Management of septic cardiomyopathy

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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
Clinical manifestation of sepsis induced cardiac dysfunction

• 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
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.

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 ScvO₂ ≥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 ≥12mmHg 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.

Buerke U et al. Shock 2008;29:497-503
• 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 vasoressor and inotropic support, infection source control.
  - What changed is not what to do, but how to do it properly?