Special features of cardiogenic failure in sepsis

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The problem in focus

- Incidence of sepsis is increasing
- Severe sepsis and septic shock are leading cause of death in ICU
- Septic patients developing myocardial dysfunction have significantly higher mortality (70%) than those without cardiovascular impairment (20%)

Topics

- Clinical manifestation of sepsis induced cardiac dysfunction
- Pathophysiological mechanisms
- Novel therapeutic strategies?
- From bench to bedside
Heart failure in sepsis

• A not adequately enhanced cardiac output
  – Decreased contractility
  – Impaired response to fluid therapy
  – Ventricular dilation

• Autonomic dysfunction

• Reduced heart rate variability

• Impaired baro- and chemoreflex sensitivity
Warm or cold shock?

- Early sepsis: decreased iv volume leads to low cardiac output
- Volume resuscitated patients develop high cardiac output due to low systemic vascular resistance
- Cold shock = inadequate volume resuscitation?
The extent of septic cardiomyopathy can be more correctly quantified by taking the afterload into consideration, thus measuring the afterload-related cardiac performance.

Werdan K et al. Clin Res Cardiol (2011) 100:661–668
Changes in myocardial function and necroenzymes are reversible in survivors in 7-10 days

Mechanisms of myocardial dysfunction in sepsis

- Hypothesis of global myocardial ischemia
- High coronary flow, decreased myocardial $O_2$ consumption
- No evidence of significant myocardial necrosis
- Functional rather than anatomical abnormalities?

Mechanisms of myocardial dysfunction in sepsis

Preincubation of beating neonatal rat cardiomyocytes in culture with TNF-α blocks βadrenoceptor-mediated increases in pulsation amplitude.
Myocardial depression in G-, G+ and fungal septic shock

- It is not so much the bacterial virulence factors but rather the common mediator network that determines the occurrence and severity of the disease.

By antagonizing and eliminating pertinent proinflammatory mediators, septic vasculopathy is more treatable than septic cardiomyopathy.

Blocking myocardial suppressant factors (TNF-α, IL-1β), the same as attempts to inhibit NO production could not prove any benefit.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CI</th>
<th>SVR</th>
<th>LVSWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin antibody (HA-1A)</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø/↓</td>
</tr>
<tr>
<td>TNF-α antibody/soluble receptors</td>
<td>Ø</td>
<td>Ø/↑</td>
<td>Ø/↑</td>
</tr>
<tr>
<td>Hemofiltration</td>
<td>Ø</td>
<td>↓</td>
<td>Ø</td>
</tr>
<tr>
<td>Plasma separation</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Ø</td>
<td>↑</td>
<td>Ø</td>
</tr>
<tr>
<td>NO synthase inhibitors</td>
<td>Ø</td>
<td>↑</td>
<td>Ø/↓/↑</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>Ø/↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td>Hemoperfusion/endotoxin absorption</td>
<td>↓</td>
<td>↑</td>
<td>Ø</td>
</tr>
</tbody>
</table>

Role of levosimendan in septic heart failure

- Theoretical advantages compared with dobutamine:
  - does not increase oxygen demand
  - correction of calcium desensitisation
  - reduction in apoptosis
  - reduction in inflammatory response
- May exacerbate hypotension (PVR↓)
- RCTs required
# RCTs with levosimendan use in septic shock

<table>
<thead>
<tr>
<th>Study, year (ref)</th>
<th>Population</th>
<th>N</th>
<th>Levosimendan dose (length of infusion)</th>
<th>Comparator dose (length of infusion)</th>
<th>Definition of septic shock and/or inclusion criteria</th>
<th>Clinical outcome(s) with levosimendan</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhashemi 2009(55)</td>
<td>Severe sepsis/septic shock</td>
<td>42</td>
<td>0.05-0.2 μg/kg/min (24 hours)</td>
<td>Dobutamine 5-20 μg/kg/min (24 hours)</td>
<td>Trial drugs increased until $\text{ScvO}_2 \geq 70%$. Rescue therapy with noradrenaline</td>
<td>ICU mortality was less (48% vs 62%). CI was less in the levosimendan group and both required similar noradrenaline rescue therapy</td>
<td>ICU length of stay</td>
</tr>
<tr>
<td>Morelli 2006(54)</td>
<td>ARDS and septic shock</td>
<td>35</td>
<td>0.2 μg/kg/min</td>
<td>Placebo</td>
<td>Septic shock (ACCP/SCCM) and ARDS</td>
<td>The combination of inotropic and pulmonary vasodilating effects of levosimendan may be beneficial with RV failure in patients with ARDS and sepsis</td>
<td>24 hours</td>
</tr>
<tr>
<td>Morelli 2005(45)</td>
<td>Refractory septic shock</td>
<td>28</td>
<td>0.2 μg/kg/min</td>
<td>Dobutamine 5 μg/kg/min</td>
<td>LVEF &gt;45%, PCWP $\geq 12\text{mmHg}$ Not fluid responsive</td>
<td>Improved haemodynamics and regional perfusion under conditions where dobutamine is no longer efficacious</td>
<td>30 days</td>
</tr>
</tbody>
</table>

Mathieu S et al. JICS 2011;12:15-24
Statins?

• Apoptosis contributes to septic cardomyopathy
  – increased release of caspases,
  – mitochondrial cytochrome c

• Statins influencing the process of apoptosis through their pleiotropic effects might turn out to be a potential therapy.
• HA-1A; Centoxin; monoclonal antibody; withdrawn 1993
• Drotrecogin alfa; Xigris; activated protein C; withdrawn 2011
• AZD9773; CytoFab; TNF-antibody; withdrawn 2012 (F IIb)
• ASEPSIS Trial; atorvastatin 40 mg; sepsis progression↓? 2012
• EUPHRATES Trial; polimyxinB HP endotoxine elim. 2013
• OASIS Trial; talactoferrin alfa; immunmodulant protein 2014
Role of mechanical circulatory support (?)

- Use of ECMO is limited to refractory pediatric septic shock and/or respiratory failure (2C)
- IABP?
- LVAD?

Changing conceptions: Volume therapy

1. Quantitative resuscitation 6-12 hours (CO)
2. Qualitative resuscitation (glycocalix)
3. De-resuscitation (oedema)

Hypervolemia could be as harmful as hypovolemia

Photo by Welsch U.
Rehm M et al. Anaesthesiology 2004;100:1211-23
Changing conceptions: Vasoactive therapy

- Norepinephrine is first choice (1B)
- Epinephrine when additional agent is needed (2B)
- Dobutamin in case of myocardial dysfunction (high filling pressure, low CO, hypoperfusion) (1C)
- Vasopressin (0.03 U/min) can be added to NE, but never initial treatment (UG)
- Dopamine in highly selected patients (2C)
  - arrhythmia

Sepsis induced cardiac dysfunction

• Leads to significantly higher mortality
• Understanding of the complex mechanism leads to potential novel therapeutic targets
• Novel drugs and mechanical circulatory support still have not brought breakthrough
• What works: early and proper volume therapy, goal-directed vasopressor and inotropic support, infection source control.
  – What changed is not what to do, but how to do it properly?
Everything should be made as simple as possible, but not simpler.

Albert Einstein

The important thing is: not to stop questioning.