Septic Acute Kidney Injury (AKI)

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Things we really, honestly know about septic AKI

AKI is common

Septic AKI is responsible for about 50% of AKI

Septic AKI is, therefore, relatively common.

We should worry about it and try to understand it.
What do we mean by AKI?

- By AKI we actually mean “loss of small solute clearance” (urea/creatinine increase in blood)
- This implies loss of GFR
- So...clinically we actually mean “likely acute decrease in GFR”
Why does GFR fall in sepsis?

- I thought we did not know, but luckily the NEJM told us (Schrier RW, Wang W. Acute renal failure in sepsis. (Review) N Engl J Med 2004; 2004; 351: 159-169)

- “...early in sepsis-related AKI, the predominant pathogenetic factor is renal vasoconstriction with intact tubular function....”

Current Dogma: Renal vasoconstriction is the first major pathogenetic event in septic AKI

- But...hang on ..in the same article: “....the hemodynamic hallmark of sepsis is **generalized arterial vasodilatation**.....”

- So... which one is true?
- **Vasoconstriction or vasodilatation?**
- It can only be vasoconstriction, right?
- How else would GFR fall?
Renal Vasculature

Look at this vessel!

Glomerulus

- Afferent arteriole
- Efferent arteriole
Vasomotor GFR control: Logical principles

- GFR can decrease if the afferent arteriole constricts no matter with the efferent does.
- GFR can decrease if the efferent arteriole dilates even if the afferent stays the same.
- GFR can decrease if the afferent arteriole dilates but the efferent arteriole dilates even more.
- All can logically cause loss of glomerular filtration pressure.
Haemodynamic measurements in conscious sheep

- Systolic, diastolic, mean arterial pressure
- Central venous pressure
- Cardiac output, heart rate, stroke volume, maximum aortic flow, dF/dt
- Regional flows and conductances
- Urinary flow
Example of induction of sepsis: hemodynamics

Induce sepsis with E. Coli

Study period

CVP 0 to 2 mmHg
Renal vasconstriction in early sepsis???

Intensive Care Med 2003; 31: 2509-13
Pre sepsis  Septic Control  Norepinephrine

Sheep 1  Sheep 2  Sheep 3  Sheep 4  Sheep 5  Sheep 6  Sheep 7  Sheep 8

Figure 2a

Crit Care Med 2003; 31: 2509-13
Figure 2c
Figure 2d

% Changes in Medullary Flow

Sheep 1
Sheep 2
Sheep 3
Sheep 4
Sheep 5
Sheep 6
Sheep 7
Sheep 8

Pre sepsis  Septic Control  Norepinephrine

Crit Care Med 2003; 31: 2509-13
Renal Blood Flow and Septic AKI

- Once we simulated the hemodynamics of human sepsis, RBF increased and renal vascular resistance decreased with simultaneous oliguria and loss of GFR.

- When we simulated profound septic shock, infusion of a powerful vasoconstrictor (norepinephrine) increased RBF and UO.

- In early (first 24 hours) experimental hyperdynamic sepsis loss of GFR occurs with renal hyperemia and vasodilatation.
New (old) Hypothesis

- Like other vascular beds the renal bed **vasodilates** in severe sepsis
- **Efferent arteriolar vasodilatation** causes loss of GFR
- Septic ARF is at least initially a **hyperemic** not an ischemic form of AKI
- If true... **vasoconstrictors should improve GFR** in septic ARF in man
macula densa

podocyte

Bowman’s space

proximal tubule
If efferent vasodilation were true....pharmacologic efferent vasconstriction should fix things
Flow goes down

- AVP effect on lumen diameter of isolated cortical afferent and efferent arterioles
- No effect on afferent arterioles which, however, responded to norepinephrine
- Concentration dependent efferent arteriolar vasoconstriction (100 times more potent than norepinephrine) – effect blocked by V1 blocker but not V2 blocker
Effect of Low-Dose Vasopressin Infusion on Vital Organ Blood Flow in the Conscious Normal and Septic Sheep

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Howard Florey Institute, University of Melbourne, Parkville and Departments of Intensive Care and Surgery, Austin Health, Heidelberg and University of Melbourne, Parkville, Victoria

SUMMARY

The effect of low-dose vasopressin (AVP) on vital regional circulations may be clinically relevant but has not been fully described. We sought to determine the effect of low-dose AVP on systemic haemodynamics, coronary, mesenteric and renal circulations in the conscious normal and septic mammal.

We studied seven Merino sheep using a prospective randomized cross-over double-blind placebo-controlled animal design. We inserted flow probes around aorta, coronary, mesenteric and renal arteries and, three weeks later, we infused low-dose AVP (0.02 IU/min) or placebo in the normal and septic state induced by intravenous E.coli. In normal sheep, AVP (0.02 IU/min) induced a 17% decrease in mesenteric blood flow (393.0±134.9 vs 472.1±163.8 ml/min, P<0.05) and a 14% decrease in mesenteric conductance (P<0.05). In septic sheep, AVP decreased heart rate and cardiac output by 28% and 22%, respectively (P<0.05). It also decreased mesenteric blood flow and mesenteric conductance by 23% (flow: 468.5±159.7 vs 611.3±136.3 ml/min, P<0.05; conductance: 6.3±2.7 vs 8.2±2.7 ml/min/mmHg; P<0.05). Renal blood flow was unchanged but urine output and creatinine clearance increased (P<0.05). We conclude that low-dose AVP infusion has similar effects in the normal and septic mammalian circulation: bradycardia, decreased cardiac output, decreased mesenteric blood flow and conductance and increased urine output and creatinine clearance. This information is important to clinicians considering its administration in humans.
P < 0.05
In early hyperdynamic mammalian sepsis or septic shock GFR can be lost in the presence of increased RBF and renal vasodilatation. Vasoconstrictors seem to help function.

Does this happen in man?
RBF in human sepsis with AKI

- Only one series in the last 40 years!
True Renal Plasma Flow (TRPF) in early sepsis

- TRPF = 154% of normal
- TRPF tightly correlated with CO
- Similar findings in humans given "pyrogen" (Combos et al. Circulation 1967; 36: 555-569)
All this was already described by Homer Smith
J Clin Invest 1945; 24: 749-758

"Derivatives of bacterial protein...lead to...a marked increase in renal blood flow, reduction in arterial pressure and an increase in cardiac index......renal hyperemia occurred in each instance studied...."
Diodrast clearance

Fig. 1. Subject P. H. The systemic and renal circulatory effects of the pyrogenic reaction, normal, male, 52 years.

BP, blood pressure (Hamilton manometer) in mm. Hg, the thick line being the mean pressure; HR, heart rate; SV, stroke volume in ml.; CI, cardiac index (ballistocardiograph) in liters per minute per square meter of body surface; R, peripheral resistance in dynes cm.** sec.; FF, filtration fraction (fraction of renal plasma flow filtered at the glomerulus); Cm, mannitol clearance (glomerular filtration rate in ml. per minute); Cn, diodrast clearance (renal plasma flow in ml. per minute). Values of the renal fraction (per cent of the cardiac output passing through the kidneys) are inserted below each diodrast clearance period figure; °F, rectal temperature in degrees of Fahrenheit. The arrows at the top of the figure indicate times at which hemodynamic data were obtained. All subjects described here were premedicated with amidopyrine.
Low-dose vasopressin increases glomerular filtration rate, but impairs renal oxygenation in post-cardiac surgery patients

Department of Cardiothoracic Anesthesia and Intensive Care, Sahlgrens University Hospital, Göteborg, Sweden
Low-dose AVP and kidney in cardiac surgery
Fig. 2. Shows the individual data on the correlation between the vasopressin-induced increases in renal filtration fraction and renal oxygen extraction ($r^2 = 0.86, P<0.001$).
The effects of vasopressin on acute kidney injury in septic shock
VASST trial – patients in RIFLE R class
VASST study – Patients in RIFLE R class
So...global flow is dissociated from function..

- What is the mechanism for such dissociation?
- Is it really efferent arteriolar vasodilatation?
- What is happening inside the kidney?
- Is this a model dependent finding?
Ultrastructural demonstration of a connection between afferent and efferent juxtamedullary glomerular arterioles

Arne Ljungqvist

Institute of Pathology, Karolinska Sjukhuset, Stockholm, Sweden

In the juxtamedullary unit, the previous observation of a direct vascular connection between the afferent and efferent vessels bypassing the glomerular tuft was confirmed. In a previous report [3], it was emphasized that in the uninjected specimen the lumen of this connecting segment is usually collapsed and that this explains why the connecting segment has been demonstrated only by workers using injection techniques [1-3, 12, 13]. This view was further
Look at this vessel!
The functional significance of the continuous juxtedullary vessel as a glomerular bypass mechanism for medullary blood flow has been discussed in detail previously [1]. The present observation that the wall of the connecting segment is devoid of smooth muscle cells suggests that this will largely passively convey the blood from the afferent to the efferent arteriole, although a certain contractile activity may well be exerted by the lacis cells to judge from their cytoplasmic
Shunting in Renal Microvasculature of the Rat: A Scanning Electron Microscopic Study of Corrosion Casts

D. CASELLAS and A. MIMRAN
Department of Medicine D, CHR Saint-Charles, Montpellier, France
Fig. 7. Corrosion cast of a juxtamedullary glomerulus (539 g body weight). An agglomerular vessel (AV) arises from the afferent arteriole (AA) at the glomerular vascular pole. Note the presence of an efferent arteriole (EA). Bar: 100 μm. VR, vasa recta.
Fig. 2. Glomerular and peritubular microvascular connections. 3-D reconstruction of the outer portion of a surface glomeruli in a Munich-Wistar F344 rat using 2-photon microscopy to acquire individual 1-μm planes. A 150-kDa fluorescent dextran provides the fluorescence detected only within the arteriole and capillary/venous microvasculature. Note the many connections between surface vessels and capillaries. Additional studies will be needed to interrelate the functional and anatomic aspects of these vessels and their importance in AKI.
Microcirculation: What happens in sepsis?
Cortical and Medullary Tissue Perfusion and Oxygenation in Experimental Septic Acute Kidney Injury

Paolo Calzavacca, MD, PhD\textsuperscript{1,2,3,4}; Roger G. Evans, PhD\textsuperscript{5}; Michael Bailey, PhD\textsuperscript{6}; Rinaldo Bellomo, MD, PhD\textsuperscript{2,3}; Clive N. May, PhD\textsuperscript{1}

(Crit Care Med 2015)
The septic kidney: global renal blood flow
Intra-renal oxygenation

Cortico-medullary dissociation

Knowing global
Or even intra-renal blood flow says little about medullary oxygenation

Also simultaneous major fall in GFR!
Long-term measurement of renal cortical and medullary tissue oxygenation and perfusion in unanesthetized sheep

Philo Calzavara,1,2,4 Roger G. Evans,2 Michael Bailey,7 Yugesh R. Lankadeva,2 Ronaldo Bellomo,2 and Clive N. May4

1Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia; 2Department of Intensive Care and Department of Medicine, Austin Health, Heidelberg, Victoria, Australia; 3Department of Anaesthesia and Intensive Care, AO Molengo, Padua, Como and Bassano, Italy; 4Department of Physiology, Monash University, Clayton, Victoria, Australia; and 5Australian and New Zealand Intensive Care Research Centre, School of Epidemiology and Preventive Medicine, Monash University, Clayton, Australia
So...global flow is dissociated from function...and from histology...which is also dissociated from function in sheep and man!

- What is the mechanism for such dissociation?
- Is it really efferent arteriolar vasodilatation?
- What is happening inside the kidney?
- **Is there intra-renal shunting?**
LPS in rats
Does any medullary hypoxia cause tubular injury?
Table 1. Human studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cause</th>
<th>AKI Definition</th>
<th>Method</th>
<th>AKI/Patients (%)</th>
<th>ATN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotchkiss [10]</td>
<td>Sepsis/septic shock</td>
<td>SCr&gt;2mg/dL and UO&lt;20mL/kg/hr x 6 hr</td>
<td>PM</td>
<td>12/20 (60)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Sato T [12]</td>
<td>Sepsis</td>
<td>NA</td>
<td>PM</td>
<td>6/6 (100)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Mustonen [9]</td>
<td>Sepsis/shock/hypovolemia</td>
<td>NA</td>
<td>Biopsy</td>
<td>57/57 (100)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Rosenberg [11]</td>
<td>Sepsis</td>
<td>SCr&gt;3.5mg/dL and U/P osm &gt;1</td>
<td>Biopsy</td>
<td>1/1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Zappacosta [13]</td>
<td>Sepsis</td>
<td>NA</td>
<td>Biopsy</td>
<td>1/1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diaz de Leon [14]</td>
<td>Severe sepsis</td>
<td>SCr, Urine Output, U/P osm (not specified)</td>
<td>Biopsy</td>
<td>107/332 (32)</td>
<td>20 (50)</td>
</tr>
</tbody>
</table>

Table 2. Primate studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cause</th>
<th>AKI/Animals (%)</th>
<th>ATN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carraway [17]</td>
<td>Heat shocked E. Coli and live E. Coli</td>
<td>6/6 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Coalsen [16]</td>
<td>E.coli endotoxin infusion</td>
<td>4/4 (100)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Coalsen [15]</td>
<td>Live E. Coli infusion</td>
<td>3/8 (38)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Welty-Wolf [18]</td>
<td>Heat shocked E. Coli and live E. Coli/gentamicin administration</td>
<td>6/6 (100)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Reference</td>
<td>Induction of sepsis</td>
<td>ATN</td>
<td></td>
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<tr>
<td>-----------</td>
<td>------------------------------------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>[32]</td>
<td>Salmonella enteritidis endotoxin</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>[33]</td>
<td>CLP/LPS</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>[34]</td>
<td>E. coli</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>[35]</td>
<td>LPS induced sepsis</td>
<td>no</td>
<td></td>
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<tr>
<td>[36]</td>
<td>LPS induced sepsis</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>[37]</td>
<td>LPS induced sepsis</td>
<td>yes</td>
<td></td>
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<tr>
<td>[38]</td>
<td>E. coli septicemia</td>
<td>no</td>
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<tr>
<td>[39]</td>
<td>LPS induced sepsis</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>[40]</td>
<td>LPS induced sepsis</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>[41]</td>
<td>CLP</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>[42]</td>
<td>LPS induced sepsis</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>[35]</td>
<td>LPS induced sepsis</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>[43]</td>
<td>LPS induced sepsis</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms of Cardiac and Renal Dysfunction in Patients Dying of Sepsis

Osamu Takasu\(^1\)*, Joseph P. Gaut\(^2\)*, Eizo Watanabe\(^3\), Kathleen To\(^3\), R. Eliot Fagley\(^1\), Brian Sato\(^1\), Steve Jarman\(^3\), Igor R. Efimov\(^4\), Deborah L. Janks\(^4\), Anil Srivastava\(^5\), Sam B. Bhayani\(^6\), Anne Drewry\(^1\), Paul E. Swanson\(^7\), and Richard S. Hotchkiss\(^1,3,8\)

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patients with sepsis-induced cardiac and renal failure. The vast majority of septic patients (32 of 38) were in shock, requiring the use of inotrope and/or vasopressors to maintain adequate mean arterial pressure and/or oxygen delivery (Table
Renal tubular injury is common in sepsis but presents focally; renal tubular regeneration possibly driven by mTOR also appears to be occurring. Renal tubular cell death occurs by necrosis and not by apoptosis or autophagy. Calcium phosphate crystals occur in renal tubules in approximately 50% of patients and may be contributing to renal failure. Although in some septic patients the degree of renal tubular injury was sufficient to explain renal failure, in most septic patients the majority of renal tubular cells appeared normal by light microscopy. Thus, the degree of cell injury and death may not account for the severity of renal failure in all patients with sepsis. This suggests that much of the organ injury is potentially reversible and that efforts to control infection and improve host immunity could decrease mortality.
Renal Histopathology During Experimental Septic Acute Kidney Injury and Recovery

Christoph Langenberg, MD, PhD³; Glenda Gobe, PhD²; Sally Hood, MSc¹; Clive N. May, PhD¹; Rinaldo Bellomo, MD, PhD³

Objectives: Our understanding of septic acute kidney injury is limited. We therefore assessed renal histopathological changes induced by septic acute kidney injury and their evolution during recovery.

Design: Prospective experimental study.

Setting: Physiology Research Institute.

Subjects: Twenty-two Merino sheep.

Intervention: We induced septic acute kidney injury by continuous IV infusion of Escherichia coli. We studied histology, immunohistochemistry, markers of apoptosis, and expression of nitric oxide synthase isoforms and hypoxia-inducible factor-1α. Analysis was performed on kidneys from normal sheep, sheep with septic acute kidney injury, and sheep after recovery from septic acute kidney injury.
DISCUSSION
Histopathological and biochemical changes, including measurement of markers of apoptosis, NOS isoforms, and HIF-1α, were assessed in the renal cortex and medulla from normal sheep, sheep after 48 hours of severe hyperdynamic sepsis, and sheep after 48-hour recovery from sepsis. Septic AKI was severe with a close to four-fold increase in serum creatinine over 48 hours. In spite of this, renal histopathology in septic animals and in animals after recovery from sepsis was indistinguishable from that in normal animals. In particular, we found no evidence of ATN or immunohistochemical evidence of macrophage or fibroblast infiltration, caspase activation, or neutrophil gelatinase-associated lipocalin expression. We also quantified apoptosis and found no increases in the septic AKI or recovery groups. Finally, we found that cortical, but not medullary, expression of all NOS isoforms was increased during septic AKI compared with the normal and recovery groups and that nNOS expression correlated with RBF. Although cortical HIF-1α expression also increased in septic AKI, it showed no correlation with RBF.
Figure 3. Relative levels of gene expression (LGE) for inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS) as measured by reverse transcriptase-polymerase chain reaction in kidneys from...
Figure 4. Relative levels of gene expression (LGE) for neuronal nitric oxide synthase (nNOS) and hypoxia-inducible factor (HIF)-1α as measured by reverse transcriptase-polymerase chain reaction in kidneys from the
What about bioenergetic failure despite high flows?
Renal Flow and Mean Arterial Pressure change over time in Septic Coil sheep

Time (min)

Renal Flow (ml/min)

MAP (mmHg)

1st Injection of E. coli

2nd Injection of E. coli

IV KCl

IJAO 2005
Sepsis

Immediately After CA

15 minutes of CA
Renal bioenergetics during early gram-negative mammalian sepsis and angiotensin II infusion

Abstract Purpose: To measure renal adenosine triphosphate (ATP) (bioenergetics) during hypotensive sepsis with or without angiotensin II (Ang II) infusion. Methods: In anaesthetised sheep implanted with a renal artery flow probe and a magnetic resonance coil around one kidney, we induced hypotensive sepsis with intravenous Escherichia coli injection. We measured mean arterial pressure (MAP), heart rate, renal blood flow (RBF) and renal ATP levels using magnetic resonance spectroscopy. After 2 h of sepsis, we randomly assigned sheep to receive an infusion of Ang II or vehicle intravenously and studied the effect of treatment on the same variables. Results: After E. coli administration, the experimental animals developed hypotensive sepsis (MAP from 92 ± 9 at baseline to 58 ± 4 mmHg at 4 h). Initially, RBF increased, then, after 4 h, it decreased below control levels (from 175 ± 28 at baseline to 138 ± 27 mL/min). Despite decreased RBF and hypotension, renal ATP was unchanged (total ATP to inorganic phosphate ratio from 0.69 ± 0.02 to 0.70 ± 0.02). Ang II infusion restored MAP but caused significant renal vasoconstriction. However, it induced no changes in renal ATP (total ATP to inorganic phosphate ratio from 0.79 ± 0.03 to 0.80 ± 0.02). Conclusions: During early hypotensive experimental Gram-negative sepsis, there was no evidence of renal bioenergetic failure despite decreased RBF. In this setting, the addition of a powerful renal vasoconstrictor does not lead to deterioration in renal bioenergetics.

Keywords: Acute kidney injury - Angiotensin II - Magnetic resonance spectroscopy - Renal blood flow - Septic shock
All these studies are too short

- We need model of sepsis that lasts >24 hrs
- We need model of sepsis that induces clear cut AKI (at least double creatinine)
Renal blood flow in experimental septic acute renal failure

C Langenberg¹, L Wan², M Egi², CN May³ and R Bellomo²

¹Department of Nephrology, Charité Campus Mitte, Berlin, Germany; ²Department of Intensive Care and Department of Medicine, Austin Hospital and University of Melbourne, Heidelberg, Melbourne, Australia and ³Howard Florey Institute, University of Melbourne, Parkville, Melbourne, Australia
Extended sepsis

- In an extended hyperdynamic sepsis model of septic AKI:
  - 1. Creatinine increased 3 times
  - 2. RBF increased 3 times
  - 3. Renal vascular conductance increased 3 times
- Dissociation between flow and function
Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: A pilot investigation

John R. Prowle, MB, BChir, MRCP, FFICM; Maurice P. Molan, MBBS, FRACR; Emma Hornsey, BSc; Rinaldo Bellomo, MD, FCICM

Objective: In septic patients, decreased renal perfusion is considered to play a major role in the pathogenesis of acute kidney injury. However, the accurate measurement of renal blood flow in such patients is problematic and invasive. We sought to overcome such obstacles by measuring renal blood flow in septic patients with acute kidney injury using cine phase-contrast magnetic resonance imaging.

Design: Pilot observational study.

Setting: University-affiliated general adult intensive care unit.

Patients: Ten adult patients with established septic acute kidney injury and 11 normal volunteers.

Interventions: Cine phase-contrast magnetic resonance imaging measurement of renal blood flow and cardiac output.

Measurements and Main Results: The median age of the study patients was 62.5 yrs and eight were male. At the time of magnetic resonance imaging, eight patients were mechanically ventilated, nine were on continuous hemofiltration, and five required vaso-pressors. Cine phase-contrast magnetic resonance imaging examinations were carried out without complication. Median renal blood flow was 482 mL/min (range 335–1137) in septic acute kidney injury and 1260 mL/min (range 791–1750) in healthy controls ($p = .003$). Renal blood flow indexed to body surface area was 244 mL/min/m$^2$ (range 165–662) in septic acute kidney injury and 525 mL/min/m$^2$ (range 438–869) in controls ($p = .004$). In patients with septic acute kidney injury, median cardiac index was 3.5 L/min/m$^2$ (range 1.6–8.7), and median renal fraction of cardiac output was only 7.1% (range 4.4–10.8). There was no rank correlation between renal blood flow index and creatinine clearance in patients with septic acute kidney injury ($r = .26$, $p = .45$).

Conclusions: Cine phase-contrast magnetic resonance imaging can be used to noninvasively and safely assess renal perfusion during critical illness in man. Near-simultaneous accurate measurement of cardiac output enables organ blood flow to be assessed in the context of the global circulation. Renal blood flow seems consistently reduced as a fraction of cardiac output in established septic acute kidney injury. Cine phase-contrast magnetic resonance imaging may be a valuable tool to further investigate renal blood flow and the effects of therapies on renal blood flow in critical illness. (Crit Care Med 2012; 40: 000–000)

Key Words: acute kidney injury; cine phase-contrast; critical care; magnetic resonance imaging; renal blood flow; sepsis
Oops...renal blood flow is dissociated from GFR!
Dissociation between global flow and function
PINK1/Parkin mediated

Damaged mitochondrial

PINK1

Ub

Mitophagy

NIX and BNIP3 mediated

Erythrocyte maturation

Beclin

Hypoxia

Bcl-2

NIX

Beclin

BNIP3

Bcl-2

Beclin

Mitophagy
Renal effects of treatment with a TLR4 inhibitor in conscious septic sheep

Johan Fenhammar¹, Mats Rundgren², Kjell Hultenby³, Jakob Forestier¹, Miael Taavo⁴, Ellinor Kenne⁵, Eddie Weitzberg², Stefan Eriksson², Volkan Ozenci⁷, Annika Wernerson⁸ and Robert Frithiof²,⁹
Figure 2 Changes in diuresis (A), creatinine clearance (Crea Clear) (B), filtration fraction (C), blood urea nitrogen (BUN) (D), plasma creatinine (P-Crea) (E), and urinary concentrations of N-acetyl-β-D-glucosaminidase (U-NAG) (F) in response to sepsis and treatment with either the selective TLR4 inhibitor TAK-242 (n = 7) or vehicle (n = 7). Data are expressed as mean and 95% confidence interval. Asterisk indicates a significant difference between TAK-242 and control in response to sepsis. Analysis of variance (ANOVA) repeated measures from 12 to 36 hours.
Conclusions

- Global renal blood flow in sepsis may initially be high driven by renal vasodilatation.
- What drives such vasodilatation remains unknown.
- Human data suggest that global blood flow and function and/or histology are dissociated.
- They may be dissociated because of decreased filtration pressure or because of shunting.
- Knowing about the macro-circulation may not be enough and AKI may mostly be a disease of the micro-circulation. But if so, how do we manipulate it?
Is it all about hemodynamics?

- It seems far too “simple”
- Sepsis is a complex and toxic state
- This data only relates to the first 24-48 hrs
- It is mostly from models
- Much more is likely to be at work
- Septic AKI is also inflammatory disease
Septic Acute Renal Failure

We do not know or understand the macro-circulation, micro-circulation, histology or pathogenesis of AKI in general.

We need to consider septic AKI as a specific entity.

We need to stop pretending that clamping of the renal artery ischemia models of AKI tell us what happens in septic AKI.

We need to start questioning old paradigms.
Reflections for those who still believe that ischemia causes septic Aki and leads to ATN...and have no doubts.

- The difficulties lie not in new ideas, but in escaping old ones... which ramify into every corner of our minds (John Maynard Keynes)
- Doubt is not a pleasant condition, but certainty is absurd (Voltaire)
- Doubt is one of the names of intelligence (Jorge Luis Borges)