⚕ Biochemistry of Cardiac Muscle – 1

Specificity of Cardiac Metabolism

General Features

- The heart is one of the most active and highly oxidative organs in the body.
- Myocardial function depends on a fine equilibrium between the work the heart has to perform to meet the requirements of the body, which conjugates a series of electrophysiological, biochemical, and mechanical events, resulting in the pumping of blood to all bodily tissues and the energy to be synthesized and transferred as **ATP** molecules to **sustain excitation-contraction coupling.**
- To support high rates of cardiac power, metabolism is designed to generate large amounts of ATP by **oxidative phosphorylation** to meet the energetic demand for generating the needed mechanical force and for maintaining cellular homeostasis.

Energetic Metabolism of the Cardiomyocyte

The energetic metabolism of the cardiomyocyte consists of three key components:

1. **Capture and utilization of primary substrates, with incorporation of their metabolites into the TCA cycle.**
2. **Oxidative phosphorylation**, which occurs in the **ETC** within the **internal** mitochondrial membrane.
3. **Phosphocreatine (PC)-creatine kinase (CK) energy transference system**, a network for phosphate transference from ATP to creatine ("energy-storing" molecule), through mitochondrial CK, yielding **PC** (an important source of energy under high-demand conditions).

Note: Mitochondria occupy ~30% of cardiomyocyte space.

Oxidative Capacity

- The metabolic machinery of the heart utilizes oxygen **up to 80–90% of the maximum capacity of ETC;** however, at resting state, the heart operates at **only 15–25% of its maximum oxidative capacity.**
- Cardiomyocytes show an elevated rate of ATP hydrolysis, which is strongly linked to oxidative phosphorylation because under non-ischemic conditions, over 95% of ATP is produced by this process.

Energy Source Distribution (**Basal Aerobic Conditions)**

1. **Fatty Acids (FAs): 60% of energy**
   - The capacity for FA synthesis is low.
   - Cardiomyocytes depend on the influx of FAs from plasma.
   - The rate of FA consumption is determined by plasma concentration of **non-esterified FAs.**
2. **Carbohydrates: 35%**
3. **Amino Acids and Ketone Bodies: 5%**

ATP Utilization:

- ~60–70% for muscle contraction
- ~30–40% for SR Ca^{2+}-ATPase and other ion pumps

Regulation of Metabolic Pathways in the Heart

- CAC is fueled by **acetyl-CoA** formed by oxidative decarboxylation of pyruvate (10–40%) and β-oxidation of FA (60–90%).
  - The reducing equivalents **NADH and $FADH_2$** (generated by glycolysis, lactate, pyruvate, and FA oxidation) deliver electrons to the ETC → ATP (**oxidative phosphorylation**).

Carbohydrate Metabolism

Glucose Source and Transport

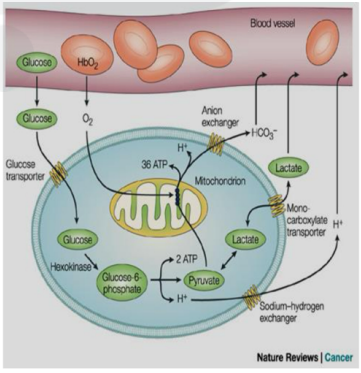
- Glycolytic substrate is derived from exogenous glucose and glycogen stores.
- Cardiac **glycogen** pool is **small** (~30 mmol/g wet wt vs. ~150 mmol/g in skeletal muscle).
- Glucose transport is regulated by transmembrane glucose gradient and the content of glucose transporter (**GLUT-4).**
- **GLUT-4** translocates to the membrane **in response to insulin, increased work demand, or ischemia.**
- **GLUT-1** plays an accessory role.

Glycolytic Pathway

- Converts **glucose-6-phosphate** and **NAD^+** to **pyruvate** and **NADH,** producing **2 ATP per glucose**.
- Under **anaerobic** conditions: Pyruvate → Lactic acid (non-oxidative glycolysis).
- Under **aerobic** conditions: Pyruvate and NADH → Mitochondria → CO_2 + NAD^+.

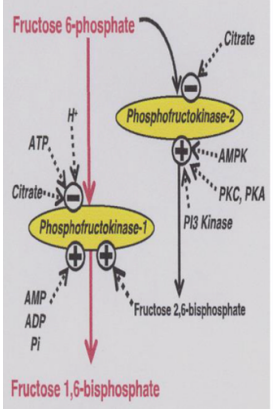
Enzyme: Glyceraldehyde-3-phosphate dehydrogenase

- **GAPDH** converts glyceraldehyde-3-phosphate → 1,3-diphosphoglycerate → NADH.
- Inhibited by NADH accumulation; activated by NAD^+.
- **Severe ischemia** → lactate & NADH accumulation → **cessation** of oxidative metabolism & lactate production.



Phosphofructokinase-1 (PFK-1) Regulation

- Catalyzes the second irreversible step in glycolysis.
- **Uses** ATP → fructose 1,6-bisphosphate.
- Activated by ADP, AMP, and Pi.
- Inhibited by ATP and fall in pH.
- **Stimulated by fructose 2,6-bisphosphate** (formed from fructose 6-phosphate by PFK-2).



Pyruvate Metabolism

In mitochondria, pyruvate can be:

1. **Oxidatively decarboxylated** → Acetyl-CoA (by PDH)
2. **Carboxylated** → Oxaloacetate (by pyruvate carboxylase)
3. **Reduced** → Lactate (by lactate dehydrogenase, cytosolic)

PDH Control:

- **PDH is a mitochondrial multienzyme complex regulated by work, substrate, and hormones.**
- **Lactate** is released to blood via specific transporters maintaining intracellular pH by **removing protons from glycolysis.**

Lactate Metabolism

- During starvation, lactate → pyruvate (NAD^+ reduced to NADH = **2.5 ATP**).
- Pyruvate → CAC → **12.5 ATP per cycle.**
- Only ~2% of heart's ATP is produced by glycolysis, but glycolysis becomes crucial under anaerobic or ischemic conditions.
- In heart failure or hypertrophy → metabolic switch **toward carbohydrate metabolism.**

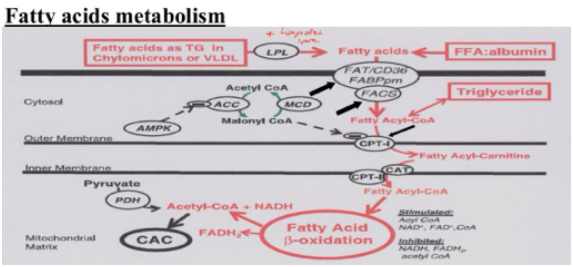
Additional Glucose Pathways

- *Pentose Phosphate Pathway (PPP):*
- G6P enters PPP → NADPH (oxidative phase) + 5-carbon sugars (non-oxidative phase).
- NADPH maintains reduced glutathione → antioxidant defense.
- Ribose-5-phosphate → nucleotide synthesis.
- Xylulose-5-phosphate → transcriptional signaling.

- *Polyol Pathway:*
- G6P → Sorbitol (via aldose reductase).
- **Increased in diabetes → abnormal glucose metabolism & cardiac dysfunction.**
- **Implicated in ischemia-reperfusion injury.**

- *Hexosamine Pathway:*
- Fructose 6-phosphate → UDP-N-acetylglucosamine (via glutamine fructose 6-phosphate amidotransferase).
- Involved in O-linked glycosylation of proteins.
- **Observed in diabetes, alters insulin sensitivity & FA oxidation.**

Fatty Acids Metabolism



FA Uptake

- FAs enter cardiomyocytes by:

1. **Passive diffusion**
2. **Protein-mediated transport** (**FAT or FABP**)

- Fatty acyl-CoA synthase (FACS) activates FAs → fatty acyl-CoA.

FAT/CD36:

- **Major FA translocase** (80 kDa membrane glycoprotein).
- Translocates to membrane under high energy demand.
- **Excess expression** → ↓ insulin sensitivity, ↓ glucose uptake, ↑ FA uptake → **lipotoxicity** (retention of GLUT-4).

peroxisome proliferator-activated receptor

Regulation by PPARs

- PPARs and coactivators (PPAR-γ coactivator 1-α) regulate genes for:
- **FA storage (diacylglycerol acyltransferase)**
- **FA oxidation (medium-chain acyl-CoA dehydrogenase)**
- **Glucose metabolism (PDH kinase 4)**
- **PPARα/γ also regulate oxidative stress** by activating antioxidant enzymes (Cu/Zn-SOD, Mn-SOD, catalase).
- **PPARα enhances IGF-1 transcription** → activates IGF-1/PI3K pathway → inhibits apoptosis & protects cardiomyocytes under ischemia.

Fate of Long-Chain Fatty Acyl-CoA

1. Esterification to triacylglycerols → intracardiac TG pool (10–30%).
2. Conversion to long-chain acylcarnitine (via CPT-I) between inner and outer mitochondrial membranes.

- Carnitine acyltranslocase (CAT): transports acylcarnitine across inner membrane.
- CPT-II: regenerates acyl-CoA. Carnitine palmitoyltransferase II
- CPT-I inhibited by malonyl-CoA (cytosolic). carnitine palmitoyltransferase -I
- Isoforms: Liver CPT-Iα & Heart CPT-Iβ (30× more sensitive to malonyl-CoA).

Malonyl-CoA Regulation

- Key physiological regulator of FA oxidation.
- ↓ **Malonyl-CoA** → ↑ **FA uptake & oxidation.**
- Formed by acetyl-CoA carboxylase (ACC) from extramitochondrial acetyl-CoA.
- ACC inhibited by AMPK phosphorylation → **accelerates** FA oxidation.
- β-oxidation generates NADH & $FADH_2$; acetyl-CoA enters TCA → more NADH.

Interregulation of FA and Carbohydrate Oxidation

- FA oxidation inhibits PDH via ↑ acetyl-CoA/free CoA & NADH/NAD^+ ratio → activates PDH kinase.
- Inhibition of FA oxidation increases glucose and lactate oxidation by:

1. Decreasing citrate levels → activating PFK.
2. Lowering mitochondrial acetyl-CoA and/or NADH.

Fatty Acids vs. Glucose as Energetic Substrates

- Substrate selection is essential for constant ATP generation and depends on dynamic metabolic requirements.
- During **fetal** development → **glucose** predominant.
- **After birth → FAs become main substrate** (due to oxygen and dietary fat availability).
- FA metabolism defects → cardiomyopathy under stress. Infants with mutations in genes involved in FAs metabolism
- **Heart failure or hypertrophy → shift to glucose metabolism** (due to reduced mitochondrial oxidative capacity).

Efficiency:

- Cardiac efficiency (O_2 consumption) is higher when oxidizing glucose/lactate vs. FAs.
- FA oxidation increases O_2 use without improving contractility → lower efficiency.
- FA oxidation causes more oxidative stress (due to higher O_2 consumption).

ATP Yield:

- Glucose: 30 ATP / 12 O atoms → 3.17 ATP/O_2
- Lactic acid: 3.00 ATP/O_2
- Palmitate: 92 ATP / 46 O atoms → 2.80 ATP/O_2
- Oleate: 2.86 ATP/O_2

→ FAs yield more ATP but require more oxygen.

Pathophysiological Effects

- β-oxidation of FAs increases lipid peroxidation → superoxide anion production.
- Elevated free FAs in ischemia worsen myocardial damage (especially in AMI).
- Obesity → ↑ serum free FAs → excessive FA oxidation → lipotoxicity → contractile dysfunction, insulin resistance, apoptosis (via ceramide accumulation).

Therapeutic Implications

- Partial inhibition of FA oxidation protects myocardium under ischemia/reperfusion, diabetic cardiomyopathy, or AMI.
- Shifting metabolism toward glucose → ↓ O_2 demand by 11–13% → ↑ cardiac efficiency & mitochondrial protection.

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