Clinically observed phenomena on cardiac energetics in heart failure emerge from simulations of cardiac metabolism

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Physiological Control Oxidative ATP Synthesis in the Heart

Data from intact tissues with high oxidative phosphorylation capacities (i.e., heart, brain, and kidney) indicate that the cytosolic concentration of ADP and Pi do not change significantly with work. These data imply that a simple feedback model is not adequate to explain the regulation of energy metabolism in these tissues.

These (and other) data are consistent with our hypothesis oxidative phosphorylation in the heart is controlled primarily through inorganic phosphate levels.
Mechanisms of activation by Pi

What have we learned about the *physiological* control of oxidative phosphorylation?

1. The metabolic stability hypothesis is disproved.

2. *In vitro* (purified mitochondria) and *in vivo* data are consistent with the hypothesis that cardiac energy metabolism is primarily regulated through feedback of substrates for oxidative phosphorylation.

3. Inorganic phosphate is key signal.

4. Maximal cardiac oxygen consumption is an *emergent property* of the integrated metabolic and transport system. (The supply-side “Vmax” is not reached in vivo.)

\[ \Delta G_{\text{CRIT}} \approx -63 \text{ kJ mol}^{-1}. \]
Analysis of Cardiac Energetics in **Heart Failure** Using an Integrated Simulation of Mitochondrial Energy Metabolism and Oxygen Transport in the Heart
## Depletion of Metabolic Pools in LVH

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Early LVH</th>
<th>Mod LVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CR}_{\text{tot}}$ (mmol/liter cell)</td>
<td>35.04</td>
<td>35.56</td>
<td>30.26 (-14%)</td>
</tr>
<tr>
<td>Basal ATP (mmol/liter cell)</td>
<td>7.23</td>
<td>6.81 (-5.8%)</td>
<td>5.27 (-27%)</td>
</tr>
<tr>
<td>Basal CrP (mmol/liter cell)</td>
<td>15.33</td>
<td>15.05</td>
<td>8.16 (-47%)</td>
</tr>
</tbody>
</table>


Model Predictions for “Early LVH” Case


Solid lines are model predictions. (Model assumptions?)
Model Predictions for “Mod. LVH” Case


Solid lines are model *predictions*.
Cardiac Energetics During Evolution of Heart Failure

Assume steady depletion of metabolites:

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Canine model of Ingwall and coworkers

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TAN, TEP, and CR$_{tot}$ in units of mmol s$^{-1}$ (l cell)$^{-1}$
“Based on analysis of human biopsy specimens, we now know that [ATP] is 25% to 30% lower in the failing human heart…Why [ATP] decreases by only 25% is not known...” Ingwall & Weiss. Circ Res, 2004. 95:135-45
Downstream signaling tied to metabolic remodeling.

Potential effects on AMPK and oxidative stress?
Possible metabolic therapy for heart failure?

“creatine and PCr levels are...maintained within a narrow range in the healthy...myocardium. We postulate that any disturbance of this fine balance, irrespective of the direction of change, leads to energetic and subsequently functional impairment.”

Key Findings—Progression of Heart Failure

There are two distinct phases associated with the gradual depletion of adenine nucleotides and creatine from the heart: an early “adaptive” phase and a later “maladaptive” phase.

Metabolic reserve and ATP hydrolysis potential are maintained (or improved) in the adaptive phase and are significantly diminished in the maladaptive phase.

The critical transition between the adaptive and maladaptive phases occurs when the adenine nucleotide pools is approximately 30% depleted compared to baseline.

Inorganic phosphate concentration decreases in the heart failure models we have examined.

Wu et al., PNAS USA. 106:7143-7148, 2009.
Thanks

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