# Acute Kidney Injury in Sepsis

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# Disclosures

- I have received speaking, consultation and grant fees from
- Baxter
- BBraun
- Edwards Lifesciences

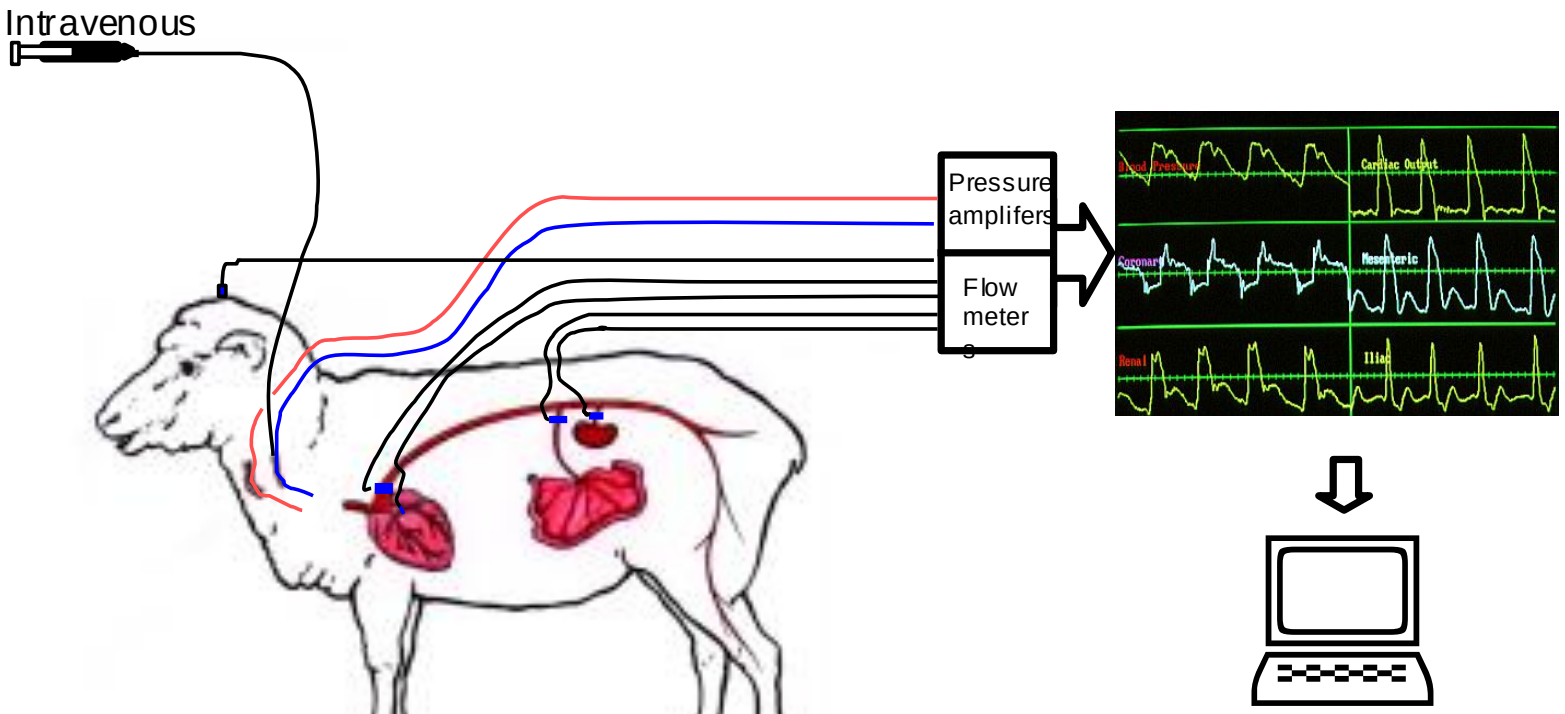
# Why does AKI develops in sepsis?

- Septic AKI is the most common form of severe AKI in developed countries
- It makes up >50% of all cases of severe AKI in ICU
- If combined with the need to deliver RRT, it carries a >50% mortality
- There is no specific therapy. Only treatment of septic focus and supportive care.
- A major problem in developing therapies arises from our **limited understanding of its pathogenesis**

# Why limited understanding?

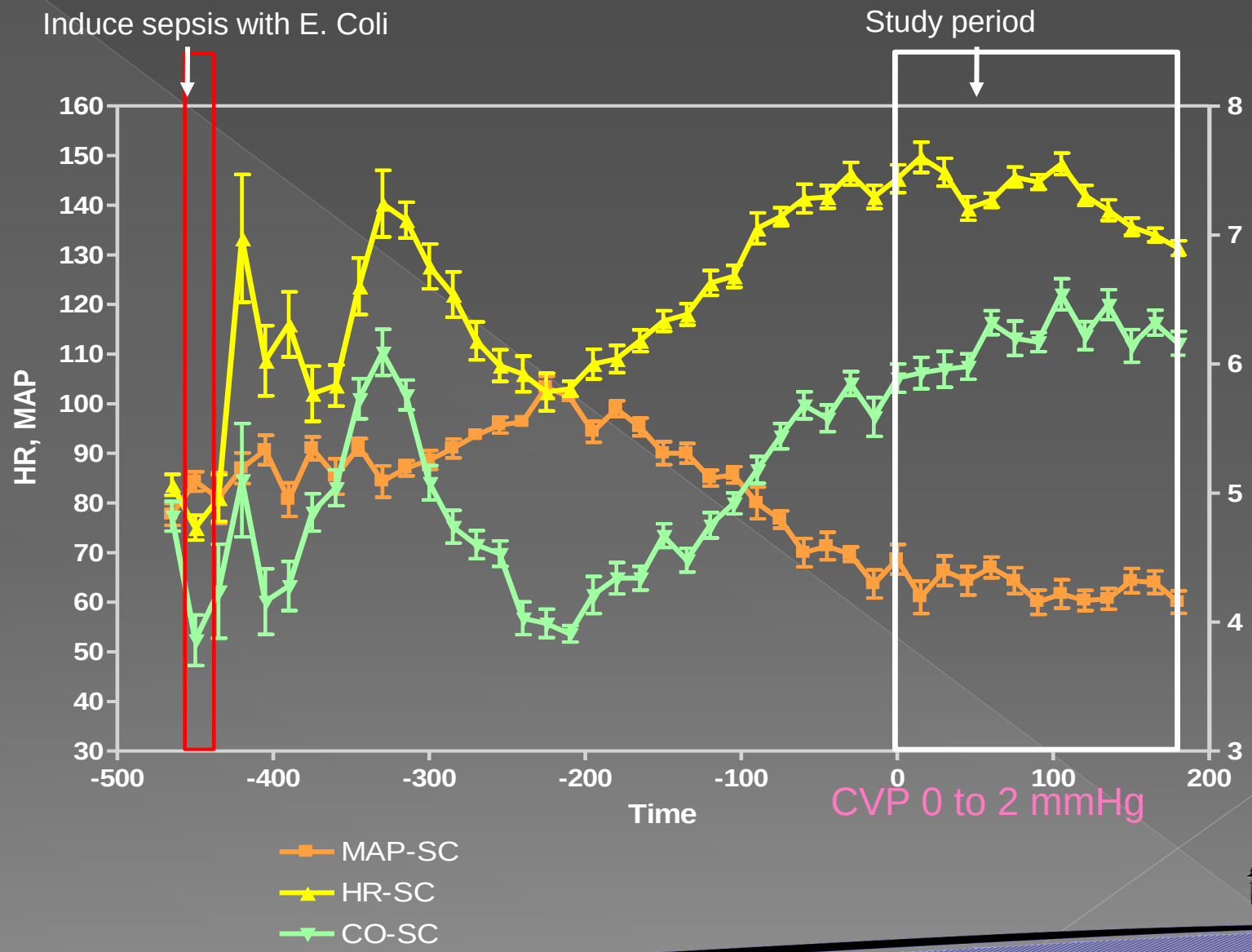
- Can't get tissue
- Can't monitor global blood flow
- Can't monitor regional renal blood flow
- Urinary flow is of limited information
- Urinary biochemistry is of limited value
- Urinary microscopy is of limited value
- Functional measured become abnormal only when >50% of function is lost

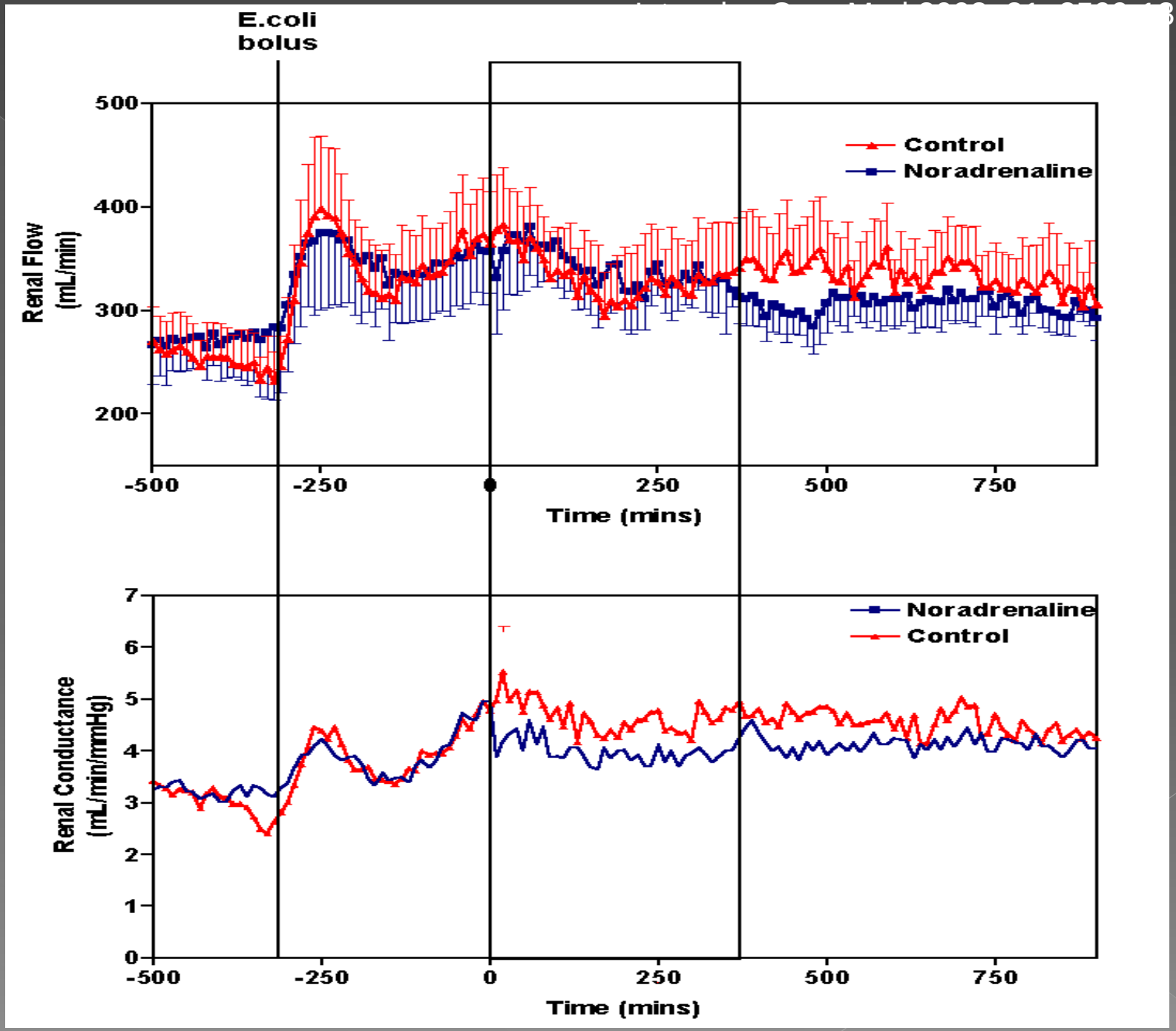
# Haemodynamic measurements in conscious sheep




- 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

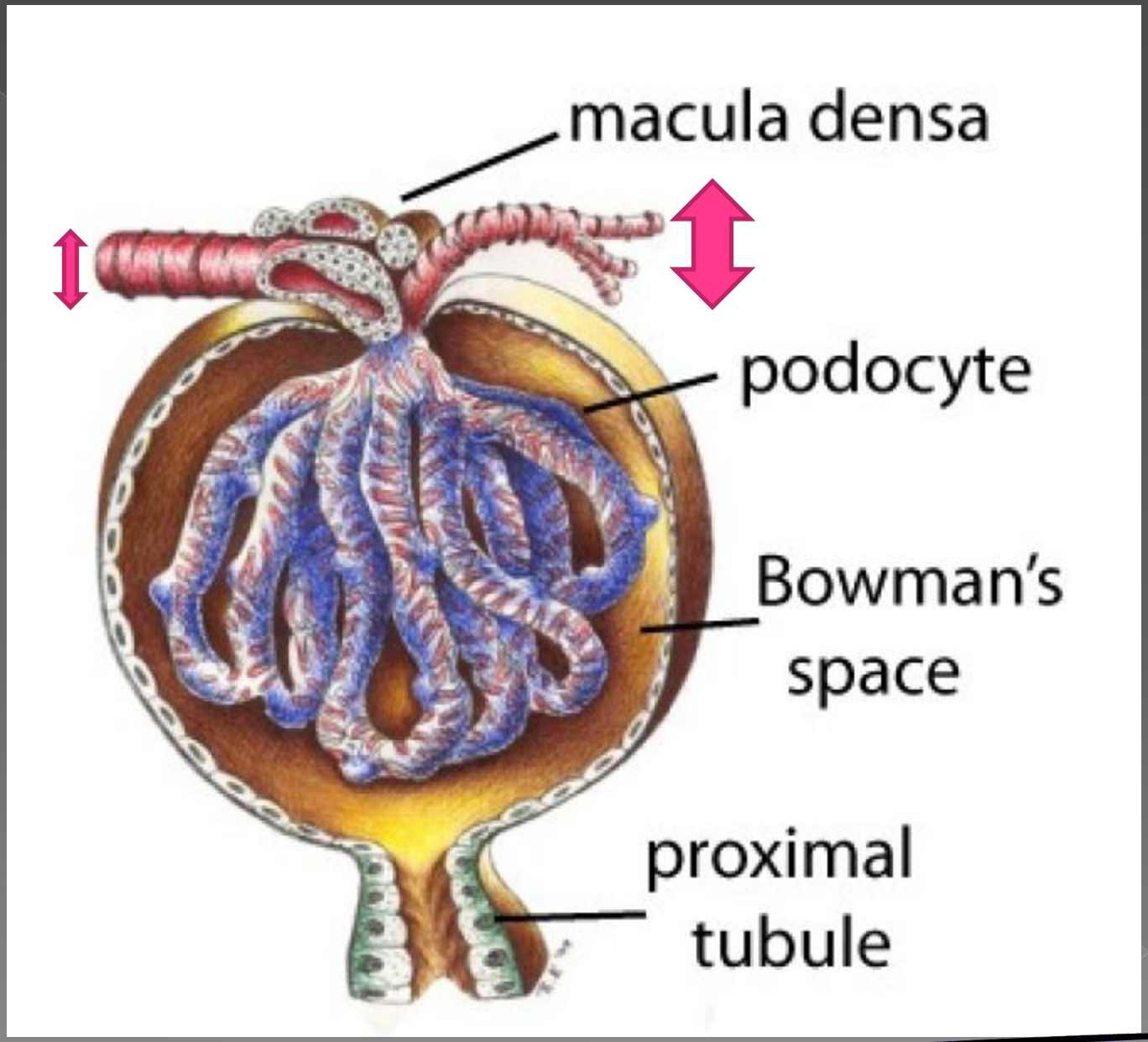
# Example of induction of sepsis: hemodynamics




E.coli
bolus
Renal Flow
(mL/min)
500
400
300
200
Control
Noradrenaline
-500
-250
250
500
750
Time (mins)
Renal Conductance
(mL/min/mmHg)
7
6
5
4
3
2
1
0
Noradrenaline
Control
-500
-250
0
250
500
750
Time (mins)

# Renal Blood Flow and Septic AKI

- In experimental gram negative bacteremia with AKI, RBF increased and renal vascular resistance decreased with simultaneous oliguria and loss of GFR
- In early (first 24 hours) experimental hyperdynamic sepsis loss of GFR occurs with renal **hyperemia** and **vasodilatation**


macula densa
podocyte
Bowman's space
proximal tubule

# Hypothesis

- Like other vascular beds the renal bed **vasodilates** in severe sepsis
- **Efferent arteriolar vasodilatation** may cause such loss of GFR
- Septic ARF is at least initially a ***hyperemic*** not an ischemic form of AKI
- Loss of function (loss of GFR) is due to **decreased filtration pressure**
- If true….**vasoconstrictors should improve GFR in septic ARF**

# If efferent vasodilation were true….pharmacologic efferent vasconstriction should improve function

Research

Open Access

## Angiotensin II in experimental hyperdynamic sepsis

Li Wan[1,2,3,4], Christoph Langenberg[1], Rinaldo Bellomo[2,3] and Clive N May[1]

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[2]Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Burnett Building, Commercial Road, Prahran, Melbourne, Victoria, Australia
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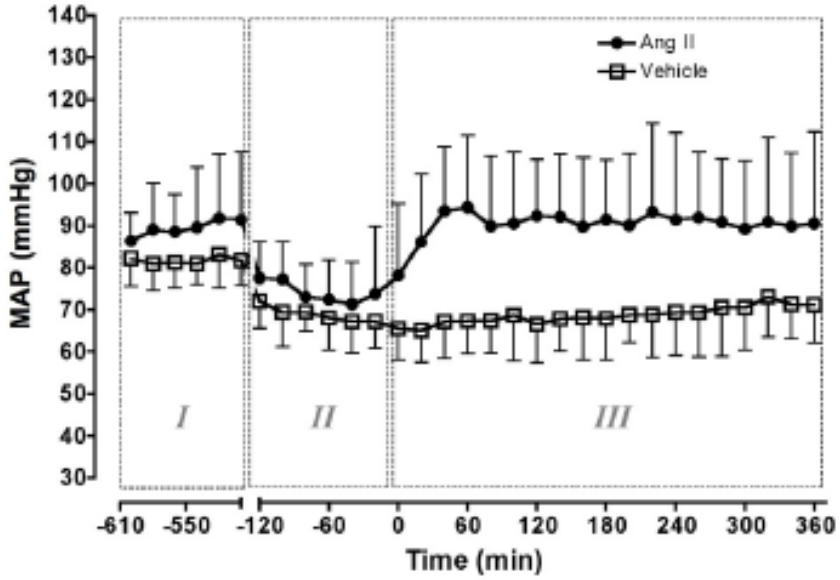
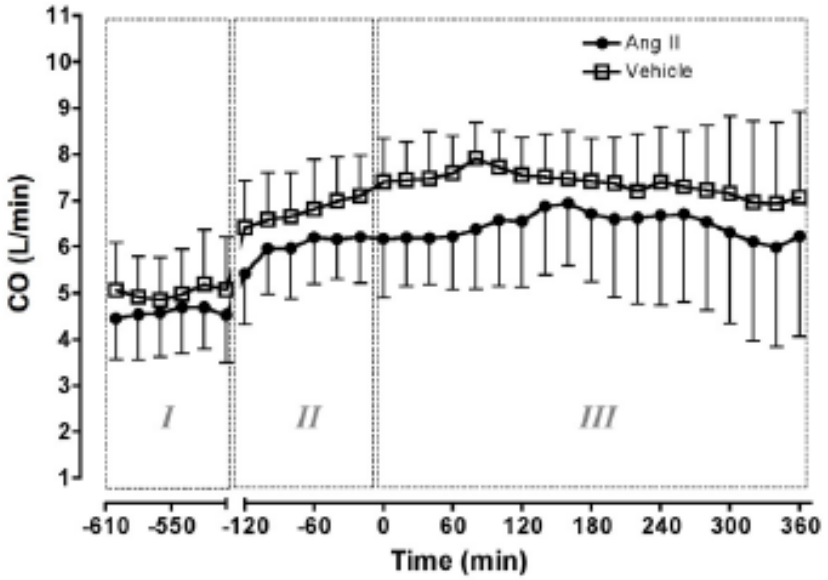
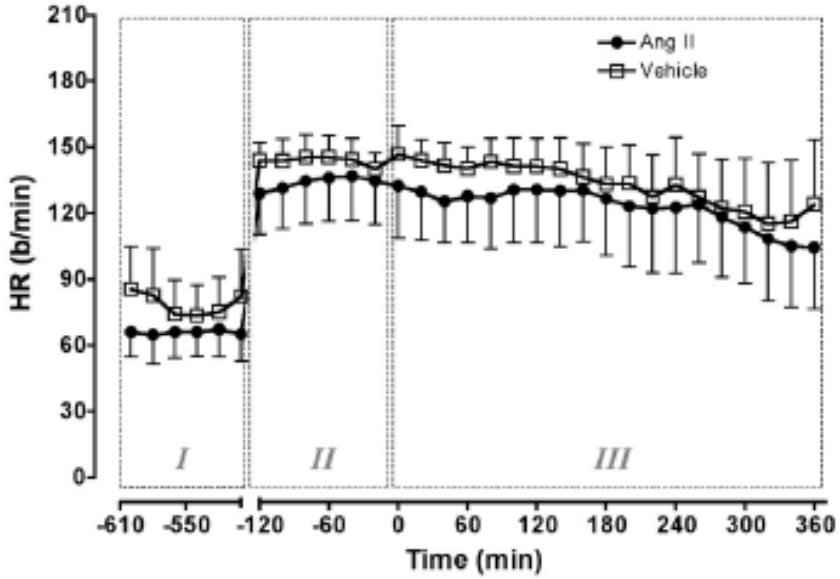
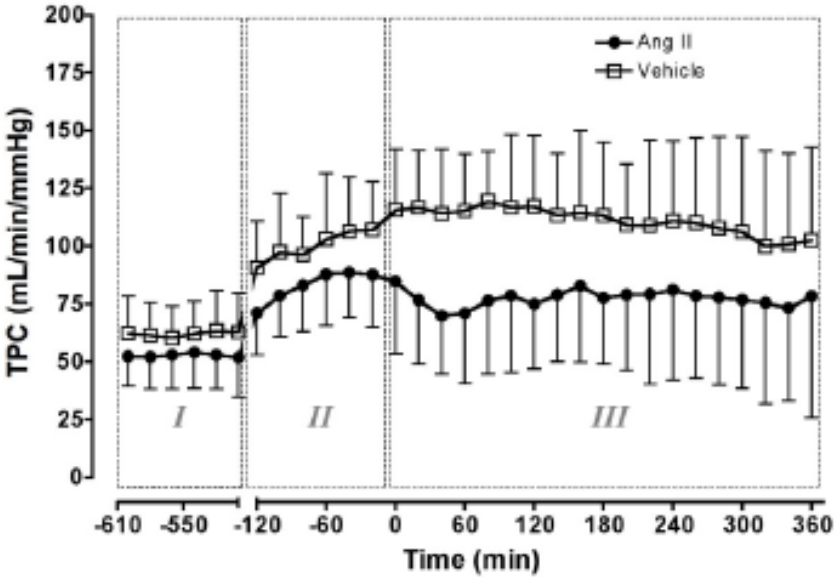
*Critical Care* 2009, **13**:R190 (doi:10.1186/cc8185)
This article is online at: http://ccforum.com/content/13/6/R190

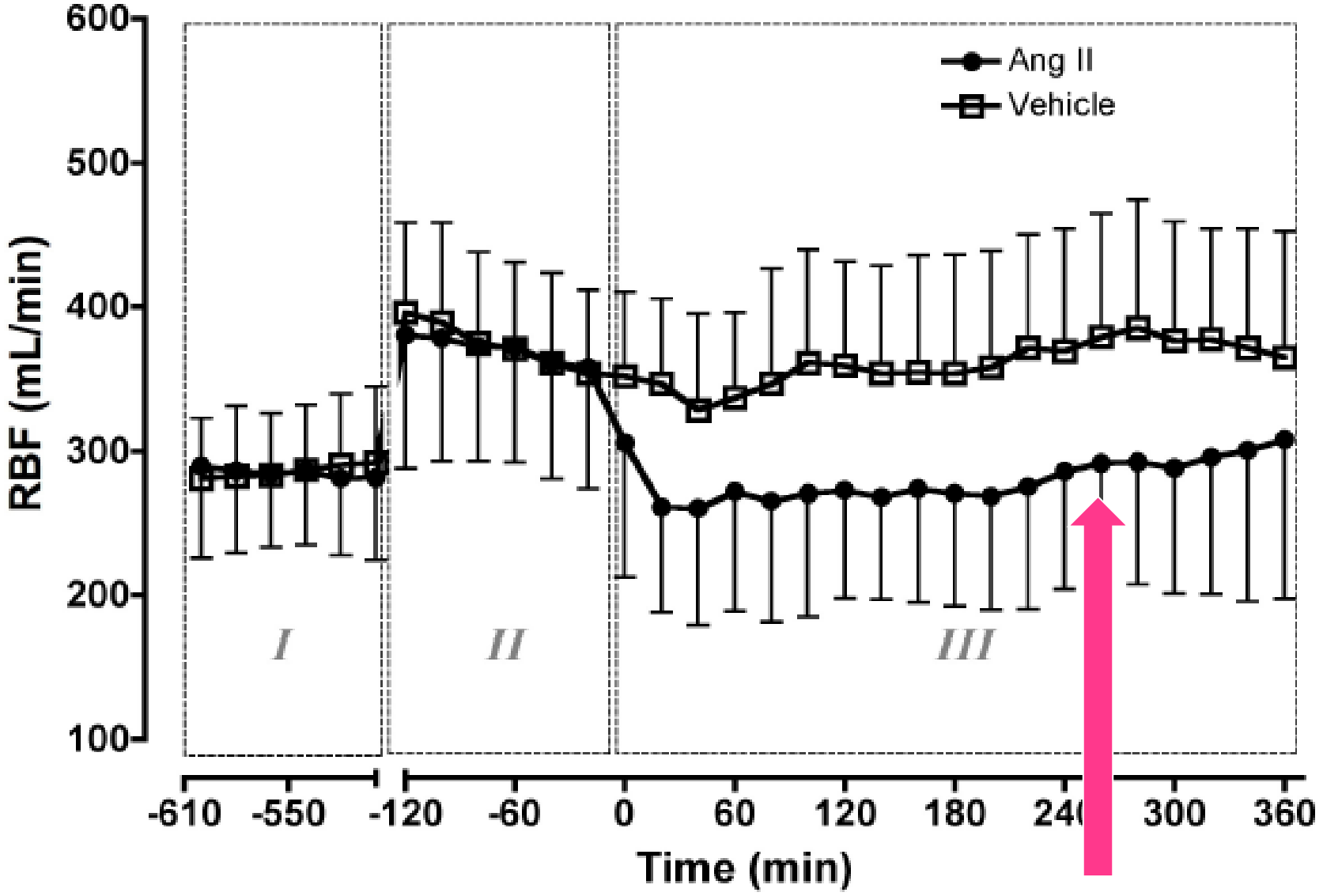
**Figure 1**


MAP (mmHg)
Ang II
Vehicle
I
II
III
Time (min)

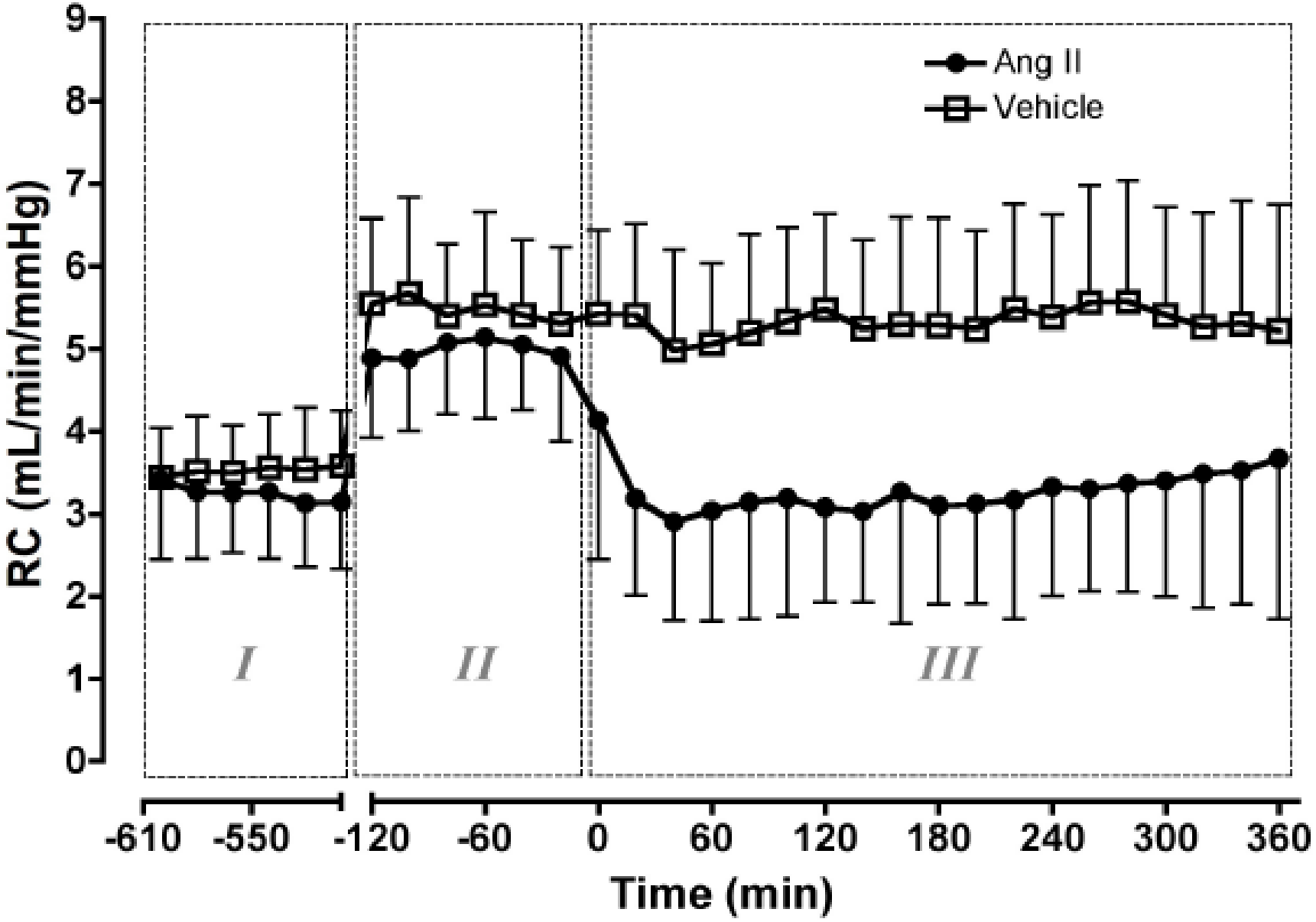

CO (L/min)
Ang II
Vehicle
I
II
III
Time (min)

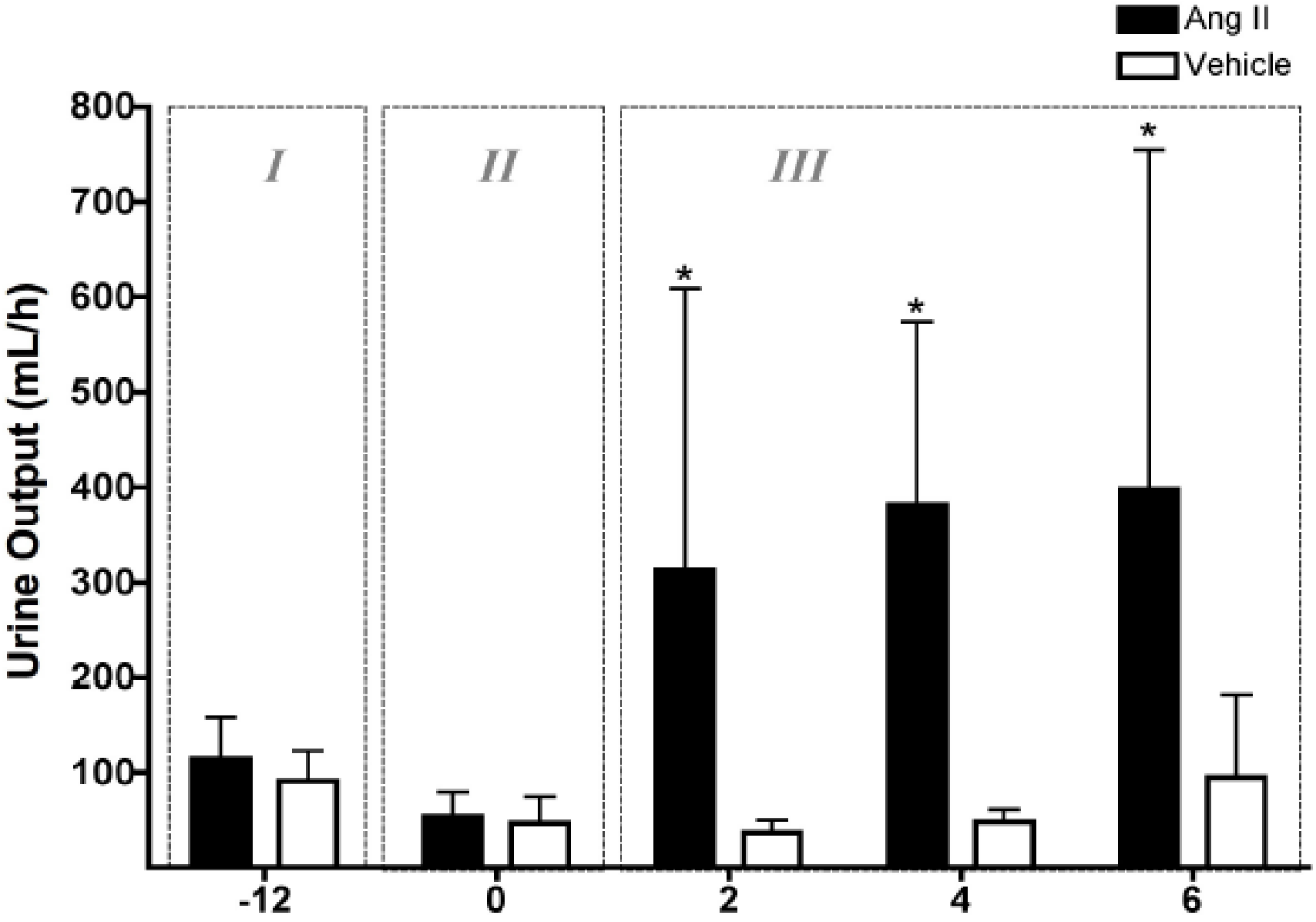

HR (b/min)
Ang II
Vehicle
I
II
III
Time (min)

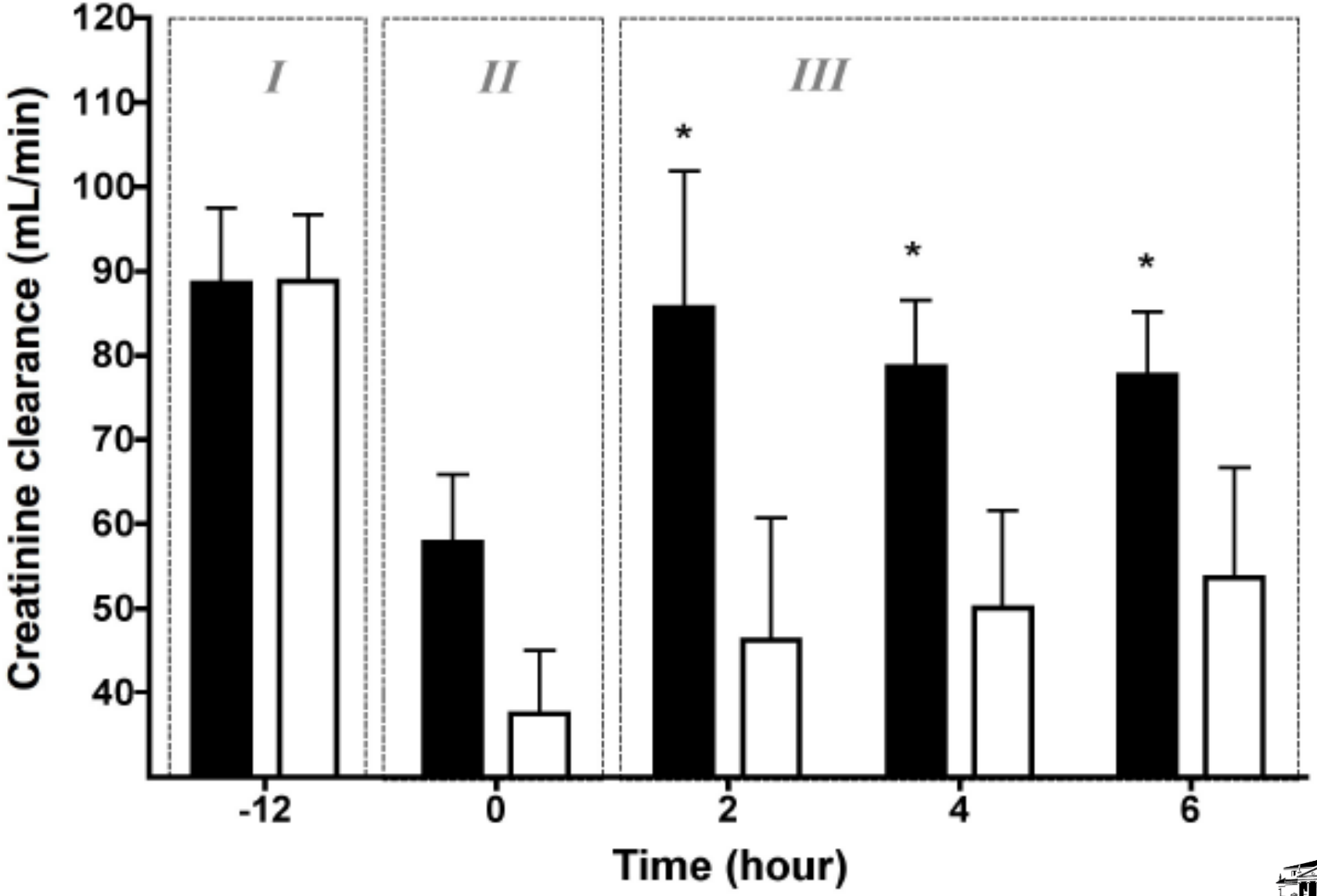

TPC (mL/min/mmHg)
Ang II
Vehicle
I
II
III
Time (min)




Flow goes down


Ang II
Vehicle
RC (mL/min/mmHg)
9
8
7
6
5
4
3
2
1
0
I
II
III
-610
-550
-120
-60
0
60
120
180
240
300
360
Time (min)


Ang II
Vehicle
Urine Output (mL/h)
800
700
600
500
400
300
200
100
I
II
III
*
*
*
-12
0
2
4
6


120
110
100
90
80
70
60
50
40
Creatinine clearance (mL/min)
I
II
III
*
*
*
-12
0
2
4
6
Time (hour)

# Proof of concept

- In early hyperdynamic mammalian sepsis or septic shock function (GFR) can be lost in the presence of increased RBF and renal vasodilatation.
- Ang II seems to help function.

**Does this happens in man?**

# RBF in human sepsis with AKI

- Only one series in the last 40 years!
- **11 patients with intra-abdominal sepsis** using para-amino hippurate and inulin clearance (renal vein sampling needed for accurate calculation of true renal plasma flow-TRPF- in sepsis) (Lucas et al. Arch Surg 1973; 106: 444-449)

# True Renal Plasma Flow (TRPF) in early sepsis

- TRPF = **154% of normal**
- TPRF tightly correlated with CO
- Similar findings in humans given **"pyrogen"** (Combos et al. Circulation 1967; 36: 555-569 and Smith H in J Lab Clin Invest 1945)

# So…global flow appears 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?

# 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.

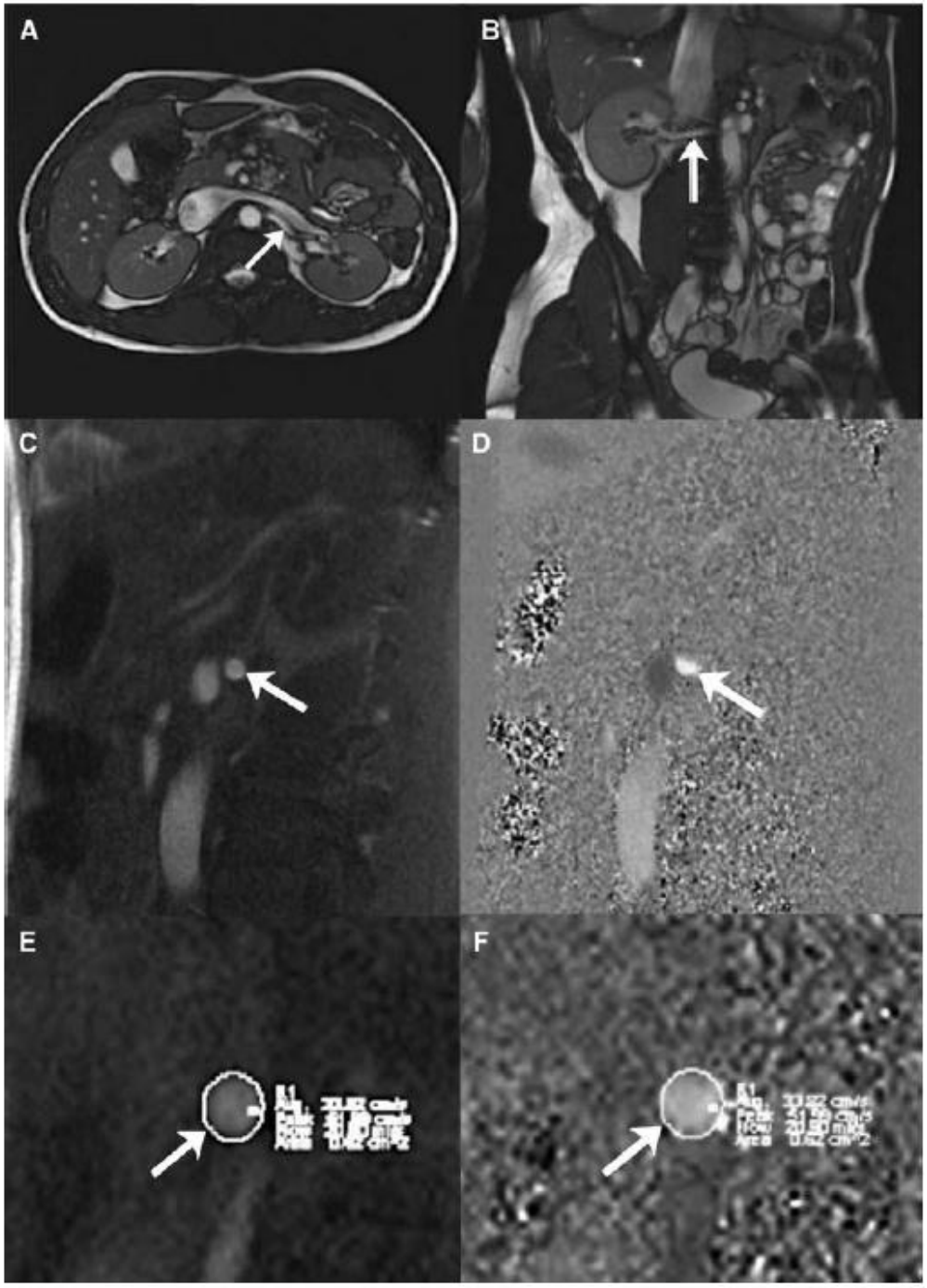
*Patients:* Ten adult patients with established septic acute kidney injury and 11 normal volunteers.

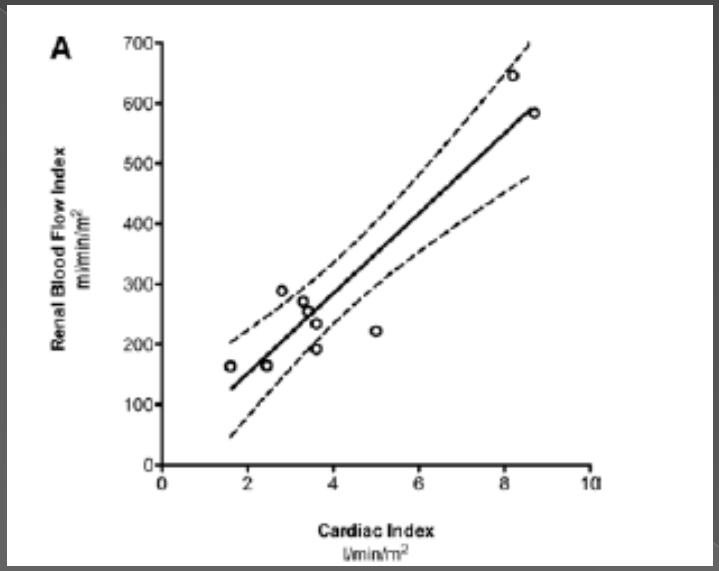
*Interventions:* Cine phase-contrast magnetic resonance imaging measurement of renal blood flow and cardiac output.

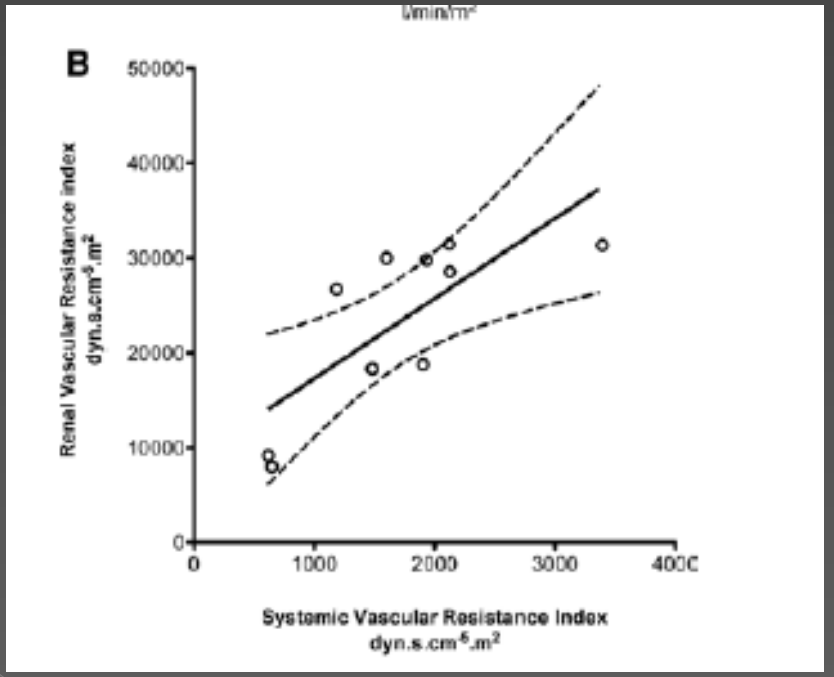
*Measurements and Main Results:* The median age of the study patients was 62.5 yrs and eight were male. At the time of magnetic resonance imaging, eight patients were mechanically ventilated, nine were on continuous hemofiltration, and five required vasopressors. Cine phase-contrast magnetic resonance 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 ($r = .26$, $p = .45$).

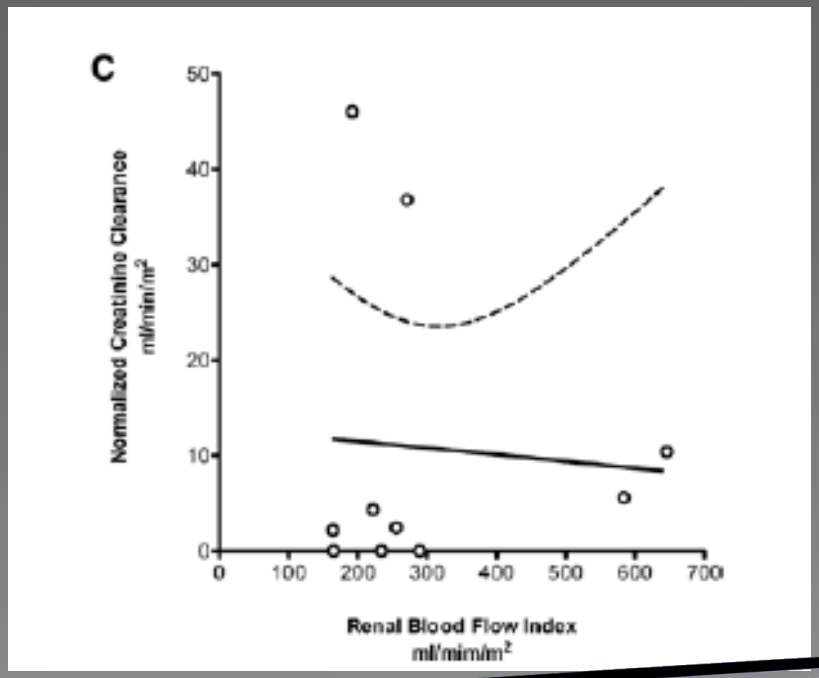
*Conclusions:* Cine phase-contrast magnetic resonance imaging can be used to noninvasively and safely assess renal perfusion during critical illness in man. Near-simultaneous accurate measurement of cardiac output enables organ blood flow to be assessed in the context of the global circulation. Renal 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


A
B
C
D
E
F



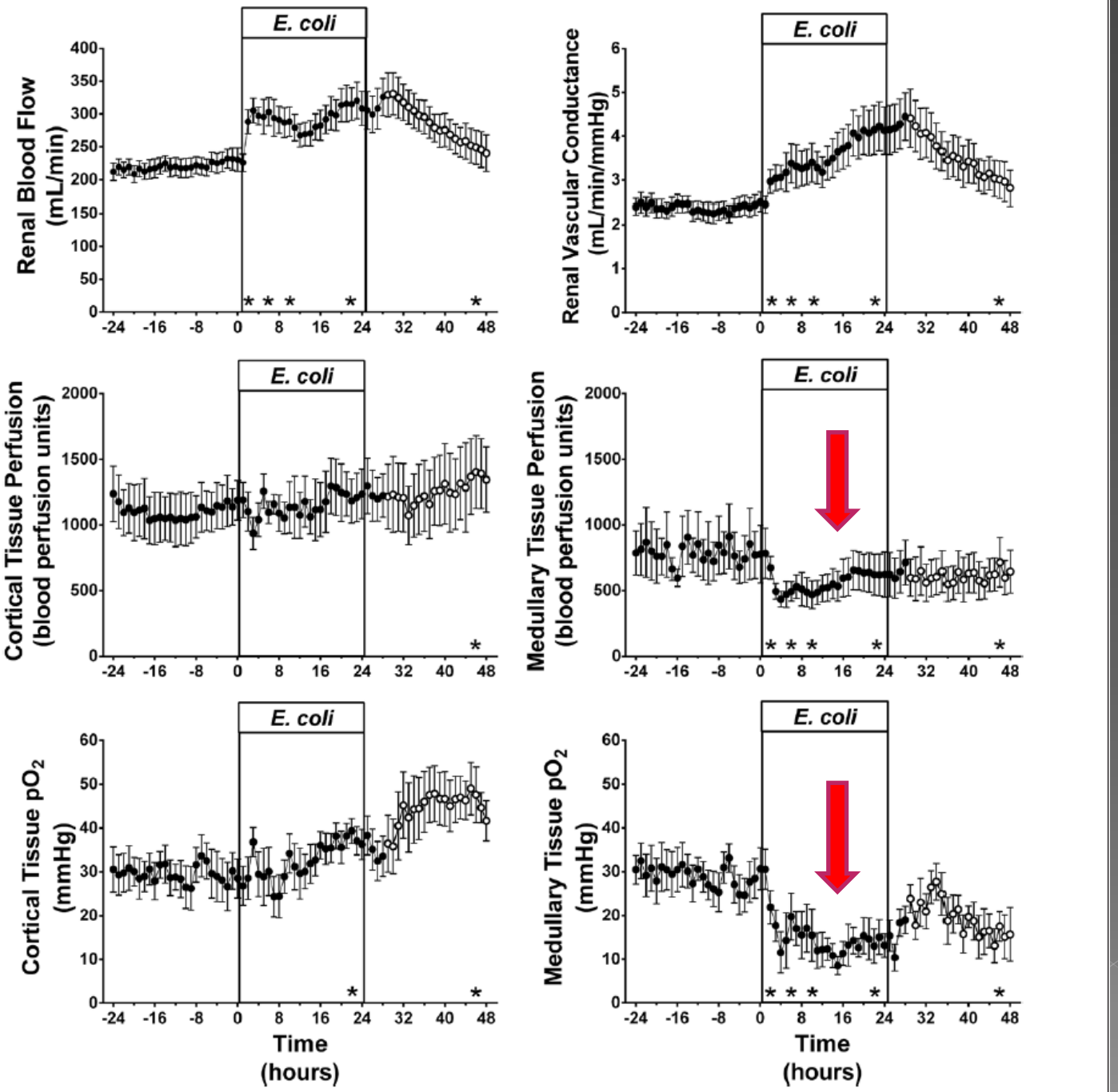

**Oops…renal blood flow is dissociated from function (GFR)!**

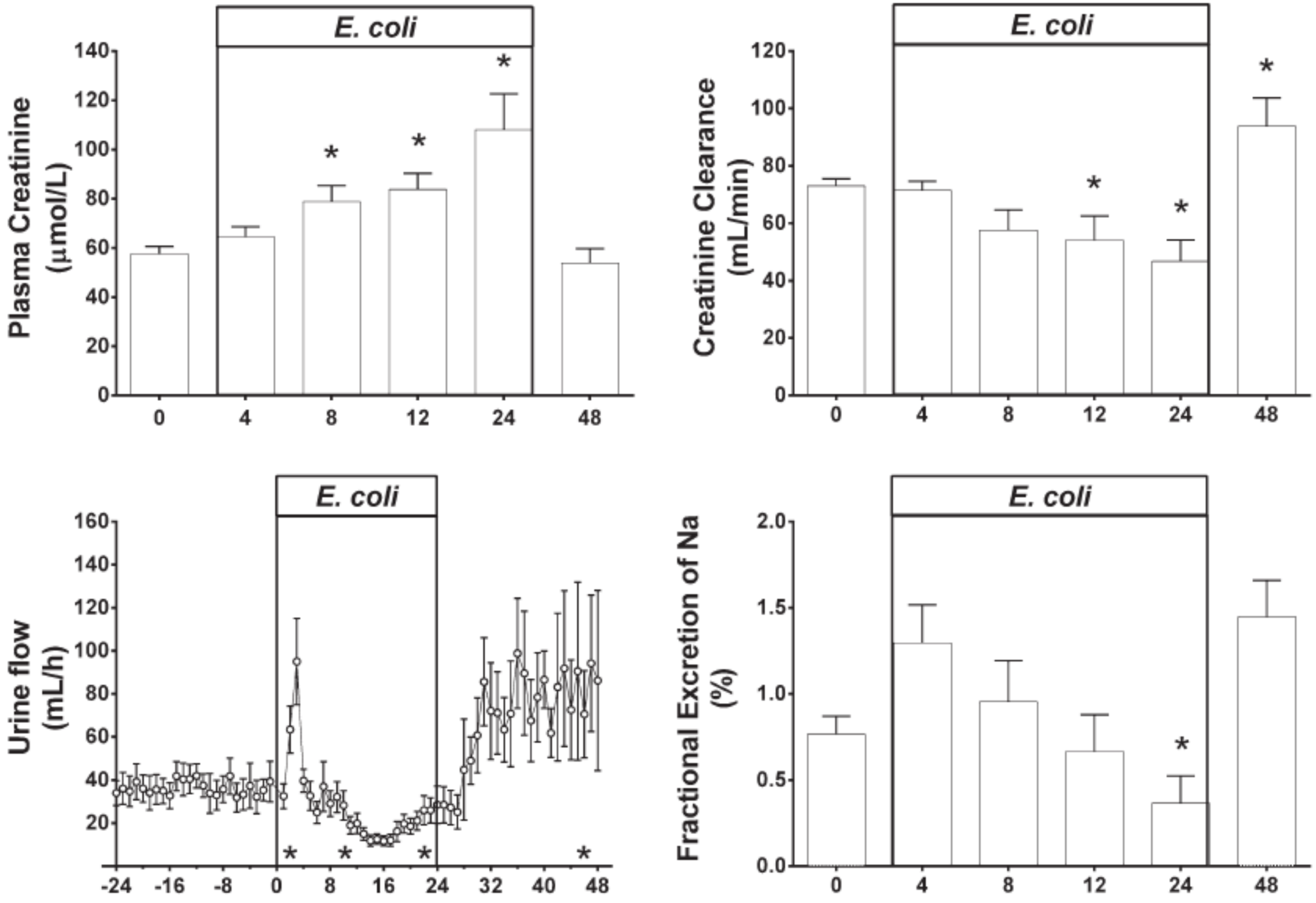
# Microcirculatory changes as the cause of loss of function

# Cortical and Medullary Tissue Perfusion and Oxygenation in Experimental Septic Acute Kidney Injury

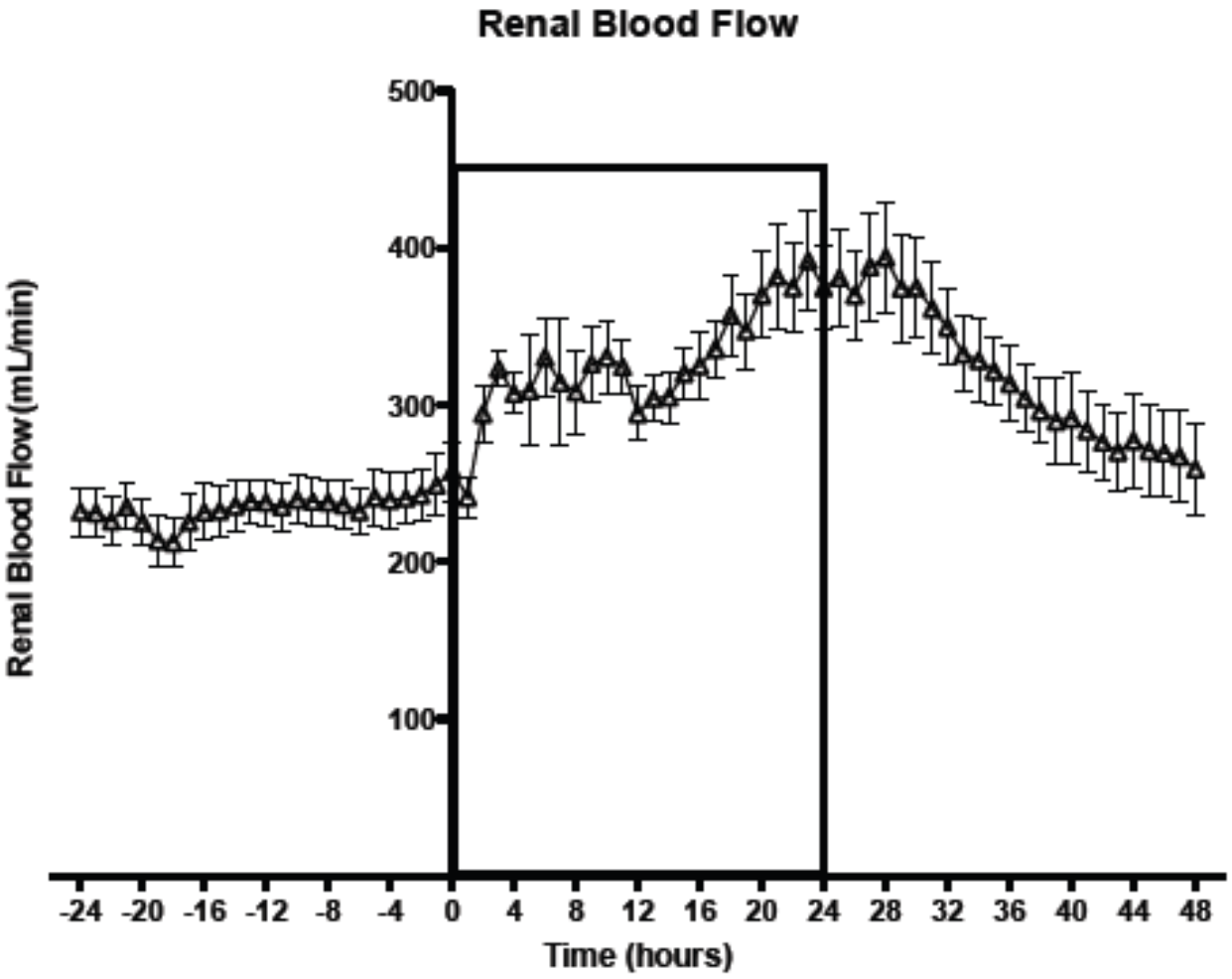
Paolo Calzavacca, MD, PhD[1,2,3,4]; Roger G. Evans, PhD[5]; Michael Bailey, PhD[6]; Rinaldo Bellomo, MD, PhD[2,3]; Clive N. May, PhD[1]

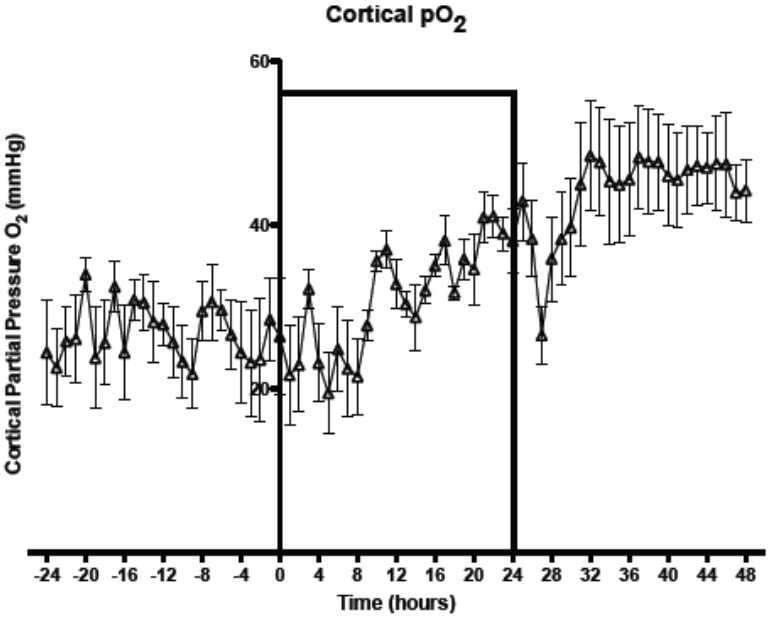
(*Crit Care Med* 2015


E. coli
Renal Blood Flow (mL/min)
Renal Vascular Conductance (mL/min/mmHg)
Cortical Tissue Perfusion (blood perfusion units)
Medullary Tissue Perfusion (blood perfusion units)
Cortical Tissue pO2 (mmHg)
Medullary Tissue pO2 (mmHg)
Time (hours)


E. coli
Plasma Creatinine (µmol/L)
0
20
40
60
80
100
120
140
0
4
8
12
24
48
*
E. coli
Creatinine Clearance (mL/min)
0
20
40
60
80
100
120
0
4
8
12
24
48
*
E. coli
Urine flow (mL/h)
20
40
60
80
100
120
140
160
-24
-16
-8
0
8
16
24
32
40
48
*
E. coli
Fractional Excretion of Na (%)
0.0
0.5
1.0
1.5
2.0
0
4
8
12
24
48
*

# The septic kidney: global renal blood flow



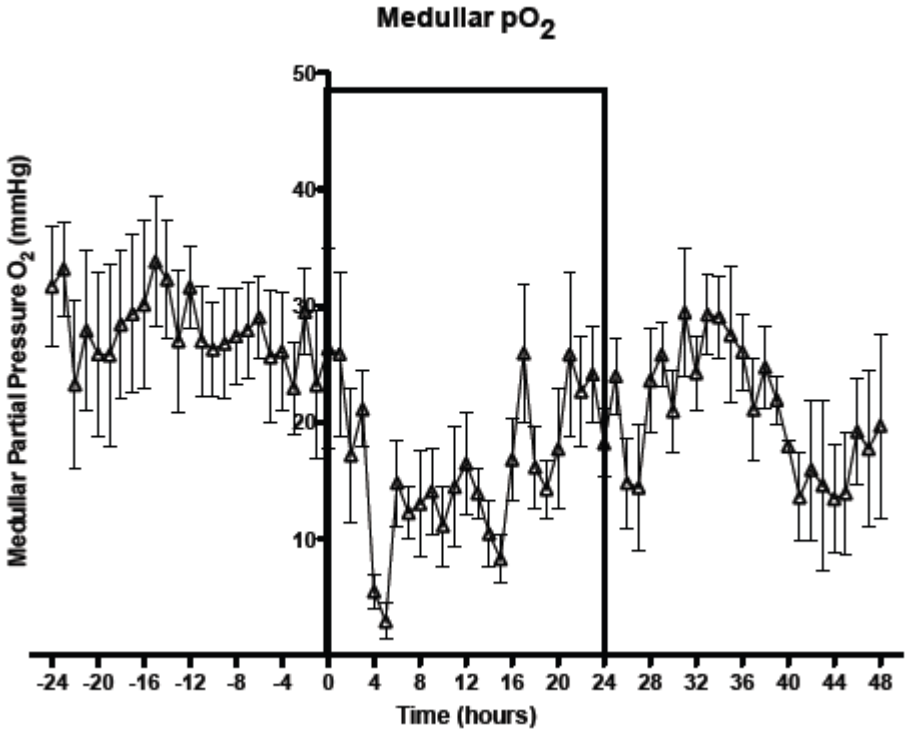



**Intra-renal oxygenation**

**Cortico-medullary dissociation**

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

**Also simultaneous major fall in GFR!**

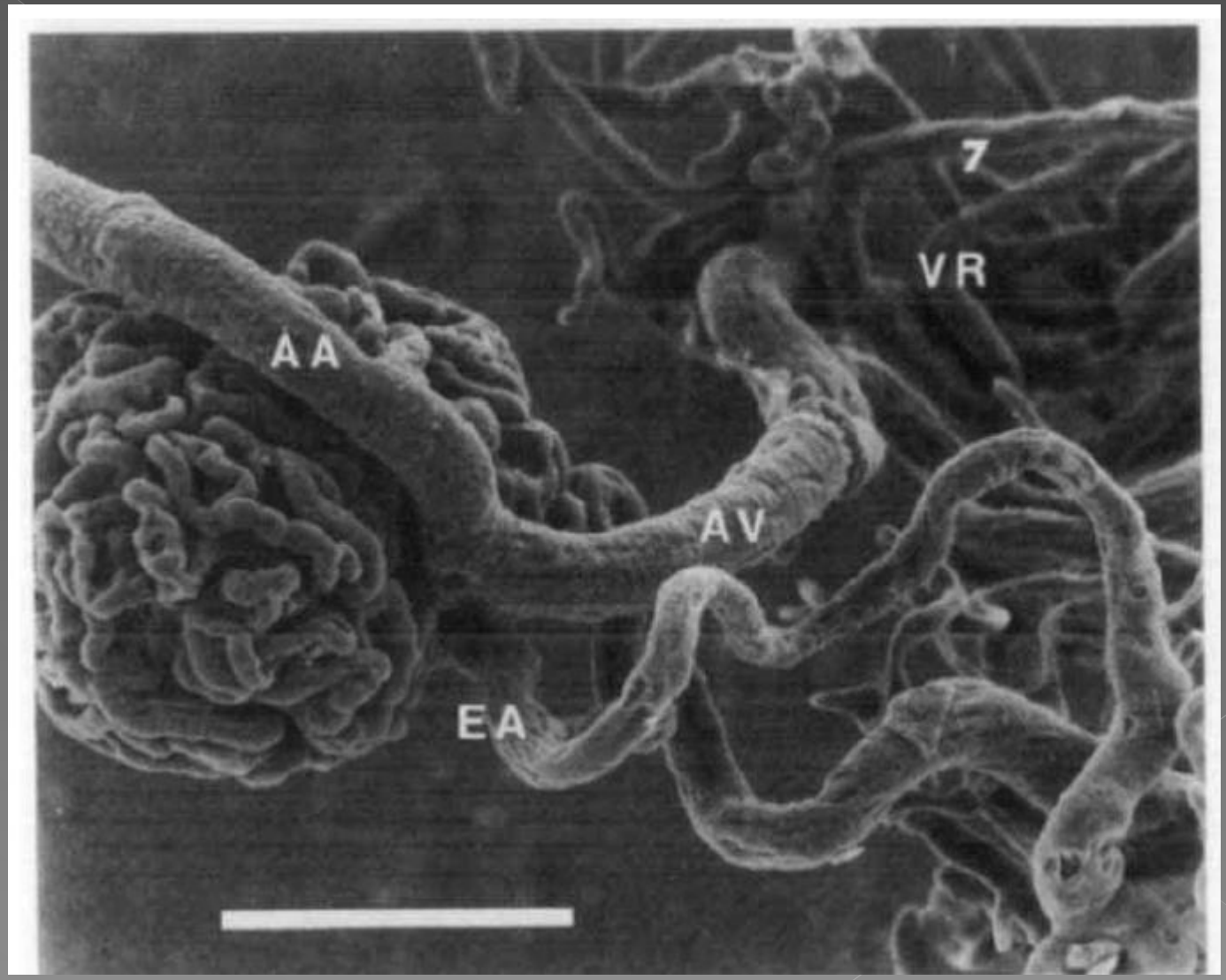


THE ANATOMICAL RECORD 201:237–248 (1981)

# 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 aglomerular 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.

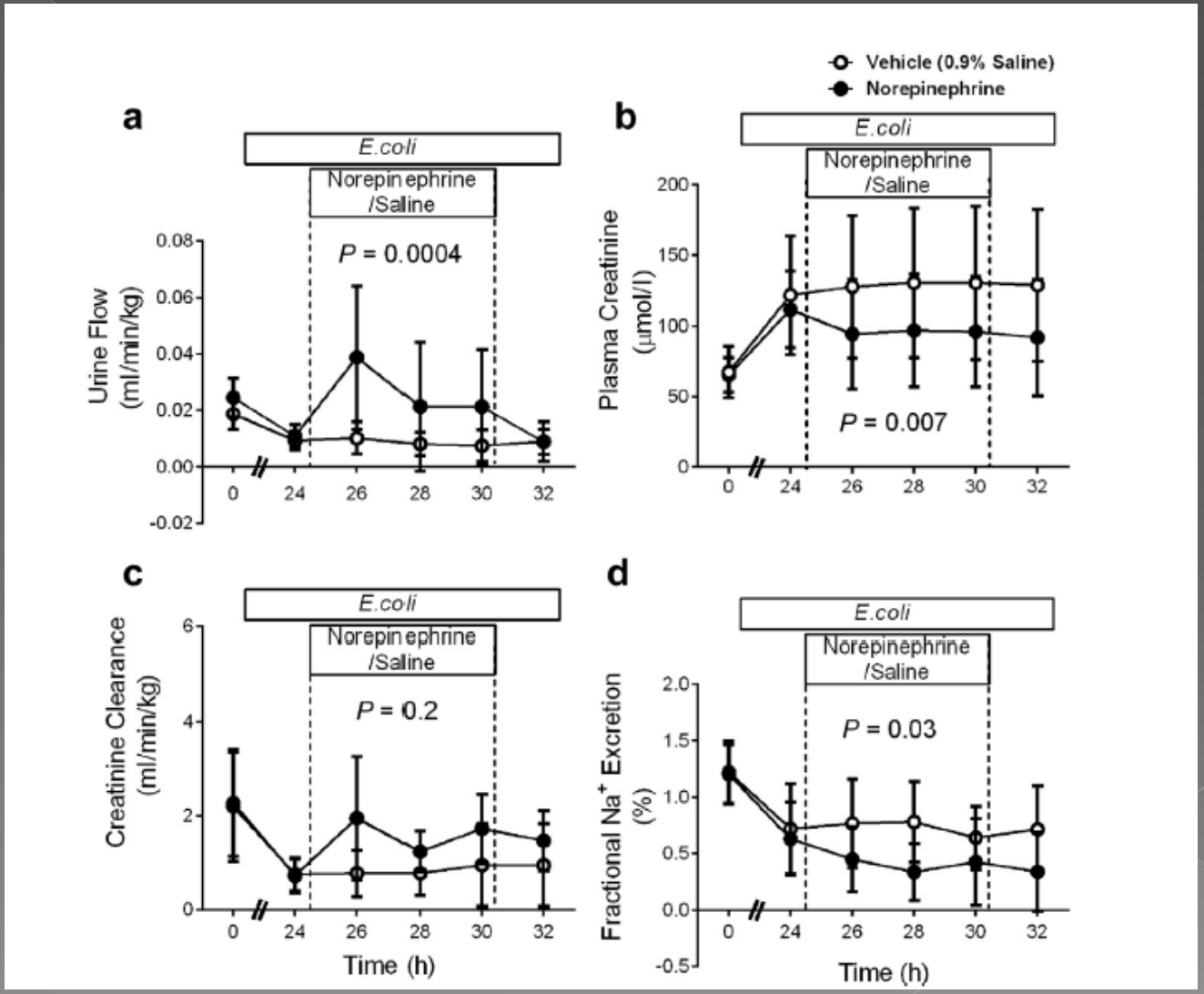


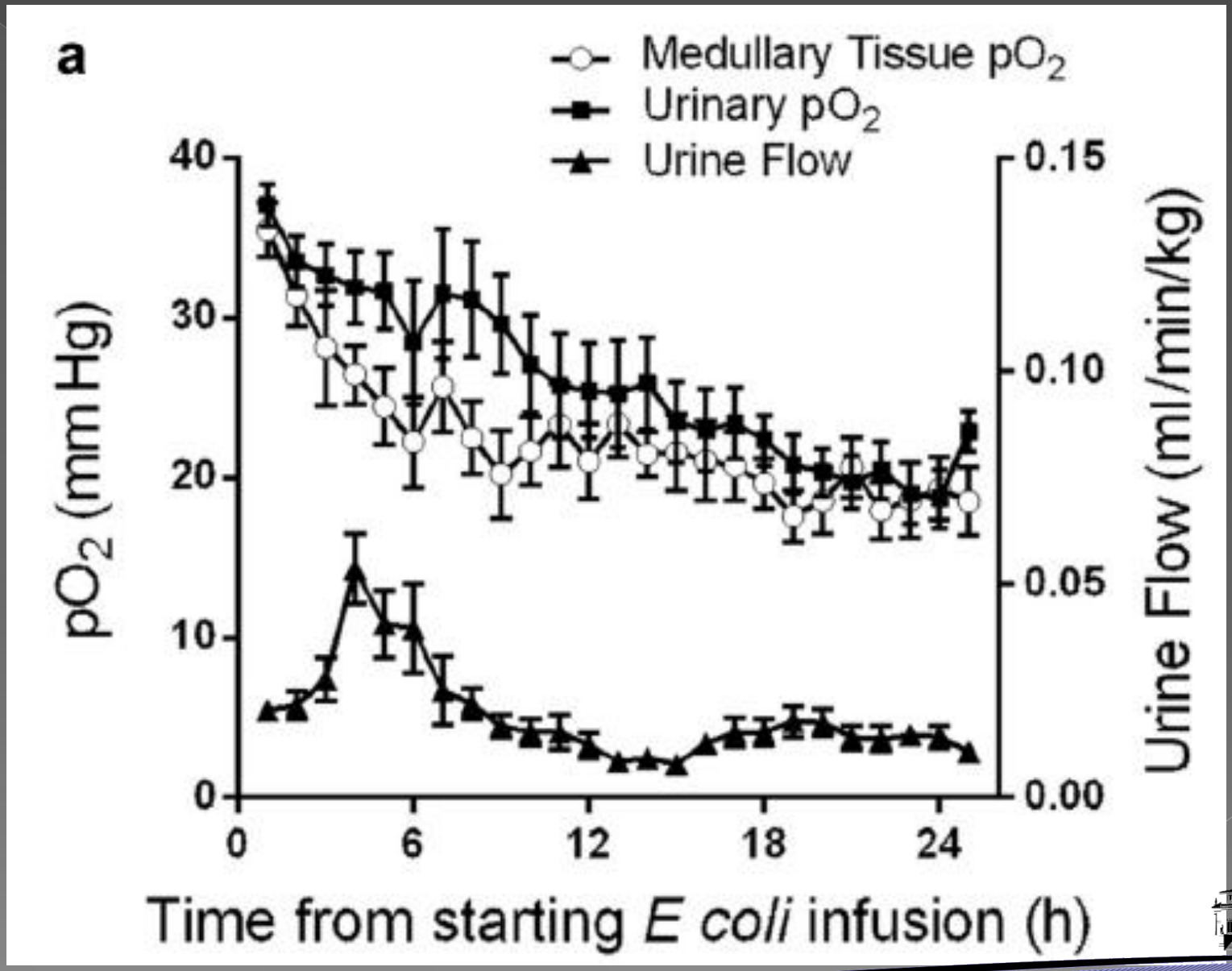
# Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury

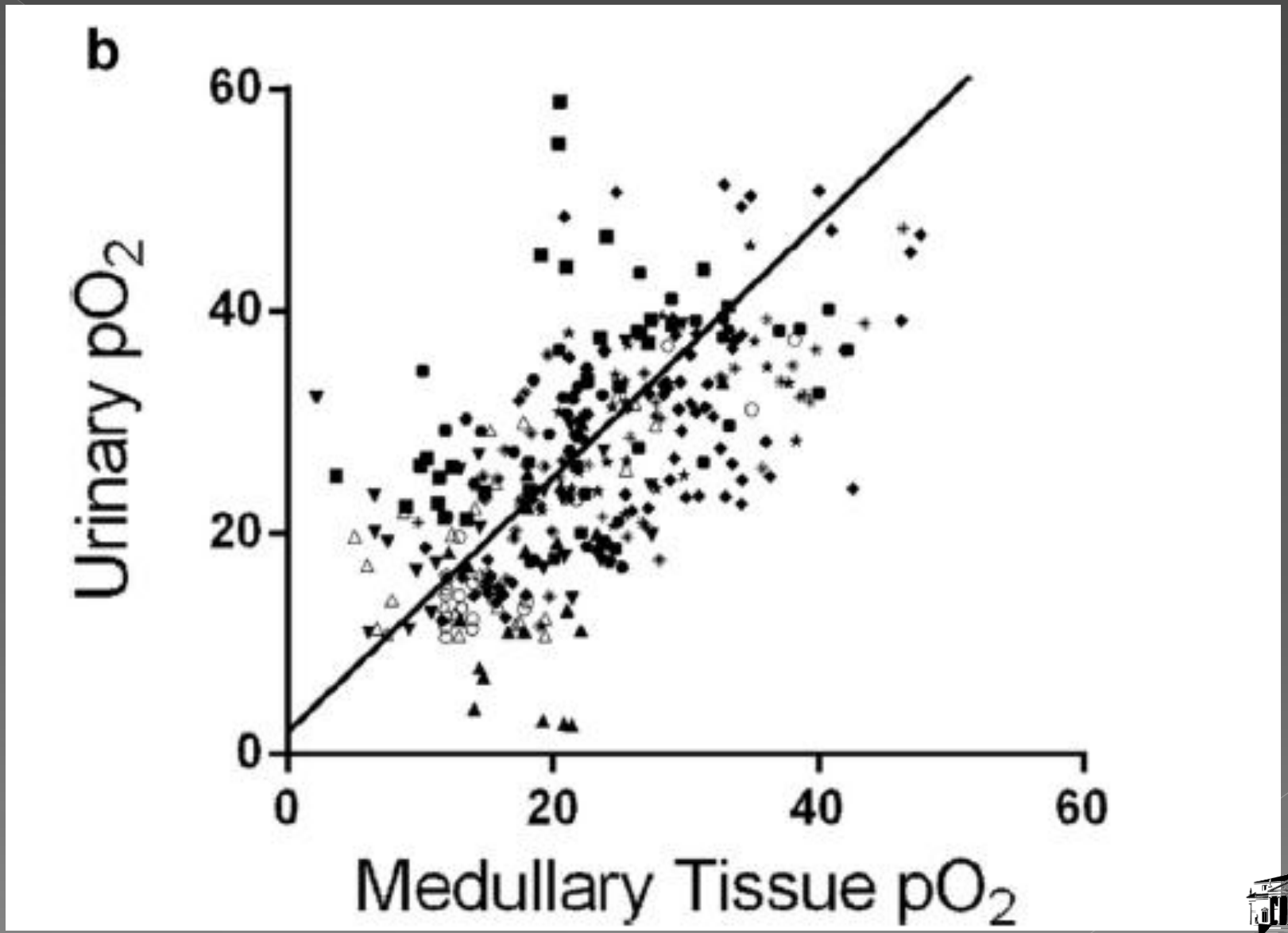
see commentary on page 22

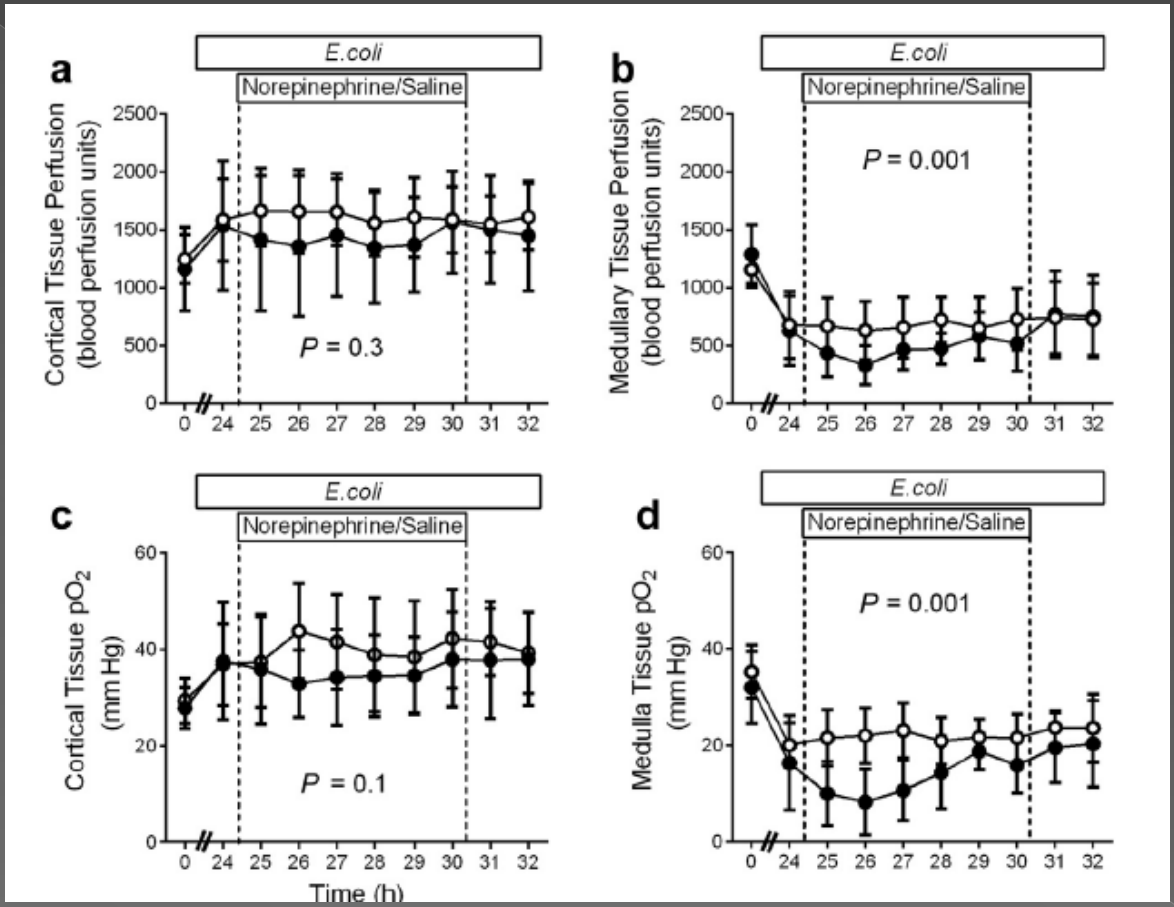
Yugeesh R. Lankadeva[1], Junko Kosaka[1], Roger G. Evans[2], Simon R. Bailey[3], Rinaldo Bellomo[4] and Clive N. May[1]

*Kidney International* (2016) **90,** 100–108

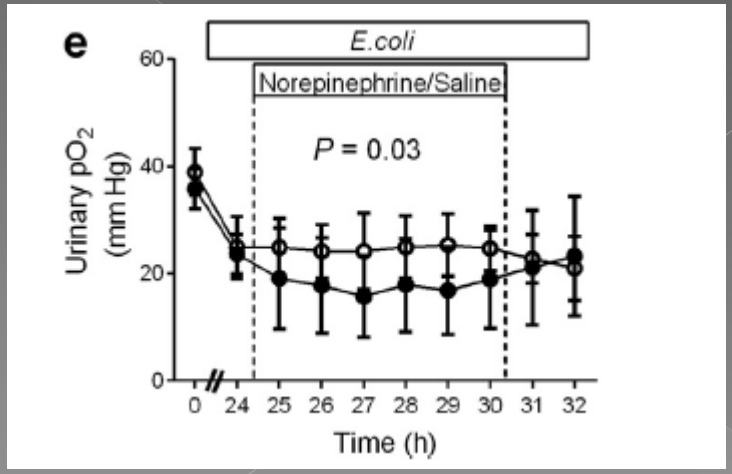


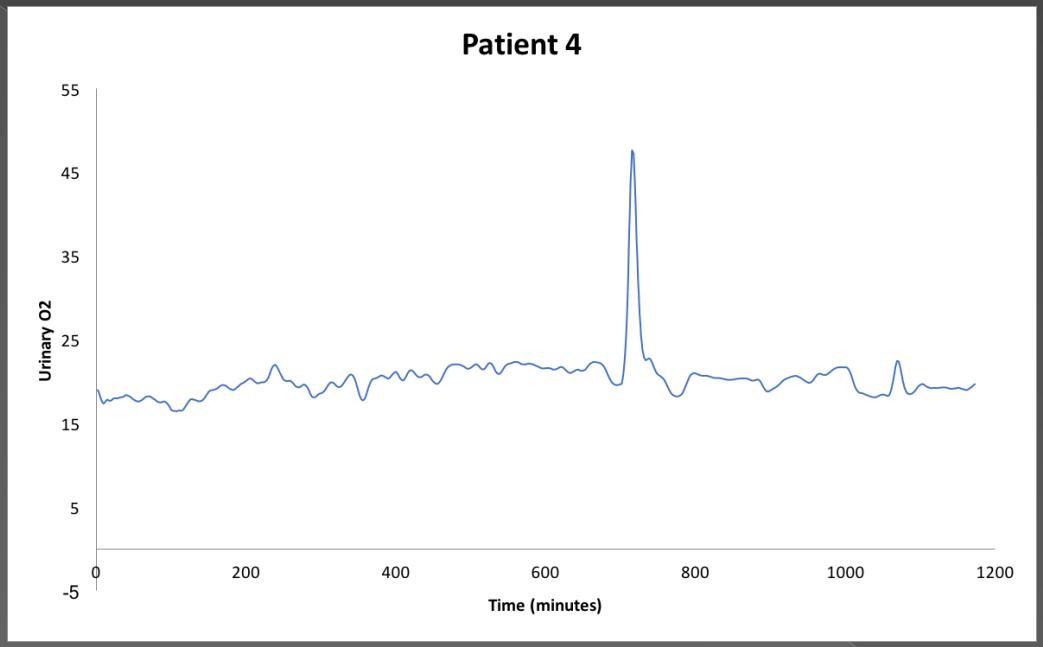

a
Medullary Tissue $pO_2$
Urinary $pO_2$
Urine Flow
40
30
20
10
0
0.15
0.10
0.05
0.00
$pO_2$ (mm Hg)
Urine Flow (ml/min/kg)
0
6
12
18
24
Time from starting *E coli* infusion (h)


b
60
40
20
0
0
20
40
60
Urinary $pO_2$
Medullary Tissue $pO_2$



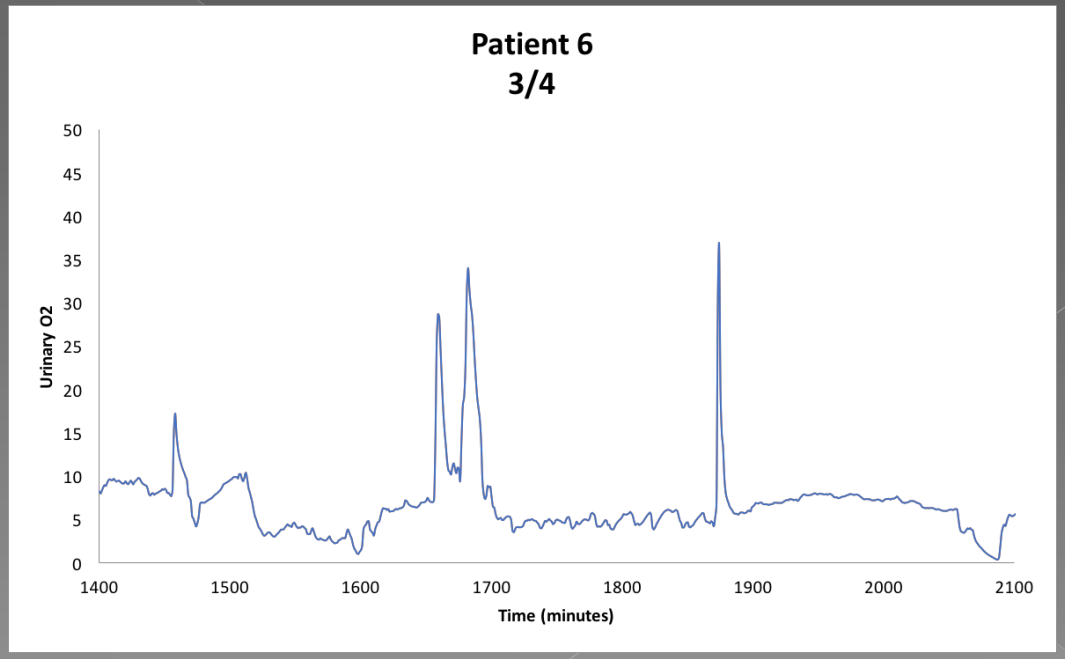

Urinary O2 below 20 mmHg with norepinephrine infusion






PuO2 in patients with Septic AKI

PuO2 is similar to what is seen in septic sheep



# Histopathology of Septic Acute Kidney Injury: A Systematic Review of Experimental Data

Junko Kosaka, MD, PhD[1]; Yugeesh R. Lankadeva, PhD[1]; Clive N. May, PhD[1]; Rinaldo Bellomo, MD, PhD[2]

(*Crit Care Med* 2016; 44:e897–e903)

**Objective:** The histopathologic changes associated with septic acute kidney injury are poorly understood, in part, because of the lack of biopsy data in humans. Animal models of septic acute kidney injury may help define such changes. Therefore, we performed a systematic review of the histopathologic changes found in modern experimental septic acute kidney injury models.

**Data Sources:** MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, and PubMed (from January 2007 to February 2015).

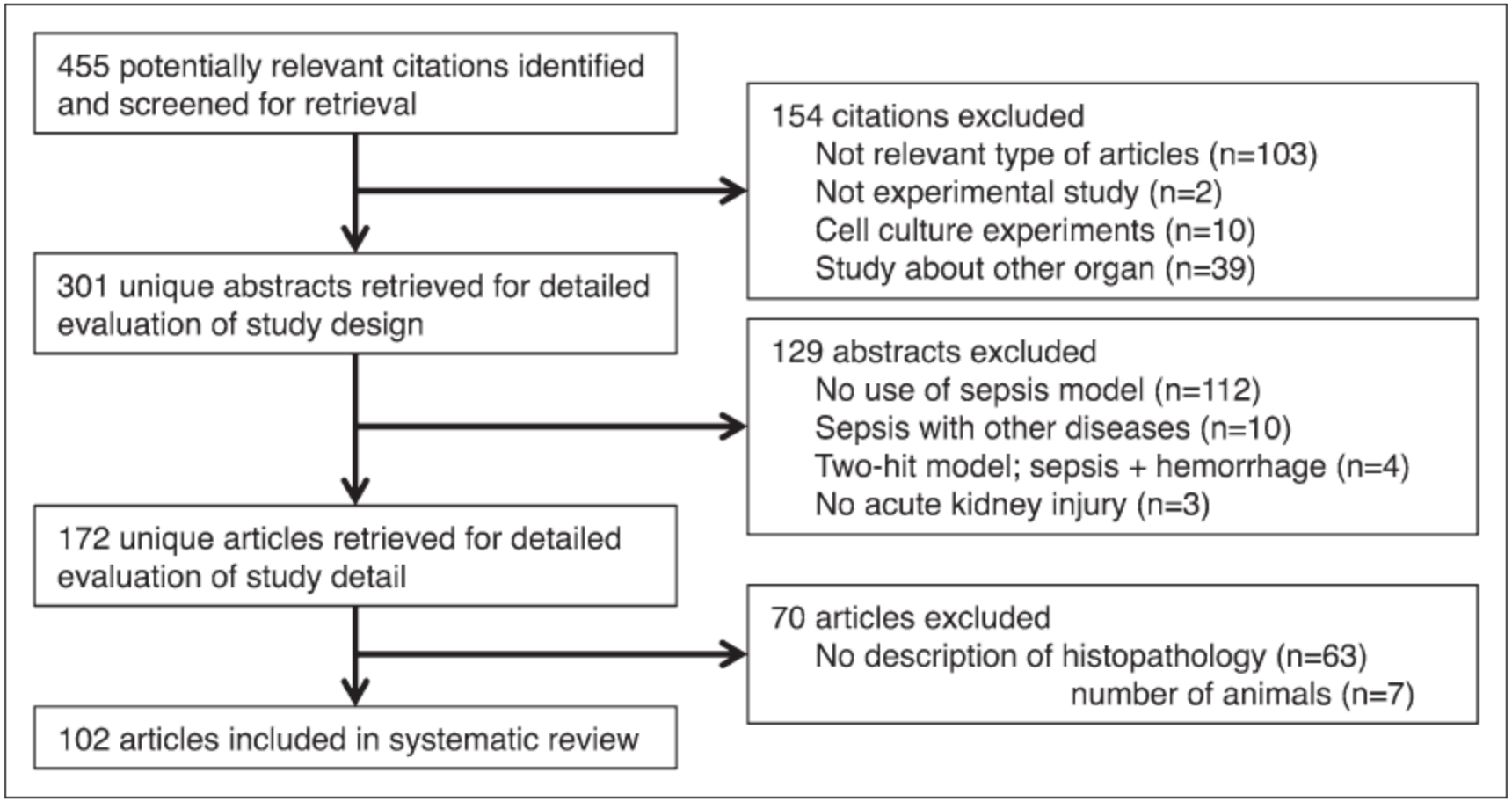



**Figure 1.** Flow diagram summarizing article selection and reasons for exclusion.

# There are tubular changes but they are "bland" given the loss of GFR

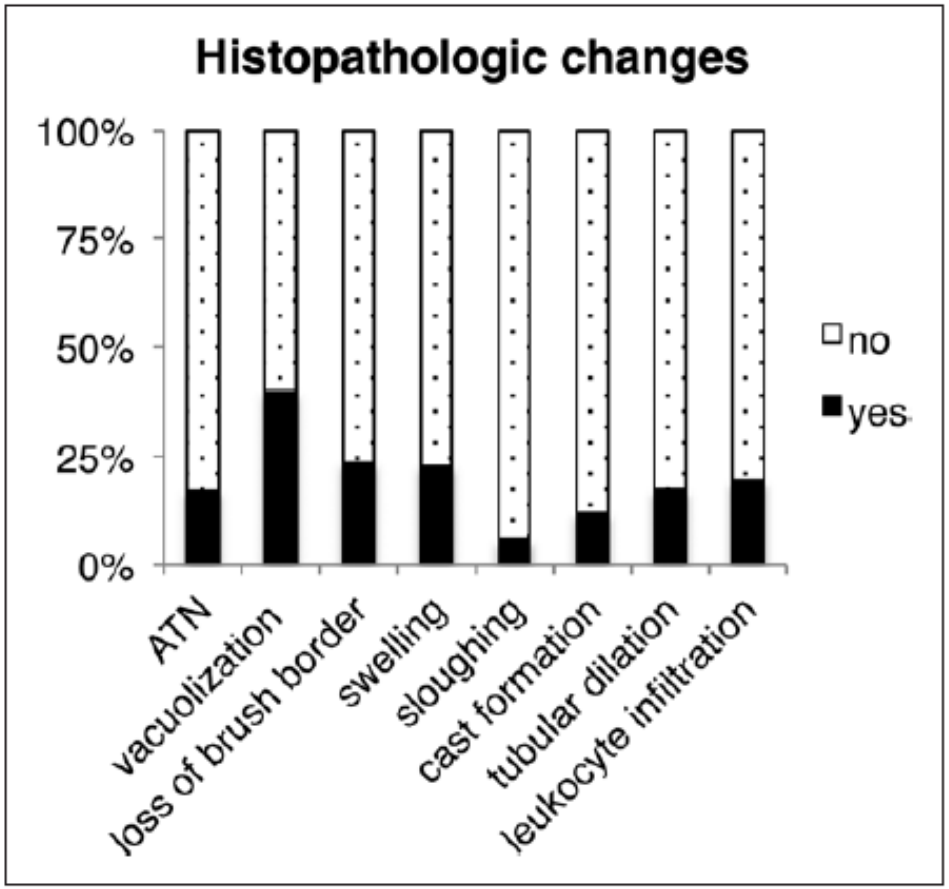



**Figure 4.** Percentage of acute tubular necrosis (ATN) and other histopathologic changes in septic acute kidney injury. ATN ($n = 184$ animals), vacuolization ($n = 423$), loss of brush border ($n = 250$), swelling ($n = 243$), sloughing ($n = 60$), cast formation ($n = 127$), tubular dilation ($n = 183$), and leukocyte infiltration ($n = 205$).

## Human histology

# 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]

Am J Respir Crit Care Med Vol 187, Iss. 5, pp 509–517, Mar 1, 2013

patients with sepsis-induced cardiac and renal failure. The vast majority of septic patients (32 of 38) were in shock, requiring the use of inotropic agents 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.

American Journal of Respiratory and Critical Care Medicine Volume 194 Number 6 | September 15 2016

ORIGINAL ARTICLE

# Structure and Function of the Kidney in Septic Shock

## A Prospective Controlled Experimental Study

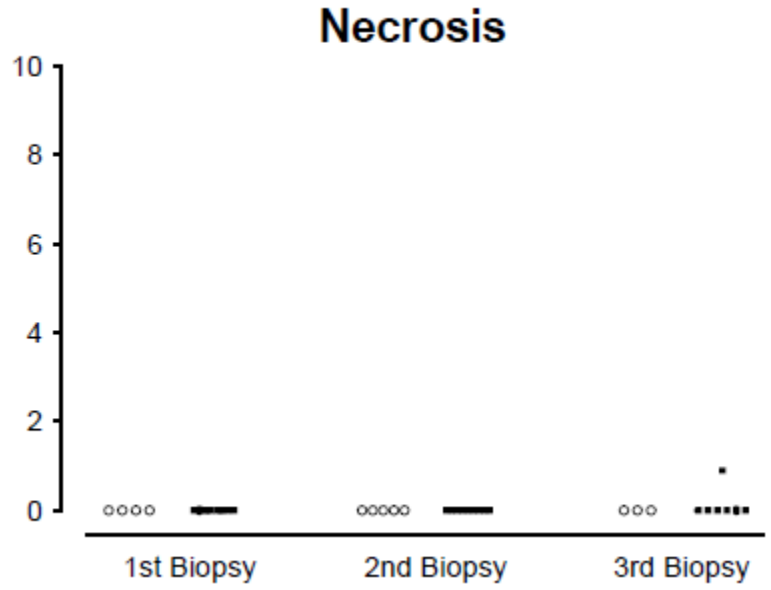
Matthew J. Maiden[1,2], Sophia Otto[3], John K. Brealey[3], Mark E. Finnis[1,2], Marianne J. Chapman[1,2], Tim R. Kuchel[4], Coralie H. Nash[2], Jason Edwards[1], and Rinaldo Bellomo[5]

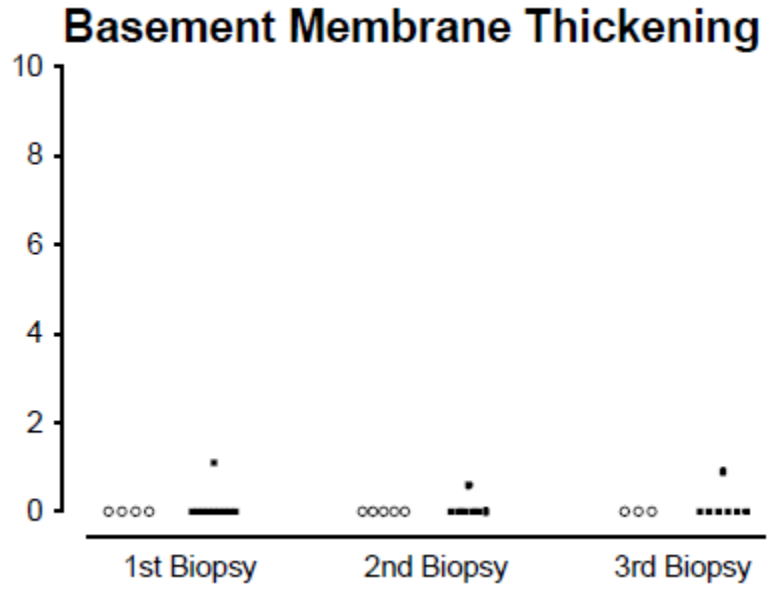
**Rationale:** It is unclear how septic shock causes acute kidney injury (AKI) and whether this is associated with histological change.

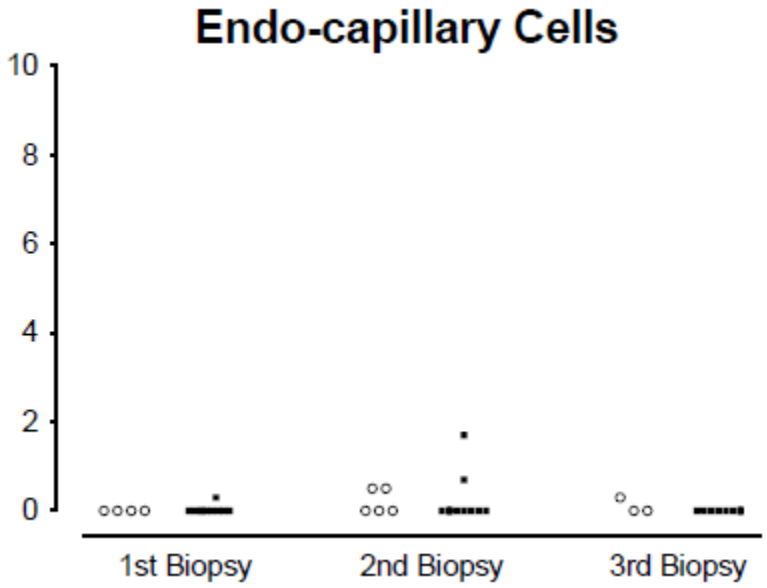
**Objectives:** We aimed to determine the nature and extent of changes in renal structure and function over time in an ovine model of septic shock.

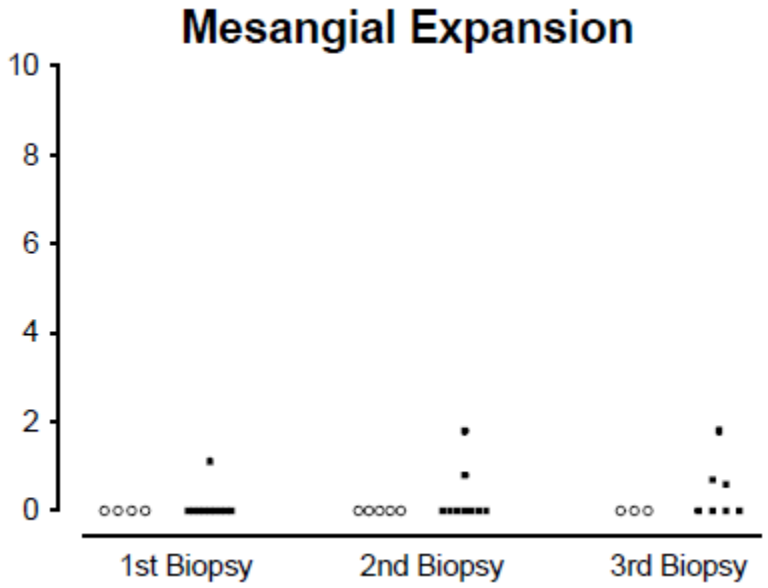
**Methods:** Fifteen sheep were instrumented with a renal artery flow probe and renal vein cannula. Ten were given intravenous *Escherichia coli* to induce septic shock, and five acted as controls. Animals were mechanically ventilated for 48 hours, while receiving protocol-guided parenteral fluids and a norepinephrine infusion to maintain mean arterial pressure. Renal biopsies were taken every 24 hours or whenever animals were oliguric for 2 hours. A renal pathologist, blinded to tissue source, systematically quantified histological appearance by light and electron microscopy for 31 prespecified structural changes.

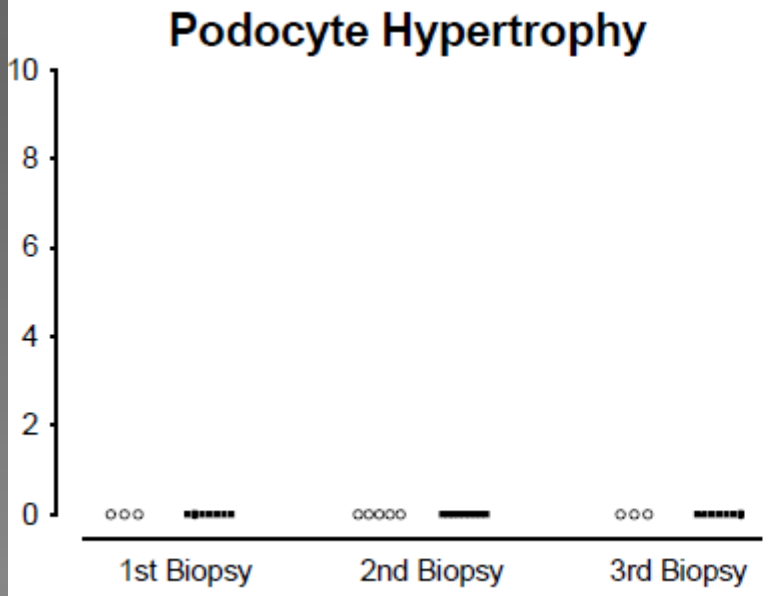
| | Biopsy 1 | | Biopsy 2 | | Biopsy 3 | |
|---|---|---|---|---|---|---|
| | Non Septic | Septic | Non Septic | Septic | Non Septic | Septic |
| Time of biopsy after *E. coli* | 0 hrs | 0 hrs | 24 hrs | 21 ± 4 hrs | 48 hrs | 42 ± 10 hrs |
| Number of animals biopsied | n=5 | n=10 | n=5 | n=9 | n=4 | n=7 |
| Urine Output preceding each biopsy (mL/kg/hr) | | | 1.5 ± 0.8 | 0.6 ± 0.5 | 1.8 ± 1.1 | 0.3 ± 0.4 |

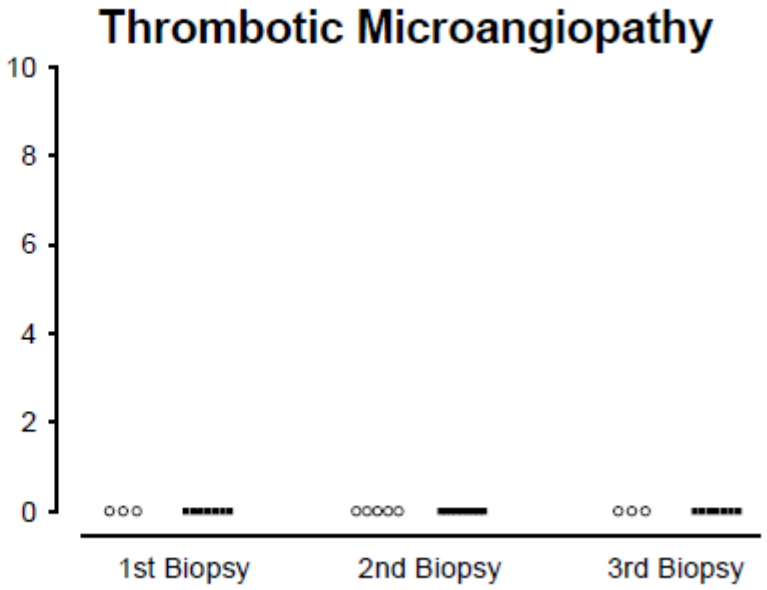


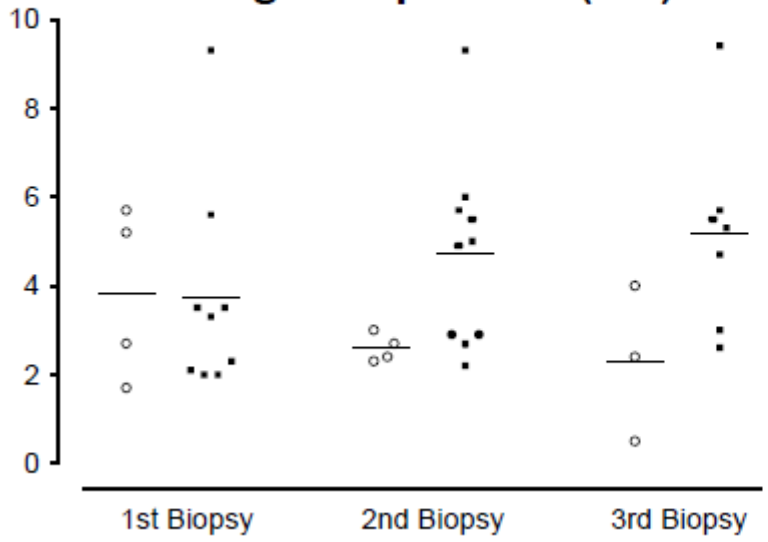

Endo-capillary Cells
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

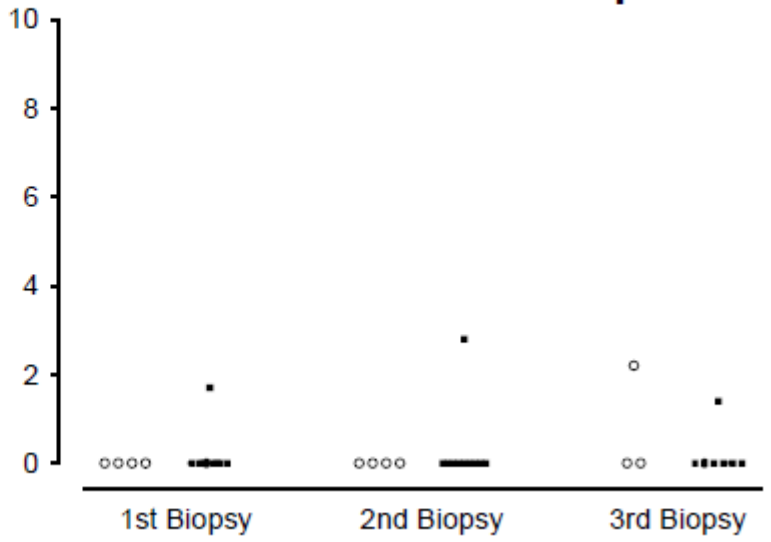

Mesangial Expansion
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

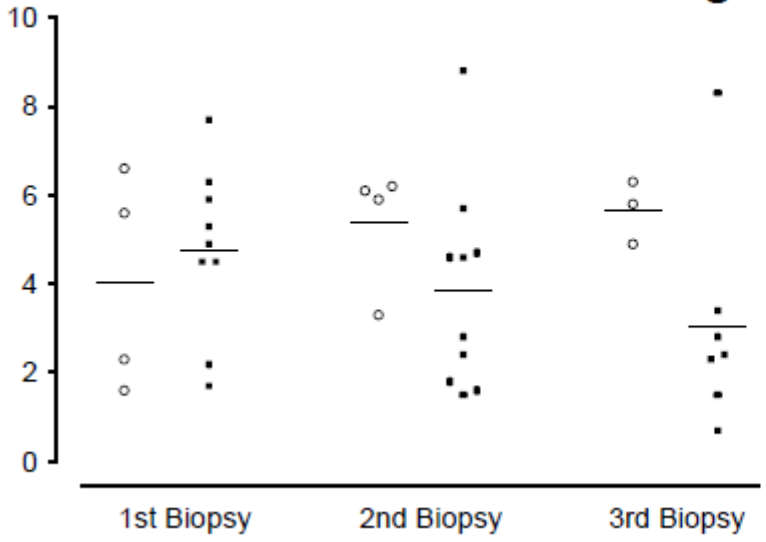

Podocyte Hypertrophy
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

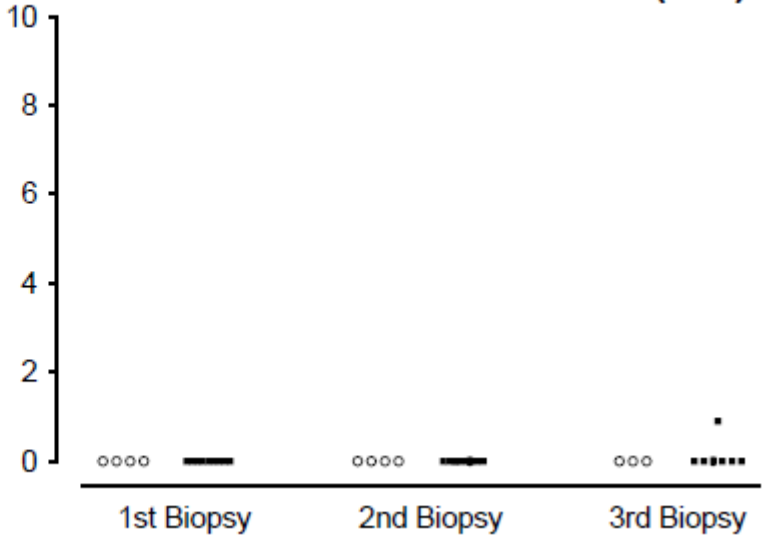

Thrombotic Microangiopathy
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

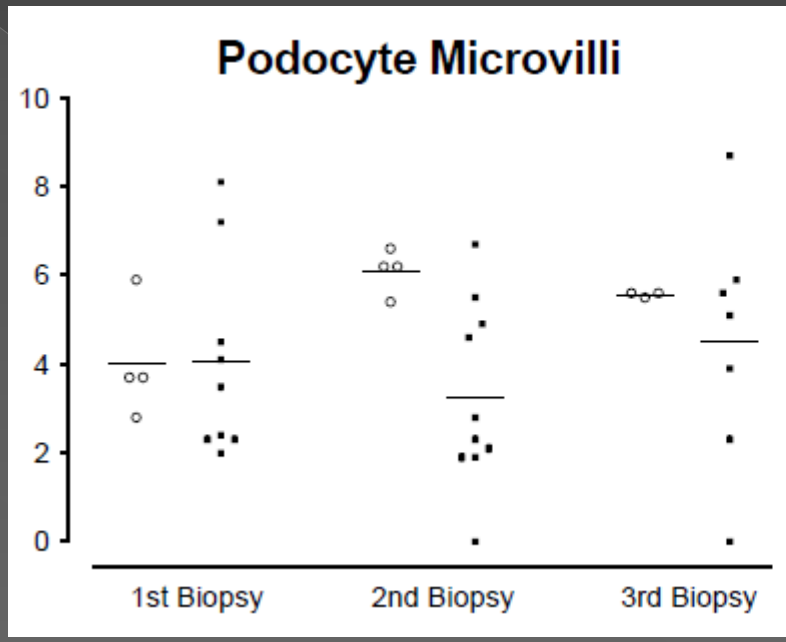
B

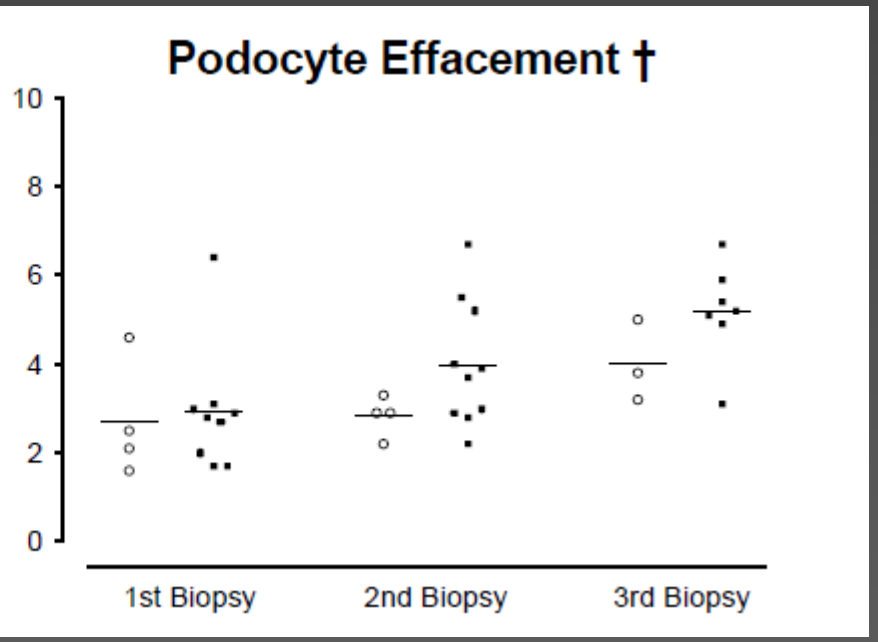

Mesangial Expansion (EM) *
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

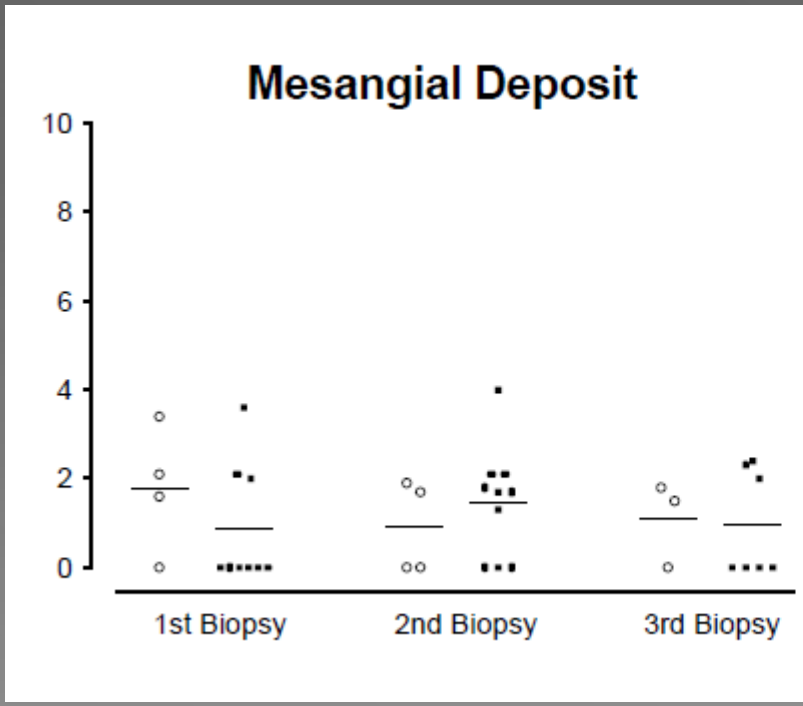

Basement Membrane Deposit
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

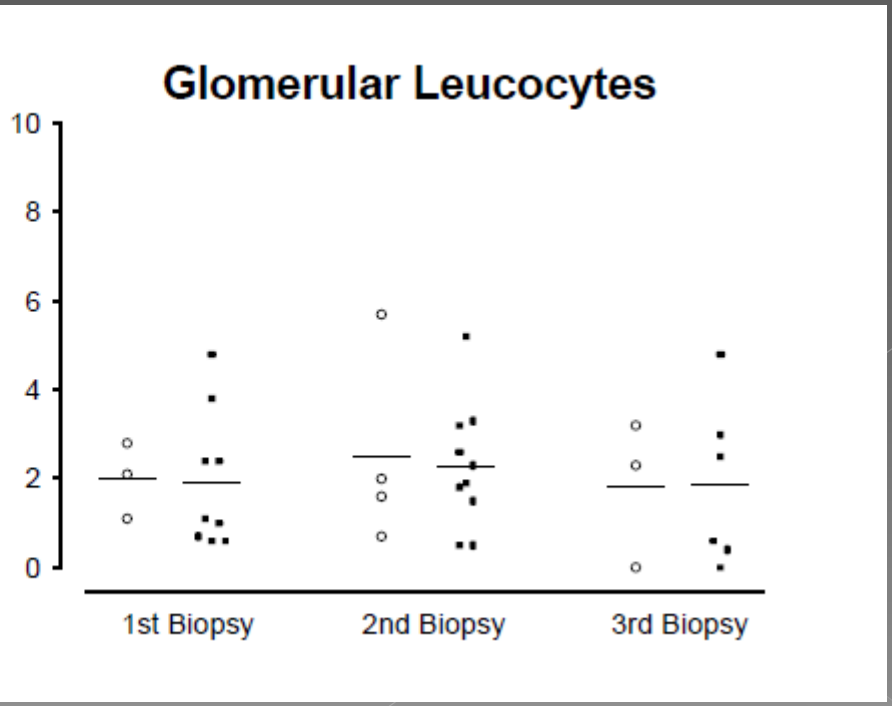

Basement Membrane Thinning
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy


Basement Membrane Thick (EM)
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

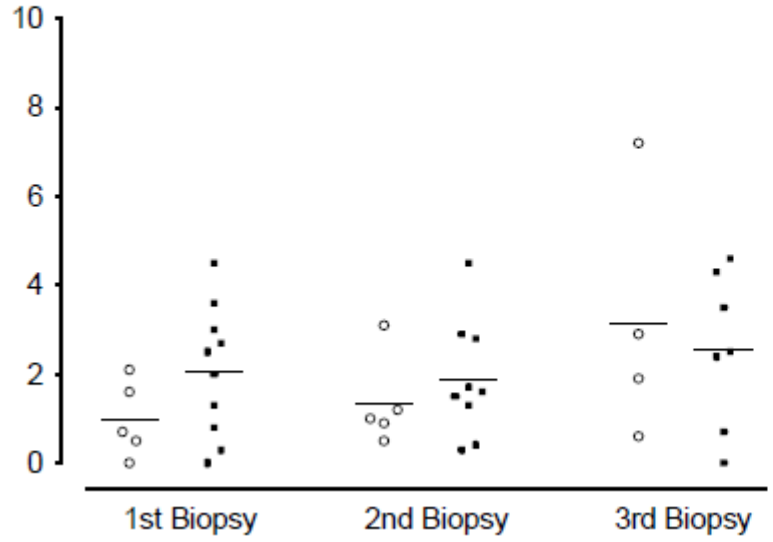

Podocyte Microvilli
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

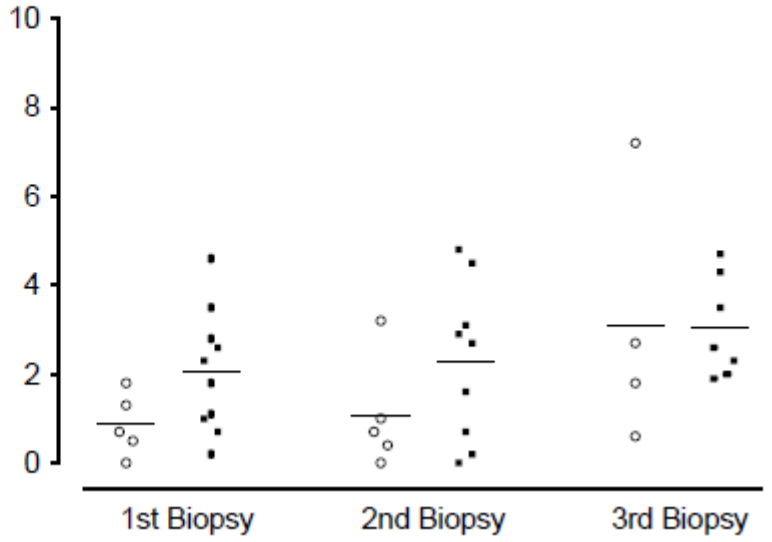

Podocyte Effacement †
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

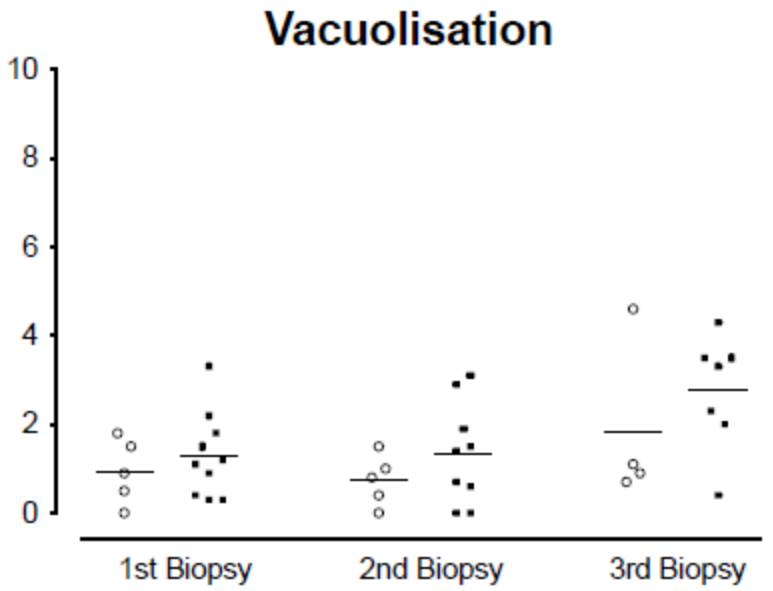

Mesangial Deposit
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

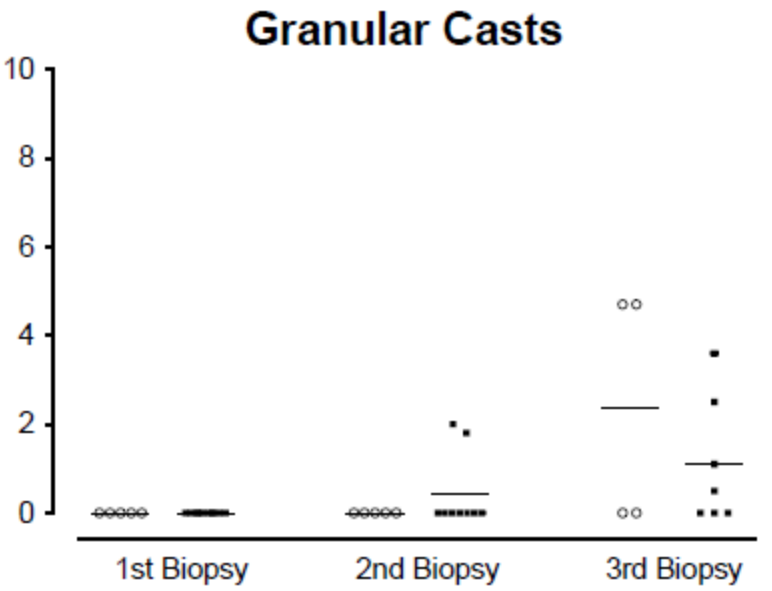

Glomerular Leucocytes
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

C


Dilation
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy


Nuclear Loss
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy


Vacuolisation
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy


Granular Casts
10
8
6
4
2
0
1st Biopsy
2nd Biopsy
3rd Biopsy

# Loss of renal function sepsis

- Global renal blood flow in Gram negative sepsis **may initially be high** driven by decreased vascular resistance
- What drives such vasodilatation remains **unknown but may include shunting and efferent vasodilatation**
- Human data suggest that **global blood flow and function are dissociated and both renal blood flow and function are dissociated from histology and that ATN is uncommon**

# Loss of renal function in sepsis

- Knowing about the macro-circulation may not be enough and **AKI may mostly be a disease of the micro-circulation**
- **Urinary O2 may provide a window on such microcirculatory changes**
- **But if they exist and we can indirectly observe their consequences on medullary O2, can we manipulate them?**