Mitochondrial Malfunction in Heart Failure and Sudden Death

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Disclosures: none
ROLE OF MITOCHONDRIA IN PHYSIOLOGY AND DISEASE

1. PRODUCE ENERGY (ATP)
2. PRODUCE/SCAVENGE ROS
3. CONTROL CELL DEATH

Image source: http://www.lhsc.on.ca/Patients_Families_Visitors/Genetics/Inherited_Metabolic/Mitochondria/index.htm
Coupled ion circuits of the cardiomyocyte

- **Potassium circuit**: 
  - K$^+$ channels
  - MIM
  - K+ efflux

- **Sodium circuit**: 
  - Na$^+$/K$^+$ ATPase
  - Na$^+$ channel

- **Calcium circuit**: 
  - Ca$^{2+}$ ATPase
  - Ca$^{2+}$ uniporter

- **Proton circuit**: 
  - Proton leak
  - Respiratory chain
  - ATP synthase
  - Na$^+$/H$^+$ exchanger
  - K$^+$/H$^+$ exchanger

- **Mitochondrial matrix**
  - NADH
  - TCA cycle
  - Scavenging

- **Cell membrane**
  - Sodium-potassium pump
  - Ca$^{2+}$-ATPase
  - ER Ca$^{2+}$
  - PTP

- **NADPH → ROS scavenging**
Blocking MCU causes NADH oxidation under load

Liu and O'Rourke Circ Res. 2008;103:279-288
Digression: Dual role of $P_i$ - acceleration of $Ca^{2+}$ uptake and buffering

Mitochondrial Ca\textsuperscript{2+} efflux is Na\textsuperscript{+},\textsubscript{i}-dependent (isolated mitochondria)

Wei, A. C. et al. (2011). Biochim Biophys Acta
In HF, Mitochondrial Ca load is low... but so is PTP Ca activation threshold

Ca load after single addition

Ca load triggering mPTP

An-Chi Wei, Poster 389 Weds
Mitochondrial Ca$^{2+}$ response is blunted in HF (Rhod2 method)

Guinea Pig Aortic Constriction (AC) model - data from Liu et al, Circ Res 2008
Mitochondrial Ca\(^{2+}\) response is blunted in HF
(MityCam method; ACi model)

Liu et Al Circ Res. 2014. 115(1):44-54
CGP-37157 corrects $[\text{Na}]_i$-induced NADH and ROS imbalance in Heart Failure (ACi)

Liu et Al Circ Res. 2014. 115(1):44-54
• Arrhythmias
• Ca^{2+} dysregulation
• Cell death
Cellular electrophysiological remodeling in ACi model

- **I\textsubscript{Ca}**
  - SHAM vs ACi
- **I\textsubscript{K1}**
- **I\textsubscript{K}**
- E-4031
- Difference

**Graphs:**
- APD50 and APD90
- mV vs msec
- 20 pA/pF vs 100 ms
**Sudden cardiac death: prevention by CGP**

Baseline | Iso | Recovery
--- | --- | ---
SHAMi | ![SHAMi baseline](image) | ![SHAMi iso](image) | ![SHAMi recovery](image)
ACi | ![ACi baseline](image) | ![ACi iso](image) | ![ACi recovery](image)
ACi+CGP | ![ACi+CGP baseline](image) | ![ACi+CGP iso](image) | ![ACi+CGP recovery](image)

Week 4

Baseline PVB (counts/hour)

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline PVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAMi</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>ACi</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>ACi+CGP</td>
<td>10 ± 3</td>
</tr>
</tbody>
</table>

Post-ISO PVB (counts/hour)

<table>
<thead>
<tr>
<th>Group</th>
<th>Post-ISO PVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAMi</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>ACi</td>
<td>90 ± 5</td>
</tr>
<tr>
<td>ACi+CGP</td>
<td>20 ± 4</td>
</tr>
</tbody>
</table>

* p < 0.05 vs baseline
† p < 0.05 vs ACi
Overall Mortality: prevention by CGP
**Integrated Omics Analysis of the ACi model of HF/SCD**

D. Brian Foster

![Graphs showing analysis of proteomics and transcriptomics for HF/SCD](https://example.com/graphics.png)

**Proteins**
- MYLK
- TMEM205
- SNRPD3
- TARS
- MGEA5
- UQCR11
- DSG2
- BASP1
- MYOM3
- FBLN5
- EPHX2
- EIF3A
- SGCE
- EIF3B

**Transcripts**
- ALDH1L1
- COL1A1
- ECHDC3
- C11orf54
- Enpp6
- Lrc14b
- Col6a6
- ADSSL1
- ECHDC3
- TMEM126B
- Cer1
- Tyr16
- Trpm1
- Sorcs1
- C9ORF10
- TTC38
- TFAM

**Tables showing gene IDs and descriptions**

**Epicardial Fatty Acid Metabolism**
- EIF3A
- MYLK3
- NUDT4
- Cltcl1
- Bphl
- Lsmem1

**Gene Descriptions**
- (top 50 up or down p<0.05)
- (top 50 up or down p<0.05)
- (top 50 up or down p<0.05)
Decreased levels of Mitochondrial Fatty Acid Transport and β-oxidation enzymes explain FA accumulation/acyl-carnitine depletion.

FA Transport & and β-oxidation programs are controlled transcriptionally by…
Metabolome-Proteome Integration II

Pyruvate carboxylase

Pyruvate dehydrogenase*

Acetyl-CoA

Citrate Synthase**

Citrate

Aconitase**

Cis-aconitate

Malate dehydrogenase **

Malate

Fumarase **

Fumarate

Sucinate dehydrogenase**

Sucinate

Isocitrate

Isocitrate dehydrogenase**

2-methylcitrate

Aspartate aminotransferase**

α-ketoglutarate

α-Ketoglutarate dehydrogenase**

Adenylosuccinate

Adenylosuccinate Lyase**

Methylmalonyl CoA Mutase**

Methylmalonyl CoA

From Odd Chain Fatty Acids & Amino Acid Metabolism

Glutamate

Glutamate dehydrogenase**

Glutamate from Amino Acid Metabolism

Pyruvate dehydrogenase*

Citrate Synthase**

Citrate

Aconitase**

Cis-aconitate

Malate dehydrogenase **

Malate

Fumarase **

Fumarate

Sucinate dehydrogenase**

Sucinate

Isocitrate

Isocitrate dehydrogenase**

2-methylcitrate

Aspartate aminotransferase**

α-ketoglutarate

α-Ketoglutarate dehydrogenase**

Adenylosuccinate

Adenylosuccinate Lyase**

Methylmalonyl CoA Mutase**

Methylmalonyl CoA

From Odd Chain Fatty Acids & Amino Acid Metabolism

Glutamate

Glutamate dehydrogenase**

Glutamate from Amino Acid Metabolism
Towards an Integrated Understanding of HF/SCD

**Signaling**
- β-AR → AC → cAMP → PKA → CREB

**Ca^{2+}/Ions Handling**
- ΔIons
  - Ca^{2+} → Na^{+}

**Myofilament Function**
- EC Coupling

**Metabi/Redox States**
- ↓ Ca^{2+} Mito
- ↓ NAD(P)H
- ↓ ATP
- ↑ ROS Overflow
- ↑ Death Signals

**Mito Protein Synthesis**
- Incorporate nuclear-encoded subunits

**Cyto Protein Synthesis**
- a) SIRT1 deacetylation
  - PTM activation
- b) Co-activation of transcription factors
- c) Expression of multiple mitochondrial genes
- d) Mito transcription factors
- e) Bioenergetic feedback

**Pathophysiological Outcomes**
- HF (Cell death, wound healing, decompensation); SCD (ROS production, fibrosis, ionic remodeling)
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GCaMP6f in NRVMs (3 sec cycle length)
Adult GP Ventricular Myocyte - mitoGCaMP6f

[Graph showing voltage changes over time for 0.33 Hz and 1 Hz stimulations, with markers for 'on' and 'off' events.]