The role of the microcirculation in acute kidney injury

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Purpose of review

Alterations of the renal microcirculation can promote the development of acute kidney injury through the interlinked occurrence of renal hypoxia and activation of inflammatory pathways. This review focuses on the recent advances in this area, and discusses the possible therapeutic interventions that might be derived from these insights.

Recent findings

Endothelial injury acts as a primary event leading to renal hypoxia with disturbances in nitric oxide pathways playing a major role. The unbalanced homeostasis between nitric oxide, reactive oxygen species and renal oxygenation forms a major component of the microcirculatory dysfunction. Furthermore, injury leads to leukocyte–endothelial interaction that exacerbates renal hypoxia at a microcirculatory level.

Summary

Knowledge of the pathophysiological mechanisms of acute kidney injury emphasizes the importance of the role of the microcirculation in its development. Preventive and therapeutic approach should be based on restoring the homeostasis between nitric oxide, reactive oxygen species and renal oxygenation.

Keywords

acute kidney injury, acute renal failure, endothelium, microcirculation, nitric oxide, oxygenation, reactive oxygen species

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Introduction

Acute kidney injury (AKI) occurs in 1–35% of hospitalized patients and yields a high mortality rate [1]. Whereas the incidence after a general surgery has been reported to be about 1%, the incidence among critically ill patients reaches 35%, with an in-hospital mortality rate above 50% when AKI develops as a part of multiple organ dysfunction syndrome [2]. AKI appears as an independent risk factor of death [3•] and can ultimately lead to chronic kidney disease. AKI is further associated with higher cost, especially related to demand of transplantation and renal replacement therapy [4].

Ischemia is the most common cause of AKI in both native and transplanted organs [5], with kidney transplantation, treatment of supra-renal aneurysms, cardiac surgery and renal artery reconstructions, contrast-agent nephropathy, cardiac arrest, sepsis and shock being all common situations exposing the kidney to ischemic injury. The appreciation that altered vascular function and ischemic-induced hypoxia contribute to AKI is not new but has gained recent insight with potential therapeutic targets emerging. The aim of this review is to describe how the renal microcirculatory alterations can promote the development of AKI through the interlinked occurrence of renal hypoxia and activation of inflammatory pathways. Further potential therapeutics implications are discussed.

Ischemic-induced renal hypoxia

One of the primary functions of the microcirculation – a network of vessels less than 150 μm in diameter comprising arterioles, capillaries and venules – is to ensure adequate oxygen delivery to meet the metabolic demand of every single cell. The unique microvasculature architecture of the kidney, associated with a high oxygen demand from the tubular salt-water reabsorption, makes it an organ highly sensitive to hypoxia [6•]. The chief function of the kidney (i.e. filtration of plasma and formation of urine) dictates the renal blood flow to be much higher than necessary to meet the metabolic requirement (the kidneys receive approximately 20% of cardiac output but they account only for 0.5% of total body weight). However, oxygen tensions in the kidney are low, from 70 mmHg in the cortex, to 20 mmHg in the medulla [7]. The reason for this remarkable discrepancy between blood supply and oxygenation is the unique architecture of the renal microvasculature which is regionally specialized. The cortex receives a large amount of blood for the filtration function. In contrast, maintenance of the corticomedullary osmotic gradients

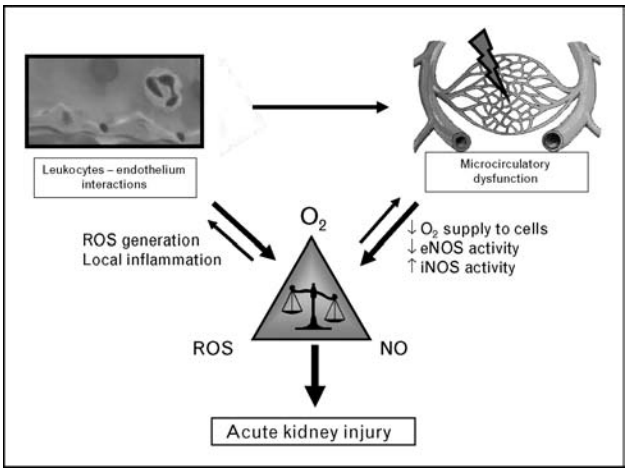
requires low blood flow through the vasa recta. Therefore, the renal microcirculation is found serially organized with almost all descending vasa recta emerging from the efferent arterioles of the juxtamedullary glomeruli. This combined with O_2 arterio-venous shuntings between the descending and ascending vasa recta further compromises oxygen supply to the medulla [8].

The effects of limited O_2 supply are aggravated by the high O_2 demand within the kidney. Under normal physiological conditions, approximately 80% of renal oxygen consumption is being used to drive Na-K-ATPase in the proximal tubule, the site of reabsorption of approximately two-thirds of the NaCl that enters the tubular fluid by glomerular filtration. Thus, factors involved in the glomerular filtration rate strongly influence medullary oxygenation by modifying the amount of solute delivered to the tubules [9]. To summarize, adequate renal oxygenation depends upon the balance between microcirculatory oxygen supply and renal oxygen consumption driven by the electrolytes reabsorption activity.

Ischemic AKI mainly results from severe reductions in renal blood flow. After reperfusion, incomplete recovery of renal blood flow is commonly observed, which is known as the 'no-reflow' phenomenon. Recent image analysis techniques have shed light on the physiopathology of ischemia–reperfusion injury showing morphological signs of vascular injury and flow cessation in both peritubular and glomerular capillaries, both in animal study and human transplanted kidneys [10,11,12•]. Disruption of the endothelial cell–cell junctions, alterations of endothelial glycocalyx or endothelial actin cytoskeleton have all been reported in AKI [13] and can lead to increased microcirculatory permeability and interstitial edema [14]. In the same line, endothelial cell swelling, activation of the coagulation pathway and subsequent red blood cells trapping can result in obstruction of the lumen of microvessels. These morphological alterations of the microcirculatory architecture and the perfusion defects at the microcirculatory level are believed to impair oxygen delivery to the cells and promote organ damage [15•] (Fig. 1).

Brodsky *et al.* [16] have underlined the central role of endothelial cell dysfunction in AKI in infusing endothelial cells from the umbilical vein after release of the renal artery and demonstrated protection of the kidney against subsequent loss of function. One of the main functional consequences of endothelial injury is the impairment of endothelium-dependent vasorelaxation and increased reactivity to vasoconstrictive agents. Numerous mediators are involved in this dysfunction, such as prostaglandins, endothelium-derived hyperpolarizing factor, endothelin, angiotensin II, thromboxane A2, sympathic nerve stimulation and nitric oxide [17]. As an example, endothelin-1 is a potent vasoconstrictor produced primarily in the kidney in response to hypoperfusion and anoxia, and endothelin-receptor antagonism has been reported to reduce renal injury after ischemia–reperfusion [18]. More recently, the imbalance between these vasoconstrictors, the nitric oxide system and oxidative stress is receiving considerable attention as a major contributor to AKI [19,20,21•]. However, the respective contribution of these pathways can depend on the nature of the injury. Whereas selective inhibition of inducible nitric oxide synthase (iNOS) has been found effective in preventing renal hypoxia after ischemia–reperfusion in rats, our group has demonstrated that this strategy did not restore renal oxygenation after lipopolysaccharide (LPS) challenge in rats, neither did exogenous nitric oxide donors [22]. In the same model, the exogenous prostacyclin analog iloprost as well as dexamethasone restored renal blood flow and corrected the LPS-induced renal hypoxic defects [23,24]. Whereas artery constriction resulting in decrease of renal blood flow (i.e. the classic 'prerenal' state of AKI) has very little impact on the renal microvascular oxygenation, a LPS infusion leading to a similar decrease of renal blood flow induces renal microvascular hypoxia [15•]. These findings suggest that the microcirculation is directly affected in septic AKI independently, at least partially, of the renal macrohemodynamic.

Figure 1 Schematic representation of our hypothesis concerning the role of the microcirculatory oxygen homeostasis and inflammation in the development of acute kidney injury



The ischemic insult will trigger leukocyte–endothelium interactions and microcirculatory dysfunction (vasoconstriction, vasodilatation, platelets-red blood cells aggregates, glycocalyx damage, and increased permeability). Activation of leukocytes will result in generation of ROS and inflammatory pathways leading to tissue and endothelial damage. Increase of the inducible nitric oxide synthase activity and uncoupling of the endothelial nitric oxide synthase will then decrease generation of eNOS-derived nitric oxide and promote generation of ROS, further compromising the renal O_2 supply and impairing the metabolic efficiency of the kidney. O_2, oxygen; ROS, reactive oxygen species; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase.

In apparent opposition to the above-mentioned concepts, dysfunction of the microcirculation might not only be viewed as a damaging process but also as an adaptive and even protective mechanism under certain conditions. In an elegant study evaluating ascending lower urinary tract infection, prevention of microcirculatory flow disturbance with heparin led to fatal urosepsis with spread of infection. The microcirculatory dysfunction might therefore be compartmentalized, analogous to the compartmentalization of inducible nitric oxide synthase, tumor necrosis factor (TNF)-α, and interleukin (IL)-1b expression in patients with septic shock caused by cellulitis [25•].

Ischemic-induced microvascular injury: the local inflammation primer

Activation of inflammation is an important component of both the initiation and extension of injury in AKI. It has become obvious that the microcirculatory dysfunction interplays with the inflammatory response through the hypoxic insults resulting from the microcirculatory flow breakdown [26].

Endothelial injury plays an active role in the recruitment of leukocytes. Numerous studies in animal models have demonstrated that ischemic-induced endothelial injury enhances endothelial expression of molecules that increase leukocytes adhesion; the first step in the diapedesis process leading to tissue infiltration [27]. Adhesion of leukocytes on the endothelium is mediated by a class of adhesion molecules known as selectins whose blockage has been demonstrated to attenuate ischemia–reperfusion injury [28]. E-selectin, specifically induced on the endothelium upon inflammatory stimulation, has been demonstrated to play a major role in leukocytes recruitment to inflammatory sites [29]. The intercellular adhesion molecule-1 (ICAM-1) appears to be particularly important for the firm attachment and transendothelial migration of leukocytes [30]. Fractalkine, a chemokine expressed on injured endothelium, acts as a chemoattractant and adhesion molecule and its inhibition has been shown to protect against kidney injury, mainly through macrophage depletion [31]. The co-stimulatory pathway B7-CD28 is another example of the central role of the endothelium in enhancing the inflammatory response: B7-1 is expressed on endothelial cells and interacts with CD28 expressed on activated antigen-presenting cells and mediates T-cell and monocytes adherence at the level of ascending vasa recta of the medullary circulation [32]. The respective contribution of neutrophils and monocytes/lymphocytes upon ischemic-induced kidney damage and dysfunction remains a matter of debate. Neutrophil infiltration was believed to occur early in the course of ischemic AKI, whereas macrophages and T cells infiltrate later in and persist into the recovery phase. This view has been recently challenged with infiltration of T cells described in the early course of AKI [33]. Further details on this topic can be found in dedicated reviews [34,35].

There is also evidence that activation of adhesion molecules is associated with changes in the cell surface glycocalyx, coating the luminal surface of the capillaries and having a significant impact on hemodynamic, coagulation, inflammation, and vascular permeability [13]. The vascular basement membrane is composed of various components, including proteoglycans such as heparin sulfate proteoglycans, which are known for their ability to bind important proteins for the inflammatory response, including L-selectin expressed on activated leukocytes and monocyte chemoattractant protein-1 expressed on activated monocytes [36]. However, the function of the glycocalyx in the renal microcirculation remains largely unknown and is a potentially fruitful area for investigation.

Whereas the hypoxic insult can result in local inflammation, endothelial–leukocyte interactions have potential paracrine effects with disturbance of the nitric oxide system which can in turn affect the renal microcirculation. The nitric oxide system which acts as a regulator of the intrarenal microcirculation and renal oxygen consumption regulation can be severely disturbed in AKI [37]. Endothelial eNOS-derived nitric oxide is essential for sustaining the renal oxygen supply after ischemia–reperfusion. It acts in a paracrine fashion, affecting surrounding cells and preventing vascular dysfunction by a direct vasodilatory effect, by inhibiting platelet aggregation and leukocytes activation [38•]. On one hand, nonselective inhibitors blocking eNOS activity have been shown to exacerbate organ ischemia [39]. On the other hand, ischemic-induced activation of iNOS, mainly in leukocytes, vascular smooth cells and epithelial tubular cells, participates in the vascular dysfunction. Selective inhibition of the iNOS component of nitric oxide generation can prevent renal injury following ischemia–reperfusion [40]. The two main pathways of iNOS-derived nitric oxide-induced damage are thought to be the inhibition of e-NOS-derived nitric oxide generation and the formation of reactive oxygen species (ROS) such as peroxynitrite [38•]. Of most importance is the interaction between the nitric oxide system and oxidative stress in the promotion of AKI. Superoxide combines rapidly with nitric oxide which results in decrease of bioavailability of nitric oxide and production of the cell-damaging compound peroxynitrite [41]. The superoxide-dependent quenching of nitric oxide is thought to decrease nitric oxide-dependent vasorelaxation following ischemia–reperfusion [42]. Various antioxidant strategies such as the use of tempol, a superoxide dismutase mimetic which scavenges intracellular radicals by permeating biological membranes, have been shown to provide beneficial

actions on AKI [43]. Traditionally, ROS have been considered to exert their effects through a direct toxic action on target cells. The basic constituents of cell, lipids, carbohydrates, proteins, and nucleic acids can be altered by ROS, leading to the loss of cell viability either by necrosis or apoptosis. However, by directly injuring the endothelium and damaging extracellular structures such as cell membranes and glycocalyx [44], ROS can also impair the endothelium-dependent vasoreactivity. In addition, ROS mediate the vasoconstrictive action of other agonists such as endothelin-1 [45], and modulate nitric oxide-dependent action. Finally, activation of the complement system in the peritubular capillaries has been described in mice. Animal studies suggest that renal ischemia–reperfusion induces changes in endothelial cells that favor complement activation in the peritubular capillaries. Once activated the complement system can generate a number of inflammatory signals [46].

Microcirculation-targeted therapeutics perspective

Several factors affecting the renal microcirculation during the process of AKI have emerged as potential therapeutic targets. However, so far translation into clinical practice has been found ineffective [47] probably due to the absence of suitably sensitive markers of developing AKI. The significance and strategies for management of AKI are currently rapidly changing with the development of new biomarkers [48] and new imaging techniques [49]. This new area will bring opportunities for new therapeutic strategies to be applied in the early course of AKI.

Correcting intravascular volume depletion with fluid administration and maintaining adequate renal perfusion pressure with vasopressors in vasoplegic states are both first-line strategies to preserve renal oxygen supply. However, the volume and choice of fluid remains a matter of debate including the need to maintain adequate renal oxygenation by blood transfusion. There is increasing evidence that hemodilution is detrimental for oxygenation of the kidney and is associated with an increased risk of AKI [50]. On the contrary, the low capacity of hemoglobin from banked blood to off-load oxygen at the microcirculatory level due to the lack of 2,3-diphosphoglycerate raises concerns about the efficacy of blood transfusion to improve tissue oxygenation and prevent organ damage [51]. This dilemma puts the physician in a delicate situation in which hemodilution should probably be limited and blood conservation strategies be encouraged. In contrast to cardiac output, no reliable test can assess renal blood flow responsiveness to fluid or vasopressor challenges. Exploration of renal vasculature resistance using renal Doppler at the bedside may prove to be a new physiological endpoint while resuscitating the kidney. Recently, Deruddre *et al.* [52] have proposed renal Doppler as a tool to titrate norepinephrine in septic shock patients based on the renal arterial resistance to determine the optimal mean arterial pressure. However, whether improvement of regional blood flow will prevent tubular damage remains to be proven.

Use of pharmacological interventions that act at the microcirculatory level may be a successful strategy to overcome ischemia-induced vascular damage and prevent AKI. Activated protein C (APC), an endogenous vitamin K-dependent serine protease with multiple biological activities, may meet these criteria. Along with antithrombotic and profibrinolytic properties, APC can reduce the chemotaxis and interactions of leukocytes with activated endothelium [53]. However, although APC has been shown to improve survival in septic shock and to shorten the time to resolution of cardiovascular and respiratory dysfunction, renal dysfunction (defined as oliguria) was not improved in the largest study published so far [54]. However, animal studies have suggested a protective effect of APC in sepsis-induced kidney injury [55]. Drugs with pleiotropic effects on the vasculature, such as erythropoietin [56] and statins [57], have the potential to prevent ischemia-induced renal failure by enhancing eNOS expression and/or improving vascular permeability, leading to improved microcirculatory function. On the basis of the mechanisms mentioned above, the use of immunosuppressive drugs and approaches to inhibit leukocyte adhesion warrant further investigation [58,59]. However, we should bear in mind that cellular components of the inflammatory response contributing to tissue damage during the early stage of injury can later provide necessary signals for the resolution of injury.

Finally, despite being an attractive pathophysiological model, neither drugs with renal vasodilatory effects (i.e. dopamine, fenoldopam, endothelin receptor blockers, adenosine antagonists) nor agents that decrease renal oxygen consumption (i.e. loop diuretics) have been shown to protect the kidney from ischemic damage [60].

In the light of the mechanisms of injury involved, of the variety of modulating each other to some degree, and interindividual differences, it is unlikely that a single treatment modality may emerge as a magic bullet in the treatment of AKI. Development of tools available at the bedside to study the perfusion and oxygenation of the renal microcirculation or of other microcirculatory compartments which may reflect altered renal function, together with the use of new biomarkers for renal injury, is needed to gain insight into the pathophysiology of AKI and for an individually tailored therapeutic strategy.

To the best of our knowledge, none of the tools assessing the microcirculation at the bedside currently under

investigations (i.e. sublingual microcirculation using Sidestream Dark-Field imaging or orthogonal polarization spectral imaging and transcutaneous tissue oxygenation or carbon dioxide techniques) has been specifically studied in the context of AKI. The recent development of new biomarkers (mainly neutrophil gelatinase-associated lipocalin and kidney injury molecule-1) for early detection of AKI is promising but is far from being specific for microvascular injury. Whether their rise can correlate with microvascular dysfunction in the context of AKI is unknown. More specific markers of vascular injury such as endothelial microparticles shedding have been shown to be associated with endothelial dysfunction in end-stage renal disease [61]. The possible relationship between circulating endothelial microparticle levels and endothelial dysfunction in AKI warrants research.

The AKI-associated microcirculatory alterations have been found to develop within a few minutes after the initial hit [10] and decrease of peritubular capillary density has been observed several months afterward [62]. However, the time sequence for microcirculatory abnormalities remains mostly elusive and so are the potential temporal windows for therapeutic interventions.

Conclusion

The renal microcirculation is recognized as a key actor in the initiation and development of AKI. Ensuring the adequate perfusion and oxygenation of the kidney is central in the prevention of AKI. The complex interplay between microvascular alterations and inflammation has emerged with microcirculatory breakdown initiating the inflammatory response and renal damage through the renal hypoxic insult. The endothelial injury appears then to be of most importance in the initiation and development of AKI through the nitric oxide pathways, ROS, leukocyte adhesion, and inflammatory response leading to regional renal hypoxia and renal dysfunction. Targeting the components of the renal microcirculation may be found an effective strategy in preventing and/or treating AKI.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 598–599).

1 Bellomo R, Ronco C, Kellum JA, *et al.* Acute renal failure: definition, outcome measures, animal models, fluids therapy and information technology needs: the second international consensus conference of acute dialysis quality initiative group. Crit Care 2004; 8:R204–212.

2 Osterman M, Chang RWS. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007; 35:1837–1843.

3 • Hoste EA, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? Crit Care Med 2008; 36:S146–S151.
This recent article provides an overview of the literature on the epidemiology of AKI in hospitalized patients.

4 Bagshaw SM. Short and long-term survival after acute kidney injury. Nephrol Dial Transplant 2008; 23:2126–2128.

5 Rosenberger C, Rosen S, Heyman SN. Renal parenchymal oxygenation and hypoxia adaptation in acute kidney injury. Clin Exp Pharmacol Physiol 2006; 33:980–988.

6 • Evans RG, Gardiner BS, Smith DW, *et al.* Intrarenal oxygenation: unique challenge and the biophysical basis of homeostasis. Am J Physiol Renal Physiol 2008; 295:F1259–F1270.
This review describes the key determinants of the oxygenation of the kidney including arterio-venous shunting.

7 Johannes T, Mik EG, Ince C. Dual-wavelength phosphorimetry for determination of cortical and subcortical microvascular oxygenation in rat kidney. J Appl Physiol 2006; 100:1301–1310.

8 Leong CL, Anderson PW, O'Connor PM, *et al.* Evidence that renal arteriovenous shunting contributes to dynamic regulation of renal oxygenation. Am J Physiol Renal Physiol 2007; 292:1726–1733.

9 Brezis M, Agmon Y, Epstein FH. Determinants of intrarenal oxygenation. 1. Effects of diuretics. Am J Physiol 1994; 267:F1059–F1062.

10 Yamamoto T, Tada T, Brodsky SV, *et al.* Intravital videomicroscopy of peritubular capillaries in renal ischemia. Am J Physiol Renal Physiol 2002; 282:F1150–F1155.

11 Wu L, Tiwari MM, Messer KF, *et al.* Peritubular capillary dysfunction and renal tubular epithelial cell stress following lipopolysaccharide administration in mouse. Am J Physiol Renal Physiol 2007; 292:F261–268.

12 • Schmitz V, Schaser KD, Olschewski P, *et al.* In vivo visualization of early microcirculatory changes following ischemia/reperfusion injury in human kidney transplantation. Eur Surg Res 2008; 40:19–25.
In this study, using orthogonal polarization (OPS) imaging, authors have shown that intraoperative disturbance of peritubular capillaries flow occurred after cold ischemia–reperfusion in kidney transplants and may be predictive of postoperative renal dysfunction.

13 Sutton TA, Mang HE, Campos SB, *et al.* Injury of the renal microvascular endothelium alters barrier function after ischemia. Am J Physiol Renal Physiol 2003; 285:F191–198.

14 Sutton TA. Alteration of microvascular permeability in acute kidney injury. Microvasc Res 2009; 77:4–7.

15 • Johannes T, Mik EG, Ince C. Nonressuscitated end endotoxemia induces microcirculatory hypoxic areas in the renal cortex in the rats. Shock 2009; 31:97–103.
In this study, using a phosphorescent quenching technique in a rat model, the authors have described that intrarenal oxygenation heterogeneity can occur after LPS challenge with occurrence of cortical microcirculatory hypoxia areas.

16 Brodsky SV, Yamamoto T, Tada T, *et al.* Endothelial dysfunction in ischemic acute renal failure: rescue by transplanted epithelial cells. Am J Physiol Renal Physiol 2002; 282:F1140–1149.

17 Bonventre JV, Weinberg JM. Recent advances in the physiopathology of ischemic acute renal failure. J Am Soc Nephrol 2003; 14:2199–2210.

18 Jerkic M, Miloradovic Z, Jovovic D, *et al.* Relative roles of endothelin-1 and angiotensin II in experimental postischemic acute renal failure. Nephrol Dial Transplant 2004; 19:83–94.

19 Legrand M, Mik EG, Johannes T, *et al.* Hypoxia and dysoxia after reperfusion of ischemic kidney. Mol Med 2008; 14:502–516.

20 Miloradovic Z, Jerkic M, Jovovic D, *et al.* Bosentan and losartan ameliorate acute renal failure associated with mild but not strong NO blockage. Nephrol Dial Transplant 2007; 22:2276–2484.

21 • Gulmen S, Kiris I, Narin C, *et al.* Tezosentan reduces the renal injury induced by abdominal aortic ischemia-reperfusion in rats. J Surg Res 2009; 22:4804–4809.
In this animal study, specific endothelin-receptor antagonism attenuates ischemic-induced renal injury. This beneficial effect may act via reduction of oxidative stress and leukocytes infiltration.

22 Johannes T, Mik EG, Ince C, *et al.* Effects of 1400W and/or nitroglycerin on renal oxygenation and kidney function during endotoxemia in anesthetized rats. Clin Exp Pharmacol Physiol 2009; Apr 27. [Epub ahead of print]

23 Johannes T, Ince C, Mik EG, *et al.* Iloprost preserves renal oxygenation and restores kidney function in endotoxemia-related acute renal failure in the rat. Crit Care Med 2009; 37:1423–1432.

24 Johannes T, Mik EG, Ince C, *et al.* Low dose dexamethasone-supplemented fluid reverses endotoxin induced acute renal failure and prevents cortical microvascular hypoxia. Shock 2009; 31:521–528.

25 Melican K, Boekel J, Mansson LE, *et al.* Bacterial infection-mediated mucosal • signalling induces local renal ischemia as a defence against sepsis. Cell Microbiol 2008; 10:1987–1998.
This elegant study provides significant insights into the pathophysiology of ascending urinary tract infection. The authors demonstrate how the systemic spread of the infection is prevented by a shutdown of the microcirculation. Prevention of microcirculatory flow deterioration by anticoagulation led to fatal urosepsis.

26 Cao CC, Ding XQ, Zhu CF, *et al.* In vivo transfection NF-kappaB decoy oligodeoxynucleotides attenuates renal ischemia/reperfusion injury in rats. Kidney Int 2004; 65:834–845.

27 Jang HR, Rabb H. The innate immune response in ischemic acute kidney injury. Clin Immunol 2009; 130:41–50.

28 Jayle C, Milinkevitch S, Favreau F, *et al.* Protective role of selectin ligand inhibition in a large animal model of kidney ischemia-reperfusion injury. Kidney Int 2006; 69:1749–1755.

29 Kato N, Yuzawa Y, Kosugi T, *et al.* The E-selectin ligand basigin/CD147 is responsible for neutrophil recruitment in renal ischemia-reperfusion. J Am Soc Nephrol 2009; 10:1046.

30 Kelly KJ, Williams WW Jr, Colvin RB, *et al.* Intercellular adhesion molecule-1-deficient mice are protected against ischemic renal injury. J Clin Invest 1996; 97:1056–1063.

31 Oh DJ, Dursun B, He Z. Fractalkine receptor (CX3CR1) inhibition is protective against ischemic acute renal failure in mice. Am J Physiol Renal Physiol 2008; 294:F264–271.

32 De Greef K, Ysebaert S, Dauwe S, *et al.* Anti-B7-1 blocks mononuclear cell adherence in vasa recta after ischemia. Kidney Int 2001; 60:1415–1427.

33 Ysebaert DK, De Greef KE, Vercauteren SR, *et al.* Identification and kinetics of leukocytes after severe ischaemia/reperfusion renal injury. Nephrol Dial Transplant 2000; 15:1562–1574.

34 Ysebaert DK, De Greef KE, De Beuf A, *et al.* T cells as mediators in renal ischemia/reperfusion injury. Kidney Int 2004; 66:491–496.

35 Thurman JM. Triggers of inflammation after renal ischemia/reperfusion. Clin Immunol 2006; 123:7–13.

36 Celie JW, Rutjes NW, Keuning ED, *et al.* Subendothelial heparin sulfate proteoglycans become major L-selectin and monocyte chemoattractant protein 1 ligands upon renal ischemia/reperfusion. Am J Pathol 2007; 170:1865–1878.

37 Guan Z, Gobe G, Willgoss D, *et al.* Renal endothelial dysfunction and impaired autoregulation after ischemia-reperfusion injury result from excess nitric oxide. Am J Physiol Ren Physiol 2006; 291:F619–628.

38 Legrand M, Payen D, Ince C, *et al.* L-NIL prevents microvascular hypoxia and • increase of renal oxygen consumption after ischemia-reperfusion in rats. Am J Physiol Renal Physiol 2009; 296:1109–1117.
This animal study showed that whereas ischemic-induced iNOS-derived nitric oxide generation could be detrimental in compromising renal microvascular oxygenation eNOS-derived nitric oxide is protective.

39 Agmon Y, Peleg H, Greenfeld Z, *et al.* Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast nephrotoxicity. J Clin Invest 1994; 94:1069–1075.

40 Chatterjee PK, Patel NSA, Kvale EO, *et al.* Inhibition of inductible nitric oxide synthase reduces renal ischemia/reperfusion injury. Kidney Int 2002; 61:862–871.

41 Aurojo M, Welch WJ. Oxidative stress and nitric oxide in kidney function. Curr Opin Nephrol Hypertens 2006; 15:72–77.

42 Myers SI, Wang L, Liu F, *et al.* Oxygen-radical regulation of renal blood flow following suprarenal aortic clamping. J Vasc Surg 2006; 43:577–586.

43 Chatterjee PK, Cuzzocrea S, Brown PAJ, *et al.* Tempol, a membrane-permeable radical scavenger, reduces oxidant stress-mediated renal dysfunction and injury in the rat. Kidney Int 2000; 58:658–673.

44 Rubio-Gayosso I, Platts SH, Dulling BR. Reactive oxygen species mediate modification of glycocalyx during ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 2006; 290:H2247–2256.

45 Hughes AK, Stricklett PK, Padilla E, *et al.* Effect of reactive oxygen species on endothelin-1 production by human mesangial cells. Kidney Int 1996; 49:181–189.

46 Yamada K, Miwa T, Liu J, *et al.* Critical protection from renal ischemia reperfusion injury by CD55 and CD59. J Immunol 2004; 172:3869–3875.

47 Bellomo R. The epidemiology of acute renal failure: 1975 versus 2005. Cur Opin Crit Care 2006; 12:557–560.

48 Trof RJ, Di Maggio F, Leemreis J, *et al.* Biomarkers of acute renal failure. Shock 2006; 26:245–253.

49 De Backer D, Hollenberg S, Ince C, *et al.* How to evaluate the microcirculation: report of a round table conference. Crit Care 2007; 11:R101.

50 Johannes T, Mik EG, Ince C, *et al.* Acute decrease in renal microvascular PO2 during acute normovolemic hemodilution. Am J Physiol renal Physiol 2007; 292:796–803; Crit Care 2007.

51 Tsai AG, Cabrales P, Intaglietta M, *et al.* Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. Transfusion 2004; 44:1626–1634.

52 Deruddre S, Cheisson G, Mazoit JX, *et al.* Renal arterial resistance in septic shock: effects of increasing mean arterial pressure with norepinephrine on the renal resistive index assessed with Doppler ultrasonography. Intensive Care Med 2007; 33:1557–1562.

53 Macias WL, Yan SB, Williams MD, *et al.* New insights into the protein C pathway: potential implications for the biological activities of drotrecogin alfa (activated). Crit Care 2005; 9:S38–45.

54 PROWESS study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. New Engl J Med 2001; 344:699–709.

55 Gupta A, Guerlitz B, Richardson MA, *et al.* Distinct functions of activated protein C differentially attenuate acute kidney injury. J Am Soc Nephrol 2009; 20:267–277.

56 Song YR, Lee T, You SJ, *et al.* Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery bypass grafting: a pilot study. Am J Nephrol 2009; 30:253–260.

57 Liakopoulos OJ, Choi YH, Haldenwang PN, *et al.* Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients. Eur Heart J 2008; 29:1548–1559.

58 Ventura CG, Coimbra TM, de Campos SB, *et al.* Mycophenolate mofetil attenuates renal ischemia/reperfusion injury. J Am Soc Nephrol 2002; 13:2524–2533.

59 Ysebaert DKY, De Greef KE, Vercauteren SR, *et al.* Effect of immunosuppression on damage, leukocyte infiltration, and regeneration after severe warm ischemia/ reperfusion renal injury. Kidney Int 2003; 64:864–873.

60 van der Voort PH, Boerma EC, Koopmans, *et al.* Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial. Crit Care Med 2009; 37:533–538.

61 Amabile N, Guerin AP, Leroyer A, *et al.* Circulating endothelial microparticles are associated with vascular dysfunction in patients with end-stage renal failure. J Am Soc Nephrol 2005; 16:3381–3388.

62 Basile DP, Donohoe D, Roethe K, *et al.* Renal ischemic injury results in permanent damage to peritubular capillaries and influences long-term function. Am J Physiol Renal Physiol 2001; 281:887–899.