CRITICAL CARE

Renal oxygenation in clinical acute kidney injury

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Introduction

Renal oxygenation is defined as the relationship between renal oxygen delivery (DO_2) and renal oxygen consumption (VO_2) and it can easily be shown that the inverse of this relationship is equivalent to renal extraction of O_2 (O_2Ex). An increase in renal O_2Ex means that renal DO_2 has decreased in relation to renal VO_2, i. e., renal oxygenation is impaired, and *vice versa*. When compared to other major organs, renal VO_2 is relatively high, second only to the heart. In sedated, mechanically ventilated patients, renal VO_2 is two-thirds (10 ml/min) that of myocardial oxygen consumption (15 ml/min) (Table 1) [1,2]. Renal blood flow, which accounts for approximately 20 % of cardiac output, is three times higher than myocardial blood flow in this group of patients. Renal O_2Ex in the non-failing kidney is therefore low, 10 %, compared with, e.g., the heart, in which O_2E_X is 55 % (Table 1).

Determinants of renal oxygenation

It is well known from experimental studies that tubular sodium reabsorption is the major determinant of renal VO_2 [3] and that under normal physiological conditions, approximately 80 % is used to drive active tubular transport of particularly sodium, but also glucose, amino acids and other solutes. Tubular transport processes are highly load-dependent and it has been shown in experimental studies [4] and in patients [2,5–7] that there is a close linear correlation between glomerular filtration rate (GFR), renal sodium reabsorption and renal VO_2 (Fig. 1). The filtered load of sodium is, thus, an important determinant of renal VO_2 and maneuvers that decrease GFR and the tubular sodium load act to decrease tubular sodium reabsorption and renal VO_2, and *vice versa* [8]. It has been shown that renal O_2Ex remains stable over a wide range of renal blood flows, which means that

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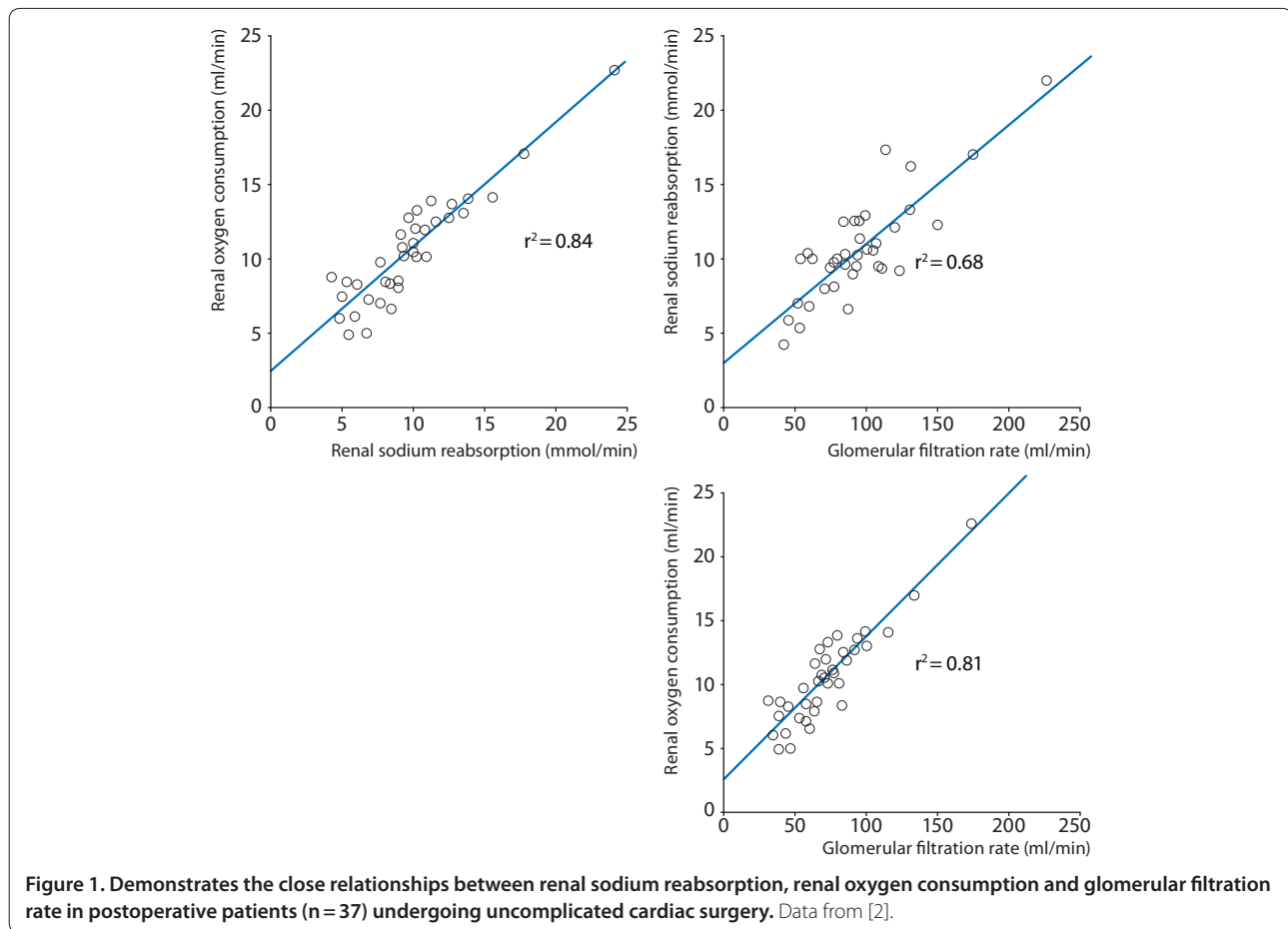**Table 1. Renal and myocardial oxygen/demand supply relationship in postoperative mechanically ventilated patients**

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

changes in renal DO_2, caused by changes in renal blood flow, are directly offset by changes in renal VO_2 [9], i. e., renal VO_2 is flow-dependent. Thus, unlike other organs where increases in blood flow will improve oxygenation, increased renal blood flow augments GFR and the filtered load of sodium, which will increase renal VO_2. Due to this flow-dependency of renal VO_2, renal oxygenation will remain constant, as long as renal blood flow and GFR change in parallel.

Regional intrarenal oxygenation and medullary hypoxia

The relatively high renal blood flow is directed preferentially to the cortex to optimize the filtration process and solute reabsorption. In contrast, blood flow in the outer medulla is less than 50 % of the cortical blood flow to preserve osmotic gradients and to enhance urinary concentration [10]. The combination of low medullary perfusion, high oxygen consumption of the medullary thick ascending limbs (mTAL) and the countercurrent exchange of oxygen within the vasa recta, results in a poorly oxygenated outer medulla [11]. Oxygen availability is, therefore, low in the outer medulla, which has an oxygen tissue partial pressure (PO_2) of 10–20 mm Hg compared to 50 mm Hg in the cortex. Thus, as the outer medulla is on the border of hypoxia already under normal conditions, it is particularly sensitive to prolonged or intermittent episodes of low renal DO_2, caused by hypoperfusion or hemodilution. This condition may occur, in particular, after major surgery (especially cardiac or vascular surgery) or severe heart failure, which are

Figure 1. Demonstrates the close relationships between renal sodium reabsorption, renal oxygen consumption and glomerular filtration rate in postoperative patients (n = 37) undergoing uncomplicated cardiac surgery. Data from [2].

common causes of ischemic acute kidney injury (AKI) in the intensive care unit (ICU).

Cardiovascular surgery is a 'clinical model' of human AKI. Because it is known when postoperative AKI may occur, in this group of patients, timely, therapeutic interventions for prevention and treatment of early AKI could be instituted. In this situation, it would be logical to improve the renal oxygen supply/demand relationship by augmenting renal DO_2 and/or reducing renal VO_2, i. e., to improve renal oxygenation.
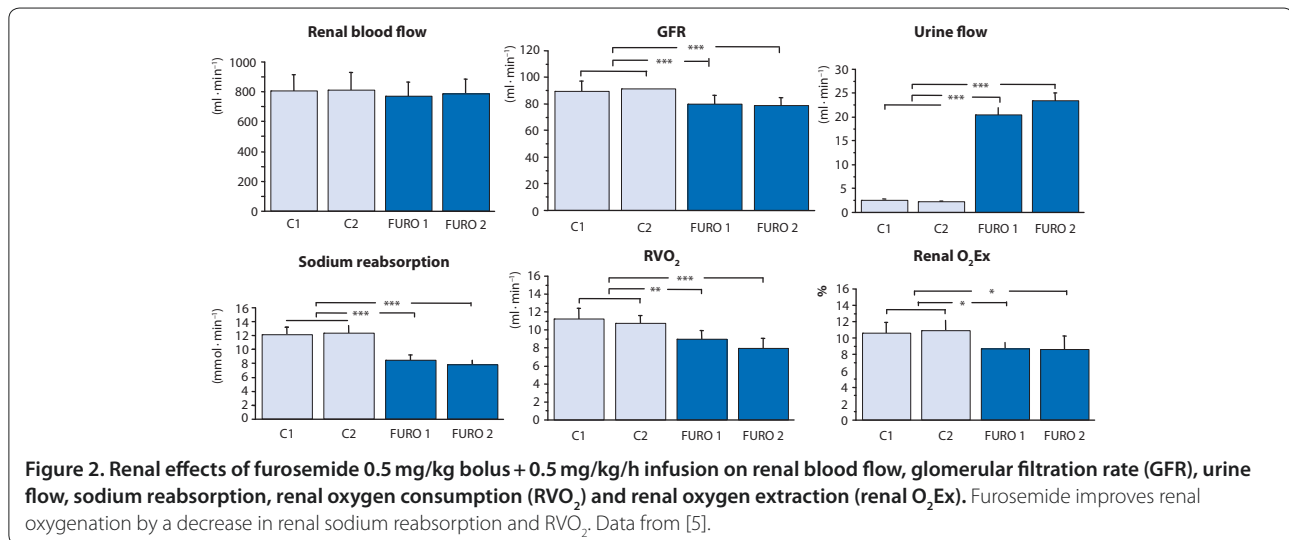
Effects of diuretics on renal oxygenation in the postoperative patient

It has repeatedly been shown in experimental studies that furosemide and other loop-diuretics (ethacrynic acid, bumetanide) inhibit renal sodium reabsorption and VO_2 in the mTAL (e.g., [12]). This decrease in reabsorptive work will increase oxygen availability and consequently increase the tissue PO_2 of the medulla [11]. Because of this decrease in renal oxygen demand, furosemide could potentially exert preventive renoprotective effects. Indeed, several reports have demonstrated that furosemide causes renoprotection in experimental ischemic AKI

(e.g., [13,14]). Most likely this is mediated by a decrease in medullary VO_2 which will increase the tolerance to renal ischemia, but it has also been suggested that the greater urine flow may 'flush out' tubular casts and thereby reduce intratubular obstruction and the back-leak of filtered urine [15].

Prasad et al. demonstrated in conscious volunteers that 20 mg of furosemide increased medullary oxygenation, using the blood oxygen level-dependent magnetic resonance imaging technique (BOLD MRI) [16]. In contrast, acetazolamide, which inhibits tubular reabsorption of the proximal tubules in the cortex and which does not affect medullary PO_2 in experimental studies, did not affect medullary oxygenation.

Swärd et al. evaluated the renal effects of a bolus dose of furosemide (0.5 mg/kg) followed by an infusion (0.5 mg/kg/h) in the early period after cardiac surgery with cardiopulmonary bypass (CPB), using the retrograde renal vein thermodilution technique and renal extraction of [51]chromium-ethylene-diaminetetraacetic acid (^{51}Cr-EDTA) for rapid bedside estimation of RBF and GFR without the need for urine collection [5] (Fig. 2). Furosemide increased fractional excretion of sodium (excreted

Figure 2. Renal effects of furosemide 0.5 mg/kg bolus + 0.5 mg/kg/h infusion on renal blood flow, glomerular filtration rate (GFR), urine flow, sodium reabsorption, renal oxygen consumption (RVO_2) and renal oxygen extraction (renal O_2Ex). Furosemide improves renal oxygenation by a decrease in renal sodium reabsorption and RVO_2. Data from [5].

sodium/filtered sodium) from 2 % to 25 % and caused a 10-fold increase in urine flow because of a 28 % decrease in tubular sodium reabsorption. These changes were in turn associated with a 23 % decrease in renal VO_2. Thus, furosemide decreased renal O_2Ex and improved renal oxygenation as renal blood flow was not significantly affected by the diuretic. Interestingly, GFR decreased by 12 % with furosemide, which could be explained by an increased delivery of sodium to the distal tubules activating the tubuloglomerular feedback mechanism, eventually inducing a constriction of the afferent arterioles and a decrease in GFR [17]. This mechanism could explain the findings of Lassnigg et al., who demonstrated in low-risk cardiac surgery patients with normal renal function that furosemide lowered creatinine clearance postoperatively [18]. The authors, therefore, suggested that loop-diuretics could be detrimental to the patients in terms of renal function and outcome. Another hypothesis would be that furosemide improves the renal oxygen demand/supply relationship and, thus, could increase the tolerance to perioperative renal ischemia, and that the mild to moderate fall in GFR with furosemide is a direct pharmacological consequence (tubuloglomerular feedback activation) of the agent which, if anything, would further decrease renal VO_2. In future studies, the potential preventive renoprotective effects of furosemide should be evaluated in high-risk surgical patients. Furthermore, GFR or creatinine clearance should not be used as the early primary end-point in such studies, because of the furosemide-induced pharmacological activation of the tubuloglomerular feedback mechanism, which will *per se* decrease GFR. Instead markers of tubular injury should be measured, to evaluate whether or not the improved renal oxygenation with furosemide could prevent tubular ischemic cell injury in high-risk surgical patients.

Effects of dopaminergic agents on renal oxygenation in the postoperative patient

Dopamine has been used to prevent acute renal dysfunction in cardiac surgery in the belief that dopamine increases renal blood flow. The preventive effect has, however, been questioned [19–21]. A prospective, randomized controlled trial showed that low-dose dopamine did not affect renal outcome in septic patients with early AKI [22]. It has also been speculated that a dopamine-induced inhibition of proximal tubular Na^+ reabsorption may increase delivery of Na^+ to potentially ischemic distal tubular cells in the medulla, which would increase their oxygen demands [19]. Thus, a dopamine-induced increase in renal VO_2 may have the potential to impair renal oxygenation, which could be detrimental in the treatment of early ischemic acute renal failure [19].

Redfors et al. recently studied the effects of low-dose (2–4 μg/kg/min) dopamine on renal blood flow, GFR, tubular sodium reabsorption, renal VO_2 and the renal oxygen demand/supply relationship in post-cardiac surgery patients [23]. Renal blood flow was estimated by two independent techniques, the retrograde renal vein thermodilution technique and the paraaminohippuric acid (PAH) infusion clearance technique, with correction for renal extraction of PAH. Interestingly, low-dose dopamine induced pronounced renal vasodilation with a 45–55 % increase in renal blood flow. One would expect that such a marked increase in renal blood flow would be accompanied by a proportional increase in GFR (Fig. 3). However, GFR was not significantly affected by dopamine. Thus, because of the lack of effect of dopamine on GFR, renal VO_2 was not affected and, consequently, renal oxygenation was improved (Fig. 3). Thus, the hypothesis put forward by Jones and Bellomo [19], that dopamine may
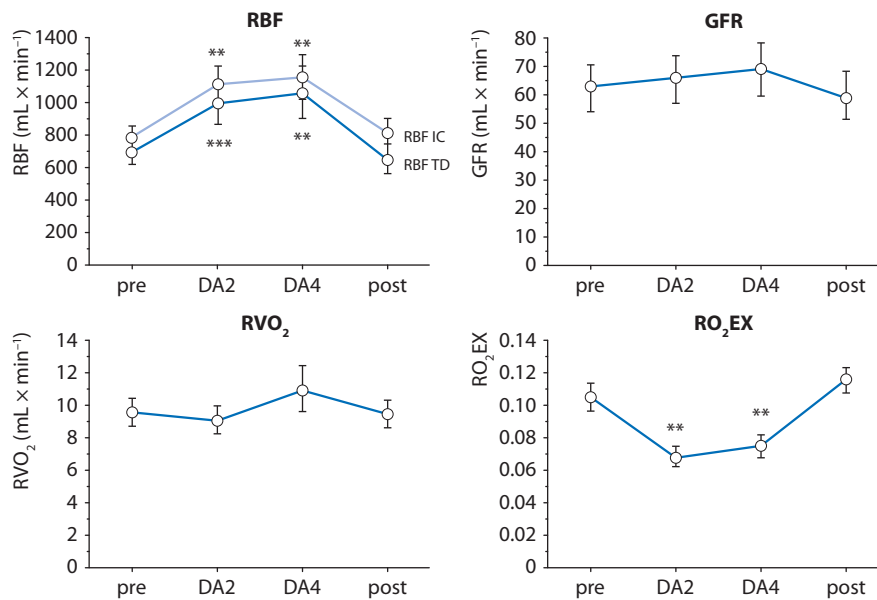
Figure 3. Effects of 2 and 4 µg/kg/min of dopamine (DA2, DA4) on renal blood flow (RBF), glomerular filtration rate (GFR), renal oxygen consumption (RVO₂) and renal oxygen extraction (RO₂Ex) in postoperative patients. RBF was measured by two independent techniques, retrograde renal vein thermodilution (RBF-TD) and infusion clearance for paraaminohippuric acid (PAH), with correction for renal extraction of PAH (RBF-IC). Note that low-dose dopamine improved renal oxygenation by a profound renal vasodilation with no changes in GFR or RVO₂. From [23] with permission.

impair renal oxygenation is not supported by the data from Redfors et al. [23].

The lack of effect of dopamine on GFR in postoperative patients highlights the common misunderstanding that an increase in renal blood flow by a renal vasodilator is always accompanied by an increase in GFR. The effect of a renal vasodilator on GFR is dependent on its effect on the longitudinal distribution of renal vascular resistance. The dopamine-induced increase in renal blood flow with no significant effect on GFR is explained by a renal vasodilatory action on pre- and postglomerular resistance vessels. Experimental studies have revealed that dopamine-mediated renal vasodilation predominantly is effected at the post-synaptic dopamine-1 (DA-1) receptors and that dopamine and other DA-1-receptor agonists dilate afferent and efferent arterioles to the same degree [24]. Studies on the effects of low-dose dopamine in volunteers or patients on renal plasma flow and GFR, as measured by clearance techniques are listed in Table 2. Note that in all studies, renal plasma flow increased, whereas in half the studies, GFR was not affected; in the remaining half, the increase in GFR was considerably lower than the increase in renal plasma flow.

The capacity of dopamine to improve renal oxygenation in postoperative patients would make it suitable for prevention of AKI, as it would increase the tolerance to renal ischemia in major surgery. However, the potential preventive effect of dopamine has not been evaluated in high-risk cardiovascular surgery. Although interest in the use of dopamine for renoprotection has decreased, interest in the use of another dopaminergic agent, fenoldopam, which exerts the same renal effects as dopamine [24], is, strangely enough, increasing. Fenoldopam is a selective dopamine-1 receptor agonist with no β-1 or α-adrenergic receptor agonistic effects and similar to dopamine, it increases renal plasma flow with no effects on GFR, as demonstrated in healthy volunteers [25]. In three preventive, randomized controlled trials in abdominal aortic surgery [26] and high-risk cardiac surgery [27], fenoldopam improved creatinine clearance compared to placebo. These beneficial effects on renal outcome with fenoldopam and the lack of similar beneficial effects with dopamine (see above), despite similar pharmacological actions, could be explained by the fact that the potential preventive renal effects with dopamine and fenoldopam were evaluated in low-risk and high-risk patients, respectively. Bove et al. compared the preventive effects of fenoldopam and dopamine (2.5 µg/kg/min) on renal excretory function in high-risk cardiac surgery and found, not surprisingly, no difference between the two dopaminergic agents on percentage postoperative increase in serum creatinine [28].

Renal oxygenation in clinical ischemic acute kidney injury

Patients undergoing cardiac surgery with CPB are at high risk of developing postoperative AKI, with a reported

Table 2. Effects of low-dose dopamine on renal plasma flow (RPF) and glomerular filtration rate (GFR) in healthy volunteers and patients, as assessed by clearance techniques

Author [ref]	Year	Patients	RPF	GFR
Ter Wee [51]	1986	Volunteers	Increase	Increase
Schoors [52]	1990	Volunteers	Increase	No effect
Olsen [53]	1993	Volunteers	Increase	No effect
Olsen [54]	1993	Volunteers	Increase	Increase
Olsen [55]	1994	Volunteers	Increase	No effect
Richer [56]	1996	Volunteers	Increase	No effect
McDonald [57]	1964	Heart failure	Increase	Increase
Rosenblum [58]	1972	Heart failure	Increase	Increase
Schwartz [59]	1988	Vascular surgery	Increase	Increase
Graves [60]	1993	Burn injury	Increase	No effect
Ungar [61]	2004	Heart failure	Increase	Increase
Redfors [23]	2010	Cardiac surgery	Increase	No effect

Table 3. Renal perfusion, filtration and oxygenation in postoperative acute kidney injury (AKI) [2]

	Control group (n = 37)	AKI group (n = 12)	p-value
Mean arterial pressure (mm Hg)	73.9 ± 1.1	73.5 ± 0.7	ns
Cardiac index (l/min/m²)	2.63 ± 0.08	2.77 ± 0.16	ns
RBF (ml/min)	758 ± 40	477 ± 54	< 0.001
RVR (mm Hg/ml/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

RBF: renal blood flow assessed by the thermodilution technique; RVR: renal vascular resistance; GFR: glomerular filtration rate. Values are means ± SEM.

incidence of 15–30 %, causing significant morbidity and mortality [29,30]. In patients undergoing major cardio-vascular surgery, even minor changes in serum creatinine are associated with increased in-patient mortality [31]. Postoperative AKI in this group of patients is considered a consequence of impaired renal DO_2, in turn caused by intra-operative hypotension and hemodilution-induced anemia [32], as well as perioperative low cardiac output [29].

It has provocatively been stated that "acute renal failure is acute renal success" [33,34], as 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. In patients with AKI, there are few data on renal VO_2, renal blood flow, GFR and renal oxygenation and current views on renal oxygenation are presumptive and largely based on experimental studies.

Redfors et al. recently studied renal perfusion, filtration and oxygenation in patients with preoperative normal renal function developing early AKI (50–200 % increase in serum creatinine) after complicated cardiac surgery [2]. Renal blood flow was measured by renal vein retro-grade thermodilution and by infusion clearance of PAH corrected for renal extraction of PAH. In spite of a normalization of cardiac index (CI) with inotropic treat-ment with or without intra-aortic balloon pump (IABP), renal oxygenation was severely impaired in patients with early AKI, as demonstrated by a 70 % relative increase in renal O_2Ex, compared to uncomplicated post-cardiac surgery patients with normal renal function This was, in turn, caused by a pronounced renal vasoconstriction and a 40 % lower renal blood flow, in combination with a renal
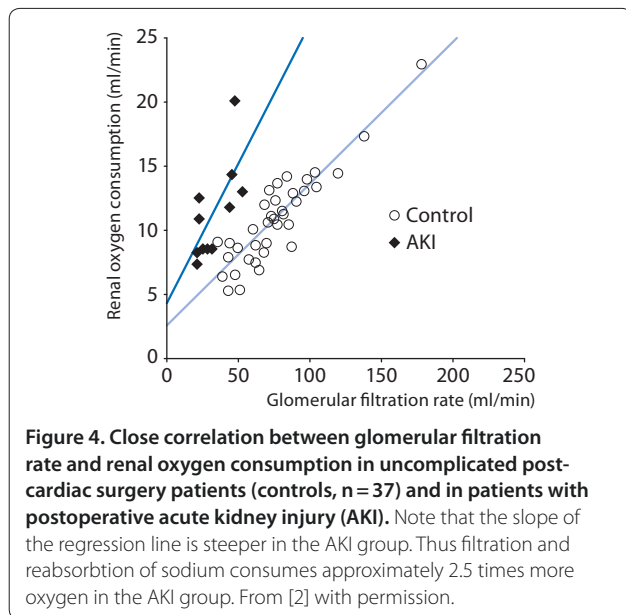
VO_2 that was not significantly different from the control group, despite the 60 % decrease in GFR and renal tubular sodium reabsorption (Table 3). Thus, the renal VO_2 of the AKI patients was 1.9 ml/mmol reabsorbed sodium, a value that was 2.4 times higher than in the uncomplicated control group (0.82 ml/mmol reabsorbed sodium). Figure 4 shows the close correlation between GFR and renal VO_2 in patients with early AKI after cardiac surgery versus those undergoing uncomplicated surgery with no renal impairment. According to the "acute renal success"-hypothesis [42–44], as put forward by several researchers, AKI patients should operate on the lower part of the regression line of the control patients. However, the regression line of the AKI patients is clearly shifted to the left, i. e., at a certain GFR, renal VO_2 is higher, speaking against this hypothesis. On the contrary, the 40 % decrease in renal DO_2 in combination with a tubular sodium reabsorption at a high oxygen demand, suggests that renal hypoxia is present after the initiation phase of ischemic AKI.

One can only speculate on the mechanisms underlying the leftward shift of the GFR/renal VO_2 relationship in AKI patients. A potential explanation could be loss of epithelial cell-polarization and tight junction integrity in AKI, as has been shown in experimental studies and after human renal transplantation [35], making tubular sodium reabsorption less efficient [36]. Another explanation may be diminished renal nitric oxide (NO) generation because of endothelial damage and downregulation of endothelial NO synthase (eNOS/NOS-3). NO is a major regulator of microvascular oxygen supply and renal VO_2 [37]. Through vasodilation, NO increases renal blood flow and hence DO_2. Furthermore, contemporary work suggests that NO acts as a 'brake' on oxidative metabolism at various sites, including direct competition of NO with oxygen for mitochondrial respiration and inhibition of cytochrome c oxidase [38].

Figure 4. Close correlation between glomerular filtration rate and renal oxygen consumption in uncomplicated post-cardiac surgery patients (controls, n = 37) and in patients with postoperative acute kidney injury (AKI). Note that the slope of the regression line is steeper in the AKI group. Thus filtration and reabsorbtion of sodium consumes approximately 2.5 times more oxygen in the AKI group. From [2] with permission.
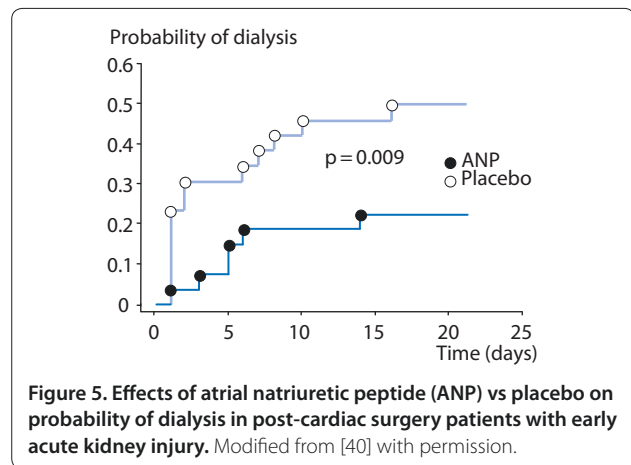

Figure 5. Effects of atrial natriuretic peptide (ANP) vs placebo on probability of dialysis in post-cardiac surgery patients with early acute kidney injury. Modified from [40] with permission.
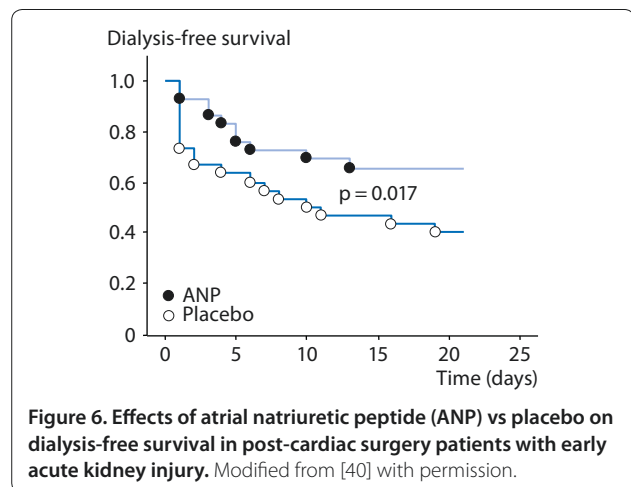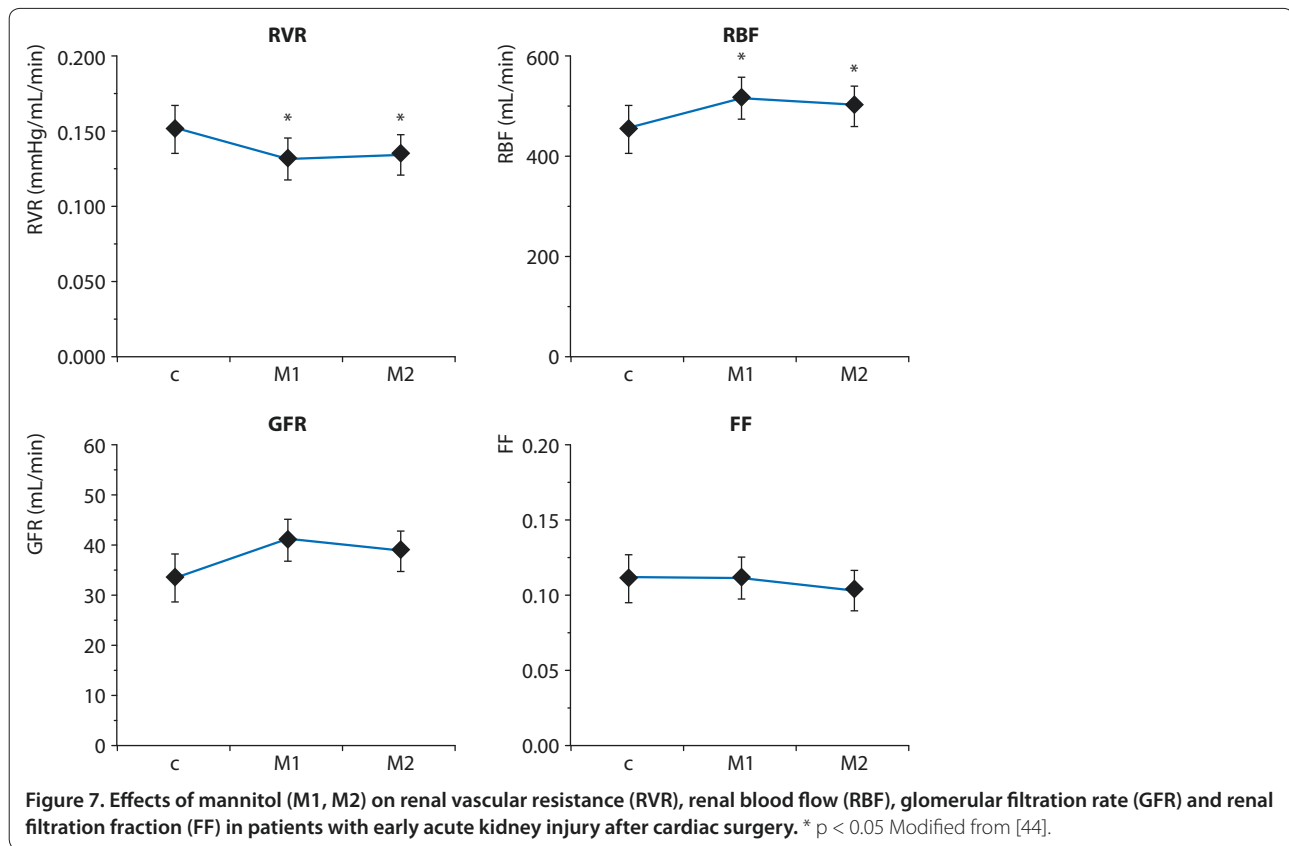

Figure 6. Effects of atrial natriuretic peptide (ANP) vs placebo on dialysis-free survival in post-cardiac surgery patients with early acute kidney injury. Modified from [40] with permission.

Treatment of clinical ischemic AKI

The major goal in the management of early AKI is to increase GFR. However, because of the close association between GFR, tubular sodium reabsorption and renal VO_2 in humans [5–7], a pharmacologically-induced increase in GFR will increase renal VO_2 and potentially further impair renal oxygenation in patients with AKI. Thus, an ideal agent to treat ischemic AKI would be one that increases both renal blood flow and GFR, i. e., an agent that preferentially induces vasodilation of the preglomerular resistance vessels. Such an agent will not only increase GFR but also meet the increased renal metabolic demand of the medulla by an increase in renal DO_2. It is not likely that the potent renal vasodilator, dopamine, will improve GFR in early clinical ischemic AKI as it exerts a non-specific renal vasodilation of pre- and postglomerular resistance vessels with a pronounced effect on total renal vascular resistance and renal blood flow but with no or minor effects on glomerular hydraulic pressure and GFR (see above). This could explain why low-dose dopamine (2 μg/kg/min) does not improve renal outcome, measured as peak serum creatinine, in ICU patients with systemic inflammatory response syndrome and early AKI [22].

Atrial natriuretic peptide (ANP) is a renal vasodilator, which causes a balanced 30–40 % increase in both renal blood flow and GFR in patients with early ischemic AKI after complicated cardiac surgery [39]. Although, the effects of ANP on renal oxygenation have not been studied, it is less likely that ANP would impair renal oxygenation because of its preferential action on the preglomerular resistance vessels. This is further supported by the findings from a prospective, randomized, blinded trial by Swärd et al., who showed that infusion of ANP enhanced renal excretory function, decreased the probability of dialysis and improved dialysis-free survival in early, ischemic AKI after complicated cardiac surgery [40] (Figs. 5 and 6).

Another approach for the treatment of clinical ischemic AKI would be to target the vascular endothelium and tubular epithelium. Experimental studies have shown that mannitol may decrease ischemia-induced swelling of tubular cells, which might obstruct the tubular lumen [41]. Mannitol treatment has been shown to increase GFR in patients after severe trauma or surgery [42]. In addition, our group has shown that mannitol increases GFR in postoperative cardiac surgery patients possibly by a de-swelling effect on tubular cells [6]. Furthermore, it has been suggested that outer medullary hypoxia may cause endothelial ischemic injury and endothelial cell swelling contributing to congestion and impaired perfusion of this region [43], which could, at least to some extent, explain the high renal vascular resistance seen in clinical early AKI [2]. The effects of mannitol treatment

Figure 7. Effects of mannitol (M1, M2) on renal vascular resistance (RVR), renal blood flow (RBF), glomerular filtration rate (GFR) and renal filtration fraction (FF) in patients with early acute kidney injury after cardiac surgery. * $p < 0.05$ Modified from [44].

on renal perfusion, filtration and oxygenation were recently studied in patients with normal preoperative creatinine, who developed early AKI after complicated cardiac surgery, requiring inotropic support with or without IABP [44]. Mannitol induced a 60 % increase in diuresis, which was accompanied by decrease in renal vascular resistance and a 12–15 % increase in renal blood flow, while no effects were seen on cardiac index or cardiac filling pressures. Mannitol did not affect filtration fraction or renal oxygenation, suggestive of balanced increases in perfusion/filtration and renal oxygen demand/supply (Fig. 7).
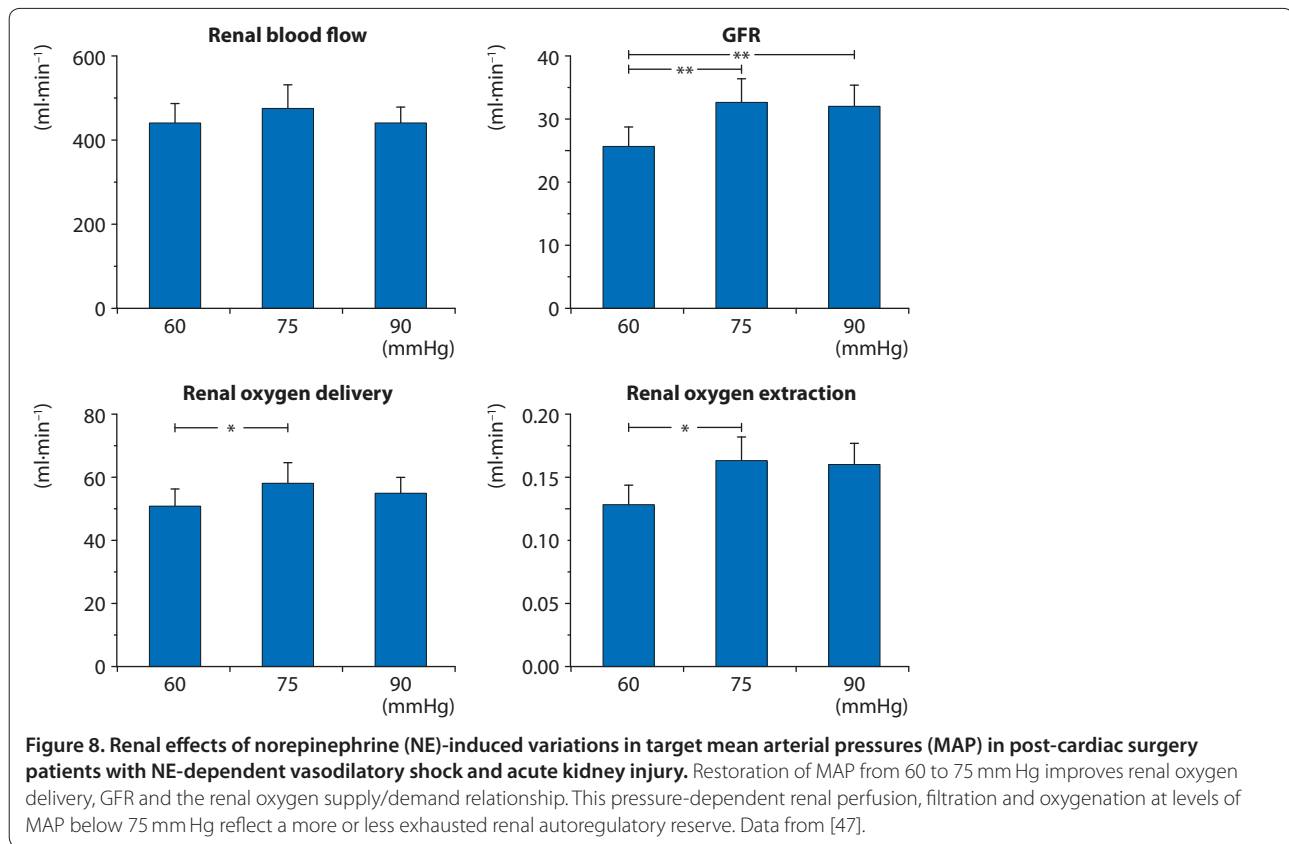
Vasodilatory shock and AKI: role of norepinephrine

Vasodilatory shock is not uncommon after complicated cardiac surgery with CPB and occurs often in conjunction with postoperative heart failure [45]. The recommended agent for treatment of volume-resuscitated vasodilatory shock is norepinephrine [46]. Patients with vasodilatory shock after cardiac surgery with CPB may suffer from concomitant AKI. The use of norepinephrine for treatment of vasodilatory shock in patients with ischemic AKI with impaired renal oxygenation is a "two-edged sword" as it may further aggravate renal ischemia. On the other hand, too low a dose of norepinephrine may result in an arterial blood pressure that may be below the limit of

renal autoregulation, i. e., when renal blood flow becomes pressure-dependent.

In a recent study in post-cardiac surgery patients with norpinephrine-dependent vasoplegia and concomitant AKI, the effects of norepinephrine on renal perfusion, filtration and oxygenation were evaluated [47]. Norepinephrine infusion rate was randomly and sequentially titrated to target a mean arterial pressures (MAP) of 60, 75 and 90 mm Hg. At each target MAP, data on renal blood flow, GFR and renal O_2Ex were obtained by the renal vein thermodilution technique and by renal extraction of ^{51}Cr-EDTA. At a target MAP of 75 mm Hg, renal DO_2 (13 %), GFR (27 %) and urine flow were higher and renal O_2Ex was lower (−7.4 %) compared with a target MAP of 60 mm Hg. However, the renal variables did not differ when compared at target MAPs of 75 and 90 mm Hg (Fig. 8). Thus, restoration of MAP from 60 to 75 mm Hg improves renal DO_2, GFR and renal oxygenation in patients with vasodilatory shock and AKI. The pressure-dependent renal perfusion, filtration and oxygenation at levels of MAP below 75 mm Hg reflect a more or less exhausted renal autoregulatory reserve.

Low-dose vasopressin and renal oxygenation
Resistance to norepinephrine and other catecholamines may develop in vasodilatory shock because of adrenergic

Figure 8. Renal effects of norepinephrine (NE)-induced variations in target mean arterial pressures (MAP) in post-cardiac surgery patients with NE-dependent vasodilatory shock and acute kidney injury. Restoration of MAP from 60 to 75 mm Hg improves renal oxygen delivery, GFR and the renal oxygen supply/demand relationship. This pressure-dependent renal perfusion, filtration and oxygenation at levels of MAP below 75 mm Hg reflect a more or less exhausted renal autoregulatory reserve. Data from [47].
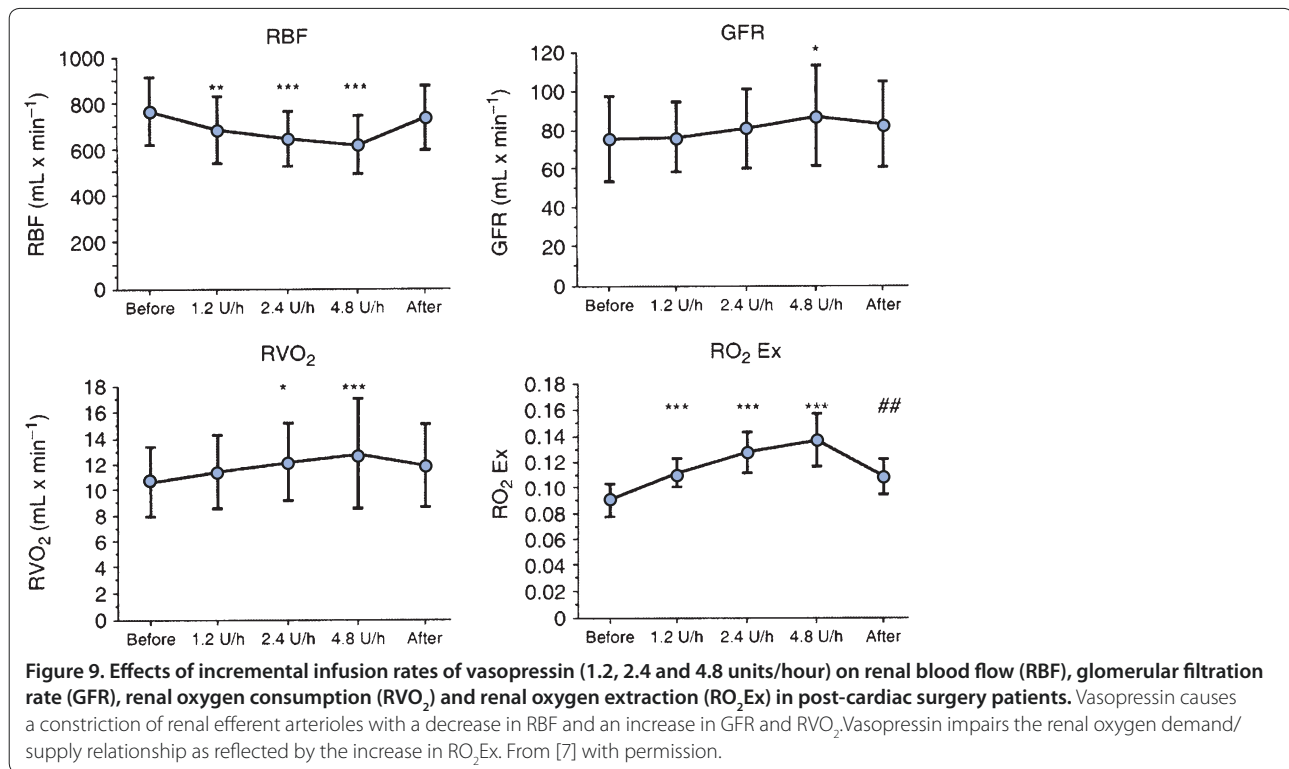
receptor downregulation and endogenous vasodilators. Furthermore, plasma levels of vasopressin are low in post-cardiotomy vasodilatory shock and in septic shock in contrast to hypovolemic and cardiogenic shock [48]. Vasopressin has, therefore, been suggested as an additional or an alternative therapy in catecholamine-dependent vasodilatory shock [49]. It has also been reported that vasopressin increases creatinine clearance, a surrogate variable of GFR, in these patients [50]. A more detailed analysis on the effects of low-dose vasopressin on renal oxygenation is lacking.

Bragadottir et al. evaluated the renal effects of low-doses (1.2, 2.4, 4.8 U/h) of vasopressin in post-cardiac surgery patients, doses that did not affect systemic blood pressure [7]. Vasopressin exerted a dose-dependent increase in GFR, sodium reabsorption, renal VO_2, renal O_2Ex and renal vascular resistance, whereas renal blood flow decreased. Thus, vasopressin considerably impaired renal oxygenation by postglomerular vasoconstriction, which induced a decrease in renal blood flow and an increase in both GFR and renal VO_2 (Fig. 9). From a renal point of view, vasopressin should be used with caution in the treatment of vasodilatory shock, because it has the potential to cause considerable renal oxygen supply/demand mismatch.

Conclusion

In spite of the apparent luxury oxygenation of the kidneys, with a high renal DO_2 in relation to renal VO_2, the outer medulla is on the border of hypoxia in the normal situation. Outer medullary hypoxia, caused by low medullary perfusion, high VO_2 of the medullary thick ascending limbs and the countercurrent exchange of oxygen, is the price the kidneys have to pay for the urine concentration mechanism. The outer medulla is, therefore, particularly sensitive to prolonged or intermittent episodes of low renal DO_2. Dopaminergic agents (dopamine/fenoldopam) and loop-diuretics improve renal oxygenation, and potentially prevent ischemic AKI, whereas vasopressin impairs renal oxygenation in postoperative patients.

Renal oxygenation is impaired in early clinical ischemic AKI because of a low renal blood flow, caused by vasoconstriction and endothelial swelling, in combination with a tubular reabsorption at a high oxygen demand. ANP is ideally suited for treatment of ischemic AKI, as it preferentially dilates the preglomerular resistance vessels; this will increase GFR but also renal blood flow, meeting the increased oxygen demand of the medulla by an increase in renal DO_2. Mannitol increases renal blood flow and GFR in clinical ischemic AKI most likely by endothelial and epithelial de-swelling effects.

Figure 9. Effects of incremental infusion rates of vasopressin (1.2, 2.4 and 4.8 units/hour) on renal blood flow (RBF), glomerular filtration rate (GFR), renal oxygen consumption (RVO$_2$) and renal oxygen extraction (RO$_2$Ex) in post-cardiac surgery patients. Vasopressin causes a constriction of renal efferent arterioles with a decrease in RBF and an increase in GFR and RVO$_2$. Vasopressin impairs the renal oxygen demand/supply relationship as reflected by the increase in RO$_2$Ex. From [7] with permission.

Competing interests
The authors declare that they have no competing interests.

List of abbreviations used
AKI: acute kidney injury; ANP: atrial natriuretuc peptide; BOLD MRI: bold oxygen level-dependent magnetic resonance imaging; CI: cardiac index; CPB: cardiopulmonary bypass; Cr-EDTA: chromium-ethylene-diaminetetraacetic acid; DA-1: dopamine-1; DO$_2$: oxygen delivery; GFR: glomerular filtration rate; IABP: intra-aortic balloon pump; ICU: intensive care unit; MAP: mean arterial pressure; mTAL: medullary thick ascending limbs; NO: nitric oxide; O$_2$Ex: renal extraction of O$_2$, PAH: paraaminohippuric acid; PO$_2$: oxygen tissue partial pressure; RBF: renal blood flow; RVR: renal vascular resistance; VO$_2$: renal oxygen consumption.

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