Brain Perfusion in Sepsis

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Sepsis associated brain dysfunction
**Sepsis associated brain dysfunction**

**Inflammatory mechanisms**
- Endothelial activation
- Increased permeability of BBB
- CNS entry of circulating leukocytes
- Activation of CNS innate and adaptive immune systems
- Microglial activation

**Neuronal mechanisms**
- Changes in neurotransmitter synthesis, release, reuptake
- Changes in synaptic strength/efficiency
- Changes in neuronal excitability
- Excitotoxicity
- Neuronal cell death

**Vascular mechanisms**
- **Macrovascular**
  - Changes in cerebral blood flow
  - Vasospasm
  - Neurovascular uncoupling
  - Loss of pressure autoregulation
  - Loss of CO2 reactivity

- **Microvascular**
  - Endothelial activation
  - Microthrombosis
  - Decrease in capillary density
  - Brain tissue hypoxia
  - Ischemia
Blood Pressure

Vascular reactivity

PaCO2

PaO2

Functional activation

Blood Pressure

Cardiac output

Temperature

Cerebral blood flow
Vascular reactivity

- Stroke
- Sepsis
- Neuro-inflammation
- Trauma
- Dementia
- Age
- Medications

Cerebral blood flow
## Methods to assess cerebral perfusion

<table>
<thead>
<tr>
<th>Noninvasive</th>
<th>Invasive</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcranial Doppler</td>
<td>Thermal diffusion flowmetry</td>
<td>Xenon CT</td>
</tr>
<tr>
<td>Near infrared spectroscopy (cerebral oximetry)</td>
<td>Laser Doppler flowmetry</td>
<td>Perfusion CT</td>
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<td></td>
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<td>Perfusion MRI</td>
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<tr>
<td></td>
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<td>PET</td>
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<td>SPECT</td>
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</tbody>
</table>
Brain perfusion in sepsis

Variables
1. Cerebral blood flow
2. Pressure autoregulation
3. CO2 reactivity
4. Neurovascular coupling

Study paradigms
1. Experimental sepsis: LPS, CLP
2. Health human volunteers: LPS
3. Human sepsis
Cerebral blood flow
Rat LPS challenge
FDG PET
LPS challenge in rhesus monkey

Weiner D. Am J Physiol 1970
LPS challenge in mongrel dog

Decrease in CBF (%)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>2 hrs</th>
<th>4 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pons</td>
<td>-60</td>
<td>-50</td>
</tr>
<tr>
<td>Medulla</td>
<td>-50</td>
<td>-50</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>-40</td>
<td>-40</td>
</tr>
<tr>
<td>Thalamus</td>
<td>-30</td>
<td>-30</td>
</tr>
<tr>
<td>Cortex</td>
<td>-20</td>
<td>-20</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>-10</td>
<td>-10</td>
</tr>
<tr>
<td>Pituitary</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
LPS challenge in mongrel dog

Ekstrom-Jodal, B. Acta Anaesthesiol Scand 1982
Septic shock

Hemorrhagic shock

Cerebral Blood Flow (ml/100 gm/min)

Baseline

Shock

Human septic shock
CBF assessed with $^{133}$Xe clearance

Cerebral blood flow (ml/100g/min)

- Healthy controls: 44.9 ml/100g/min
- Septic shock: 29.6 ml/100g/min

Human healthy volunteers
Intravenous LPS challenge

![Bar chart showing CBF (ml/100g/min) and PaCO2 (mmHg) before and after endotoxin challenge.](Moller et al. J Cereb Blood Flow Metab 2002)
Human healthy volunteers: Intravenous LPS challenge

Pressure autoregulation
Pressure autoregulation
S. pneumoniae bacteremia (rat)
Human sepsis

Static pressure autoregulation

MCA CBFV (cm/s)

MAP = 75 mmHg

MAP = 98 mmHg

Matta B and Stow P. Br J Anaesth 1996
Human septic shock
Pressure autoregulation

PaCO2 < 40 mmHg
PaCO2 > 40 mmHg
Sepsis-associated delirium

Dynamic pressure autoregulation

Sepsis-associated delirium

Dynamic pressure autoregulation

Schramm et al. Crit Care 2012
Methods
Static and dynamic autoregulation assessed with MCA FV assessed with TCD in
1. Healthy volunteers before LPS (n=9)
2. Patients with sepsis (n=16)

Findings
No difference in static autoregulation between groups
*Increased* dynamic autoregulation in HV after LPS
*Decreased* dynamic autoregulation in patients

Consistent with separate results of Brassard et al.

Ronan M. G. Berg,1,2,3 Ronni R. Plovsing,3 Andreas Ronit,4 Damian M. Bailey,5 Niels-Henrik Holstein-Rathlou,2 and Kirsten Møller1,6
CO2 reactivity
Human septic shock
CO2 reactivity

Matta B and Stow P. Br J Anaesth 1996
Human septic shock
CO2 reactivity assessed with acetazolamide test

![Graph showing cerebrovascular reserve capacity for sepsis and control groups. The graph indicates a statistically significant difference (p<0.01) between the two groups.](image-url)
Human septic shock

CO2 reactivity

<table>
<thead>
<tr>
<th></th>
<th>Sepsis</th>
<th>No sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO2 reactivity index (TCD)</td>
<td>11</td>
<td>30,7</td>
</tr>
<tr>
<td>CO2 reactivity index (NIRS)</td>
<td>0,7</td>
<td>2,3</td>
</tr>
</tbody>
</table>

Teborg et al. Intensive Care Med 2001
Neurovascular coupling
Changes in neurovascular coupling associated with community acquired pneumonia (CAP)
Simultaneous TCD-EEG during visual stimulus paradigm (N=43)
Changes in neurovascular coupling associated with community acquired pneumonia (CAP) Simultaneous TCD-EEG during visual stimulus paradigm (N=43)

*Gain represents the flow velocity difference between conditions of rest and activation under stable hemodynamic conditions
Microcirculation
Microcirculatory dysfunction in sepsis

Cell/tissue markers of microcirculatory dysfunction
  - Reactive hyperemia
  - Functional capillary density
  - Brain tissue oxygen
  - Lactate, pyruvate, glutamate

Molecular markers of endothelial activation in sepsis
  - Toll-like receptor expression and activation
  - Inducible and endothelial NOS expression
  - Cyclooxygenase-2 expression
  - Cell adhesion molecules (ICAM, VCAM) expression
  - Adenosine receptor activation
Association between Endothelial Dysfunction and Acute Brain Dysfunction during Critical Illness

Christopher G. Hughes, M.D.,* Alessandro Morandi, M.D.,† Timothy D. Girard, M.D.,‡ Bernhard Riedel, M.D., Ph.D.,§ Jennifer L. Thompson, M.P.H.,II Ayumi K. Shintani, Ph.D.,# Brenda T. Pun, M.S.N.,**, E. Wesley Ely, M.D.,†† Pratik P. Pandharipande, M.D.‡‡

N=134 Shock or Respiratory Failure
Functional capillary density, n/mm

- SEPSIS
- SHAM

Baseline  6 hours  12 hours  Shock
Optical methods to assess CBF

Near-infrared spectroscopy

Diffuse correlation spectroscopy

Photoacoustic tomography

Optical intrinsic signal imaging

Laser speckle contrast imaging

Optical coherence tomography

Two-photon microscopy
Take home

1. Disturbances in cerebral perfusion represent a key component for the development of brain dysfunction in sepsis and may be observed at the macrovascular and microvascular level.

2. Pressure autoregulation may be impaired in a subset of septic patients in particular those with delirium.

3. Reactivity of cerebral vasculature to CO2 may be affected in a subset of patients with sepsis.

4. Coupling of neuronal activity with hemodynamic responses may be impaired in sepsis.

5. Evidence of tissue disturbance in sepsis includes decreased capillary density, brain tissue hypoxia, and increased lactate/pyruvate.
Next Steps

1. Develop/validate accurate and reliable methods to assess cerebral perfusion and autoregulation at the bedside
2. Determine relationship between cerebral perfusion abnormalities and imaging or biochemical markers of brain damage
3. Identify relationship between cerebral perfusion abnormalities and clinical outcomes
4. Evaluate targeted therapies to correct perfusion abnormalities in sepsis
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