Cardiac Metabolism – Key Concepts

General Features

- The heart is one of the **most active** and highly oxidative organs in the body.

Its **function depends on a balance between:**

- Electrical activity
- Biochemical reactions
- Mechanical contraction

- All of these require continuous **ATP production to pump blood and maintain cellular function.**
- The heart generates **large amounts of ATP mainly through oxidative phosphorylation** to meet its high energy needs.

Three Main Components of Heart Energy Metabolism

1. **Substrate utilization**

- Heart uses substrates like **fatty acids and glucose**
- Their products enter the **TCA** (**Krebs**) **cycle**

2. **Oxidative phosphorylation**

- Happens in the **mitochondria**
- **Produces most** of the **ATP**

3. **Creatine-phosphate system**

- Transfers phosphate from **ATP** → **Creatine** → **Phosphocreatine**
- Acts as an **energy reserve** during **high demand**

(The heart has ~**30% of its volume as mitochondria**)

Energy Sources at Rest

- The heart uses **80–90%** of its **max oxidative capacity**
- But **normally** works at only **15–25%** of that capacity
- **>95% of ATP** is made by **oxidative phosphorylation** (**aerobic**)

ATP source distribution

Source % of ATP

Fatty acids → 60%
Carbohydrates → 35%
Amino acids + ketone bodies → 5%

ATP use

Use % of ATP

Muscle contraction → 60–70%
Ca^{2+} pumps + ion pumps → 30–40%

Regulation of Cardiac Metabolism

- **TCA cycle** driven by **acetyl-CoA**
- From **fatty acids** (60–90%)
- From **glucose via pyruvate** (10–40%)

NADH & **$FADH_2$ donate electrons to ETC → ATP production**

Carbohydrate Metabolism

Glucose Sources

From **blood** and **small glycogen stores** (smaller than skeletal muscle)

Glucose Transport

GLUT-4 → **activated** by **insulin**, **exercise**, **ischemia**
GLUT-1 → **minor role**

Fate of Glucose

Aerobic: pyruvate → mitochondria → CO_2 + ATP
Anaerobic: pyruvate → lactate (when **oxygen is low**)

Important Enzymes

GAPDH

- Produces **NADH**
- **Inhibited** by ↑**NADH** and **activated** by ↑**NAD^+**

PFK-1

- **Rate-limiting enzyme** of glycolysis
- **Activated** by: **AMP, ADP, Pi, Fructose-2,6-BP**
- **Inhibited** by: **ATP, ↓pH (acidosis)**

Pyruvate Fate

To **acetyl-CoA (by PDH)**
To **oxaloacetate**
To **lactate**

PDH Regulation

- Controlled by **workload**, **substrates**, and **hormones**
- **Key step** in glucose metabolism
- **Lactate** helps **remove protons** → **maintains pH**

Importance of Glycolysis in the Heart

- Only ~**2%** of **ATP** at rest comes from **glycolysis**
- But becomes **critical** **in ischemia & heart failure**
- In **HF** and **hypertrophy** → **shift toward** **using carbohydrates**

Other Glucose Pathways

Pentose Phosphate Pathway (PPP)

- Makes NADPH → antioxidant defense
- Produces ribose-5-phosphate → nucleotide synthesis

Polyol Pathway

- G6P → sorbitol
- **Increased** in **diabetes**, linked to **cardiac dysfunction**

Hexosamine Pathway

- Produces **UDP-N-acetylglucosamine**
- **Important** for protein glycosylation
- **Increased** in **diabetes** → affects **insulin sensitivity** and FA oxidation

Fatty Acid Metabolism

FA Entry into Heart Cells
Passive diffusion
Transport proteins***: FAT/CD36, FABP***

Activation

Fatty acids → **fatty acyl-CoA (by FACS)**

FAT/CD36

Main FA transporter
Moves to membrane when **energy demand increases**
Too much activity → **excessive FA uptake** → lipotoxicity + **↓GLUT4**

PPAR Regulation

- PPARs regulate **long-term FA oxidation**
- **PPAR-α** **increases** FA oxidation enzyme expression
- PPARs also increase antioxidant enzymes:
  Cu/Zn SOD
  Mn-SOD
  Catalase

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