The renal microcirculation in sepsis

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ABSTRACT

Despite identification of several cellular mechanisms being thought to underlie the development of septic acute kidney injury (AKI), the pathophysiology of the occurrence of AKI is still poorly understood. It is clear, however, that instead of a single mechanism being responsible for its aetiology, an orchestra of cellular mechanisms failing is associated with AKI. The integrative physiological compartment where these mechanisms come together and exert their integrative deleterious action is the renal microcirculation (MC). This is why it is opportune to review the response of the renal MC to sepsis and discuss the determinants of its (dys)function and how it contributes to the pathogenesis of renal failure. A main determinant of adequate organ function is the adequate supply and utilization of oxygen at the microcirculatory and cellular level to perform organ function. The highly complex architecture of the renal microvasculature, the need to meet a high energy demand and the fact that the kidney is borderline ischaemic makes the kidney a highly vulnerable organ to hypoxaemic injury. Under normal, steady-state conditions, oxygen (O2) supply to the renal tissues is well regulated; however, under septic conditions the delicate balance of oxygen supply versus demand is disturbed due to renal microvasculature dysfunction. This dysfunction is largely due to the interaction of renal oxygen handling, nitric oxide metabolism and radical formation. Renal tissue oxygenation is highly heterogeneous not only between the cortex and medulla but also within these renal compartments. Integrative evaluation of the different determinants of tissue oxygen in sepsis models has identified the deterioration of microcirculatory oxygenation as a key component in the development AKI. It is becoming clear that resuscitation of the failing kidney needs to integratively correct the homeostasis between oxygen, and reactive oxygen and nitrogen species. Several experimental therapeutic modalities have been found to be effective in restoring microcirculatory oxygenation in parallel to improving renal function following septic AKI. However, these have to be verified in clinical studies. The development of clinical physiological biomarkers of AKI specifically aimed at the MC should form a valuable contribution to monitoring such new therapeutic modalities.

Keywords: AKI, microcirculation, nitric oxide, oxygenation, oxygen radicals

INTRODUCTION

Sepsis is a condition characterized by progressive systemic haemodynamic deterioration and a massive increase in inflammatory mediators and activated leucocytes, which together cause severe microcirculatory dysfunction and disrupt oxygen homeostasis, leading to oxidative stress and hypoxaemia [1]. One of the most frequent and serious complications for septic patients is acute kidney injury (AKI), a disorder characterized by a rapid failure of the kidneys to adequately filter the blood, regulate the ion and water balance, and generate urine [2]. Although there is appropriate supportive therapy for the treatment of sepsis associated with AKI, the underlying mechanisms are poorly understood and the mortality rate remains considerably high. Recently, a multinational prospective observational study including 29,269 critically ill patients revealed that the most frequent contributing factor to AKI was sepsis (50%) [3]. Other reports have shown that between 45 and 70% of all AKI is associated with sepsis [4, 5]. Many studies have indicated that the pathogenesis of sepsis-induced AKI is initiated by renal microcirculatory dysfunction [6, 7].

There are two specialized microcirculatory structures in the kidney, the glomerulus and peritubular microcirculatory networks located in the renal cortex and renal medulla, which play a key role in the homeostasis of the haemodynamic...
regulation and function of the kidney. Several different pathophysiological mechanisms have been proposed for sepsis-induced AKI, such as vasodilation-induced glomerular hyperperfusion, dysregulation of the circulation within the peritubular capillary network, inflammatory reactions by systemic cytokines or local cytokine production [8], and tubular dysfunction by oxidative stress [9]. These effects on the cellular functions affect the renal microcirculation (MC) and impair the main function of the renal MC of transporting oxygen to the respiring renal cells.

The oxygen requirement of the kidney is mainly determined by the ATP production needed for Na/K pump function [10]. Microcirculatory dysfunction can severely limit the ability of the circulation to provide adequate oxygen for fueling oxidative phosphorylation for the production of ATP and can directly impair the function of the Na/K ATPase pump. However, inflammation and oxidative stress can also severely alter the delicate balance between the oxygen supply and consumption in the kidney [11, 12]. In addition, a disturbance in the homeostasis between reactive oxygen species (ROS), nitric oxide (NO) and renal oxygenation fuelled by renal inflammation may contribute to kidney dysfunction and lead to renal failure [6]. Many other studies on renal injury have also reported that the common pathway to renal failure includes microcirculatory failure [13]. The success of microcirculatory function involves the successful interaction of many cellular and subcellular systems matched to the needs for renal function.

Septic insults have been shown to influence almost all cellular and subcellular compartments needed to achieve adequate renal microcirculatory function for renal function. Different pathogenic factors are associated with sepsis, which can result in renal dysfunction. In this paper, we review the renal MC and its response to sepsis as well as potential therapeutic strategies that may protect vulnerable renal MC in sepsis.

**THE PATHOPHYSIOLOGY OF SEPSIS**

Sepsis is characterized by a number of circulatory disorders, including decreased systemic vascular resistance, hypotension, impaired oxygen utilization, lactic acidosis and misdirection of blood flow in MC [14–16]. Importantly, sepsis is commonly caused by stimulating the host immune system cells and leads to the production of many types of important mediators such as cytokines, eicosanoids, complement and coagulation components, kinins, platelet activating factor, NO, and oxygen radicals that can have profound effects on the vascular tone and permeability, resulting in microcirculatory disturbances, cell damage, shock and organ dysfunction [17, 18]. Furthermore, endothelial/platelet-derived ROS enhance platelet activation and adhesion and promote coagulation during inflammation [19]. Another important aspect of sepsis is the alteration of the procoagulant–anticoagulant balance [20], stimulating endothelial cells to up-regulate tissue factor and activating coagulation factors such as fibrin, which leads to the formation of microvascular thrombi. These effects might contribute to the renal microcirculatory injury.

Numerous studies have shown that sepsis attenuates the arteriolar diameter response to vasoconstrictors [21–23] and vasodilators [24, 25]. In the case of sepsis, the pooling of blood in the venous system also promote capillary leak, which can lead to the progression of tissue oedema and compromise tissue oxygenation and microvascular barrier caused by inflammatory and oxidative insult associated with sepsis.

Several studies have indicated that inflammatory mediators also alter the barrier function of the MC, including junctions between cells and possibly the endothelial glyocalyx, leading to tissue oedema and further oxygen extraction deficiency [26, 27]. Endothelial glyocalyx components such as Syndecan-1 and glycosaminoglycans levels also increase in septic shock patients. The increase of these components in the blood has been found to correlate with albuminuria and mortality [28]. The best described effects of endothelial glyocalyx degradation have included increased vascular permeability, interstitial oedema formation, increased rolling and adhesion of leucocytes and increased platelet adhesion [29]. Red blood cells (RBC) also play an important role in the regulation of microcirculatory blood flow by their ability to release NO in the presence of hypoxia and, thus, cause vasodilatation [30, 31]. Studies have shown evidence that RBCs become less deformable and aggregate during sepsis [32, 33] promoting microcirculatory dysfunction.

These described sequel of events lead to massive microcirculatory collapse, which specifically influences the renal function, whereby the physiological vascular mechanism responsible for the vasotone regulation necessary for meeting oxygen needs is no longer functional and microcirculatory patency becomes impaired.

**RENAL MICROVASCULAR STRUCTURES**

The functional morphology of the microcirculatory networks in the different organ systems is highly heterogeneous, having adapted itself to the metabolic demand and function of each organ type [34] as illustrated in Figure 1. In the kidney, the renal artery branches continue to the inter-lobar artery, arcuate artery and interlobular artery which supplies blood to the afferent artery. A unique arteriolar capillary network in the present glomerulus is fed by the afferent arteriole in both the cortex and medulla. The nephron, consisting of the glomerulus, Bowman capsules and tubules, maintains the excretion, re-absorption and secretion functions of the kidney. In addition to the glomerular arteriolar structure, the renal cortex has a peritubular capillary network arising from efferent arterioles surrounding the proximal and distal convoluted tubules to maintain large reabsorption of glomerular filtrate. In contrast, the vasa recta is located specifically in the medulla and is fed by efferent arterioles, and peri-glomerular shunt pathways located at juxta-medullary glomeruli follows to the loops of Henle and collecting ducts deep into the medulla. The parallel arrangement of descending vasa recta (DVR) and ascending vasa recta with descending limbs and ascending limbs gives rise to a counter-current exchange system that maintains the
The cortico-medullary osmotic gradient established from countercurrent multiplication by the loops of Henle crucial for concentrating the urine [35–37] while maintaining adequate oxygen and nutrient delivery as well as metabolic clearance [38]. Moreover, this parallel arrangement has a key role in regulating regional perfusion between the outer versus inner medulla [35]. Contraction of the DVR results in the redirection of blood to the outer medullary inter-bundle capillaries [36] (Figure 1). A consequence of this structural arrangement is that there is a low oxygen tension in the medulla with medullary partial pressure of oxygen between 30 and 40 mmHg compared with that of the 40–60 mmHg in the cortex [39]. Renal blood flow (RBF) is also regionally specific, and tightly regulated by tubuloglomerular feedback mechanism in the cortex. Although only a small fraction (~10%) of the total RBF enters the renal medulla, the regulation of medullar flow is important because RBF seems to play a key role in the regulation of tubular function, sodium excretion, fluid volume control, and ultimately blood pressure regulation [40] which is locally adjusted by renin secretion from juxtaglomerular cells (Figure 2). Proper reabsorption of water and electrolytes is dependent on optimal blood flow through specific regions of the kidney. Consequently, blood flow is regulated differently in the cortex and medulla [41]. Additionally, the afferent and efferent arteriole tone is regulated by complex interactions between vasodilators such as NO and prostaglandin E2 (PGE2) and vasoconstrictors such as endothelin, angiotensin II and adenosine [42–45]. Importantly, the altered tonicity of both afferent and efferent arterioles including the vasa recta can directly affect both the renal function and distribution of oxygen transport in the kidney (Figure 1).

**RENAL HISTOPATHOLOGY AND ULTRASTRUCTURAL CHANGES IN SEPSIS**

Histopathological studies have shown that sepsis or septic shock can lead to ischaemic necrosis of tubular cells [46] or acute tubular necrosis (ATN) in the renal cortex and medulla [47] because of hypoxia and the overproduction of reactive oxygen and nitrogen species and cytokines [6, 12]. The consequences of ATN can be tubular obstruction and back-leak of the ultra-filtrate proximal from the obstruction by an increase in the intra-tubular pressure and loss of part of the anatomical...
barrier between the tubular lumen and the post-glomerular efferent capillaries surrounding the tubules [48]. Other studies have described that the alterations of sepsis-induced AKI consist of the predominantly mononuclear immune cell infiltration, some degree of tubular cell vacuolization, loss of brush border and polarity, apoptosis [47, 49], and dysfunction of the intracellular junction and basal membrane with the consequent detachment of cells into the tubular lumen [50]. Additionally, LPS and cytokines also increase the expression of P-selectin at the endothelial cell surface and initiate platelet adhesion in sepsis [51]. Thus, platelet activation, aggregation and platelet–endothelial adhesion in sepsis could contribute to microthrombi formation and cause plugging of the capillaries.

Under normal conditions, blood plasma is filtered from the capillaries of the glomerulus into the Bowman capsule’s lumen and vascular permeability is regulated by glomerular hydrostatic pressure, oncotic pressure and the glomerular filtration barrier (GFB). The latter consists of fenestrated glomerular endothelial cells, podocytes and the glomerular basement membrane. GFB is selectively permeable, allowing the passage of water and small solutes but not the passage of macromolecules such as albumin. The permselectivity of GFB is achieved by the contribution of the glyocalyx [52]. The microvascular endothelium is covered by a glyocalyx layer, which consists of proteoglycans (syndecan and glypicán), negatively charged glycosaminoglycans (hyalurunan, heparin sulphate and chondroitin sulphate) and soluble constituents. Under normal physiological conditions, the endothelial glyocalyx plays an active role in maintaining vascular homeostasis by inducing endothelial cells to synthesize shear-induced NO and preventing the adhesion of platelets and leucocytes as well as regulating vascular permeability and tone [53]. Adembri et al. reported that sepsis is also associated with a significant alteration in the composition of the GFB-associated glyocalyx. The authors observed a decrease in the expression of syndecan-I, the hyaluruan content and the total amount of sialic acid in the kidney tissue; they also observed an increase in the plasma TNF-α levels and urinary albumin level with loss of GFB permselectivity in an experimental rat model of polymicrobial sepsis [52]. Consequently, all these physiological and structural changes contribute to renal microvascular deterioration and dysfunction in sepsis-induced AKI. It is clear that the physiological function of the kidney relies on a delicate balance between oxygen transport and utilization, reactive oxygen and nitrogen metabolism and that this balance results in effective renal MC that is essential for renal function (Figure 3) [6].

IMPARED RENAL MICROVASCULAR PERFUSION DURING SEPSIS

Microcirculatory dysfunction in sepsis is characterized by heterogeneous abnormalities in RBF in which some capillaries are under-perfused, while others have normal or abnormally high blood flow [11, 54, 55]. Langenberg et al. have shown that hyperdynamic sepsis may cause an increase of RBF in a sheep model of sepsis and have suggested [56], in contrast to the general belief [8, 13], that renal ischaemia may not play a central role in sepsis-induced AKI [57]. However, in a rat model of sepsis-induced AKI with maintained constant renal arterial blood flow, we identified using speckle imaging of the cortex, microcirculatory perfusion alterations. We then showed that the origin of the ischaemic component of AKI was indeed located at the cortex microcirculatory level. Chvojka et al. in a porcine model of septic AKI using micro-laser probe showed similar results [58]. The ischaemic component is not found in global renal arterial blood flow but rather in a defect in the distribution of renal cortex MC with patchy areas of micro-ischaemia [11]. Indeed, these heterogeneous conditions can occur during septic shock but can also be the result of therapy such as the administration of fluids. Additionally, Fivre et al. showed that whereas arginine vasopressin consistently reduced renal medullar blood flow with or without pre-treatment with levosimendan as a calcium sensitizing agent and saline, neither arginine vasopres- sin or norepinephrine changed cortical RBF after pre-treat- ment with levosimendan and saline challenge in septic rabbits [59]. Thus, although fluid resuscitation can normalize the renal arterial flow, it can cause heterogeneous microcirculatory flow in the renal cortex, resulting in heterogeneous hypoxic areas that contribute to renal oxygen extraction dysfunction [11].

IMPARED RENAL MICROVASCULAR OXYGENATION DURING SEPSIS

Fluid administration can contribute to renal dysfunction by reducing the renal microcirculatory oxygenation causing an imbalance between the renal oxygen consumption and sodium reabsorption, which is indicative of a loss of tubular polarity [60]. These insights have been gained by our introduction of the non-invasive quenching of palladium (Pd) porphyrin phosphoresence technique. This technique allows in vivo quantitative measurement of microcirculatory oxygen pressure in rat kidneys [61, 62]. The heterogeneous nature of oxygen pressure distribution, measured in the cortex and medulla, as well as the non-invasive assessment of oxygen levels in the renal vein to determine renal O2 consumption (VO2) allowing the calculation of the important functional parameter of the kidney mainly oxygen consumption per tubular Na+ reabsorption (VO2/TNa+) were studied with this technique [63–65].

Johannes et al. showed in an endotoxemia model that the rat cortex microcirculatory μPO2 was preserved despite endotoxemia causing hypotension and a drop in renal arterial flow. Interestingly, fluid resuscitation in this model resulted in a correction of blood pressure and the restoration of RBF, but paradoxically at the expense of decrease in cortex μPO2 [61]. Recently, Leong et al. determined that RBF could be reduced or increased by ~30% without detectable changes in tissue PO2 in the cortex or medulla under normoxic, hypoxic and hyperoxic conditions. Changes in RBF induced by renal arterial infusion of angiotensin II (ang II) and acetylcholine were accompanied by changes in renal O2 delivery and efflux but not in renal O2 consumption. Thus, arterial-to-venous (AV) shunting may be a contributing factor in the regulation of renal oxygenation and bioavailability of MC [66]. Moreover, Johannes et al. found that renal cortical tissue PO2 fell during
normovolemic haemodilution to a much greater extent than the PO₂ of renal venous blood. The authors reasoned that the increased 'gap' between the tissue and venous PO₂ during haemodilution indicated increased AV oxygen shunting [62]. Evans et al. suggested that AV shunting is an adaptation to prevent hyperoxia and the overproduction of ROS due to the high renal perfusion needed to sustain glomerular filtration rate (GFR) [67]. Nonetheless, a decrease in RBF either at the renal arterial level and/or at the microcirculatory level in the kidney cortex can be regarded as central to the pathogenesis of septic AKI.

The highly complex structure of the renal microvasculature, its high-energy demand and borderline hypoxaemic nature of renal medulla makes the kidney highly vulnerable to injury, and adequate microcirculatory oxygenation is important [68]. Under normal conditions, ~80% of renal oxygen consumption (VO₂) is used to drive Na/K ATPase in the proximal tubules, which is responsible for Na reabsorption. Approximately two-thirds of NaCl is reabsorbed by the proximal tubule as a result of glomerular filtration [69]. Thus, renal oxygen consumption is dominated by the requirements of Na/K ATPase, which, in turn, drives most active and passive reabsorptive processes in the kidney [10]. Na/K ATPase leads not only the active transport of sodium but also the dependent transport processes of glucose, amino acids and other solutes [69]. The loss of tubular polarity associated with sepsis-induced AKI can result in an increase VO₂/TNa⁺ with Na/K pump being ineffective in achieving Na⁺ reabsorption [13]. The heterogeneous nature of microcirculatory oxygenation and hypoxia may then result in an inactivation of the Na/K ATPase pump due to reduced ATP levels.

The medullary thick ascending limb (mTAL) has higher Na/K ATPase activity than the proximal tubules, and the metabolic energy is mostly used by TAL in addition to the proximal tubules and is further increased in the distal tubule [60]. Increased Na⁺ transport in the TAL without an increase in oxygen delivery through the vasa recta can exacerbate medullary hypoxia. Brezis et al. clearly demonstrated that inhibition of Na⁺ transport in the TAL and proximal tubule by diuretics elevates PO₂ in the renal medulla and cortex [70]. Apparently, there is a positive correlation between renal oxygen consumption (VO₂), oxygen delivery (DO₂), tubular sodium reabsorption and GFR.

**IMPACT OF RENIN–ANGIOTENSIN ALDOSTERONE SYSTEM ON RENAL MICROCIRCULATION**

Activation of the renin–angiotensin aldosterone system (RAAS) with elevated levels of angiotensin II (Ang II) and a
rise in vasopressin levels is often part of the host response [71]. Even if these mechanisms are largely responsible for the systemic vasoconstriction and hyperdynamic circulation, the local production of Ang II also takes place in the kidneys [72], which leads to a reduction in the GFR because of the vasoconstriction of the glomerular afferent and efferent arterioles. Thus, RAAS activation gives rise to a greater increase in the vascular resistance and the transglomerular hydraulic pressure [73]. Importantly, Patzk et al. have shown the relationship between angiotensin II and NO in which intraluminal perfusion of angiotensin II decreased dose dependence in isolated afferent arteriolar diameters and simultaneously enhanced NO fluorescence in mice [74]. Additionally, low doses of aldosterone induces both afferent and especially efferent arteriolar constriction [75], elevating the glomerular capillary pressure and renal vascular resistance contributing to glomerular dysfunction and glomerular structural damage in renal diseases [76].

The afferent and efferent arteriolar vasoconstriction induced by RAAS causes regional micro-ischaemia resulting in reduced cortical μPO2, medullar μPO2 and oxygen delivery (DO2) in the kidney. This condition might be an important contributing factor to AV shunting [12].

### EFFECTS OF REACTIVE OXYGEN AND NITROGEN SPECIES ON THE RENAL MC IN SEPSIS

NO is a major regulator of the microvascular oxygen supply and VO2 and increases the RBF via vasodilatation, which in turn increases the oxygen delivery. Non-specific NO synthase (NOS) blockade reduces the GFR and TNα+ and enhances the renal VO2 in dogs [77]. In contrast to many other organs, inducible NO synthase (iNOS) is constitutively expressed in both mouse and human renal tubule cells [78, 79], and contributes to subsequent renal haemodynamic changes and reduction in GFR during the first stage of sepsis-induced AKI. However, the overexpression of iNOS and excessive production of nitrogen species can induce nitrosative stress, resulting in pathological shunting of flow [80, 81], arteriolar responsiveness [22], impairment of capillary blood flow [82] and cell function during sepsis. However, constitutive NOS isoforms are susceptible to inhibition by elevated levels of NO. For this reason, some studies have suggested that an elevated value of iNOS might actually inhibit endothelial NOS (eNOS) activity, which results in impaired microvascular homeostasis and renal function in sepsis [83, 84]. Recently, Langenberg et al. demonstrated that production of all NOS isoforms are increased during sepsis in the renal cortex but not in the renal medulla. Thus, they hypothesized that overexpression of NOS isoforms in the cortex may lead to intrarenal shunting. Indeed, blood is carried away from the medulla and induces medullar hypoxia during sepsis [85]. We demonstrated the elevated NOS isoforms in a rat model of sepsis-induced AKI as well [86, 87]. Thus, excessive NO produced by cells can, besides causing nitrosative damage, inhibit mitochondrial respiration by competing with oxygen for binding mitochondrial cytochrome oxidase in a dose-dependent manner [88]. NO reacts immediately with elevated levels of superoxide ions and can generate peroxynitrite radicals. Peroxynitrite is a powerful oxidant, capable of oxidizing thiol groups and DNA bases and modifying protein and lipids by nitration. As a result, peroxynitrite leads to direct inhibition of the mitochondrial respiratory chain enzyme, DNA damage, inhibition of membrane Na/K-ATPase activity and activation of apoptotic enzymes [89]. Interestingly, Lowes et al. demonstrated that treatments with antioxidants to preserve mitochondrial function and structure, such as MitoQ, MitoE and melatonin are able to reduce mitochondrial damage, organ dysfunction and attenuate inflammatory responses in a rat model of sepsis [90].

Oxidative stress is an imbalance between oxidants and antioxidants that favours oxidants and causes a disruption in redox signalling and control, leading to damage of the cellular molecular structures [67, 91]. Under normal circumstances, ROS are released at low concentrations and are neutralized by endogenous antioxidant compounds. Both high and low levels of oxygen tension, however, promote oxidative stress, making it necessary to keep the levels of tissue oxygen tensions at physiological levels to avoid the detrimental effects of oxidative stress [89]. The dependency of ROS activity on oxygen availability was recently demonstrated in a model of oxidative stress in spontaneously hypertensive rats wherein a loss of bioactive NO by high ROS production interfered with normal oxygen usage in the kidney. In addition, superoxide produced by NADPH oxidase is inhibited when oxygen tensions drop <20 mmHg [92].

Consequently, the close relationship between NO and ROS, the inhibition of membrane Na/K-ATPase by peroxynitrite, mitochondrial damage and shunting seems to play a critical role in the microcirculatory process by reducing the oxygen consumption and delivery as well as tubular sodium reabsorption in the septic kidney.

### THERAPEUTIC APPROACHES

AKI develops within the first 24 h in 64% of patients with sepsis with hypotension [93]. Protecting the kidney during sepsis could significantly reduce morbidity and mortality in patients with severe sepsis. Treatment of sepsis and especially sepsis-induced AKI has advanced little in recent decades [94]. Our working hypothesis states that in order for a microcirculatory therapy to be effective in protecting the kidney from AKI, an integrative therapeutic improvement of all the factors shown in Figure 3 would need to be targeted, including an anti-inflammatory agent in combination with effects for restoring the homeostasis between oxygen and oxygen and nitrogen reactive species [6]. Fluid resuscitation is a cornerstone of the treatment of sepsis because it is considered crucial for the preservation of adequate intravascular volume, the maintenance of blood pressure with the ultimate aim of promoting tissue perfusion and oxygenation [95]. However, the extent to which fluid therapy is effective in promoting renal oxygenation has recently been questioned [96, 97]. The limited effects of fluids in this respect are caused not only by the poor oxygen...
solubility in fluids but also by the haemodilution it causes which reduces renal capillary density due to reduced viscosity [98]. Fluid resuscitation can have severe deleterious effects on MC [61] and haemodilution may contribute to AKI [99]. In sepsis, excessive fluid administration has been found to be associated with renal failure [100], although restrictions in fluid use can, on the other hand, lead to hypovolaemia which can equally contribute to renal failure. Therefore, determining the optimal fluid volume to administer during sepsis to treat hypovolaemia remains a source of uncertainty.

Recently, Legrand et al. have shown that endotoxaemia could induce alterations in the microvascular perfusion distribution and reduce oxygenation in the renal cortex in rats, and these alterations appear to be weakly dependent on systemic and renal macrohaemodynamics. Importantly, prevention of endotoxaemia-induced hypotension and reduction of RBF by immediate colloidal fluid resuscitation did not prevent systemic inflammation activation but did reduce renal inflammation such as the iNOS level in the kidney [11]. Other studies showed that treatment with low-dose dexamethasone (DEX) having iNOS inhibitory and anti-inflammatory properties in combination with fluid (hydroxyethyl starch) resuscitation therapy significantly improved the reduced value of the systemic and renal haemodynamic and oxygenation parameters compared with standard fluid resuscitation in LPS-induced septic rats. Although the average microvascular oxygen levels were unaffected by treatment with DEX, the appearance of the microcirculatory hypoxic areas in the cortical oxygen histogram was reversed after treatment with DEX in parallel with improved renal function as demonstrated by restoration of the creatinine clearance and normalization of the tubular sodium reabsorption [87]. Indeed in an ischaemia-reperfusion model, a specific inhibitor of iNOS, L-N6-iminoethyllysine (L-NIL) was found to be effective in restoring renal oxygenation, nitrosative homeostasis and renal functional markers [86]. Moreover, Choi et al. have shown that glucocorticoids induce a decrease in pro-inflammatory cytokines, apoptosis and mitochondrial damage in a cecal ligation and puncture model of sepsis [101].

Finally, compounds which have an anti-inflammatory effect in combination with vasoactive properties promoting tissue perfusion may be beneficial in correcting the various pathogenic mechanisms involved in microcirculatory dysfunction. Indeed two compounds we found to be highly effective in this respect for the septic kidney were iloprost and activated protein C both having such multiple actions [102, 103].

CONCLUSION

Renal oxygen consumption usually changes in response to altered arterial pressure, RBF, GFR and sodium balance. The oxygen supply to the renal tissues is well regulated and utilized not only for the mitochondrial production of ATP to maintain the Na/K ATPase activation needed for Na-reabsorption but also for the production of NO and the ROS needed for the physiological control of renal function. In sepsis, the balance between these physiological determinants of renal function becomes disturbed mainly due to the inflammatory insult resulting in abnormal levels of these compounds which then exert pathogenic effects, such as hypoxaemia, oxidative and nitrosative stress. This sequel of events results in a deterioration of the renal MC function and oxygenation leading to acute renal failure. Although there is experimental evidence for effective therapeutic procedures for prevention of sepsis-induced AKI, further clinical investigations are needed. Fluid resuscitation therapy supplemented with antioxidants or other vasoactive and anti-inflammatory substances may provide an integrative therapeutic platform to prevent renal microcirculatory dysfunction and sepsis-induced AKI.

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REFERENCES