Glomerular haemodynamics, the renal sympathetic nervous system and sepsis-induced acute kidney injury

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ABSTRACT

Background. To describe recent insights into glomerular haemodynamics in septic acute kidney injury (AKI).

Methods. We reviewed the literature with particular emphasis on recent findings in animal experiments and human studies in relation to renal macro- and micro-renal haemodynamics during septic AKI.

Results. The dominant paradigm is that septic AKI is due to decreased renal perfusion with ischaemic loss of glomerular filtration rate (GFR), ischaemic tubular cell injury and acute tubular necrosis (ATN). However, recent experimental and human studies challenge this view of the pathogenesis of septic AKI. In addition, rapid post-mortem and experimental histological studies do not support ATN as the histological substrate of septic AKI. Finally, more recent experimental evidence suggests that changes in the glomerular and peri-glomerular haemodynamics provide a more likely explanation for the loss of GFR seen in the early phases of septic AKI.

Conclusions. Despite a long-standing paradigm that septic AKI is due to renal hypo-perfusion and associated ATN, experimental and human studies increasingly suggest that changes in the state of the glomerular and peri-glomerular haemodynamics provide a more likely explanation for the loss of GFR seen in the early phases of septic AKI.

Keywords: acute kidney injury, afferent arteriole, efferent arteriole, renal blood flow, sepsis

INTRODUCTION

Despite several decades of research, the pathophysiology of septic acute kidney injury (AKI) remains obscure. Septic AKI has been traditionally considered a disease of the renal macro-circulation [1] resulting from global renal ischaemia (decreased renal artery blood flow), cellular damage and acute tubular necrosis (ATN). However, human studies have not confirmed decreased renal blood flow (RBF) in sepsis [2], and animal models have shown that septic AKI develops despite an increase or no fall in total RBF [3]. In this review, we will present the available evidence of the renal vascular changes induced by sepsis, discuss the role of the sympathetic nervous system (SNS) in the control of the renal vascular response to sepsis and propose some alternative pathophysiologic hypotheses to explain septic AKI. In particular, we will speculate whether septic AKI may be caused by a derangement of glomerular and peri-glomerular haemodynamics. In order to address these issues, we begin with a brief focused review of the renal vasculature.

KEY ASPECTS OF THE RENAL MACRO- AND MICRO-VASCULATURE

In 1842, Bowman provided the first accurate description of the glomerular tuft [4]. Through a series of injections and microscopic observations, he arrived at the conclusion that ‘all the blood of the renal artery… enters the capillary tufts of the Malpighian bodies (glomeruli as we now call them); thence it passes into the capillary plexus surrounding the uriniferous tubes, and it finally leaves the organ through branches of the renal vein’ [4]. He also described that the kidney had ‘two perfectly distinct systems of capillary vessels’ [4] (the glomerular capillaries and the vasa recta). The vascular anatomy of the renal medulla is particularly complex. It is estimated that only 5–15% of total RBF is directed to the medulla, with the outer medulla
having higher blood flow (130–340 mL/100 g tissue/min) than the inner medulla (22–69 mL/100 g tissue/min) [5]. This wide range of medullary blood flow is considered to be partly dependent on the fluid status and mediated by arginine vasopressin (AVP), with the highest flow during conditions of water diuresis [6, 7]. However, such flow estimates vary widely and are largely dependent on limitations of the different techniques used [5].

Importantly, the entire vascular supply to the medulla appears to originate from the efferent arterioles of the glomeruli located at the junction of the cortex and the medulla, the juxtamedullary glomeruli. These efferent arterioles are larger and have a thicker endothelial layer than other cortical efferent arterioles. The arterial vessels originating from the juxtaglomerular efferent arterioles descend in parallel into the medulla and laterally give rise to a capillary plexus. In the inner medulla, each vasa recta has a hairpin turn and returns in parallel to the descending vessels as ascending venous vessels. These descending and ascending vessels (vasa recta) are fundamental to the generation of the counter-current gradient needed for solute control.

**The Renal Sympathetic Nervous System**

The SNS is a key controller of renal function, as described long ago by Claude Bernard [8]. Since then, numerous studies have demonstrated that the SNS plays an important role in regulating renal vascular tone, as well as water and electrolyte reabsorption and renin secretion [9–12]. An anatomical substrate from these actions is indicated by extensive sympathetic innervation throughout the whole vascular tree, from the main renal artery to the glomerular arterioles and vasa recta, and of the juxtaglomerular renin secreting cells, mesangium, the proximal and distal tubules and the loop of Henle [13–15].

The level of sympathetic nerve activation (SNA) is one of the determinants of RBF [11] and glomerular filtration rate (GFR) through innervation of the afferent and efferent arterioles [10]. Electrical stimulation of the renal nerves has been shown to decrease single nephron GFR [16, 17], whereas reflex simulation of renal sympathetic nerve activation (RSNA) with hypoxia can selectively increase or decrease glomerular capillary pressure and, hence, GFR by differentially activating separate populations of renal nerves [18, 19]. The finding that noradrenaline has similar vasoconstrictor actions on isolated rat efferent and afferent arterioles [20] suggests that any differential action of the sympathetic nervous system on the pre- and post-glomerular vessels must result from the different levels of innervation of the two types of vessel. The SNS also regulates renal function through innervation of the proximal tubules where it is an important regulator of sodium excretion, and thus indirectly of water, reabsorption. Increased SNA enhances proximal tubular Na+ reabsorption and decreases urine volume [21–27]. Finally, a major role of the SNS is in the control of renin release, as indicated by its dense innervation of the juxtaglomerular cells and of the macula densa [14, 15, 28].

Renal SNA is increased by sepsis and its activation is associated with oliguria (Figure 1). Such activation releases noradrenaline from sympathetic catecholaminergic terminals.

Noradrenaline release is modulated through several different renal pre-junctional and post-junctional receptors [10, 17, 29–31]. The most important pre-junctional modulation is through α2-adrenoceptors, with their activation leading to inhibition of noradrenaline release [32, 33]. Post-junctionally, noradrenaline binds to α1-adrenoceptors in the vasculature to induce vasoconstriction, β-adrenoceptor on juxtaglomerular cells to cause renin release and both α1 and α2-adrenoceptors in the proximal tubule to promote sodium reabsorption.

Circulating and locally released humoral factors also have major effects on renal function. Angiotensin II has a pronounced preferential vasoconstrictor effect on the efferent compared with the afferent arteriole, leading to reduction in total RBF but an increase in GFR [34–36]. The vasoconstrictor effects of noradrenaline and angiotensin II are counterbalanced by NO (nitric oxide) release (formerly known as endothelium-derived relaxing factor), the most important vasodilator in the renal vasculature. Several other mediators have also been identified that modulate vascular tone and regional renal perfusion, including prostaglandins, adenosine, endothelin and natriuretic peptides [4, 37, 38]. The role of the renal SNA in the regulation of glomerular haemodynamics requires detailed investigation.

**Sepsis Acute Kidney Injury: Challenging Dominant Paradigms**

From a physiologically logical point of view, at least three possible fundamental mechanisms can be offered to explain septic AKI: (i) septic AKI could be a consequence of cell damage (structural injury), (ii) septic AKI could be a consequence of partial or complete loss of function with minimal cell injury (functional injury) or (iii) septic AKI could be a combination of both the above processes which is dynamic in nature and varies in composition according to the stage and intensity of disease (more severe disease causing greater cell injury).

![Graph](image-url)

**Figure 1**: Changes in RSNA after the induction of Gram-negative sepsis by intravenous administration of E. coli. The initial response is one of decreased activity for several hours, followed by rebound increase in activity. Such changes are associated with increased urinary output (UO) during suppression and decreased UO during increased discharge.
In turn, cellular injury may be due to:

(i) hypoxia,
(ii) mitochondrial dysfunction and reduced energy production,
(iii) damage by reactive oxygen species,
(iv) autophagy to recycle damaged organelles and macromolecules,
(v) excessive inflammation, or cell death by apoptosis or necrosis.

Functional injury may result from regional perfusion mismatches leading to altered perfusion of critical sites such as the glomerulus that can alter renal function, and/or local ischaemia. Such changes in intra-RBF distribution may happen as a consequence of changes in the levels of circulating and local hormones, activation of the SNS, micro-vascular alterations with local areas of vasodilatation and of vasoconstriction, opening of vascular shunts, development of micro-thrombi, or because of interstitial oedema that slows down oxygen diffusion, or most likely a variable combination of these mechanisms.

Despite all of the above logical theoretical possibilities, at present and over the last 50 years, ischaemia has been widely accepted as the primary cause of septic AKI [1, 39]. According to this commonly accepted paradigm [1, 39], sepsis causes a decrease in total RBF due to renal arterial vasoconstriction and/or decreased systemic delivery of blood to vital organs, and this event, in turn, causes renal ischaemia, and tubular cell death with loss of function. As a consequence of such ischaemia, ATN is believed to occur.

However, whether a decrease in total RBF leading to ATN could be the initiating cause of septic AKI in humans is questionable. Little, if any, human evidence supports this hypothesis [2, 40–42]. Cardiac output is typically increased in sepsis when AKI develops, but unfortunately, due to technical limitations, little is known about changes in RBF in human sepsis [2]. Similarly, contradictory findings on the changes in kidney histology in septic AKI have been reported [43, 44], with the majority of findings even in rapid post-mortem studies reporting a lack of ATN. In view of the lack of validated, accurate, non-invasive techniques to assess RBF at the bedside in humans, animal models have been used to investigate sepsis-induced changes in RBF and to understand the histopathology of AKI in sepsis (Figure 2).

A range of contradictory haemodynamic and histopathologic changes have been described in animal models of sepsis [45, 46], likely due to the different models used. In particular, about half of the animal evidence available is from studies of ‘hypo-dynamic sepsis in anaesthetised animals’. Hypo-dynamic sepsis is a pattern only rarely encountered in human sepsis [45], as sepsis is more often characterized by a hyper-dynamic state. In fact, a review of studies on conscious animals with hyper-dynamic models of sepsis that more closely mimics the clinical and haemodynamic phenotype of human sepsis, found that RBF was increased [45]. In particular, previous experiments in our laboratory using highly accurate transit time flow probes (Figure 3) have found that RBF in a sheep model of sepsis achieved with intravenous infusion of Escherichia coli was markedly increased (Figure 4) [47, 48] and studies of porcine sepsis have shown development of AKI with normal RBF [3].

Further evidence that renal ischaemia is not responsible for inducing bio-energetic failure is suggested by the finding that renal ATP availability measured using magnetic resonance spectroscopy was unchanged in the first hours of sepsis in anaesthetized sheep (Figure 5). Importantly, the use of a renal vasoconstrictor agent, (angiotensin II) in this early phase of sepsis did not change renal ATP availability [49]. Finally, 2 h of 80% occlusion of the renal artery in conscious sheep did not cause AKI [50], and complete occlusion of the renal artery in humans for more than 30 min does not cause structural changes [51]. All the findings which challenge the ischaemia–ATN paradigm are listed in Table 1. All of the above experimental data raise serious questions about the dogma that septic AKI is a disease of the macro-circulation (renal artery vasoconstriction and/or global hypo-perfusion). In conjunction with evidence that ATN is an uncommon finding in septic AKI and that the initial characteristic of the syndrome is actually loss of GFR, they
suggest instead the need to explore alternative hypotheses and to focus on the glomerulus.

**THE GLOMERULAR ARTERIOLES IN SEPSIS**

The main control of GFR is through the regulation of afferent and efferent arteriolar tone. Thus, a decrease in GFR can logically be the consequence of either:

(i) an increase in afferent arteriolar tone or
(ii) a decrease in efferent arteriolar tone or
(iii) combination of the two with these changes leading to decreases in the hydrostatic gradient for filtration.

suggest instead the need to explore alternative hypotheses and to focus on the glomerulus.

**FIGURE 4:** Changes in mean arterial pressure, cardiac output and renal artery flow after the induction of experimental Gram-negative sepsis in the sheep. The systemic haemodynamic phenotype is the same as typically seen in intensive care in septic man. However, in septic man, renal blood flow cannot be measured continuously on a beat-by-beat basis as was done in this sheep. Such monitoring reveals clear cut renal hyperaemia. Given the decrease in mean arterial pressure, such hyperaemia must reflect decreased renal vascular resistance.

**FIGURE 5:** Graphic representation of changes in ATP during experimental Gram-negative septic shock causing severe AKI and anuria and in the sheep. No changes in ATP occurred. The spectra were of high quality (see right-hand corner) with preservation of γ, α and β peaks indicating that there was no global bio-energetic failure in this setting.

**Table 1. Evidence challenging the concept of global hypo-perfusion causing septic AKI**

- There is ‘no’ robust evidence that RBF is decreased in human sepsis;
- There is ‘no’ reliable evidence of ATN in septic man or animals;
- No treatment aiming at improving global renal perfusion has proved effective in septic AKI;
- Renal ATP availability is ‘unchanged’ in the first 4 h of sepsis in sheep and is not when RBF is reduced by infusion of angiotensin II;
- Severe and prolonged occlusion (80% reduction in RBF, for 2 h) of the renal artery does ‘not’ cause AKI in sheep;
- Complete occlusion of the renal artery for more than 30 min in humans does ‘not’ cause renal parenchymal damage;
- Human sepsis is characterized by a ‘hyper-dynamic’ state with a high cardiac output;
- It is possible to reproduce septic AKI even in the face of markedly ‘increased total renal blood flow’.

(iv) A decrease in afferent arteriolar tone with even greater decrease efferent arteriolar tone.
(v) Intra-renal shunting with peri-glomerular blood flow.

In a hyper-dynamic animal model with demonstrable hyperaemia as repeatedly reported and yet loss of GFR, the only explanations that make physiological sense are hypotheses (iv) and (v). If, in sepsis, efferent vasodilatation was more pronounced than afferent vasodilatation, this could explain the rapid loss of GFR seen clinically (Figure 6). A treatment that can increase efferent arteriole tone more than afferent arteriole tone would then be expected to restore GFR in sepsis. In support of this hypothesis, we have shown that angiotensin II can improve GFR in an early phase of sepsis in sheep despite a
creases or increases in GFR, respectively. Increases in RSNA on the stimulus 
arteriolar vasoconstriction, and can induce either preferential
sepsis in changes in RSNA that occur in the early and late stages of 
increased. It is currently unknown whether the 
crease in SNA, as shown by the increase in plasma catechol-
Sepsis, like other stress conditions, is characterized by an in-
crease sodium reabsorption at tubular level [22, 64], which can
reduce urine output. Moreover, an increase in SNA can cause a shift of the relation of RBF and GFR to renal perfusion pres-
ture to the right so that auto-regulation is reduced at higher
pressure. Thus, the initial decrease in RSNA in sepsis could account for the initial diuresis, and the later increase in RSNA could contribute to the decrease in GFR and development of oliguria in sepsis.

Although the cardiovascular effects of an increase in SNA would be expected to be beneficial by helping to maintain arterial pressure, there is also evidence that a protracted and ex-
cessive increase in SNA during prolonged critical illness may become maladaptive and exert adverse effects. Support for the use of sympatholytics in sepsis comes from recent studies of the effects of the centrally acting α2-adrenoceptor agonists in sepsis. Preliminary clinical evidence showed that inhibition of sympath-
thetic outflow with a centrally acting sympatholytic drug (either clonidine or dexmedetomidine) improved outcome in sepsis [66–70]. Dexmedetomidine, an alpha-2 receptor agonist, has been introduced as a sedative agent and to prevent/treat ICU delirium [71]. This drug has less effect on the cardiovascular system than clonidine and therefore could be easier to manage in sepsis with cardiovascular derangement and might be the subject of further investigations.

FIGURE 6: Schematic representation of what might be happening at a micro-vascular level to explain the presence of hyperaemia and loss of GFR in experimental ovine sepsis. Under normal conditions [schema 1], there is normal ultrafiltration (UF) and a normal state of the afferent (AA) and efferent (EA) arterioles. In sepsis with hyper-
aemia and decreased vascular resistance, there may be AA dilatation. However, such AA vasodilatation would be expected to increase UF. For UF to simultaneously decrease (small UF arrow), the EA must dilate even more than the AA and thus decrease intra-glomerular filtration pressure (a state similar to the administration of angiotensin-converting enzyme inhibitors) [schema 2]. Another possibility is that low resistance shunt pathways open during sepsis. These pathways can then divert blood away from the glomerulus [schema 3]. It is of course possible that scheme 2 and 3 operate simultaneously.

reduction in total RBF [52]. Similarly, vasopressin preferential-
ly vasoconstricts the efferent arteriole, and AVP and Terlipres-
sin, an analogue with a longer half-life, have been shown to 
prove renal function in experimental and clinical sepsis [53, 54]. These observations, however, do not exclude shunting and do not explain the mechanisms behind such changes in arteriolar tone. They invite consideration (among several po-
tential mechanisms) of the role of the renal nervous sympa-
thetic system.

SYMPATHETIC NERVOUS SYSTEM AND GLOMERULAR FUNCTION IN SEPSIS

Sepsis, like other stress conditions, is characterized by an in-
crease in SNA, as shown by the increase in plasma catechol-
amine levels and in directly recorded SNA [55–57]. Our laboratory showed that SNA is differentially increased in heart and kidney during sepsis [58]: cardiac SNA (CSNA) was in-
creased while RSNA was initially inhibited and only subse-
quently increased. It is currently unknown whether the 
changes in RSNA that occur in the early and late stages of 
sepsis influence RBF and renal function [58–62]. It is known that an increase in RSNA in physiologic conditions causes ar-
teriolar vasoconstriction, and can induce either preferential 
vasoconstriction of the afferent or efferent arteriole depending on the stimulus [9–11, 18–21, 63, 64], which could lead to decreases or increases in GFR, respectively. Increases in RSNA also stimulate renin release from juxtaglomerular cells, and in-
crease sodium reabsorption at tubular level [22, 64], which can reduce urine output. Moreover, an increase in SNA can cause a shift of the relation of RBF and GFR to renal perfusion pres-
ture to the right so that auto-regulation is reduced at higher
levels of perfusion pressure [65]. Thus, the initial decrease in RSNA in sepsis could account for the initial diuresis, and the later increase in RSNA could contribute to the decrease in GFR and development of oliguria in sepsis.

Currently, we have little understanding of the control of intra-
RBF, or intra-renal oxygen delivery, oxygen extraction and 
tissue oxygenation in the normal state, and even less knowl-
dge in septic AKI. In sepsis, local mismatches in oxygen supply/demand due to perfusion derangements may occur 
[72, 73], and these may contribute to the development of AKI.
The development of probes that simultaneously measure 
tissue perfusion and tissue partial pressure of oxygen has 
allowed recent investigation of these processes. In a series of 
studies utilizing such probes, Evans et al. [37, 74–76] have shown that numerous hormones including angiotensin, en-
dothenin, vasopressin, acetylcholine and noradrenaline have 
differential effects on cortical and medullary perfusion. A role 
for neural mechanisms in the control of intra-RBF was de-
monstrated by the finding that, in conscious rabbits, stimula-
tion of the nasopharyngeal reflex, decreased both cortical and 
medullary flow [37].

It has long been recognized that the level of blood flow differs 
in the cortex and in the medulla [5, 37]. Importantly, for this 
review, anatomical evidence has accumulated that in addition to 
this classical description of renal vascular anatomy, other shunt-
ing peri-glomerular vessels may exist. Several authors have 
described peri-glomerular vessels directly connecting the affer-
ent to the efferent arteriole (therefore circumventing the glom-
erator circulation) as well as vessels which directly link the 
arcuate arteries to veins in different species [77–81]. Opening of 
such shunt vessels would result in a reduction in GFR in the 
presence of an increase in RBF as occurs in ovine hyper-
dynamic sepsis [45, 47]. At present, the existence of such ‘shunt vessels’ is controversial and it is unknown what mechanisms control their vascular tone, and further investigation is required to determine their relevance in normal and pathological conditions.

This review has indicated that there are now a number of hypotheses proposing that micro-vascular mechanisms may contribute to the early loss of GFR in septic AKI. They include a greater efferent than afferent vasodilatation thereby inducing a fall in GFR with renal hyperaemia. It is also possible that, for some glomeruli, afferent arteriolar vasoconstriction occurs or peri-glomerular shunt vessels open leading to a fall in GFR but increased RBF, although identification of these vessels is required. All these putative responses may either be adaptive or maladaptive. These questions will require careful and targeted experimental, physiological and anatomical work in the next decade.

CONCLUSIONS

In conclusion, previous paradigms that renal hypo-perfusion and ATN are responsible for septic AKI have little support from experimental and human investigations. In a hyperdynamic large mammal model of severe sepsis, total RBF increased from experimental and human investigations. In a hyperdynamic sepsis model of severe sepsis, total RBF increased. To better understand the causes of septic AKI, it is necessary to improve our knowledge of the haemodynamic changes in the renal micro-vasculature, the role of increased SNA and hormonal systems and to investigate the importance of intra-renal shunting. In the next decade, investigations of the pathogenesis of septic AKI will likely focus on the regulation of microvascular flow and renal tissue oxygenation.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received for publication: 28.9.2013; Accepted in revised form: 5.2.2014