Microcirculation in Sepsis

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What is the microcirculation?
Why is there “Hypoxia” in Sepsis?

1. Macrocirculatory Failure
2. Microcirculatory Failure
3. Mitochondrial Dysfunction
Why Is the microcirculation Important?

**Oxygen Utilization**

1. **Macrocirculation**
   - Oxygen Supply
   - $\text{DO}_2 = (\text{CO})(\text{Hb})(\text{SaO}_2)$

2. **Microcirculation**
   - Oxygen extraction/diffusion

3. **Mitochondria**
   - Oxygen use

ScvO2 measurement
Bedside Use of Video-Microscope

- User needs to remain still at microscopic level
- Patient needs to remain still at microscopic level
- Can’t apply too much pressure
- Can’t apply too little pressure
- Need to get right vessels, in focus with correct light contrast
Healthy Volunteer

Brisk Flow
Septic Patient

Non-continuous and stopped flow
Comparison of buccal microcirculation between septic and hemorrhagic shock

Xiangshao Fang, MD; Wanchun Tang, MD, FCCM; Shijie Sun, MD, FCCM; Lei Huang, MD; Yun-Te Chang, MD; Carlos Castillo, MSEE; Max Harry Weil, MD, PhD, FCCM
Controlled Macrocirculation (MAP)

Fang et al. Crit Care Med 2006:34:12 (suppl)

Pressure (MAP)

Microvascular Perfusion
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
Microcirculatory Perfusion Predicts Death

Table 5. Area under the curve (AUC) of the receiver operating characteristics curves of changes over time (between first and second day of shock and first and last day of shock) in the main hemodynamic and biologic variables

<table>
<thead>
<tr>
<th></th>
<th>AUC Second-First</th>
<th>AUC Last-First</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0.57</td>
<td>0.66</td>
</tr>
<tr>
<td>Mean arterial blood pressure</td>
<td>0.53</td>
<td>0.64</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>Pulmonary artery occlusion pressure</td>
<td>0.64</td>
<td>0.52</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.51</td>
<td>0.57</td>
</tr>
<tr>
<td>SvO₂</td>
<td>0.52</td>
<td>0.53</td>
</tr>
<tr>
<td>Do₂</td>
<td>0.52</td>
<td>0.56</td>
</tr>
<tr>
<td>VO₂</td>
<td>0.50</td>
<td>0.55</td>
</tr>
<tr>
<td>Lactate</td>
<td>0.63</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Microvascular perfusion</strong></td>
<td><strong>0.77</strong></td>
<td><strong>0.83</strong></td>
</tr>
<tr>
<td>SOFA score</td>
<td>0.61</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Sakr, Dubois, De Backer et al. Crit Care Med 2004:32
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators

- Trial of alternative resuscitation strategies (EGDT vs protocolized non-invasive versus usual care)
- 1350 subjects
- No difference in mortality
ProCESS Endothelial Cell Signaling Ancillary Study – Investigator Team

- **U Pitt ProCESS Coordinating Center**
  - Dr. Derek Angus
  - Dr. David Huang
  - Dr. John Kellum
  - Dr. Don Yealy

- **Beth Israel Deaconess**
  - Dr. William Aird
  - Dr. Michael Massey
  - Bjorn Fabian-Jessing

- **Enrolling Sites**
  - U Pitt – Dr. Peter Simon
  - Brigham – Dr. Peter Hou
  - Mass General – Dr. Michael Filbin
  - U of Alabama – Dr. Henry Wang
  - University of Florida – Dr. David Orban
  - Christ Hospital – Dr. Erik Kulsted
ProCESS Microcirculatory Flow Ancillary Study

- **Objective 1**: To study the impact of alternative fluid resuscitation strategies on microcirculatory flow in sepsis
- **Objective 2**: To study the association between microcirculatory flow parameters over the first 72 hours and mortality in severe sepsis
- **Objective 3**: To study the association between leukocyte rolling and adhesion with septic shock and mortality
Study Methods

• **Design:** Prospective observational sub-study of ProCESS trial
• **Setting:** 6 participating centers
• **Population:** 205 Severe Sepsis patients enrolled in ProCESS
• **Intervention:** Random assignment to 3 different resuscitation strategies
• **Primary outcome:** 28 day in-hospital mortality
Microcirculation Assessment

1. Acquisition at Site with Microscan (Microvision Medical, Netherlands)
2. Sent via internet for centralized analysis
3. Videos were quality scored – any video with failing parameter rejected
4. Passing videos clipped and de-identified
5. Imported into AVA software and Vessels Hand Traced and flow scored visually 0-3
Microcirculation Assessment

- Microvascular Flow Index (MFI)
  - 0 = stopped flow
  - 1 = intermittent flow
  - 2 = sluggish
  - 3 = fast
- Proportion Perfused Vessels (PPV)
- Debacker Score
- Total Vascular Density (TVD)
- Perfused Vascular Density (PVD)
- Heterogeneity Index

Debacker et al. Critical Care. 11:5:2007:
## Results

<table>
<thead>
<tr>
<th></th>
<th>6 Hour (n=225)</th>
<th>24 Hour (n=222)</th>
<th>72 hour (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired Images</td>
<td>205</td>
<td>200</td>
<td>147</td>
</tr>
<tr>
<td>Analyzed Images</td>
<td>162 (79%)</td>
<td>147 (74%)</td>
<td>118 (80%)</td>
</tr>
</tbody>
</table>

- **225 patients included overall**
- **86% of available time points attempted**
- **77% passed quality check and analyzed**
Microcirculatory Flow by Arm

mfi-arm-line

TVD

ppv

pvd_small
MFI and Mortality

- Top graph: Box plot showing mfi over time (6, 24, 72 hours) for dead and alive groups.
- Bottom graph: Log scale showing mfi over time (0, 6, 24, 72 hours) for dead and alive groups.
PPV and Mortality
DeBacker Score

- Box plot showing DEbacker levels over time (6, 24, 72 hours) for dead and alive groups.
- Log scale plot showing DEbacker levels over time (0, 6, 12 hours) for dead and alive groups.

Legend:
- Dead
- Alive

* Statistical significance indicated.
Perfused Vascular Density

![Box plot showing perfused vascular density over time for dead and alive subjects.](image1)

![Line graph showing log of perfused vascular density over time for dead and alive subjects.](image2)
TVD and Mortality
## Summary Results

<table>
<thead>
<tr>
<th>Microcirculation Parameter</th>
<th>Alive at discharge</th>
<th>Dead at discharge</th>
<th>overall model alive vs dead</th>
<th>beta</th>
<th>*p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 hours N=138</td>
<td>24 hours N=128</td>
<td>72 hours N=108</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 hours N=128</td>
<td>6 hours N=32</td>
<td>24 hours N=21</td>
<td>72 hours N=12</td>
<td></td>
</tr>
<tr>
<td>TVD, mean±SD</td>
<td>22.6±4.2</td>
<td>23.0±5.4</td>
<td><strong>22.1±4.0</strong></td>
<td>21.1±3.7</td>
<td>21.7±5.7</td>
</tr>
<tr>
<td>PVD, mean±SD</td>
<td>21.1±4.8</td>
<td>21.8±5.7</td>
<td><strong>21.0±4.2</strong></td>
<td>20.8±4.9</td>
<td>19.3±7.5</td>
</tr>
<tr>
<td>DeBacker, mean±SD</td>
<td>14.8±2.6</td>
<td>15.1±3.2</td>
<td><strong>14.6±2.5</strong></td>
<td>14.5±2.6</td>
<td>14.4±2.3</td>
</tr>
<tr>
<td>Hetero, median [IQR]</td>
<td>0.08 [0.00-0.43]</td>
<td>0.18 [0.00-0.46]</td>
<td>0.17 [0.00-0.49]</td>
<td>0.00 [0.00-0.51]</td>
<td>0.27 [0.00-0.67]</td>
</tr>
<tr>
<td>MFI, median [IQR]</td>
<td>2.92 [2.59-3.00]</td>
<td>2.85 [2.61-3.00]</td>
<td>2.88 [2.51-3.00]</td>
<td>2.96 [2.56-3.00]</td>
<td>2.67 [2.18-3.00]</td>
</tr>
<tr>
<td>PPV, median [IQR]</td>
<td>0.90 [0.83-0.97]</td>
<td>0.90 [0.85-0.96]</td>
<td>0.91 [0.83-0.95]</td>
<td>0.91 [0.82-0.95]</td>
<td>0.91 [0.83-0.95]</td>
</tr>
</tbody>
</table>
Leukocyte Rolling
Leukocyte Adhesion
Impaired Leukocyte Movement—In vitro

Image Courtesy of Chris Carman, PhD and Roberta Martinelli, PhD
Leukocyte Rolling and Sepsis

Roling: Severe Sepsis v. Control

# of rolling leukocytes

Control
n=32

Sepsis
n=64

Patient Group

*** p<0.001

Fabian-Jessing, Massey, et al – Unpublished data
Leukocyte Adhesion and Sepsis

Adhered: Severe Sepsis v. Control

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Control</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>32</td>
<td>64</td>
</tr>
</tbody>
</table>

# of adhered leukocytes

*** p<0.001

Fabian-Jessing, Massey, et al – Unpublished data
Leukocyte Rolling and Mortality in Sepsis

Rolling: Alive v. Dead

# of rolling leukocytes

Alive
Dead

n=53
n=11

Patient Group

*p=0.32

Fabian-Jessing, Massey, et al – Unpublished data
Leukocyte Adhesion and Mortality in Sepsis

Adhered: Alive v. Dead

* *p<0.05

# of adhered leukocytes

Alive n=53

Dead n=11

Patient Group

Fabian-Jessing, Massey, et al – Unpublished data
Study Conclusions

• No difference in microcirculatory flow among the 3 structured resuscitation arms

• There was an association at 24 and 72 hours between impaired microcirculatory flow and mortality in some parameters

• There was increased leukocyte rolling and adhesion in septic shock patients compared to non-infected controls

• There was increased adhesion in sepsis fatalities
Questions?