Cardiac metabolism

- Heart is **highly oxidative** (elevated rate of ATP hydrolysis by Oxidative phosphorylation), there is a fine equilibrium between the work the heart has to do and the energy to be synthesized.
- Metabolism of heart is designed to generate a large amount of ATP by oxidative phosphorylation
- ▼ Three key components of cardiac metabolism
  1. Capture and utilization of substrates to use them in the TCA cycle (citric acid/kreb's)
  2. Oxidative phosphorylation in mitochondria
  3. Phosphocreatine-creatine kinase system (transferring phosphate from ATP to creatine to make PC (phosphocreatine which is a source of energy under high demand)
- Metabolism of heart can use O2 up to 80-90% of ETC capacity, but at resting state, heart operates at 15-20% of maximum oxidative capacity
- ▼ **Energy sources** of heart under basal aerobic conditions
  1. **60% from Fatty acids**
     - Synthesising capacity of fatty acids in heart is low
     - heart depends on influx of fatty acids from blood vessels
     - So, rate of FA consumption is determined by concentration of non-esterified fatty acids in plasma
  2. **35% from carbohydrates**
  3. **5% from amino acids and ketone bodies**

- Uses of energy (ATP) in heart
  - **60-70%** used for **muscle contraction**
  - **30-40%** for **Ca+2 ATPase** in sarcomplasmic reticulum and **other pumps**
- **General steps** of metabolic pathways in heart
  - **10-40%**: Oxidative decarboxylation of **pyruvate in glycolysis** → Acetyl CoA (discussed below)
  - 60-90%: **B-oxidation of fatty acids** → Acetyl CoA (discussed in lecture 2)
  - Acetyl CoA → Citric acid cycle → Forms NADH and FADH2 → Deliver electrons to electron transport chain → ATP
- Carbohydrate metabolism
  - Depends on glycogen stores and exogenous glucose
    - **Glycogen stores are small** (30mmol/g)
    - **Exogenous glucose is transported by GLUT4** (found in sarcolemma and translocated to membrane in response to Insulin, Work demand, and Ischemia) **GLUT1 plays an accessory role**
      - Factors regulating transport: Transmembrane gradient of glucose + Content of GLUT4
  - ***Glycolytic pathway*** (Glucose-6-phosphate + NAD+ → Pyruvate and NADH)
    - Generates **2 ATP per glucose**
    - In Anaerobic conditions: Pyruvate → Lactic acid
    - In Aerobic conditions: Pyruvate + NADH → CO2 + NAD+ (in mitochondrial matrix)

- Only **2% of ATP is produced in glycolytic pathway**, but it's important in Anerobic or ischemic status
- In **heart failure and hypertrophy**, shift of metabolism towards carbohydrates not FAs

▼ Regulatory steps

▼ Glyceraldehyde-3-phosphate dehydrogenase **(GAPDH)**

- Major regulatory step
- Produces NADH
- Inhibited by excess NADH (-ve feedback), Activated by NAD+
- Accumulation of NADH and lactate in ischemia → Stop oxidative metabolism and lactate production

▼ **PFK-1:** KEY regulatory enzyme

- Catalyzes second irreversible step
- **Activated by low forms of energy** (ADP, AMP, Pi (inorganic phosphate)) + Fructose 2,6-bisphosphate (formed by PFK-2)
- **Inhibited by high forms of energy** (ATP and low pH)

- Pyruvate fates in mitochodria
  1. Oxidatively ***decarboxylated*** by Pyruvate dehydrogenase (PDH) → **Acetyl CoA**
     - Control of PDH (mitochondrial multicomplex) activity is essential in control of glucose metabolism
     - Controlled by work, substrate and hormones
  2. ***Carboxylated*** by Pyruvate carboxylase → **oxaloacetate**
  3. (in cytosol) ***Reduced*** by Lactate dehydrogenase → **Lactate**
     - Lactate is then released into blood by transporter (this has a critical role in maintaining cellular pH)
     - During starvation, lactate can be recycled into pyruvate (produces 2.5 ATP since it forms NADH) → This pyruvate is then burned aerobically in Citric acid cycle (produces 12.5 ATP per cycle)
- Fates of Glycolytic intermediates (pathways that don't make ATP)
  - **PPP pathway**
    - **Glucose-6-phosphate** from hexokinase reaction enters → **Produces NADPH** (in oxidative phase) + **5-carbon sugars** (in non-oxidative phase)
      - ***NADPH*** important for antioxidant effect (as it maintains level of reduced glutathione)
      - ***Ribose-5-phosphate*** (non-oxidative phase product) → substrate for nucleic acid synthesis
      - ***Xylulose-5-phosphate*** (non-oxidative product) → Transcriptional signaling molecule

- **Polylol pathway**
  - **G6P → Sorbitol**, by aldose reductase
  - Role of this pathway is **unknown**, but diabetic patients have increased flux to this pathway + Associated with abnormal glucose metabolism and cardiac dysfunction
  - Increased aldose reductase: implicated in myocardial response to ischemia-reperfusion injury
- **Hexosamine biosynthetic pathway**
  - **Fructose-6-phosphate → Uridine diphosphate-N-Actylglucosamine**, by glutamine fructose-6-phosphate amidotransferase
  - Product of this reaction (uridine...) Participates in O-linked glycosylation reactions of proteins
    - **Observed in diabetes**, could be responsible for alteration of insulin sensitivity and fatty acid oxidation