Editorial Review

Cellular adaptive changes in AKI: mitigating renal hypoxic injury

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Abstract

Hypoxia plays a role in ischemic, toxic and sepsis-induced acute kidney injury. Evolving hypoxia triggers renal adaptive responses that may mitigate the insult, leading to sub-lethal forms of cell injury. The unique capability of the kidney to downregulate oxygen consumption for tubular transport could represent one such adaptive response which promotes maintenance of renal oxygenation, thereby preserving cellular integrity. Tran et al. recently explored a novel mechanism that might prevent tubular damage by downregulation of mitochondrial biogenesis and oxygen consumption. Using expression profiling of kidney RNA in endotoxemic rodents and complementary studies in vitro and in PGC-1α knockout mice, they found a sepsis-related decline in PPARγ coactivator-1α (PGC-1α) expression and of PGC-1α-dependent genes involved in oxidative phosphorylation. This response may explain their observation of a paradoxical preservation of kidney oxygenation and structural integrity in sepsis, despite reduced renal blood flow and oxygen delivery. Thus, resetting of mitochondrial respiration and oxygen consumption during sepsis might be added to the growing list of adaptive responses that occur during hypoxic stress. This review will focus on these mechanisms that mitigate evolving hypoxic injury, even at the expense of transient renal dysfunction.

Keywords: hypoxia; hypoxia-inducible factors; kidney failure, acute; microcirculation; PGC-1α

Introduction

Homeostasis of renal parenchymal oxygenation is maintained by complex systems, which regulate and match regional blood perfusion and oxygen expenditure, principally for tubular transport. These systems are especially important in the renal outer medulla, where limited blood supply and oxygen delivery are barely sufficient for tubular transport demand and consequent oxygen consumption [1]. Renal hypoxic stress may evolve from suppressed regional perfusion, increased oxygen utilization for tubular transport or their combination. The physiologically low medullary pO2 leads to a particular vulnerability of this region to hypoxic injury, which predominantly involves S3 proximal tubules in experimental warm ischemia and reperfusion and medullary thick ascending limbs (mTALs) in acute kidney injury (AKI) models characterized by medullary hypoxia and continued tubular transport [1–3]. This difference in tubular susceptibility to injury reflects diverse cellular metabolism in different tubular segments. Proximal tubules are highly sensitive to hypoxia because they principally depend on oxidative catabolism, whereas distal tubular segments, especially mTALs, which are able to use glycolysis, endure severe hypoxia, provided that transport activity diminishes [4].

Renal hypoxia has also been recognized in chronic kidney disease, in part due to rarefaction of peritubular microvasculature, and is believed to participate in the progression of derangements in kidney structure and function [5].

Some of the adaptive responses to intensified renal parenchymal hypoxia in the chronic and acute settings involve whole-organ physiological changes. Additional adaptive changes that facilitate endurance of the hypoxic stress occur at the cellular level. Recently, one such process, the downregulation of PPARγ coactivator-1α (PGC-1α), has been identified by Tran et al. [6] to lead to the attenuation of mitochondrial respiration and oxygen consumption during sepsis. The aim of this review is to examine renal adaptive responses to hypoxia and to suggest that they might represent novel therapeutic targets for AKI.

The physiological control of renal parenchymal oxygenation at the organ level

As illustrated in Figure 1 and Table 1, nitric oxide (NO), adenosine, dopamine and vasodilator prostaglandins have long been recognized as chief regulators of renal regional perfusion and tubular transport activity under normal physiological conditions. NO, dopamine and PGE2 enhance medullary blood flow and suppress tubular transport and oxygen consumption. Furthermore, adenosine as well as other vasoconstrictors reduce cortical blood flow and...
glomerular filtration rate (GFR), leading to diminished downstream solute delivery and consequent decreases in tubular transport and oxygen consumption. Prostaglandins, nitric oxide and dopamine enhance oxygen delivery and downregulate tubular transport. GFR may decline by activated TGF and adenosine release, which induces cortical vasoconstriction, while maintaining medullary blood flow. Other neurohumoral stimuli, including sympathetic activity, angiotensin II and endothelin also reduce cortical blood flow and GFR while maintaining or even increasing medullary blood flow and may also directly reduce tubular transport (endothelin). Enhanced ROS generation may disrupt these homeostatic systems, compromising the microcirculation and dysinhibiting tubular transport. Black arrows and red-dashed lines represent enhancing and suppressing effects, respectively. TGF, tubuloglomerular feedback; ATP, adenosine triphosphate. *Cortical vasoconstrictors, such as endothelin, angiotensin II or adenosine, spare or even enhance medullary blood flow due to disparate expression of different receptor types with opposing effects upon microvascular tone in the cortex and medulla [1].

**Table 1.** Renal adaptive responses which ameliorate hypoxic stress

<table>
<thead>
<tr>
<th>Responses at the organ level</th>
<th>Mechanism</th>
<th>Mediators</th>
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<tbody>
<tr>
<td>Reduced GFR</td>
<td>-Reduced downstream tubular transport and oxygen consumption</td>
<td>-Sympathetic activity, angiotensin II, endothelin, vasopressin and adenosine [1, 2]</td>
</tr>
<tr>
<td>Maintained medullary flow</td>
<td>-Maintained oxygen supply</td>
<td>-Prostaglandins (PGE2 and PGI2), NO and adenosine [1, 2]</td>
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<tr>
<td>Downregulation of tubular transport</td>
<td>-Reduction of oxygen consumption</td>
<td>-Prostaglandins, dopamine, NO and endothelin [1, 2]</td>
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<tr>
<td>Improving oxygen delivery</td>
<td>-Stimulation of RBC formation -Vasodilation -Enhancement of local microcirculation</td>
<td>-HIF-mediated EPO induction -HIF-mediated NOS induction -HIF-mediated VEGF synthesis [7]</td>
</tr>
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**Responses at the tubular cell level**

| Downregulation of tubular transport | -Reduction of oxygen consumption | -Prostaglandins, dopamine, NO and endothelin [1, 2] |
| Downregulation of mitochondrial respiration | -Reduction of oxygen consumption and reduction of ROS formation | -PGC-1α [6] |
| Improving antioxidant capacity    | -Attenuation of oxidative stress | -HIF-mediated HO-1 synthesis [7] |
| Changing membrane cholesterol content | -Reduction of mitochondrial ROS formation | -Induction of HO-1 [7] |

*aVEGF, vascular endothelial growth factor; EPO, erythropoietin.*
oxygen utilization and may be disadvantageous in the situation of acute or chronic renal failure. Indeed, in clinical trials measures that enhance GFR were not found renoprotective in AKI. By contrast, diminished GFR might be regarded as a principal mechanism promoting maintenance of homeostasis of renal parenchymal oxygenation. This notion fits well with the term ‘acute renal success’ rather than ‘failure’, suggested decades ago by Thurauf [9], whereby reduced GFR might be considered renoprotective in AKI. However, renal oxygen consumption has recently been found to be unaffected in post-cardiac surgery patients with AKI, despite reduced GFR and renal blood flow [10]. This probably underscores the impact of other factors, detailed below, that may lead to enhanced oxygen consumption by tubular cells, so counteracting the anticipated reduced tubular transport activity, resulting from diminished GFR.

**Adaptive responses to hypoxic stress at the cellular level**

Cellular hypoxia leads to functional and structural derangements, related both to hypoxia and to excess formation of reactive oxygen species (ROS). As illustrated in Figure 2, ROS enhance tubular transport with a feed-forward loop of oxygen consumption and ROS formation [11, 12]. Loss of cell polarity during hypoxic damage might also result in uncontrolled transport activity. Additionally, the initiation of processes, such as poly (ADP-ribose) polymerase (PARPP)-mediated DNA repair or programmed cell death, consumes energy and might intensify oxygen expenditure. On the other hand, various conditions lead to reduced oxygen needs for tubular transport, such as tubular atrophy with reduced mitochondrial mass and ion transporters in the case of chronic salt depletion [13], inhibition of glycolysis and Na/K/ATPase by acidosis, the closing of chloride exit channels in mTALs, produced by ATP hydrolysis in hypoxic cells or the physiological downregulation of tubular transport discussed above [1, 2, 4].

Hypoxia markedly affects the expression of numerous potentially protective genes which participate in tissue oxygenation, cell metabolism and survival. Hypoxia-inducible factors (HIFs), heterodimers consisting of α and β subunits, are key regulators of gene expression in response to declining pO2 [14]. Under normoxia, oxygen-sensitive HIF-prolyl-hydroxylases promote HIFα proteasomal degradation. Upon hypoxia HIF-prolyl-hydroxylases are inhibited, so HIFα rapidly accumulates and binds to HIFβ. The HIFαβ dimers translocate into the nucleus where they transactivate a myriad of genes, many of which can promote hypoxia adaptation. As reviewed elsewhere [2], renal HIF accumulation can be detected by immunostaining following acute hypoxic stress, such as systemic hypoxia, global or segmental renal ischemia, acute inhibition of NO or prostaglandin synthesis or after the administration of nephrotoxins which hamper renal oxygenation, such as radiocontrast agents, cisplatin or myoglobin. HIF-mediated genes are subsequently upregulated in affected renal regions, some of which act to ameliorate hypoxia, counteract oxidative stress and improve cell survival [2, 14].

Interestingly, HIFα expression, detected by immunohistochemistry, is absent or barely detectable under normal conditions, despite the uneven distribution of renal oxygenation, with low pO2 in the renal medulla. Moreover, various tubular cell types differ in their capacity to mount an HIF response [15, 16]. Thus, seemingly, the set point of HIFα stabilization and the initiation of the HIF response cascade differ in various renal regions and among cell types and is dependent on specific oxygen levels, sensed by varied HIF-proly hydroxylases as oxygen insufficiency.

Cellular control of mitochondrial respiration is an additional potential adaptive response to hypoxic stress. We have recently found evidence for renal HIF cross-talk with signal transducer and activator of transcription (STAT)-3, an additional master regulator of gene expression responses [17]. HIF and STAT-3 stimulate each other and together form a transcription complex with p300, inducing dependent genes such as vascular endothelial growth factor (VEGF) in tumor cell lines [18]. Interestingly, pSTAT3 was recently found to translocate into mitochondria and to affect the mitochondrial electron transport chain [19]. Hence, a direct link may extend from cellular hypoxia to the control of mitochondrial energy expenditure and ROS formation.

ROS generation may also directly affect mitochondrial respiration and oxygen expenditure. While NO, generated by endothelial NO synthase (eNOS), normally competes with oxygen on cytochrome oxidase [20] and diminishes oxidative stress, its production by inducible NO synthase

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**Fig. 2.** Mechanisms involved in tubular cell non-physiological hypoxic stress and adaptive responses: hypoxic sublethal injury results from altered microcirculation (1) and/or excessive transport activity and oxygen consumption (2). Ischemia and reoxygenation leads to enhanced ROS generation that may disrupt cell integrity and intensify hypoxia and ROS generation in a feed-forward loop (3), in part through enhanced transport activity (4) and dysregulation of mitochondrial respiration (5). ROS may also induce endothelial dysfunction and hamper regional microcirculation (6). Enhanced reparative processes (7), such as PARPP activation and autophagy, may also intensify hypoxic stress. On the other hand, protective pathways are activated: HIF-mediated systems (8) include improved oxygen delivery (9) through the induction of erythropoiesis, vasodilation and microvascular proliferation and the maintenance of cell metabolism and protective properties (10), such as the generation of antioxidants and genes regulating intracellular pH. Downregulation of mitochondrial respiration (11) by the downregulation of PGC-1α-dependent genes and enhanced membranal cholesterol content. ROS and HIF interactions (12) are complex and to some extent controversial. While HIF-mediated genes, such as heme-oxygenase I, counteract ROS generation, ROS may enhance or attenuate HIF stabilization by various pathways. Black and red arrows represent positive and negative effects, respectively.
(iNOS) is markedly upregulated during sepsis [21], leading to the formation of the highly toxic free radical peroxynitrite and ROS-mediated cell injury. Very little is known regarding cellular oxygen consumption in these settings, but it is believed that dysregulation of mitochondrial respiration may develop, with relatively inefficient oxygen utilization and enhanced oxygen consumption, which may further enhance ROS formation. Thus, there appears to be a complex interplay between hypoxia signaling, cellular redox state, NO and mitochondrial function that likely has profound roles in renal oxygen regulation and dysregulation under normal circumstances and during hypoxic or septic AKI, respectively [22, 23].

Sublethal cell injury and renal failure also induce adaptive changes in the cellular plasma membrane with increased membrane cholesterol content, conferring resistance to ischemic injury [8]. Indeed, excess production of cholesterol esters affects mitochondrial energy production, decreasing the generation of ROS [24]. Mitochondrial toxicity and altered cytochrome oxidase activity seem to be a general response to sepsis, with the development of a disappointing understood cellular metabolic derangement with defective utilization of energy substrates beyond the bioavailability of oxygen. Debate exists regarding the nature of the consequent metabolic downregulation, termed ‘mitochondrial hibernation’ or ‘cytopathic hypoxia’, and whether it is a pathologic response or an adaptive mechanism [25]. Tran et al. [6] studied renal oxygen consumption and mitochondrial respiration in sepsis. Renal blood flow markedly declined in mice during endotoxemia, whereas renal oxygenation [determined by blood oxygen level-dependent functional magnetic resonance imaging (BOLD MRI)] was well maintained, implying possible attenuation of oxygen expenditure. In fact, renal cytochrome oxidase content and activity were markedly suppressed during endotoxic AKI, in parallel with declining nicotine adenine dinucleotide oxidase. Expression profiling of kidney RNA revealed consistent changes in genes related to oxidative phosphorylation, ubiquinone biosynthesis and mitochondrial function. The expression of PGC-1α, a regulator of mitochondrial biogenesis and metabolism, substantially declined in AKI, in proportion to renal dysfunction and reactivated upon normalization of kidney function. Furthermore, a parallel suppression of PGC-1α-dependent oxidative phosphorylation genes was noted, and some, such as Cox5b, remained depressed throughout recovery [6]. A further mechanistic link between endotoxemia, PGC-1α suppression and reduced oxygen consumption was provided by the observation that tumor necrosis factor-α reduced PGC-1α expression and oxygen consumption in cultured tubular cells, an effect reversed by PGC-1α transfection. Furthermore, global- and tubule-specific PGC-1α-knockout mice suffered persistent renal dysfunction following endotoxemia [6]. Interestingly, increased levels of asymmetric dimethylarginine (ADMA), as shown in experimental diabetes [26] and following inflammation [27], were found to attenuate hepatic mitochondrial biogenesis and respiration, in parallel with reduced levels of PGC-1α [26]. Furthermore, acute administration of ADMA increased hypoxia tolerance in mice [28]. This implies that ADMA might be an additional regulator of mitochondrial oxygen expenditure through PGC-1 suppression.

Taken together, these findings are in concordance with attenuation of mitochondrial respiration and oxygen consumption during sepsis, which could explain the preserved renal oxygenation despite reduced renal blood flow. Maintained renal oxygenation could also explain the near absence of morphological evidence for tubular damage, suggesting the substitution of hypoxic injury with sublethal forms of cell damage.

Sublethal hypoxic tubular cell injury

Morphologically, acute sublethal tubular changes in experimental models of AKI include the loss of brush border, cell and mitochondrial swelling, cytoplasmic vacuolization and nuclear pyknosis. Some of these changes were shown to be reversible in hypoxic isolated perfused kidneys, following the restoration of oxygen supply [29]. In more intense or protracted hypoxia, cells may become committed to energy consuming autophagy or apoptosis. When hypoxic stress exceeds a certain point of no return, frank necrosis will ultimately develop. Importantly, all these morphological patterns of tubular cell damage can coexist within the injured kidney, reflecting gradients of tissue hypoxia and diversity of resistance to hypoxia among different nephron segments, as illustrated in rat models of hypoxic medullary injury induced by iodinated radiological contrast media [30]. Cell attachment to the basal membrane may also be altered with damaged tubular cells, some of them still viable [31] sloughed into the tubular lumen. Elimination of injured cells from the tubular lining epithelium (single-cell dropout) and their replacement by regenerated cells can lead to the illusion of an intact parenchyma in AKI.

Biomarkers of tubular damage in the urine or plasma may also herald tubular injury, appearing at very early phases of evolving AKI [32]. Some of these markers evidently reflect stress responses of viable tubular cells. Indeed, novel experimental approaches, such as incorporation of the luciferase reporter gene into the neutrophil gelatinase-associated lipocalin locus, have enabled the real-time detection of reversible tubular cellular stress [33]. Sublethal injury might also be evaluated by the assessment of real-time tubular dysfunction. Indeed, the loss of sodium gradient along the renal medulla, detected by sodium MRI, evolves in the presence of minimal focal tubular damage [34] and may resolve if hypoxic stress is transient and sublethal [35].

Other forms of sublethal injury, lacking distinct morphologic hallmarks, may be traced by identification of the tissue response to hypoxia. HIF stabilization and upregulation of hypoxia/HIF-triggered genes may help to assess the timing and spatial distribution of evolving hypoxic stress. Importantly, the capacity to generate detectable HIF responses, as detected by immunostaining differ among various tubular segment types (collecting ducts >> proximal tubules >> medullary thick limbs). Furthermore, dying and dead cells would not be expected to express HIF or related upregulated genes. Most likely, the HIF response only occurs in cells that have a reasonable chance of surviving hypoxia. Thus,
HIF-negative cells may either experience no hypoxia or very deep and protracted hypoxia [36].

Expression profiling of kidney-derived RNA is also a highly sensitive tool to identify cellular stress responses in what might be regarded as sublethal injury. Indeed, downregulation of the expression of genes involved with the mitochondrial electron transport chain was associated with very limited cell injury [6].

The vascular component

Studies of renal hypoxia and hypoxic damage have traditionally been focused on tubular cells. Indeed, the usual toxic and ischemia reflow AKI models show high levels of tubular injury. In contrast, biopsies of human AKI show very limited damage. Even in delayed graft function in the human, tubular injury is minimal compared to the degree of renal failure [3]. It seems logical to presume, therefore, that a major mediator of renal failure is injury and dysfunction of the microcirculation, particularly in sepsis and following profound hypotension [37]. Endothelial damage, as reflected by an altered endocalyx and defective nitrovasodilation, may be induced by systemic inflammation, hypoxia and ROS formation. Indeed, evaluation of the human renal microcirculation during transplantation has provided evidence for reduced capillary blood flow and loss of glocalyx integrity [38]. In vivo visualization of peritubular blood flow enables the detection of altered microcirculation, and endocapillary leak can be detected with the use of fluorescein-labeled dextran [39]. These methods have shown that endotoxemia in rodents is associated with a rapidly developing derangement of renal peritubular blood flow and a compromised endothelial cell barrier, particularly localized to areas with oxidative stress [21]. Interstitial edema may develop and the distribution of renal oxygenation becomes markedly heterogeneous, with scattered areas of profound hypoxia as opposed to intact regions with preserved pO2 [40]. The importance of endothelial injury in septic AKI is underscored by the attenuation of renal dysfunction by the maintenance of endothelial integrity [41, 42]. ROS, generated in endothelial cells or in adjacent tubular cells, markedly hinder nitrovasodilation, which can be restored by selective iNOS inhibition [43].

Altered vasa recta function seemingly plays a central role in chronic medullary hypoxic stress, such as in diabetes [44], and in multiple forms of AKI, including radiocontrast nephropathy [45]. Isolated vasa recta perfused by radiocontrast media display vasoconstriction, mediated to a large extent by ROS, since pericyte relaxation occurs upon application of antioxidants [46]. Thus, sublethal microvascular injury might be manifested by endothelial dysfunction, leading to a feed-forward loop of intensified hypoxia, ROS formation and damage. Such endothelial sublethal stress leads to HIF stabilization, detected by immunostaining, which might be endothelial cell protective and organ protective simultaneously. Indeed, renal blood flow was substantially improved in isolated perfused hypoxic kidneys when HIF stabilization was primed by the inhibition of HIF-prolyl hydroxylases [16].

The study by Tran et al. [6] provided strong evidence for a role of PGC-1α in the tubular response to sepsis but did not directly address cell type specificity of protective mitochondrial down regulation during sepsis. It is tempting to speculate that this phenomenon might also occur in endothelial cells.

Potential clinical implications

Tubular cell oxygen expenditure might be attenuated by therapeutic interventions. Indeed, under experimental settings, inhibition of tubular transport with diuretics has been shown to improve renal parenchymal oxygenation [47] and to attenuate hypoxic damage [48], and might be renoprotective in clinical practice, provided that fluid balance is maintained [49]. Inhibition of energy-consuming PARPP activation might also be renoprotective [50].

Enhancement of cellular adaptive responses to hypoxia might also become a therapeutic option in AKI. HIF transfection is renoprotective [51], and as reviewed elsewhere [5], intense research has been focused on HIF prolyl-hydroxylase inhibitors in experimental animal models of organ injury. These studies have shown amelioration of AKI in toxic nephropathies, following ischemia and reperfusion and in transplanted kidneys. Erythropoietin, a HIF-dependent gene was also found to exert protective properties in experimental AKI models. The report of Tran et al. [6] suggests that PGC-1α attenuation might be a reasonable additional approach to be tested in the treatment of septic AKI.

Attenuation of cellular oxidative stress might improve cellular HIF stabilization, as shown in the diabetic kidney [52], though this issue currently remains controversial. Antioxidants may also restore endothelial function and improve microcirculatory function and oxygenation [45]. Finally, the protective efficacy in AKI of newer antioxidants with preferential penetration into the mitochondria [53, 54] might to some extent be related to restoration of mitochondrial function and oxygen expenditure [23].

Comments and conclusions

Hypoxia plays a role in ischemic, toxic and sepsis-induced AKI. Evolving hypoxia activates renal adaptive responses that may mitigate the insult transforming potentially lethal cellular insults into sublethal forms of cell injury. A prototype of such self-preserving processes is HIF stabilization with the induction of protective HIF-dependent genes.

An additional mechanism of cell preservation during sepsis-induced hypoxic stress is downregulation of oxygen expenditure. The assessment of total renal oxygen supply, oxygenation and oxygen extraction is quite feasible [55]. However, since global cellular oxygen consumption reflects several coexisting physiological pathways, in vivo determination of the sum of cellular oxygen expenditure does not provide us with a clear distinction of the relative impact of each of these pathways on total oxygen utilization. The findings of Tran et al. [6] regarding tubular cell mitochondrial respiration are intriguing, but their clinical
important is yet to be defined in the perspective of other important issues, not addressed in their study. For example, while Tran et al. relate the lack of decline in renal oxygenation, despite reduced renal blood flow, to downregulation of mitochondrial oxygen expenditure, reduced GFR and diminished downstream tubular transport activity might be a much more important factor. Unlike Tran, additional reports show diminished renal pO2 following endotoxin administration in rats [55, 56], determined both in the cortex and medulla. These studies have demonstrated marked reductions in total renal blood flow (and oxygen delivery) but increased oxygen extraction and thus relatively little change in total renal oxygen consumption [55]. Furthermore, if tubular transport activity during sepsis diminishes (due to reduced GFR), it remains unclear as to exactly what happens to the degree of mitochondrial respiration. Notably, two phases of oxygen expenditure conceivably exist in sepsis [57]. During early stages, enhanced NO production may improve overall renal parenchymal oxygenation by vasodilation and by reduction of mitochondrial respiration and oxygen consumption in well-oxygenated regions. Thus, oxygen availability to adjacent hypoxic regions might improve. However, in more advanced phases of sepsis, abundant iNOS expression leads to overwhelming NO production and nitrosative stress, with consequent cellular injury and dysregulation of cell physiology and mitochondrial respiration [23, 57] that might be associated with enhanced oxygen consumption.

NO downregulates mitochondrial respiration by competing with oxygen at cytochrome C. Tran et al. propose an additional mode of mitigation of mitochondrial oxygen expenditure by PGC-1α. Yet, several issues in the work of Tran et al. warrant further clarification: how effective is this mechanism in the more advanced phases of sepsis? By what mechanisms does sepsis attenuate PGC-1α expression? Is it through evolving hypoxia or might there be other factors involved, such as inflammatory cytokines, acting directly or through enhanced ROS formation? Additional studies of renal gene expression in other non-inflammatory conditions of renal ischemia as well as the addition of antioxidants might address these issues. In order to explore the possibility that hypoxia is the initiating factor and acts through HIF, HIF manipulation, such as with the administration of prolyl-hydroxylase inhibitors or the use of HIF knockout mice, might be useful. Another point of critique is the determination of renal oxygenation in sepsis. Though Tran et al. report that renal blood oxygenation (determined by BOLD MRI) remains intact in murine sepsis, yet more direct methods have shown much lower tissue oxygenation [55], which might further decline substantially during sepsis [55, 56]. Hemodynamic status and the degree of renal hypoperfusion might explain to some extent these discrepancies. Furthermore, direct determination of oxygenation in comparable settings does show heterogenous distribution of renal parenchymal oxygenation, with discrete areas of altered microcirculation and oxygenation [40, 56]. Thus, the ability of BOLD MRI to reflect scattered tissue hypoxia at the cellular level, especially at regions with uneven oxygenation, remains questionable.

Additionally, whereas sepsis models in rodents are characterized by profound renal vasoconstriction [40], renal blood flow is maintained or is even increased in hyperdynamic sepsis in large animals and probably at early stages in human sepsis as long as cardiac function remains intact [58, 59]. Whether renal tissue hypoxia occurs in humans and other large animals during sepsis, and even the factors leading to failure of GFR, remain to be determined.

Finally, an intriguing question to be addressed is whether downregulation of mitochondrial activity by PGC-1α during sepsis is indeed cell protective. Tran et al. reported very limited tubular injury in septic animals, including vacuolar changes related to mitochondrial swelling, rare single cell necrosis and scant apoptosis, in agreement with previous reports [60], yet they did not address the impact of PGC-1α manipulations upon renal morphology.

In summary (Table 2), the kidney is unique in its complex structure that predicates limited parenchymal oxygen availability, particularly in the medulla, requiring complicated regulatory systems which match oxygen supply and expenditure. Dysregulation of renal oxygenation generates adaptive responses at both organ and cellular levels, which attenuate oxygen demand and enable renal parenchymal endurance, even at the price of reduced renal function. Attenuation of oxygen expenditure, enhancement of hypoxia-adaptive mechanisms and reparation of endothelial dysfunction are plausible goals in AKI prevention and treatment. The report of Tran et al. sheds light upon one such aspect of oxygen expenditure at the mitochondrial level. Yet, the clinical importance of these findings is yet to be assessed, especially since renal oxygenation might be

Table 2. List of main conclusions

1. AKI, caused by various forms of ischemic, toxic or sepsis-related insults, as well as chronic renal disease, leads to renal hypoxia and tubular hypoxic stress.
2. Hypoxic stress triggers adaptive responses at the organ level, such as redistribution of intrarenal blood flow, reduced GFR and diminished tubular transport.
3. Additional adaptive responses, many of them hypoxia/HIF-dependent, are activated at the renal cellular level, mitigating the insult and converting potential lethal cell damage to sublethal forms of cell injury.
4. Microvascular injury and dysfunction play central roles in the pathogenesis of AKI, forming a feed-forward loop of hypoxia and ROS formation. Restoration of microvascular function is essential in the attenuation of renal parenchymal hypoxia and the prevention of AKI.
5. One such adaptive response during sepsis, at least in mice, is suppression of mitochondrial oxygen consumption by the downregulation of genes involved in mitochondrial biogenesis and respiration. This response is possibly mediated by suppressed PGC-1α expression.
6. Renal oxygenation and oxygen expenditure during AKI reflect the net balance of altered microcirculation, together with counteracting processes that enhance or mitigate oxygen consumption at the whole organ or at the tubular cell levels. An ultimate goal in the understanding and prevention of AKI might be the ability to determine the individual impact of modifications of these coexisting processes on renal oxygenation.
affected by various additional factors governing renal oxygen supply and expenditure.

Conflict of interest statement. None declared.

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Received for publication: 30.12.11; Accepted in revised form: 27.2.12