Metabolomics in Heart Failure

I have no conflict of Interest

Ioannis A. Paraskevaidis
The age-adjusted rates for heart failure-related deaths declined from 2000 through 2012 but increased from 2012 through 2014.

Figure 1. Number of and crude and age-adjusted rates for heart failure-related deaths: United States, 2000–2014

Interventions According to Level of Evidence and Classification of HF

V. Katsi et al Heart Fail Rev 2017
Energy Supply–Demand Matching in Health and HF


H. Ardehali et al. European Journal of Heart Failure 2012; 14,:120–129
**Metabolomics** The metabolome represents the collection of all metabolites in a biological cell, tissue, organ or organism, which are the end products of cellular processes. It gives an instantaneous snapshot of the physiology of that cell.
Metabolomics in HF

J.R. Ussher et al. J Am Coll Cardiol 2016;68:2850–70
Metabolic Shift in HF

Cardiomyocyte Signalling Pathways Involved in the Pathophysiology of HF


Myocardial Energy Metabolism

R Witteles et al. JACC 2008;51:93-102

Witteles R et al., JACC 2008;51:93

WWW.HCS.GR

70 ΧΡΟΝΙΑ ΚΑΡΔΙΟΛΟΓΙΑΣ (ΕΚΕ)
70 YEARS OF CARDIOLOGY (HSC)
ΠΑΝΕΛΛΗΝΙΟ ΚΑΡΔΙΟΛΟΓΙΚΟ ΣΥΝΕΔΡΙΟ
PANHellenic Congress of Cardiology
Possible Mechanisms Connected to the Development of the Failing Heart

A. Gupta et al. Heart Fail Rev 2017
Organelle Dynamics and Phenotypic Changes in the CV System

Physiological condition
- Glucose-GLUT4
- ATP
- Krebs cycle
- Mitochondrion
- Plasma membrane

Organelle dysfunction
- Fragmentation
- Altered signalling
- Reduced calcium
- Reduced metabolism
- Reduced calcium uptake
- Uncoupling

Cellular alterations
- Reduced metabolic activity
- ↓AKT
- ↓ATP
- ↑Lactate
- Apoptosis resistance

Pathological manifestations
- Insulin resistance
- Cardiac hypertrophy
- Atherosclerosis
- Increased proliferation
- Pulmonary artery hypertension

C. Lopez-Crisosto et al. Nature Reviews/Cardiology 2017
Changes in Cardiac Energy Metabolism in H F


myofibrillar creatine kinase isoenzyme
Multifaceted Symptoms of HF

HF — A Multi-systemic Disease.

Advanced Heart Failure

Endocrine systems impairment
Elevated pro-inflammatory cytokines

Liver
- Cardiac hepatopathy (CH)
- Acute cardiogenic liver injury (ACLI)
- Altered drugs pharmacokinetics
- Decreased albumin synthesis
- Prolonged PT

Kidney
- RAAS activation
- Fluid overload

Bone
- Reduced bone mass
- Enhanced lipolysis
- Insulin resistance (IR)
- Cardiac lipotoxicity

Adipose Tissue
- Limited exercise capacity

Diaphragm
- Weight loss (katabolism)
- Limited exercise capacity

Skeletal Muscle

Metabolites Profile
(e.g. urine, serum, plasma)
Studies of Metabolomics in CVD

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Principal Metabolic Finding</th>
<th>Method of Metabolite Profiling</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFpEF patients</td>
<td>Circulating acylcarnitines are increased in HFpEF patients and further increased in HFrEF patients</td>
<td>MS/MS</td>
</tr>
<tr>
<td>(LVEF &gt;45%)</td>
<td></td>
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<tr>
<td>HFpEF patients</td>
<td>Circulating C16 and C18:1 acylcarnitines are increased in end-stage HF vs. chronic HF, and are corrected via LVAD placement</td>
<td>MS</td>
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<tr>
<td>(LVEF &lt;45%)</td>
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<tr>
<td>Chronic HF patients</td>
<td>S-C, M-C, and L-C acylcarnitines are decreased in transmural LV myocardial biopsies from end-stage HF patients</td>
<td>LC/MS</td>
</tr>
<tr>
<td>(LVEF 20%-30%)</td>
<td>β-Hydroxybutyryl-CoA is increased in transmural LV myocardial biopsies from end-stage HF patients</td>
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<td>End-stage HF patients with nonischemic cardiomyopathy</td>
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<tr>
<td>(mean LVEF 17.5%)</td>
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<tr>
<td>HFpEF patients</td>
<td>Circulating ketone bodies are decreased in HFpEF patients and further decreased in HFrEF patients</td>
<td>LC-MS/MS and (^1)H-NMR</td>
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<td>(LVEF &gt;45%)</td>
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<tr>
<td>HF patients</td>
<td>BCKAs are increased in LV biopsies of HF patients with dilated cardiomyopathy</td>
<td>LC/MS</td>
</tr>
<tr>
<td>(LVEF ≤30%)</td>
<td></td>
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</tbody>
</table>

J.R. Ussher, J Am Coll Cardiol 2016;68:2850–70
Plasma Long-chain Acylcarnitine Contributions to the HF Phenotype

Major metabolic impairments identified in metabolomics investigations of human HF

The Action of Therapeutic Agents

A.Gupta et al. Heart Fail Rev 2017
Integration of Various Omics Platforms for pts Phenotyping

J.R. Ussher, J Am Coll Cardiol 2016;68:2850–70

A.T. Turer. Journal of Molecular and Cellular Cardiology 2012
Historical Knowledge

- «...Τίποτα δεν γίνεται ούτε χάνεται, αλλά συντίθεται και διαχωρίζεται από προϋπάρχοντα όντα». 
  Αναξαγόρας (~500-428 π.Χ)

- “The sum of the actual and potential energies in the universe is unchangeable.”
  William J.M. Rankine, 1853

The heart is a self-renewing biological pump that converts chemical energy into mechanical energy, with some energy loss as heat and kinetic energy.