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Acute renal failure in sepsis

Prof. Dr. J.G. van der Hoeven
Radboud University Nijmegen Medical Centre
j.vanderhoeven@ic.umcn.nl or hahoe@mac.com

Sepsis and mortality

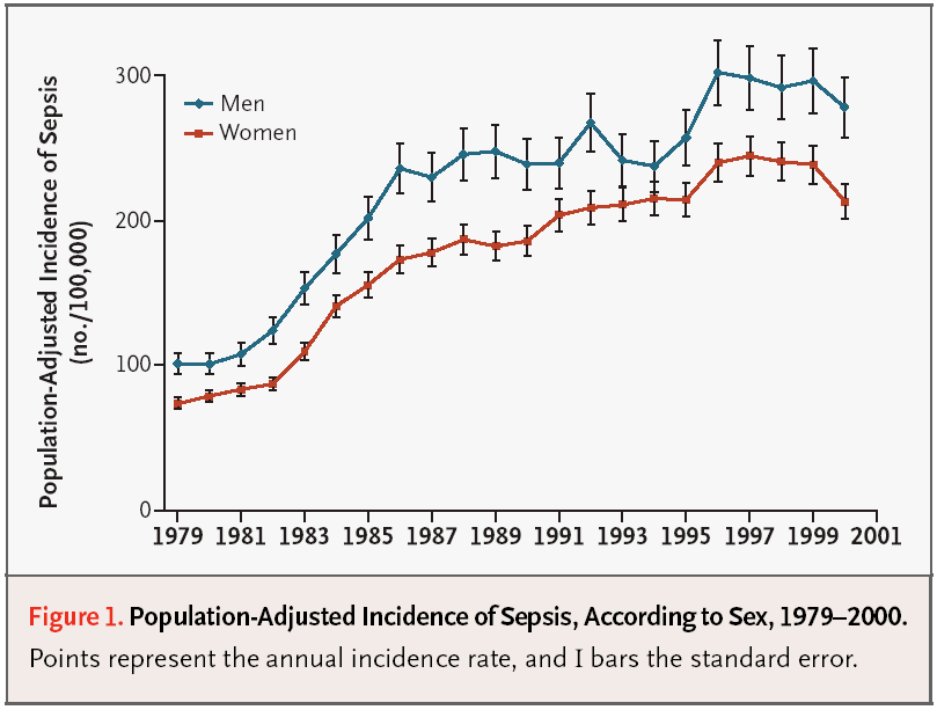


Figure 1. Population-Adjusted Incidence of Sepsis, According to Sex, 1979–2000.
Points represent the annual incidence rate, and I bars the standard error.

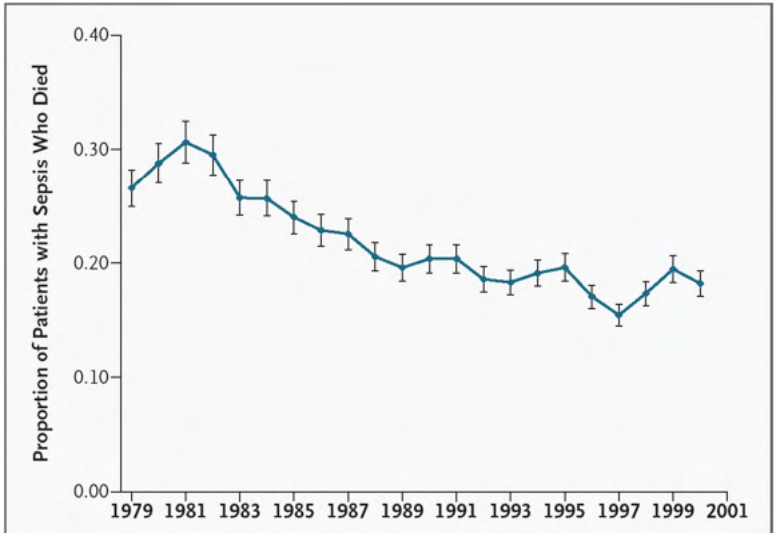


Figure 4. Overall In-Hospital Mortality Rate among Patients Hospitalized for Sepsis, 1979–2000.
Mortality averaged 27.8 percent during the first six years of the study and 17.9 percent during the last six years. The I bars represent the standard error.

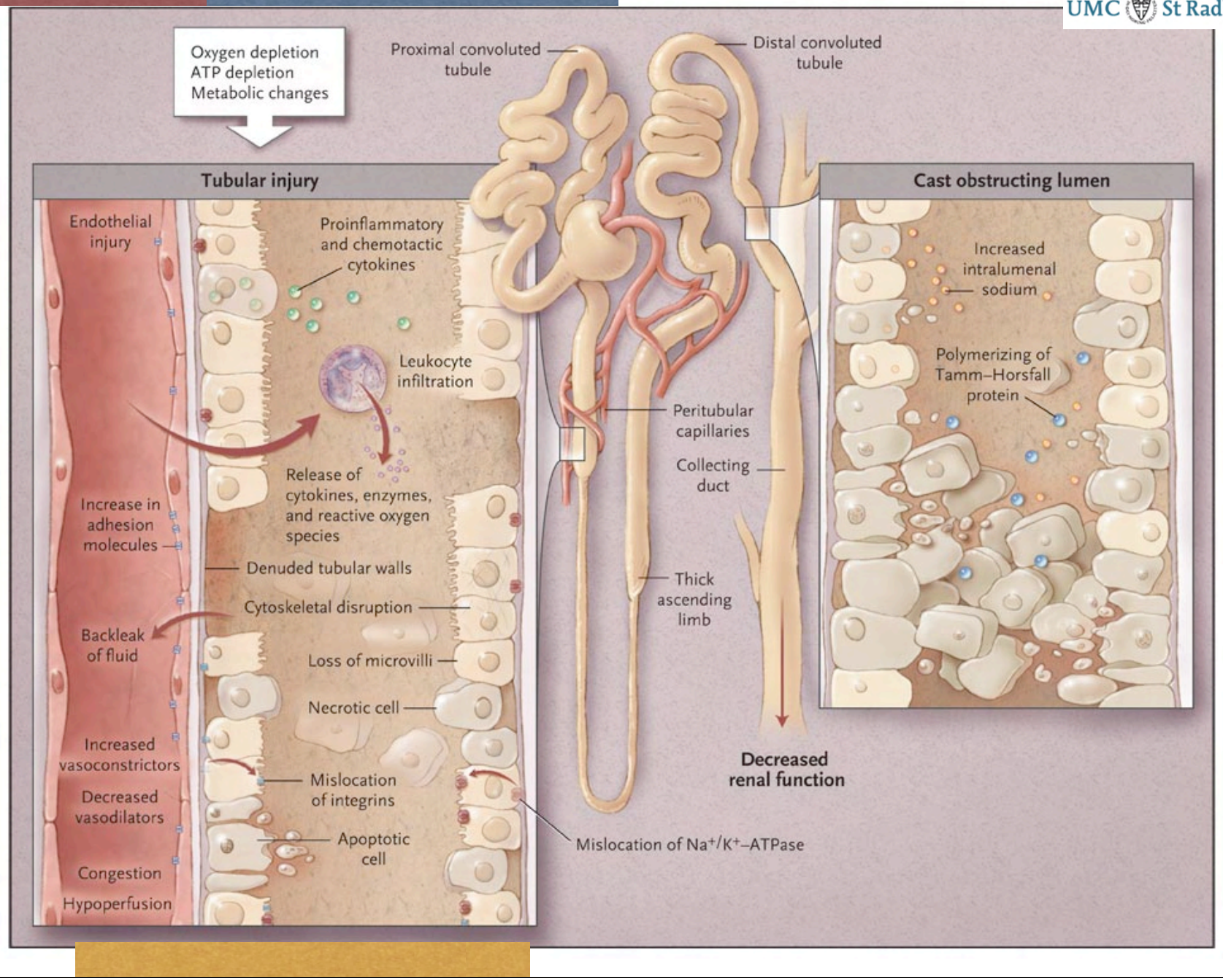
Netherlands 8500 - 9000 cases of severe sepsis/yr

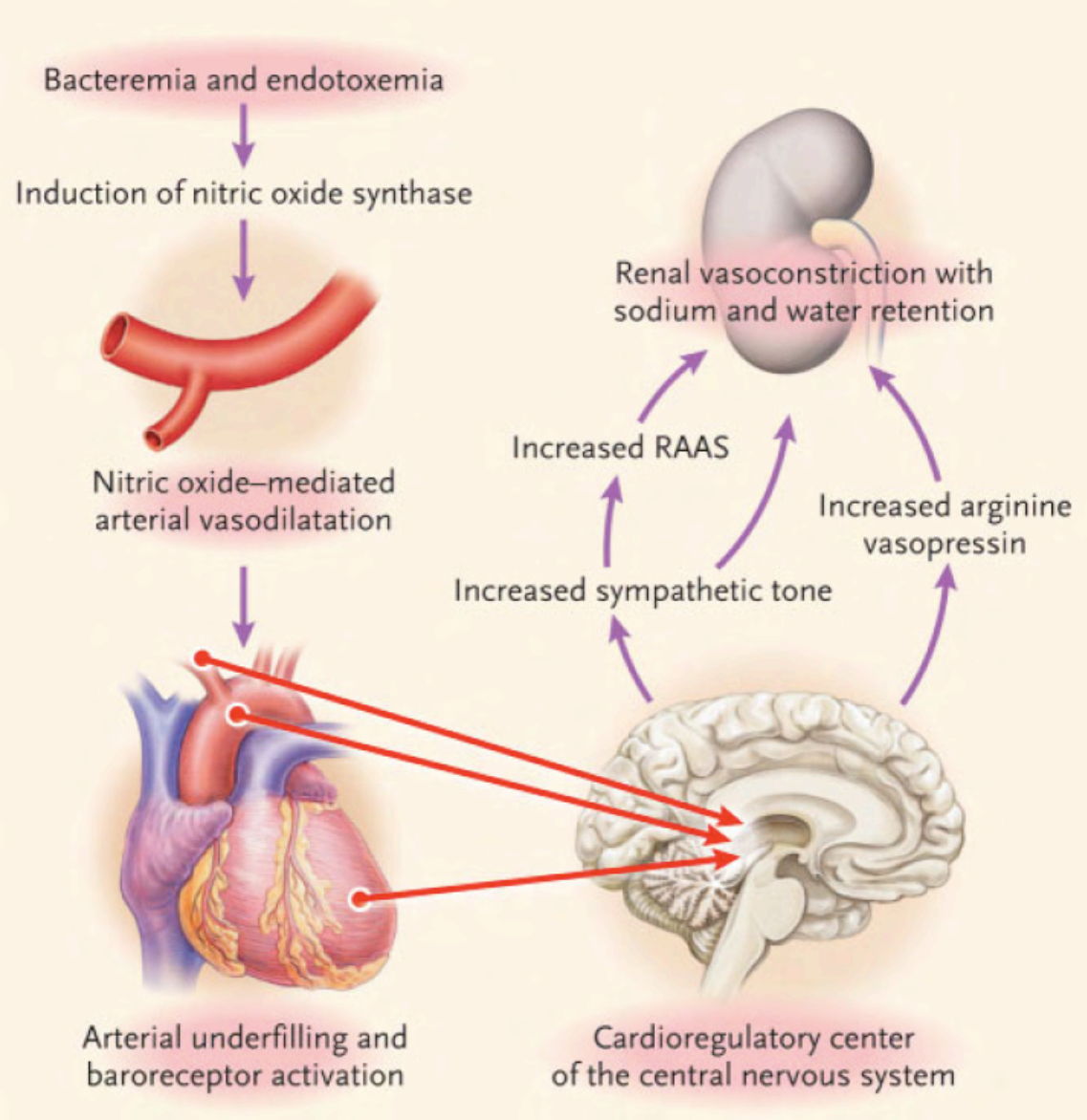
ARF in sepsis

	Moderate sepsis N = 649	Severe sepsis N = 467	Septic shock N = 110
Acute renal failure			
•Positive culture	19%	23%	51%
•Negative culture	5%	16%	38%
ARDS			
•Positive culture	6%	8%	18%
•Negative culture	3%	4%	18%

ARF in sepsis

- Mortality 50 - 70%
- Pathophysiology is complex and includes hemodynamic changes and renal inflammation


Oxygen depletion
ATP depletion
Metabolic changes
Proximal convoluted tubule
Distal convoluted tubule
Tubular injury
Endothelial injury
Proinflammatory and chemotactic cytokines
Leukocyte infiltration
Release of cytokines, enzymes, and reactive oxygen species
Increase in adhesion molecules
Denuded tubular walls
Cytoskeletal disruption
Backleak of fluid
Loss of microvilli
Necrotic cell
Increased vasoconstrictors
Mislocation of integrins
Decreased vasodilators
Apoptotic cell
Congestion
Hypoperfusion
Peritubular capillaries
Collecting duct
Thick ascending limb
Mislocation of Na+/K+–ATPase
Decreased renal function
Cast obstructing lumen
Increased intralumenal sodium
Polymerizing of Tamm–Horsfall protein



- Predominant afferent constriction
- High risk with NSAID's, ACEi
- Tubular function initially intact

Schrier RW. N Engl J Med 2004;351:159-169

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Renal blood flow in human sepsis

PAH-RPF/true RPF (n/n)	PAH-RPF (ml/min)	True RPF (ml/min)
6 (0)	-	690
40 (11)	475	1116
22 (6)	474	1238

True RPF includes renal vein sampling for PAH - normal RPF 600 - 700 ml/min)

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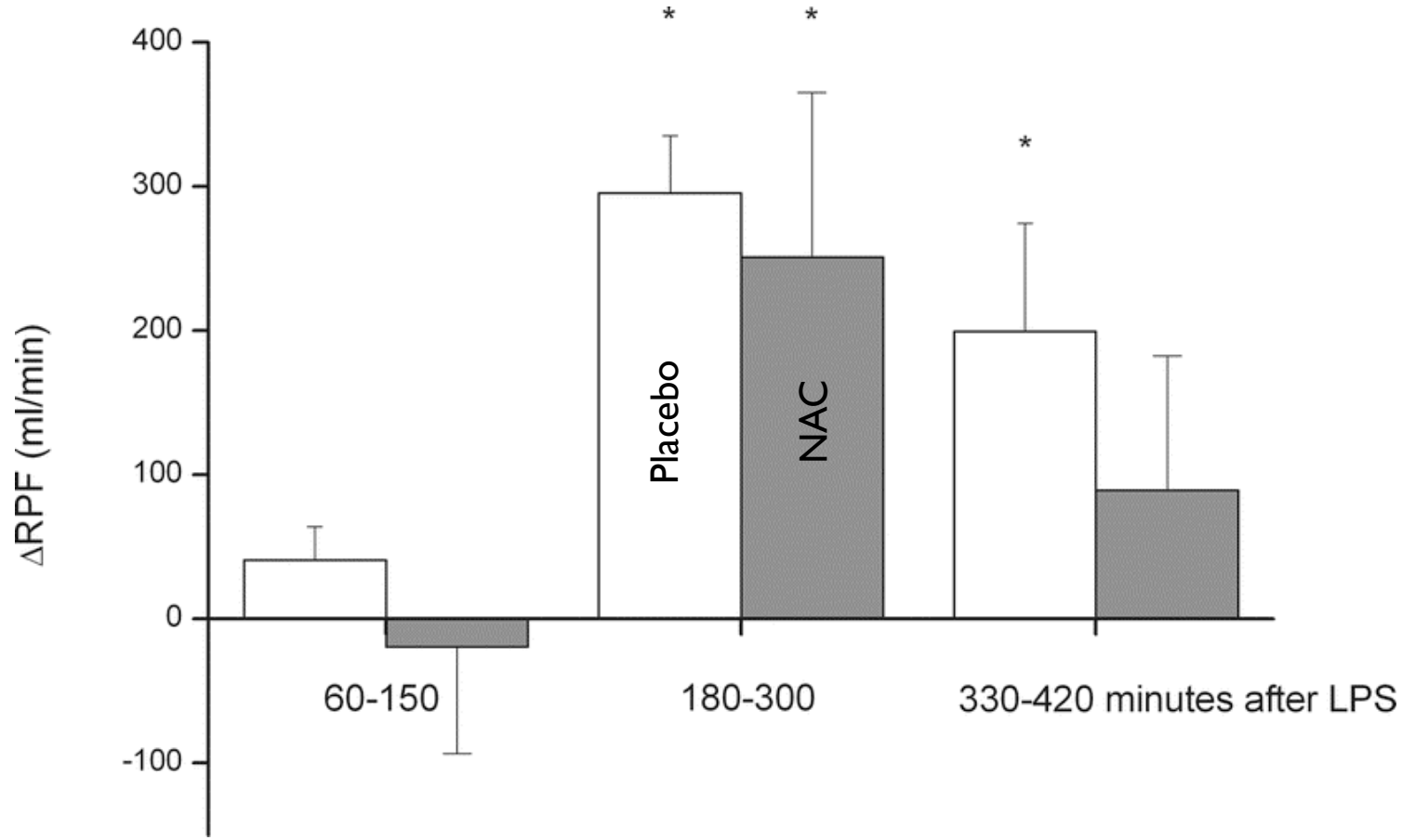
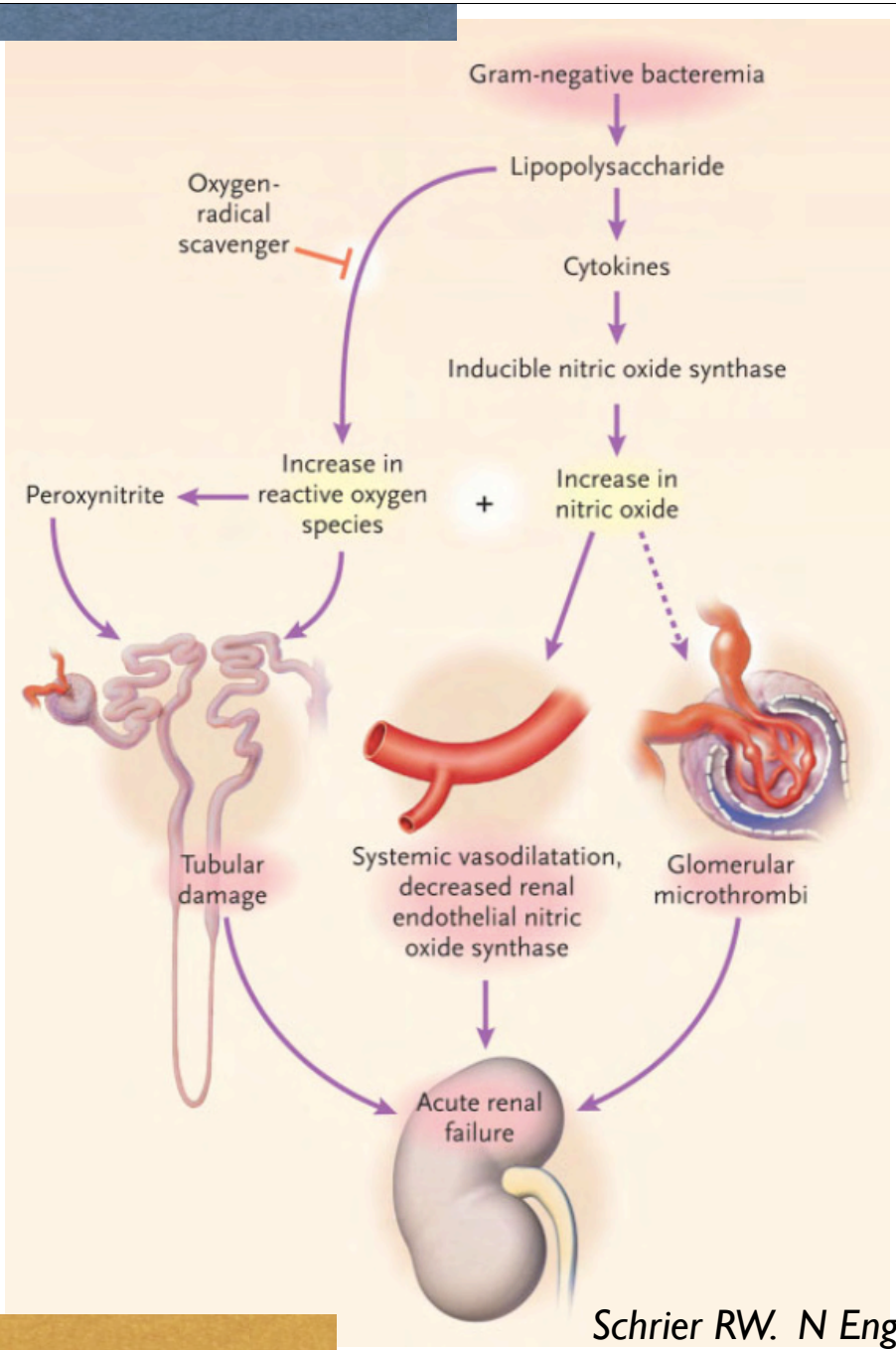
Renal blood flow after endotoxin infusion



Schaller G. Crit Care Med 2007;35:1869-1875



Schrier RW. N Engl J Med 2004;351:159-169

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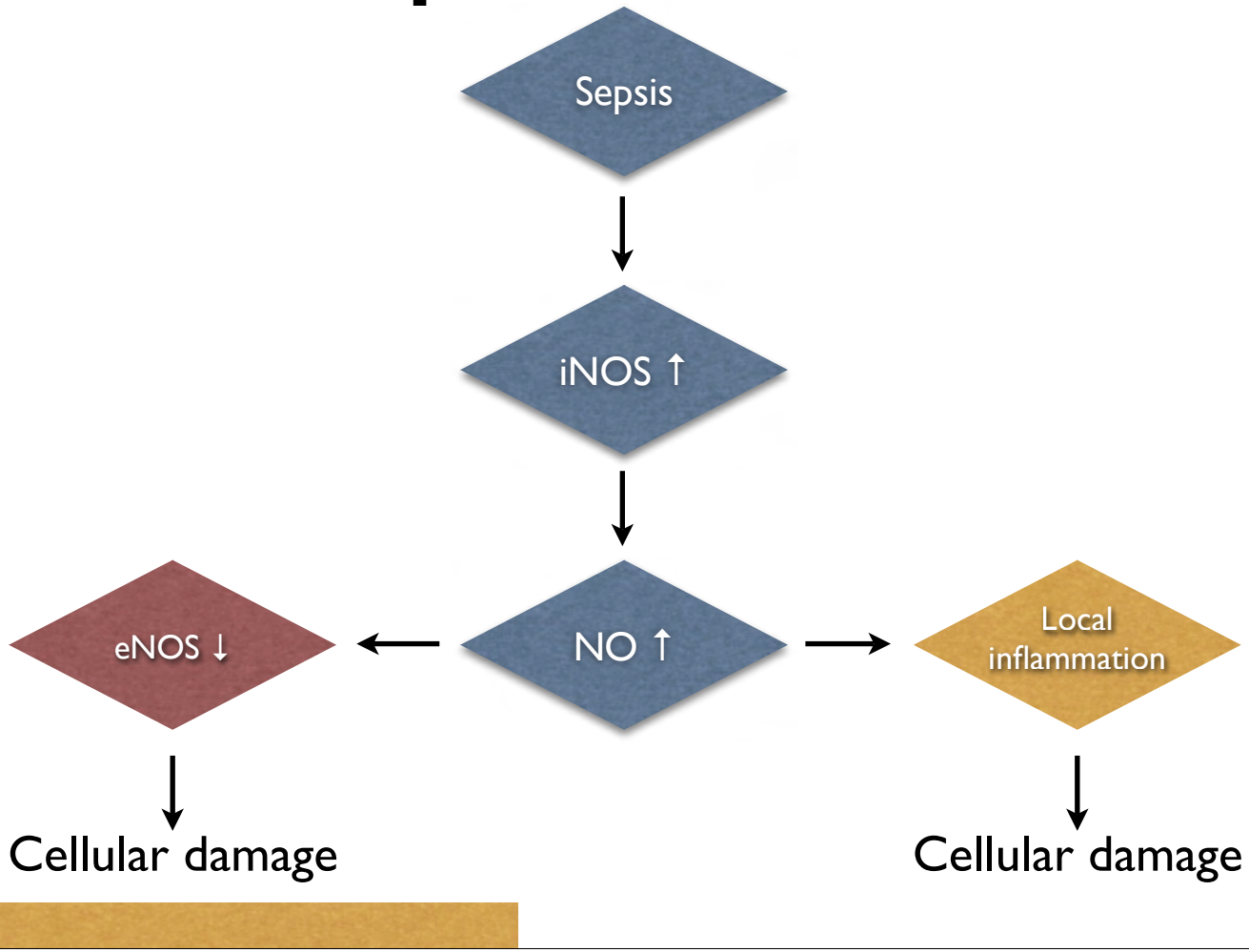
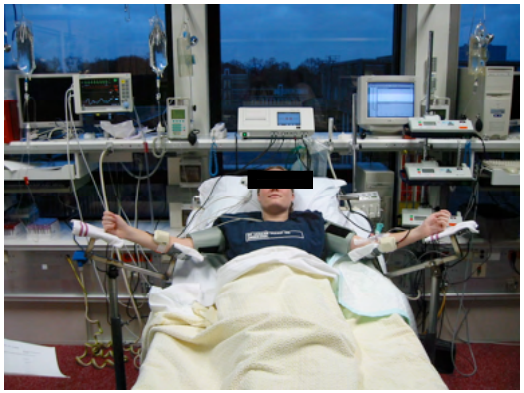
Hypothesis from animal experiments





Blood

- Creatinine and urea ⟶ Clearance
- Cytokines (TNF-α, IL-β)
- C-Reactive Protein
- Leukocytes and trombocytes
- NO metabolites (nitrate, nitrite)

Urine

- Creatinine and urea ⟶ Clearance
- GST-α and GST-π (ELISA)
- NO metabolites (nitrate, nitrite)

Isolation

Protein

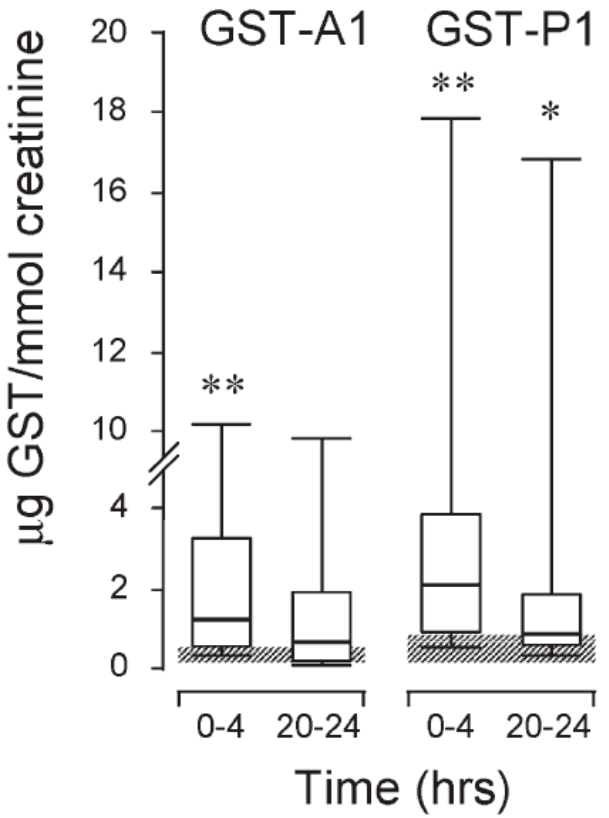
RNA

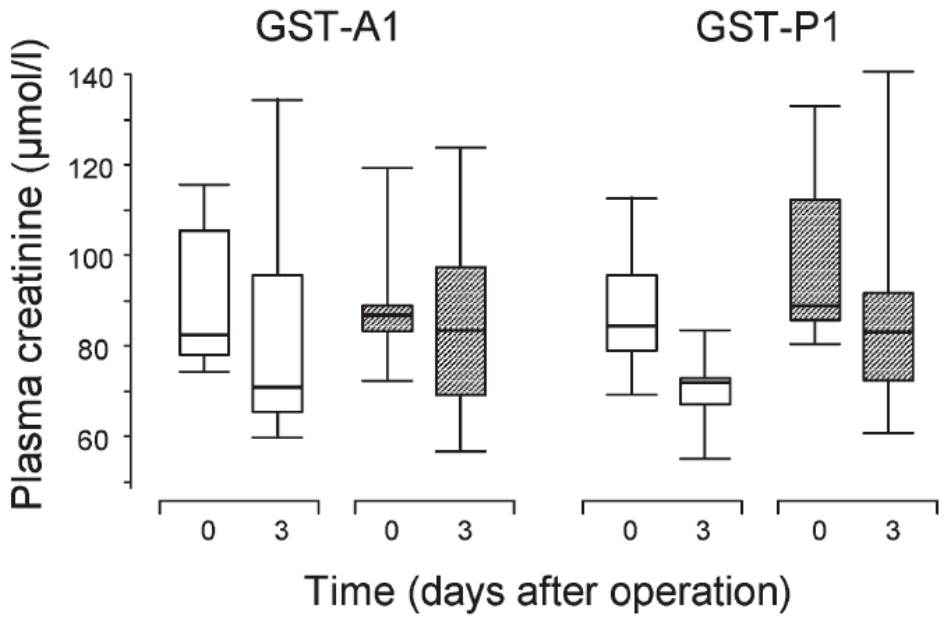
Western blot

Real Time PCR

Expression iNOS

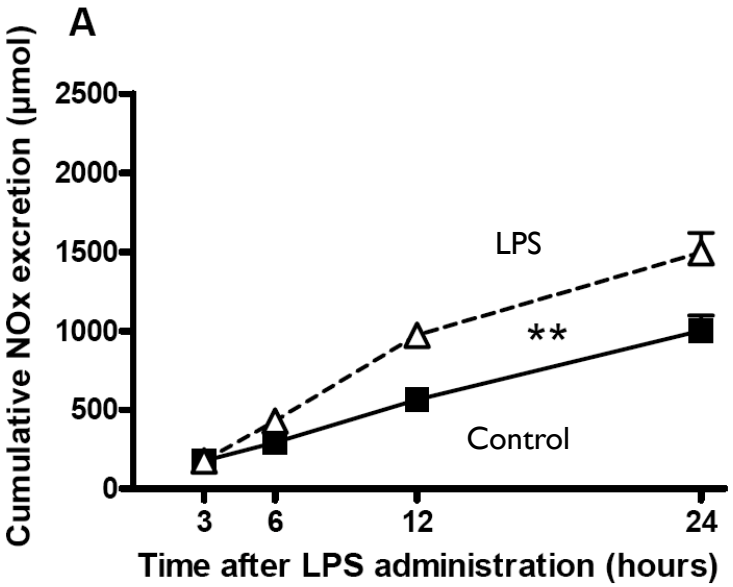
Early renal damage

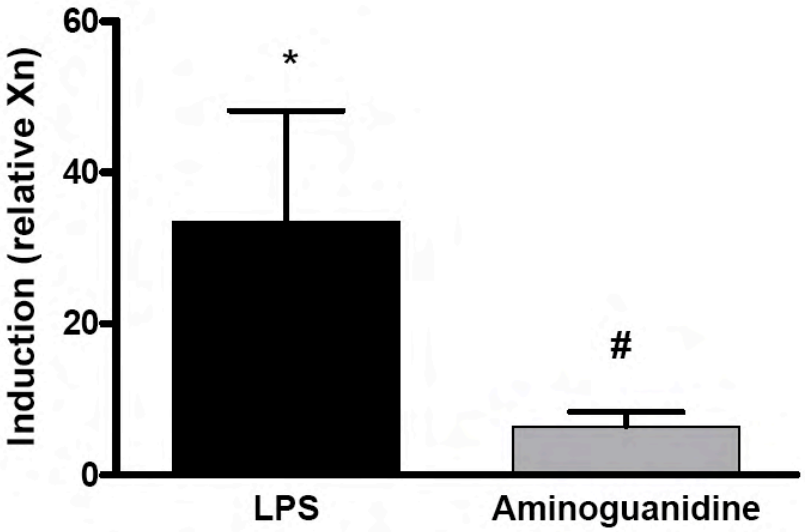


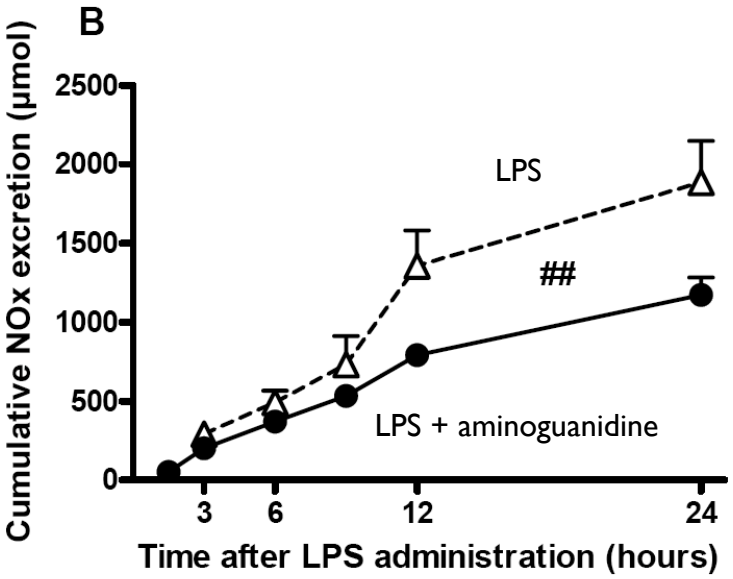


White = lowest 10
Gray = highest 10

Eijkenboom JJA. Intensive Care Med 2005;31:664-667



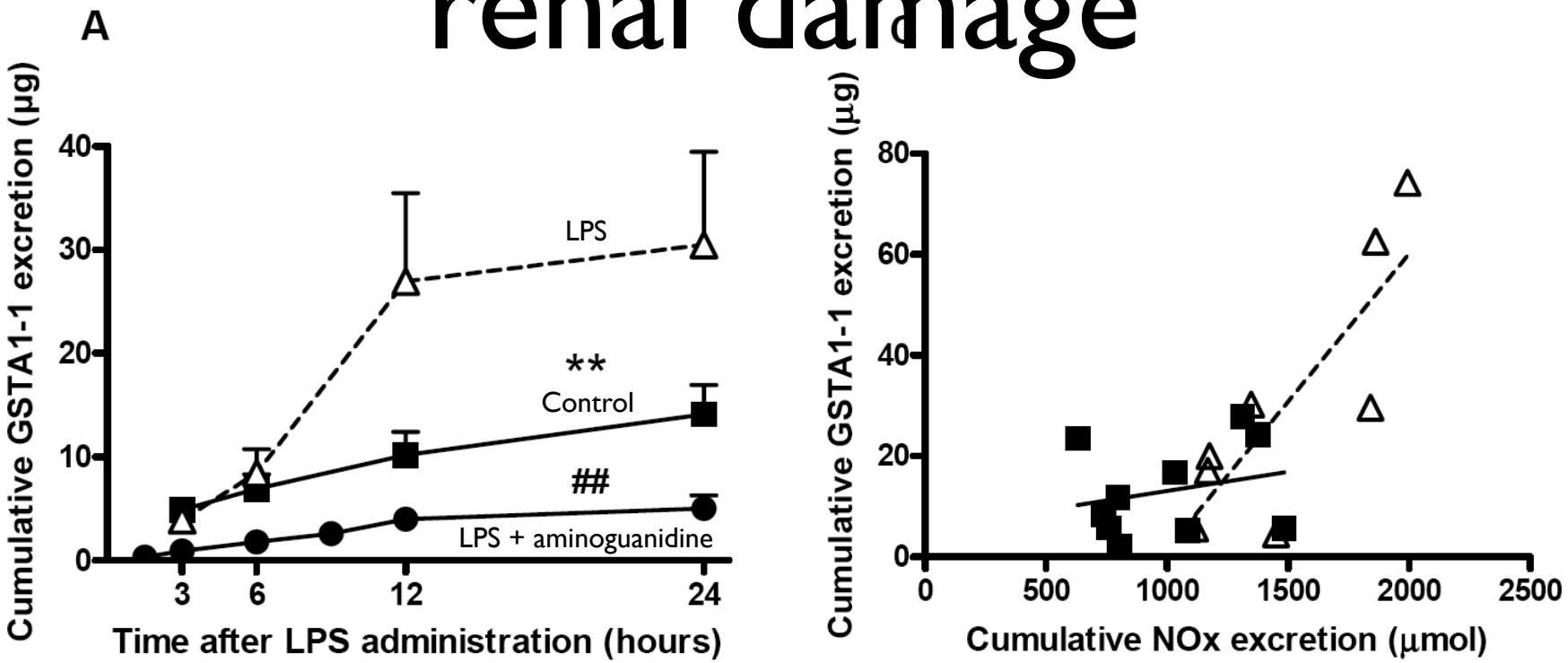




Correlation between cumulative NOx excretion and GST A1 ($r = 0.67$, $p = 0.013$)

Heemskerk S. Clin J Am Soc Nephrol (2006), 1: 853-862

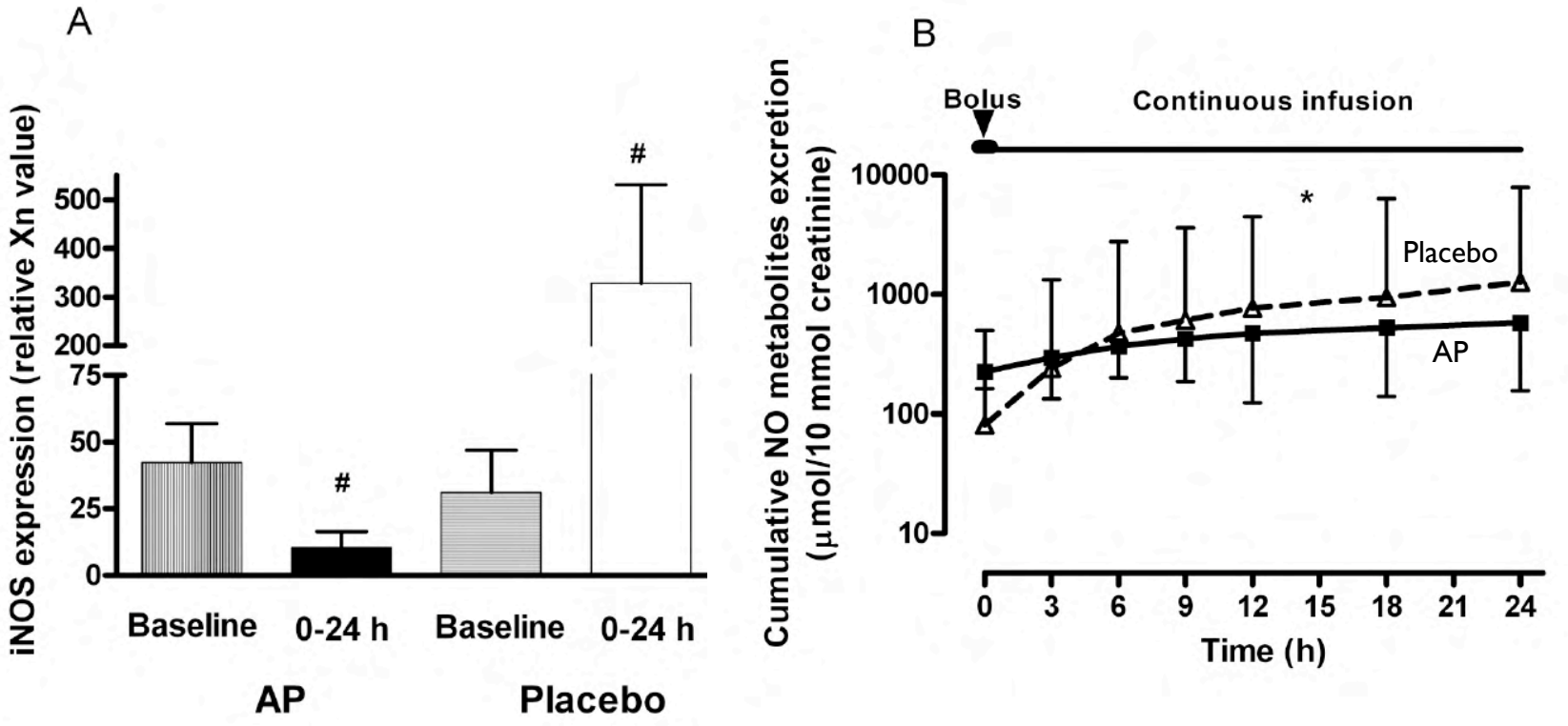
NOx excretion and renal damage



Correlation between cumulative NOx excretion and GST A1 only after LPS ($r = 0.67$, $p = 0.013$)

Heemskerk S. Clin J Am Soc Nephrol (2006), 1: 853-862

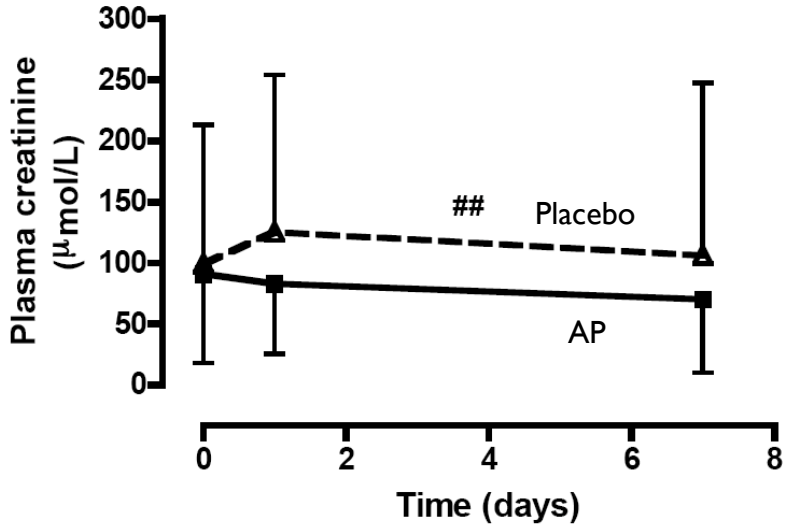
Human septic shock

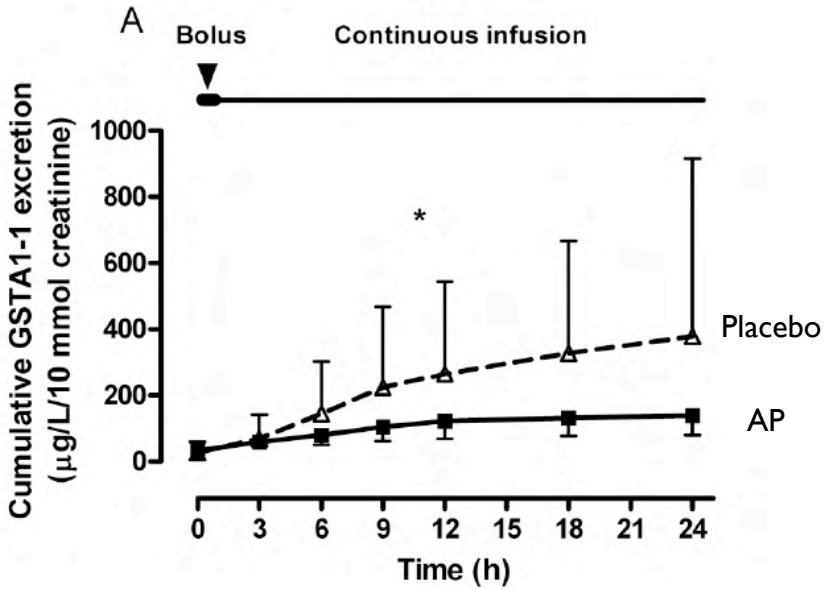


Heemskerk S. Clin J Am Soc Nephrol 2007 (submitted)

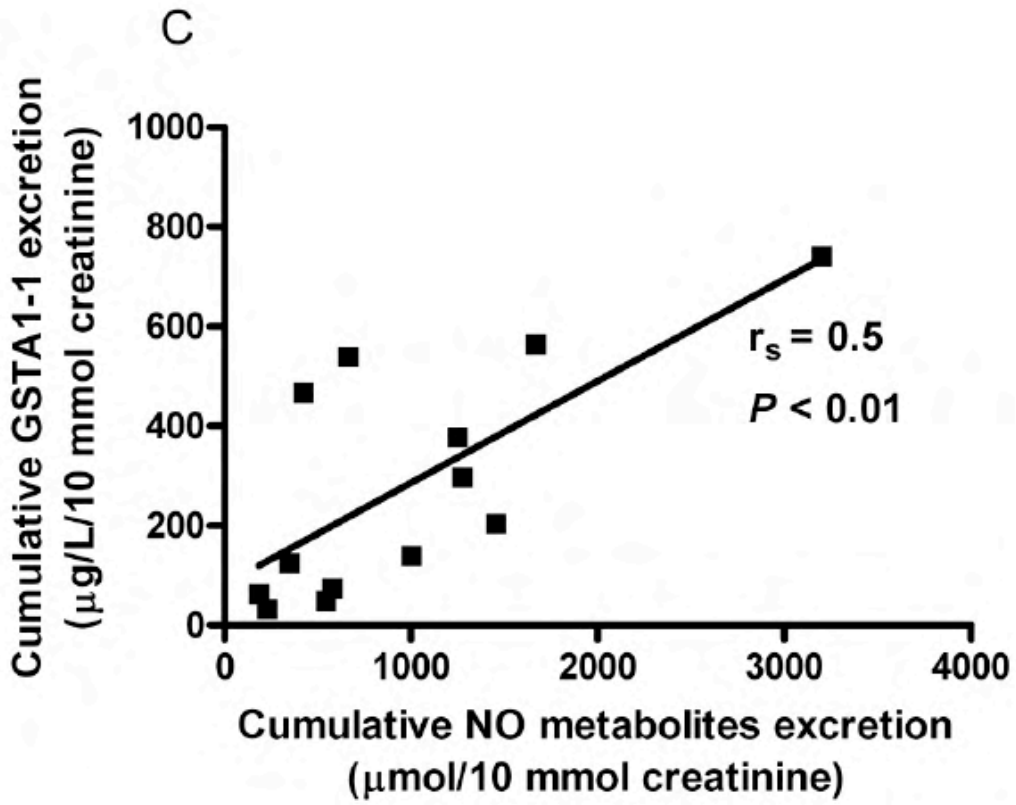
Kidney function	Time	AP (n=10)	Placebo (n=5)
Total urine volume (ml)	0-24 h	1876 [940-2227]	1470 [1115-2775]
Protein excretion (mg/day)	0-24 h	454 [330-533]	447 [414-769]
Creatinine clearance (ml/min)	Baseline	54 [24-84]	80 [77-91]
	0-24 h	76 [25-101] *	59 [45-59]

Data are expressed as median [25-75% range]. * $P<0.05$, significantly different compared to the placebo group.





Heemskerk S. Clin J Am Soc Nephrol 2007 (submitted)

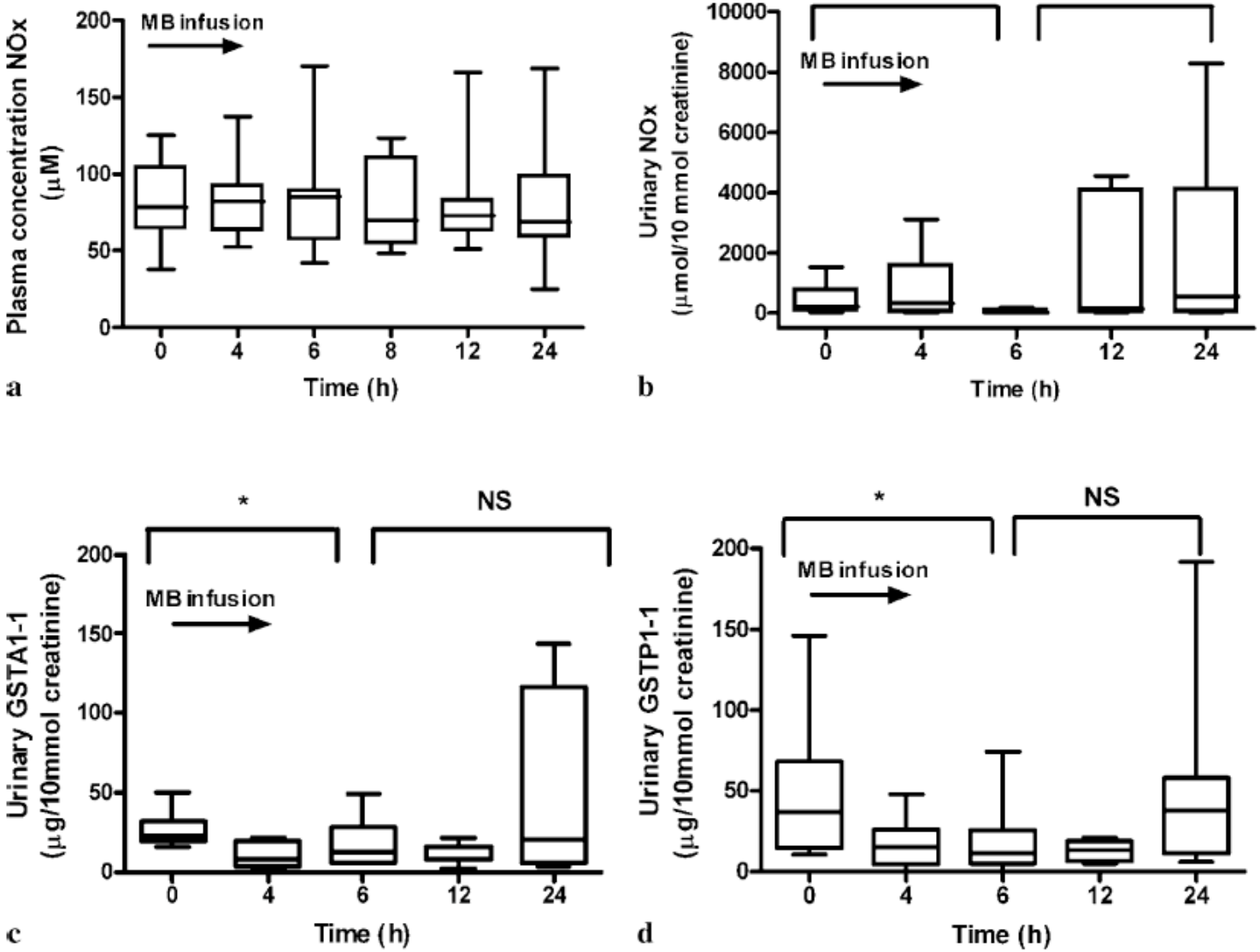


Heemskerk S. Clin J Am Soc Nephrol 2007 (submitted)

Methylene blue

- Nine patients with norepinephrine refractory septic shock
- Infusion of methylene blue 1 mg/kg/hr for 4 hrs
- 90% decrease in urinary NO metabolites
- Decrease in GST-A1 and GST-P1 of 45 and 70%
- Increase in creatinine clearance of 51%

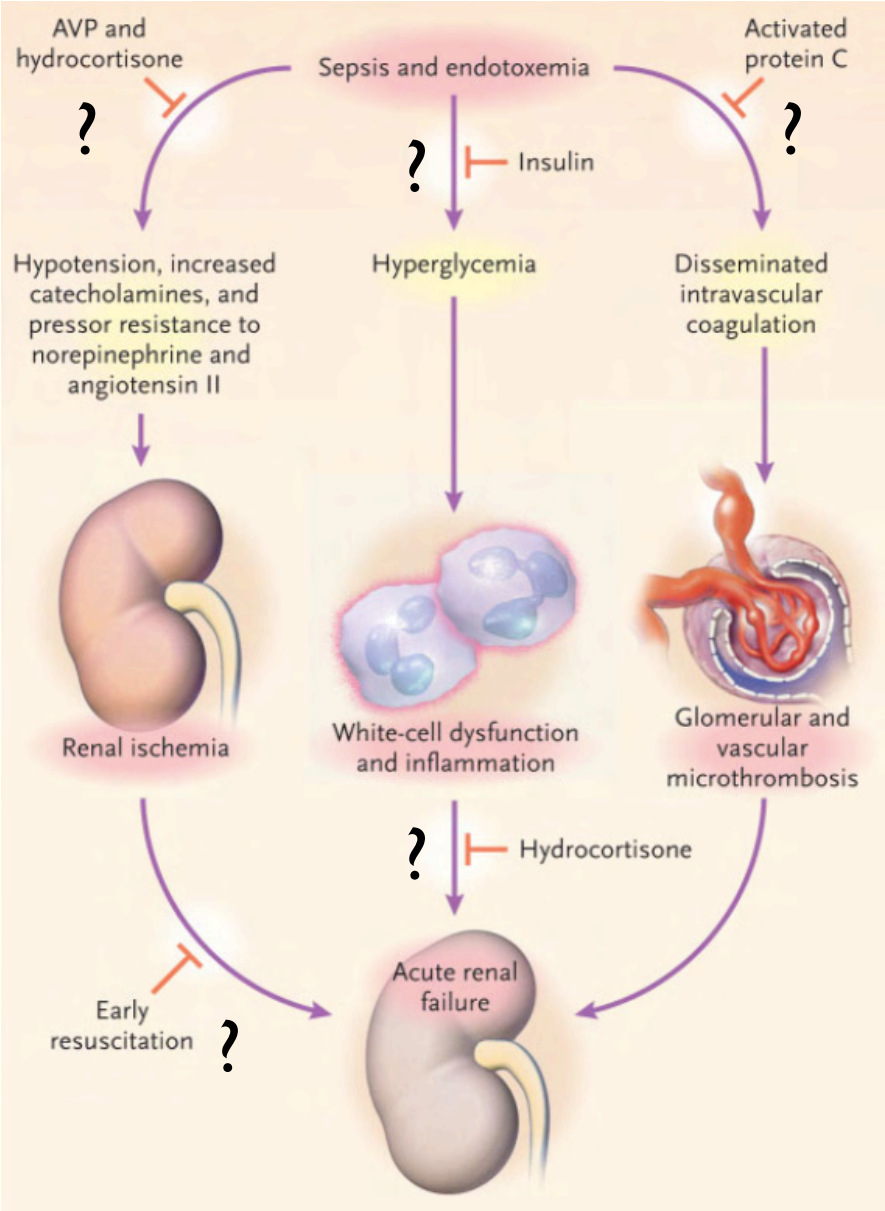
Heemskerk S. Intensive Care Med 2007



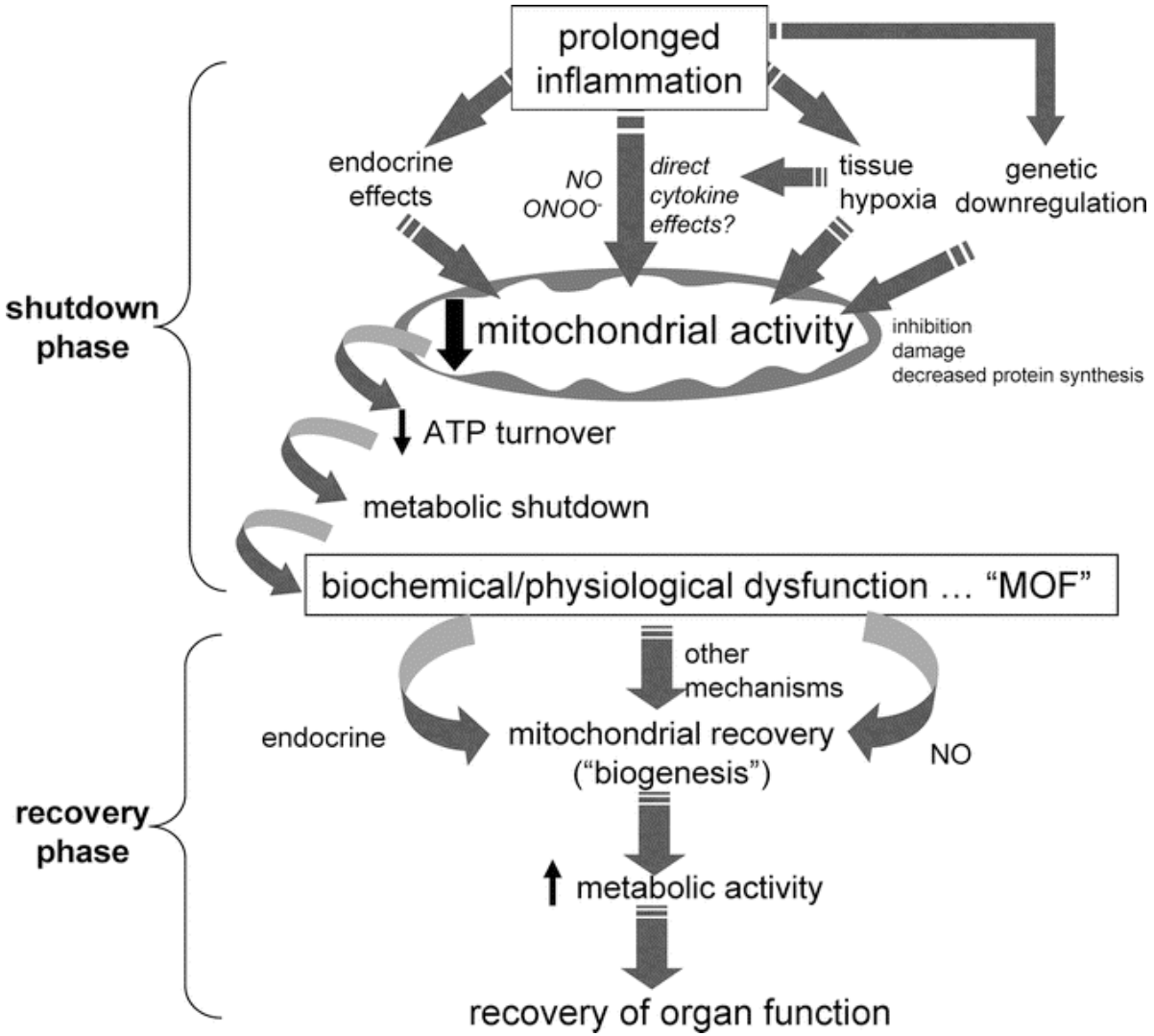
Heemskerk S. Intensive Care Med 2007

What does not work?

- Frusemide
- Low dose dopamine
- N-Acetyl Cysteine

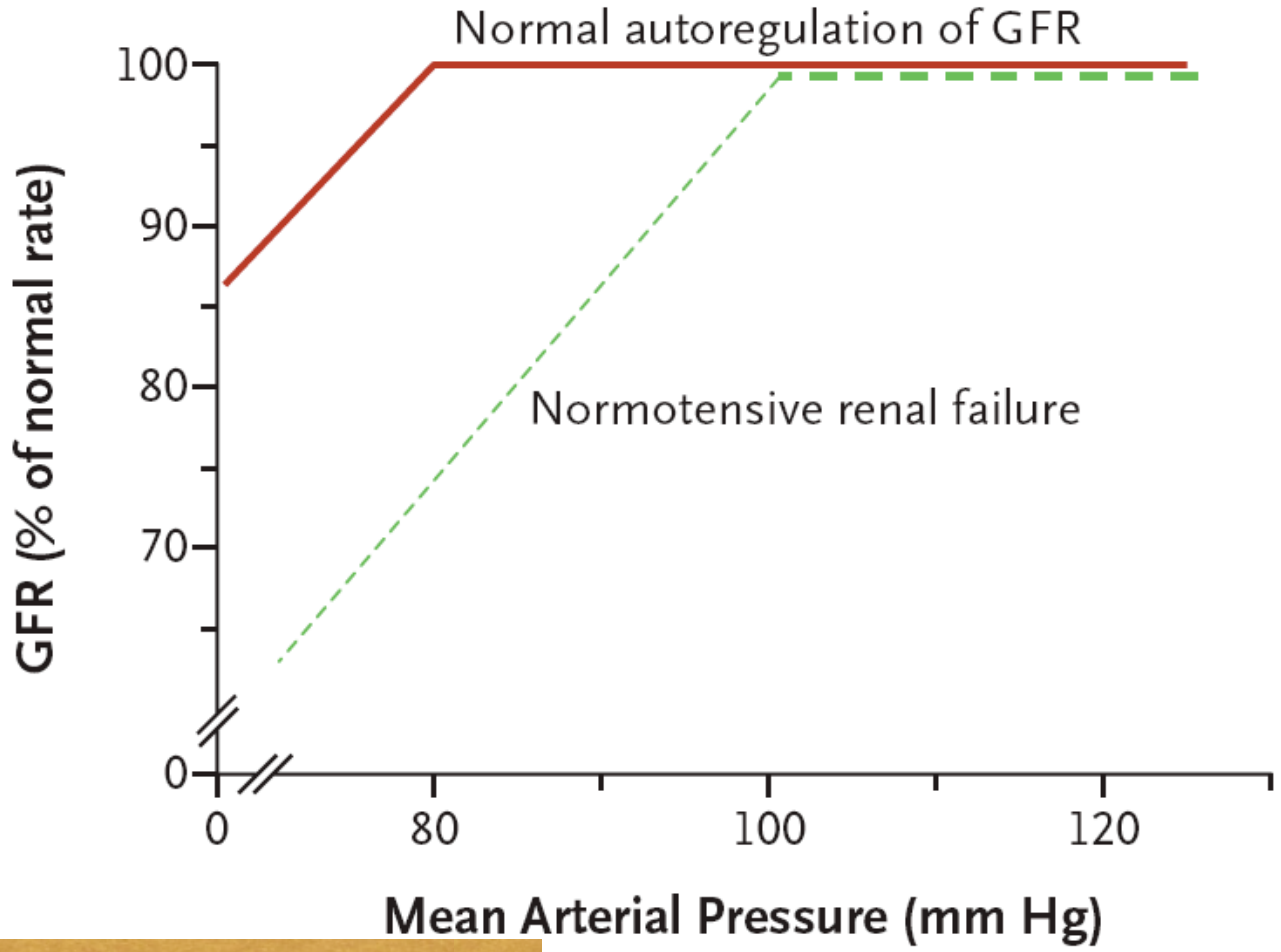


Schrier RW. N Engl J Med 2004;351:159-169



Singer M. Crit Care Med 2007;35:S441-S448

Autoregulation

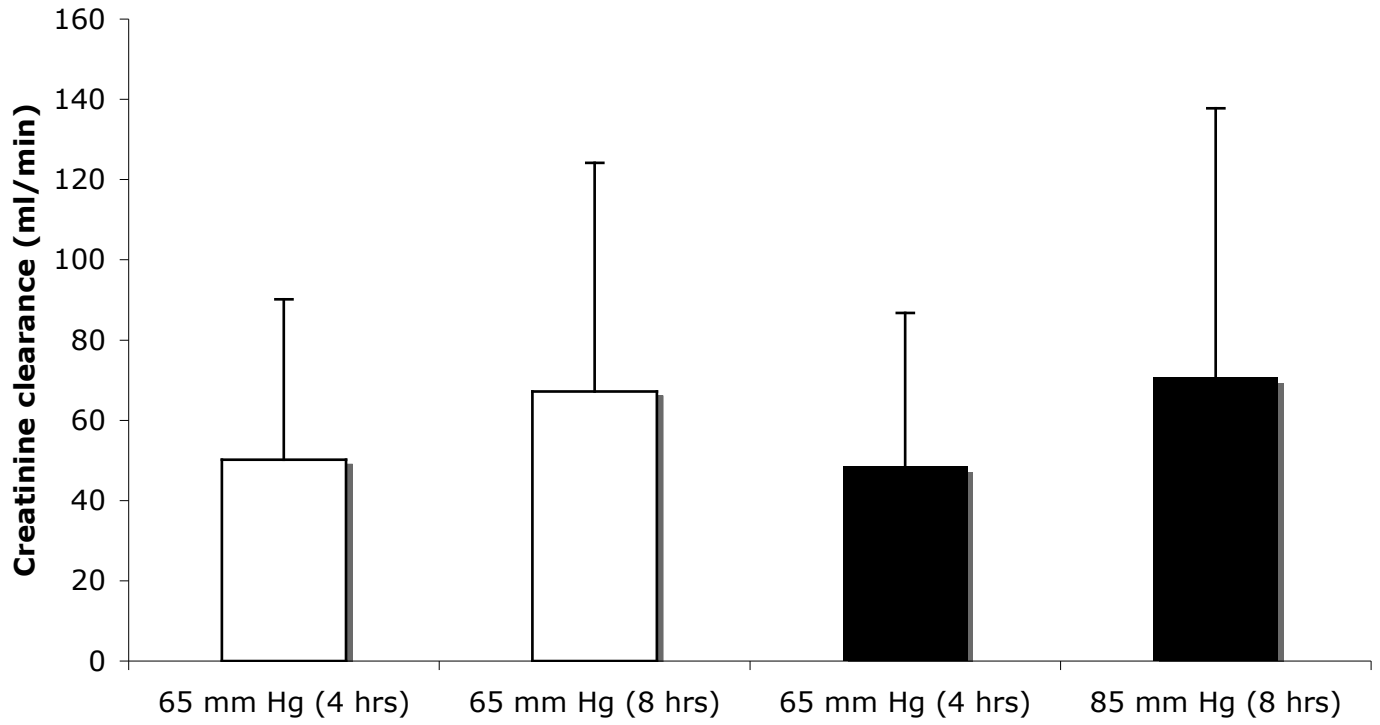


Optimal MAP in sepsis

	MAP 65	MAP 75	MAP 85
Lactate (mmol/l)	3.1 ± 0.9	2.9 ± 0.8	3.0 ± 0.9
Urine (ml/hr)	49 ± 18	56 ± 21	43 ± 13
Capillary blood flow (ml/min/100 gr)	6.0 ± 1.6	5.8 ± 1.2	5.3 ± 0.9
PiCO2 (mm Hg)	41 ± 2	47 ± 2	46 ± 2
Pa-PiCO2 (mm Hg)	13 ± 3	17 ± 3	16 ± 3

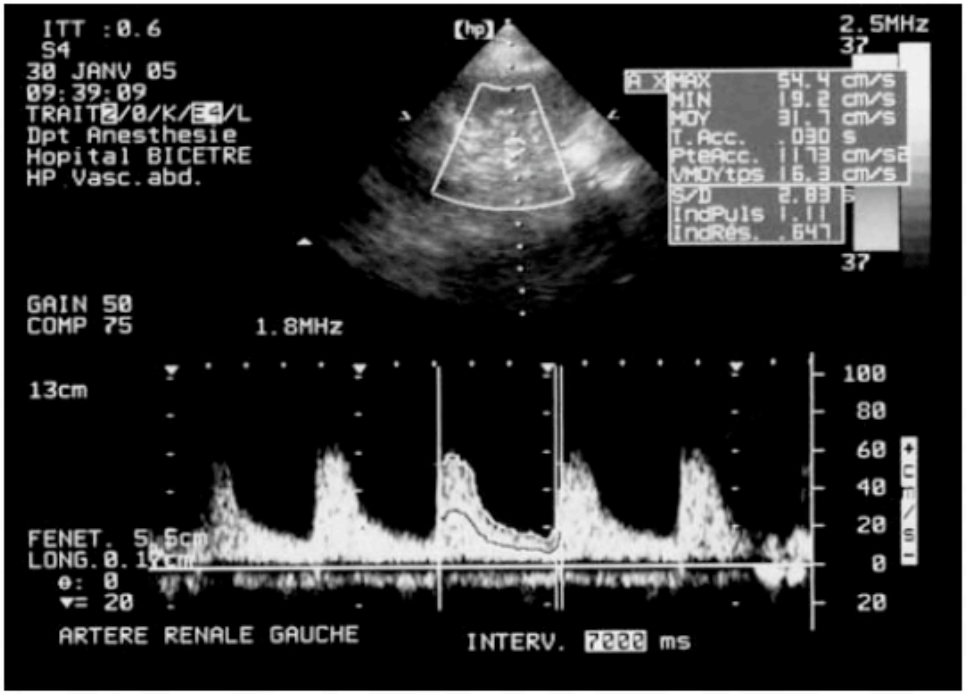
LeDoux D. Crit Care Med 2000;28:2729-2732

Optimal MAP in sepsis

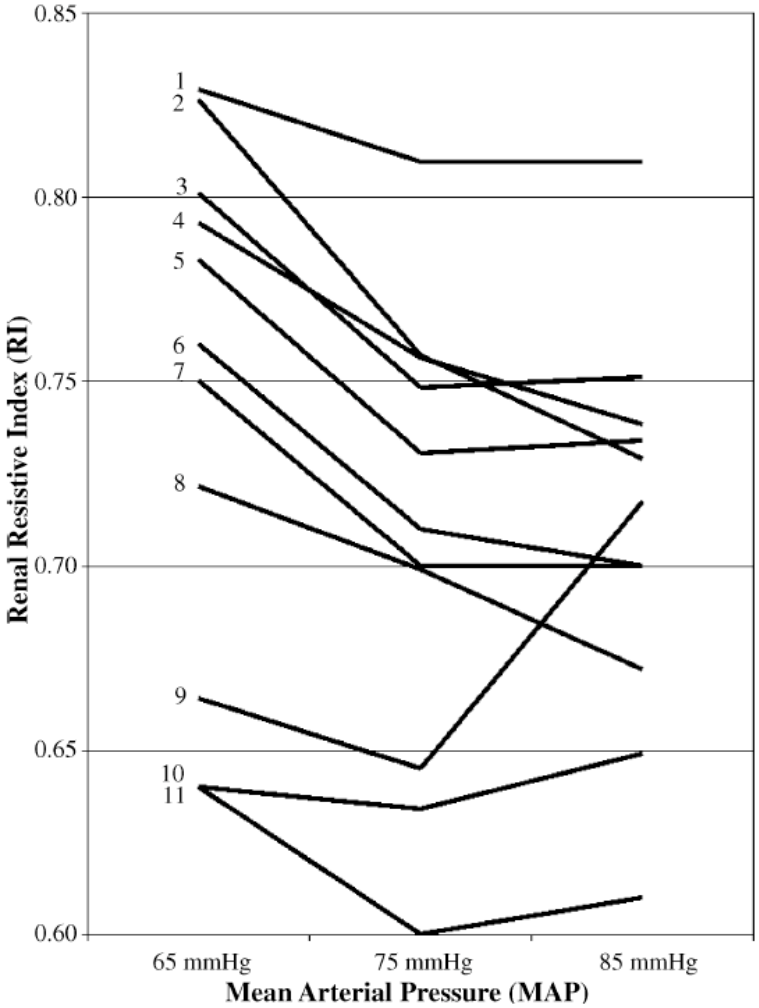


Bourgoin A. Crit Care Med 2005;33:780-786

Renal Resistive Index



Renal resistive index (PSV-EDV)/PSV



Deruddre S. Intensive Care Med 2007;33:1557-1562

Conclusions

- Local renal iNOS activation and NO production play a possible role in sepsis-induced acute kidney injury
- This opens new possibilities for the prevention and treatment of acute kidney injury
- Second study with alkaline phosfatase recently started