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M2 Mini Review
August 2008

Physiology/Pathophysiology
Of
Coronary Blood Flow

Louis G. D’ Aley, Professor of Physiology
Coronary Blood Flow Outline

1) Myocardial Ischemia
   Supply
   Demand
2) Coronary Flow Reserve
3) Determinants of Coronary Blood Flow
4) Neural (autonomic) Mechanisms
5) Endothelial Factors (Mechanisms)
6) NOS, NO and ADMA
Myocardial Ischemia (MI)

- blood flow to a tissue or organ (heart) that is inadequate to maintain function.
Heart statistics

300g / 70,000g = 0.0043 or < 0.5% Body Weight.
Heart consumes more energy than any other organ.
Coronary flow = 4% of cardiac output.
“Resting “ flow 30X flow/g tissue of skeletal muscle.

**Highest oxygen consumption per g of tissue in body.**
(arterial oxygen 20 Vol % to coronary sinus 8 Vol %)
(typical mixed venous oxygen higher at 17 Vol %)

***SEE SLIDE 37 & 38 FOR SUMMARY OF OTHER TISSUES

**Must increase coronary blood flow to increase oxygen delivery.

Vol % = mL O₂ / 100mL blood
Thus an enlarged heart has greater demand.

\[ r = \text{radius} \]
How can coronary flow remain relatively constant with an 80% "lesion"?

Fig. 6.3

Occlusion
“...proximal arterial stenosis...”
Lesion here

Compensatory Vasodilation here

Therefore series resistance and **flow** stays the same.

\[ R_s = R_1 + R_2 + R_3 \]

\[ \Delta P = P_i - P_0 \]

\[ \dot{Q} = \Delta P / R_s \]

6.3 MH
With the same perfusion pressure, the same measured flow means the overall (series) resistance is the same regardless of a focal lesion! BUT *** You have used up vasodilator reserve !!!!!!!
Correlation of coronary anatomy and physiology: The concept of coronary flow reserve

Anatomy

Normal epicardial artery

Epicardial stenosis

Microvascular disease

Physiology

Arteriolar vasodilation (Papaverine) Time

4x

4x

4x

LOST RESERVE

Lesion upstream and down stream vasodilation used up.

Lesion down stream and large vessel vasodilation used up even with no upstream lesion.

Papaverine inhibits breakdown of cGMP & cAMP by PDE
DETERMINANTS OF CORONARY BLOOD FLOW (PERFUSION)

1. DIASTOLIC PERFUSION PRESSURE $\Delta P$

2. SYSTOLIC COMPRESSSION (“Resistance”)

3. METABOLIC CONTROL (Resistance)
   - $O_2$ & adenosine

4. NEURAL CONTROL (Resistance)
   - Sympathetic & Parasympathetic
But where is the origin of perfusion pressure?
Origin of left coronary artery

Venous end is at coronary venous sinus right atrium.

Highest pressure

Lowest pressure

Source Undetermined
Systolic compression

Left coronary flow
mL/min

Right Coronary flow
mL/min

120 mmHg

Systolic Pressure

Time
DETERMINANTS OF CORONARY BLOOD FLOW

1  PERFUSION PRESSURE

2  SYSTOLIC COMPRESSION

3  METABOLIC CONTROL

4  NEURAL CONTROL
TISSUE VASCULAR RESISTANCE

(**Assume Perfusion Pressure is Constant**)

- **Vasoconstriction** ⇒ \( \downarrow r \Rightarrow \uparrow R_{\text{tissue}} \)
  \( \Rightarrow \downarrow F_{\text{tissue}} \)

- **Vasodilation**
  \( \Rightarrow \uparrow r \Rightarrow \downarrow R_{\text{tissue}} \Rightarrow \uparrow F_{\text{tissue}} \)

\[ F_{\text{tissue}} = \frac{\text{Perfusion Pressure}}{R_{\text{tissue}}} = \text{Coronary flow} \]
“Flow” vs. “Perfusion”

- Angiography
- Large surface
- “Focal”
- “Fixed” diameter
- Bypass
- Stent

- Nuc. Imaging
- Arteriolar
- Vasodilator reserve
- Functional flow
- Distributed resistance
- Collateral channels
Intrinsic Regulation of Coronary Blood Flow

“Thus any additional oxygen requirement must be met by an increase in blood flow.”

P 143 Lilly

You must use vasodilator reserve --- assuming you have any left!
Figure 6.1. Major determinants of myocardial oxygen supply and demand.

h, ventricular wall thickness; P, ventricular pressure; r, ventricular radius.

Source Undetermined
Isolated Vascular Effects

(vessel strips or rings in bath)

- Sympathetic alpha adrenergic
  \[ \alpha_1 \text{ vasoconstriction} \]

- Sympathetic beta adrenergic vasodilation
  \[ \beta_1 \text{ (evidence for innervated VSM)} \]
  \[ \beta_2 \text{ non-innervated VSM} \]

- Parasympathetic cholinergic vasodilation
BUT HOW DOES IT WORK IN VIVO ????

Parasympathetic Activation

Stimulate parasympathetic to heart >> Ach >>SA node >> ↓↓ HR >>↓↓ metabolism >> ↓↓ Coronary Blood flow

BUT

PACE heart (i.e. fixed heart rate) >> no change in HR >> no change metabolism ---------- Therefore
Stimulate parasympathetic to paced heart >> >> Ach vasodilation >> ↑↑ coronary blood flow !!
BUT HOW DOES IT WORK IN VIVO ????

**Sympathetic Activation**

Stimulate sympathetic nerves to heart $\rightarrow$ ↑↑ Norepi $\rightarrow$
$\rightarrow$ ↑↑ HR + ↑↑ inotropism $\rightarrow$ ↑↑ metabolism $\rightarrow$ $\rightarrow$
$\rightarrow$ ↑↑ ↑↑ Coronary Blood flow

BUT

Block $\beta_{1&2}$ receptors and Stimulate sympathetics to heart
$\rightarrow$ ↑↑ Norepi (stress) $\rightarrow$ no change in HR $\rightarrow$ $\rightarrow$ no change
inotropism $\rightarrow$ $\rightarrow$ no change in metabolism $\rightarrow$ potential for
$\rightarrow$ ↓↓ Coronary Blood flow

by “unmasked” $\alpha_1$ adrenergic vasoconstriction

Can Metabolic control still dominate??
Figure 6.1. Major determinants of myocardial oxygen supply and demand.

- O$_2$ content
  - Coronary blood flow
    - coronary perfusion pressure
    - coronary vascular resistance
    - external compression
    - intrinsic regulation
    - local metabolites
    - endothelial factors
    - neural innervation

- Myocardial oxygen demand
  - Wall stress
    - $P \cdot r / 2h$
  - Heart rate
  - Contractility

$h$, ventricular wall thickness; $P$, ventricular pressure; $r$, ventricular radius.
Sheer or Flow Mediated Dilation

* FMD *

Box 6.1
Page 144
Fig 6.2

Endothelial-dependent vasodilators
(e.g., ACh, serotonin, thrombin, shear stress)

Prostacyclin

EDRF-NO

Endothelin-1

SmOoth MUSCLe CELL

\( \uparrow \text{cAMP} \)

\( \uparrow \text{cGMP} \)

RELAXATION

CONTRACTION
lated that in normal individuals, the relaxation effect of EDRF-NO outweighs the direct $\alpha$-adrenergic constrictor effect of catecholamines on arterial smooth muscle, such that vasodilatation results. However, in patients with dysfunctional endothelium (e.g., atherosclerosis), an impaired release of endothelial vasodilators leaves the direct catecholamine effect unopposed, such that relative vasoconstriction occurs instead. The resultant decrease in coronary blood flow and myocardial oxygen supply contributes to ischemia. Of note, in patients with risk factors for atherosclerosis, $\alpha_1$-adrenergic constrictor effect may be “unmasked”. 
++ Drug effects ++ Endothelial Dysfunction
Asymmetrical Dimethylarginine (ADMA is a NOS Inhibitor)

Sheer or flow mediated vasodilation

Endothelial Cell

L-Arginine

Nitric oxide synthase

Nitric oxide

L-Citrulline

Nitroprusside or nitroglycerin

GTP

G-cyclase

cGMP

Smooth Muscle Cell

Relaxation
ADMA (NOS Inhibitor)

Sheer or flow mediated vasodilation

ENDOTHELIAL CELL

L-Arginine

Nitric oxide synthase

(-)

L-Citrulline

Nitric oxide

SMOOTH MUSCLE CELL

GTP → G-cyclase → cGMP

Nitric oxide

RELAXATION

Source Undetermined
Does ADMA Cause Endothelial Dysfunction?

John P. Cooke

(Arterioscler Thromb Vasc Biol. 2000;20:2032-2037.)

THEN

LATER

Asymmetrical Dimethylarginine
The Über Marker?

ADMA: A Major Cause of Endothelial Dysfunction

ADMA Regulates Vascular Resistance

(Circulation 2004;109:1813-1819.)
Asymmetrical Dimethylarginine Predicts Progression to Dialysis and Death in Patients with Chronic Kidney Disease: The Mild to Moderate Kidney Disease Study. Danilo Fliser, et al.

“ADMA…independent risk marker for progression…mortality”

Elevation of asymmetric dimethylarginine in patients with Unstable angina and recurrent cardiovascular events. Tanja K. Krempl et al.

European Heart Journal (2005) 26, 1846-1851
“ADMA … significantly elevate… reduction may indicate decreased risk.”
After PCI, Pts with decreased ADMA had greater survival!
Asymmetric Dimethylarginine Independently Predicts Fatal and Nonfatal Myocardial Infarction and Stroke in Women
24-Year Follow-Up of the Population Study of Women in Gothenburg


Figure 1. Cumulative risk of incident myocardial infarction and stroke for the top quintile (≥0.71 μmol/L) of the distribution of ADMA levels compared to bottom 4 quintiles (<0.71 μmol/L).
ADMA-NOS-NO Pathway
the newest drug target?

PRMT           DDAH

all in blood *** my laboratory interest

PRMT = Protein arginine methyltransferase
DDAH = Dimethylarginine dimethylaminohydrolase

L-arginine

NO synthase

Vasodilatation
Platelet aggregation
Monocyte adhesion
Release of superoxide radicals
Proliferation of vascular smooth muscle cells
Oxidation of LDL
Published interest in ADMA


84 Publications In 2003

111 Publications In 6 MONTHS of 2008 !!!
Look out for Limits to Compensatory VD and EC Dysfunction
Table 32-1. Resting Blood Flow and O₂ Consumption of Various Organs in a 63-Kg Adult Man with a Mean Arterial Blood Pressure of 90 mm Hg and an O₂ Consumption of 250 mL/min.

<table>
<thead>
<tr>
<th>Region</th>
<th>Mass (kg)</th>
<th>Blood Flow mL/min</th>
<th>mL/100 g/min</th>
<th>Arteriovenous Oxygen Difference (mL/L)</th>
<th>Oxygen Consumption mL/min</th>
<th>mL/100 g/min</th>
<th>Resistance (R units)²</th>
<th>Percentage of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>2.6</td>
<td>1500</td>
<td>57.7</td>
<td>34</td>
<td>54</td>
<td>2.0</td>
<td>3.6</td>
<td>9.4</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.3</td>
<td>1360</td>
<td>420.0</td>
<td>14</td>
<td>18</td>
<td>6.0</td>
<td>4.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Brain</td>
<td>1.4</td>
<td>750</td>
<td>54.0</td>
<td>62</td>
<td>46</td>
<td>3.3</td>
<td>7.2</td>
<td>10.1</td>
</tr>
<tr>
<td>Skin</td>
<td>3.6</td>
<td>462</td>
<td>12.8</td>
<td>25</td>
<td>12</td>
<td>0.3</td>
<td>11.7</td>
<td>42.1</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>31.0</td>
<td>840</td>
<td>2.7</td>
<td>60</td>
<td>50</td>
<td>0.2</td>
<td>6.4</td>
<td>198.4</td>
</tr>
<tr>
<td>Heart muscle</td>
<td>0.3</td>
<td>250</td>
<td>84.0</td>
<td>114</td>
<td>29</td>
<td>9.7</td>
<td>21.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Rest of body</td>
<td>23.8</td>
<td>336</td>
<td>1.4</td>
<td>129</td>
<td>44</td>
<td>0.2</td>
<td>16.1</td>
<td>383.2</td>
</tr>
<tr>
<td>Whole body</td>
<td>63.0</td>
<td>5400</td>
<td>8.6</td>
<td>46</td>
<td>250</td>
<td>0.4</td>
<td>1.0</td>
<td>63.0</td>
</tr>
</tbody>
</table>

²R units are pressure (mm Hg) divided by blood flow (mL/min).

Table 32-1. Resting Blood Flow and O$_2$ Consumption of Various Organs in a 63-Kg Adult Man with a Mean Arterial Blood Pressure of 90 mm Hg and an O$_2$ Consumption of 250 mL/min.

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<td>60</td>
<td>50</td>
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<td>6.4</td>
</tr>
<tr>
<td>Heart</td>
<td>0.3</td>
<td>250</td>
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<td>154</td>
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<td>25.4</td>
</tr>
<tr>
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<td>44</td>
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<td>Whole body</td>
<td>63.0</td>
<td>9400</td>
<td>8.6</td>
<td>46</td>
<td>250</td>
<td>0.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Cardiac Output | Oxygen Consumption |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>598.4</td>
<td>15.6</td>
</tr>
<tr>
<td>63.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Asymmetric Dimethylarginine Independently Predicts Fatal and Nonfatal Myocardial Infarction and Stroke in Women
24-Year Follow-Up of the Population Study of Women in Gothenburg

Tora Leong, Dimitri Zylberstein, Ian Graham, Lauren Lissner, Deirdre Ward, Jane Fogarty, Calle Bengtsson, Cecilia Björkelund, Dag Thelle; for The Swedish-Irish-Norwegian (SIN) Collaboration

Objective—Asymmetrical dimethylarginine (ADMA) reduces nitric oxide by inhibiting nitric oxide synthase and is associated with cardiovascular disease (CVD). Our study examined the association of ADMA with CVD prospectively in a healthy population-based cohort of women.

Methods and Results—We measured baseline ADMA of 880 women in the Population Study of Women in Gothenburg using high-performance liquid chromatography. After adjustment for traditional risk factors, creatinine clearance, and homocysteine using Cox models, the HR (95% CI in parentheses) of CVD end points at 24 years for a 0.15 μmol/L (1 SD) increase in ADMA were: all-cause mortality 1.12 (0.96, 1.32), fatal CVD 1.30 (1.04, 1.62), total CVD events 1.29 (1.09, 1.53). The top quintile (ADMA ≥0.71 μmol/L) compared with the bottom four-fifths, conferred a cumulative risk 22 versus 14%, relative risk 1.75 (95% CI 1.18, 2.5%) and population attributable risk 12.7% of total CVD events, and further identified individuals who are at higher than expected risk based on the SCORE and Framingham systems.

Conclusions—A 0.15 μmol/L increase in baseline ADMA levels is associated with approximately 30% increase in incident cardiovascular risk at 24 years in women after adjustment, ADMA levels ≥0.71 μmol/L enhances CVD risk assessment in women. (Arterioscler Thromb Vasc Biol 2008;28:961-967)
Slide 7: Source Undetermined
Slide 8: Source Undetermined
Slide 9: Source Undetermined
Slide 10: Source Undetermined
Slide 11: Source Undetermined
Slide 13: Source Undetermined
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Slide 30: Source Undetermined
Slide 31: Source Undetermined
Slide 32: Circulation 2004; 109:1813-1819
Slide 34: Source Undetermined
Slide 36: Source Undetermined
Slide 37: Source Undetermined
Slide 38: Source Undetermined
Slide 39: McGraw-Hill
Slide 40: McGraw-Hill