Fuel the Failing Heart: glucose or fatty acids?

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Metabolic Remodeling:

Fatty Acids ↓

PCr/ATP ↓

Carbohydrates ↑
Glucose vs. fatty acids:

Glucose:
- O2 efficient substrate, 11% saving in P:O
- C inefficient, 2/3 carbon enters TCA
- availability to the cardiac myocyte is subjected to insulin regulation

Fatty acids:
- O2 inefficient substrate, requires 11% or more O2 than glucose
- high availability and C efficient, every carbon is oxidized
- FAO is dependent on mitochondrial function
- reactive lipid species
Shifting Substrate Preference to Glucose by overexpressing GLUT1

2-deoxyglucose-phosphate (mM)

WT TG

2-deoxyglucose uptake rate (mM/min)

basal insulin-stimulated

WT TG

% Oxidation

FS%

WT TG

Survival at 90 weeks

Survival (%)
Overexpressing GLUT1 delays the transition to failure and Improves Long-term Survival Post Ascending Aortic Constriction
Glucose is not toxic.
A greater than endogenous capacity for glucose utilization is needed to compensate for impaired FAO in the adult heart.

\[
\text{PPARα}^{-/-} \text{ mice} \quad \text{whole body knockout} \quad \times \quad \text{GLUT1}^{\text{TG}} \text{ mice} \quad \text{cardiac specific}
\]

\[
\text{PPARα}^{-/-} \text{ GLUT1}^{\text{TG}}
\]
Contributions of glucose vs. fatty acids to the oxidative metabolism

Baseline
High workload
Rate Pressure Product (10³ mmHg/min)

- **WT**
- **PPARα⁻/⁻**
- **PPARα⁻/⁻-GLUT1**
- **GLUT1**

Graph showing the comparison of Rate Pressure Product under different conditions of glucose and mixed substrates. The high workload is indicated to last 25 minutes.
[ATP] (mM)

- WT
- PPARα^−/−
- PPARα^−/−GLUT1
- GLUT1

high workload 25 min.
Maladaptive:
Limited capacity for ATP synthesis

Further facilitates glucose utilization (GLUT1-TG)

Normalized FAO?

↑ use of glucose and ↓ use of fatty acids

Adaptive:
↓ O₂ demand
Strategies:

• Enhance FAO via the PPARα mechanisms
  – Cardiac PPARα-TG: cardiomyopathy
  – Pharmacological activation: worse or no effects on cardiac function in hypertrophied heart

• High fat diet
  – Delays the development of heart failure in certain models while worsens the outcome in others

FA uptake >> FAO

• Mitochondrial FAO
  – Manipulate long-chain fatty acid entry
Targeting Acetyl-CoA Carboxylase (ACC2) to Specifically Increase FAO

Fatty Acids → Lipid synthesis → MCD → Acetyl CoA

Lipid synthesis

Acetyl CoA → MCD → Acetyl CoA

Acetyl CoA

Malonyl CoA → ACC1 → ACC2

Malonyl CoA

ACC1

ACC2

ACS

CPT1

β-oxidation → TCA

Mitochondrion
Cardiac-specific deletion of ACC2 decreases Malonyl-CoA level

ACC2

CON ACC2H-/-

Heart

Gastroc

Liver

ACC1 mRNA

Fold Change (from Control)

C57 f/WT f/f -/+ -/-

CON

ACC2H-/-

0.0

0.5

1.0

1.5

2.0

2.5

Malonyl CoA

nмол/г dry weight

CON ACC2H-/-

0.0

0.5

1.0

1.5

2.0

2.5

*
Effects of ACC2 Deletion on Cardiac Metabolism

% Oxidation

Relative Contribution to Acetyl-CoA (%)

TAG Content

Glycogen Content

MVO₂

MVO₂/RPP

Gene Expression

Acylcarnitines

Fold Change (Relative to Control)

Glc+pyr mixed substrate

CON

ACC2H⁻/⁻
High Workload Challenge in Isolated Perfused Heart

**Cardiac Function**

- **LVDevP (mmHg)**
  - CON
  - ACC2H⁻/⁻

- **Heart Rate (bpm)**
  - CON
  - ACC2H⁻/⁻

**Diastolic Function**

- **EDP (mmHg)**
  - CON
  - ACC2H⁻/⁻

**Inorganic Phosphate**

- **Baseline**
- **High Workload**

**Phosphocreatine**

- **Baseline**
- **High Workload**

**ATP**

- **Baseline**
- **High Workload**

**PI (mM)**

- **Baseline**
- **High Workload**

* and ** indicate statistical significance.
Aging: Fatty acid metabolism is maintained with normal function and morphology up to 12 months of age.

**Substrate Utilization**

- **Contribution to Acetyl-CoA (%):**
  - CON
  - ACC2H⁻/⁻

**In-vivo Function**

- **Fractional Shortening (%):**
  - CON
  - ACC2H⁻/⁻

**Wall Thickness**

- **LVPW;d (mm):**
  - CON
  - ACC2H⁻/⁻
Pressure Overload: TAC

% Contribution to Acetyl-CoA

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Glucose, Fatty Acids, Other

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CON ACC2H/-

PCr/ATP

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 Function

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FS (%)

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PCr/ATP

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PCR/ATP↓

Carbohydrates ↑

Fatty Acids ↓

Alanine

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ANAPLEROISIS

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13C3-Alanine/13C1-Glucose (AU)

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Lactate

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13C-C3Lactate/13C-C1Glucose (AU)

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CON ACC2H/-

PCr/ATP

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PCr/ATP↓

Carbohydrates ↑

Fatty Acids ↓
Reduced Hypertrophy and Fibrosis in ACC2H-/- 4 weeks Post-TAC

![Graphs and images showing reduced hypertrophy and fibrosis in ACC2H-/- mice 4 weeks post-TAC.]
Optimal energy metabolism

Capacity:

to meet the high energy demand

Balance:

uptake = utilization

Flexibility:

able to utilize what is available

No “one-size-fit-all” substrate for the heart
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