Myocardial Energetics and Coronary Blood Flow

The Pressure-Volume Diagram

\[ EW = \int_{EDV}^{ESV} P(t) \, dV \]
**Myocardial Oxygen Consumption**

- Since 95% of ATP in myocytes is normal produced by aerobic metabolism (oxidative phosphorylation), myocardial oxygen consumption (MVO$_2$) is often used to determine cardiac energy utilization by multiplying coronary blood flow by the arterio-venous O$_2$ difference.

- While the energy generated by the oxidation of 1 mole of substrate varies with substrate, the energy generated per unit oxygen is fairly constant and similar to that for glucose and lactate ~20 J/ml O$_2$

- External work should be related to regional work done by the myocardium:

  \[
  \text{Regional Work} = - \int T_{ij} \, dE_{ij} \approx \int T_a \, d\ell
  \]

**Myocardial Oxygen Demand**

- Myocardial oxygen demand is related to myocardial wall stress, heart rate and contractility (affected by cytosolic Ca and myosin ATPase activity)
- Mitochondrial metabolism increases to augment oxygen uptake when myocardial oxygen demand increases
- Mitochondrial oxygen uptake is stimulated by ADP translocation to the mitochondrial matrix via ATP-ADP translocase in the inner mitochondrial membrane
- But in cardiac myocytes calcium is probably the more important regulator of mitochondrial function via Ca sensitive mitochondrial dehydrogenases acting to increase NADH.
Factors That Increase Myocardial Oxygen Demand

**TABLE 14-2. Factors increasing the heart rate and the myocardial oxygen uptake**

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>β-adrenergic stimulation</td>
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<tr>
<td>Exercise</td>
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<tr>
<td>Emotional stress</td>
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<tr>
<td>Early morning rise in heart rate</td>
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<tr>
<td>Decreased vagal inhibition</td>
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<tr>
<td>Early morning rise in heart rate</td>
</tr>
<tr>
<td>Disease states</td>
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<tr>
<td>Cardiac conditions: congestive heart failure, arrhythmias, acute myocardial infarction</td>
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<tr>
<td>Extracardiac conditions influencing the heart: thyrotoxicosis</td>
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<tr>
<td>Favors</td>
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<tr>
<td>Drug-induced tachycardia</td>
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<tr>
<td>Sympathomimetic drugs, such as bronchodilators</td>
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<tr>
<td>Vasodilators</td>
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</tbody>
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\[ MVO_2 = CBF \times AV\Delta O_2 \]
MVO₂ Increases with External Work

- Dog heart-lung preparation, Evans and Matsuoka, 1915
- Efficiency in dotted lines
- Steeper relationship when work is increased by increasing preload than when it is increased by increasing afterload
- Indices that correlate somewhat better include the rate-pressure product, tension-time index and contractility

**Pressure-Volume Area (PVA)**

- Suga (1979) used the time-varying elastance concept (Suga & Sagawa, 1974) and considered the elastic potential energy generated during an isovolumic contraction, and realized that this pressure development required metabolic energy though it did no external work. Rather it must be dissipated as heat.
- Hence Suga defined the pressure-volume area (PVA) as the sum:
  
  \[ \text{PVA} = \text{PE} + \text{EW} \]
Potential Energy

$1 \text{ mm.Hg.ml} = 1.33 \times 10^{-4} \text{ J}$

**MVO}_2 \text{ increases linearly with PVA**

$MVO_2 = 1.2 \times 10^{-5} \times \text{PVA} + 0.013$

$r^2 = 0.968$
No effect of heart rate after measuring $\text{VO}_2$ per heart beat

Effect of Inotropy

- Increased $E_{\text{max}}$ due to Ca, epinephrine shifts $\text{MVO}_2$-PVA curve up
- Beta blocker or Ca channel blocker shifts it down
- Hence slope of the $\text{MVO}_2$-PVA relation is independent of contractility too.
The Heart Accommodates An Equivalent Increase of Work Due to Volume Loading More Efficiently than Pressure Loading

Basal and activation energy

- Basal energy is oxygen consumption when heart is not beating
- Activation energy increases with contractility and is mainly the energy of calcium cycling
Efficiency

Mechanical efficiency = \frac{\text{External Work}}{\text{Total MVO}_2}

Conversion efficiency = \frac{\text{Pressure-Volume Area}}{\text{Total MVO}_2}

Myofibrillar efficiency = \frac{\text{Pressure-Volume Area}}{\text{MVO}_2 - \text{unloaded MVO}_2}

• Conversion efficiency varies from 10-30%
• Myofibrillar efficiency varies from 30-40%

Mechanical vs. Thermodynamic Efficiency

\[ -\Delta H = W + Q \]

\[ \varepsilon = \frac{W}{\Delta H} = \frac{W}{W + Q} \]

\[ \Delta G_{\text{ATP}} = RT \ln \left( \frac{[\text{ADP}][\text{Pi}]}{[\text{ATP}]} \right) \]

\[ \Delta H = \Delta G + T\Delta S \]

\[ \eta = \frac{W}{\Delta G} \]

Enthalpy change = work plus heat

Mechanical efficiency

Gibbs Free Energy of ATP

Hydrolysis (i.e. the difference in chemical potential between the [ADP] + [Pi] and [ATP] = 55 kJ/mol)

Second law of thermodynamics

Thermodynamic efficiency

Metabolic Cost of Exercise Work

Inverse of the slope is the net efficiency = 0.2 (assuming 20 kJ/L \( \text{O}_2 \))

Rate of Enthalpy Output vs. Power Output for Isolated Muscles

Inverse of the slope is the net efficiency = 0.12
Fenn Effect

- Fenn (1923) found that the total amount of external work done plus heat released by a skeletal muscle contracting from a constant initial increases and then decreases with the amount of shortening.
- This suggests an additional energy cost of ejection even though the total energy of a contracting beat is less than that of an isovolumic beat at the same end-diastolic volume.
- This can be explained by the PVA-MVO$_2$ relationship:

$$\text{PVA} = \text{EW} + \text{PE}$$

$$= P_{ES} (V_{ED} - V_{ES}) + \frac{1}{2} P_{ES} (V_{ES} - V_0)$$

$$= P_{ES} (V_{ED} - V_0 - \frac{E_{ES}}{E_{ED}}) + \frac{1}{2} P_{ES}^2 E_{ES}$$

$$= P_{ES} (V_{ED} - V_0) - \frac{1}{2} P_{ES}^2 E_{ES}$$

Here time-varying elastance is used to predict oxygen cost of ejecting vs isovolumic beats (C) and compared with experiments by Gibbs (1998) in isolated papillary muscles.
Myocardial Oxygen Delivery

FIGURE 11-5 Relationship between myocardial oxygen consumption and coronary blood flow during a variety of interventions that increased or decreased myocardial metabolic rate. (Reproduced from Berne RM, Rubio R: Coronary circulation. In Handbook of Physiology, Section 2: The Cardiovascular System—The Heart, vol 1. Bethesda, Md, 1975, American Physiological Society.)

Coronary System

A

Right coronary artery

Left main coronary artery

Aorta

Left anterior descending coronary artery

Left circumflex coronary artery

Left circumflex coronary artery

Right coronary artery

Oblique marginal branches

Diagonal branch

Pars atheroscorer coronary artery

Left circumflex coronary artery

Oblique marginal branches

Diagonal branch

B

C
Physical Factors Affecting Coronary Blood Flow

Coronary perfusion pressure (note autoregulation when BP changes)

Systolic flow impediment due to intramyocardial stress acting on coronary vessels. While coronary arterial inflow is lowest during systole, coronary venous outflow is highest.

Epicardial flow is higher than endo during systole, lower during diastole.
Neural and Neurohormonal Factors Affecting Coronary Blood Flow

Sympathetic stimulation increases CBF
- Decreases diastolic interval thereby increasing effect of flow impediment
- Increases heart rate and work therefore increasing myocardial oxygen demand and dilating coronary vessels
- Beta adrenergic receptors dilate coronary vessels but alpha adrenergic receptors constrict them and this is the dominant adrenergic effect

Vagal activity (e.g. elicited by carotid and aortic chemoreceptors) slightly dilates coronary vessels

Metabolic Factors Affecting Coronary Blood Flow

CBF is closely coupled to myocardial metabolic activity
- Decreased ratio of oxygen supply to demand stimulates release of vasodilators especially adenosine and nitric oxide, though other mediators include CO$_2$, O$_2$, H*, lactate, K$^+$
- $K_{ATP}$ channels in vascular smooth muscle open when ATP falls, causing an inward K current that reduces action potential duration and inward Ca current, decreasing smooth muscle contraction
- At low concentrations adenosine activates endothelial cell $K_{ATP}$ channels and increases NO release which dilates smooth muscle cells
- At higher concentrations adenosine acts directly on VSM cells by activating $K_{ATP}$ channels
Reduced Coronary Blood Flow

- Acute myocardial ischemia – acute reduction of CBF
- Myocardial infarction – result from ischemia exceeding 20 mins duration
- Ischemic preconditioning – protective effect of transient ischemia
- Myocardial “stunning” – functional deficit in contractile performance for days after acute ischemia
- Myocardial “hibernation” – chronic downregulation of myocardial metabolism during myocardial ischemia that preserves myocardial viability
- Area at risk > ischemic area (collateral vessels)
- Ischemic area > Infarct area (border zone sparing)
- Mechanical dysfunction area > ischemic area (functional border zone)

Cardiac Energetics and Coronary Flow: Summary of Key Points

- Myocardial oxygen demand increases in proportion to pressure-volume area (stroke work plus potential energy)
- Increased heart rate and stroke work prompt increased ATP production by mitochondria
- Mechanical efficiency varies with loading conditions
- Work over enthalpy change is a good measure of mechanical efficiency. Work over Gibbs Free Energy is a measure of thermodynamic efficiency
- The PVA-MVO$_2$ relationship explains the Fenn Effect (1923)
- Coronary Blood Flow increases with myocardial oxygen consumption and is regulated primarily by physical, and metabolic factors