Monitoring the microcirculation to guide resuscitation

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TISSUE PERFUSION: Key points

- Microcirculatory perfusion is a key determinant of tissue perfusion.
- Microvascular perfusion is under control of different mechanisms than systemic hemodynamics.
- O2 transport is driven at microcirculatory level by diffusion more than by convection.
The density of capillaries is a primary determinant of tissue oxygenation

Trzeciak et al
Crit Care 9:S20;2005
Microcirculatory alterations in experimental sepsis
EXPERIMENTAL STUDIES IN SEPSIS

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…)

Branemark et Urbaschek Angiology 18:667;1967
Lam et al. JCI 94: 2077; 1994
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
Potential mechanisms?
Potential mechanisms

Endothelial dysfunction (impaired sensitivity of vasoconstrictive/vasodilating substances)

- Flow $\gg$ O2 needs $\Rightarrow$ High SvO2
- Flow $\ll$ O2 needs $\Rightarrow$ Hypoxia

- Impaired RBC deformability
- Altered glycocalyx
- Rolling and adhesion of RBC and WBC to endothelium
- Impaired backward communication

- Red blood cell
- White blood cell
ALSO IN HUMANS?
Vascular density (all vessels)

++ p <0.01 vs volunteers

De Backer et al
AJRCCM 166:98;2002
Percentage of vessels perfused (small vessels)

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

+++ p < 0.001 vs volunteers
Heterogeneity index

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>SEPSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td>26</td>
</tr>
</tbody>
</table>

P < 0.01

Trzeciak et al

Emergency department
- 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
- 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
- Edul et al CCM 2012
- Kavundis et al ICM 2012
- Hernandez et al CCRP 2012
- Pranskunas et al ICM 2013
- Hernandez et al ICM 2013
- Hernandez et al J Crit Care 2013
- Vellinga et al BMC Anesthesiol 2013
- Filbin et al Acad Emerg Med 2014
- Vellinga et al CCM 2014
- Trzeciak et al CCM 2014
- Vellinga et al CCM 2015

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)
Endothelial reactivity is impaired in sepsis

* p < 0.001 vs volunteers and ICU control

Creteur et al
ICM 2007
Alterations of NIRS vasoreactivity test in patients with sepsis

- Girardis et al ICM 2003
- De Blasi et al ICM 2005
- Pareznik et al ICM 2006
- Podbregar et al Crit Care 2007
- Doerschung et al JAP 2007
- Creteur et al ICM 2007
- Skarda et al Shock 2007
- Nanas et al Aenesth Intens Care 2009
- Payen et al Crit Care 2009
- Donati et al Crit Care 2009
- Mesquida et al ICM 2009
- Mozina et al Crit Catre 2010
- Georger et al ICM 2010
- Shapiro et al Crit Care 2011
- Soga T et al Emerg Med J 2013
Relationship with outcome?
Vessel density, proportion of perfused vessels and heterogeneity but not velocity differ between survivors and non-survivors.

Edul et al.
CCM 2012
Association with outcome

Severe sepsis (n=252)

De Backer et al
CCM 41:791;2013
Shapiro et al
Crit Care 15 R223; 2011

168 pts at emergency dpt
Severe sepsis 24 / volunteers 15
33 pts with septic shock

- 1st SDF evaluation within 3 hours after EGDT initiation
- 2nd SDF evaluation 3 to 6 hours after EGDT initiation
- SOFA changes between 0 and 24 h
TISSUE PERFUSION: Key points

• O2 transport is driven at microcirculatory level by diffusion more than by convection.

=> Do fluids improve microcirculatory perfusion?
Fluids but not vasopressors improved FCD

Changes in FCD (%) from baseline

Hamster skinfold
LPS
Microvascular effects of fluid challenge in patients with septic shock

Ospina et al
ICM 35:949;2010

Small vessel perfusion (%)  
P<0.01

\( N = 60 \)
Microcirculation targeted therapy?

Timing of intervention?
Influence of timing of fluid resuscitation

Legrand et al
ICM 37:1534; 2011
Microvascular effects of fluid challenge in patients with septic shock

Proportion of perfused small vessels

Baseline

Fluids

Early stage (<24h) N=37

Late stage (>48h) N=23

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

Ospina et al
ICM 35:949;2010
CO (L.min⁻¹)  

Baseline 1: 5.1 ± 1.5  
PLR: 6.0 ± 1.7 *  
Baseline 2: 5.1 ± 1.5  
$\text{VE}_{\Delta \text{PP}=\text{PLR}}$: 5.9 ± 1.5*  
$\text{VE}_{\text{END}}$: 6.5 ± 1.6 *$§$‡
Relationship with systemic response

Vallée et al
Chest 138:1062;2010

Ear lobe PCO2
Microcirculation as a tool to select patients eligible for fluid therapy?

Pranskunas A et al
ICM 2013

N = 33
N = 17
Microcirculation as a tool to select patients eligible for fluid therapy?

Evolution of organ failure score during fluid therapy

Pranskunas A et al
ICM 2013
Effects of RBC transfusions
EFFECTS OF RED BLOOD CELL TRANSFUSIONS

N=35

Capillary density

Sakr et al
CCM 35:1639;2007
EFFECTS OF RED BLOOD CELL TRANSFUSIONS

Sakr et al
CCM 35:1639;2007

N=35
Vasoactive agents?
Dobutamine in experimental sepsis

Rats, liver sinusoids
β-adrenoceptor stimulation improved liver microvascular perfusion and redox state

Fink T et al
Shock 2013

Rats / Fecal peritonitis
Dobutamine 5 mcg/kg.min

Capillary Perfusion

21 patients in septic shock
<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Dobutamine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total microvascular density (n/mm)</td>
<td>11.8 [10.2-12.5]</td>
<td>11.9 [9.7-12.5]</td>
<td>0.91</td>
</tr>
<tr>
<td>Perfused vessel density (n/mm)</td>
<td>9.1 [7.9-9.9]</td>
<td>9.1 [7.9-10.1]</td>
<td>0.24</td>
</tr>
<tr>
<td>Proportion of perfused microvessels (%)</td>
<td>75 [69-79]</td>
<td>79 [72-84]</td>
<td>0.09</td>
</tr>
<tr>
<td>Microvascular flow index</td>
<td>2.1 [1.9-2.5]</td>
<td>2.1 [1.8-2.5]</td>
<td>0.73</td>
</tr>
<tr>
<td>Het Index MFI</td>
<td>0.58 [0.46-0.73]</td>
<td>0.47 [0.40-0.86]</td>
<td>0.52</td>
</tr>
</tbody>
</table>

20 patients with septic shock

Hernandez G et al ICM 39:1435;2013

Obvious individual variability
Change in Lactate

De Backer et al
CCM 34:403;2006

DOBU 5 mcg/kg.min
Vasopressor agents?
Impact of vasopressors on the microcirculation (Norepinephrine vs Vasopressine)

Friesenecker et al
Crit Care 10:R75;2006

<table>
<thead>
<tr>
<th></th>
<th>MAP (mmHg)</th>
<th>RBC velocity (mm/s)</th>
<th>Arteriolar BF (10^-4 x mm x μm^2/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NE^b</td>
<td>103 ± 8</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>AVP^b</td>
<td>98 ± 10</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NE^a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>129 ± 7</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AVP^a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>121 ± 8</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AVP^a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.2 ± 0.9</td>
</tr>
</tbody>
</table>

Hamster, control condition
Impact of vasopressors on the microcirculation

Normotensive sepsis

Rats, LPS, gut muscularis

No fluids
Doses:
NE 5 mcg/kg.min
EPI 5 mcg/kg.min
PHE 10 mcg/kg.min
DOPA 20 mcg/kg.min
Dobu 12 mcg/kg.min

Nacul F et al
Anesth Analg
110:447;2010
Does correction of hypotension result in an improved tissue perfusion?
Impact of vasopressors on the microcirculation (Norepinephrine vs Vasopressin)

Nakajima et al
CCM 34:1847;2006

**Baseline value**

**Shock value**

Rats, LPS

MAP 46 71 70 mmHg
Correction of hypotension improves microvascular reactivity (NIRS)

MAP 54 => 77 mmHg

Georger et al
ICM 36:1882;2010
What is the optimal blood pressure target for the microcirculation?
Impact of MAP/NE on microvascular perfusion

Dubin et al
Crit Care 2009

N=20
Impact of MAP/NE on microvascular perfusion

Density of perfused small vessels

FCD small vessels, n/mm

level of mean arterial pressure, mmHg

65 (baseline) 75 85 65
6
8
10
12

*
A high mean arterial pressure target is associated with improved microcirculation in septic shock patients with previous hypertension: a prospective open label study
Vasodilatory agents?
MICROCIRCULATORY ALTERATIONS IN SEPTIC PATIENTS

Proportion of perfused vessels (all vessels)

% 100
95
90
85
80
75
70
65

BASE
TOPICAL ACETYLCHOLINE (10⁻² M)

++ p <0.01 vs base

Patients with septic shock (n = 11)

De Backer et al
AJRCCM 166:98;2002

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
Proportion of Perfused Small Vessels

**BASELINE**
**BEFORE DRUG**
**SHOCK NE 1H**
**NE 2H**

* p<0.05 vs baseline and before drug
p=0.83 for trend in enalaprilat group
p=0.006 for trend in placebo group
p=0.48 for group/time interaction

ACE inhibitors? But no impact on
• outcome
• organ function

Salgado D et al
Shock 2011

Sheep
CLP
**Inhaled NO?**

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**Patients with sepsis**

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

OFA = Sequential Organ Failure Assessment.
Modulation of endothelial function?
Vitamin C

Tyml K et al
CCM 33,1823;2005

Rat / muscle
CLP

Ascorbate 7.6g/100g BW
1h or 24h post CLP
Vitamin C

The effect is related to endothelial NOS

Mice / muscle
Feces in peritoneum
Ascorbate 10-200 mg/kg
6h post peritonitis

Tyml K et al
CCM 2008
**BH4 (tetrahydrobiopterin)**

**Effect on NO metabolism at endothelial level**

Schmidt S and Alp N
Clinical Science
113: 47; 1997
BH4 (tetrahydrobiopterin)
BH4 (tetrahydrobiopterin)

Improved
- outcome
- organ function
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.

Modulation of endothelial NO synthase seems promising.