MICROCIRCULATORY ALTERATIONS: POTENTIAL MECHANISMS AND IMPLICATIONS FOR THERAPY

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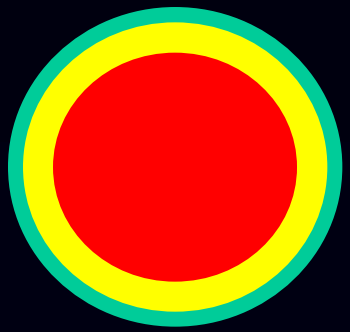
Specificities of the microcirculation

Microcirculatory DO2 cannot be predicted from global DO2

- **Hematocrit lower than systemic hematocrit**
  (+ non linear distribution along capillaries)

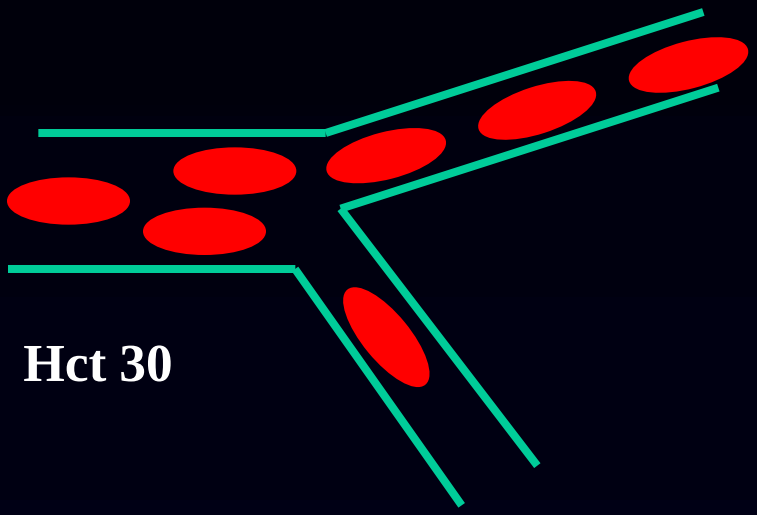
Mandatory plasma layer => hematocrit is lower is small vessels

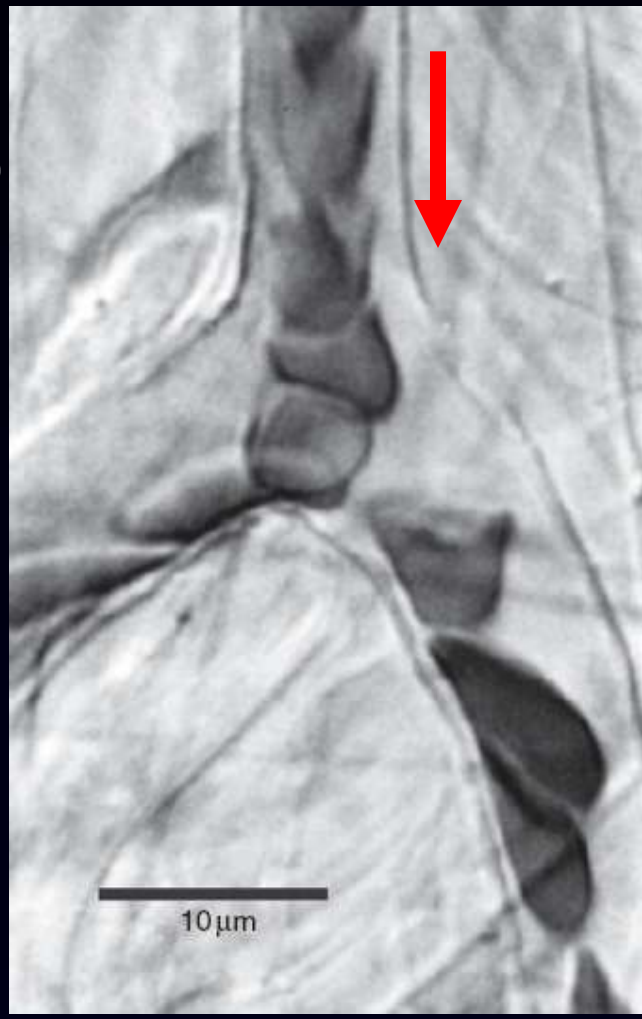


20 µm

10 µm

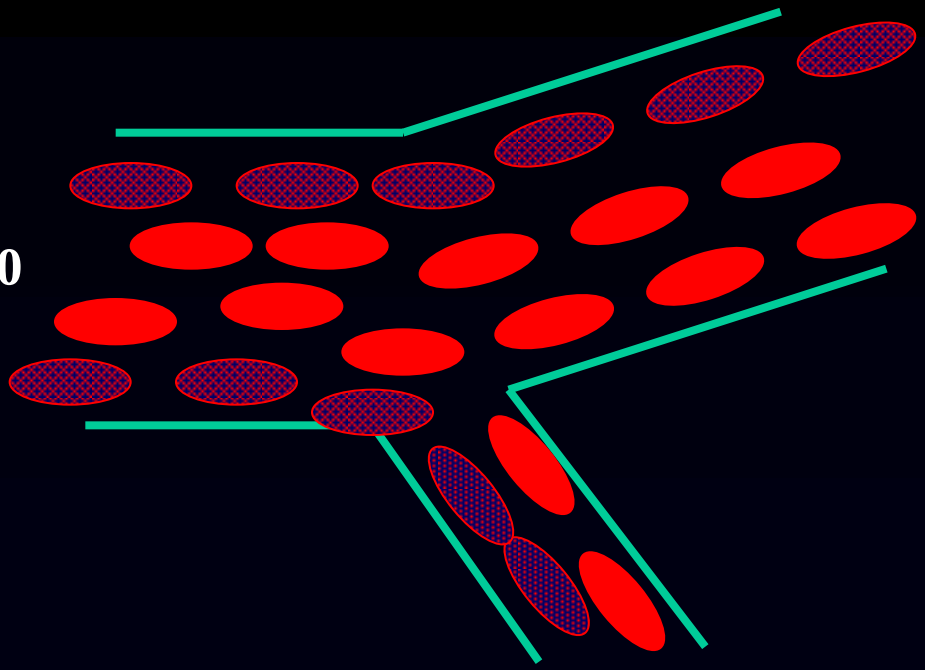
Due to kinetic inertia, red blood cells will preferentially go straightforward, accordingly the hematocrit will be lower in vessels with a large angle at origin.





Cockelet et al
Microcirculation 2:1-18;1982

Heterogeneity of PO2 at branchpoints



PO2 is lower in vicinity of vascular wall (O2 consumption by endothelium)

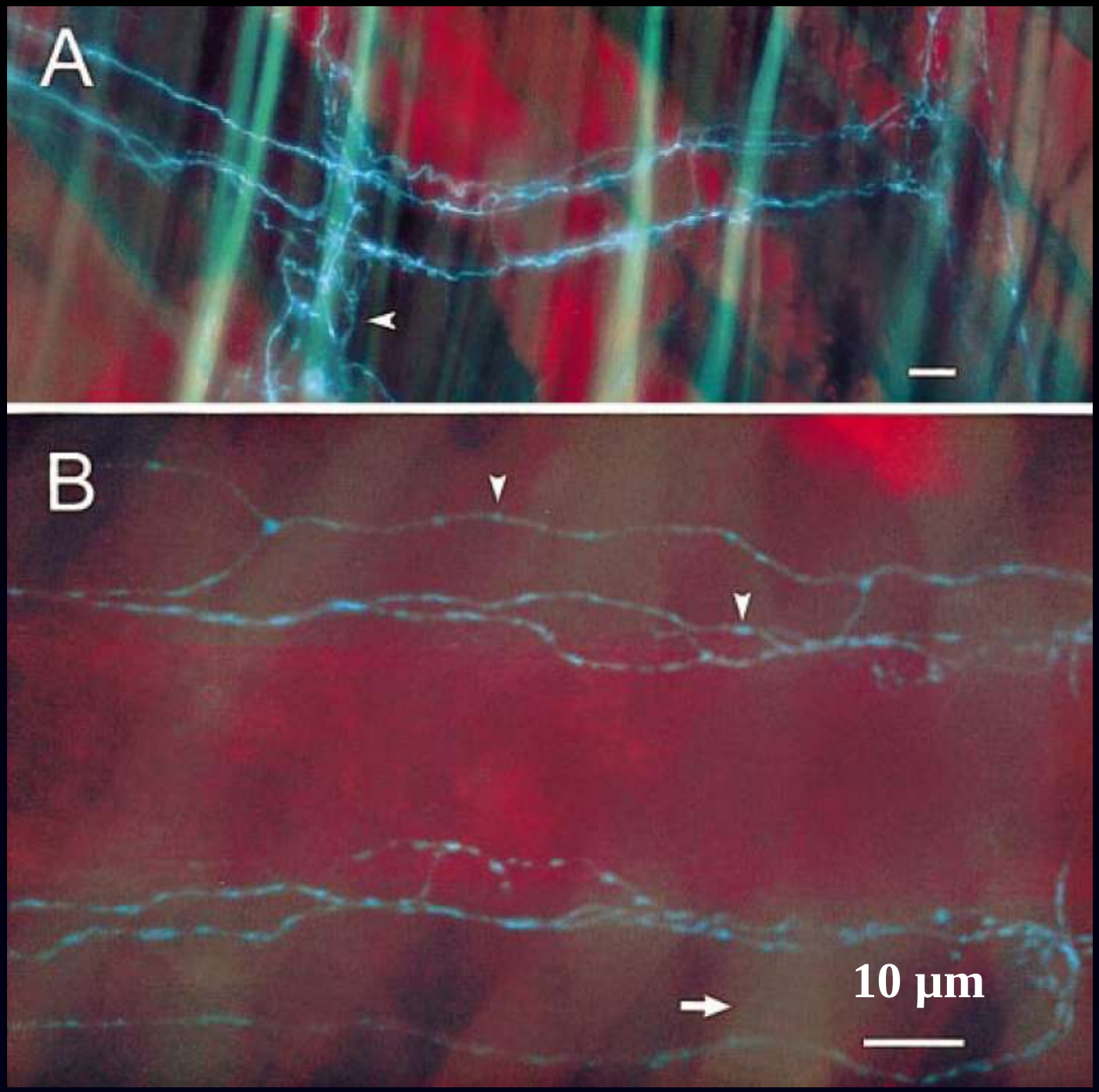
Microcirculatory DO2 cannot be predicted from global DO2

- **Hematocrit lower than systemic hematocrit (+ non linear distribution along capillaries)**
- **Control of blood flow under different mechanisms**

Determinants of microvascular blood flow

$$\dot{V} = \frac{\pi}{8} \cdot \frac{r^4}{L} \cdot \frac{1}{\eta} \cdot \Delta P$$

Blood flow is adapted to local metabolic needs through local vasodilation and upstream changes in vasomotor tone



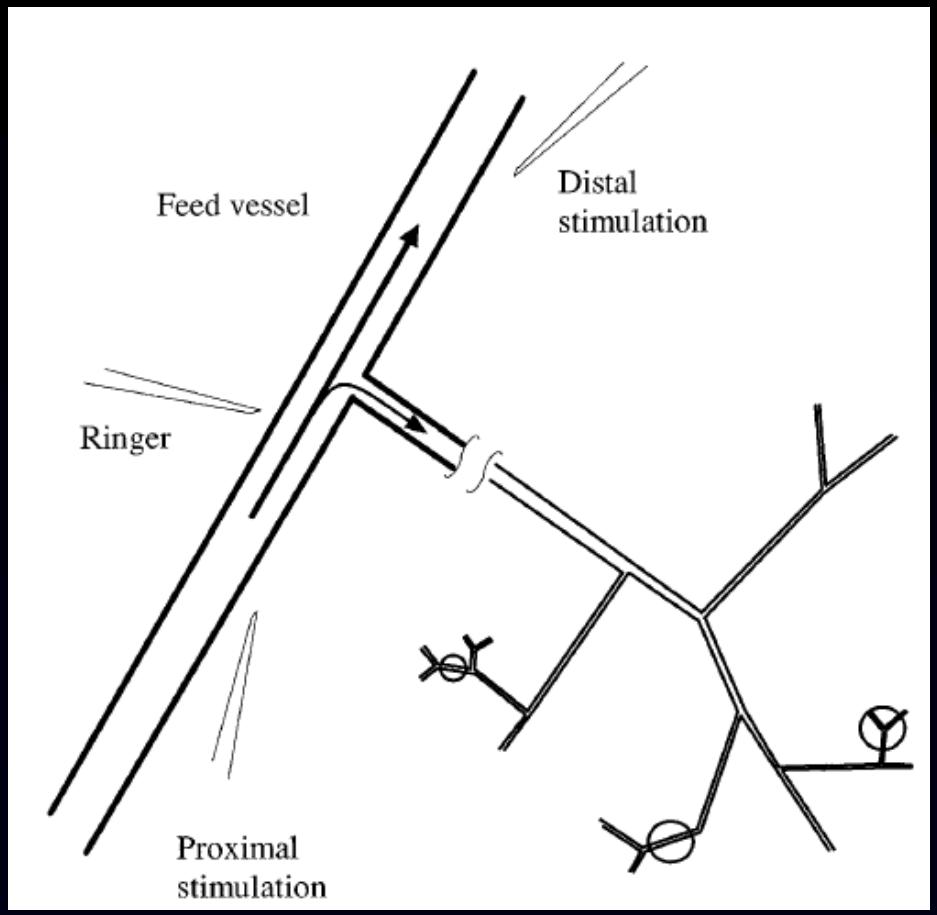
Hungerford-JE et al
FASEB 14:197;2000

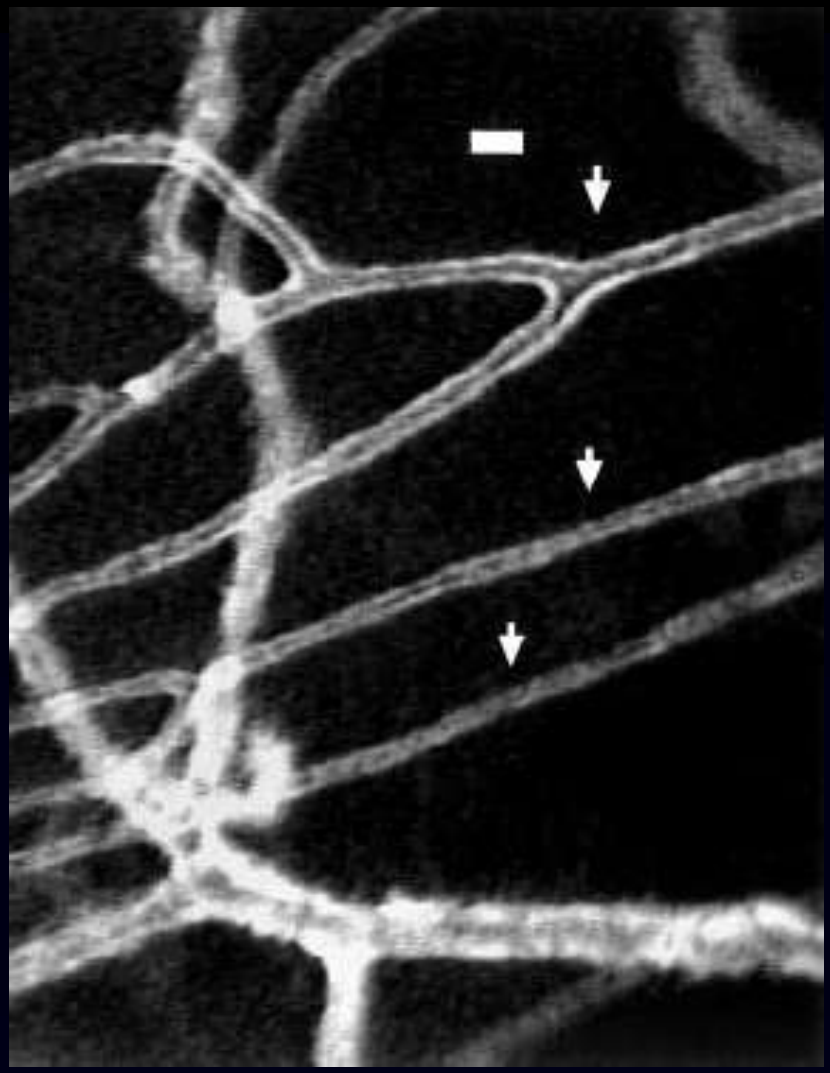
Neural control

Perivascular sympathetic nerves

Neural control

Beach-JM et al
AJP 275:H1489;1998



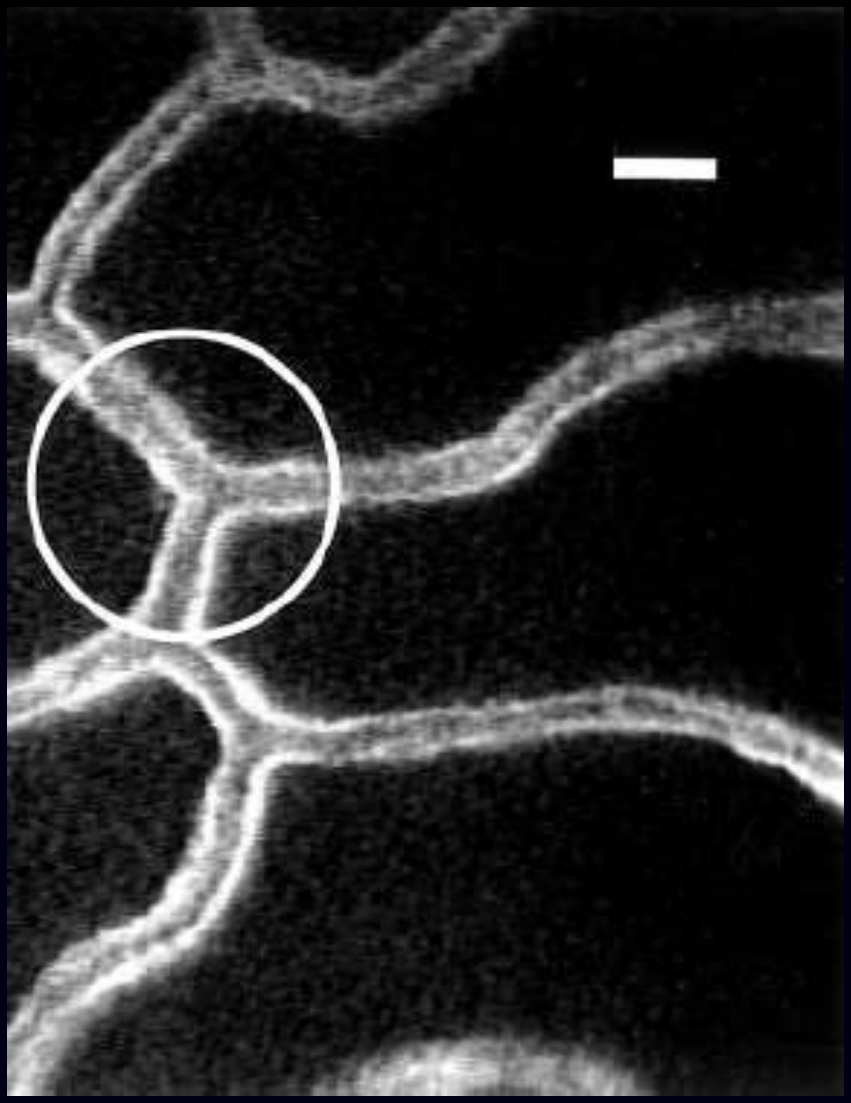


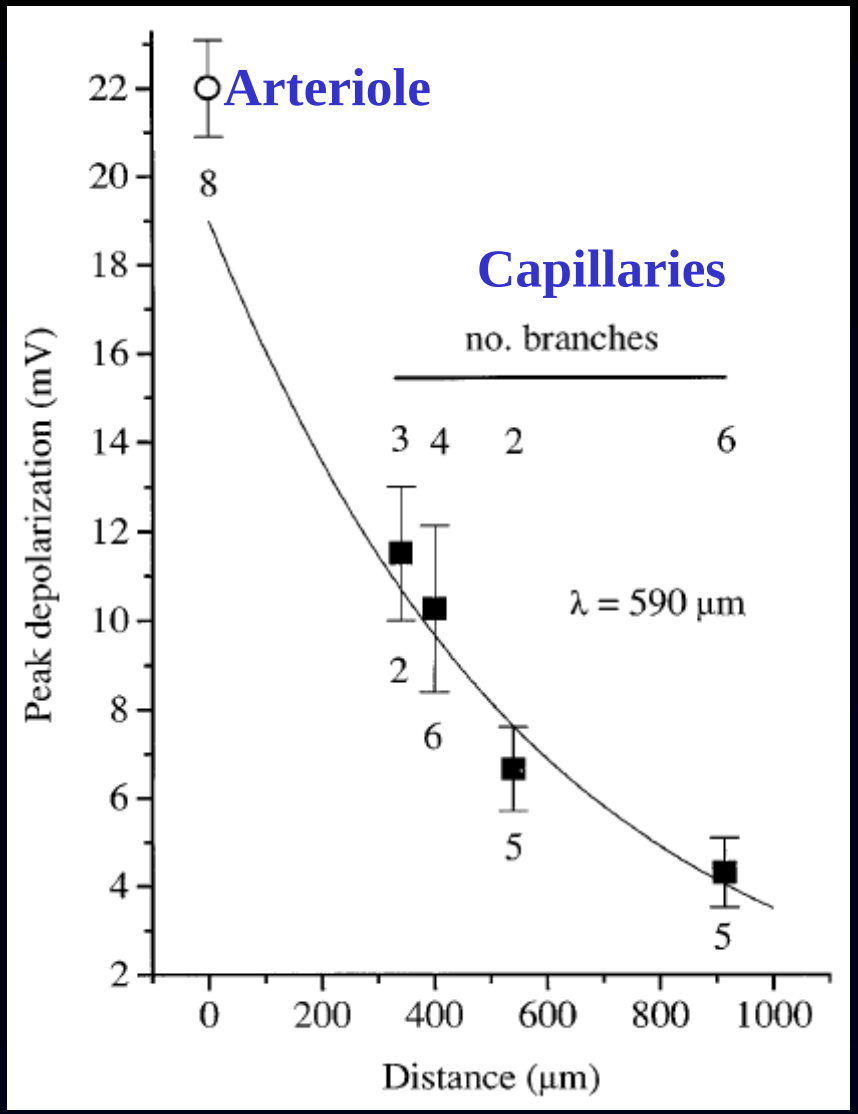
Forward and backward transmission in response to focal stimulation (Ach of PE)

Fluorescence reflects activation

Neural control

Beach-JM et al
AJP 275:H1489;1998

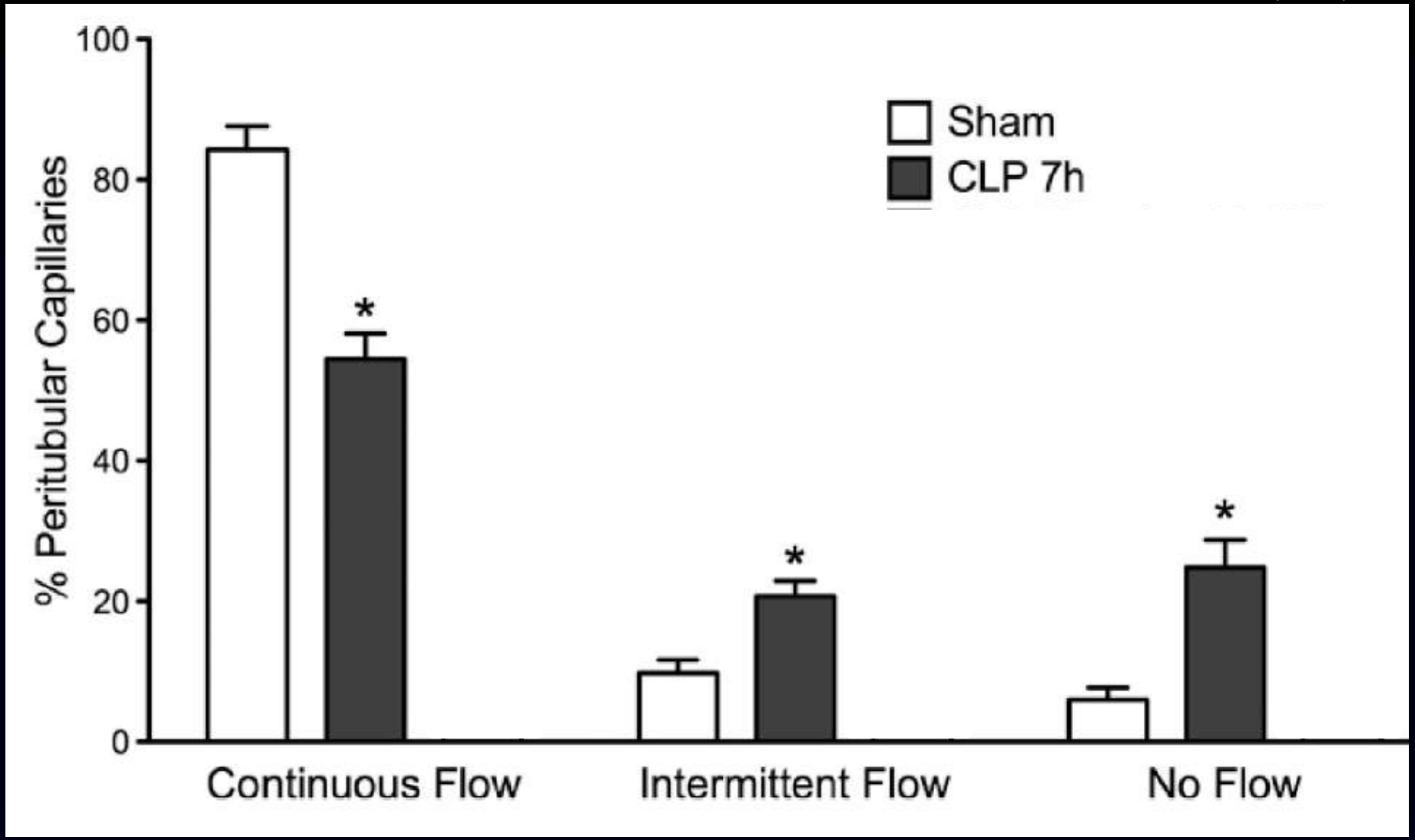




MICROVASCULAR ALTERATIONS IN EXPERIMENTAL SEPSIS

IMPAIRED RENAL MICROCIRCULATION IN EXPERIMENTAL SEPSIS

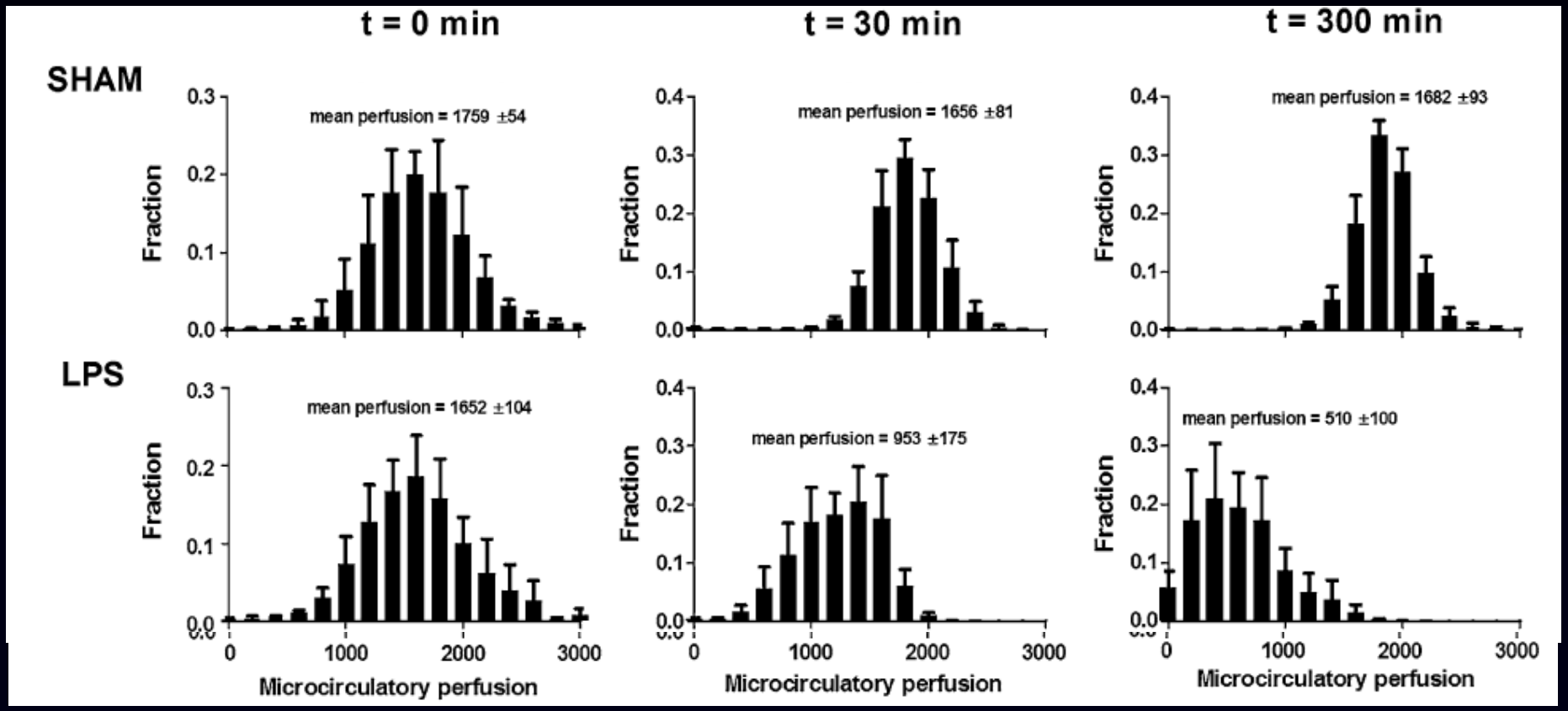
Wang Z et al
Shock 35,141;2011



Mice / CLP **LPS**

Increase heterogeneity of renal perfusion in sepsis

Legrand et al
ICM 2011



Rats
LPS

EXPERIMENTAL STUDIES IN SEPSIS

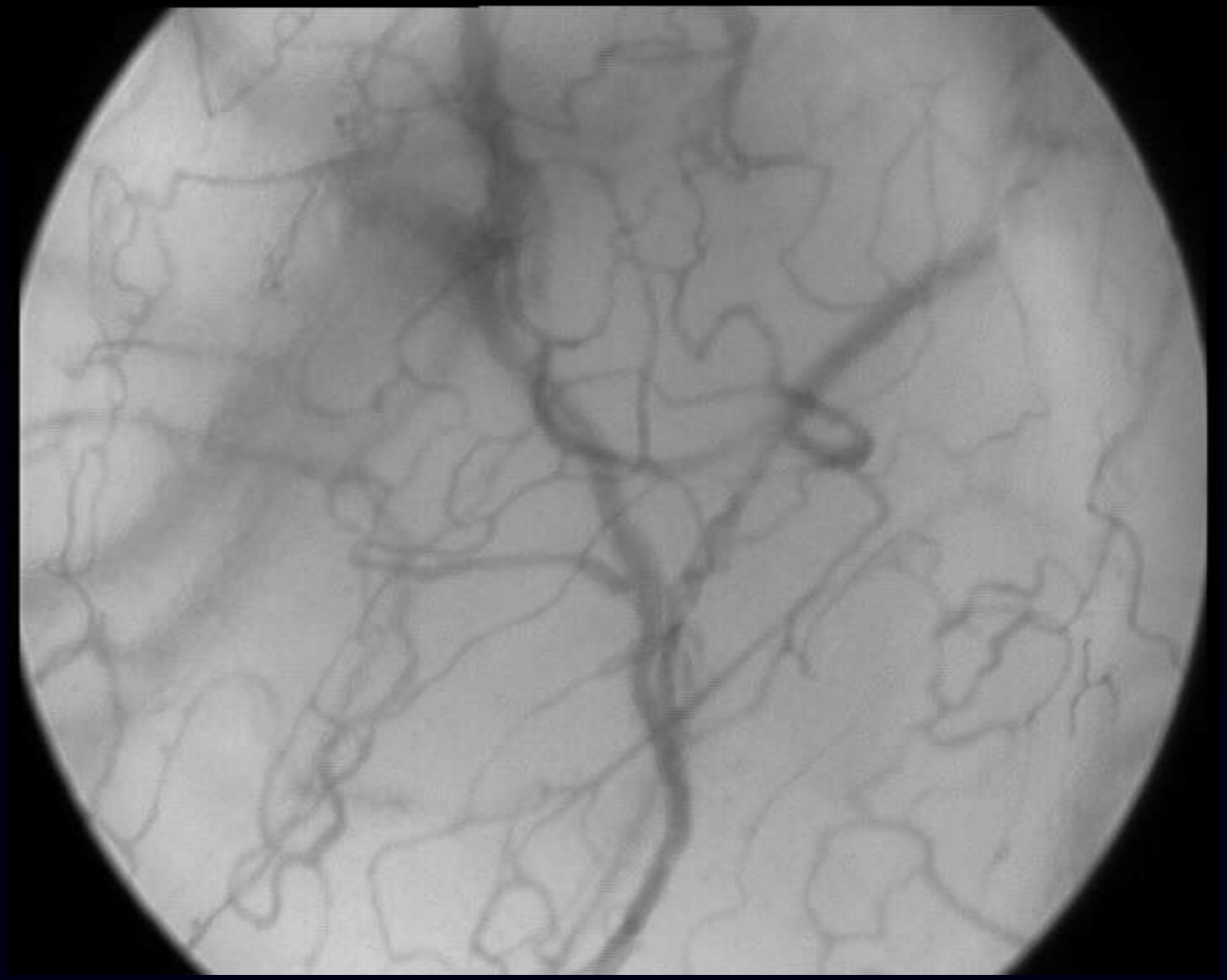
Branemark et Urbaschek Angiology 18:667;1967
Lam et al. JCI 94: 2077; 1994
Farquhar et al. J Surg Res 61: 190; 1996
Madorin et al CCM 27:394;1999
Ellis et al AJP 282:H156;2002
Verdant et al CCM 37:2875;2009
Secor et al ICM 2010

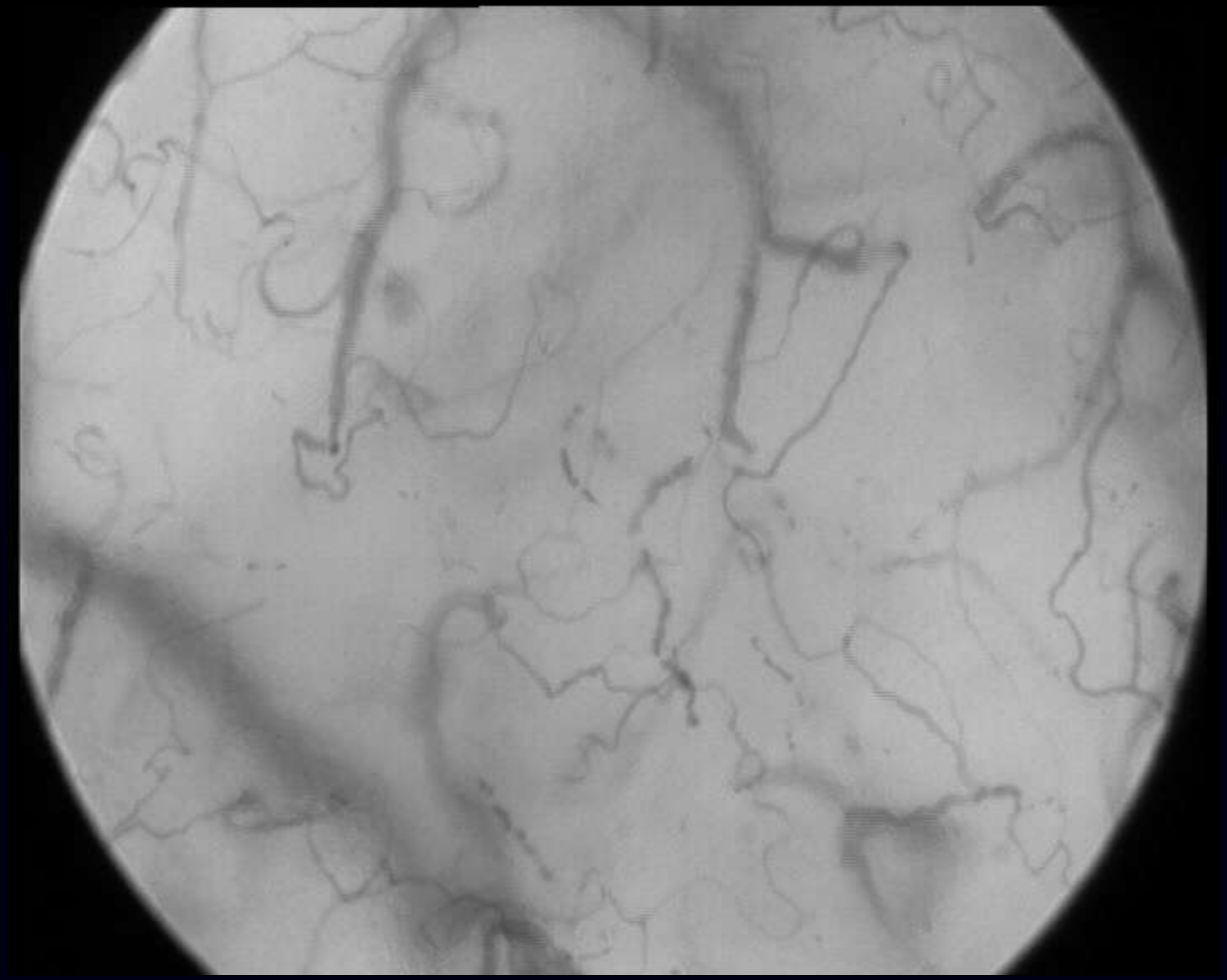
- Microvascular blood flow alterations are frequent
  - decreased vascular density
  - absent or intermittent flow in capillaries
  - heterogeneity between areas

Different models (LPS, CLP, live bacteria,…)
Various species (rats, mice, hamsters, pigs, sheep…)
Various organs (skin, gut, liver, lung, kidney, heart, brain…)

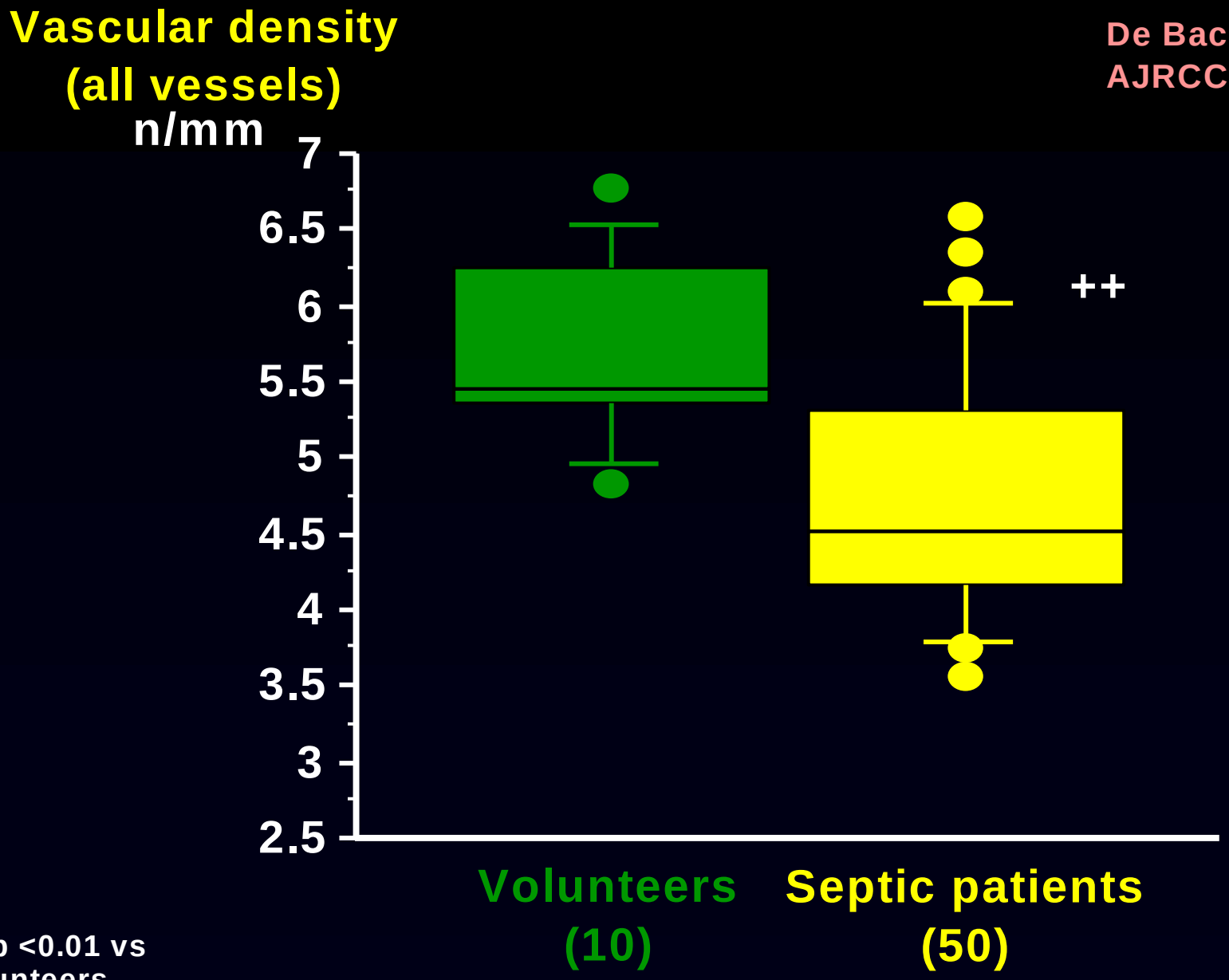
DDB USI

ALSO IN HUMANS ?





De Backer et al
AJRCCM 166:98;2002



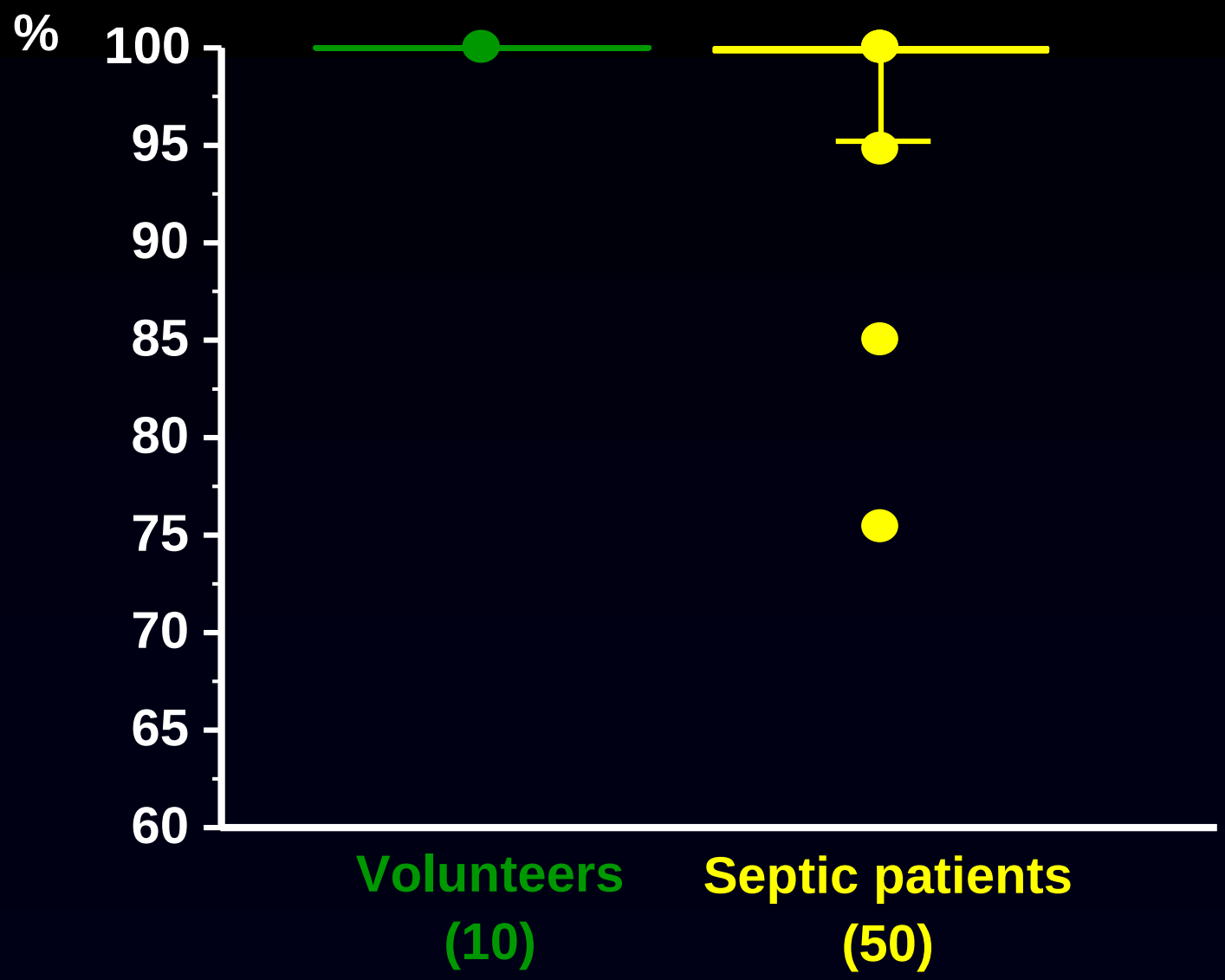
++ p <0.01 vs volunteers

DDB USI

MICROCIRCULATORY ALTERATIONS IN SEPTIC PATIENTS

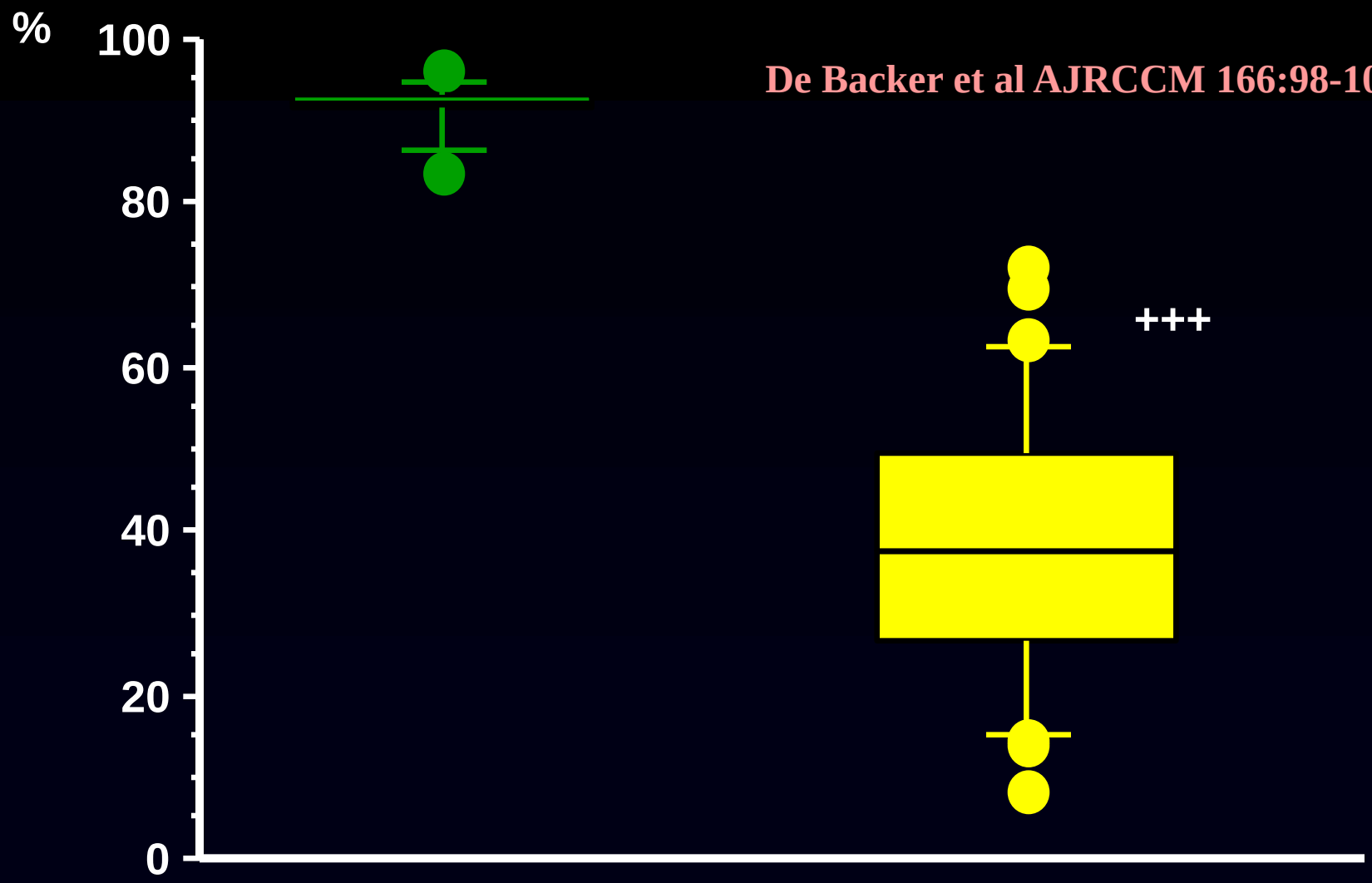
Percentage of vessels perfused (large vessels)

De Backer et al
AJRCCM 166:98;2002



DDB USI

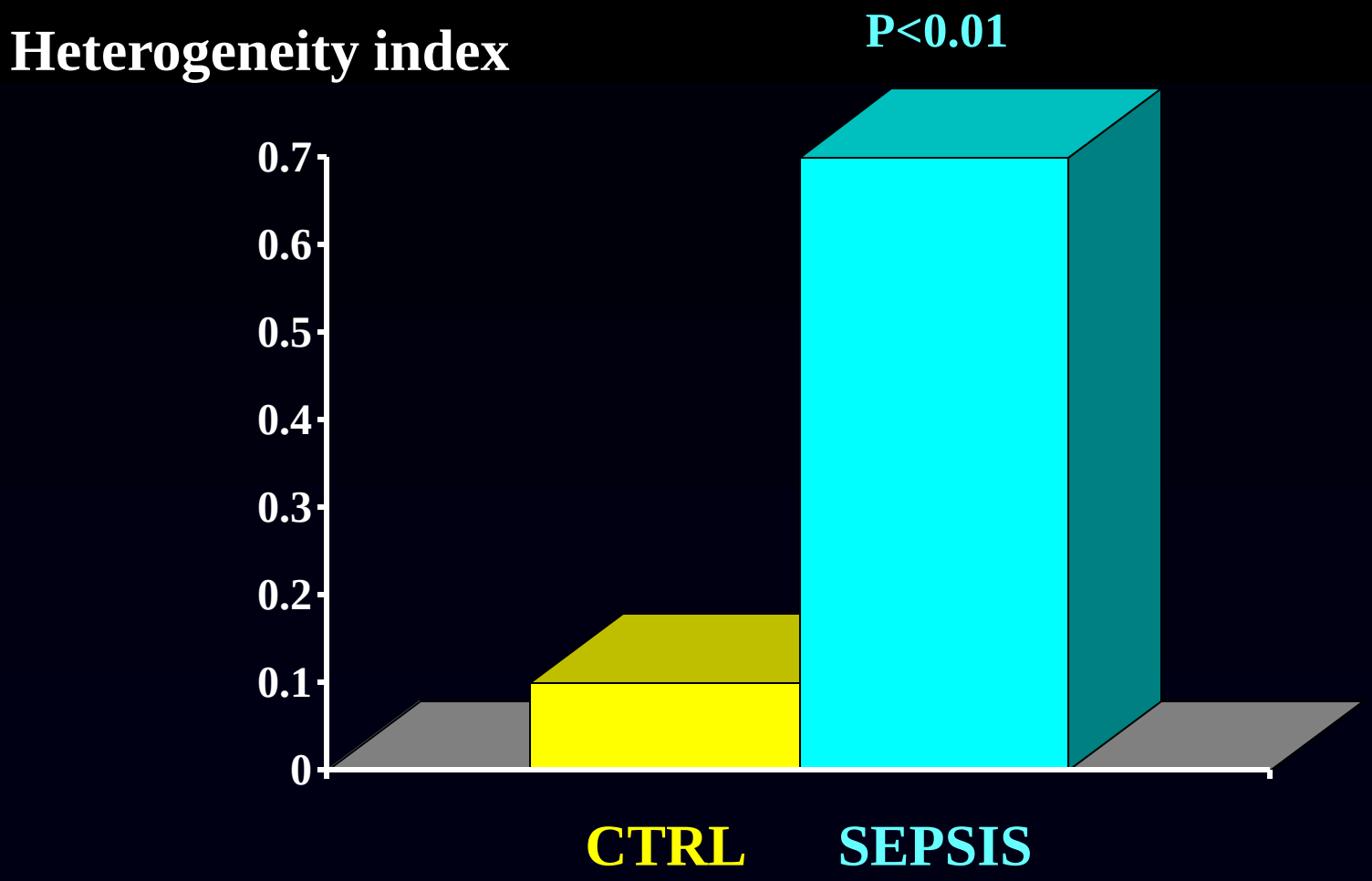
Percentage of vessels perfused (small vessels)



De Backer et al AJRCCM 166:98-104;2002

+++ p <0.001 vs volunteers

Trzeciak et al
Ann Em Med 49:1579;2007

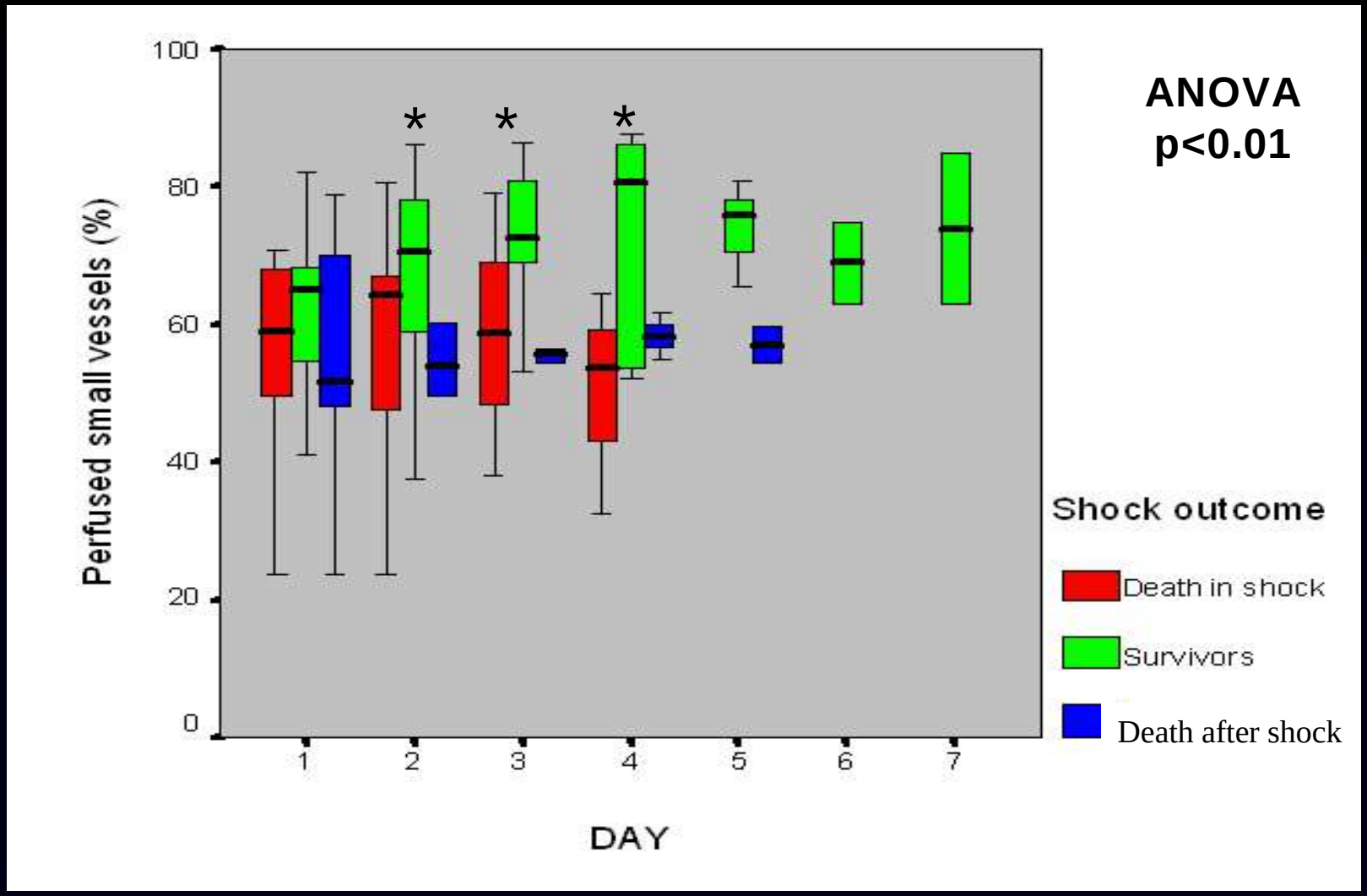


Emergency department

N=26

EVOLUTION OF MICROCIRCULATORY ALTERATIONS IN SEPTIC PATIENTS

Sakr et al
CCM 32:1825;2004



49 pts with septic shock

DDB USI

- De Backer et al AJRCCM 2002
- Spronk et al Lancet 2002
- Sakr et al CCM 2004
- De Backer et al CCM 2006
- De Backer et al CCM 2006
- Creteur et al ICM 2006
- Boerma et al CCM 2007
- Trzeciak et al Ann Emerg Med 2007
- Sakr et al CCM 2007
- Trzeciak et al ICM 2008
- Boerma et al ICM 2008
- Dubin et al Crit Care 2009
- Buchele et al CCM 2009
- Boerma et al CCM 2010
- Ospina et al ICM 2010
- Spanos et al Shock 2010
- Pottecher et al ICM 2010
- Morelli et al Crit Care 2010
- Ruiz et al Crit Care 2010
- Dubin et al J Crit Care 2010
- Morelli et al ICM 2011

Alterations of sublingual microcirculation in patients with sepsis

- **↓ total vascular density**
- **↓ perfusion of capillaries (no flow or intermittent flow)**
- **Preserved venular perfusion**
- **Heterogeneity between areas (close by a few microns)**

Potential mechanisms ?

PATHOPHYSIOLOGY OF MICROVASCULAR ALTERATIONS

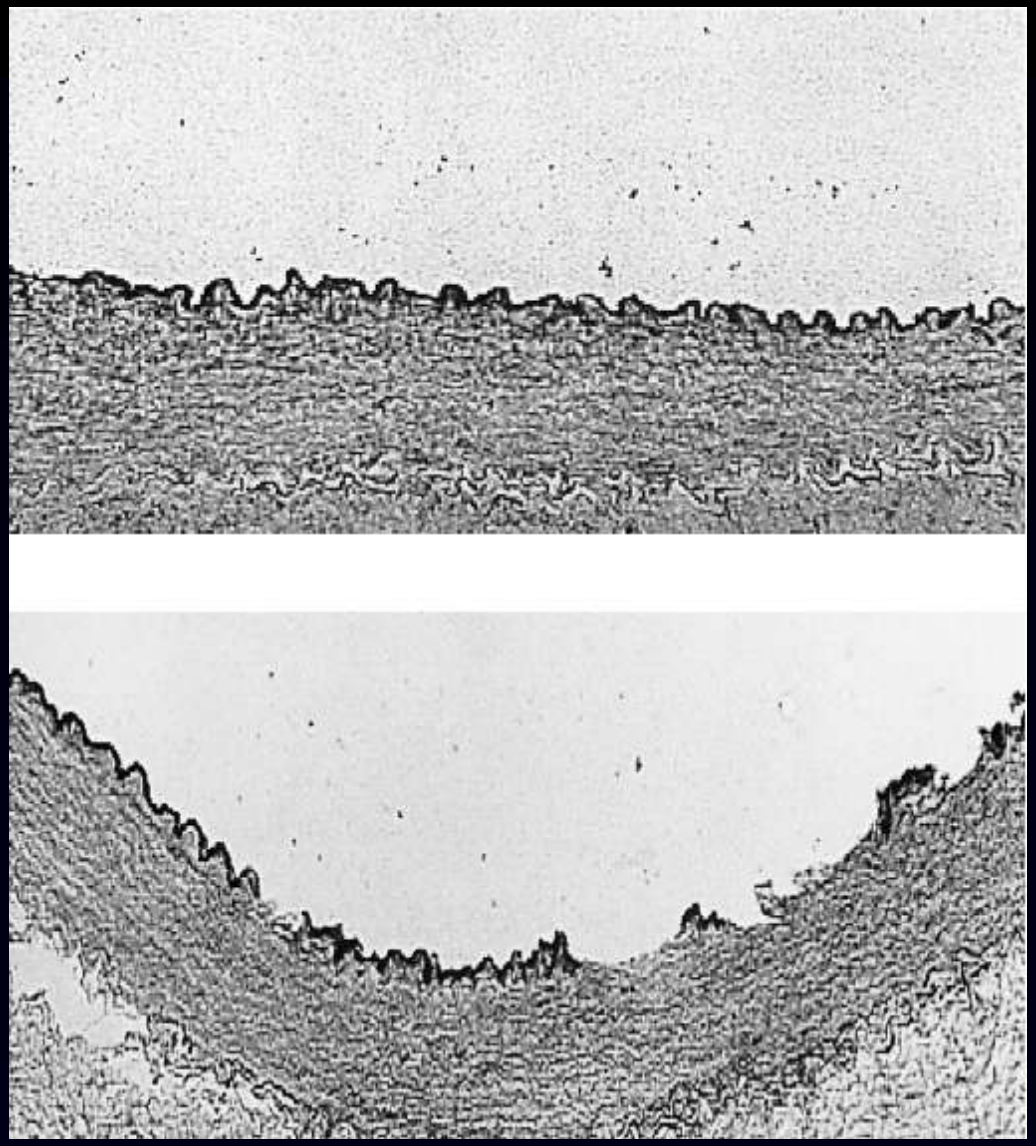
Triggered by inflammatory mediators

TNF **(Vicaut E JCI 87:1537;1991)**

ENDOTHELIAL ALTERATIONS

Leclers J et al
CCM 28:3672;2000

ctrl



5 days
post LPS

25-35%
vessels

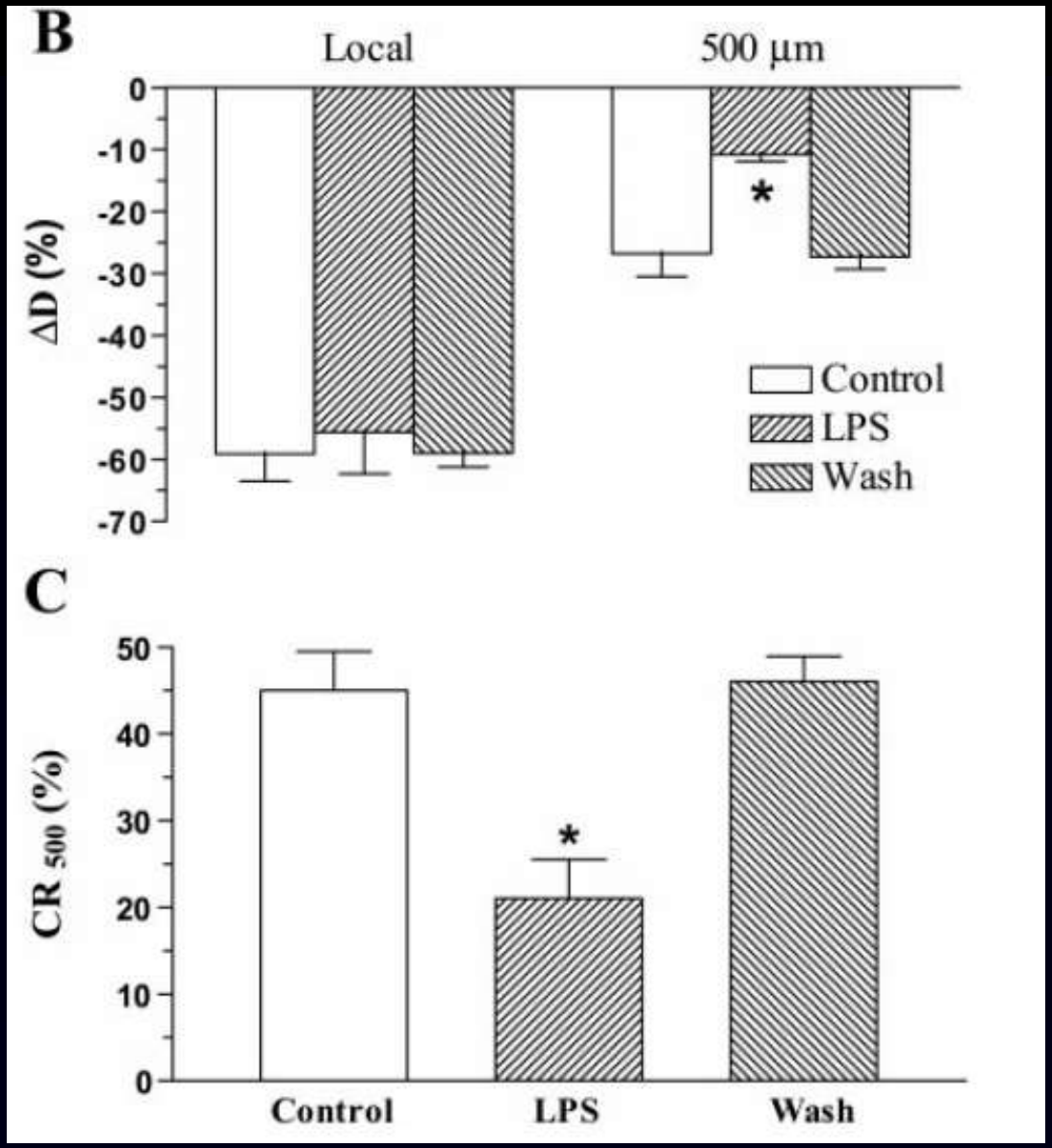
rabbits

Loss of neural control

Tyml-K et al
AJP 281:H1397;2001

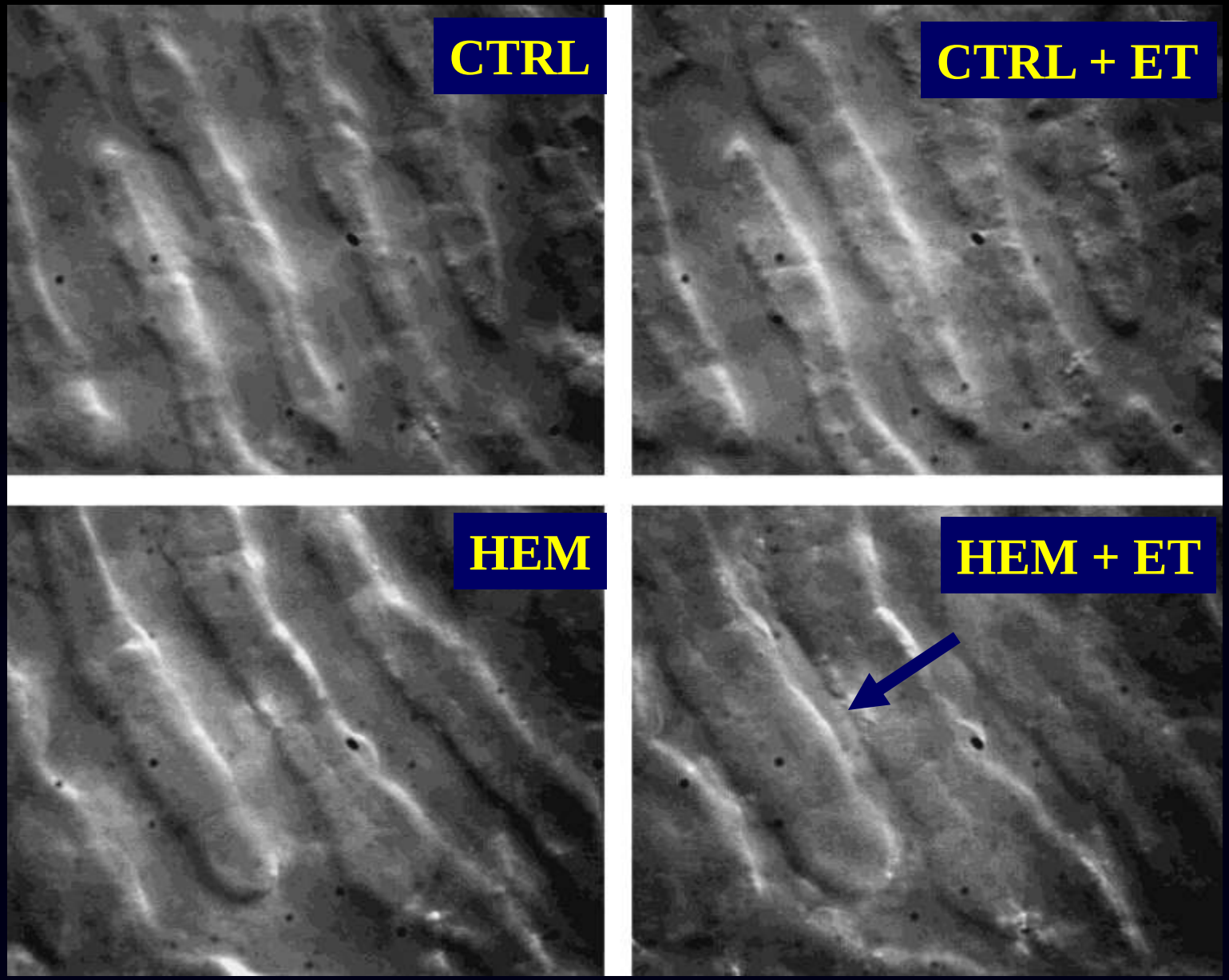
Change in diameter and communication rate (CR500) between 500 µm distant microvessels (retrograde communication)

B: cremaster muscle (mice)
C: Endothelial microlayer



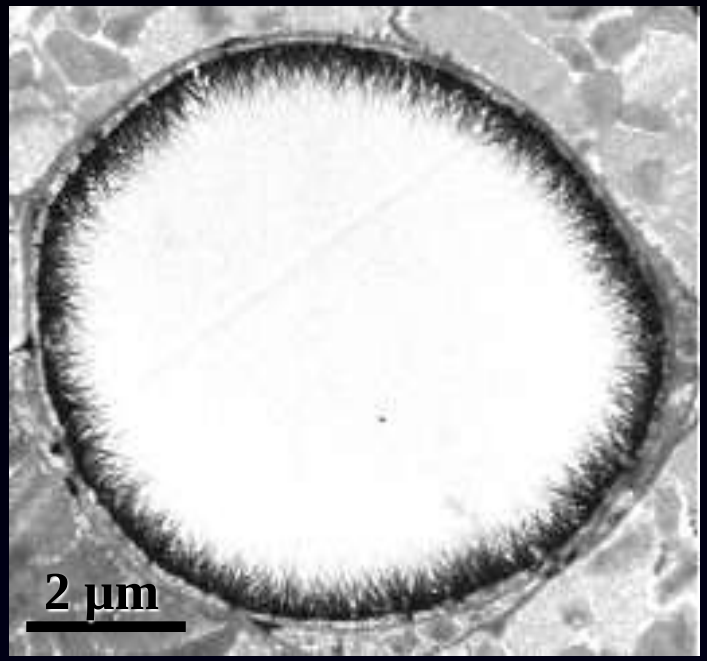
Enhanced response to vasoconstrictor substances

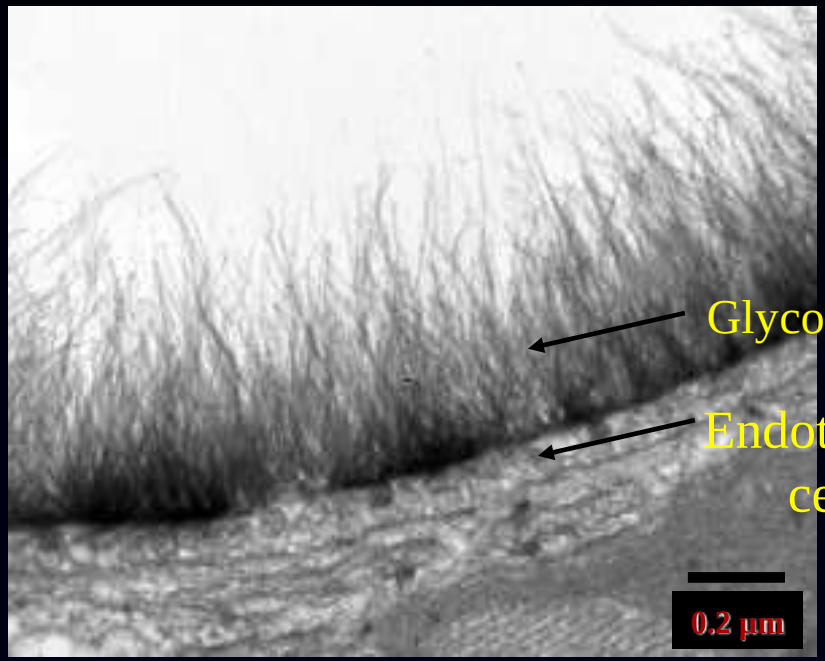
Pannen B et al
AJP 26:180;2001



Rats

GLYCOCALYX ALTERATIONS

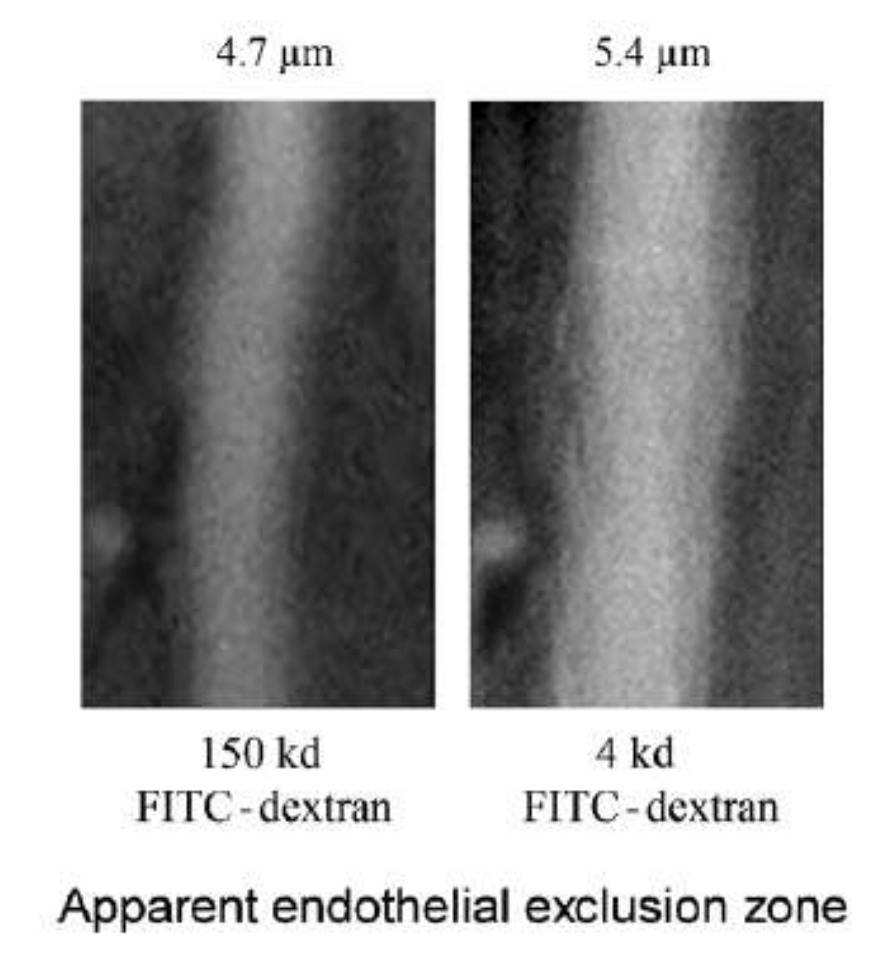


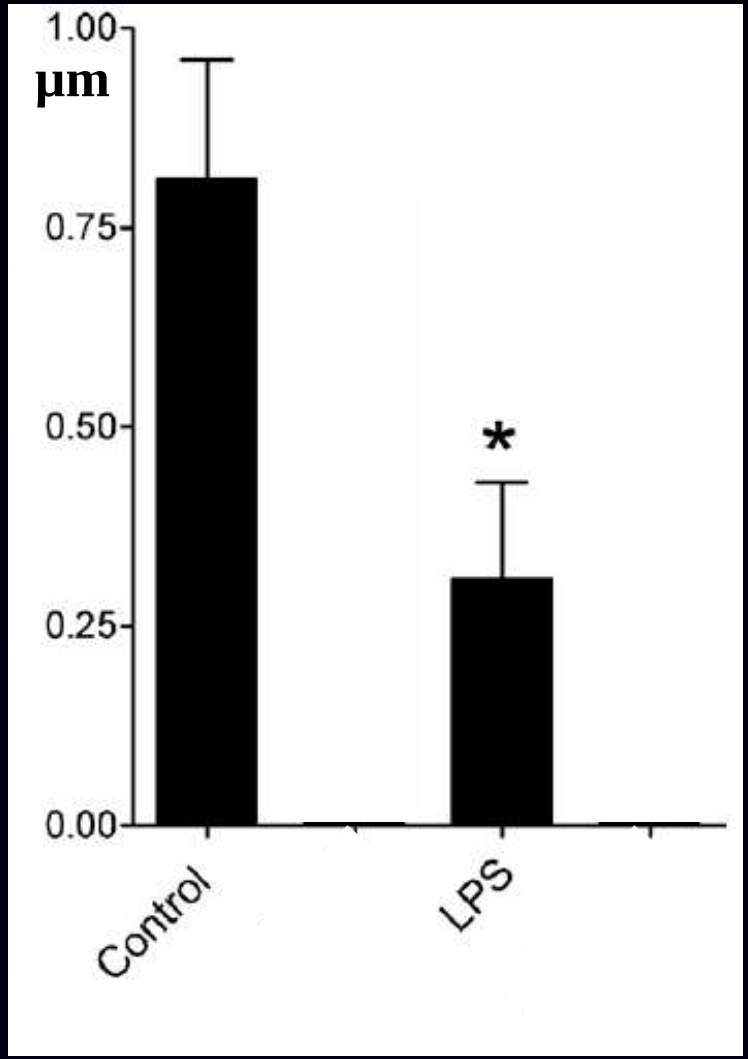


From C Ince

Role of glycocalyx in microvascular alterations

Marechal X et al
Shock 29:572;2008

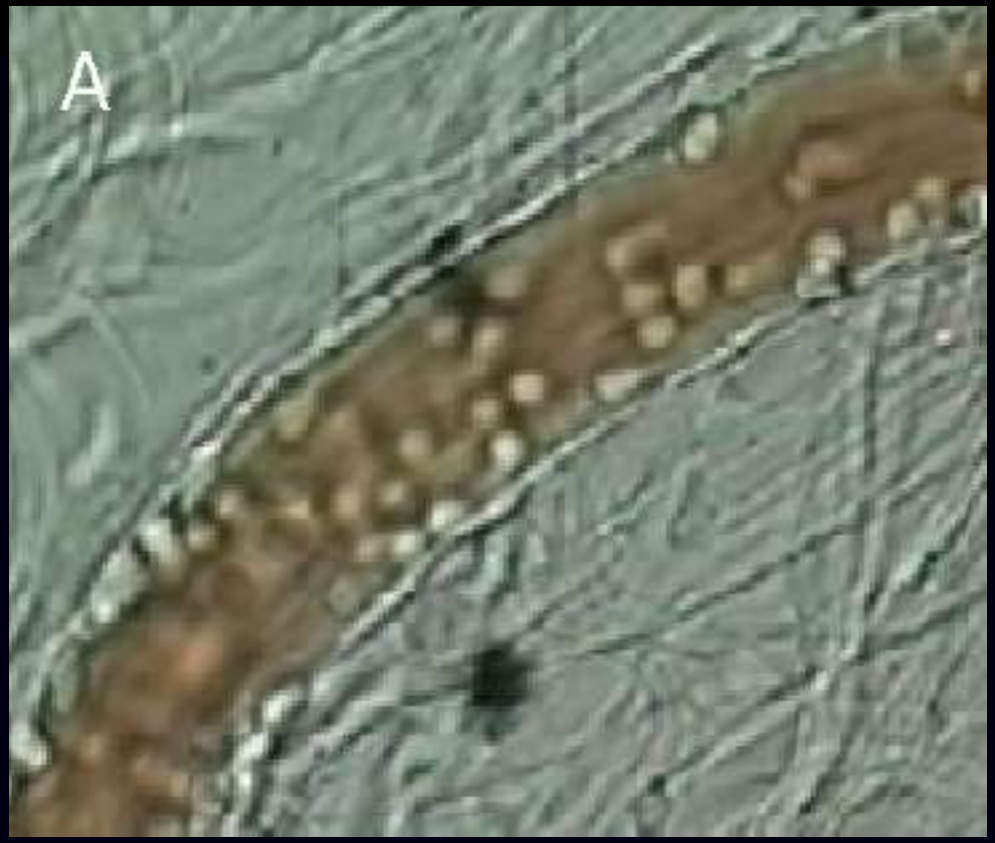




Rats, ileum

Hypoxia promotes leukocyte adhesion

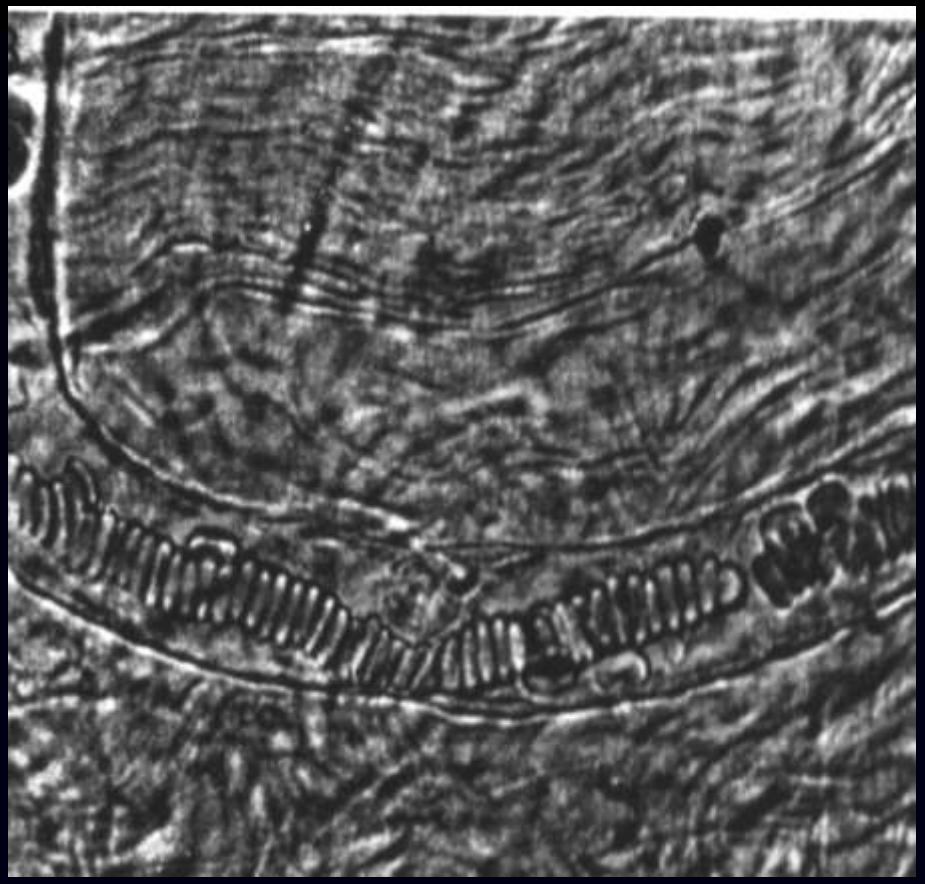
Bartolome-S et al
Shock 29:384; 2008



Mesentery
Rats
Hypoxia (FiO2 0.1)

Altered Red blood cell deformability

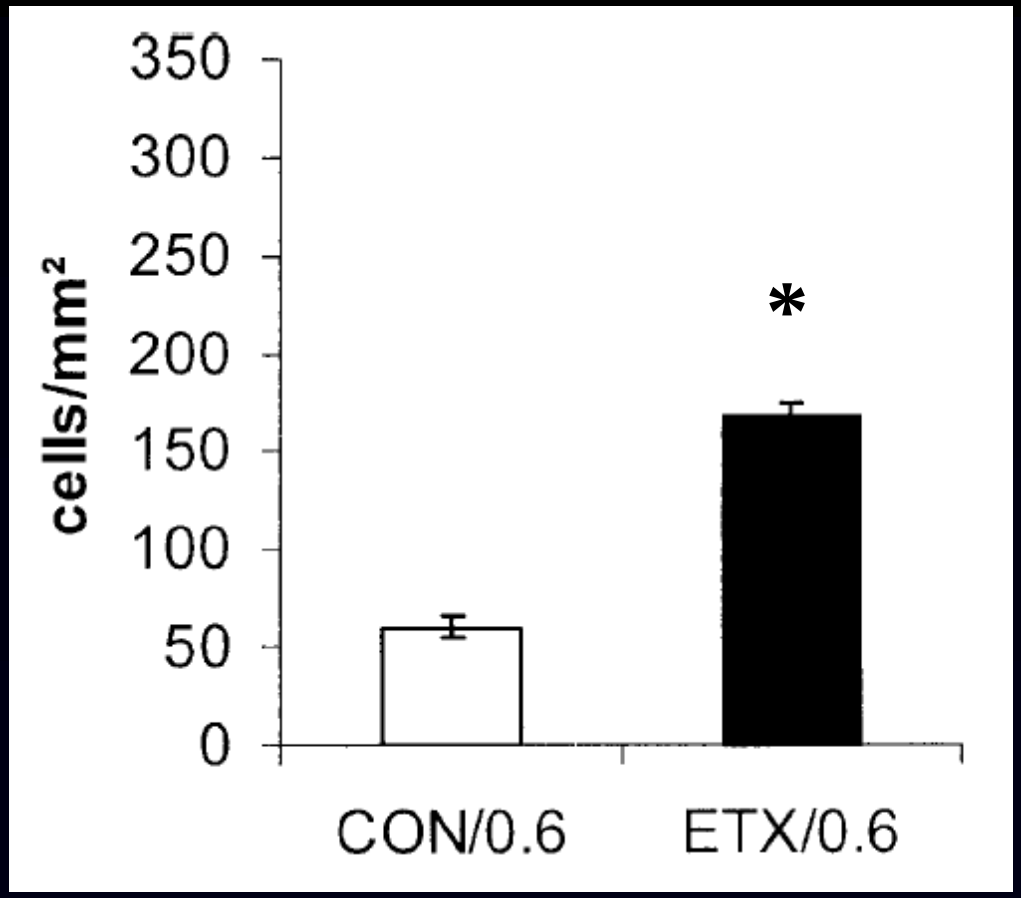
McCuskey et al
Cardiovasc Res
32:752:1996



Rouleau formation

ETX promotes adhesion of RBC to endothelium

Eichelbronner et al
ICM 29:709;2003



HUVEC

Microthrombi ?

Croner et al
Crit Care 10:R15;2006

Intravital microscopy measurements in postsinusoidal venules and liver sinusoids

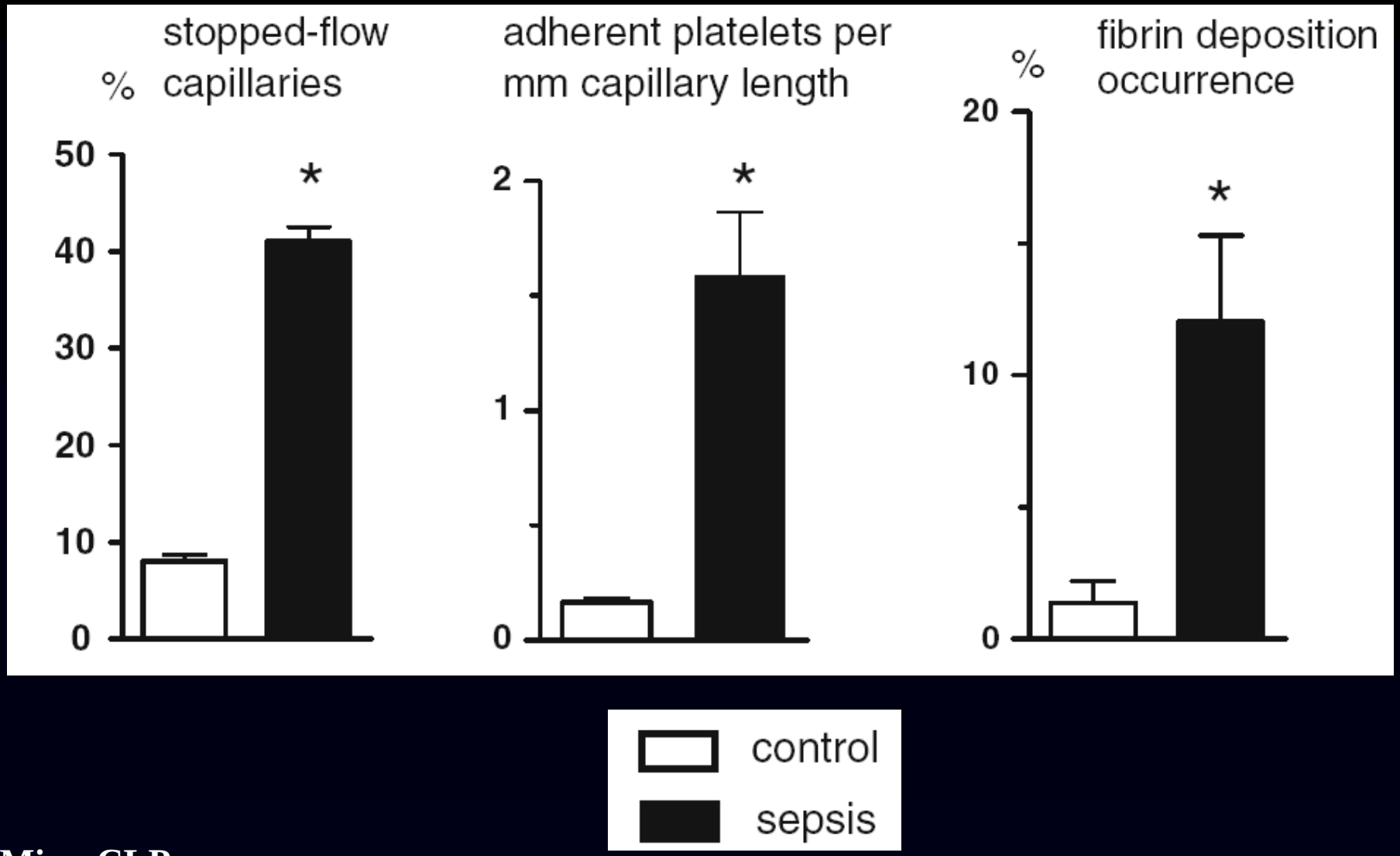
Measurement	Time point during intravital microscopy					
	0 h	1 h	3 h	5 h	10 h	20 h
MEV (mm/s)						
Venules	0.81 (0.03)	0.75 (0.03)	0.75 (0.04)	0.83 (0.03)	0.49 (0.02)[a]	0.40 (0.02)[a]
Sinusoids	0.39 (0.02)	0.38 (0.03)	0.29 (0.01)[a]	0.28 (0.02)[a]	0.25 (0.02)[a]	0.25 (0.02)[a]
Roller (mm² ES)						
Leukocytes	48 (16)	150 (36)	221 (49)[a]	111 (21)	222 (54)[a]	269 (69)[a]
Platelets	6 (4)	36 (7)[a]	37 (9)[a]	47 (11)[a]	38 (6)[a]	43 (9)[a]
Sinusoid diameter (µm)	8.00 (0.40)	7.90 (0.30)	7.20 (0.30)	7.30 (0.50)	7.00 (0.30)[a]	6.50 (0.30)[a]
Thrombotic sinusoids (%)	0 (0)	0 (1)	1 (1)	5 (1)[a]	8 (1)[a]	11 (2)[a]

Values are means with standard error of the mean in parentheses. [a]$p < 0.05$ versus 0 h. ES, endothelial surface; MEV, mean erythrocyte velocity.

Vasoconstriction
Platelet/WBC interaction with endothelium
Microthrombi not frequent

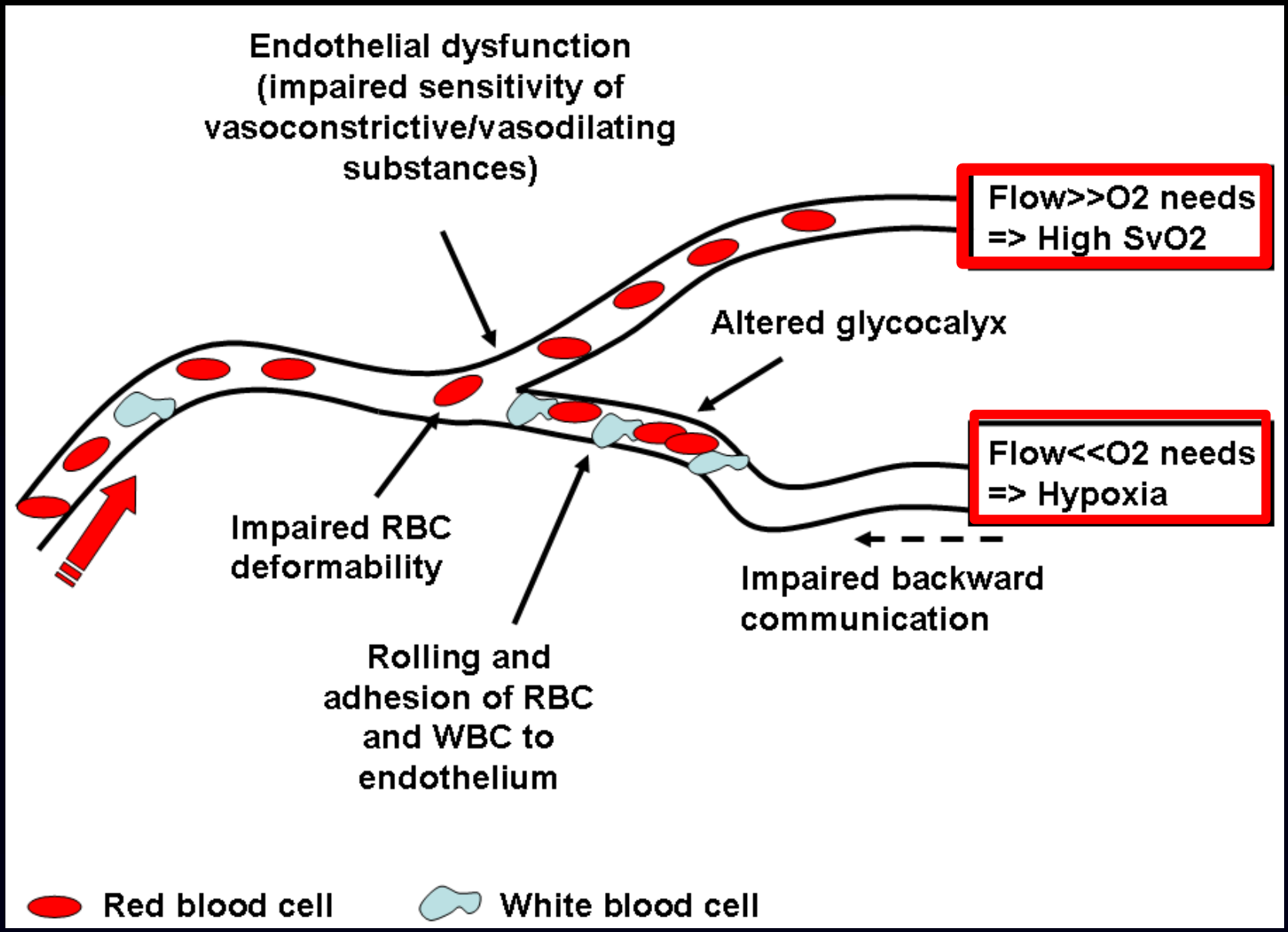
Rats, CLP

Secor et al
ICM 36:1928; 2010



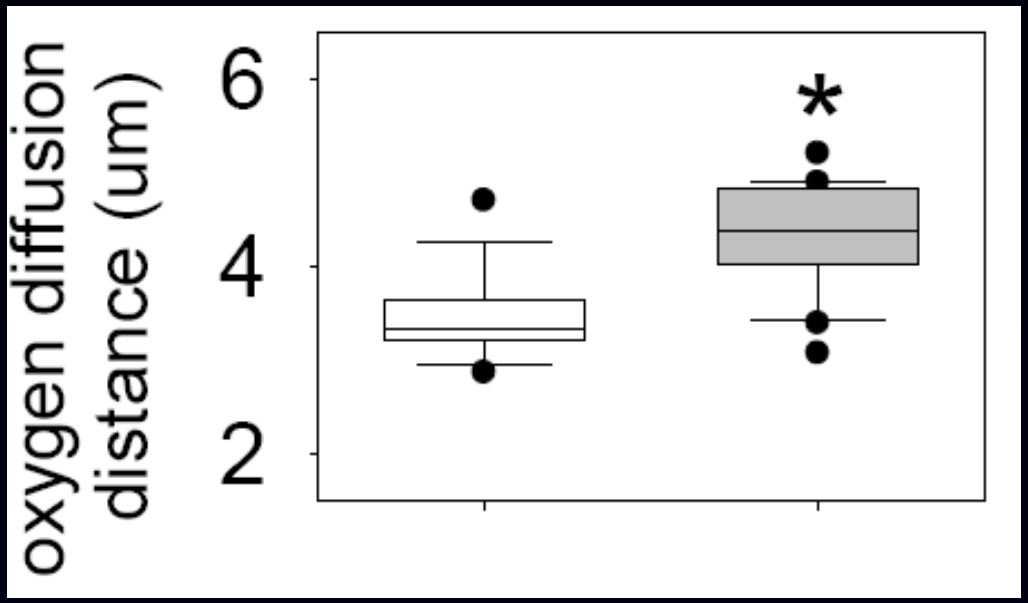
Mice, CLP

De Backer et al
Annals Intensive Care 2011



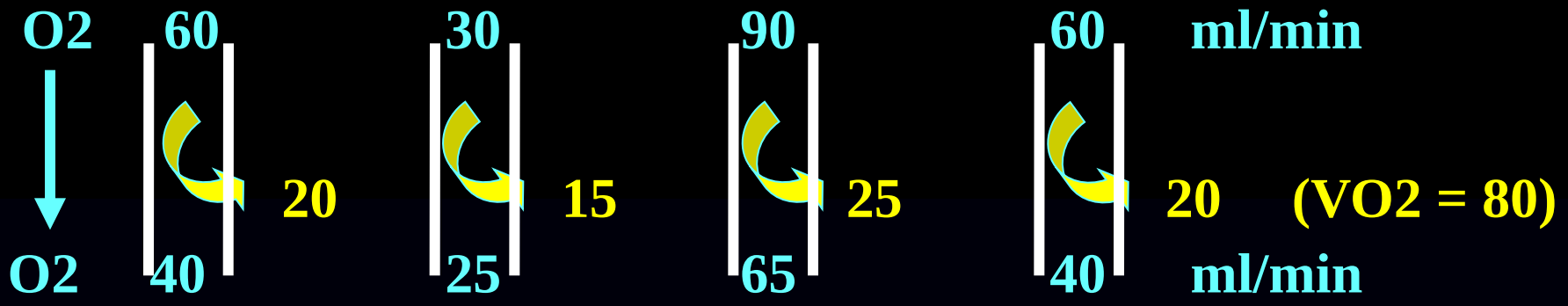
Consequences…

Bateman et al
AJP 293/H448;2007



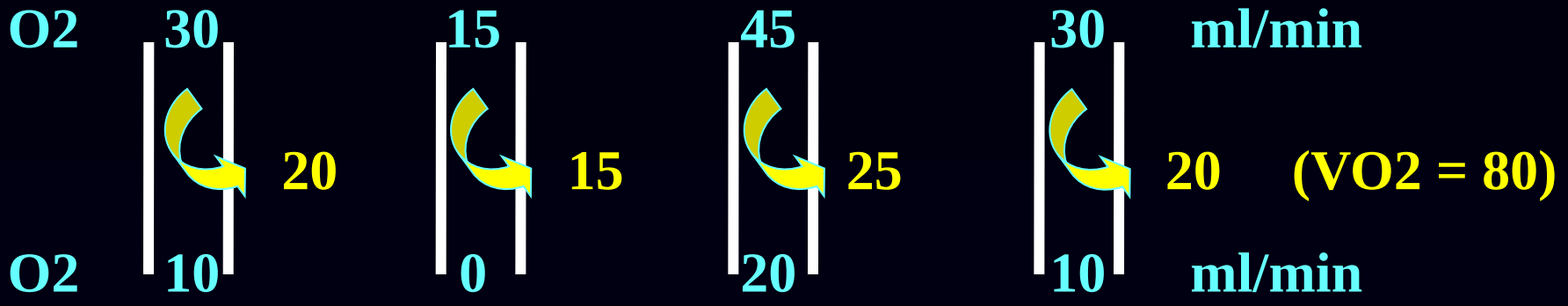
Cardiomyocytes rats

Normal moderately heterogenous (and adapted) flow



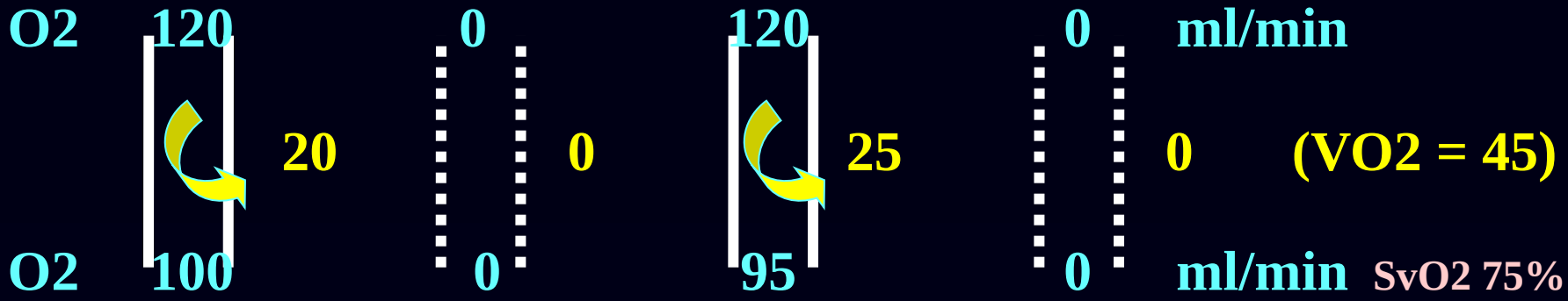
SvO2 71%

Low but relatively homogenous flow



SvO2 33%

Increased heterogeneity in flow



SvO2 75%

HOW TO TREAT MICROVASCULAR ALTERATIONS?

De Backer et al
AJRCCM 166:98-104;2002

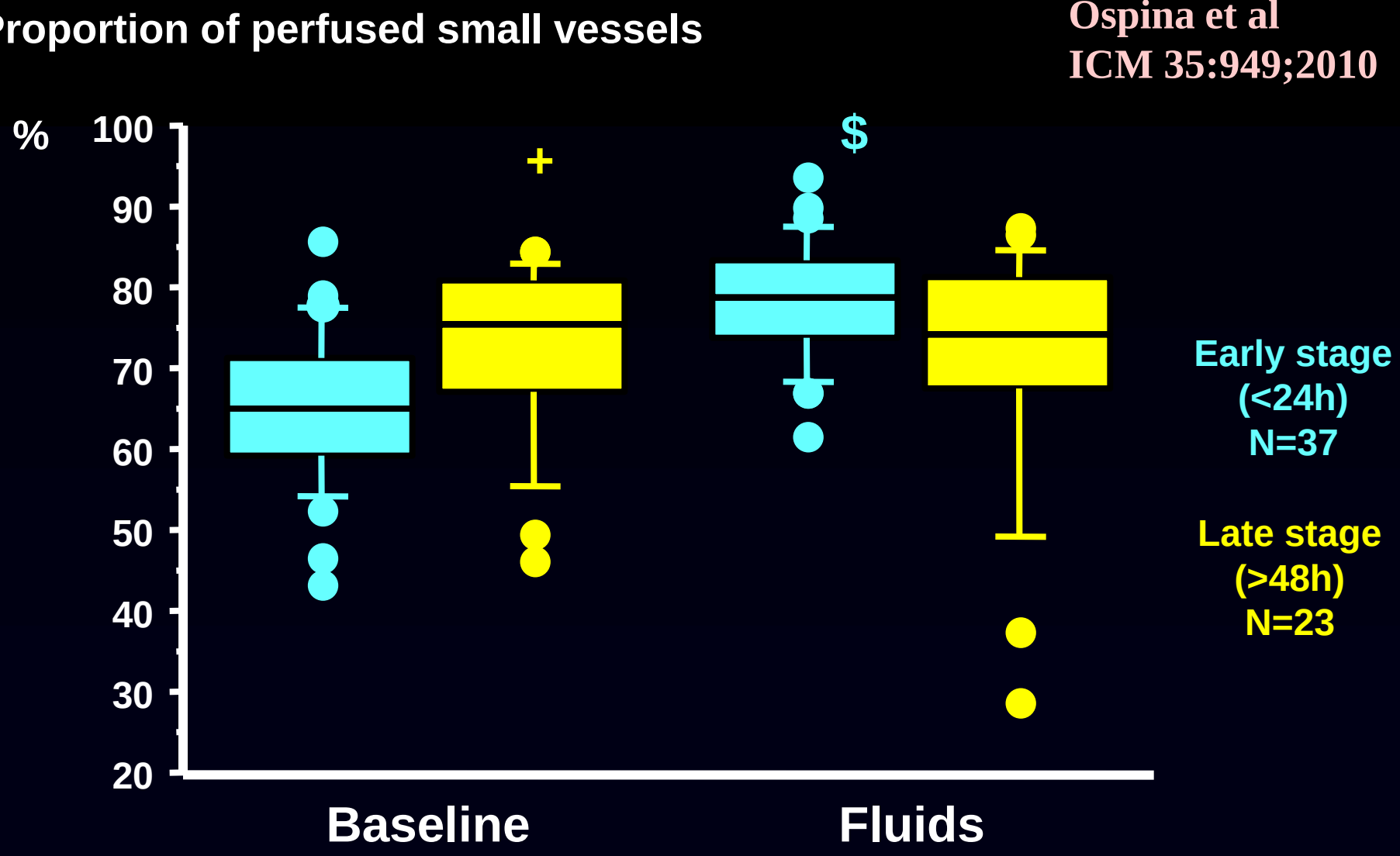
Spronk et al
Lancet 360:1395;2002

Trzeciak et al
Ann Em Med 49:1579;2007

- Decreased total vascular density
- Decreased perfusion of capillaries (no flow or intermittent flow)
- Preserved venular perfusion
- Heterogeneity between areas (close by a few microns)

Therapy should aim at recruiting the microcirculation more than at increasing flow

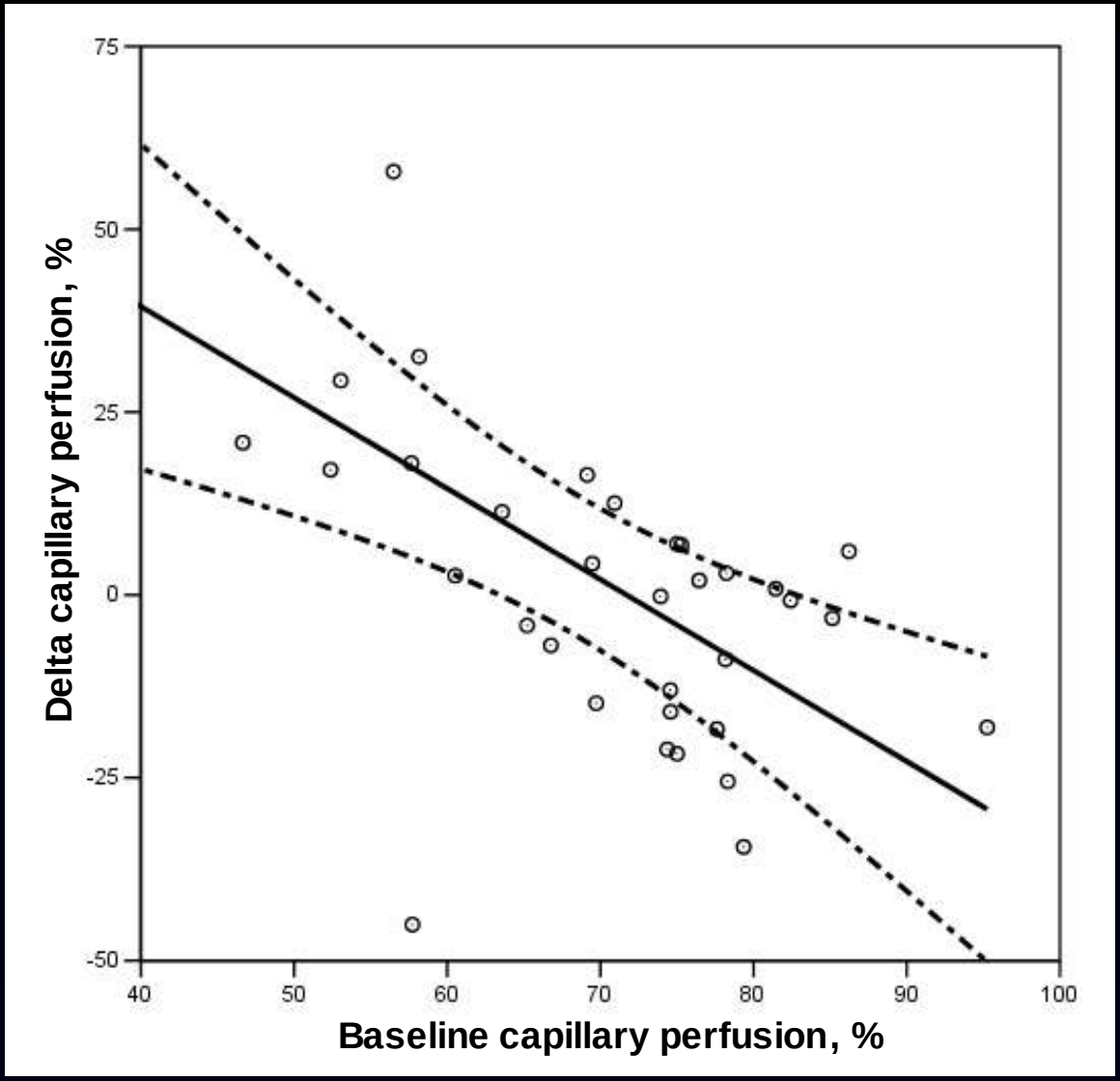
Microvascular effects of fluid challenge in patients with septic shock



$ p<0.01 fluids vs baseline and + p<0.01 late vs early

EFFECTS OF RED BLOOD CELL TRANSFUSIONS

Sakr et al
CCM 35:1639;2007

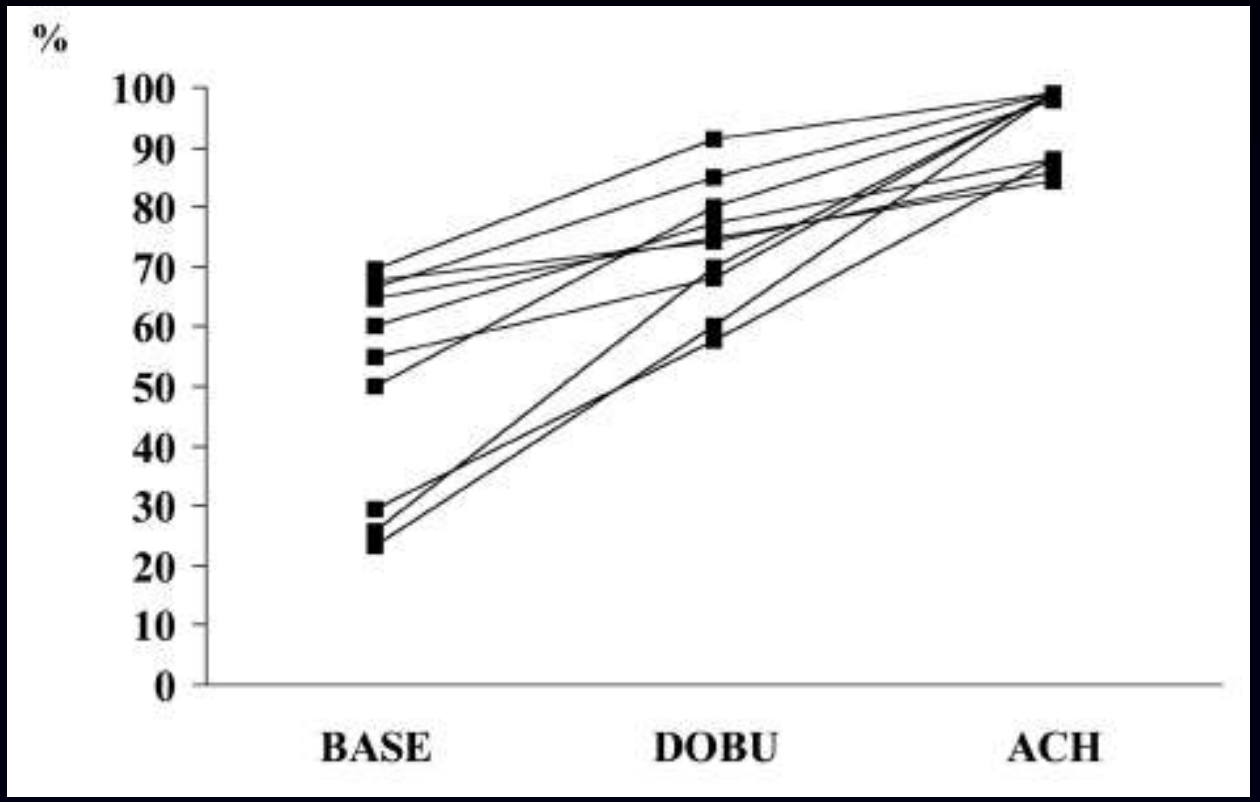


N=35

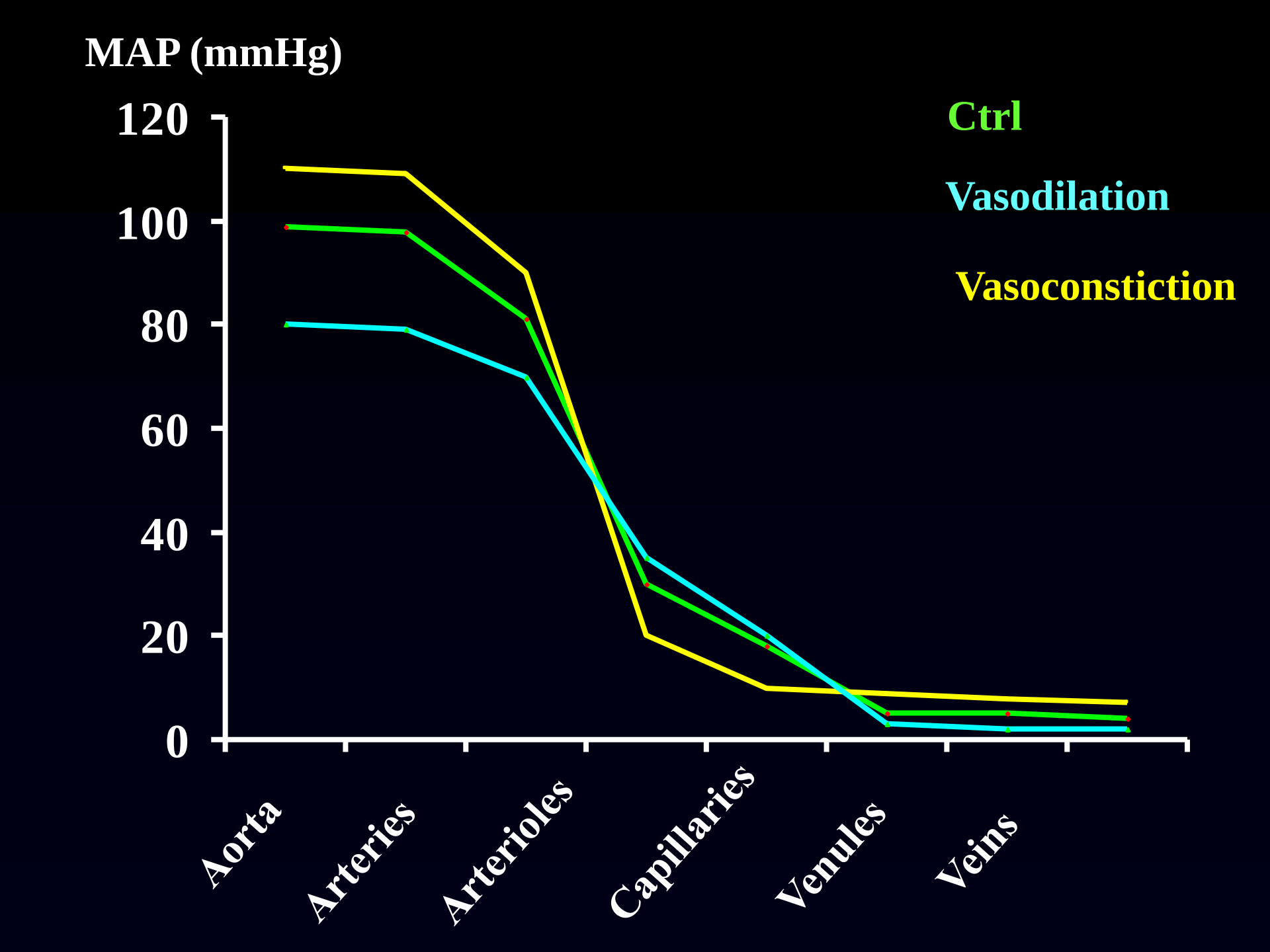
Dobutamine 5 mcg/kg.min

De Backer et al
CCM 34:403;2006

Capillary Perfusion

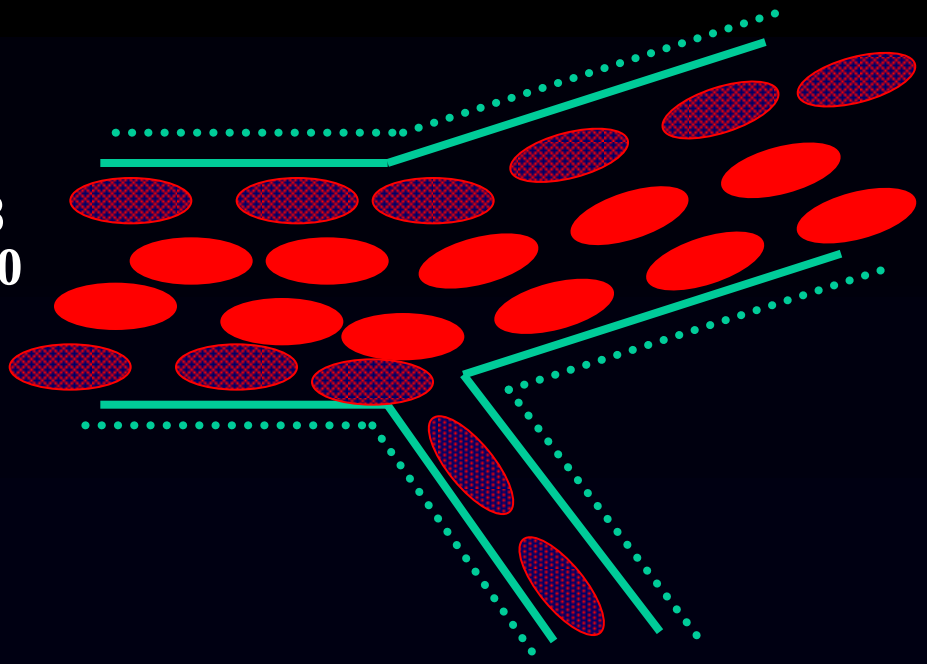


21 patients in septic shock


MAP (mmHg)
120
100
80
60
40
20
0
Ctrl
Vasodilation
Vasoconstiction
Aorta
Arteries
Arterioles
Capillaries
Venules
Veins

Heterogeneity of Hct / PO2 at branchpoints

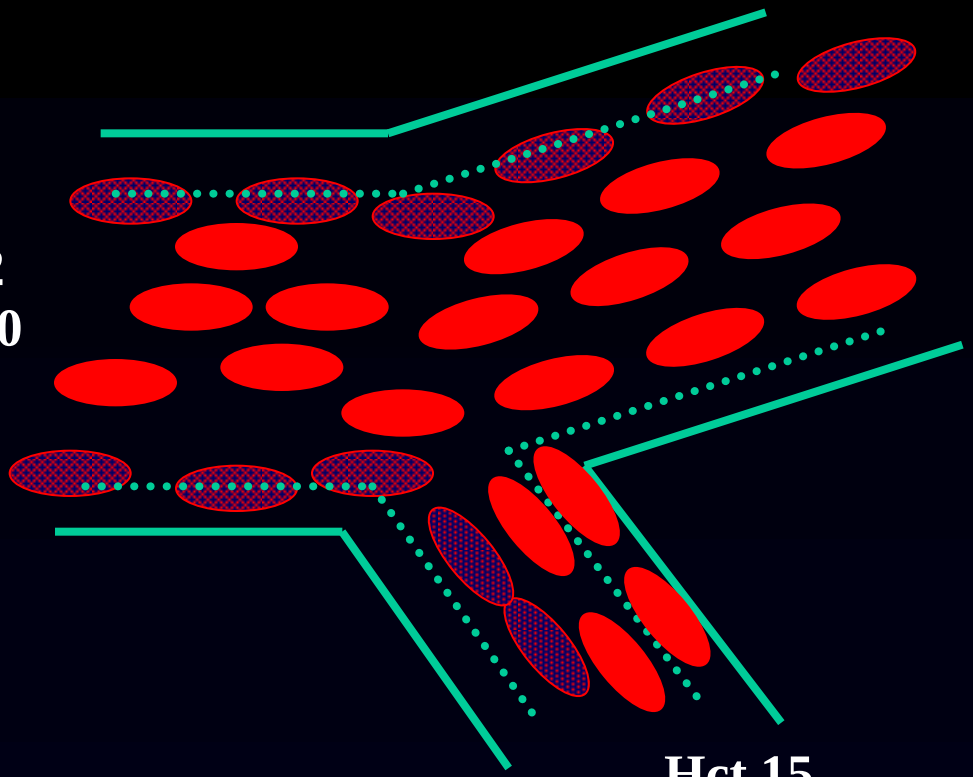
Impact of vasoconstriction



Decrease in Hct with vasoconstriction (especially in small vessels)

Heterogeneity of PO2 at branchpoints

Impact of vasodilation



Hct 32
PO2 60

Hct 32
PO2 60

Hct 15
PO2 55

Increase in Hct with vasoconstriction (especially in small vessels)

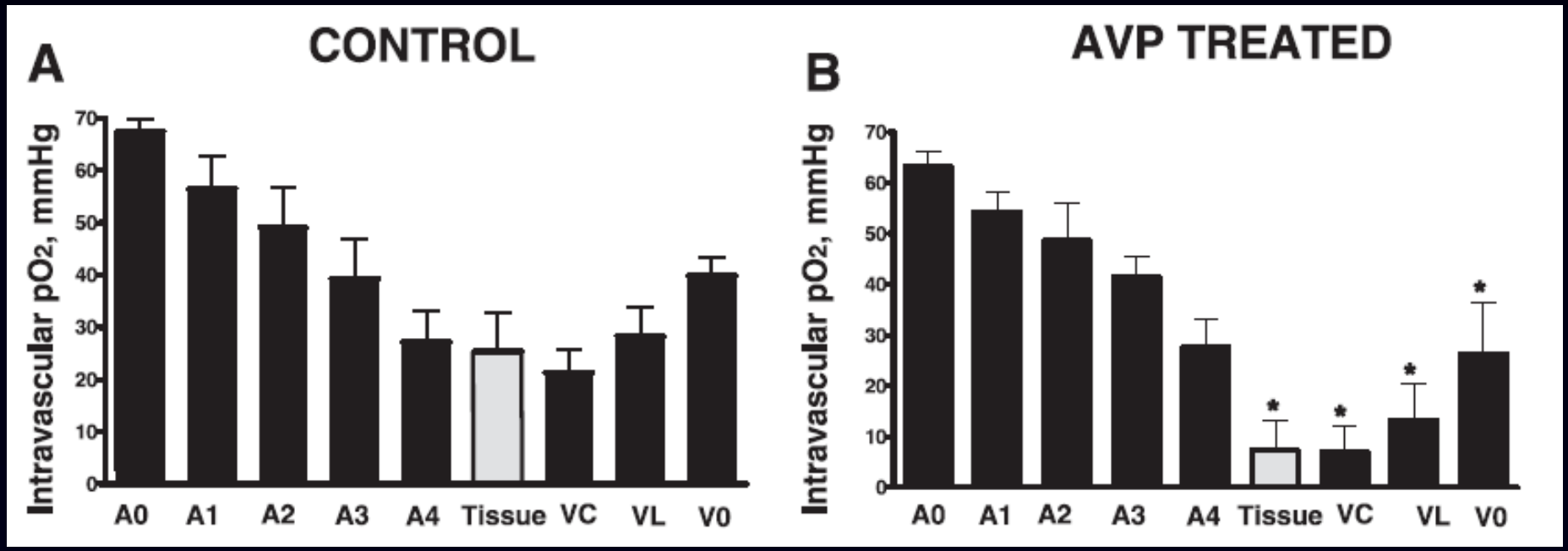
Detrimental effects in control conditions

Hamster, control condition

Friesenecker et al
Crit Care 10:R75;2006

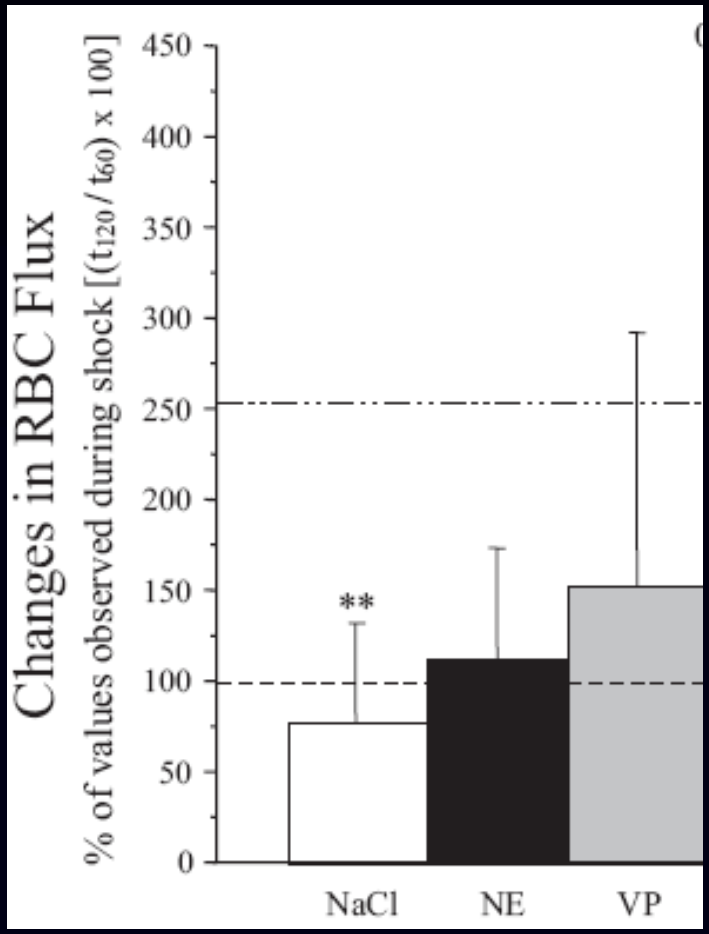
RBC velocity (mm/s)	NE[a]	1.7 ± 0.3 →	1.3 ± 0.3
	AVP[a]	1.5 ± 0.3 →	1.1 ± 0.1
Arteriolar BF (10^{-4} × mm × μm^2/s)	NE[a]	1.3 ± 1.4 →	0.4 ± 0.3
	AVP[a]	1.2 ± 0.9 →	0.5 ± 0.3

Friesenecker et al
AJP 287:H1792;2004



Impact of vasopressors on the microcirculation (Norepinephrine vs Vasopressine)

Nakajima et al
CCM 34:1847;2006



Baseline value

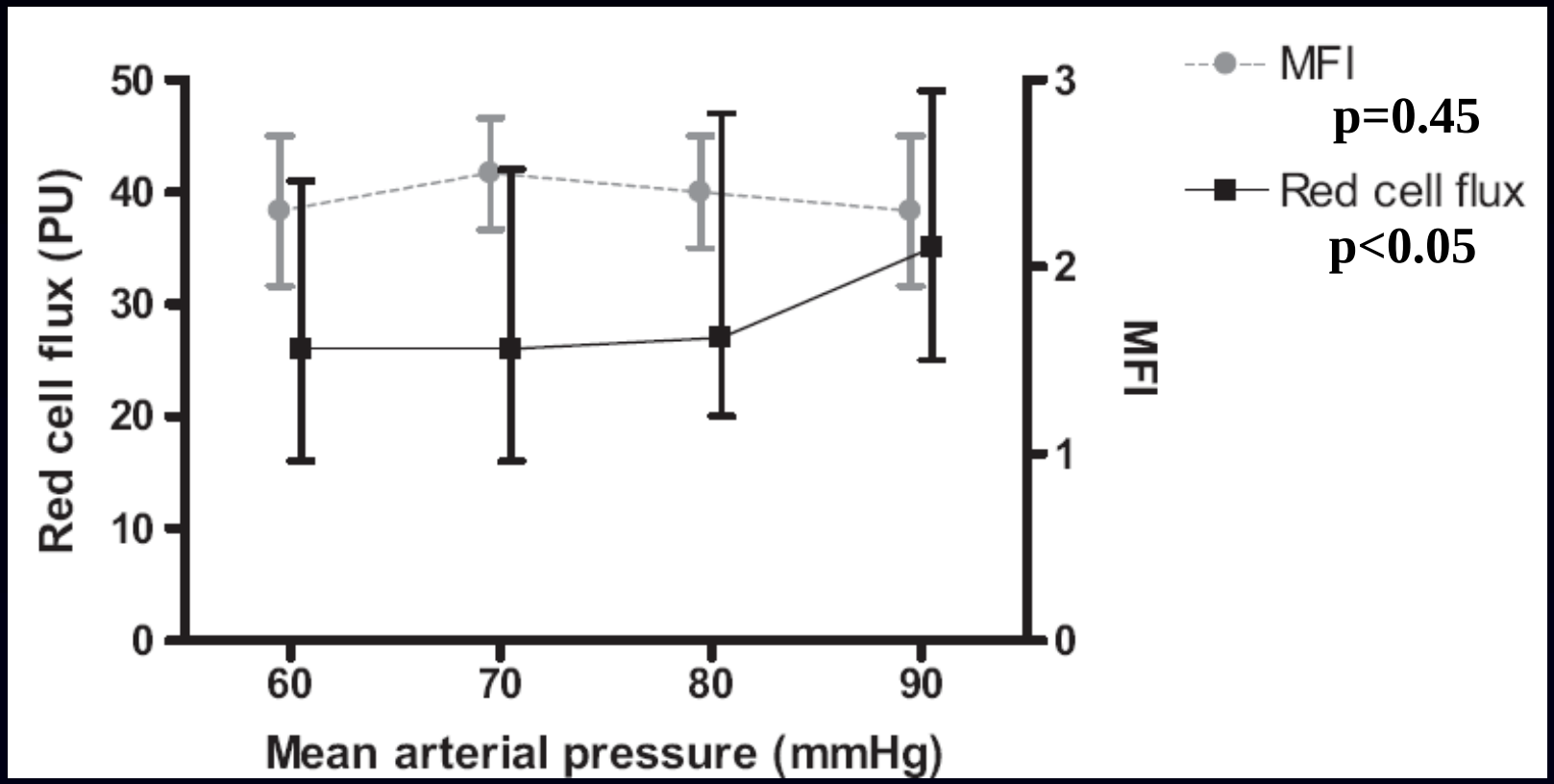
Shock value

Rats, LPS

MAP 46 71 70 mmHg

Impact of MAP/NE on microvascular perfusion

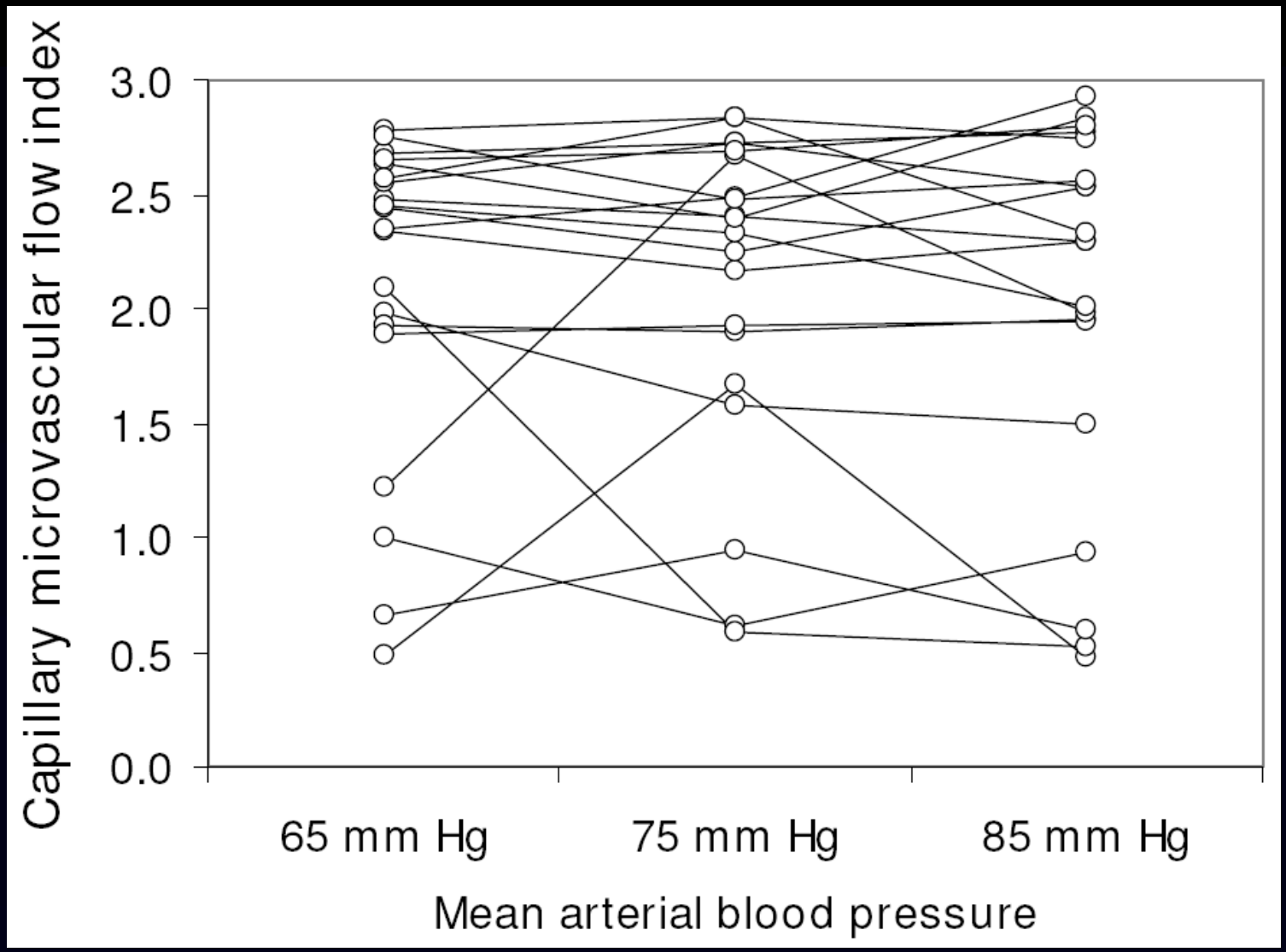
Jhanji et al
CCM 37:1961;2009



N=16

Impact of MAP/NE on microvascular perfusion

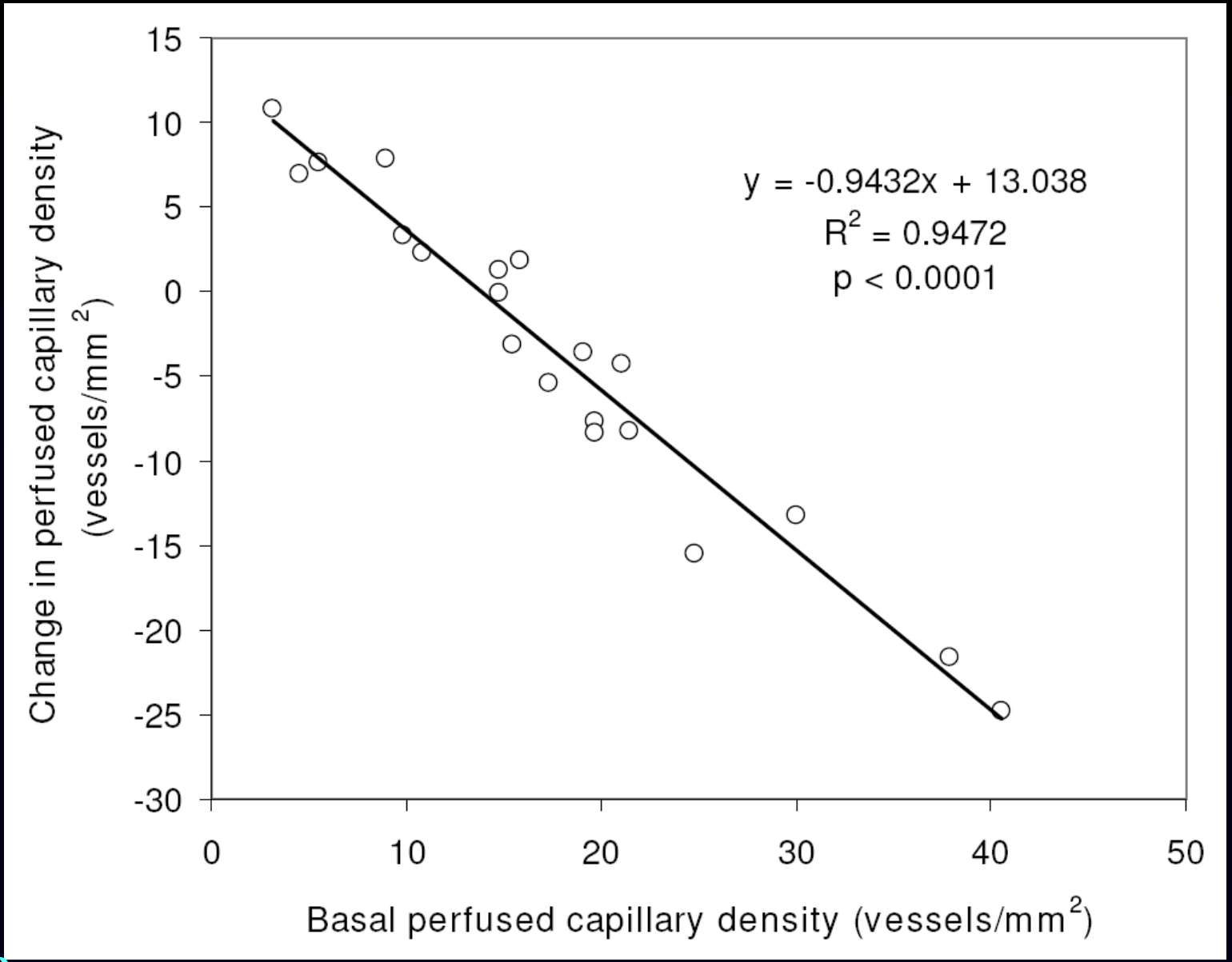
Dubin et al
Crit Care 2009



N=20

Impact of MAP/NE on microvascular perfusion

Dubin et al
Crit Care 2009

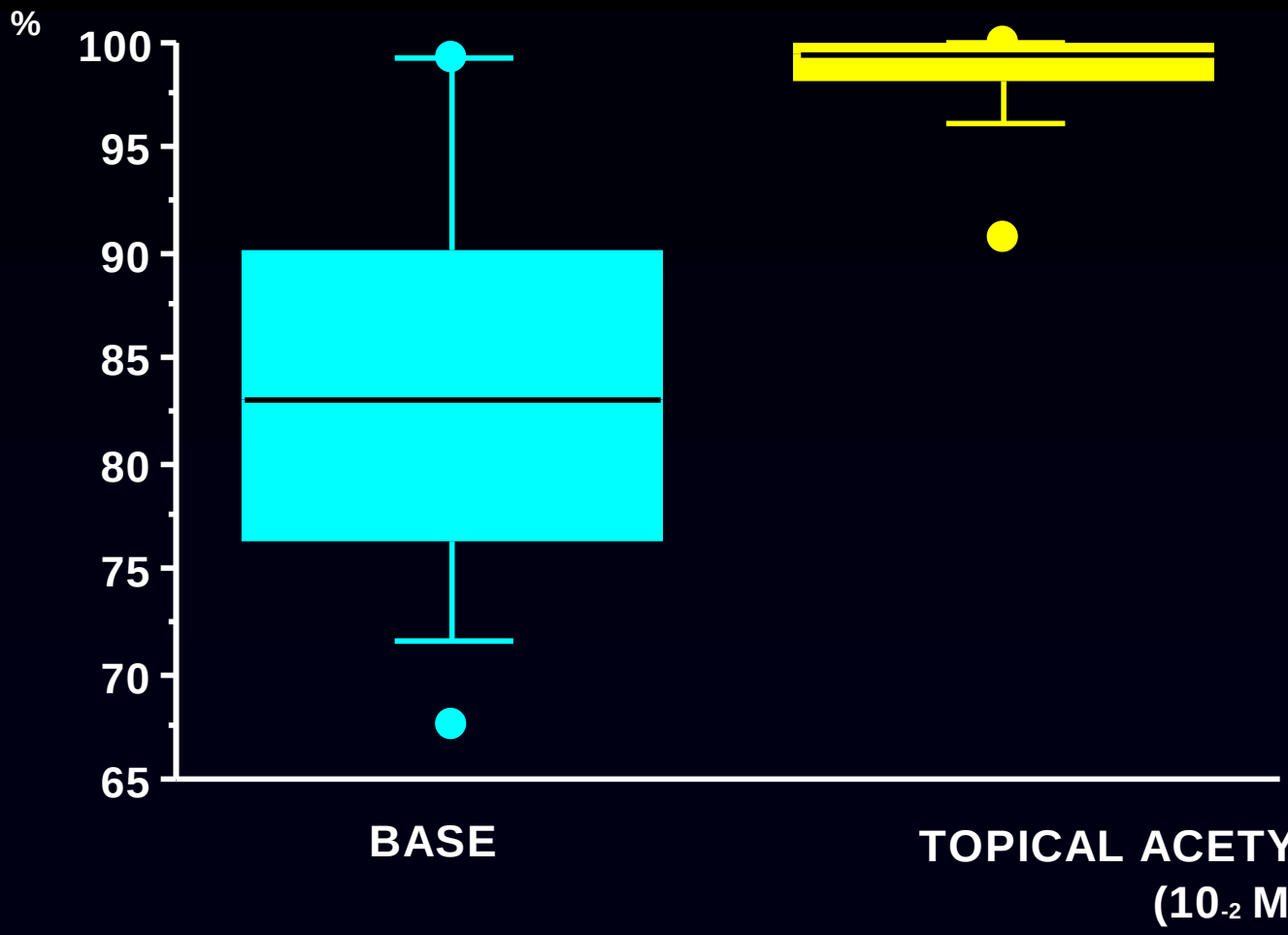


N=20

MICROCIRCULATORY ALTERATIONS IN SEPTIC PATIENTS

Proportion of perfused vessels (all vessels)

De Backer et al
AJRCCM 166:98;2002



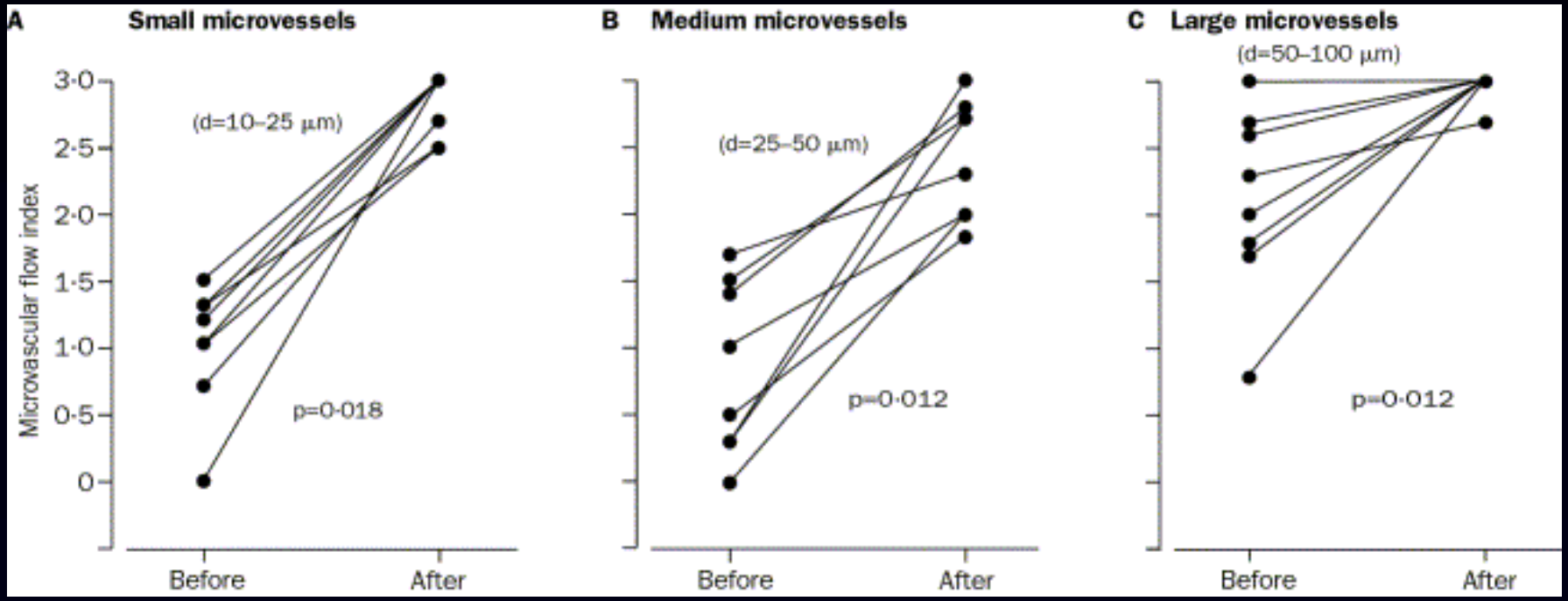
++ p <0.01 vs base

Patients with septic shock (n = 11)

DDB USI

Effects of nitroglycerin

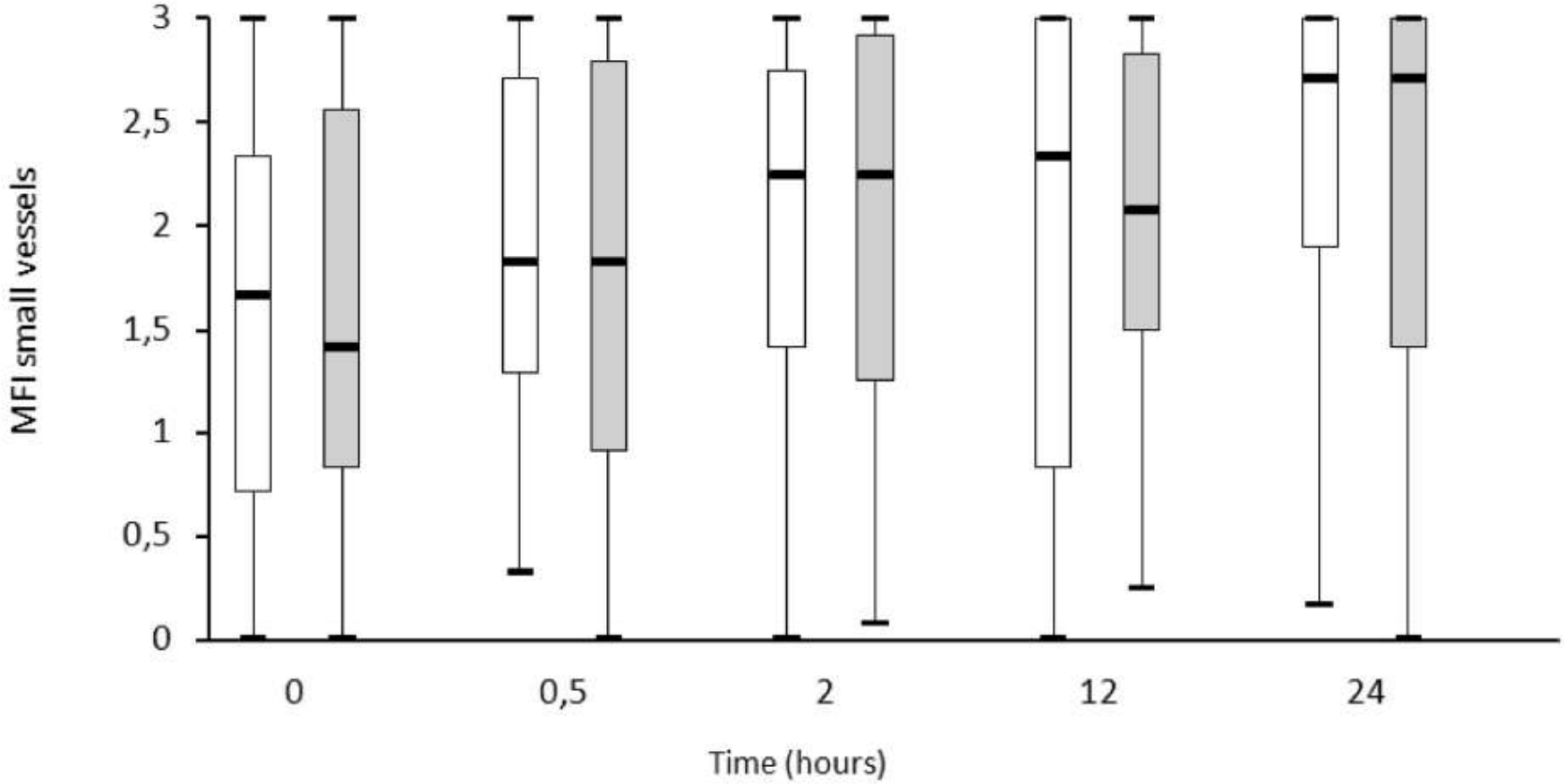
Spronk et al
Lancet 360:1395;2002



8 pts with septic shock

Effects of nitroglycerin

Boerma E et al
CCM 38:93-100;2010



70 pts with severe sepsis

Effects of nitroglycerin

Boerma E et al
CCM 38:93-100;2010

But can normal be more normal than normal ?

Variables	Baseline NTG (n = 35)	Placebo (n = 35)	30 mins NTG (n = 35)	Placebo (n = 35)	2 hrs NTG (n = 35)	Placebo (n = 35)
MFI small vessels	1.67 (0.67–2.42)	1.42 (0.83–2.63)	1.83 (1.08–2.75)	1.83 (0.83–2.83)	2.25 (1.42–2.75)	2.25 (1.25–2.92)
MFI medium vessels	2.33 (1.83–2.83)	2.33 (2–2.83)	2.67 (2.25–2.83)	2.42 (2.17–2.92)	2.83 (2.42–3)	2.75 (2.33–3)
MFI large vessels	2.92 (2.75–3)	2.92 (2.75–3)	3 (2.83–3)	3 (2.75–3)	3 (3–3)	3 (3–3)
TVD, mm/mm^2	14 (12.8–15.6)	15 (12.3–16.1)	13.9 (12.2–15)	14.1 (12.8–15.9)	14.3 (13.2–15.1)	14 (12.9–16)
PPV, %	98 (93–100)	97 (89–100)	100 (96–100)	97 (90–99)[c]	99 (96–100)	98 (93–100)
PVD, 1/mm	9.1 (8.3–10.5)	9.8 (8.4–10.8)	9.7 (8.7–10.5)	9.7 (8–10.5)	9.7 (8.4–10.7)	9.5 (8.7–11.3)
Heterogeneity index	1.76 (0.88–2.84)	1.96 (0.66–3)	1.71 (0.36–2.17)	1.53 (0.36–2.75)	0.82 (0.26–2.11)	1.24 (0.34–2.4)

70 pts with severe sepsis

CONCLUSIONS

- **Multiple experimental and clinical studies suggest that microvascular alterations play a key role in the pathophysiology of sepsis and in the development of sepsis-induced organ failure.**

- **These alterations are due to several factors (endothelial dysfunction, interaction with circulating cells) that make unlikely that classical hemodynamic resuscitation can be effective in restoring an adequate microcirculation.**