Energy metabolism in heart disease: Is it clinically relevant?

René Lerch, Geneva
Andreas Grüntzig Lecture 2016
Energy metabolism in heart disease: Is it clinically relevant?

Outline

- My first observation
- Imaging metabolism
- Metabolism and reperfusion
- Metabolism in heart failure
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Doctoral Thesis
Left ventricular dynamics, transmural blood flow and energy metabolism during coronary flow reduction and reperfusion in anesthetized dog

Rejected by Basic Res Cardiol in 1975 → Artefact!
1975, G. Heyndrickx → Stunning!

J Clin Invest 1975; 56: 978 - 85
“Myocardial stunning”
remaining questions

Dirk J. Duncker a, Rainer Schulz b, Roberto Ferrari c, David Garcia-Dorado d, Carlo Guarnieri e, Gerd Heusch b, Pieter D. Verdouw a,*

had normalized almost instantaneously. In that period there was some scepticism about the concept that myocardial function would not recover immediately upon reperfusion, illustrated by the rejection of a manuscript, in which the...

Metabolism
Myocardial energy metabolism

- **Glucose**
- **Fatty acid**
- **Lactate**
- **Ketone bodies**

**Glycolysis**

- ATP
- Triglycerides

**β-oxidation**

**Krebs cycle**

- NADH
- H$_2$O

**Oxidative phosphorylation**

**Respiratory chain**

**Contraction**

**Transport**

**Structure**

**ATP**

**O$_2$**

**CrP**
History of modern research on myocardial metabolism


Richard J. Bing (1909 – 2001)
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Positron emission tomography at WUSTL in 1978

Cyclotron

Radionuclides ($T_{1/2}$)
- Oxygen-15: 2.1 min
- Nitrogen-13: 10.0 min
- Carbon-11: 20.3 min
- Fluor-18: 110 min

Biomolecules
- $^{11}$C-palmitic acid
- $^{11}$C-acetate
- $^{11}$C-glucose
- $^{18}$F-fluoro-deoxyglucose

Michael Ter-Pogossian (1925 - 1996)

Positron emission tomography

PETT V

Dog, $^{11}$C-palmitate
Temporal Dependence of Beneficial Effects of Coronary Thrombolysis Characterized by Positron Tomography

Anesthetized dogs, Thrombus induced by intracoronary copper coil, Thrombolysis with streptokinase.

Myocardial uptake of $^{11}$C-palmitate

Reperfusion after 90 min

Reperfusion after 360 min

- Anesthetized dogs,
- Thrombus induced by intracoronary copper coil,
- Thrombolysis with streptokinase.
Localization of Viable, Ischemic Myocardium by Positron-emission Tomography with $^{11}$C-Palmitate

Rene A. Lerch, M.D., Hans D. Ambos, Steven R. Bergmann, Ph.D., Michael J. Welch, Ph.D., Michel M. Ter-Pogossian, Ph.D., and Burton E. Sobel, M.D.

Circulation 1981; 64: 689-99

Myocardial time-activity curve

Effect of pacing-induced ischemia

Anesthetized dogs, circumflex stenosis.
Effect of Flow-Independent Reduction of Metabolism on Regional Myocardial Clearance of $^{11}$C-Palmitate

Rene A. Lerch, M.D., Steven R. Bergmann, Ph.D., Hans D. Ambos, Michael J. Welch, Ph.D., Michel M. Ter-Pogossian, Ph.D., and Burton E. Sobel, M.D.

Circulation 1982; 65: 731-38
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Substrate Competition in Postischemic Myocardium

Effect of Substrate Availability During Reperfusion on Metabolic and Contractile Recovery in Isolated Rat Hearts

Christian Tamm, Richard Benzi, Irène Papageorgiou, Isabelle Tardy, René Lerch

Circ Res 1994; 75: 1103-1112

Contribution of palmitate and glucose to ATP production

- Langendorff perfused rat hearts
- Perfusate 11 mM glucose and 0.4 mM palmitate
- 40 min no-flow ischemia

means +/- SEM; * p<0.05 vs control
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Non-ischemic control

Post-ischemic reperfusion
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Metabolic remodeling in heart failure:

Shift from fatty acid to glucose oxidation

Overexpression of angiotensinogen in myocardium (TG1306/R1)

Compensated Hypertrophy ~50%  Heart Failure ~50%

Thierry Pedrazzini, UNIL

Pellieux et al, J Mol Cell Cardiol 2006; 41: 459 - 66
Metabolic remodeling in heart failure:
Reduction of enzymes of fatty acid oxidation

Transcription factors
- PPARα
- PGC-1α

Transcription

Messenger RNA (mRNA)

Protein

CPT-1M: Carnitine palmitoyltransferase 1
MCAD: Medium-chain acyl-CoA dehydrogenase

*P<0.05 vs wild type

Pellieux et al, J Mol Cell Cardiol 2006; 41: 459 - 466
Metabolic remodeling in heart failure:
Potential contribution of altered energy metabolism to contractile failure

Fatty acid oxidation

NADH → ATP

Lipotoxicity

Lack of energy
Metabolic remodeling in heart failure: 

Signs of lipotoxicity

- **Lipid droplets**:
  - Wild type: absent
  - Hypertrophy: absent
  - Heart failure: present

- **Ceramides**:
  - Control vs. High fat diet
  - Heart failure vs. Wild type

*Pellieux et al, Am J Physiol Heart - Circ Physiol 2012; 302: H1795-1805*
4 observations on energy metabolism in heart disease

1971
- Stunning

1978
- Imaging metabolism
- Metabolic protection during reperfusion

since 1982
- Restricted fatty acid oxidation in heart failure
Regard research as an end of itself – not a means to an end.

Feel deeply the thrill of the chase and the joy of discovery, i.e. answering a question.

Eugene Braunwald, 2008
Collaborators (since year 2000)

Christoph Montessuit
Nathalie Rosenblatt-Velin
Corinne Pellieux
Irene Papageorgiou
Andrea Remondino
Isabelle Tardy
Jerôme Terrand

Thierry Pedrazzini
University of Tromsoe
Terje Larsen
Ellen Aasum
Merci!