Centre Hospitalier Régional Universitaire de Lille

FACULTE DE MEDECINE Université de Lille HENRI WAREMBOURG

Microcirculation dans les états de choc : Diagnostic, implications, traitement

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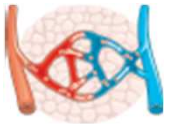
Instituts thématiques

Inserm
Institut national de la santé et de la recherche médicale

Déterminants de l'oxygénation tissulaire

- Flux sanguin (convection)
- Quantité des GR (hématocrite local)
- Qualité des GR (déformabilité)
- **Diffusion de l'oxygène (distance intercapillaire/densité capillaire)**



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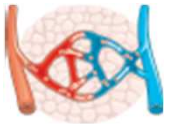
Déterminants de l’ouverture des capillaires

- Pression capillaire
- Pression interstitielle
- Thrombose intra-capillaire



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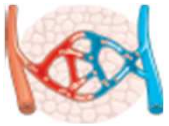
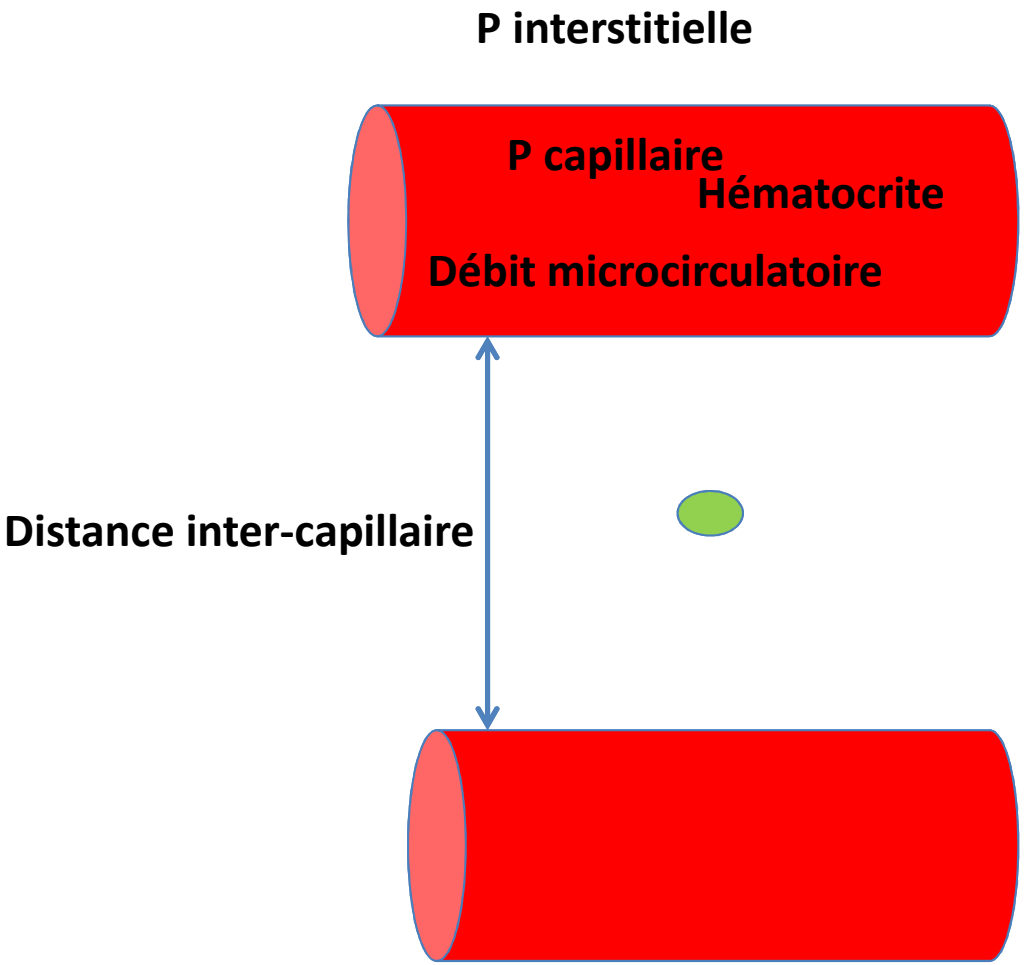
Réglage fin

- Nerfs **sympathiques** péri-vasculaires
  - Quid des sympathicomimétiques ?
- Communication rétrograde via les cellules endothéliales de proche en proche (Ca2+) jusqu'à 1mm
  - Perdue dans le sepsis sur modèles animaux

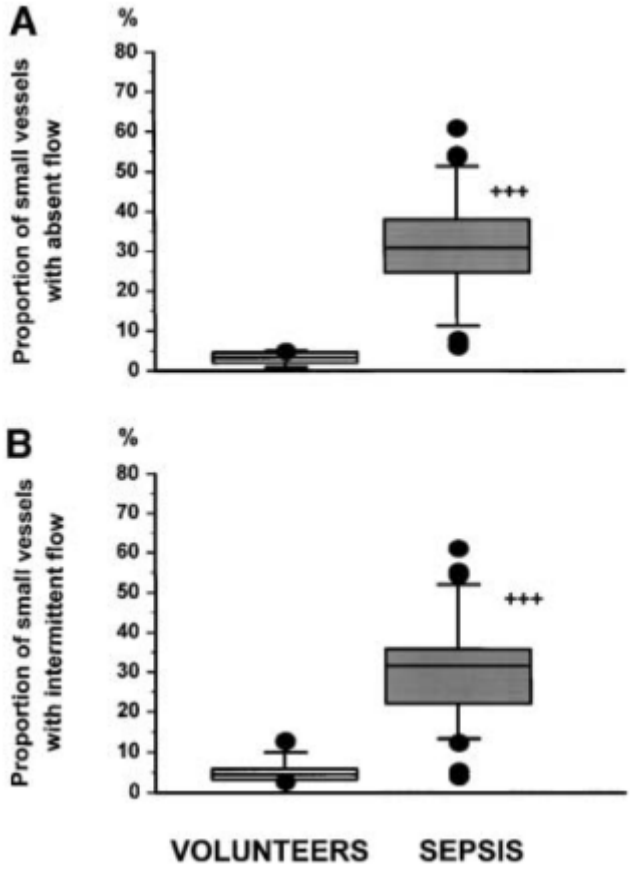


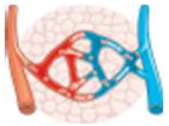


Débit= Pa-Pv ($\pi r4$) / $8\eta L$
Débit= (Pa-Pc)/Ra = (Pc-Pv)/Rv

D'où $Pc = \frac{(Pa-Pv)}{1+Ra/Rv} + Pv$

La microcirculation est altérée lors du sepsis et elle est hétérogène





De Backer AJRCCM 166; 98–104, 2002

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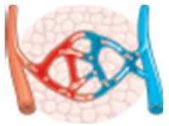
Malgré une macrocirculation « normale »

TABLE 2. PRINCIPAL PHYSIOLOGIC VARIABLES OF HEALTHY VOLUNTEERS, PATIENTS BEFORE CARDIAC SURGERY, INTENSIVE CARE UNIT CONTROL SUBJECTS, AND PATIENTS WITH SEPSIS

	Healthy Volunteers	Patients before Cardiac Surgery	ICU Control Subjects	Patients with Sepsis
Age, yr	29 (25–35)	66 (56–74)*	64 (56–69)*	61 (50–72)*
Temperature, ° C	37.0 (36.8–37.1)	36.7 (36.0–37.1)	36.8 (36.4–37.5)	37.0 (36.4–38.0)
Heart rate, bpm	69 (64–72)	68 (65–74)	69 (63–106)	105 (91–110)
Mean arterial pressure, mm Hg	82 (80–87)†	91 (79–99)‡	88 (75–94)†	71 (63–79)
Cardiac index, L/min · m^2	N/A	N/A	3.03 (2.4–3.60)	3.63 (2.62–4.69)
$\dot{D}_{O_2}$, ml/min · m^2	N/A	N/A	440 (380–499)	421 (333–525)
$\dot{V}_{O_2}$, ml/min · m^2	N/A	N/A	119 (115–134)	122 (96–152)
E_{O_2}, %	N/A	N/A	29 (27–30)	29 (24–33)
pH	N/A	N/A	7.44 (7.35–7.48)†	7.35 (7.27–7.39)
Pa_{CO_2}, mm Hg	N/A	N/A	33 (28–34)	37 (32–43)
Pa_{O_2}, mm Hg	N/A	N/A	142 (107–169)†	94 (73–108)
Sa_{O_2}, %	N/A	N/A	99 (99–99)†	97 (94–98)
$S\bar{v}_{O_2}$, %	N/A	N/A	70 (69–72.5)	68 (62–73)
Hemoglobin, g/dl	N/A	12.6 (11.5–14.5)‡	11.1 (9.2–11.8)‡	8.3 (7.4–9.9)
Lactate, mEq/L	N/A	N/A	1.4 (1.3–1.7)	2.2 (1.5–3.4)
APACHE II score§	N/A	5 (3–5)‡	10 (7–20)†	21 (17–25)
SOFA score‖	N/A	0 (0–0)‡	3 (1–8)‡	13 (10–15)

Definition of abbreviations: $\dot{D}_{O_2}$ = oxygen delivery; E_{O_2} = oxygen extraction; ICU = intensive care unit; N/A = not available; $S\bar{v}_{O_2}$ = mixed venous oxygen saturation; $_{O_2}$ = oxygen consumption.

* $p < 0.01$ versus volunteers.
† $p < 0.05$ versus sepsis.
‡ $p < 0.01$ versus sepsis.
§ Knauss and coworkers (21).
‖ Vincent and coworkers (22).



De Backer AJRCCM 166; 98–104, 2002

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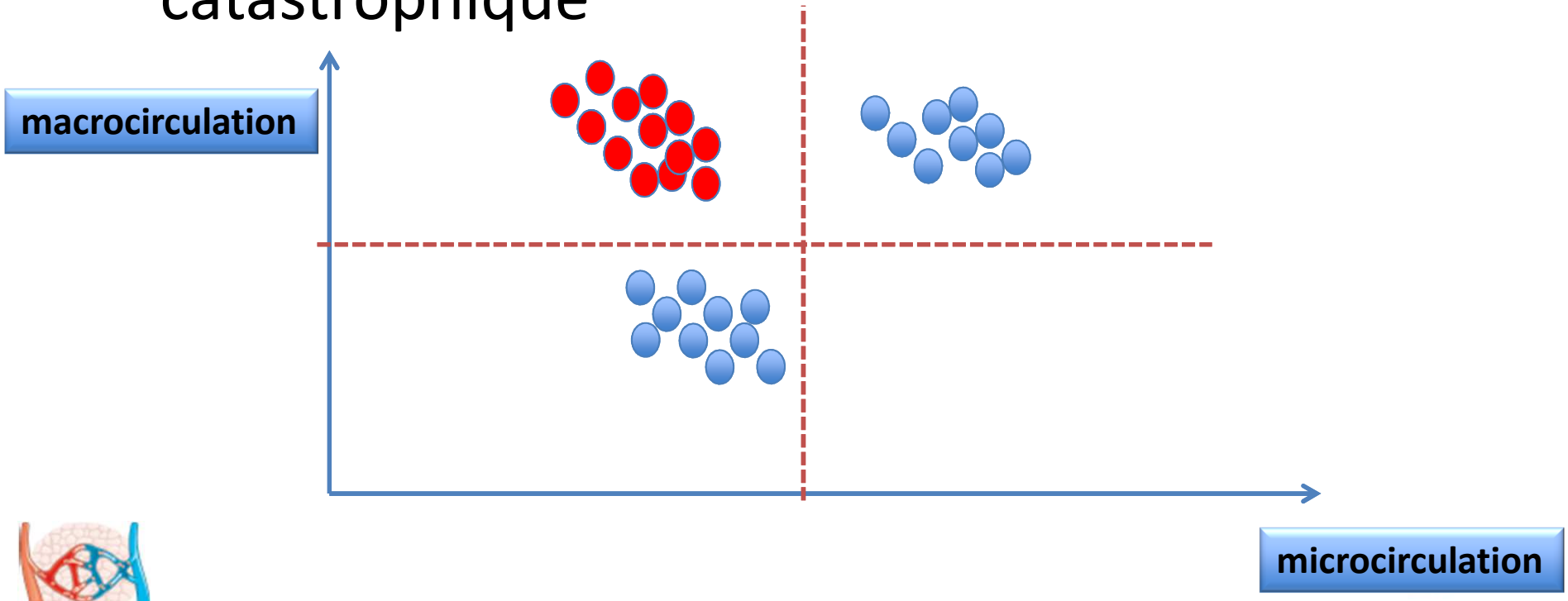
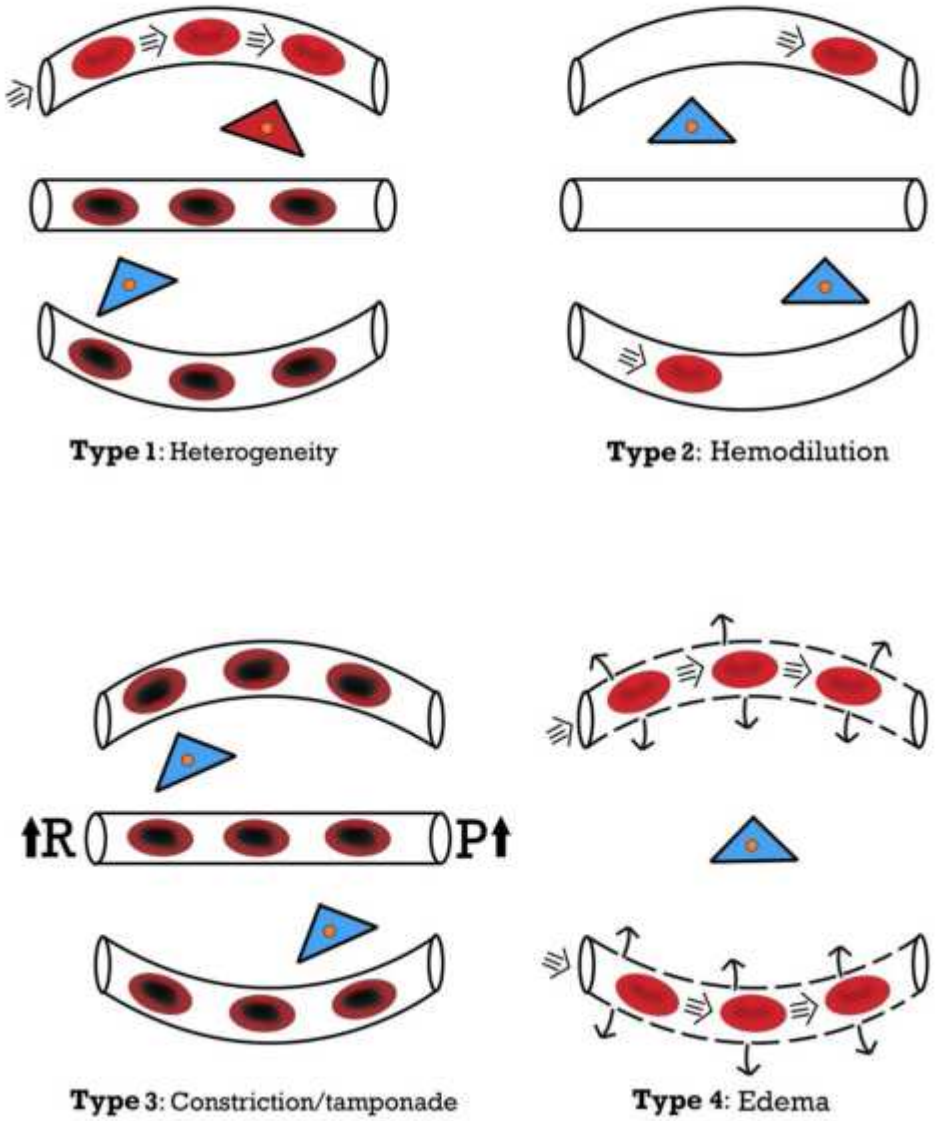
1er message

- La macrocirculation et la microcirculation sont dissociées lors des états de choc
- Sauf quand la macrocirculation est catastrophique



Microcirculatory alterations associated with loss of hemodynamic coherence.

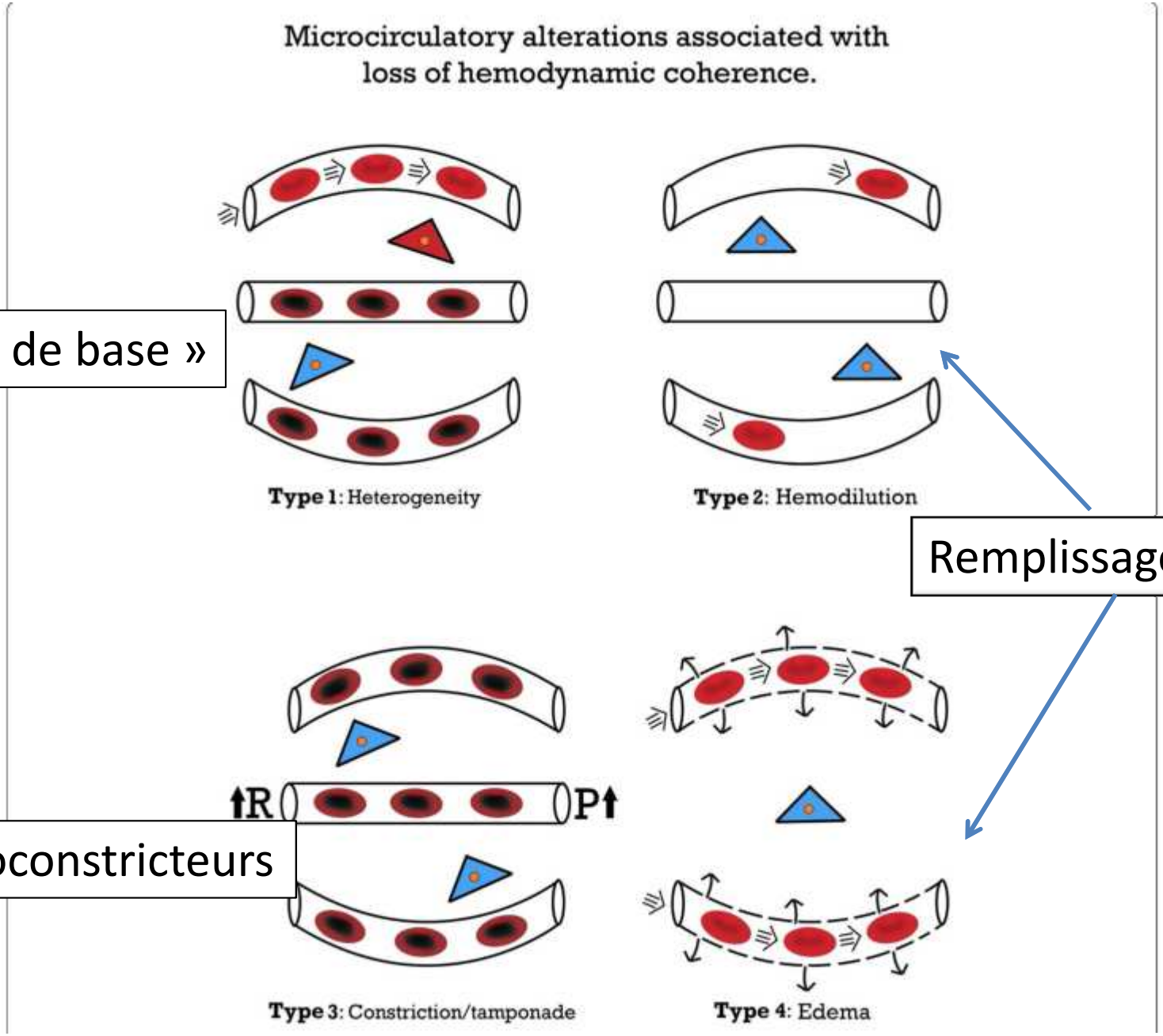


Type 1: Heterogeneity

Type 2: Hemodilution

Type 3: Constriction/tamponade

Type 4: Edema



« de base »

Remplissage massif

vasoconstricteurs

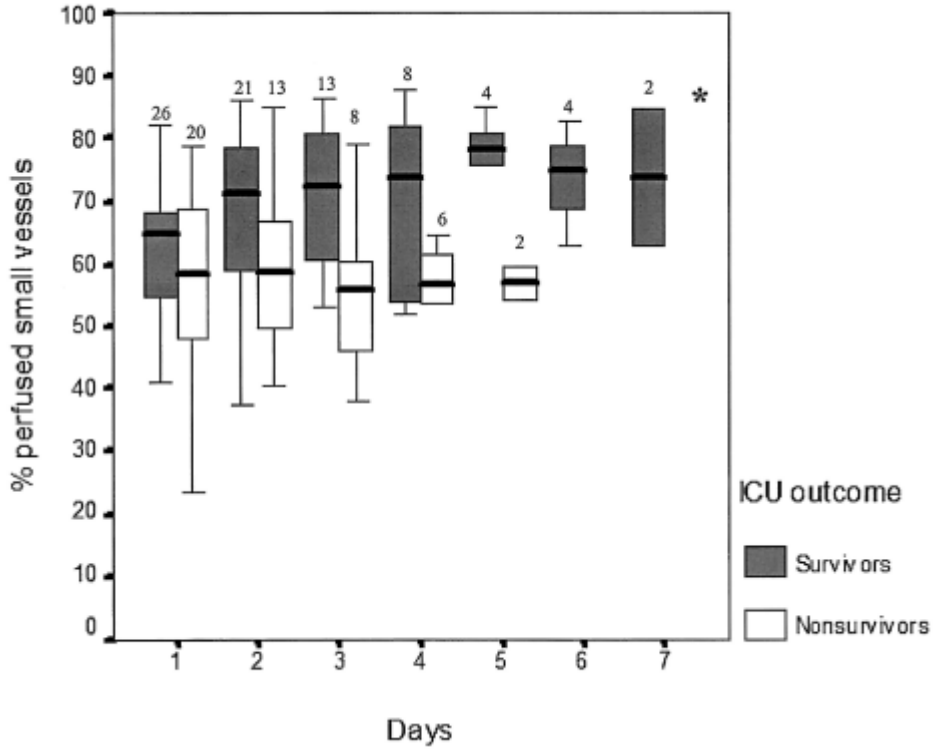
Ince *Critical Care* 2015, **19**:S8

Facteur pronostic

Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock*

Yasser Sakr, MB, BCh, MSc; Marc-Jacques Dubois, MD; Daniel De Backer, MD, PhD; Jacques Creteur, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCM

Crit Care Med 2004 Vol. 32, No. 9



Au moins une association..

J Appl Physiol 102: 2251–2259, 2007.
First published March 8, 2007; doi:10.1152/japplphysiol.01155.2006.

Microvascular and capillary perfusion following glycocalyx degradation

Pedro Cabrales,[1] Beatriz Y. Salazar Vázquez,[2,3,4] Amy G. Tsai,[1,4] and Marcos Intaglietta[4]

[1]*La Jolla Bioengineering Institute, La Jolla, California;* [2]*School of Medicine, Universidad Juárez del Estado de Durango, Durango, Mexico;* [3]*School of Medicine, Universidad de Colima, Colima, Mexico; and* [4]*Department of Bioengineering, University of California, San Diego, La Jolla, California*

Submitted 12 October 2006; accepted in final form 2 March 2007

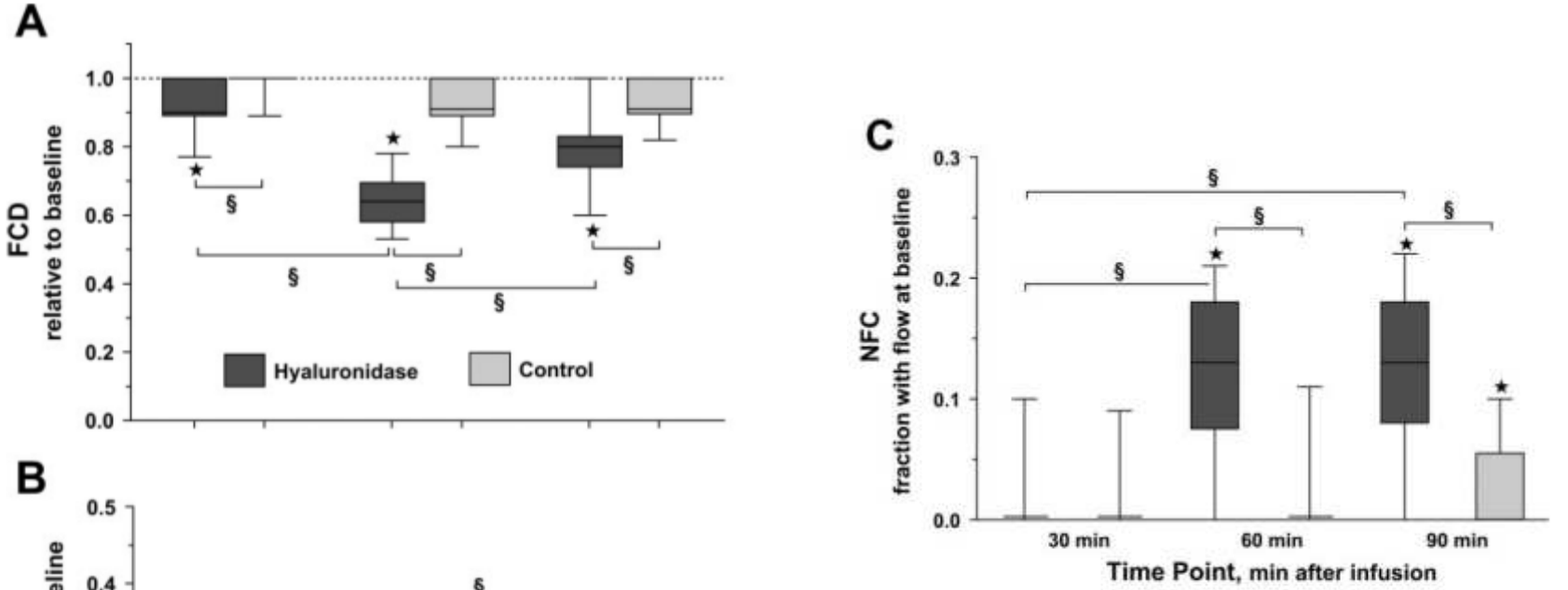
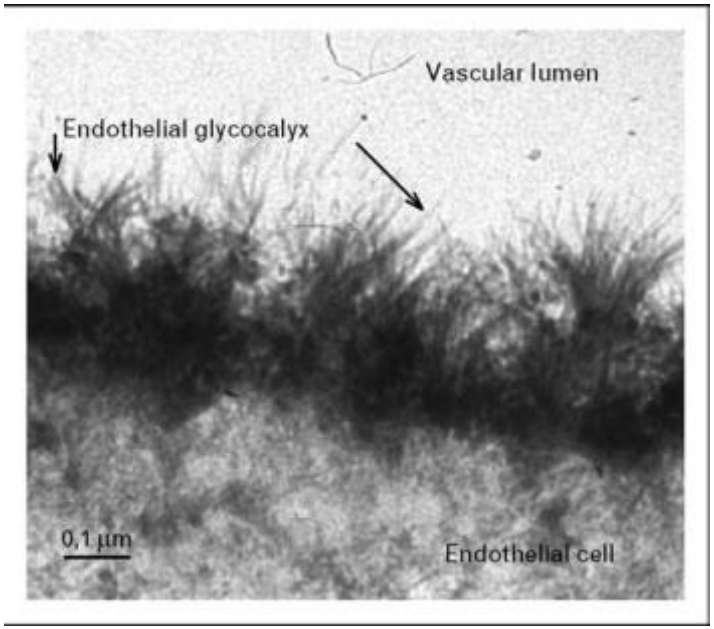
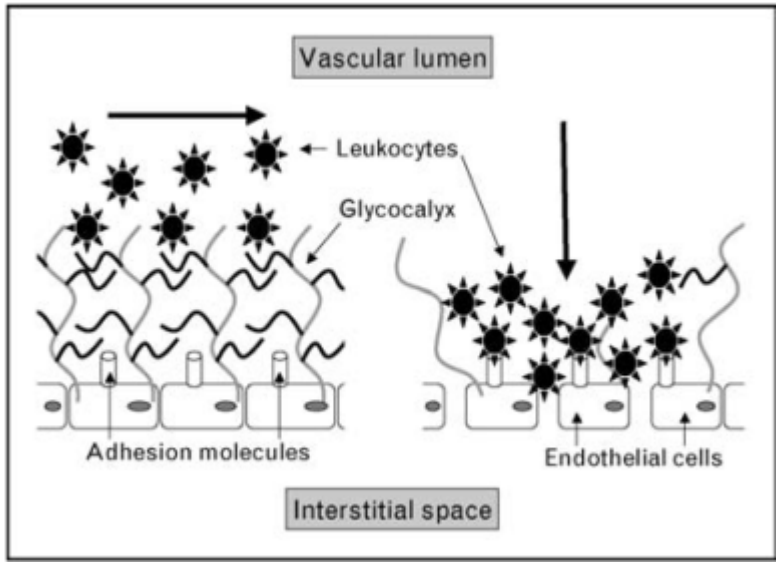


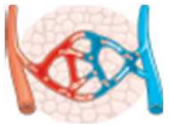
Fig. 2. Effects of enzymatic reduction of glycocalyx hyaluronan on capillary perfusion. *A*: functional capillary density (FCD) was unchanged after inactivated hyaluronidase (control). *B*: plasma-only perfused capillaries (PPC) increased 30 and 60 min after hyaluronidase infusion (hyaluronidase). *C*: nonflowing capillaries (NFC) increased 60 and 90 min after hyaluronidase infusion (hyaluronidase). FCD (cm^{-1}) at baseline in both study groups was as follows: hyaluronidase 104 (SD 14); control 106 (SD 12). $^*P < 0.05$ compare with baseline; $\S P < 0.05$ among groups.





GLYCOCALYX

- Modulation de cascades : tonus vasculaire, coagulation
- Perméabilité capillaire
- Difficile à appréhender au lit du patient : acide hyaluronique ? Syndecan 1 ? SDF (globule blanc)



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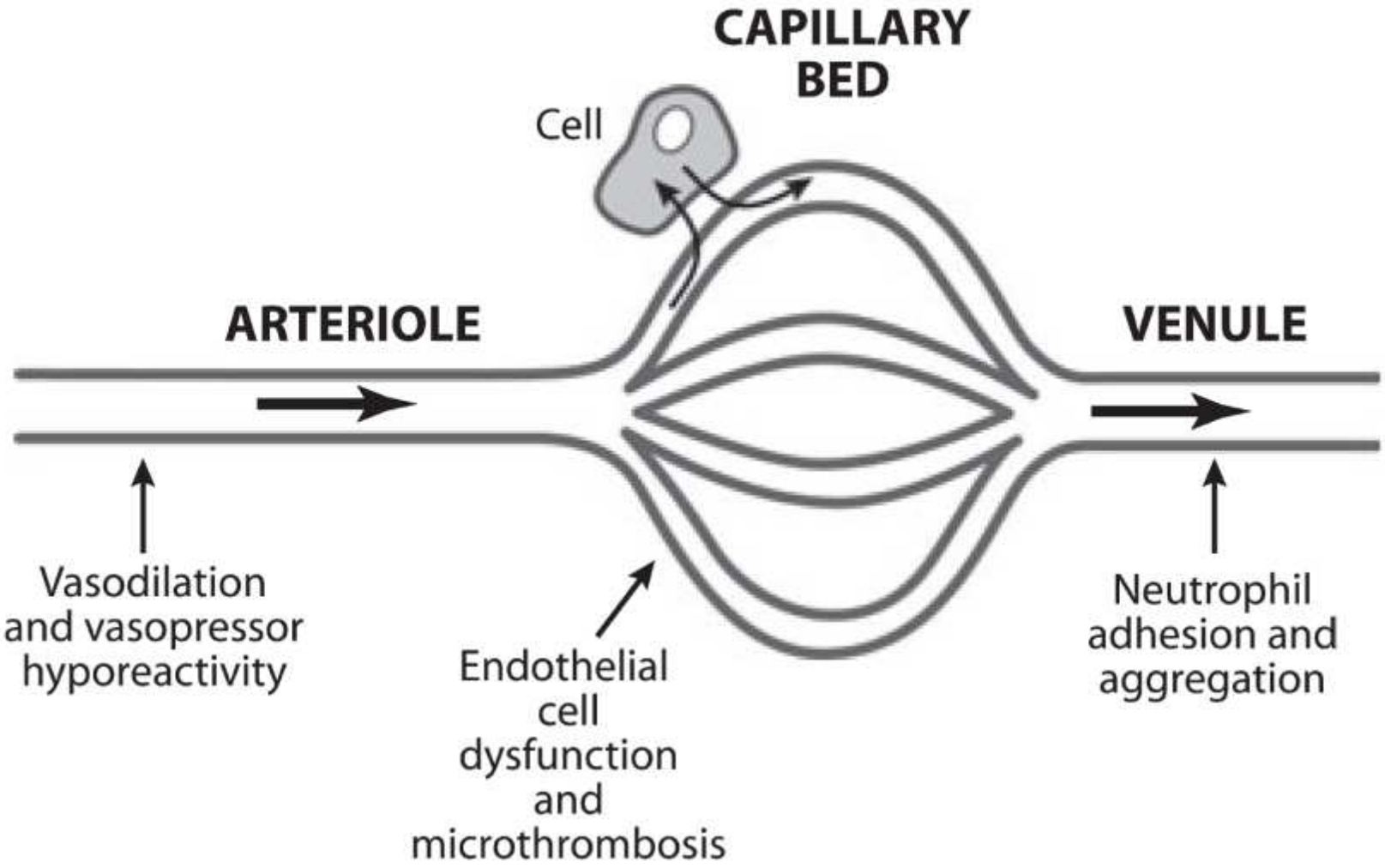

CAPILLARY BED
Cell
ARTERIOLE
VENULE
Vasodilation and vasopressor hyporeactivity
Endothelial cell dysfunction and microthrombosis
Neutrophil adhesion and aggregation

Les anomalies microcirculatoires sont réversibles

Microvascular Blood Flow Is Altered in Patients with Sepsis

Daniel De Backer, Jacques Creteur, Jean-Charles Preiser, Marc-Jacques Dubois, and Jean-Louis Vincent

Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Brussels, Belgium

Am J Respir Crit Care Med Vol 166. pp 98–104, 2002
DOI: 10.1164/rccm.200109-016OC
Internet address: www.atsjournals.org

TABLE 4. EFFECT OF TOPICAL ACETYLCHOLINE ADMINISTRATION IN 11 PATIENTS WITH SEPSIS

	Patients with Sepsis*,† (*n* = 11)		Volunteers (*n* = 10)
	Baseline	Acetylcholine (10^{-2} *M*)	
Total number of vessels, n/mm	4.9 (4.1–5.7)	6.0 (4.7–6.4)‡	5.4 (5.4–6.3)‡
Proportion of vessels perfused, %	83 (77–96)	99 (98–100)‡	98 (97–99)‡
Proportion of venules perfused, %	100 (100–100)	100 (100–100)	100 (100–100)
Proportion of capillaries perfused, %	44 (24–60)	94 (77–96)‡	94 (92–95)‡
Absent flow (capillaries), %	29 (8–44)	1 (0–3)‡	3 (2–5)‡
Intermittent flow (capillaries), %	24 (19–38)	8 (3–19)‡	5 (3–6)‡

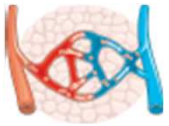
Data are presented as medians (25th–75th percentiles).

* All the patients with sepsis were treated with vasoactive agents (dopamine, n = 11, 20 [15–20] μg/kg · min; norepinephrine, n = 4, 1.23 [0.59–2.10] μg/kg · min; dobutamine, n = 7, 20 [5–20] μg/kg · min; epinephrine, n = 1, 0.1 μg/kg · min).

† The principal physiologic variables of the septic patients are reported in Table E2 in the online data supplement.

‡ $p < 0.01$ versus sepsis.

Cytopathie hypoxique vs microcirculation en détresse ?



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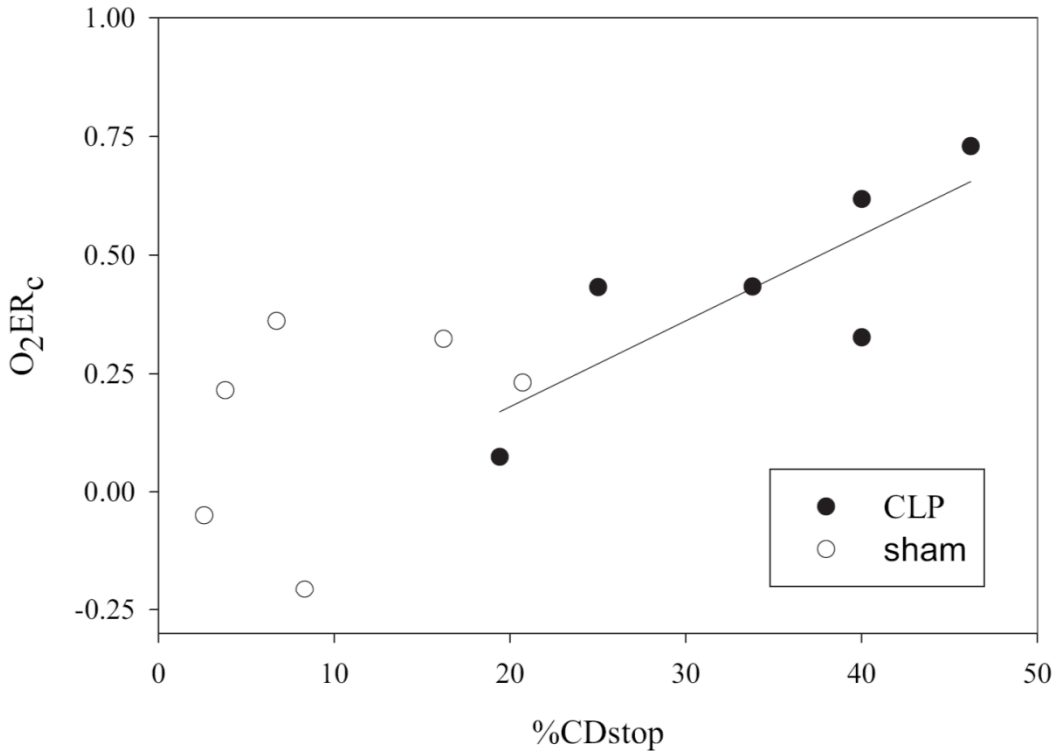
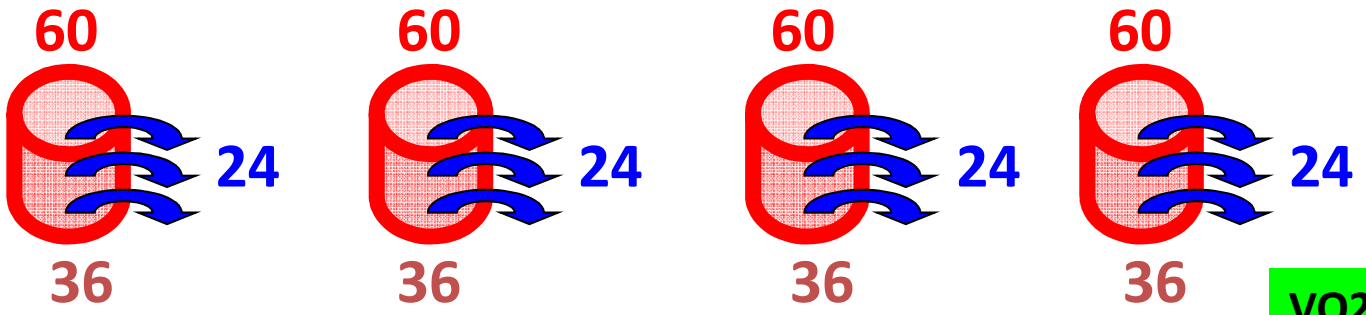


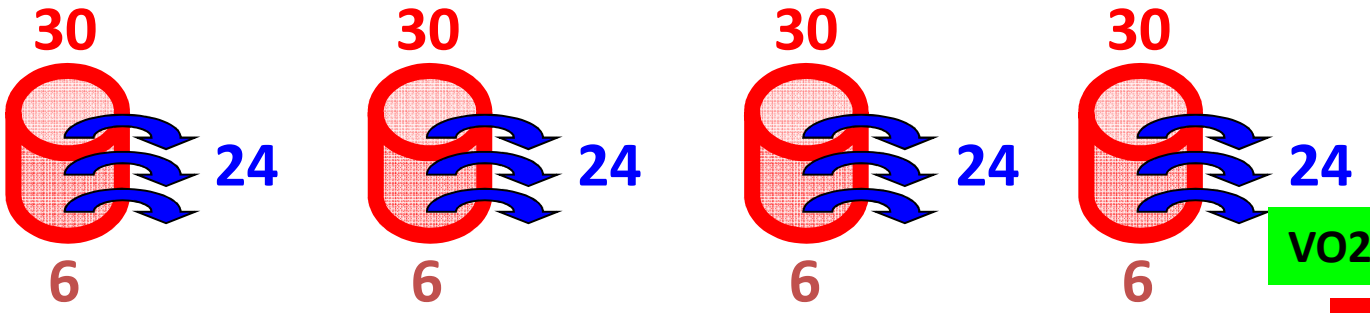
Local capillary oxygen extraction ratio (O_2ERc) versus regional capillary stopped-flow (%CDstop). In a 24-hour rat model of sepsis (cecal ligation and perforation [CLP]), capillary oxygen extraction from normally flowing capillaries (capillary velocity between 20 and 325 μm/s) was found to correlate with the degree of regional capillary stopped-flow. As capillary stopped-flow increased, the RBCs offloaded increased amounts of oxygen. (CLP group: $y = 0.018x - 0.18$; $r^2 = 0.64$; $P < 0.05$.) By permission from *Am J Physiol Heart Circ Physiol* 2002, **282**:H156-H164 [30].

Etats de bas débit et EO2

Flux normal



VO2 globale = 96

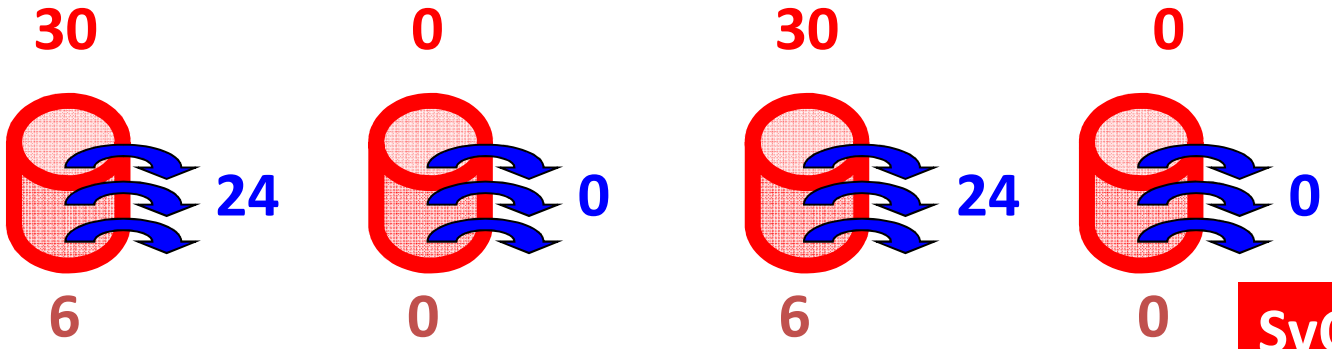


VO2 globale = 96

Bas débit homogène

SvO2 basse

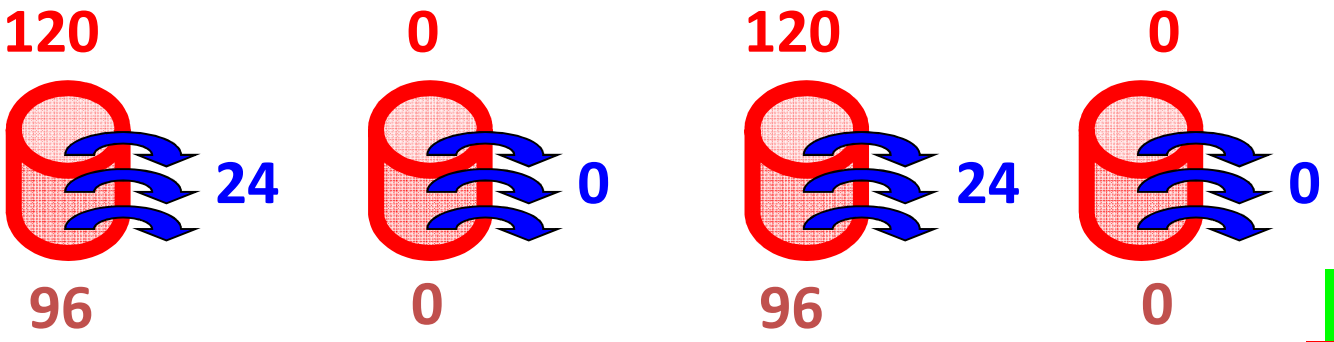
Choc distributif avant réanimation



VO2 globale = 48

SvO2 très basse

Choc distributif « réanimé »



VO2 globale = 48

SvO2 normale

Alors comment les repérer ?

L'ETUDE DE

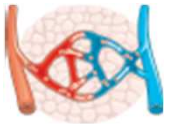
LA MICROCIRCULATION

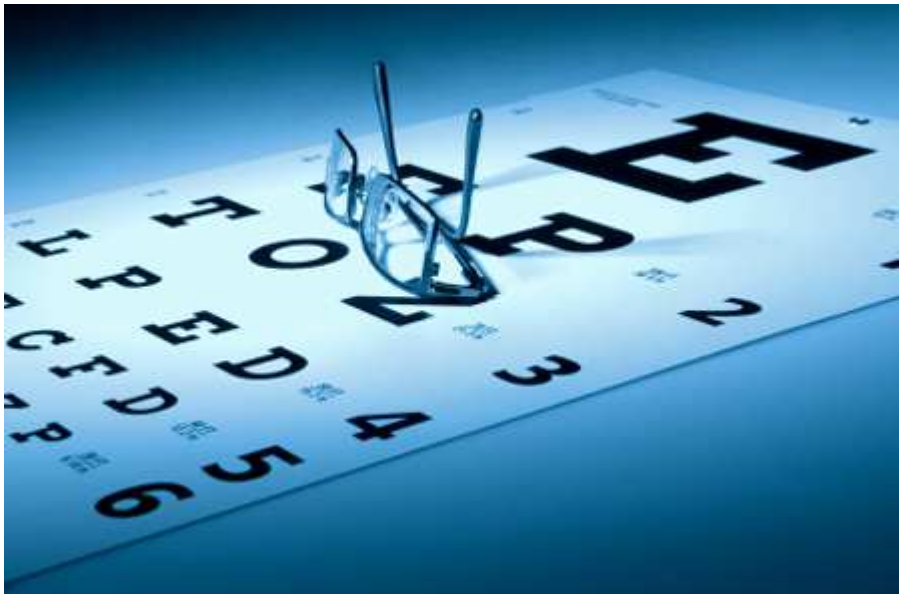
POURRAIT PERMETTRE DE MIEUX PRENDRE

EN CHARGE LES PATIENTS EN ETAT DE CHOC.

ELLE NECESSITE UN APPAREILLAGE DE PLUS EN PLUS FACILE A UTILISER AU LIT

DU PATIENT MAIS CERTAINS NECESSITENT JUSQU'À TROIS MOIS D'APPRENTISSAGE

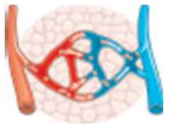




Moyens diagnostics

- Accessibles

- Inaccessibles: coût, expérience, difficultés d'interprétation → recherche



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La clinique d’abord quand c’est évident, biensûr !

Temps de recoloration cutané, marbrures, teint gris extémités froides

Intensive Care Med (2011) 37:801–807
DOI 10.1007/s00134-011-2163-y

ORIGINAL

H. Ait-Oufella
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Mottling score predicts survival in septic shock

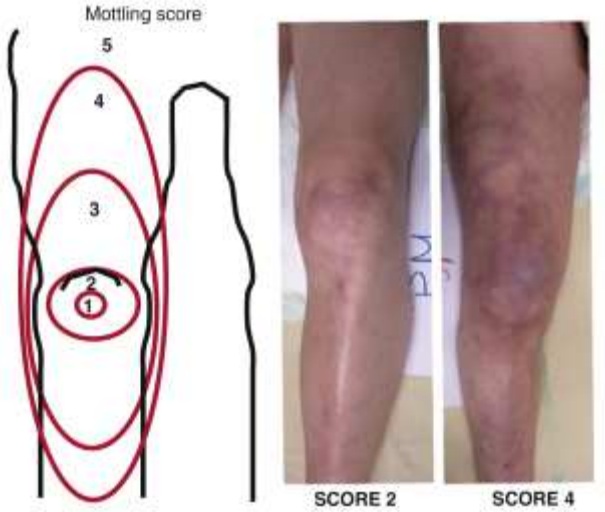
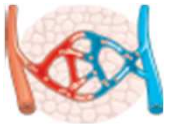


Fig. 1 *Left*: the mottling score is based on a mottling area extension on the legs. Score 0 indicates no mottling; score 1, a modest mottling area (coin size) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin. *Right*: Examples of the mottling score

Dans les études sur le remplissage, on ne nous dit jamais si les marbrures disparaissent..seulement si le débit cardiaque augmente…

Quels marqueurs biologiques ?

- Gradient de P_{CO2} (au moins initialement Ospina-Tascon ICM 2016)
- Lactate ? (pompe Na/K..)
- Lactate/SvcO2 (Jansen AJRCCM 2010)



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Intensive Care Med (2016) 42:211–221
DOI 10.1007/s00134-015-4133-2

ORIGINAL

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César Arango-Dávila
Daniel De Backer

Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock?

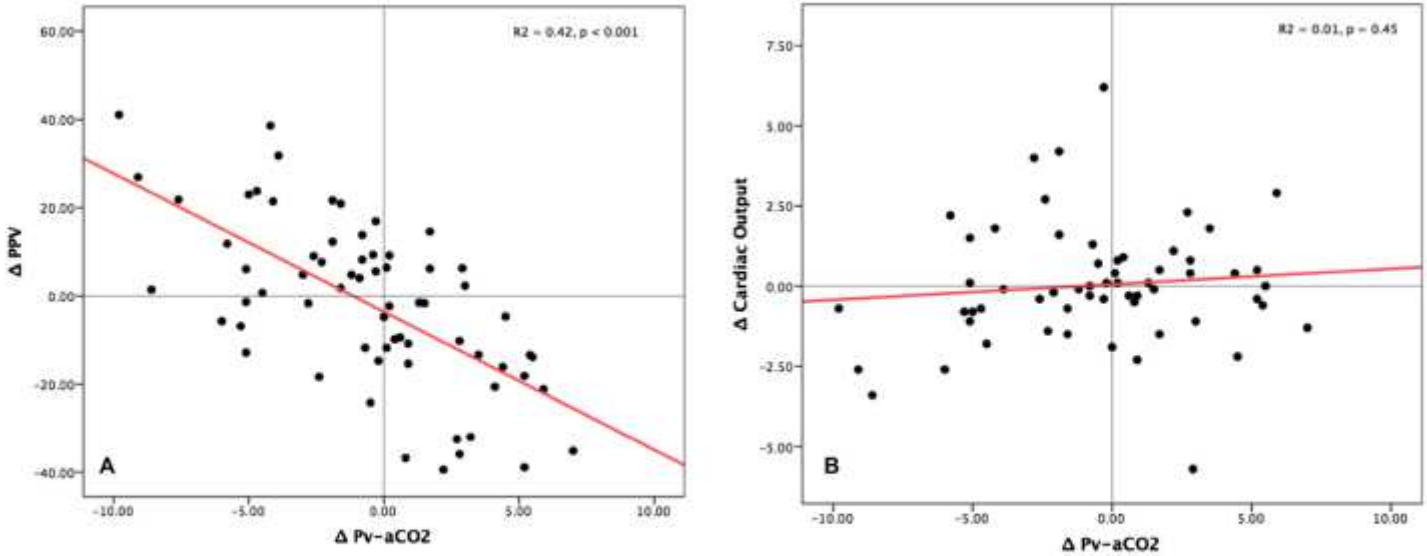
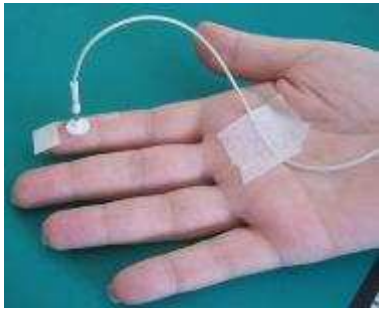


Fig. 2 Scatter plots showing the correlation of variations observed between changes in venous-to-arterial CO_2 partial pressure differences (Δ Pv-aCO_2) and **a** changes in percentage of small vessels perfused (Δ PPV) between measurements performed at T0 and T6 ($R^2 = 0.42$, $p < 0.001$) and **b** changes in cardiac output (Δ cardiac output) between measurements performed at T0 and T6 ($R^2 = 0.01$, $p = 0.45$)

Le gradient de PCO2 semble être corrélé plus à la micro qu'à la macrocirculation: ceci dit ça nous arrangerait..

Moyens « inaccessibles »

- Laser-Doppler



Réactivité vasculaire

- NIRS

- SDF/IDF

Hétérogénéité du flux

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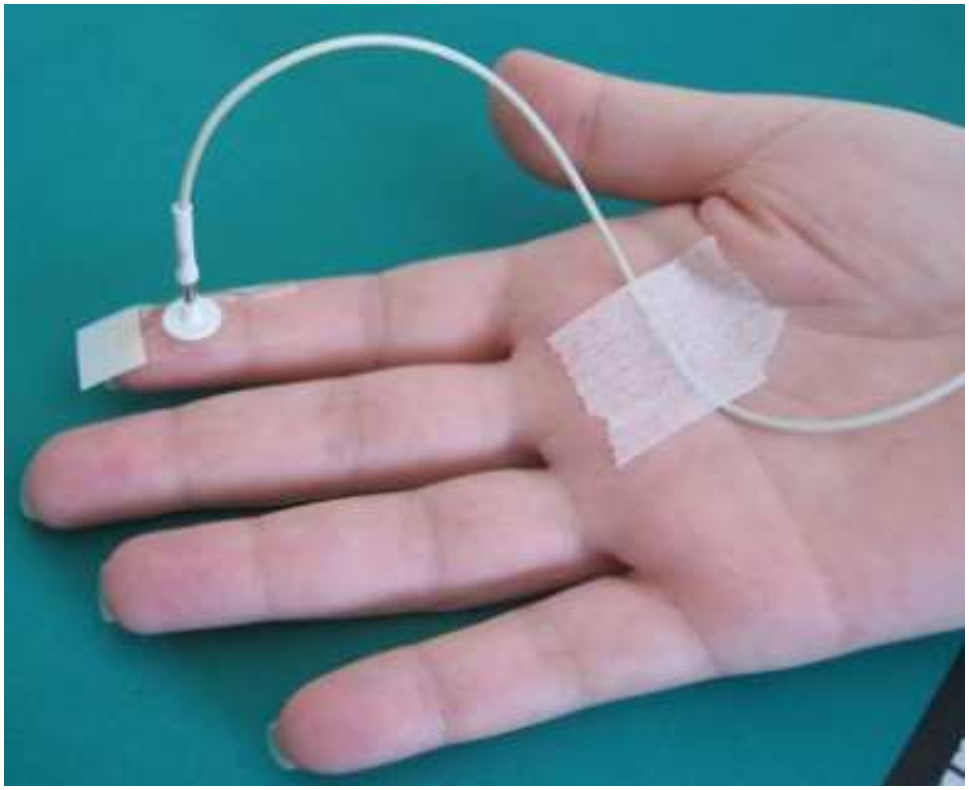
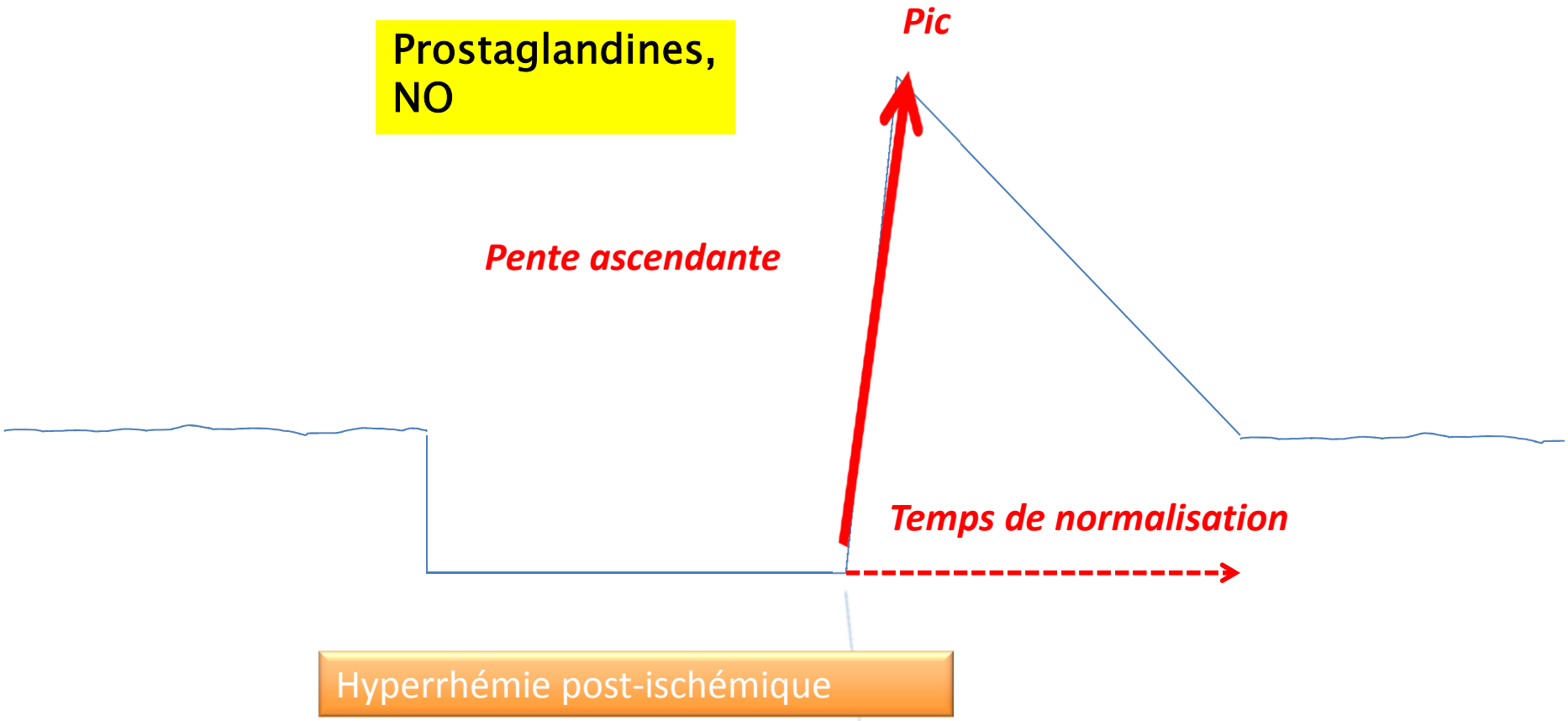
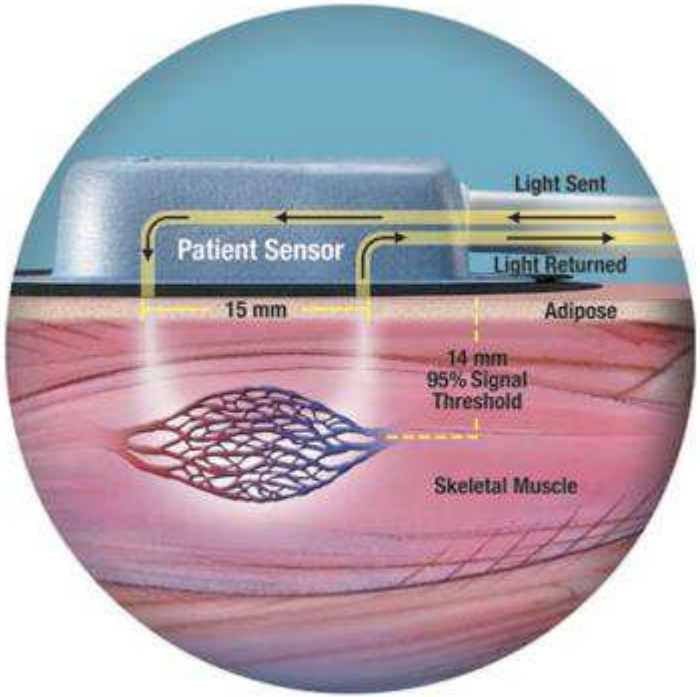
LDF:laser doppler= réactivité vasculaire

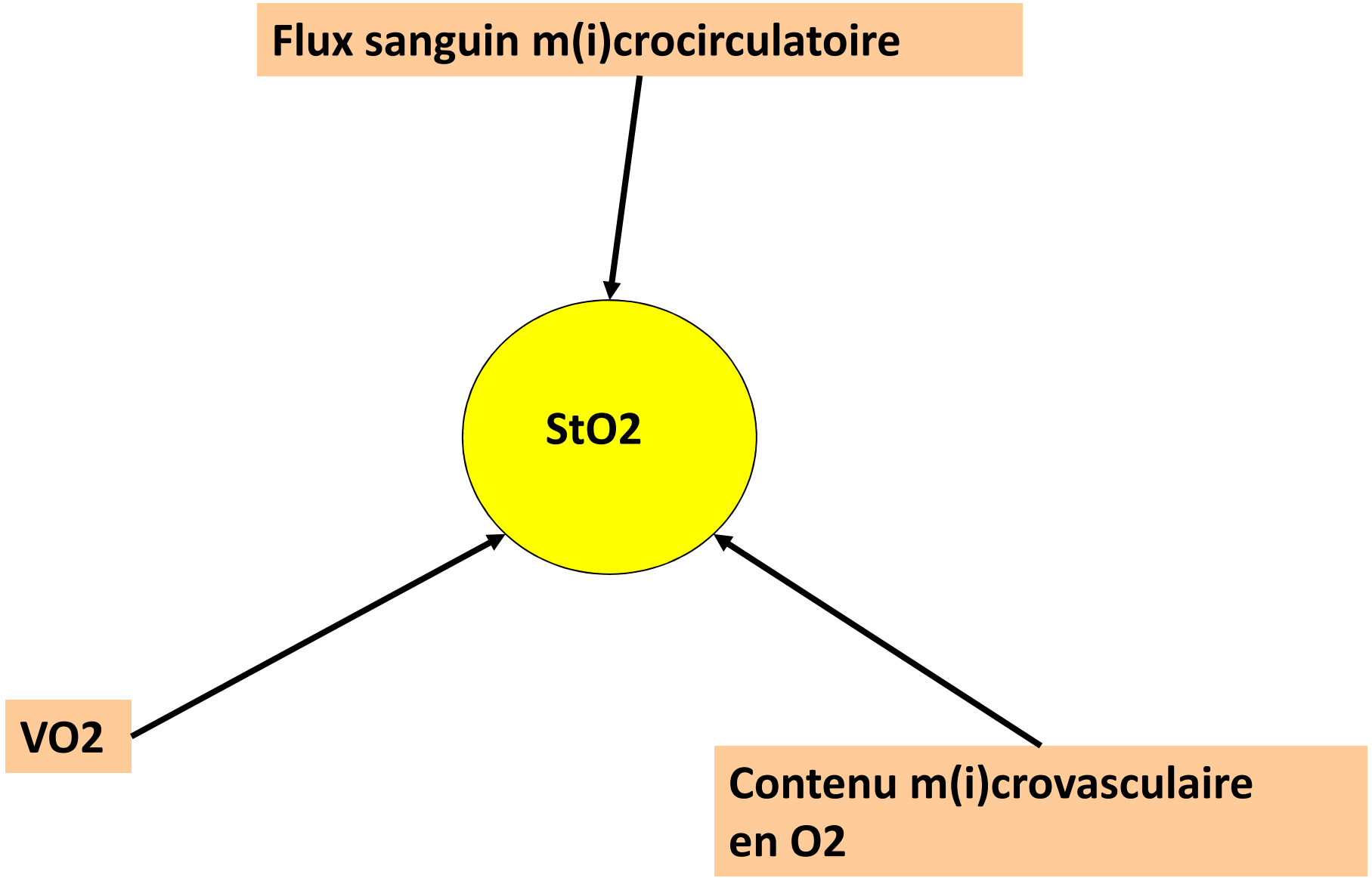


Simple, reproductible,
(mais ne tient pas compte de l'hétérogénéité du flux)



NIRS: saturation tissulaire en O_2=?




Flux sanguin m(i)crocirculatoire
StO2
VO2
Contenu m(i)crovasculaire
en O2

Intensive Care Med (2007) 33:1549–1556
DOI 10.1007/s00134-007-0739-3

ORIGINAL

Jacques Creteur
Tiziana Carollo
Giulia Soldati
Gustavo Buchele
Daniel De Backer
Jean-Louis Vincent

The prognostic value of muscle StO_2 in septic patients

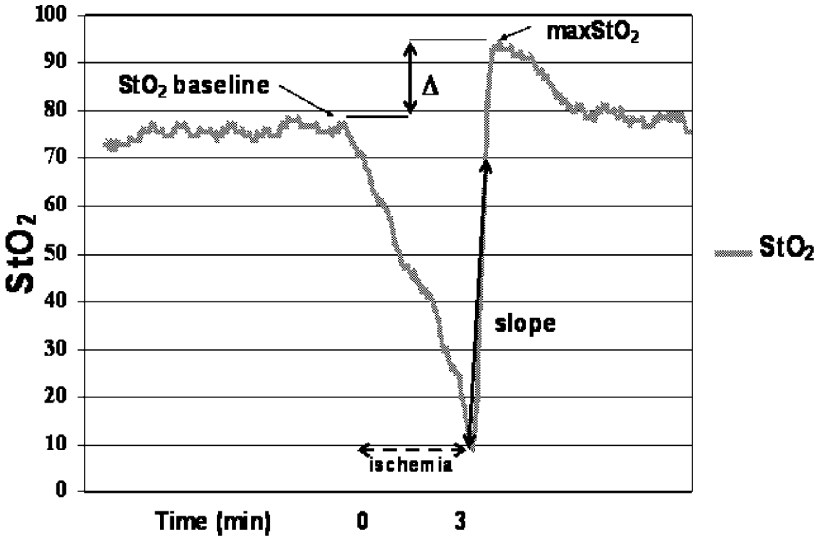


Fig. 1 Representative StO_2 curve. Δ, difference between maximum StO_2 value during the reperfusion period and baseline StO_2. *Slope*, slope of the increase in StO_2 during the first 14 s of the reperfusion period

Simple, reproductible mais probablement pas la microcirculation
Part veineuse importante, échantillon trop étendu

OPS/SDF/IDF

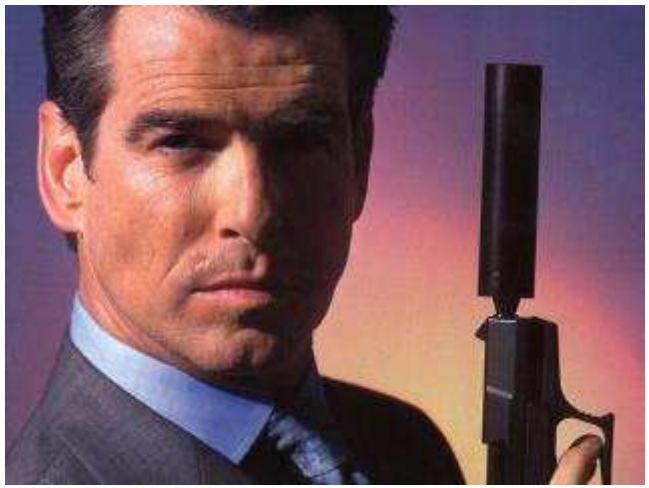


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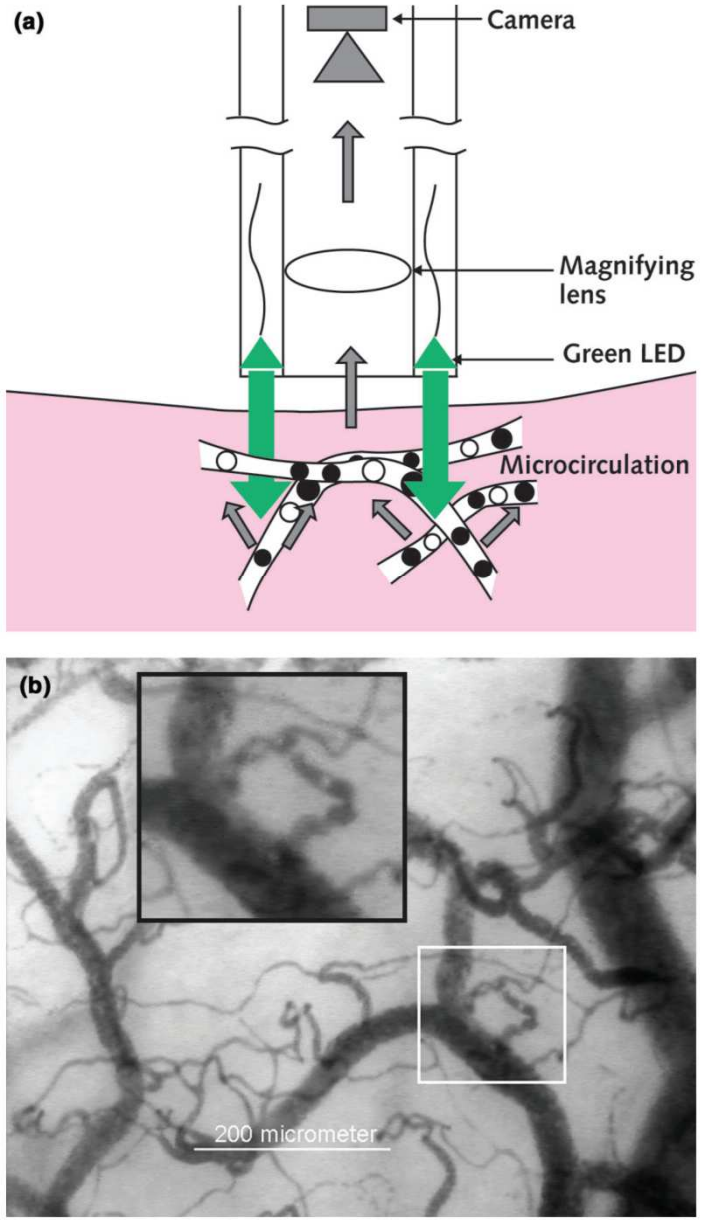
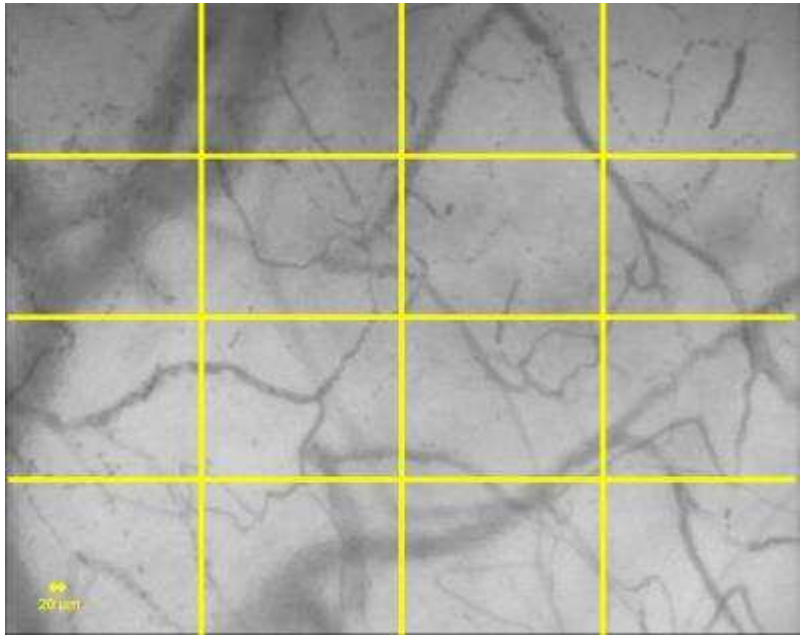
Figure 2



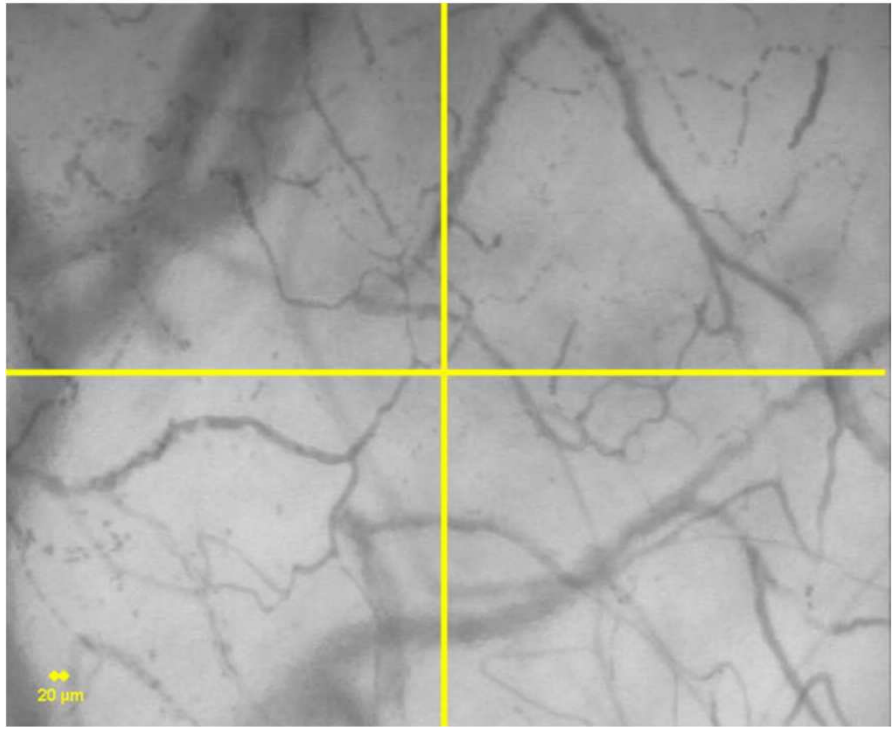
Ne permet de voir que les GR, on ne sait pas s'ils transportent de l'oxygène…



Proportion de capillaires perfusés:
PPV%
proportion de capillaires
perfusés qui croisent les lignes

5 videos de 20 secondes
Time consuming !!!

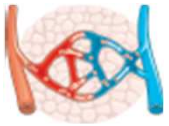
MFI: microvascular flow index
Moyenne des 4 quadrants
3:normal
2:intermittent
1:ralenti
0:pas de flux



D’accord on peut les repérer, mais possède-ton des traitements ?

vasoconstricteurs

- Noradrénaline: effet non prévisible, difficile à dissocier d'un « effet débit cardiaque »
- Phényléphrine: quand alpha-1 pur a priori délétère
- Vasopressine: à voir et dans des conditions bien précises



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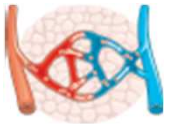
Noradrénaline

- 3 études cliniques: pas d'effets délétères majeurs
- Augmentation de la précharge sans fuite capillaire ?
- Effet débit cardiaque ?



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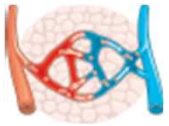
Noradrénaline

- Oui mais précautions



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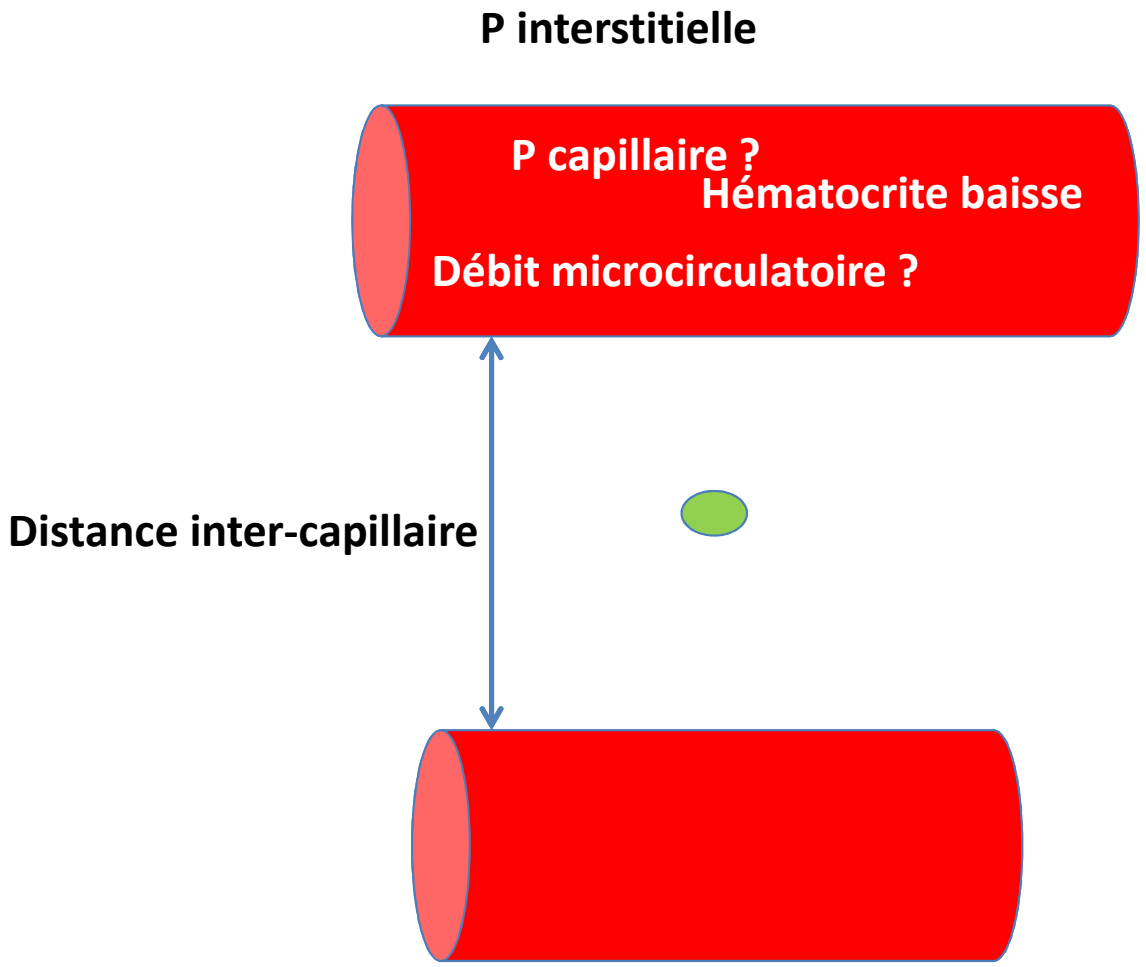
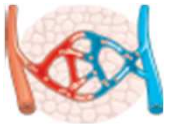
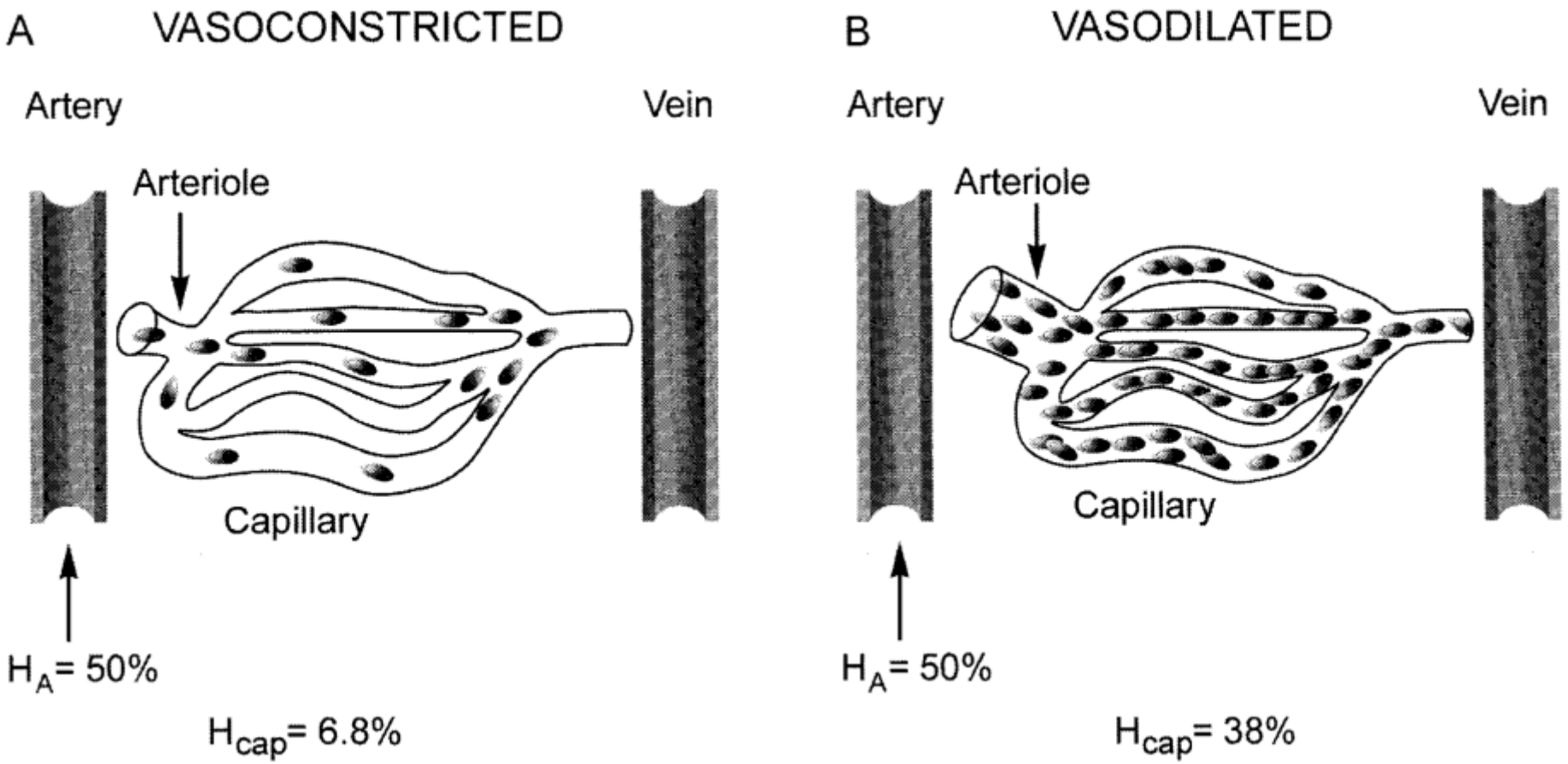


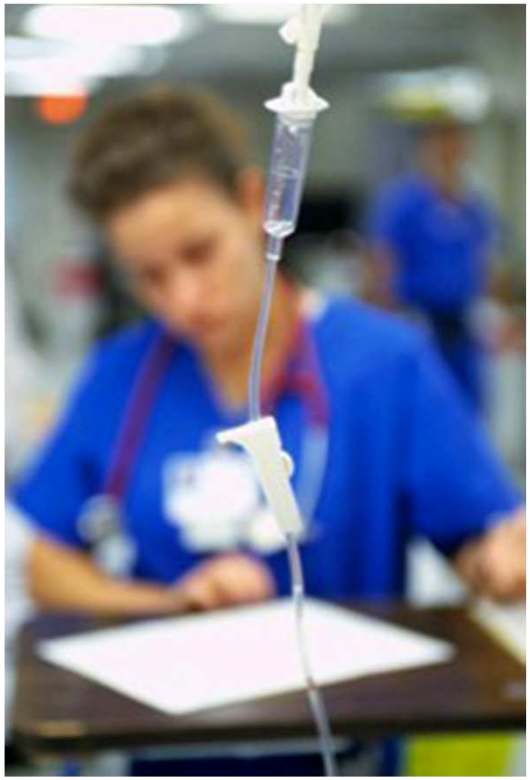
Débit= Pa-Pv (πr^4) / $8\eta L$
Débit= (Pa-Pc)/Ra = (Pc-Pv)/Rv

D'où $Pc = \frac{(Pa-Pv)}{1+Ra/Rv} + Pv$




A
VASOCONSTRICTED
Artery
Vein
Arteriole
Capillary
H_A= 50%
H_{cap}= 6.8%
B
VASODILATED
Artery
Vein
Arteriole
Capillary
H_A= 50%
H_{cap}= 38%

Rien ne sert de remplir si on est pas parti à point..



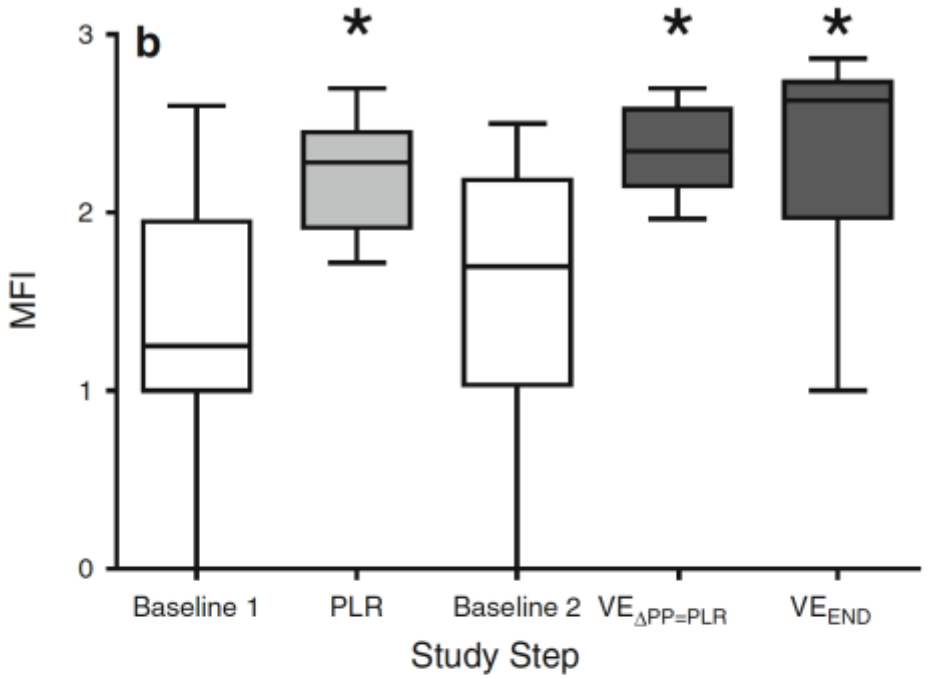
Intensive Care Med (2010) 36:1867–1874
DOI 10.1007/s00134-010-1966-6

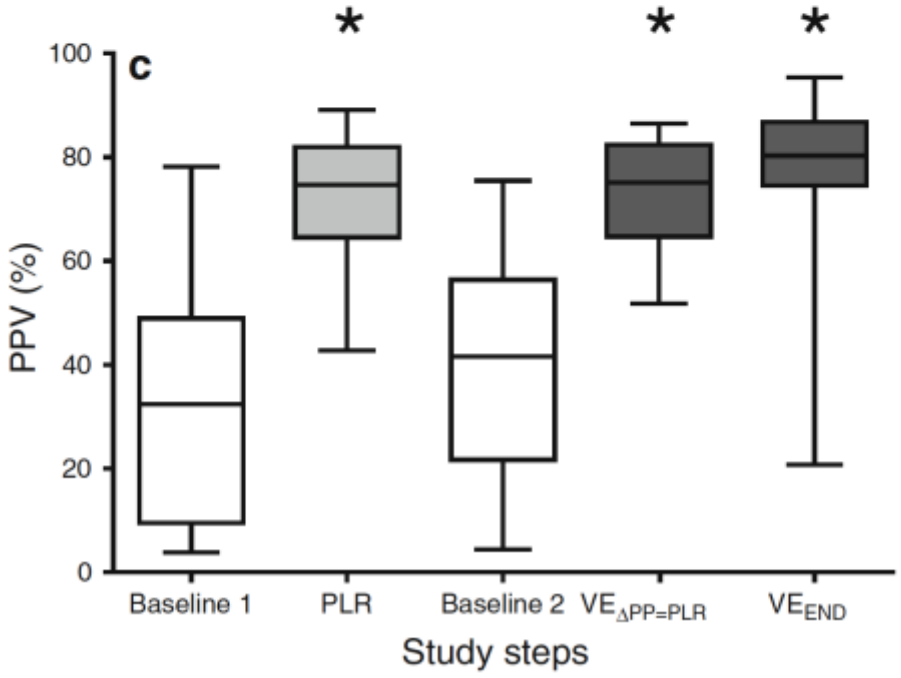
ORIGINAL

Julien Pottecher
Stéphane Deruddre
Jean-Louis Teboul
Jean-François Georger
Christian Laplace
Dan Benhamou
Eric Vicaut
Jacques Duranteau

Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients

25 patients
<24 heures
Tous précharge-dépendants





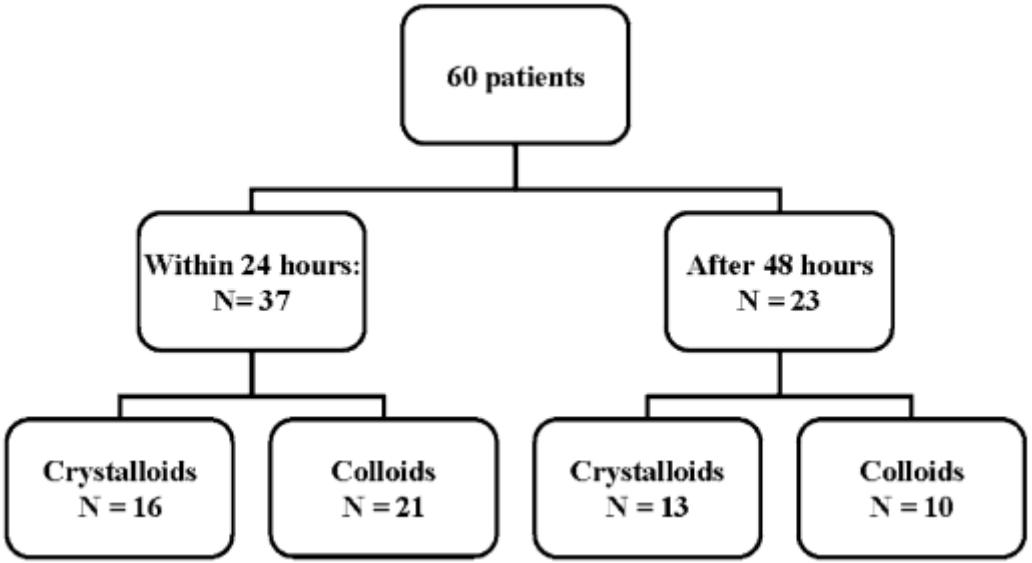
Pottecher, ICM 2010; 36: 1867-1874

Intensive Care Med (2010) 36:949–955
DOI 10.1007/s00134-010-1843-3

ORIGINAL

Gustavo Ospina-Tascon
Ana Paula Neves
Giovanna Occhipinti
Katia Donadello
Gustavo Büchele
Davide Simion
Maria-Luisa Chierego
Tatiana Oliveira Silva
Adriana Fonseca
Jean-Louis Vincent
Daniel De Backer

Effects of fluids on microvascular perfusion in patients with severe sepsis



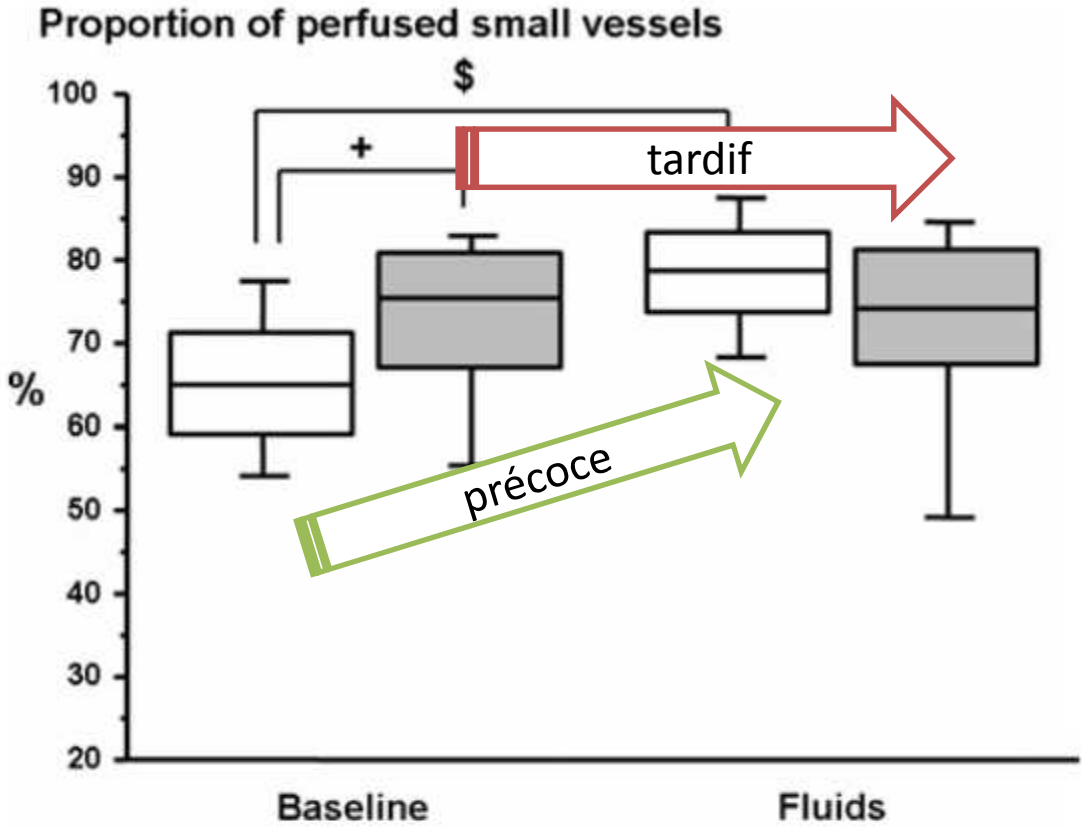


Fig. 2 Evolution of proportion of perfused small vessels in patients investigated early or late after diagnosis of severe sepsis. Patients investigated within 24 h of the diagnosis of severe sepsis (early, $n = 37$) are represented by *white rectangles*; patients investigated more than 48 h after diagnosis (late, $n = 23$) are represented by *gray rectangles*. $^{+}p < 0.01$ between the two groups, $^{\$}p < 0.01$ fluids versus baseline

Ospina-Tascon, ICM 2010; 36:949-955

P interstitielle augmente si le liquide fuit

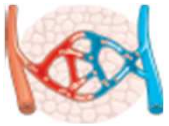
P capillaire ?
Hématocrite baisse

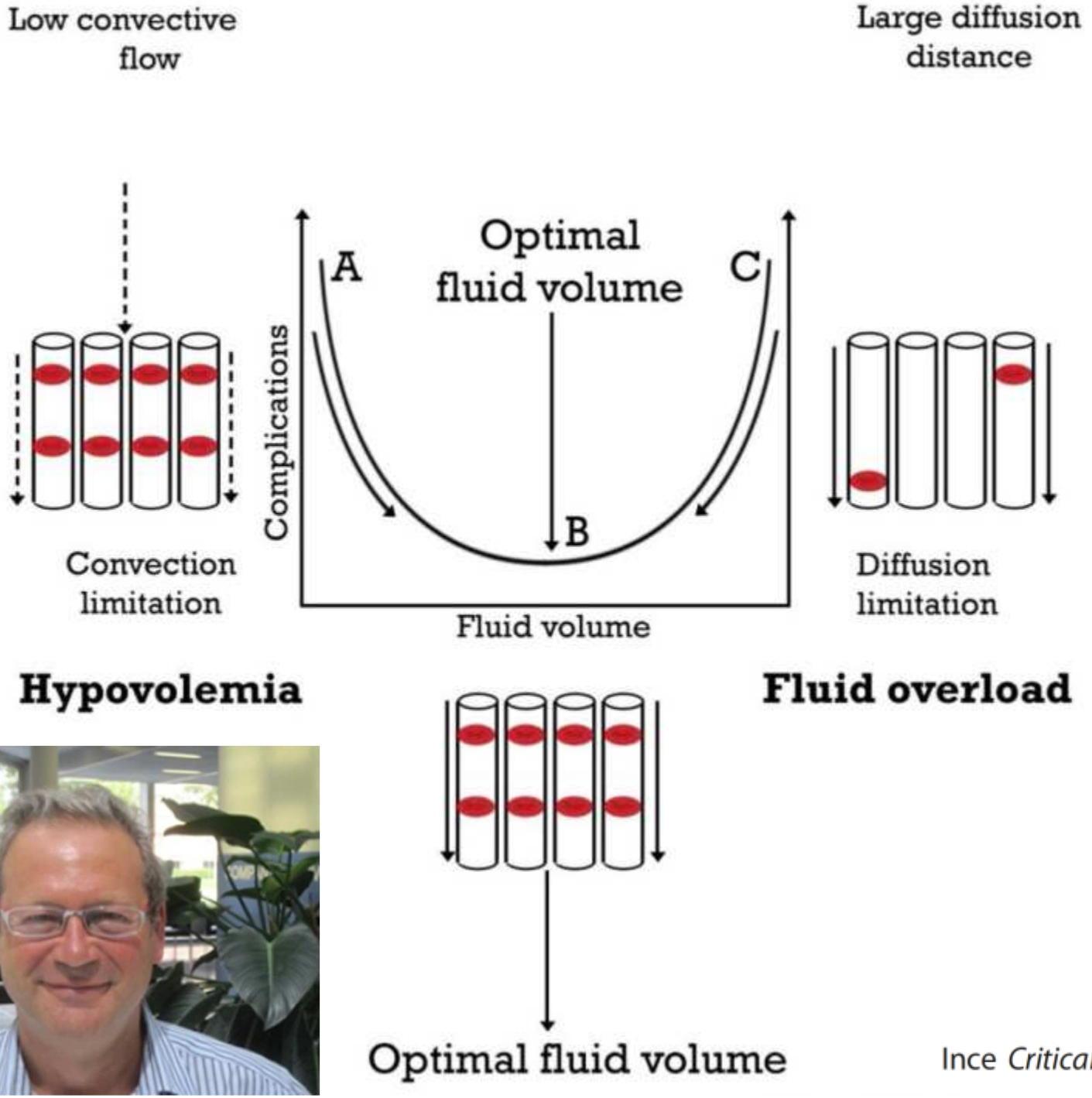
Débit microcirculatoire suit probablement le DC

Distance inter-capillaire
Augmente si la Pinterstitielle
Augmente trop

Débit= Pa-Pv (πr^4) / $8\eta L$
Débit= (Pa-Pc)/Ra = (Pc-Pv)/Rv

D'où $Pc = \frac{(Pa-Pv)}{1+Ra/Rv} + Pv$





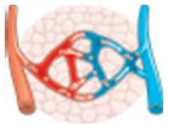
Ince *Critical Care* 2015, **19**:S8

Message : remplissage

- Oui mais ca dépend quand: au début sûrement, après pas sûr du tout…

- Lactate de sodium ?
- Hypertonic sodium lactate improves fluid balance and hemodynamics in porcine endotoxic shock.

  Duburcq et al Crit Care. 2014 Aug 14;18(4): 467e



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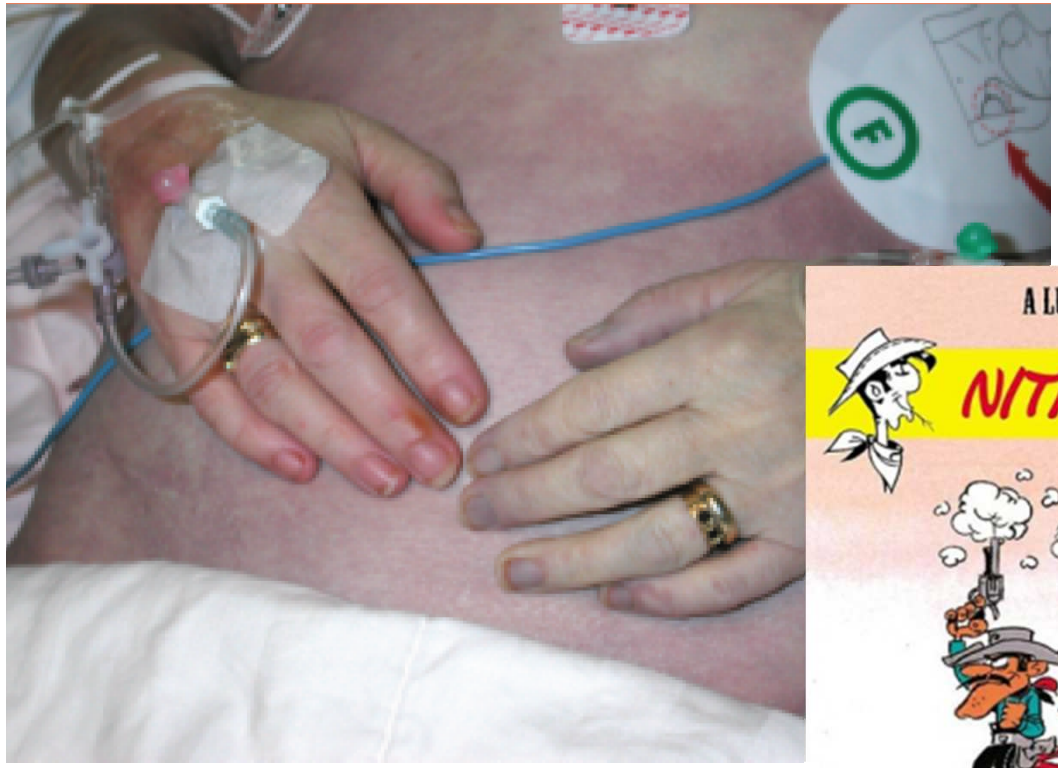
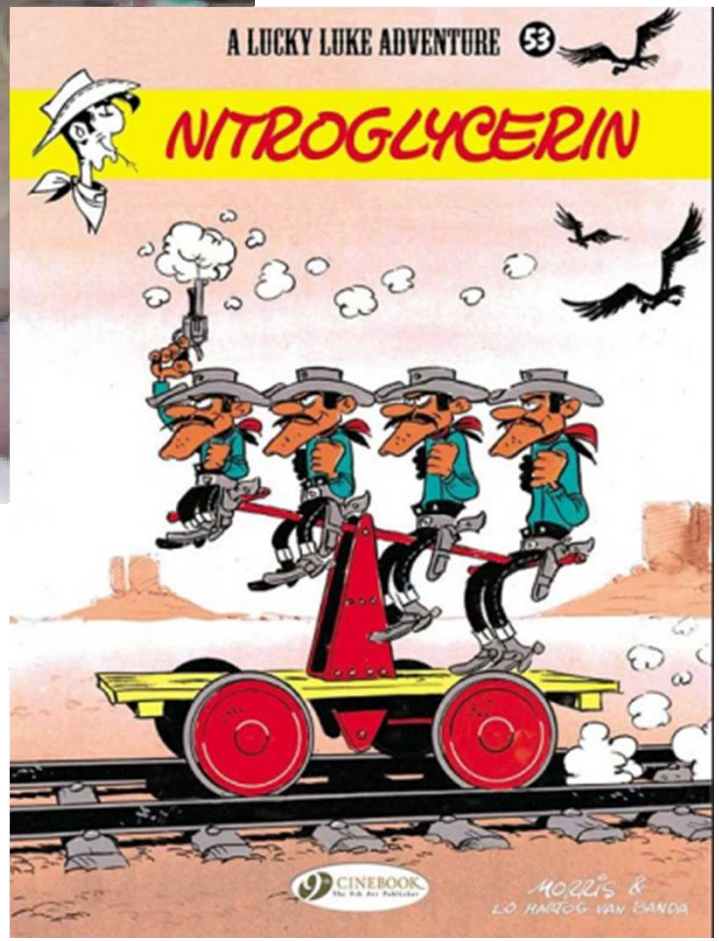




Quizz: quel traitement est perfusé sur périphérique rose ?

Vasodilatateurs

Université de Lille

Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock*

Angel López; Jose Angel Lorente; Jay Steingrub; Jan Bakker; Angela McLuckie; Sheila Willatts; Michael Brockway; Antonio Anzueto; Laurent Holzapfel; Desmond Breen; Michael S. Silverman; Jukka Takala; Jill bert Grover

l Vol. 32, No. 1

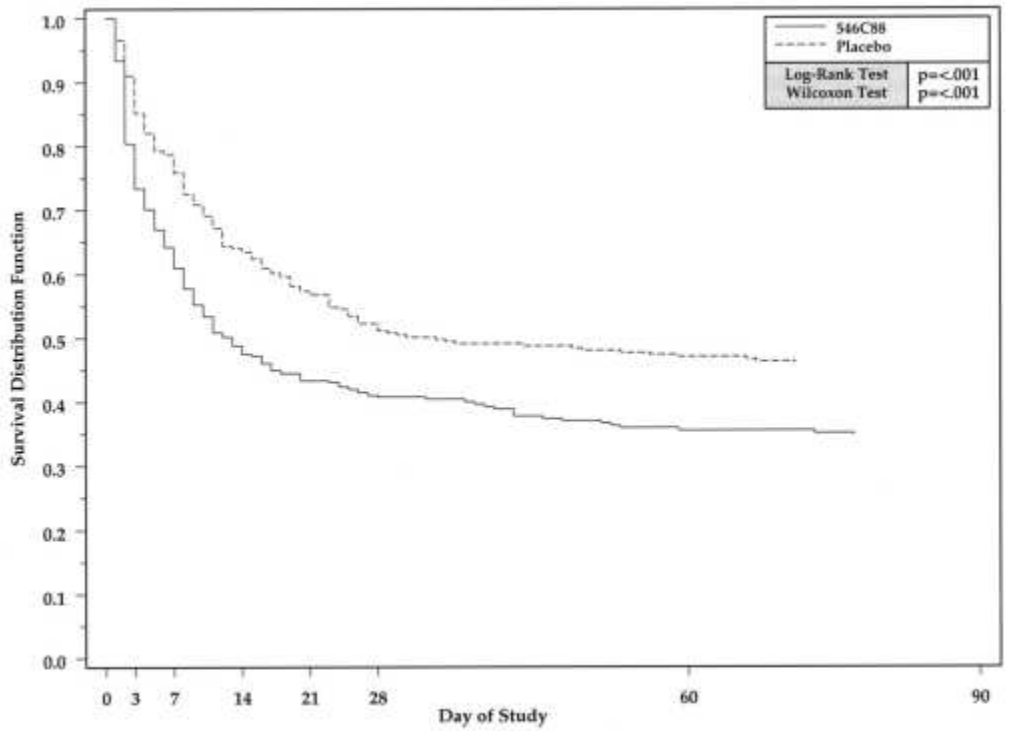
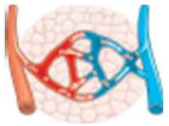


Figure 1. Kaplan-Meier survival plots up to day 90 for the 546C88 and placebo groups; stages 1 and 2 combined.



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Débit= Pa-Pv (πr4) / 8ηL
Débit= (Pa-Pc)/Ra = (Pc-Pv)/Rv

D'où $Pc = \frac{(Pa-Pv)}{1+Ra/Rv} + Pv$

P interstitielle

P capillaire
Hématocrite
Débit microcirculatoire

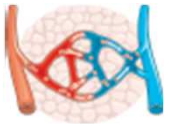
vasodilatation

Distance intercapillaire

P interstitielle

P capillaire ↗
Hématocrite ↗
Débit microcirculatoire ↗

Distance intercapillaire ↘



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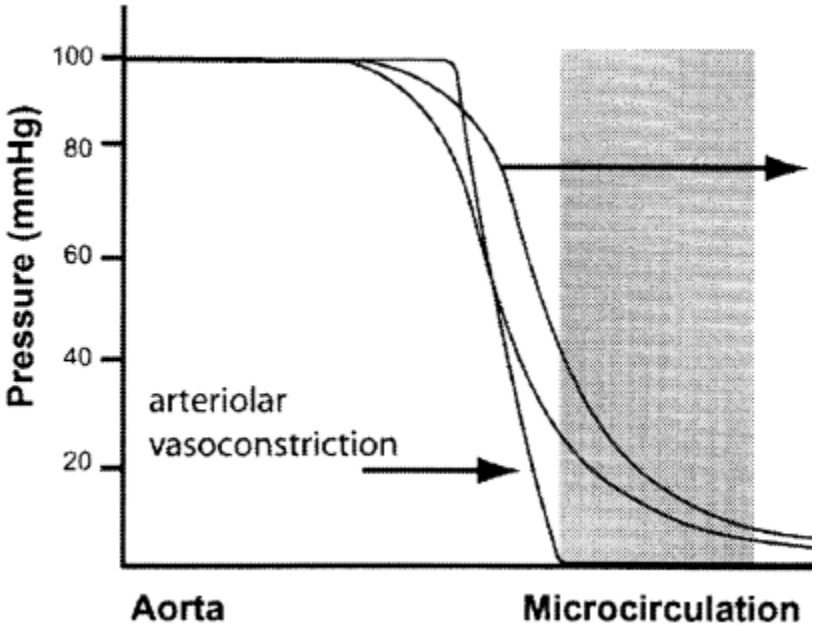
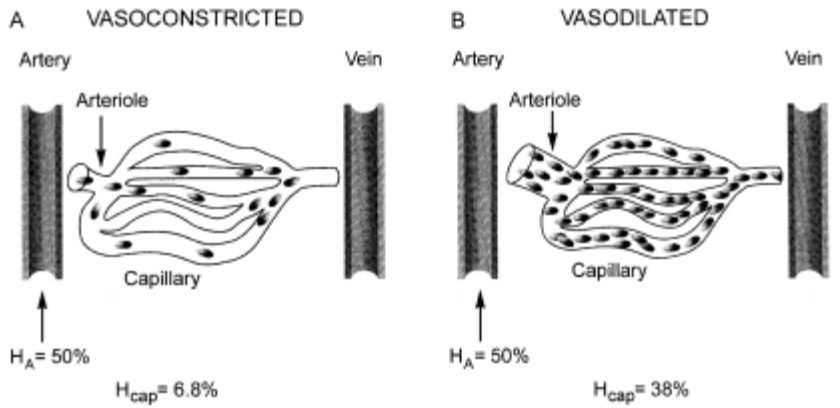
Intensive Care Med (2002) 28:1208–1217
DOI 10.1007/s00134-002-1407-2

REVIEW

Mattijn Buwalda
Can Ince

Opening the microcirculation: can vasodilators be useful in sepsis?





Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: A double-blind randomized placebo controlled trial

E. Christiaan Boerma, MD, PhD; Matty Koopmans, RN; Arjan Konijn, MD; Katerina Kaiferova, MD; Andries J. Bakker, PhD; Eric N. van Roon, PhD; Hanneke Buter, MD, PhD; Nienke Bruins, MD; Peter H. Egbers, MD; Rik T. Gerritsen, MD; Peter M. Koetsier, MD; W. Peter Kingma, MD; Michael A. Kuiper, MD, PhD, FCCP, FCCM; Can Ince, PhD

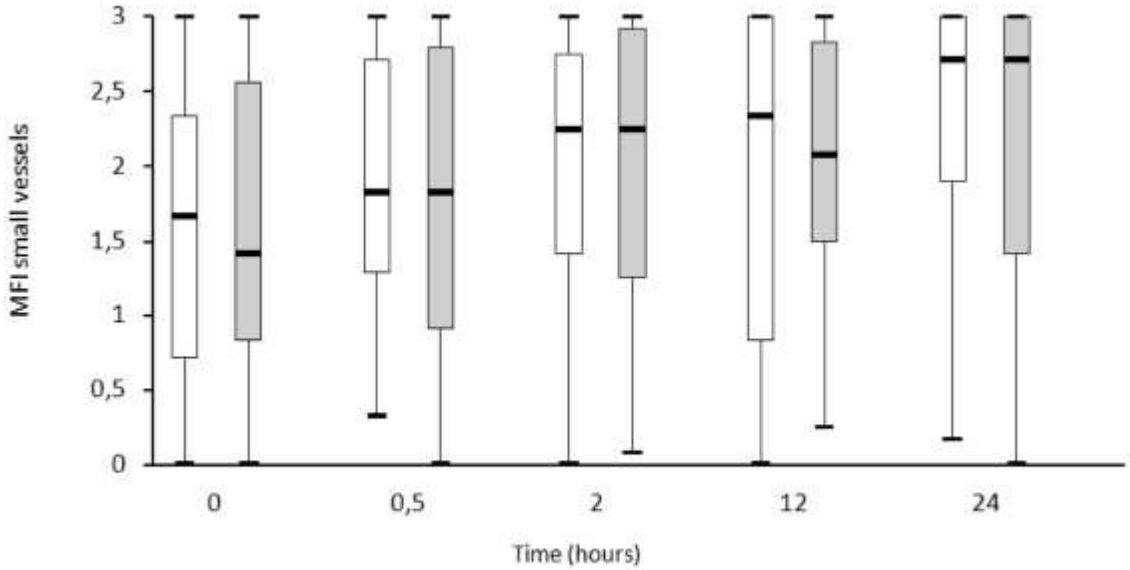


Figure 2. Box plots of sublingual microvascular flow index (*MFI*) in small vessels (<20 μm) during the 24-hr study period. *White boxes*, nitroglycerin, *gray boxes*, placebo.

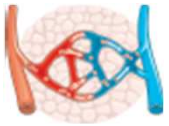


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Table 5. Morbidity and mortality outcome variables

Variables	Nitroglycerin (n = 35)	Placebo (n = 35)	p
ICU mortality, n (%)	11 (31.4)	4 (11.4)	.08
Hospital mortality, n (%)	12 (34.3)	5 (14.2)	.09
LOS ICU, all patients, median (IQR)	8 (4–12)	12 (7–16)	.03
LOS ICU, survivors, median (IQR)	9 (5–12)	18 (9–35)	.11
LOS hospital, all patients, median (IQR)	21 (8–35)	29 (17–48)	.04
LOS hospital, survivors, median (IQR)	11 (7–14)	18 (12–40)	.67
Cumulative SOFA day 1–5, all patients	30 (22–41)	46 (32–53)	.003
Cumulative SOFA day 1–5, survivors	31 (28–40)	46 (34–53)	.07
Cumulative SOFA ICU, all patients	46 (28–80)	66 (49–121)	.02
Cumulative SOFA ICU, survivors	50 (30–68)	67 (54–93)	.03
ARF RIFLE score maximum, median (IQR)	3 (0–3)	1 (0–3)	.37
CVVH, use of, n (%)	12 (34.3)	11 (31.4)	.87

ICU, intensive care unit; LOS, length of stay; SOFA, Sequential Organ Failure Assessment; ARF, acute renal failure; RIFLE, Risk, Injury, Failure, Loss, and Endstage; CVVH, continuous veno-venous hemofiltration.

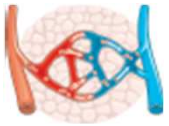
Crit Care Med 2010 Vol. 38, No. 1

Table 3. Microvascular variables over time

Variables	Baseline NTG (n = 35)	Placebo (n = 35)	30 mins NTG (n = 35)	Placebo (n = 35)	2 hrs NTG (n = 35)	Placebo (n = 35)	12 hrs NTG (n = 34)	Placebo (n = 35)	24 hrs NTG (n = 32)	Placebo (n = 34)
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)	2.34 (0.83–3)	2.08 (1.5–2.83)	2.71 (1.85–3)[b]	2.71 (1.27–3)[a]
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)	2.79 (2.08–3)	2.67 (2.5–2.92)	3 (2.75–3)[b]	2.86 (2.19–3)
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)	3 (2.81–3)	3 (2.92–3)	3 (3–3)[a]	2.89 (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)	14 (13.1–15.7)	13.9 (13.2–15.5)	13.9 (12.5–15.7)	14.7 (13.1–16.1)
PPV, %	98 (93–100)	97 (89–100)	100 (96–100)	97 (90–99)[c]	99 (96–100)	98 (93–100)	99 (93–100)	99 (93–100)	100 (98–100)	98 (86–100)[c]
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)	10 (8.3–10.8)	9.1 (8.2–10.5)	10.2 (8.7–11.2)	10.1 (8.5–10.7)
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)	1.22 (0–2.89)	1.44 (0.35–2)	0.74 (0–1.62)[b]	0.54 (0–1.76)[a]

NTG, nitroglycerin; MFI, microcirculatory flow index; TVD, total vessel density of (small) vessels; PPV, proportion of perfused(small) vessels; PVD, perfused (small) vessel density.

[a]$p < .05$; [b]$p < .0001$ after 24 hrs in comparison to baseline, nonparametric test for dependent samples; [c]$p < .05$ between groups, nonparametric test for independent samples. Cutoff value for small vessels <20 μm. All data are presented as medians (interquartile range).



Amélioration du SOFA mais augmentation (ns) de mortalité

Université de Lille

Randomized Controlled Trial of Inhaled Nitric Oxide for the Treatment of Microcirculatory Dysfunction in Patients With Sepsis*

Stephen Trzeciak, MD, MPH[1]; Lindsey J. Glaspey, BA[1]; R. Phillip Dellinger, MD[1]; Paige Durflinger, RRT[1]; Keith Anderson, RRT, MBA[1]; Cameron Dezfulian, MD[2]; Brian W. Roberts, MD[3]; Michael E. Chansky, MD[3]; Joseph E. Parrillo, MD[1,4]; Steven M. Hollenberg, MD[4]

TABLE 3. Outcome Measures

	All Patients ($n = 49$)	Inhaled Nitric Oxide ($n = 26$)	Sham ($n = 23$)	p
Δ Microcirculatory flow index (0–2 hr)	−0.06 (−0.17 to 0.07)	−0.06 (−0.20 to 0.03)	−0.03 (−0.14 to 0.15)	0.37
Lactate clearance (%) (0–2 hr)	−9 (−15 to 0)	−9 (−16 to 12)	−9 (−15 to 0)	0.59
Δ SOFA score (0–6 hr)	0 (−1 to 0)	0 (−1 to 0)	0 (−1 to 0)	0.96
Δ SOFA score (0–24 hr)	−1 (−2 to 0)	−1 (−2 to 0)	−1 (−1 to 0)	0.30
Organ dysfunction responder,[a] *n* (%)	13 (27)	8 (31)	5 (22)	0.48
In-hospital mortality, *n* (%)	15 (31)	9 (35)	6 (26)	0.52

SOFA = Sequential Organ Failure Assessment.

[a]Defined as a reduction in SOFA score of two or more points over 0–24 hours.

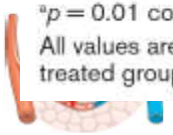
Data are expressed as median and interquartile range except where indicated otherwise.

TABLE 2. Plasma Nitrite Levels (μM) and Change in Plasma Nitrite Levels for the Inhaled Nitric Oxide and Sham Groups

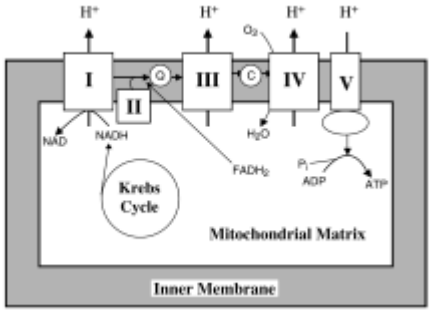
	All Patients	Inhaled Nitric Oxide	Sham
0 hr	0.20 (0.07–0.25)	0.21 (0.08–0.26)	0.14 (0.07–0.25)
2 hr	0.27 (0.15–0.52)	0.41 (0.24–0.63)	0.19 (0.12–0.31)
Δ 0–2 hr	0.09 (0.04–0.23)	0.25 (0.07–0.32)[a]	0.07 (0.03–0.10)

[a]$p = 0.01$ compared to sham group by Mann-Whitney *U* test.

All values are expressed as median and interquartile range. We found that the change in plasma nitrite was significantly increased in the inhaled nitric oxide–treated group compared with sham, $p = 0.01$.

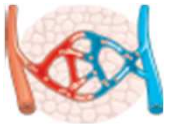


NO



- En conditions physiologiques
  - Produit par la NO synthase endothéliale: eNOS
  - Shear-stress sur les cellules endothéliales
  - Régulation par le calcium
  - Vasodilatation ET inhibition de l'adhésion et de l'aggrégation plaquettaire

- Lors du sepsis
  - iNOS
  - Cellules musculaires lisses, Macrophages, hépatocytes, cardiomyocytes
  - Non régulé autoamplifié



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Effets attendus du NO exogène

Effets bénéfiques

- Modulation du tonus vasculaire avec adaptation aux besoins métabolique locaux (?)
- Modulation de l'activité plaquettaire: activation, adhésion, agrégation
- Diminution de l'adhésion des leucocytes sur l'endothélium

Effets secondaires

- Peroxynitrite (stress oxydatif)
- S-Nitrosylation de l'albumine
- Inhibition du complexe IV de la mitochondrie (effet secondaire ?)
- Dysfonction hépatique/rénale
- Effet inotrope négatif ?

Early Lactate-Guided Therapy in Intensive Care Unit Patients

A Multicenter, Open-Label, Randomized Controlled Trial

Tim C. Jansen[1], Jasper van Bommel[1], F. Jeanette Schoonderbeek[3], Steven J. Sleeswijk Visser[4], Johan M. van der Klooster[5], Alex P. Lima[1], Sten P. Willemsen[2], and Jan Bakker[1], for the LACTATE study group*

[1]Department of Intensive Care, Erasmus MC University Medical Centre, Rotterdam, The Netherlands; [2]Department of Biostatistics, University Medical Centre Rotterdam, Rotterdam, The Netherlands; [3]Department of Intensive Care, Ikazia Hospital, Rotterdam, The Netherlands; [4]Department of Intensive Care, Reinier de Graaf Hospital, Delft, The Netherlands; and [5]Department of Intensive Care, St. Franciscus Gasthuis, Rotterdam, The Netherlands

CRITICAL CARE MEDICINE VOL 182 2010

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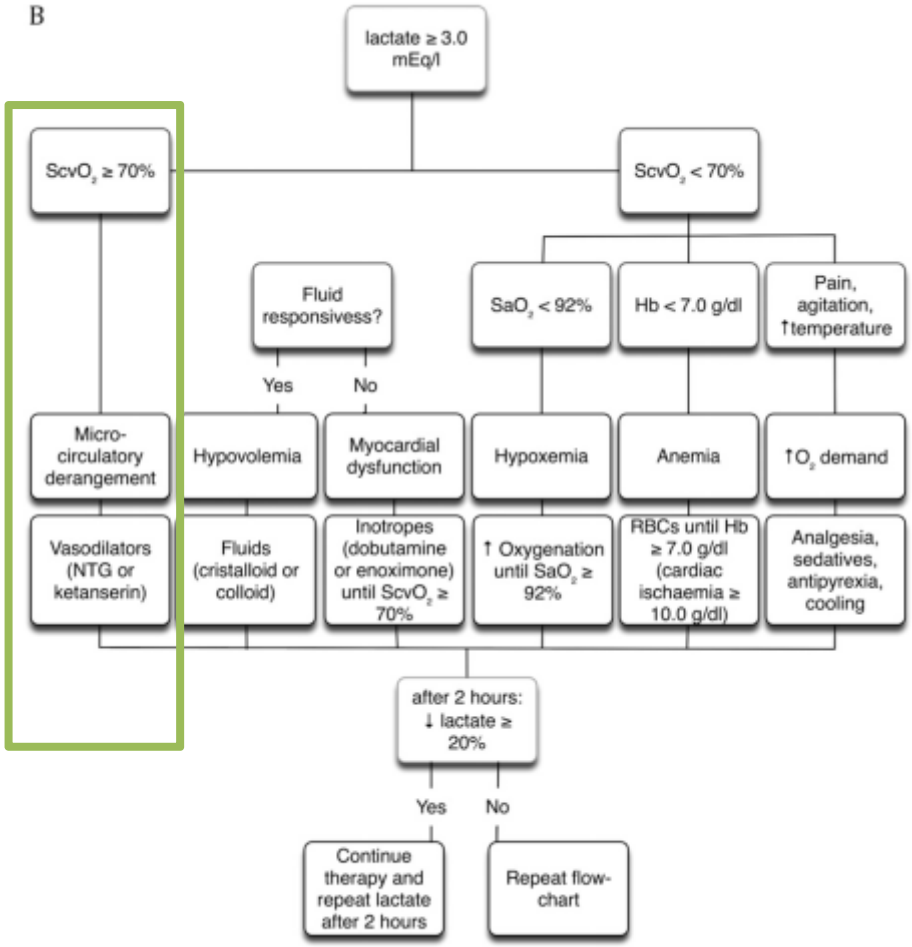


TABLE 3. FLUIDS AND VASOACTIVE MEDICATION USE DURING THE INITIAL TREATMENT PHASE AND UP TO 72 HOURS

Treatment	Control Group	Lactate Group	*P* Value
Fluids, ml*			
0–8 h†	2,194 ± 1,669	2,697 ± 1,965	0.011
9–72 h‡	10,043 ± 6,141	8,515 ± 4,987	0.055
Red blood cell transfusion, ml			
0–8 h†	196 ± 495	322 ± 1037	0.15
9–72 h‡	345 ± 667	423 ± 1300	0.59
Any inotropic agent, %§			
0–8 h†	32.9	40.1	0.17
9–72 h‖	44.2	35.2	0.12
Any vasodilator, %¶			
0–8 h†	20.2	42.5	<0.001
9–72 h‖	27.1	43.2	0.005
Any vasopressor, %**			
0–8 h†	63.6	69.5	0.25
9–72 h‖	63.7	71.4	0.16

Definition of abbreviation: ICU = intensive care unit.

P values as calculated by two-sample Student *t* test or the chi-square test, as appropriate.

* Sum of crystalloid and colloid fluids.

† Values are shown for all patients.

‡ Cumulative values (± SD) are shown for patients who were still admitted to the ICU after 72 h.

§ Dobutamine, enoximone, or epinephrine.

‖ Proportions are shown for patients who stayed for more than 8 h in the ICU.

¶ Nitroglycerin or ketanserin.

** Norepinephrine, dopamine, or phenylephrine.

Jansen, AJRCCM 2010; 182:752-761

EJA

Eur J Anaesthesiol 2014; **31**:1–10

ORIGINAL ARTICLE

Testing a conceptual model on early opening of the microcirculation in severe sepsis and septic shock

A randomised, controlled pilot study

Peter H.J. van der Voort, Mark van Zanten, Rob J. Bosman, Ilse van Stijn, Jos P.J. Wester, Rutger van Raalte, Heleen M. Oudemans-van Straaten and Durk F. Zandstra

37 vs 40 patients

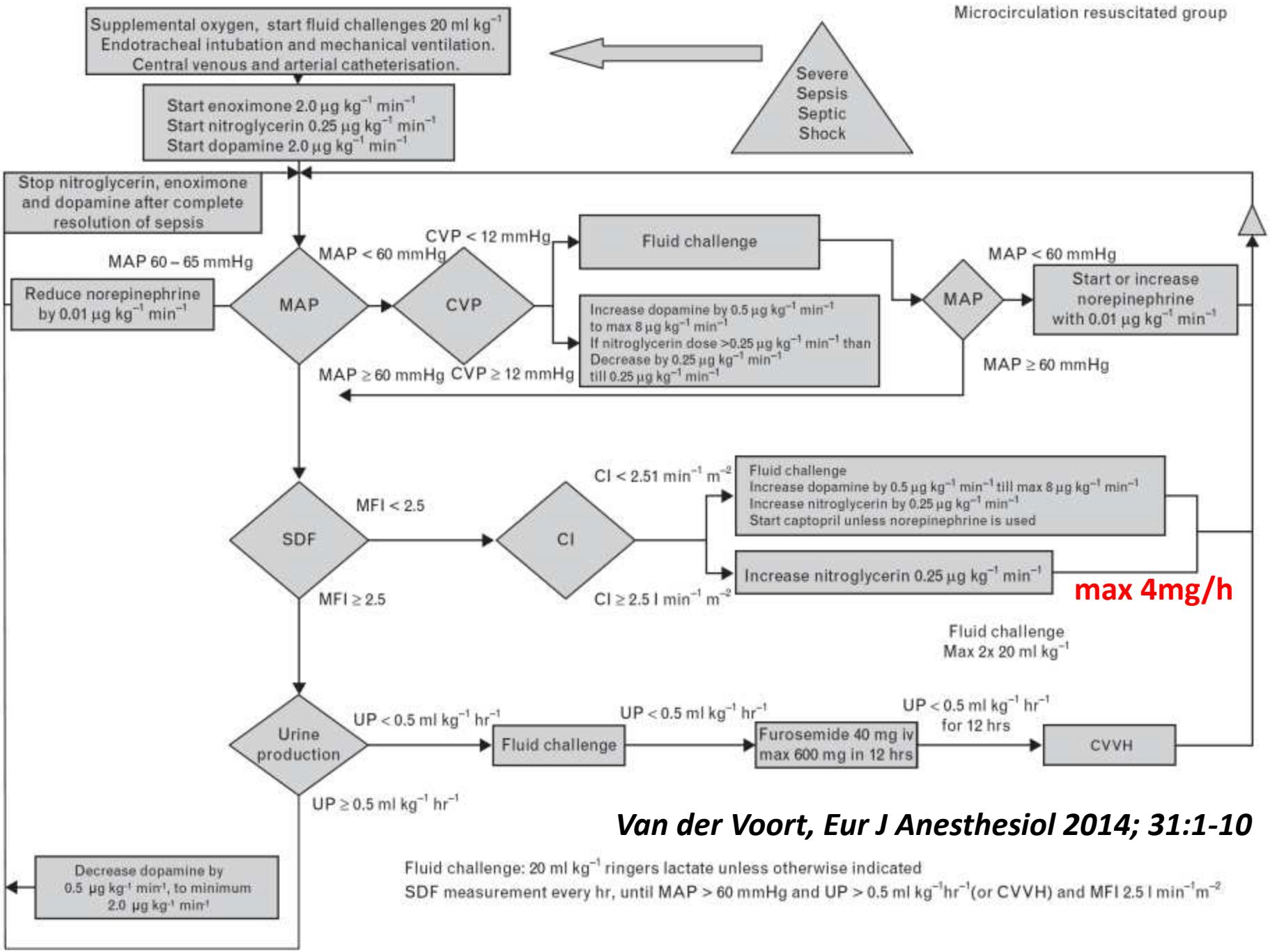

Microcirculation resuscitated group
Supplemental oxygen, start fluid challenges 20 ml kg-1
Endotracheal intubation and mechanical ventilation.
Central venous and arterial catheterisation.
Start enoximone 2.0 µg kg-1 min-1
Start nitroglycerin 0.25 µg kg-1 min-1
Start dopamine 2.0 µg kg-1 min-1
Severe Sepsis Septic Shock
Stop nitroglycerin, enoximone and dopamine after complete resolution of sepsis
MAP 60 – 65 mmHg
Reduce norepinephrine by 0.01 µg kg-1 min-1
MAP
MAP < 60 mmHg
CVP
CVP < 12 mmHg
Fluid challenge
Increase dopamine by 0.5 µg kg-1 min-1 to max 8 µg kg-1 min-1
If nitroglycerin dose >0.25 µg kg-1 min-1 than Decrease by 0.25 µg kg-1 min-1 till 0.25 µg kg-1 min-1
MAP ≥ 60 mmHg CVP ≥ 12 mmHg
MAP
MAP < 60 mmHg
Start or increase norepinephrine with 0.01 µg kg-1 min-1
MAP ≥ 60 mmHg
SDF
MFI < 2.5
MFI ≥ 2.5
CI
CI < 2.51 min-1 m-2
CI ≥ 2.5 l min-1 m-2
Fluid challenge
Increase dopamine by 0.5 µg kg-1 min-1 till max 8 µg kg-1 min-1
Increase nitroglycerin by 0.25 µg kg-1 min-1
Start captopril unless norepinephrine is used
Increase nitroglycerin 0.25 µg kg-1 min-1
max 4mg/h
Fluid challenge
Max 2x 20 ml kg-1
Urine production
UP < 0.5 ml kg-1 hr-1
Fluid challenge
UP < 0.5 ml kg-1 hr-1
Furosemide 40 mg iv
max 600 mg in 12 hrs
UP < 0.5 ml kg-1 hr-1
for 12 hrs
CVVH
UP ≥ 0.5 ml kg-1 hr-1
Decrease dopamine by 0.5 µg kg-1 min-1, to minimum 2.0 µg kg-1 min-1
Van der Voort, Eur J Anesthesiol 2014; 31:1-10
Fluid challenge: 20 ml kg-1 ringers lactate unless otherwise indicated
SDF measurement every hr, until MAP > 60 mmHg and UP > 0.5 ml kg-1hr-1(or CVVH) and MFI 2.5 l min-1m-2

Table 2 Cumulative quantity of vasoactive drugs and fluids over the first 3 days of ICU treatment

	Microcirculation resuscitated group	Standard resuscitation group	*P*
Noradrenaline (mg)	1.1 (0.01 to 5.2)	2.0 (0.13 to 4.4)	NS
Dopamine (mg)	834 (455 to 1074)	N/A	N/A
Dobutamine (mg)	N/A	5.0 (0.0 to 172.0)	N/A
Enoximone (mg)	243 (107 to 320)	N/A	N/A
Nitroglycerin (mg)	57 (33 to 80)	N/A	N/A
Crystalloids (ml)	9360 (7154 to 12 494)	6533 (4396 to 10 785)	0.028
Colloids (gelatins and albumin, ml)	5500 (1500 to 9600)	1950 (0.0 to 3300)	0.006
Red blood cell transfusion (ml)	0.0 (0.0 to 280)	0.0 (0.0 to 0.0)	NS

Data are median (IQR). N/A, not applicable; NS, nonsignificant.

L'étude est négative
Le protocole dure 3 jours…
Beaucoup de remplissage..

Van der Voort, Eur J Anesthesiol 2014; 31:1-10

Lima *et al. Critical Care* 2014, **18**:R126
http://ccforum.com/content/18/3/R126

CRITICAL CARE

RESEARCH Open Access

Nitroglycerin reverts clinical manifestations of poor peripheral perfusion in patients with circulatory shock

Alexandre Lima*, Michel E van Genderen, Jasper van Bommel, Eva Klijn, Tim Jansem and Jan Bakker

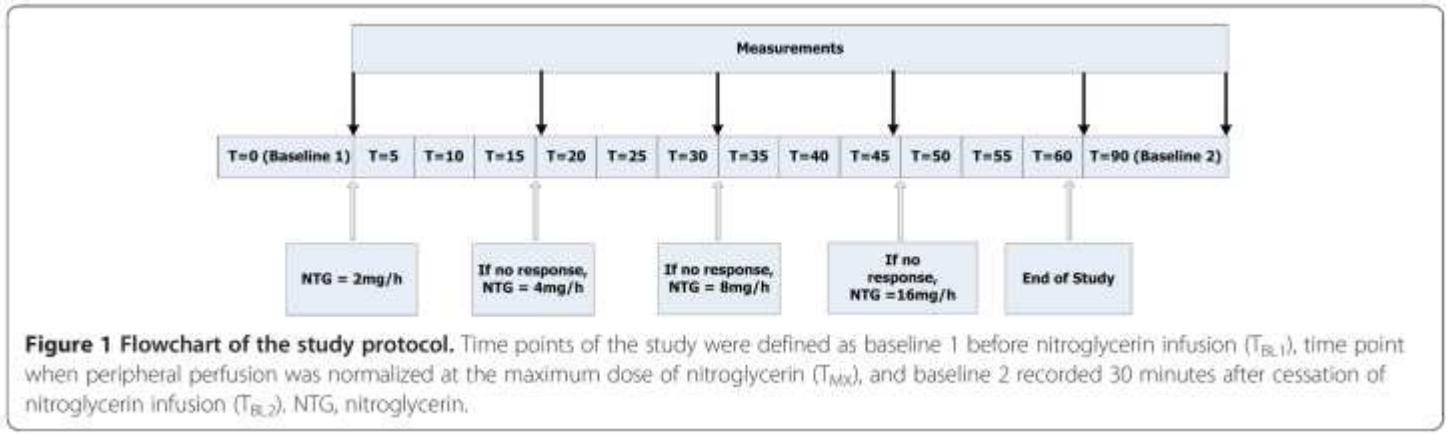


Figure 1 Flowchart of the study protocol. Time points of the study were defined as baseline 1 before nitroglycerin infusion (T_{BL1}), time point when peripheral perfusion was normalized at the maximum dose of nitroglycerin (T_{MX}), and baseline 2 recorded 30 minutes after cessation of nitroglycerin infusion (T_{BL2}). NTG, nitroglycerin.

15 patients
93% des patients sous noradrénaline

Table 2 Global hemodynamic variables recorded in the three different time points during execution of the study protocol (n = 15)

	T_{BL1}	T_{MX}	T_{BL2}
Heart rate, beats per minute	95 (4.3)	97 (4.4)	98 (4.4)
Systolic blood pressure, mm Hg	113 (4.6)	94 (4.0)[a]	111 (3.8)[a]
Diastolic blood pressure, mm Hg	52 (4.9)	49 (4.8)[a]	57 (4.9)[a]
Mean arterial blood pressure, mm Hg	75 (3.0)	61 (2.9)[a]	71 (2.3)[a]
Central venous pressure, mm Hg	12 (4.0)	9 (5.0)[a]	10 (6.0)
Cardiac index, n = 6, L/min per m^2	4.1 (0.4)	3.8 (0.5)	3.9 (0.4)
Stroke volume, n = 6, mL	78 (15)	66 (14)	77 (12)

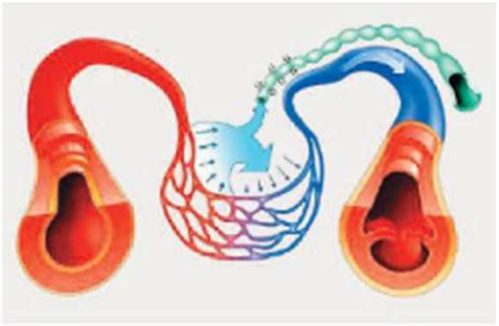
Data are presented as mean (standard error). [a]P <0.05 versus previous time point (linear model for repeated measurements). Time points are defined as before nitroglycerin infusion (T_{BL1}), at the maximum dose of nitroglycerin (T_{MX}), and 30 minutes after cessation of nitroglycerin (T_{BL2}). Cardiac index and stroke volume were measured in six patients.

Lima, Crit Care 2014; 18:R126

Table 3 Peripheral perfusion parameters recorded in the three different time points during execution of the study protocol (n = 15)

	T_{BL1}	T_{MX}	T_{BL2}
Capillary refill time, seconds	9.4 (0.6)	4.8 (0.3)[a]	7.1 (0.8)[a]
Tskin-diff, degrees Celsius	3.3 (0.7)	0.7 (0.6)[a]	1.8 (0.6)[a]
PI.log, percentage	–0.5 (0.2)	0.7 (0.1)[a]	0.2 (0.1)[a]
StO_2, percentage	75 (3.4)	84 (2.7)[a]	79 (2.8)
Tissue hemoglobine index, arbitrary units	11.1 (1.3)	13.2 (1.4)[a]	11.6 (1.2)[a]
$RincStO_2$, n = 13, percentage per second	1.9 (0.08)	2.8 (0.05)[a]	2.4 (0.09)[a]
$RdecStO_2$, n = 13, percentage per minute	8.6 (0.5)	9.2 (0.6)	9.14 (0.7)

Data are presented as mean (standard error). [a]P <0.05: previous time point (linear model for repeated measurements). Time points are defined as before nitroglycerin infusion (T_{BL1}), at the maximum dose of nitroglycerin (T_{MX}), and 30 minutes after cessation of nitroglycerin (T_{BL2}). Rate of tissue oxygen saturation increase after arterial occlusion ($RincStO_2$) and rate of tissue oxygen saturation deoxygenation during arterial occlusion ($RdecStO_2$) were collected from 13 patients. PI, perfusion index; Tskin-diff, forearm-to-fingertip skin-temperature gradient.



Timing

Précoce

- Nitroglycérine (Lima, Crit Care 2014) titrée
- Nitroglycérine avec DXM, enoximone, Dopamine (Van der Voort, Eur J of anesthesiol 2014) dose max de ntg
- Nitroglycérine avec EGDT (Jansen, AJRCCM 2009)

Après optimisation: 2 RCT

- Nitroglycérine 2mg

(Boerma, Crit Care Med 2009)

- NO inhalé 40 ppm

(Tzreciak, Crit Care Med 2014)

Pas de sélection des patients sur anomalies au départ !

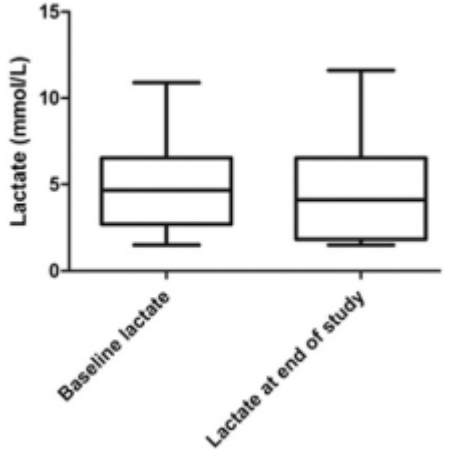
Effects of ketanserin on microcirculatory alterations in septic shock: An open-label pilot study☆

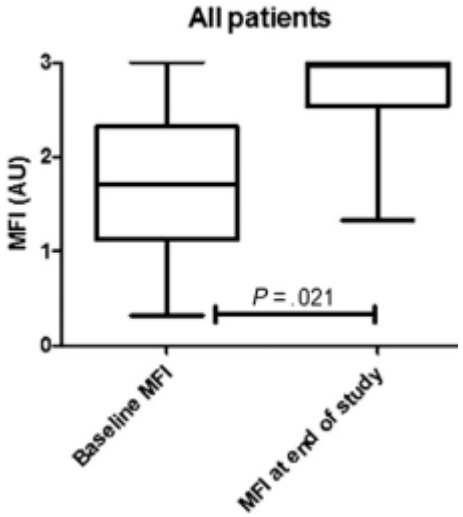
Namkje A.R. Vellinga, MD, PhD [a,b], Gerke Veenstra, MD [a], Claudia Scorcella, MD [a], Matty Koopmans, RN, MSc [a,*], Eric N. van Roon, PhD [c], Can Ince, PhD [b], E. Christiaan Boerma, MD, PhD [a,b]

[a] Department of Intensive Care, Medical Center Leeuwarden, Leeuwarden, the Netherlands
[b] Department of Translational Physiology, Academic Medical Center, Amsterdam, the Netherlands
[c] Department of Clinical Pharmacy and Pharmacology, Medical Center Leeuwarden, Leeuwarden, the Netherlands

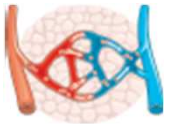
Anti R $5HT_{2A}$ sélectif (vasoD) et
diminution de l'agrégation plaquettaire
action inhibitrice iNOS (NFKB, ERK) ? *
action stimulatrice respiration mitochondriale (PTP) *

Antagoniste alpha-1





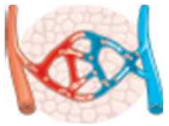
Anomalies initiales prérequis



****: Liu; Free Radic Bio Mol Med 2013: 65: 658-666***

vasodilatateurs

- Oui sûrement mais ce n'est pas encore prouvé et il ne faut pas compromettre la macrocirculation (mais ça c'est plus simple à repérer…)
- *Penser aux patchs de dérivés nitrés pour les extrémités mal perfusées*



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Intensive Care Med (2016) 42:211–221
DOI 10.1007/s00134-015-4133-2

ORIGINAL

Gustavo A. Ospina-Tascón
Mauricio Umaña
William F. Bermúdez
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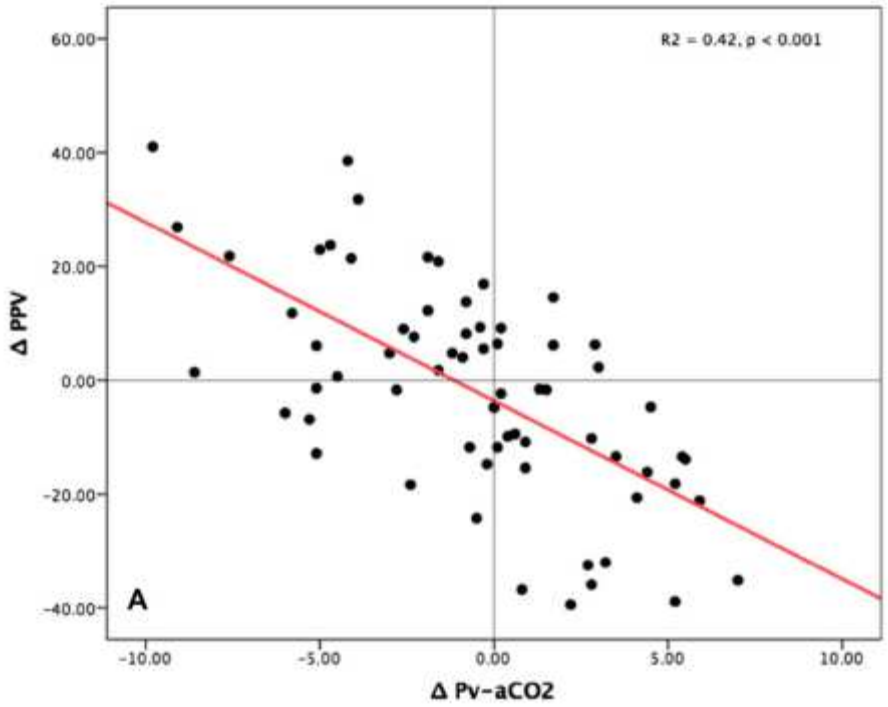
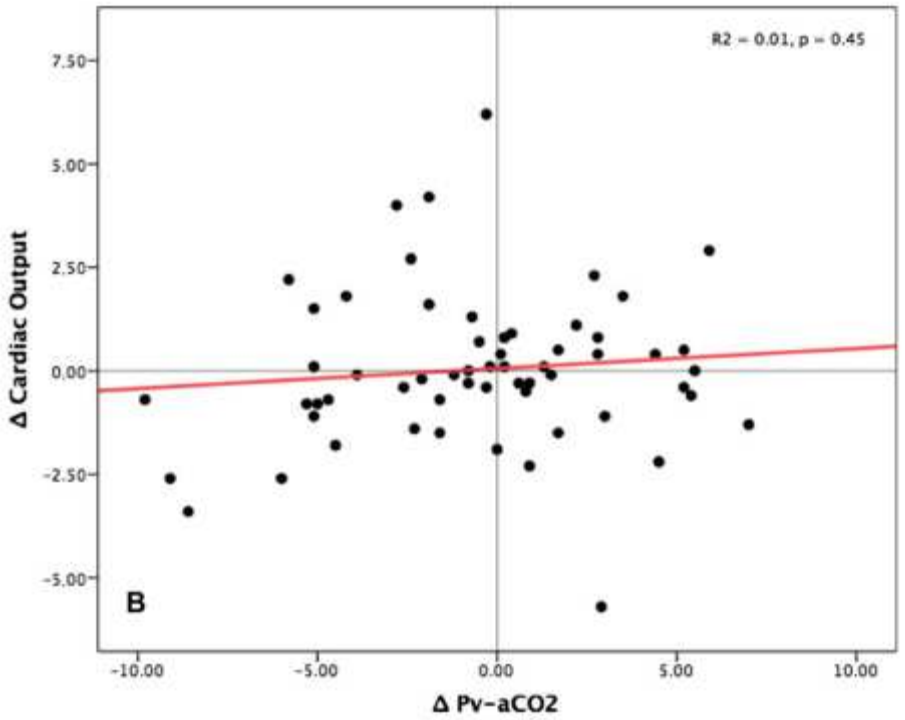
Juan D. Valencia
Humberto J. Madriñán
Glenn Hernandez
Alejandro Bruhn
César Arango-Dávila
Daniel De Backer

Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock?





Edul et al. Annals of Intensive Care 2014, 4:39
http://www.annalsofintensivecare.com/content/4/1/39

Annals of Intensive Care
a SpringerOpen Journal

RESEARCH Open Access

Dissociation between sublingual and gut microcirculation in the response to a fluid challenge in postoperative patients with abdominal sepsis

Vanina Siham Kanoore Edul[1,2], Can Ince[1], Noelia Navarro[3], Luciana Previgliano[3], Alejandro Risso-Vazquez[3], Paolo Nahuel Rubatto[3] and Arnaldo Dubin[2,3*]

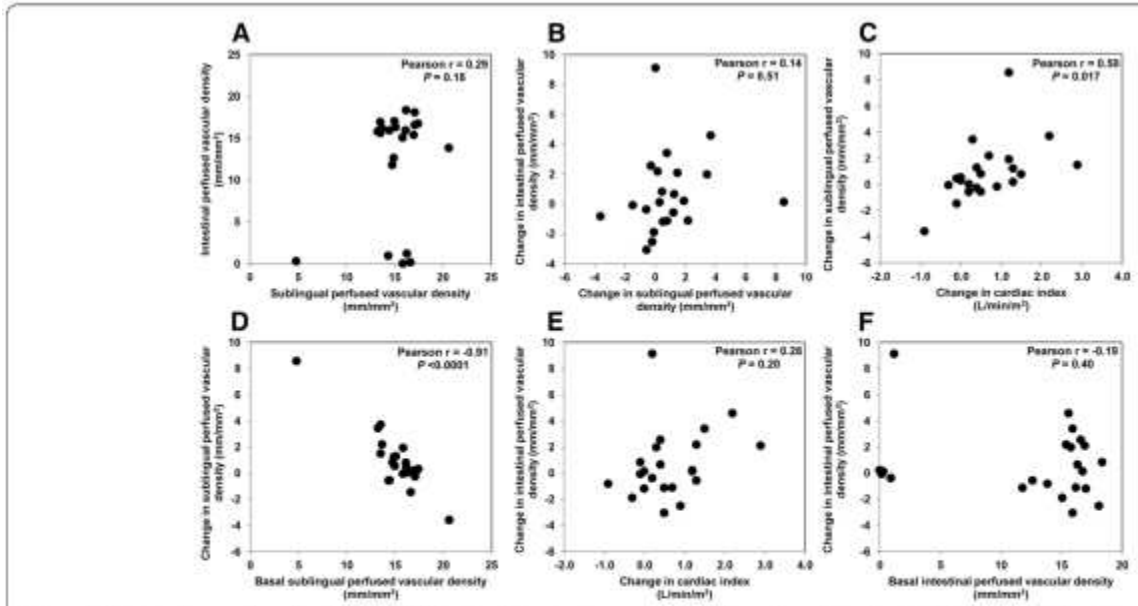


Figure 2 Perfused vascular density (PVD). (A) Correlation between basal sublingual and intestinal PVD. **(B)** Correlation between the changes in sublingual and intestinal PVD in response to the fluid challenge. **(C)** Correlation between the changes in cardiac index and sublingual PVD in response to the fluid challenge. **(D)** Correlation between the changes in sublingual PVD in response to the fluid challenge and the basal sublingual PVD. **(E)** Correlation between the changes in cardiac index and intestinal PVD in response to the fluid challenge. **(F)** Correlation between the changes in intestinal PVD in response to the fluid challenge and the basal intestinal PVD.

Table 2 Systemic cardiovascular variables and tissue perfusion parameters before and after the fluid challenge

	Before	After	P
Heart rate (beats/min)	87 ± 27	86 ± 23	0.45
Mean arterial blood pressure (mm Hg)	68 ± 11	82 ± 12	<0.0001
Central venous pressure (mm Hg)	10 ± 4	12 ± 6	<0.01
Intra-abdominal pressure (mm Hg)	8 ± 3	8 ± 3	0.33
Abdominal perfusion pressure (mm Hg)	61 ± 11	74 ± 13	<0.0001
Cardiac index (L/min/m^2)	2.6 ± 0.5	3.3 ± 1.0	<0.01
Respiratory pulse pressure variation (%)	10 ± 6	7 ± 3	<0.02
Arterial lactate (mmol/L)	2.8 ± 2.2	2.7 ± 2.3	0.29
Central venous oxygen saturation (%)	72 ± 7	74 ± 9	0.21
Central venous arterial PCO_2 (mm Hg)	6 ± 2	5 ± 2	<0.05
Central-peripheral temperature (°C)	5.0 ± 1.9	5.1 ± 2.2	0.78
Sublingual microcirculation			
Proportion of perfused vessels	0.92 ± 0.14	0.96 ± 0.05	0.23
Microvascular flow index	2.6 ± 0.5	2.8 ± 0.2	0.12
Proportion of perfused vessels	0.92 ± 0.14	0.96 ± 0.05	0.23
Microvascular flow index	2.6 ± 0.5	2.8 ± 0.2	0.12
Red blood cell velocity (μm/s)	912 ± 270	1,064 ± 200	<0.002
Heterogeneity flow index	1.2 ± 0.6	1.0 ± 0.2	0.09
CV red blood cell velocity	0.49 ± 0.24	0.40 ± 0.15	<0.03
Intestinal microcirculation			
Total vascular density (mm/mm^2)	16.9 ± 1.8	17.4 ± 1.9	0.22
Proportion of perfused vessels	0.73 ± 0.39	0.73 ± 0.37	0.88
Microvascular flow index	2.0 ± 1.1	2.1 ± 1.1	0.34
Red blood cell velocity (μm/s)	679 ± 37		0.12
Heterogeneity flow index	8.9 ± 18.0	15.4 ± 42.7	0.28
CV red blood cell velocity	0.46 ± 0.36	0.37 ± 0.26	0.31

normal

Anormal mais stomie fraiche…

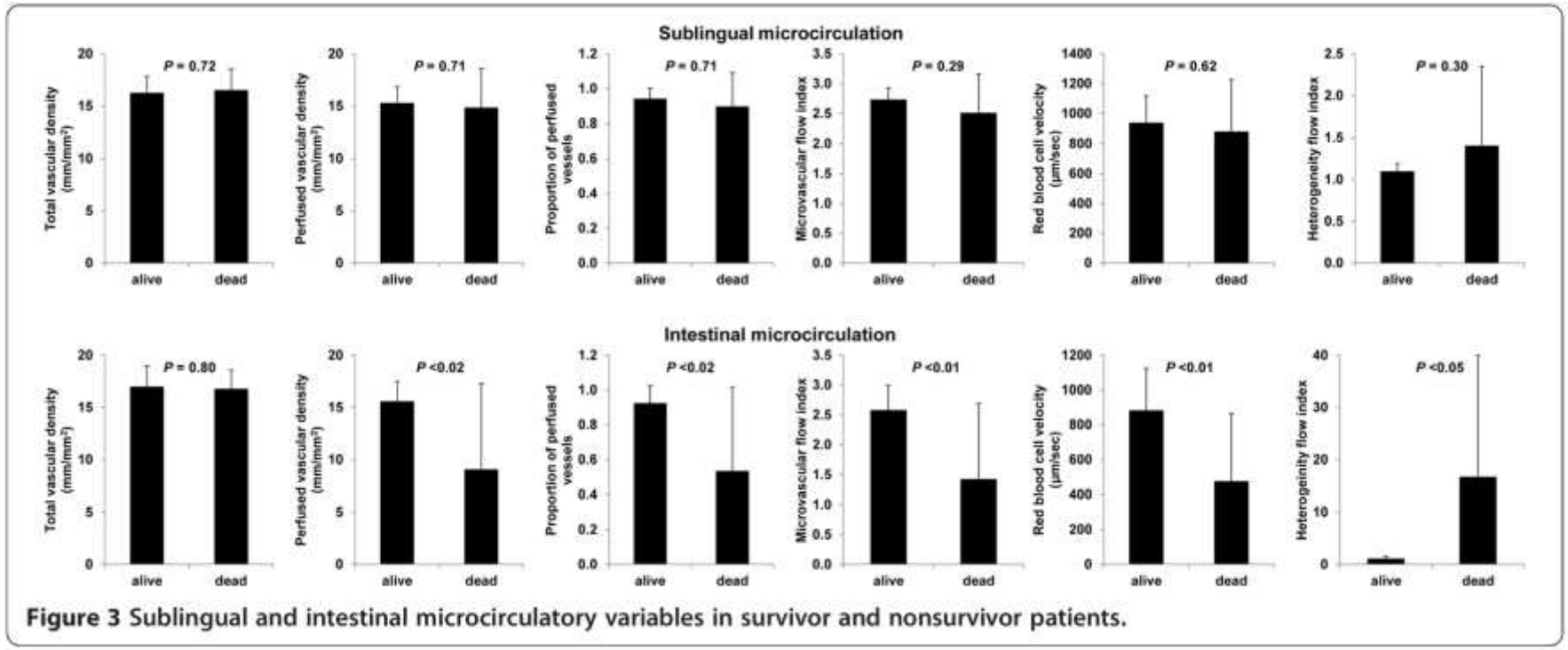


Figure 3 Sublingual and intestinal microcirculatory variables in survivor and nonsurvivor patients.

Meilleure discrimination pronostique de la microcirculation intestinale
Dissociation entre les deux microcirculations
Gros plus: avant après remplissage
Moins : stomies « fraiches », PPV sublinguale normale

Jacquet-Lagrèze et al. Critical Care 2014, 18:R153
http://ccforum.com/content/18/4/R153

CRITICAL CARE

RESEARCH Open Access

A new device for continuous assessment of gut perfusion: proof of concept on a porcine model of septic shock

Matthias Jacquet-Lagrèze[1*], Jeanne-Marie Bonnet-Garin[2], Bernard Allaouchiche[1,3], Olivia Vassal[1], Damien Restagno[2], Christian Paquet[2], Jean-Yves Ayoub[2], Jérôme Etienne[3,4], François Vandenesch[3,4], Olivier Daulwader[4] and Stéphane Junot[2]

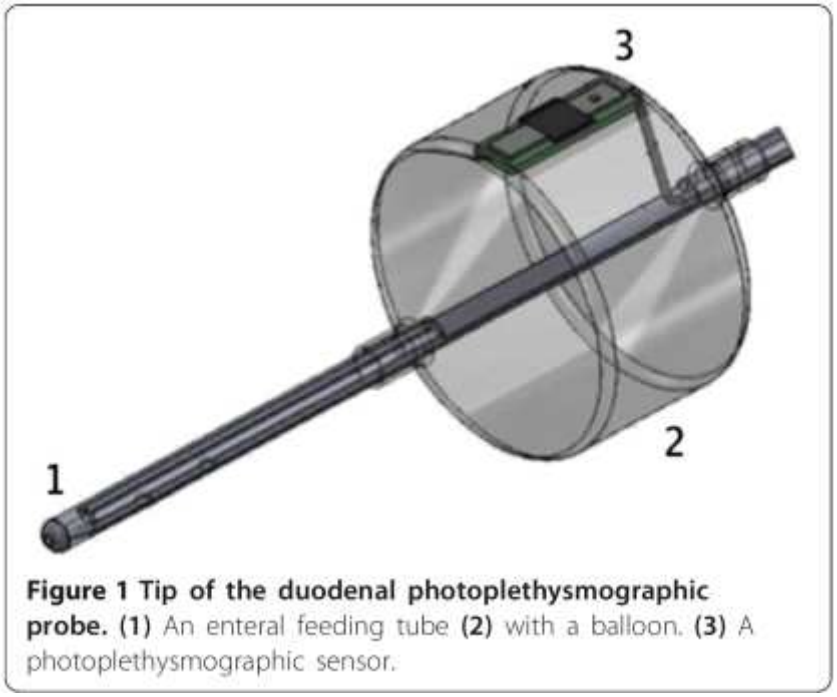
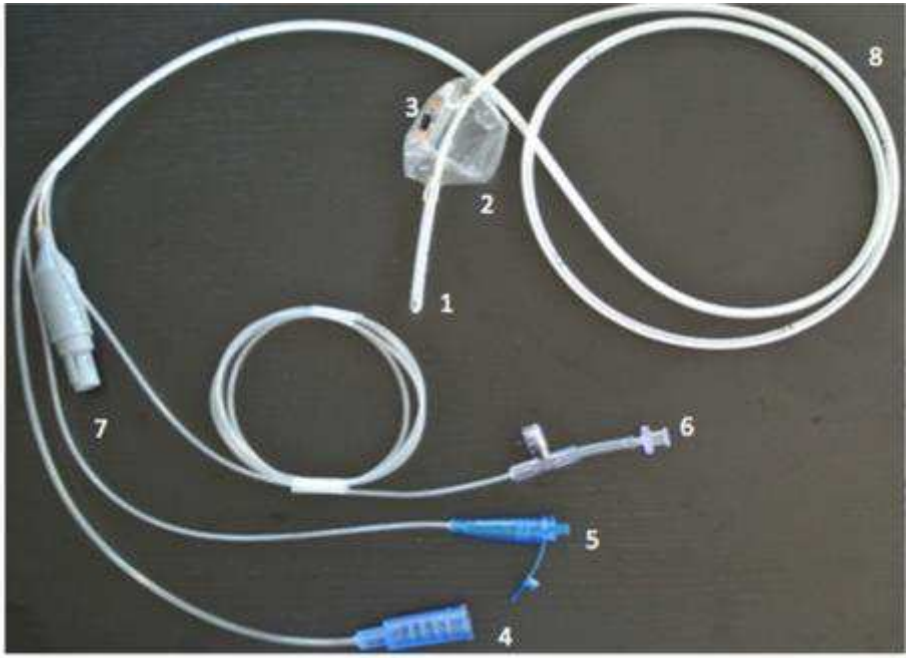
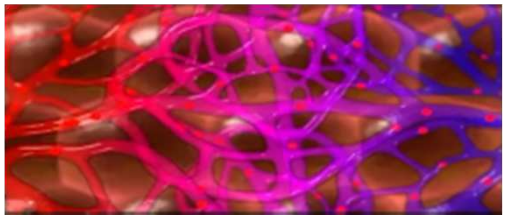


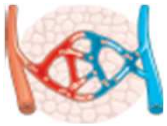
Figure 1 Tip of the duodenal photoplethysmographic probe. (1) An enteral feeding tube **(2)** with a balloon. **(3)** A photoplethysmographic sensor.





Conclusions

- La microcirculation et la macrocirculation sont dissociées en partie lors des états de choc
- L'hétérogénéité des atteintes microcirculatoires rend difficile leur détection en clinique (marbrures, $ScvO_2$ élevée plus lactate élevé, gradient de PCO_2)
- La microcirculation d'intérêt est probablement l'intestin mais on manque d'outils
- Remplissage :
  - La microcirculation est « précharge-dépendante » au départ
  - Probablement beaucoup moins après
- Vasodilatateurs (kétansérine)
- S'il n'y a pas d'anomalies microcirculatoires, probablement ne pas les traiter !
- Si on les traite, probablement très tôt et pas longtemps



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