Metabolic Resuscitation: a new approach to sepsis?

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Research Support/Disclosures

• NIH K23 HL128814-01A1 (PI)
• American Heart Association grants (co-investigator)
Trial of Early, Goal-Directed Resuscitation for Septic Shock

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Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*
In the normal state (blue line), oxygen consumption is constant over a range of DO2, and decreases only when DO2 falls below a critical level (critical DO2). Pathologic changes caused by sepsis or systemic inflammatory responses (red line) cause increased VO2 and impaired peripheral oxygen utilization, resulting in an elevation in critical DO2.
Oxygen transport patterns in patients with sepsis syndrome or septic shock: Influence of treatment and relationship to outcome.

Hayes, Michelle; MD, FRCA; Timmins, Andrew; Yau, Ernest; Palazzo, Mark; MD, FRCP; Watson, David; Hinds, Charles


<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th></th>
<th></th>
<th>Nonsurvivors</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>T1</td>
<td>Tmax</td>
<td>T0</td>
<td>T1</td>
<td>Tmax</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>82 ± 73.95</td>
<td>91 ± 80.106</td>
<td>93 ± 86.101&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69 ± 64.76&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69 ± 65.82&lt;sup&gt;b&lt;/sup&gt;</td>
<td>84 ± 80.91&lt;sup,c&lt;/sup&gt;</td>
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<tr>
<td>PAOP (mm Hg)</td>
<td>9 ± 6.11</td>
<td>16 ± 15.17&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 ± 10.14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6 ± 10.13</td>
<td>16 ± 15.17&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15 ± 13.16&lt;sup,c&lt;/sup&gt;</td>
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<tr>
<td>SVRI (dyne-s/cm&lt;sup&gt;2&lt;/sup&gt;-m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1622 ± 1417.1924</td>
<td>1480 ± 1113.1773&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1120 ± 956.1399&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1379 ± 1110.1859</td>
<td>1271 ± 1052.1843</td>
<td>1174 ± 1082.1281&lt;sup,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVSWI (g-m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>36 ± 32.52</td>
<td>40 ± 33.66&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60 ± 49.67&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23 ± 18.33&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24 ± 17.34&lt;sup&gt;c&lt;/sup&gt;</td>
<td>40 ± 33.46&lt;sup,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>C(a-τ)O&lt;sub&gt;2&lt;/sub&gt; (mL/dL)</td>
<td>3 ± 2.92, 3.98</td>
<td>2.9 ± 2.41, 3.64</td>
<td>2.6 ± 2.13, 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.23 ± 2.9, 3.72</td>
<td>3.33 ± 2.59, 3.87</td>
<td>2.43 ± 2.25, 2.77&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; extr (%)</td>
<td>0.23 ± 0.21, 0.28</td>
<td>0.21 ± 0.16, 0.28</td>
<td>0.17 ± 0.15, 0.22&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.25 ± 0.23, 0.3</td>
<td>0.24 ± 0.2, 0.29&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.15 ± 0.14, 0.17&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>CI (L/min/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>3.99 ± 2.87, 4.23</td>
<td>4.17 ± 3.9, 5.18&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.22 ± 5.1, 6.68&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.38 ± 2.79, 3.97</td>
<td>3.55 ± 2.935, 4.03&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 ± 4.28, 5.77&lt;sup,c&lt;/sup&gt;</td>
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<tr>
<td>Do&lt;sub&gt;2&lt;/sub&gt; (mL/min/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>454 ± 382.579</td>
<td>642 ± 460.739&lt;sup&gt;a&lt;/sup&gt;</td>
<td>997 ± 739, 1081&lt;sup&gt;c&lt;/sup&gt;</td>
<td>435 ± 363.577</td>
<td>489 ± 402.606</td>
<td>800 ± 691.865&lt;sup,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; (mL/min/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>120 ± 95.133</td>
<td>121 ± 112.133</td>
<td>170 ± 136.172&lt;sup&gt;c&lt;/sup&gt;</td>
<td>108 ± 101.124</td>
<td>109 ± 97.131</td>
<td>120 ± 106.139&lt;sup,e&lt;/sup&gt;</td>
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MAP: mean arterial pressure; PAOP, pulmonary artery occlusion pressure; SVRI, systemic vascular resistance index; LVSWI, left ventricular stroke work index; C(a-τ)O<sub>2</sub>, arterial-venous oxygen content difference; O<sub>2</sub> extr, oxygen extraction ratio; CI, cardiac index; Do<sub>2</sub>, oxygen delivery; VO<sub>2</sub>, oxygen consumption.

<sup>a</sup>p < .05 within group statistics, when compared with baseline; <sup>b</sup>p < .01 between group statistics; <sup>c</sup>p < .001 within group statistics, when compared with baseline; <sup>d</sup>p < .05 between group statistics; <sup>e</sup>p < .01 within group statistics, when compared with baseline; <sup>f</sup>p < .001 between group statistics.

Data are expressed as median ± 25th, 75th percentiles.
Cytopathic Hypoxia

• The breakdown of aerobic metabolism in the presence of adequate oxygen delivery

• Failure of oxygen extraction

• No known way to improve extraction
59 year-old man, found on the street, confused

T 98.6   P 110   BP 84/60   RR 32   Sat 98%

Gen: Tachyapneic, dry mucous membranes

Chest: CTA bilaterally      Heart: S1 S2 reg

Abd: Soft, mild diffuse tenderness

Neuro: A & O x 2, no focal neuro findings

Extrem: Cool, clammy
Arterial Blood Gas:
pH: 6.9    pCO₂: 10    HCO₂: 3
pO₂: 80    Sat: 96%    Lactate: 27.2 mmol/dl

Complete Blood Count:
White Cell Count: 3.4    Hemoglobin: 8.1
Platelets: 230
Glucose → Pyruvate → Cori Cycle in Liver

Pyruvate → Lactate

Anaerobic metabolism

Thiamine (essential cofactor) → PDH → Acetyl CoA

Aerobic metabolism

Acetyl CoA → Krebs Cycle

Krebs Cycle → ATP, O₂
Thiamine Deficiency in Critical Illness

- 35% (28/80) of septic shock patients with elevated lactate
- 45% (7/16) of post-arrest patients
- Inverse correlation between thiamine and lactate in:
  - Sepsis
  - Post-arrest
  - DKA
Thiamine decreased lactate and improved survival in septic shock patients with thiamine deficiency

Thiamine improved survival in mouse model of cardiac arrest
What about Coenzyme Q10?
CoQ10 is low after cardiac arrest, and associated with survival.
CoQ10 increases in vitro oxygen consumption after cardiac surgery
A cure for sepsis?

A critical-care physician at Eastern Virginia Medical School has found what he believes is a cure for sepsis. The discovery came by accident as Paul Marik, MBChB, was treating a patient who was dying of sepsis.
Where do we go from here?

• Research, research, research

• Think about possible nutritional deficiencies in refractory shock

• Better understanding of mitochondrial function and how to support it may redefine “supportive care” of the critically ill patient