Energetics of Heart Failure

Focus on the metabolism of ATP and Cr

Understanding the failing human myocardium using animal models

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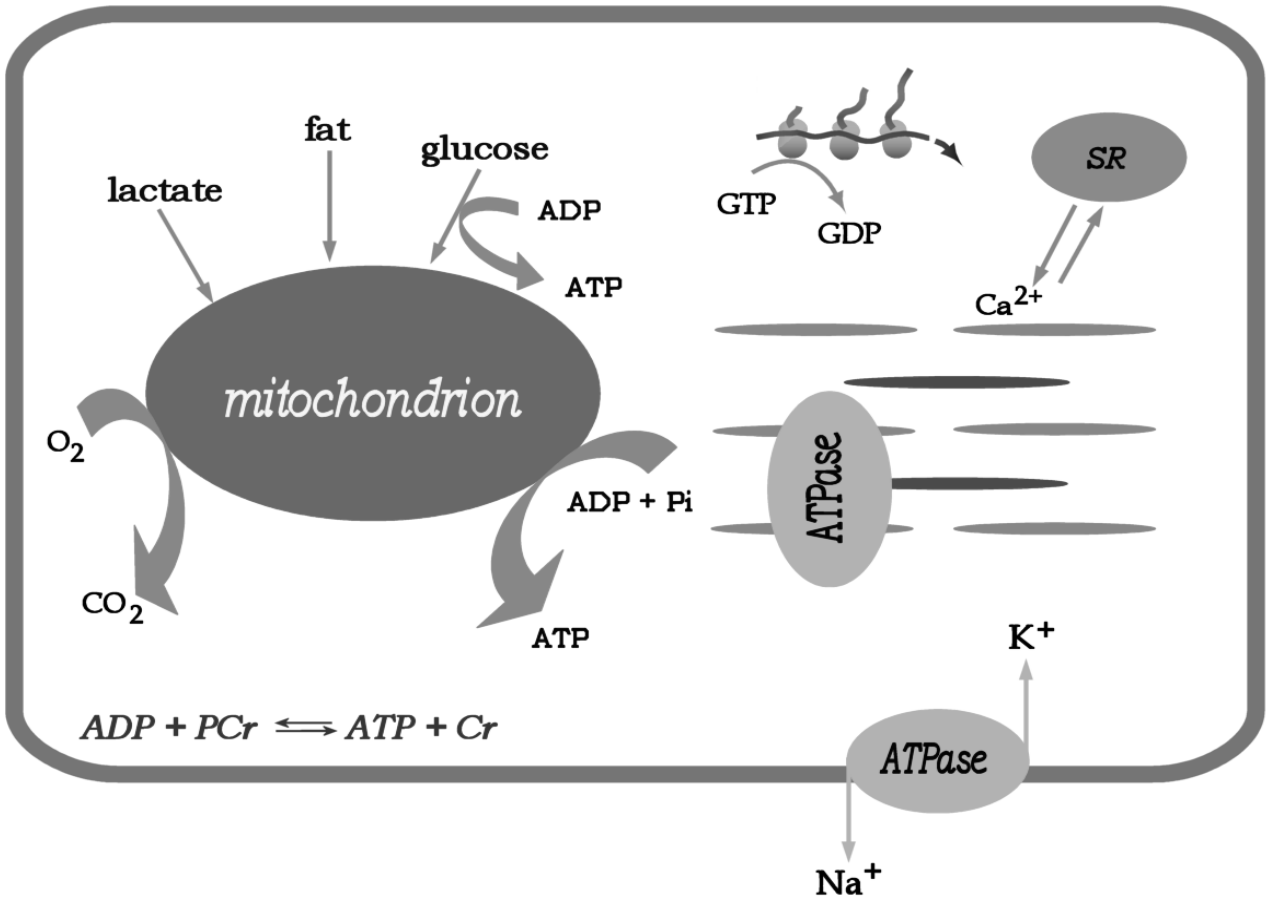
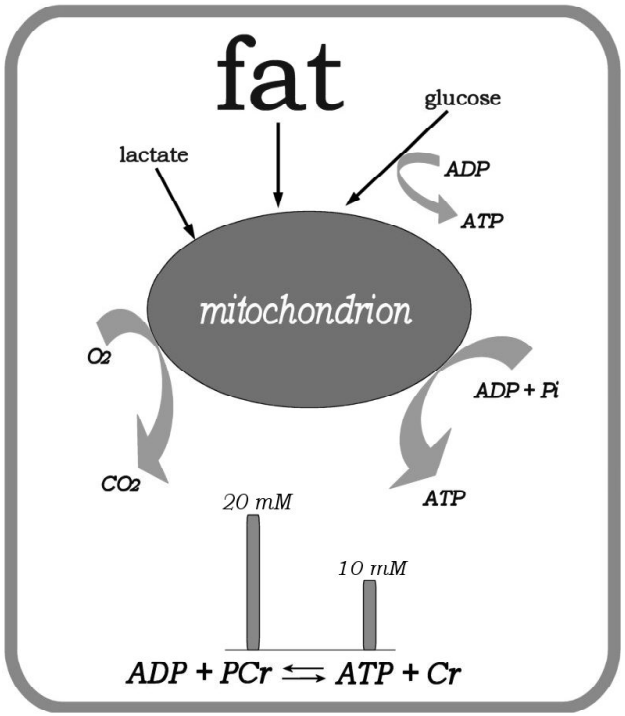
ATP supply and utilization



Two lessons:

1. Fuel utilization changes in the failing heart
2. [ATP] and [PCr] fall due to supply/demand mismatch



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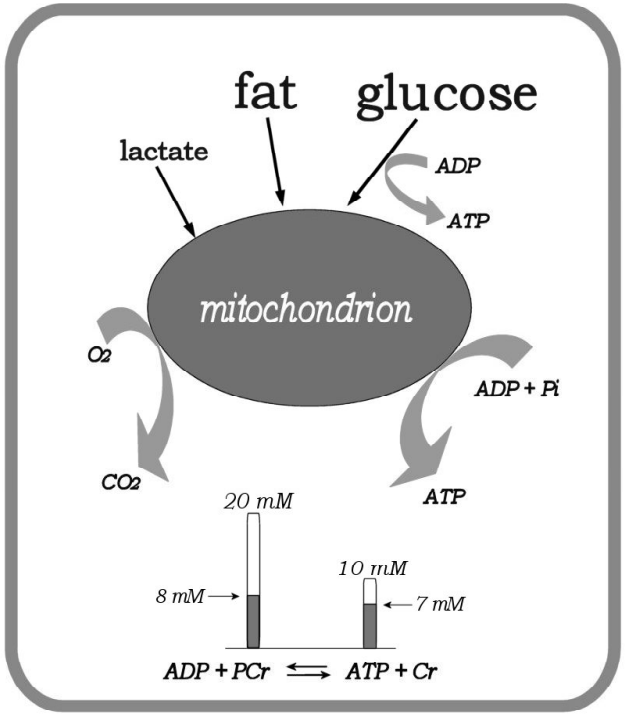


Failing

OUTLINE

- **ATP falls in the failing myocardium**
  - Proximal mechanism
  - Long-term mechanisms
  - Consequences on heart function
  - Attempts to reverse
- **Creatine and PCr fall in the failing myocardium**
  - Proximal mechanism
  - Long-term mechanisms
  - Consequences on heart function
  - Attempts to reverse

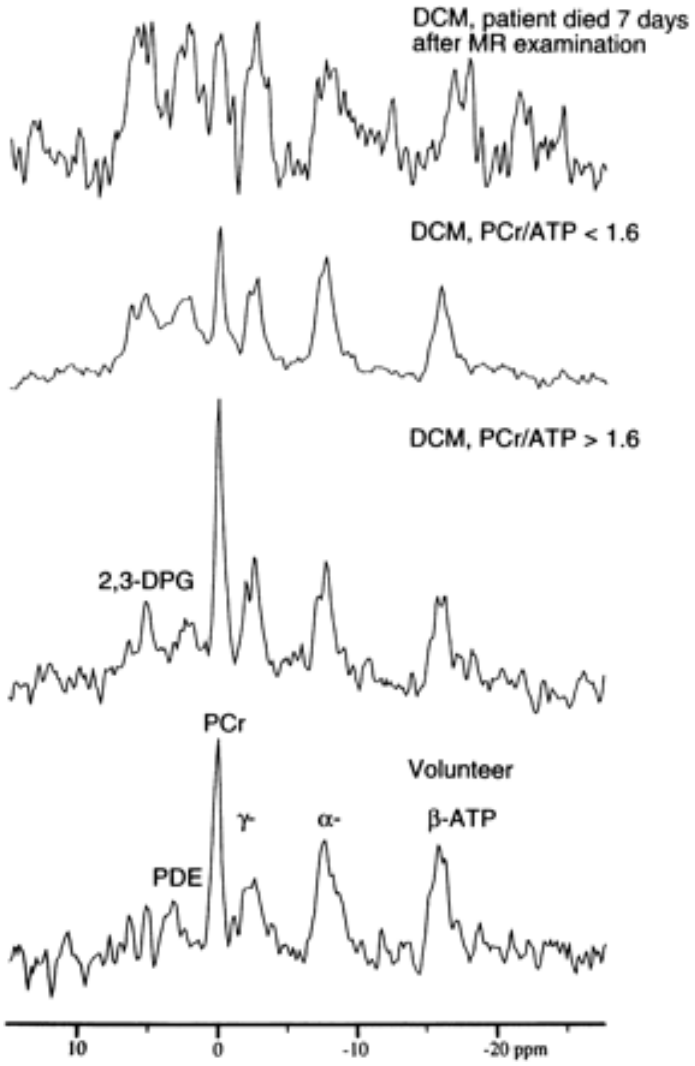
Myocardial PCr/ATP is a predictor of mortality in patients with DCM

Neubauer et al, Circulation 1997

- 39 patients with DCM followed for up to 1600 days; 26% mortality
- LVEF, NYHA class and PCr/ATP measured at entry and at end
- Each divided into 2 groups:
  - LVEF: > 30%, <30%
  - NYHA class: I and II *vs.* III
  - PCr/ATP: >1.6 (2/19 deaths); <1.6 (8/20 deaths)

Myocardial PCr/ATP is a predictor of mortality in patients with DCM

Neubauer et al, Circulation 1997 96:2190



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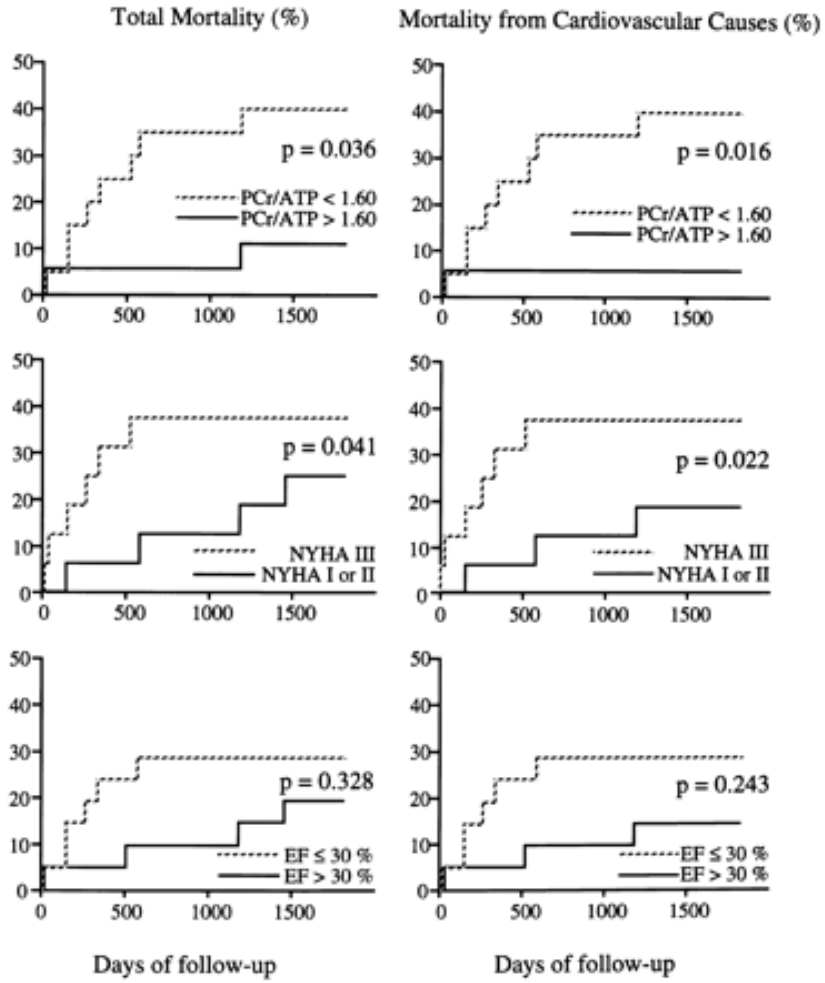


Changes in ATP in Failing Hearts

	ATP (mM)
Animal Models	
Control rat	10
50% LVH due to aortic banding	**8.8 ↓**
Control dog	10
Pacing induced HF	**8.0 ↓**
Non failing hamster	8.7
Failing hamser	**6.4 ↓**
Control turkey	8.5
Furazolidine DCM	**6.5 ↓**
Human Myocardium	
Control	10
Failing	**7.6 ↓**

LVH, left ventricular hypertrophy
HF, heart failure
DCM, dilated cardiomyopathy

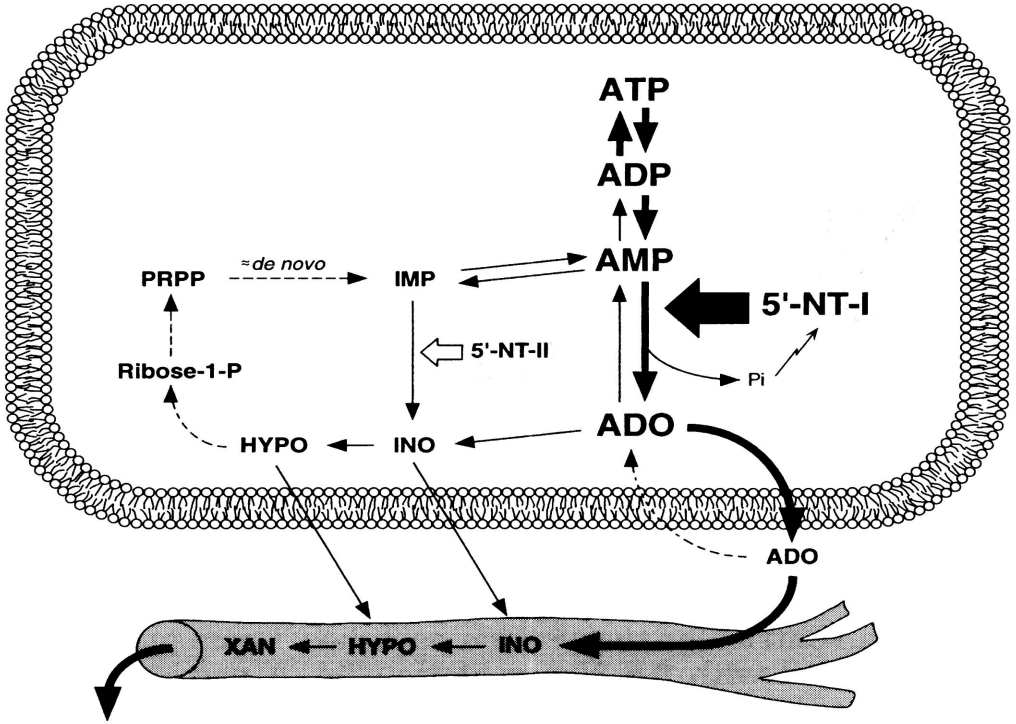
OUTLINE

ATP falls in the failing myocardium

- **Proximal mechanism**
- Long-term mechanisms
- Consequences on heart function
- Attempts to reverse

Pathway for ATP degradation in ischemic myocardium

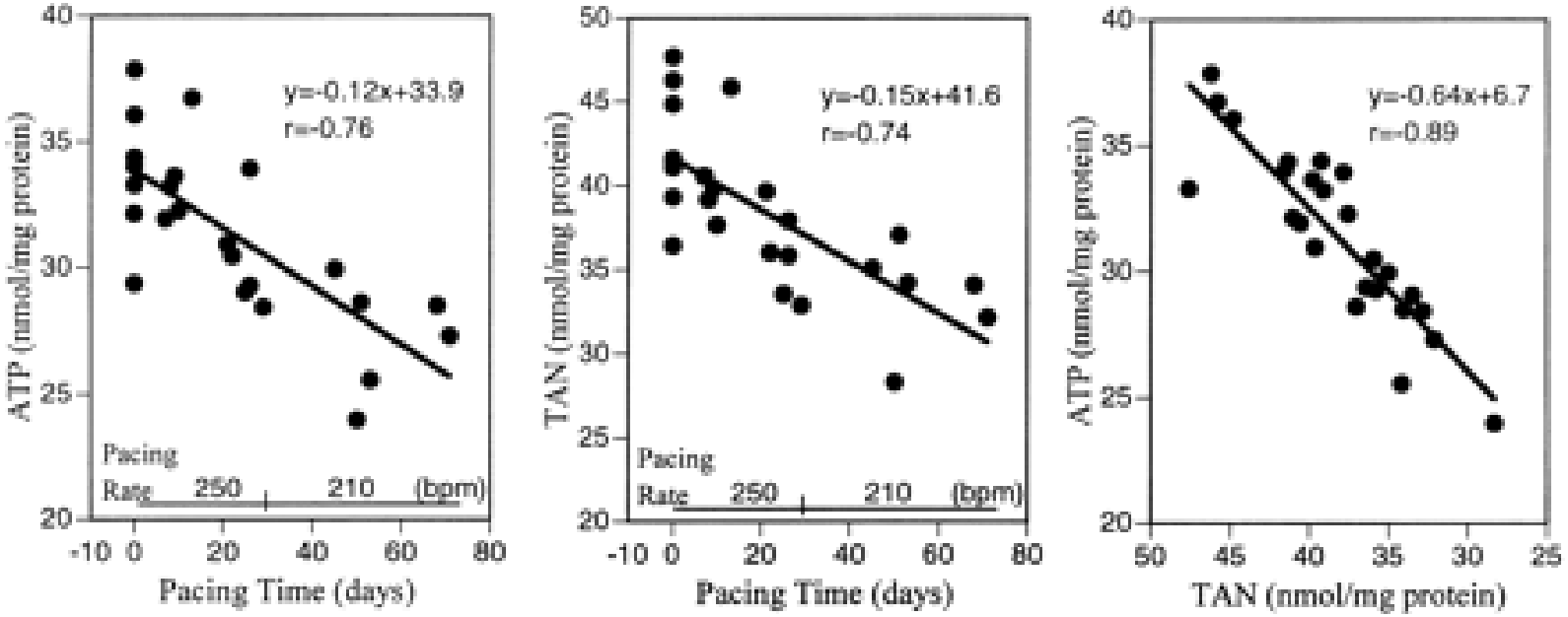
Bak & Ingwall, J Clin Invest 1994



Does this also occur in the failing heart?

Progressive loss of myocardial ATP due to loss of total purines during the development of heart failure in dogs

Shen et al, Circulation 1999



Changes in ATP, ADP and AMP in failing heart

	ATP (mM)	→	ADP (μM)	→	AMP (μM)
Animal Models					
Control rat	10		11		0.01
50% LVH due to aortic banding	**8.8 ↓**		**39**		**0.16 ↑**
Control dog	10		64		0.42
Pacing induced HF	**8.0 ↓**		**49**		**0.34 ↓**
Non failing hamster	8.7		74		0.60
Failing hamser	**6.4 ↓**		**36**		**0.20 ↓**
Control turkey	8.5		47		0.25
Furazolidine DCM	**6.5 ↓**		**23**		**0.08 ↓**
Human Myocardium					
Control	10		43		0.17
Failing	**7.6 ↓**		**31**		**0.14 ↓**

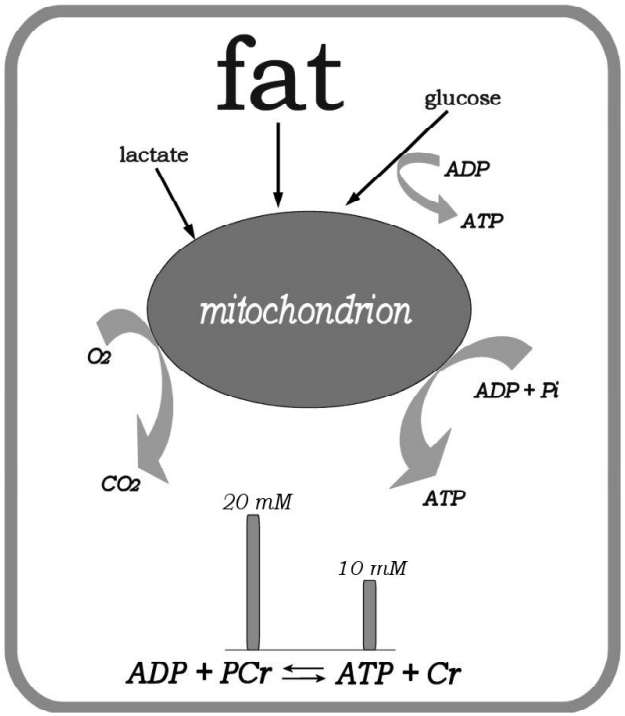
LVH, left ventricular hypertrophy
HF, heart failure
DCM, dilated cardiomyopathy

OUTLINE

ATP falls in the failing myocardium

- **Proximal mechanism**
- **Long-term mechanisms**
- **Consequences on heart function**
- Attempts to reverse

Fuel utilization changes in the failing heart



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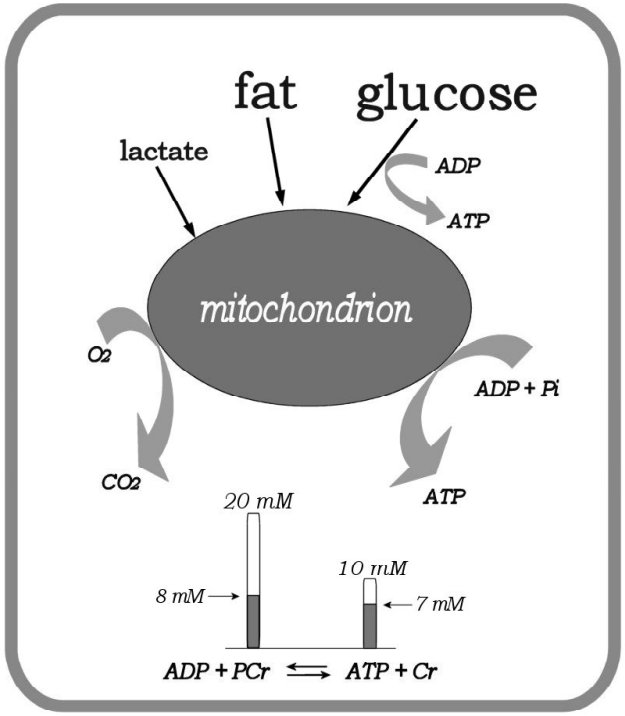
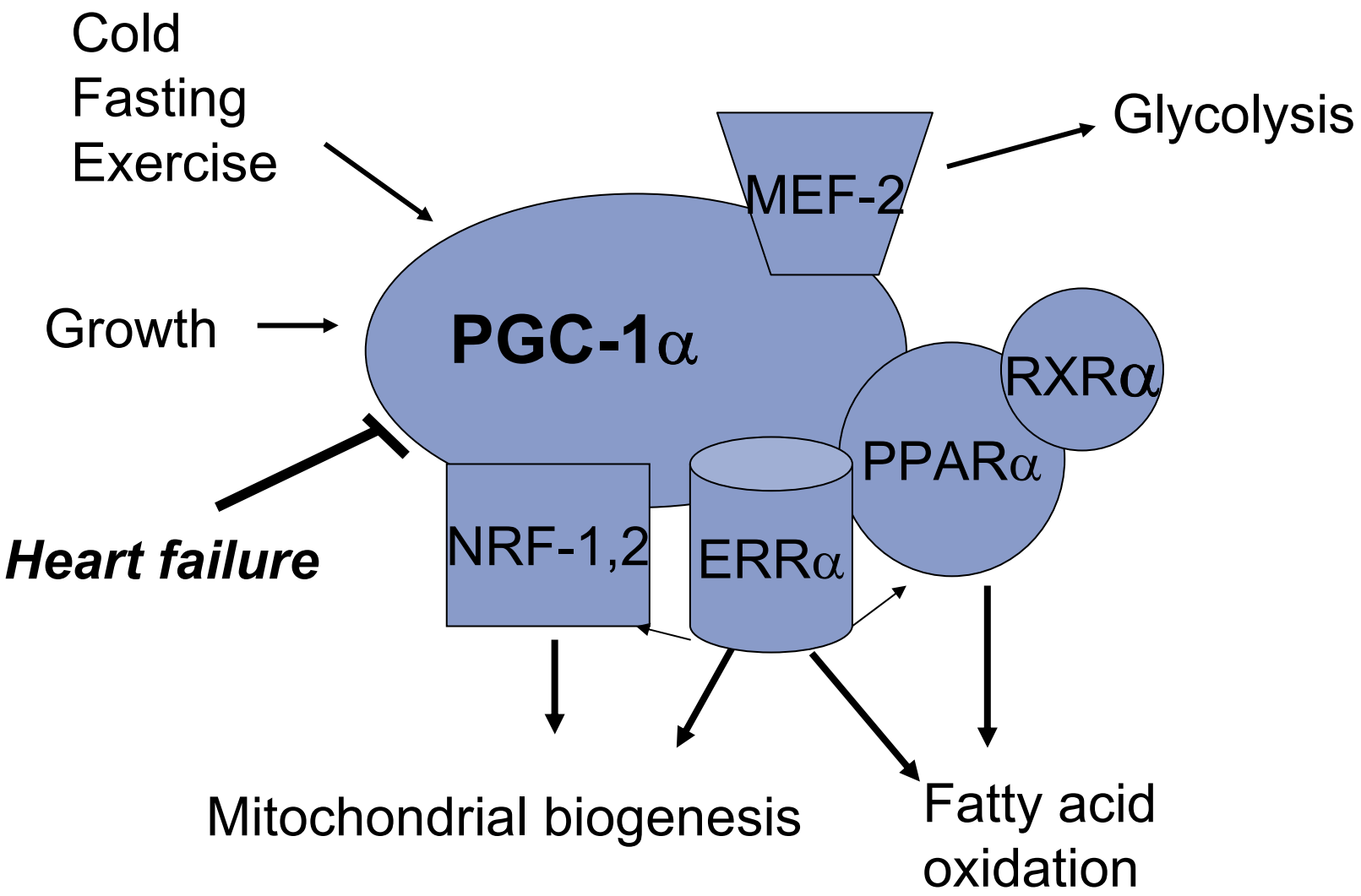


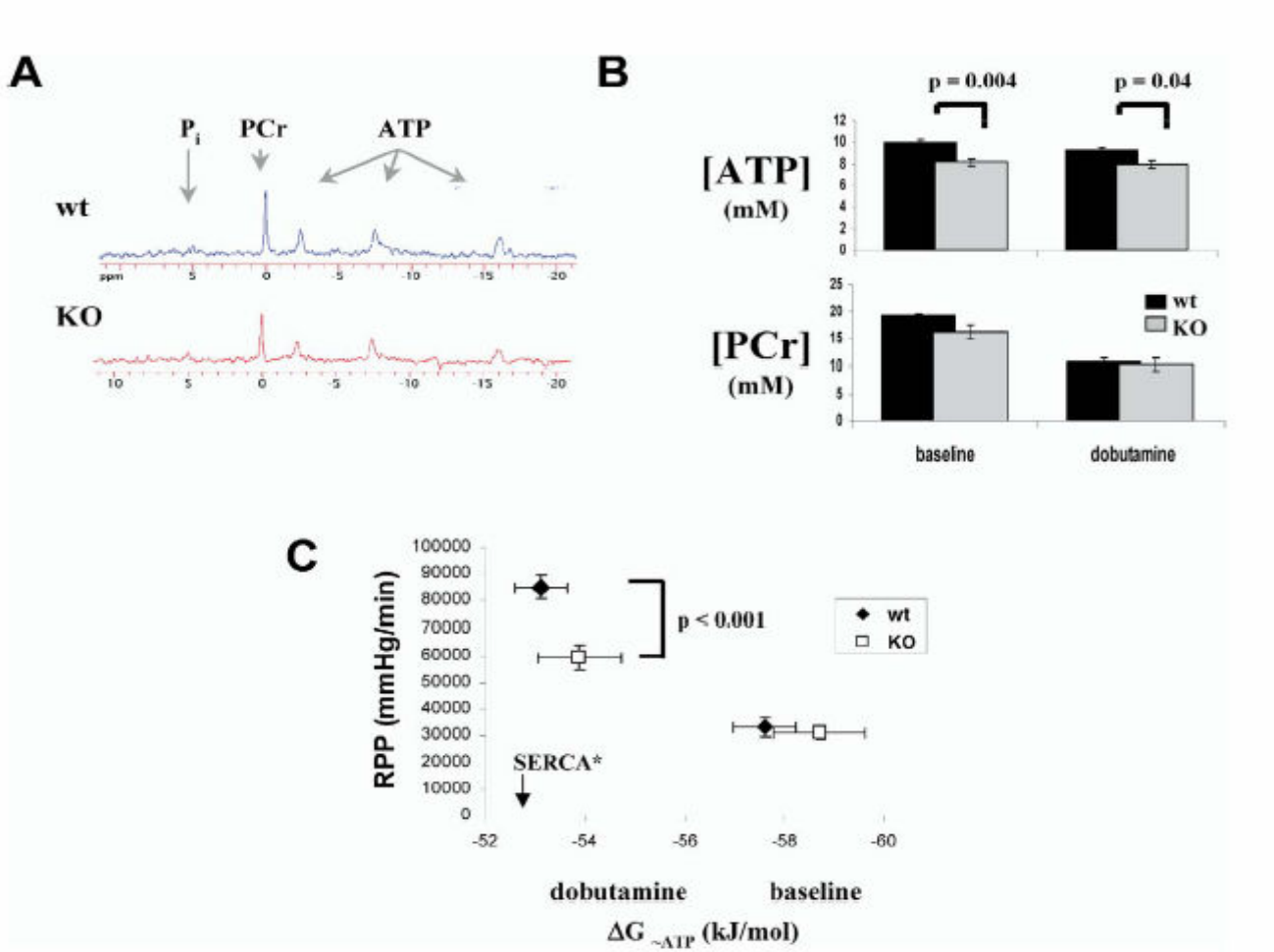
Failing

TRANSCRIPTIONAL CONTROL OF FATTY ACID METABOLISM
Role of the transcriptional co-activator PGC-1α



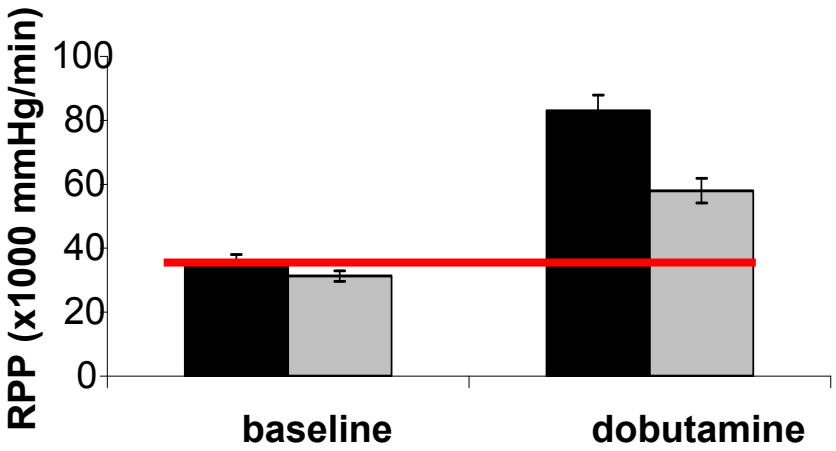
Hearts from PGC-1α KO mice are energy deficient

Arany et al, Cell Metabolism 2005

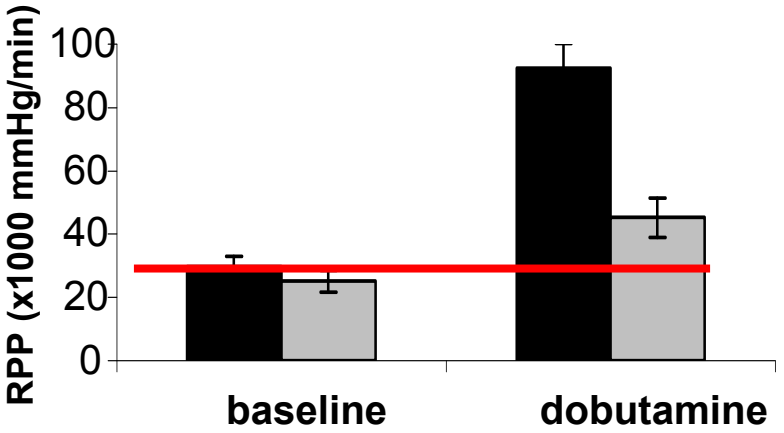


Functional consequence of deleting PGC-1α in mouse hearts

Glucose/Pyruvate



Glucose/Free Fatty Acid/ Lactate/Ketone

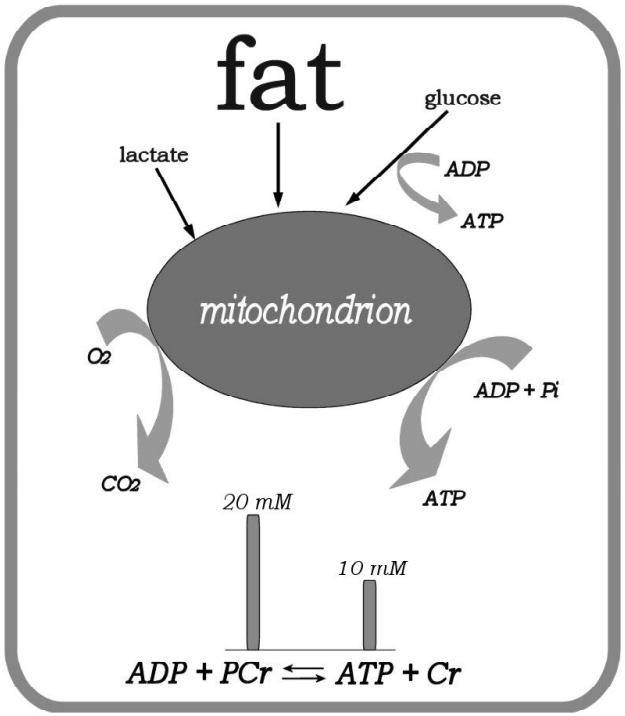


OUTLINE

ATP falls in the failing myocardium

- Proximal mechanism
- Long-term mechanisms
- Consequences on heart function
- **Attempts to reverse fall in ATP**

Fuel utilization changes in the failing heart



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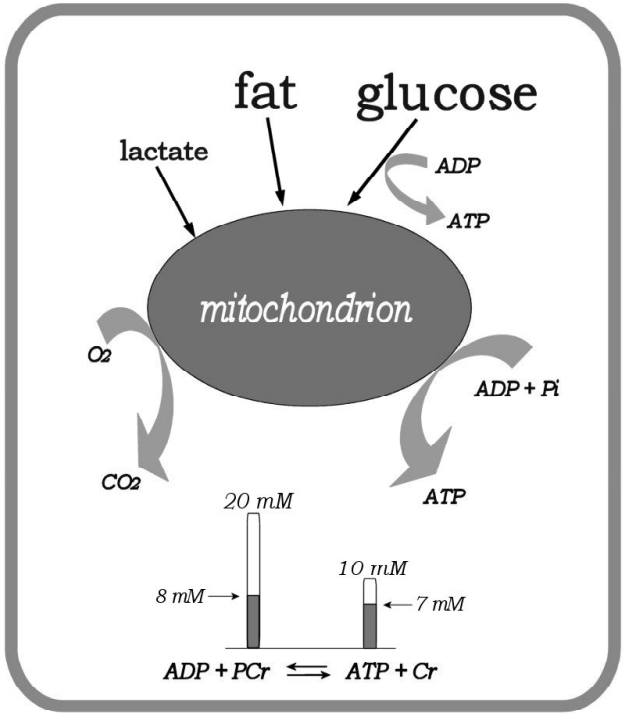
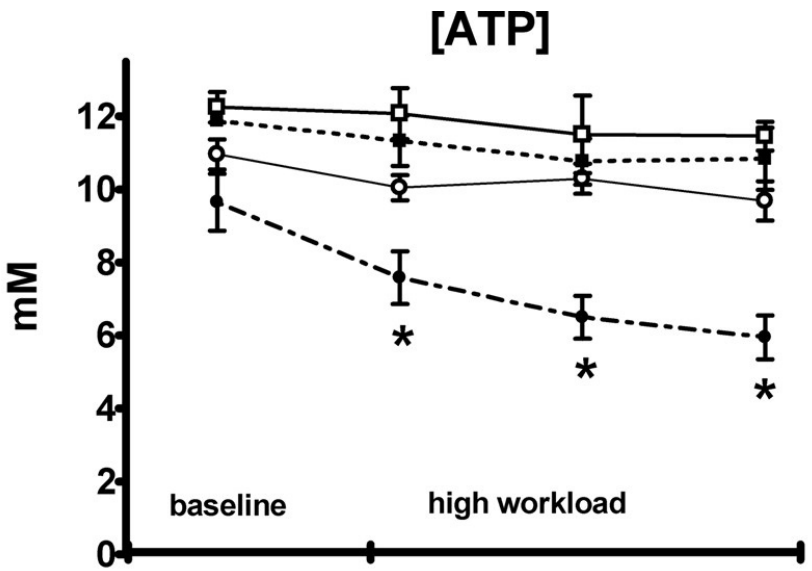
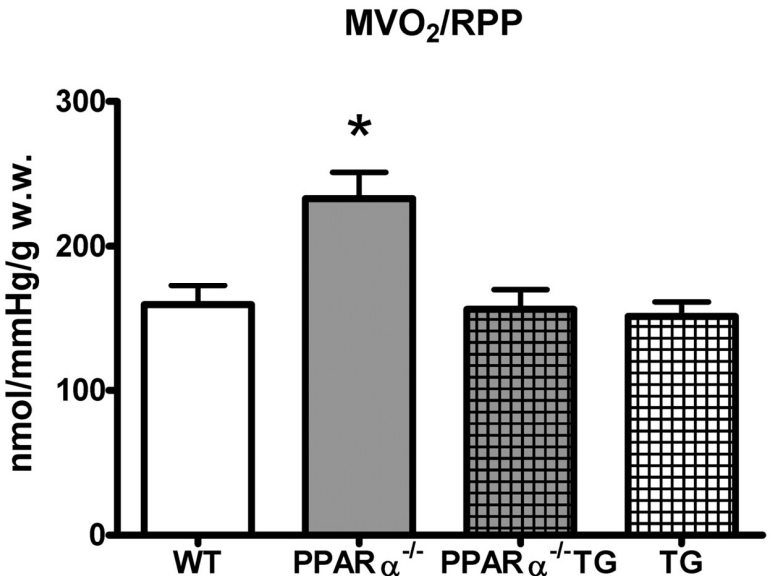


Failing

Increasing glucose uptake and metabolism rescues PPARα deficient mouse hearts

Luptak et al, Circulation 2005





Conclusions: on ATP

ATP falls in the failing myocardium

- Proximal mechanism: *loss of purines*
- Long-term mechanisms: *transcriptional control by PGC-1α, PPARα*
- Consequences on heart function: *decreased function*
- Is there a future for therapeutic strategies based on metabolism? *YES*

OUTLINE

- **ATP** falls in the failing myocardium

  Proximal mechanism

  Long-term mechanisms

  Consequences on heart function

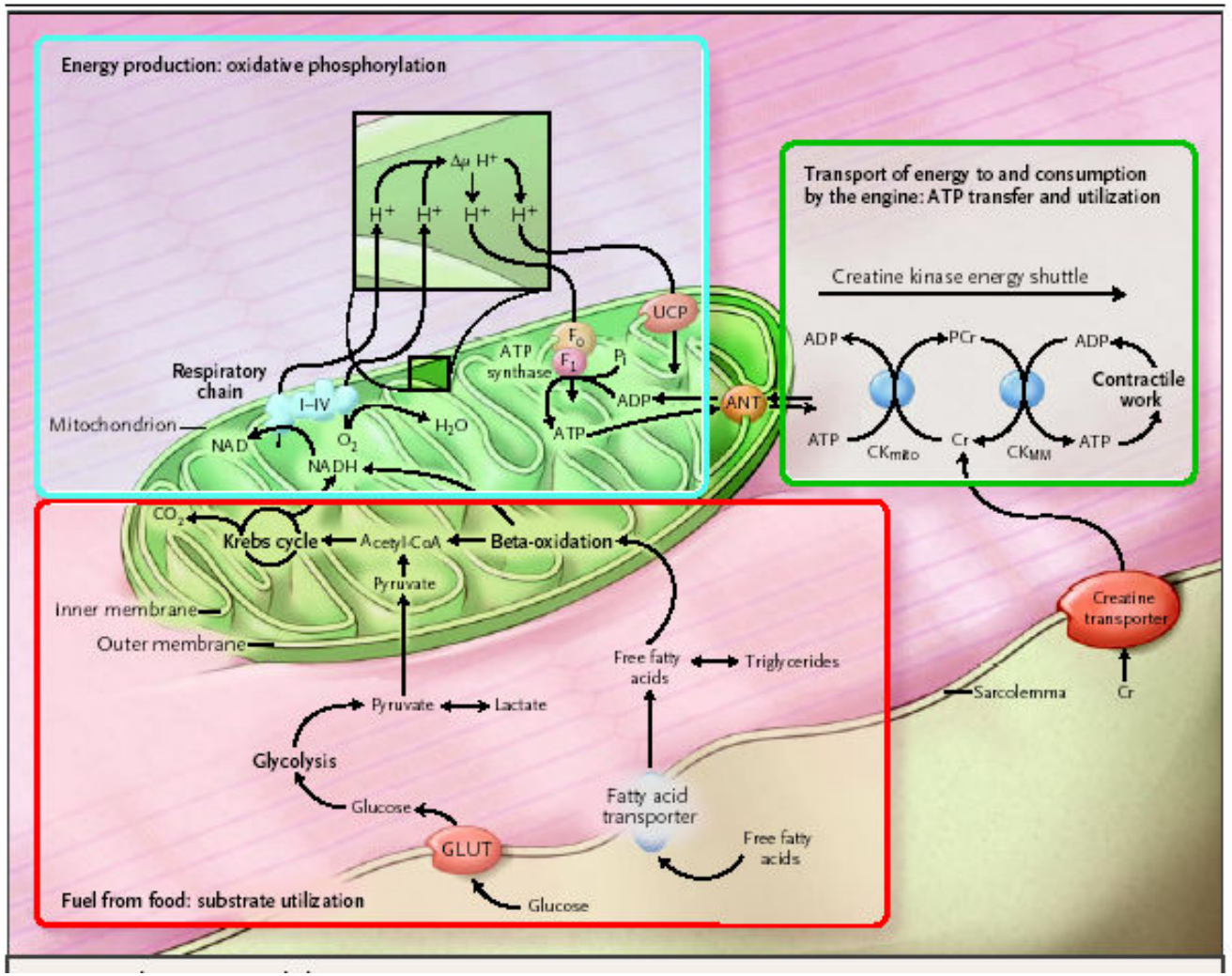
- **Creatine** falls in the failing myocardium

  Proximal mechanism

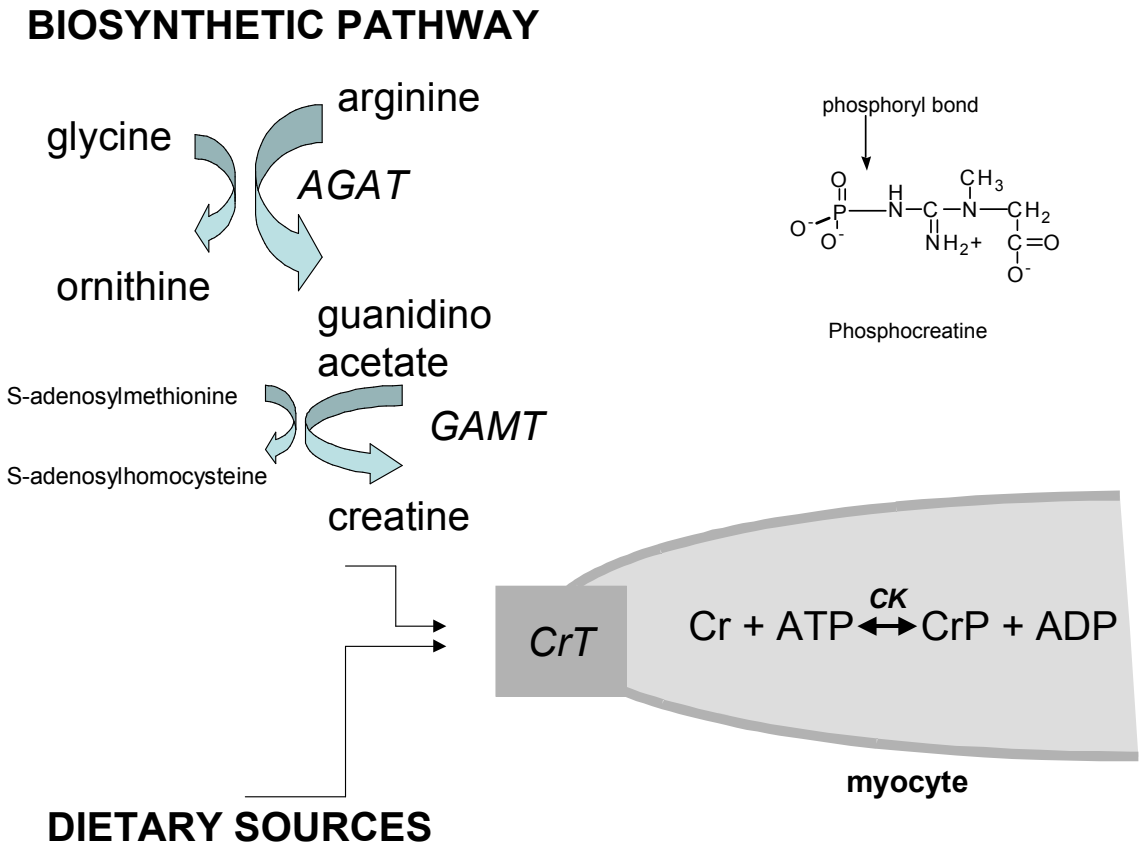
  Long-term mechanisms

  Consequences on heart function

Primary Energy Supply and Transfer Pathways



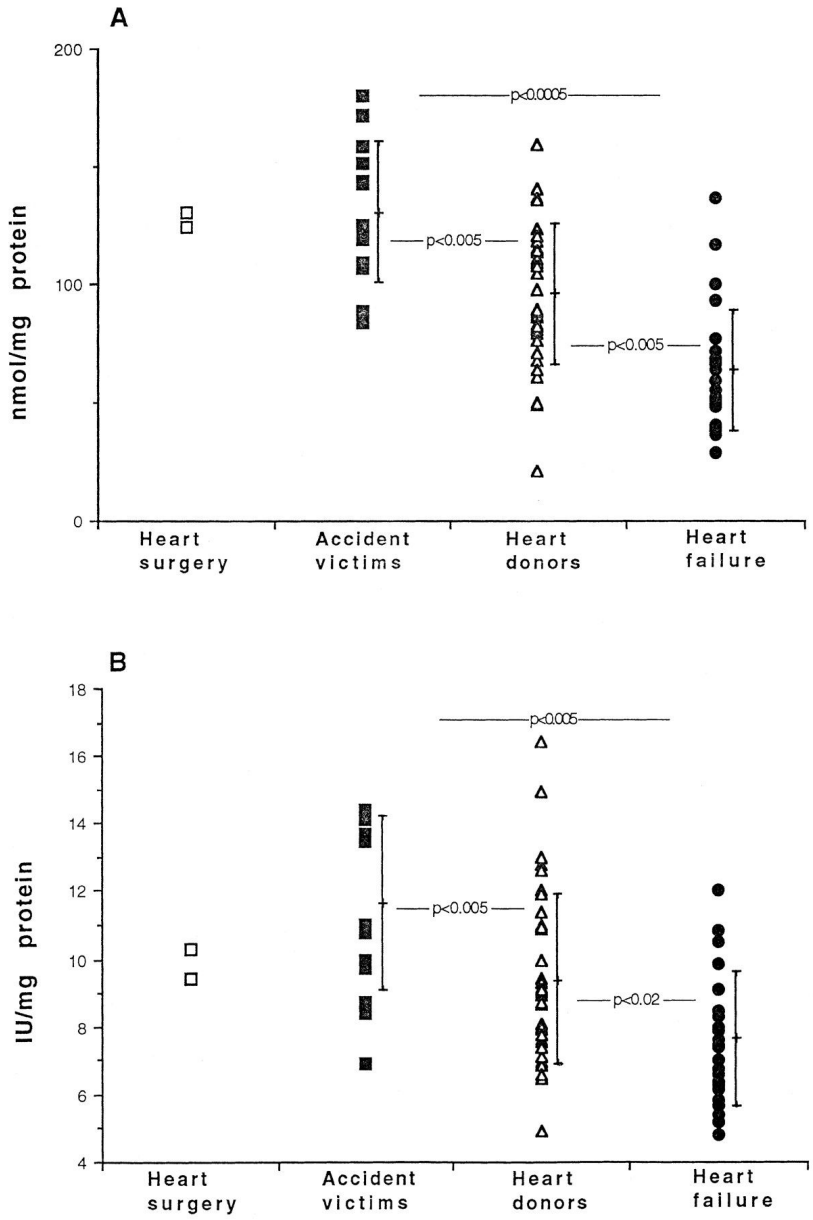
Sources for Creatine



Ways to manipulate [PCr]/[Cr]

- **Loss of function: decreased in LVH and HF**
- Gain of function: reversed in recovery from HF

- Bioengineered mouse hearts:
  - Loss of function: delete GAMT
  - **Gain of function: over express CrT**

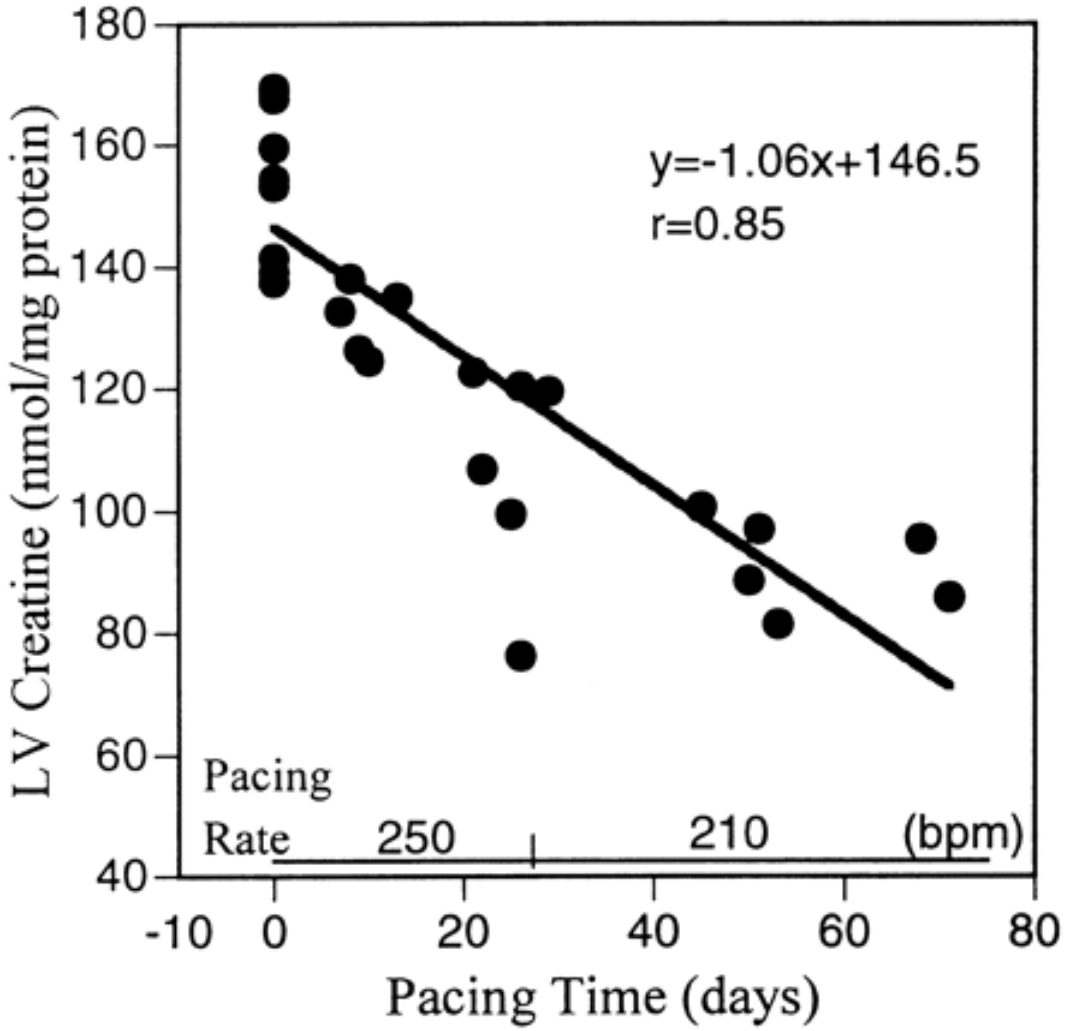


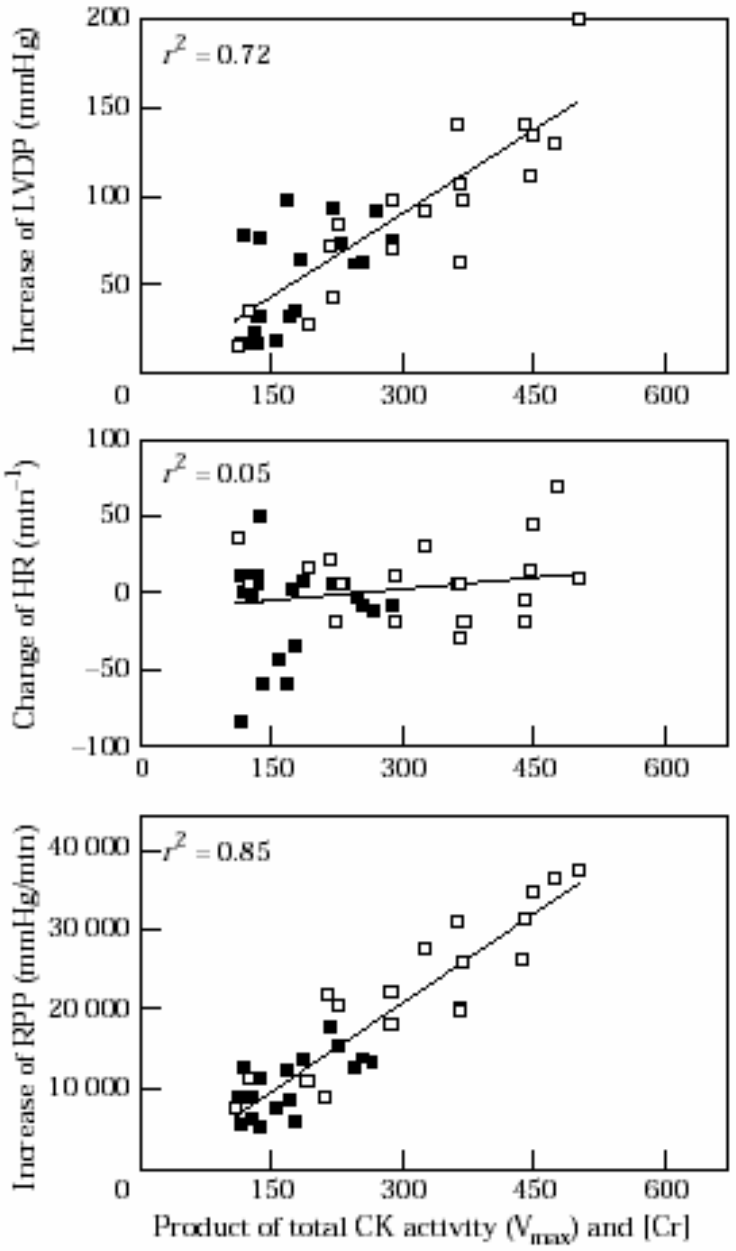
Total creatine and total CK activity in myocardium of LVs of control, donor, and failing hearts

Nascimben et al, Circulation 1996

Progressive rapid loss of myocardial creatine during the development of heart failure in dogs

Shen et al, Circulation 1999



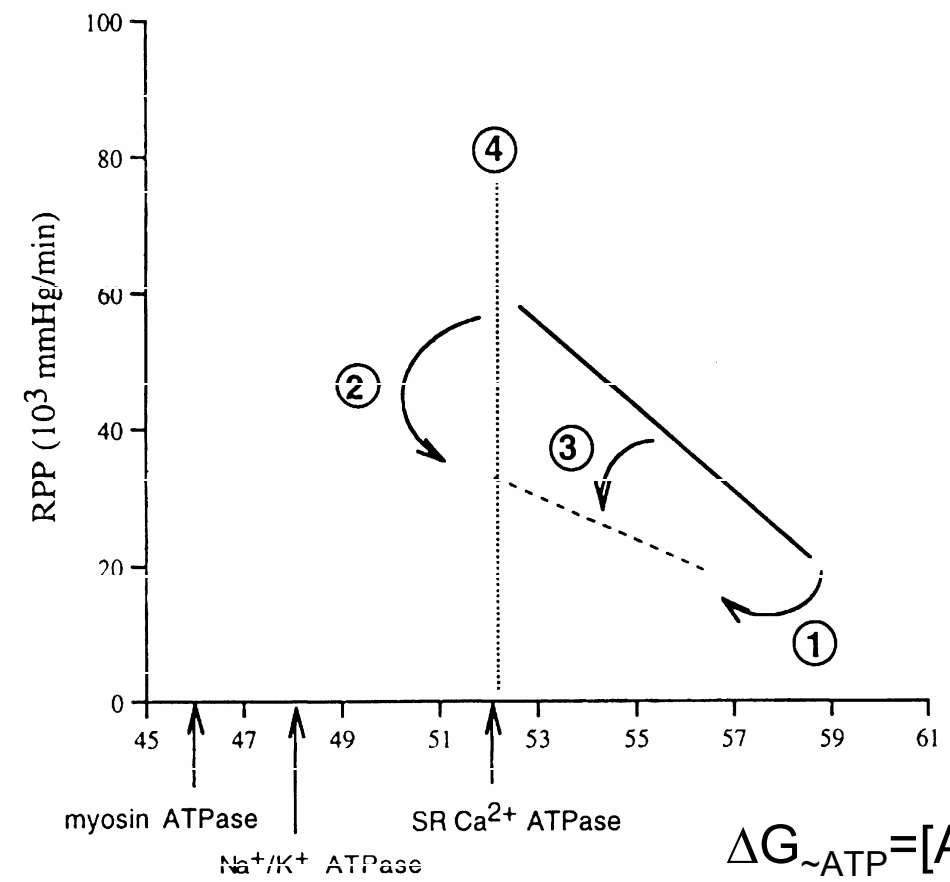


Decreased CK flux and decreased contractile reserve in failing TO2 Syrian hamster hearts

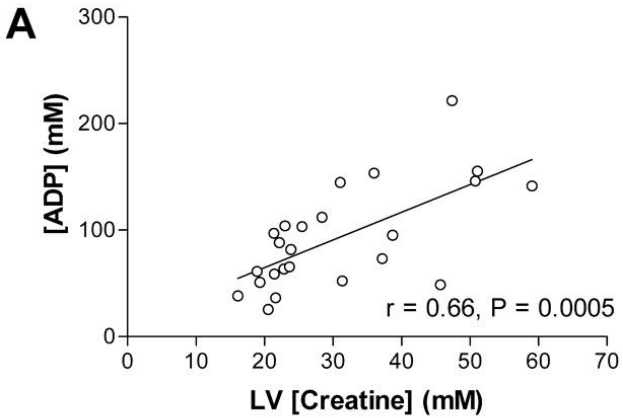
Tian et al, JMCC 1996

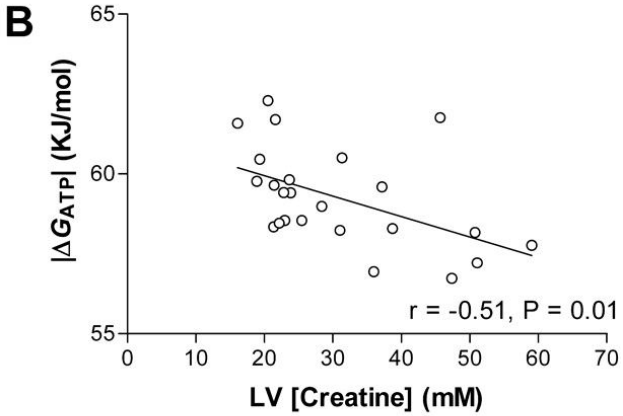
Relationship between $\Delta G_{\sim ATP}$ and contractile reserve in hearts with inactive CK

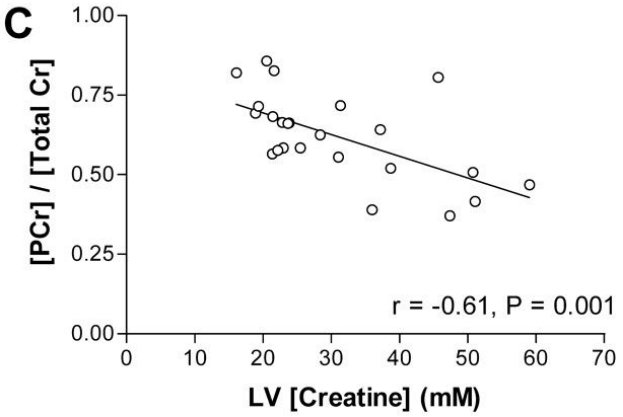
Ingwall JS. Kluwer Academic Publisher: Norwell, 2002



$\Delta G_{\sim ATP}=[ATP]/[ADP][Pi]$





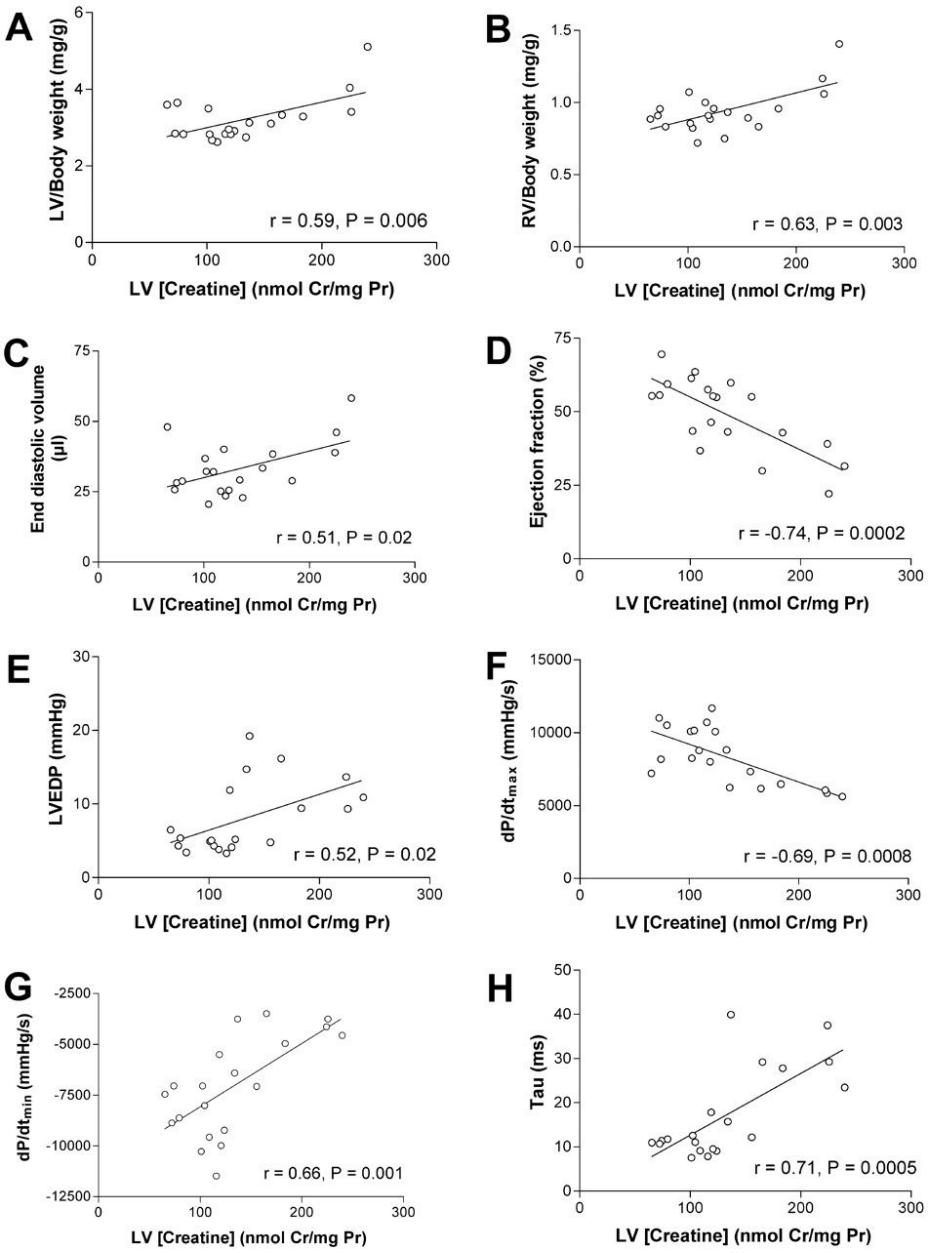


Over expression of CrT also disturbs energy balance because PCr/Cr low

Wallis et al, Circulation 2005

[ADP], μM	78	148
$\Delta G_{\sim ATP}$, kJ/mol	60	58

Normal Failing



Supra normal [Cr] with low PCr/Cr leads to LVH and heart failure

Wallis et al, Circulation 2005

Conclusions: on Creatine

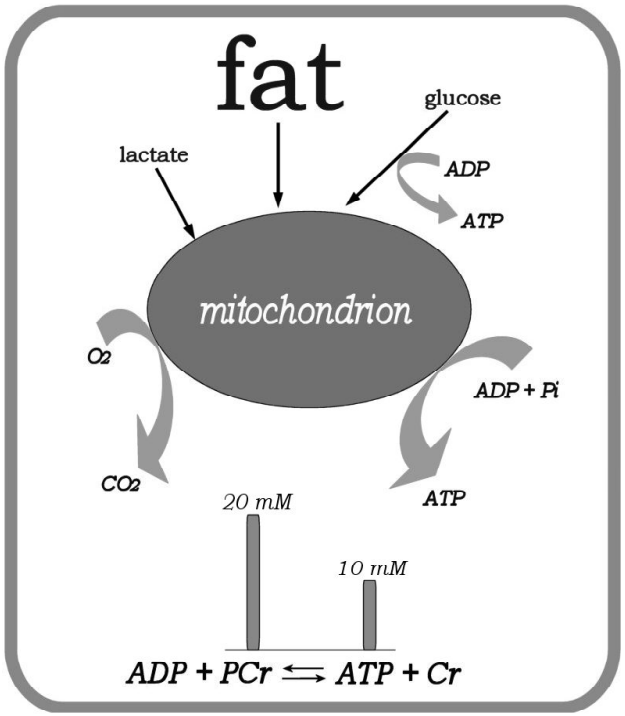
Cr and PCr *fall* in the failing myocardium,

PCr falls > ATP

- Proximal mechanism: *decreased Cr transporter*
- Long-term mechanisms: *transcriptional control*
- Consequences on heart function: *decreased energy reserve defined as low PCr/Cr leads to decreased contractile reserve*
- Will Cr be basis for therapeutic strategies? *uncertain*

Two lessons:

1. [ATP] and [PCr] fall due to supply/demand mismatch
2. Fuel utilization changes in the failing heart



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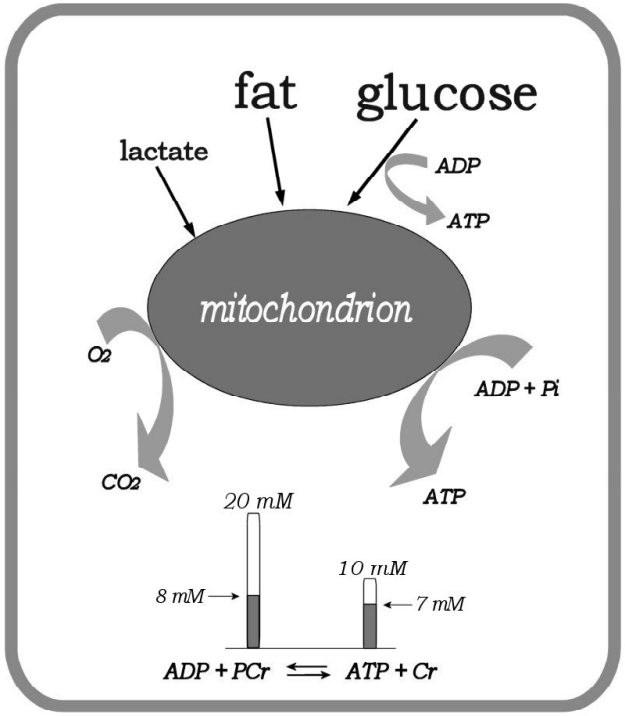

Failing