Control of Myocardial Blood Flow

“Blood goes where it is needed”


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ETP, Sofia Antipolis, April 2013
The Control of Resting Myocardial Blood Flow

**Neuro-humoral factors**
- Noradrenaline
- Adrenaline
- Acetylcholine
- Arterial Pressure
- Coronary pressure
- RAP, LVDP and Pf=0
- Systolic compression
- Diastolic compression

**Endo- and paracrine factors**
- Adenosine
- PO$_2$
- PCO$_2$, H$, K^+$
- Angiotensine II
- Histamine
- Bradykinine

**Physical factors**

Adapted from D.J.G.M. Duncker
The Control of Resting Myocardial Blood Flow

The balance between supply and demand depends on mechanisms which are multiple, interacting, cumulative, nonlinear.

Adapted from D.J.G.M. Duncker

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...Myocardial blood flow during resting conditions ... in normal human subjects is generally reported in the range of 0.5–1.5 ml/min/g of myocardium. The wide range of resting values of left ventricular blood flow in awake animals appears to be related to the state of alertness. Animals conditioned to rest quietly in the laboratory have the lowest reported values, whereas animals standing on a treadmill ready to run have higher heart rates and higher coronary flow rates...

(Dunker DJ and Bache RJ Physiol Review 2008)
ABC of Coronary Physiology
For the Interventionalist

1. About Pressure, flow, mass, resistance, etc, ...

2. Epicardial vs microvascular compartments

3. Flow-function relationship

4. Coronary autoregulation
The Control of Resting Myocardial Blood Flow

Neuro-humoral factors
- Noradrenaline
- Adrenaline
- Acetylcholine

Metabolic factors
- Adenosine
- $\text{PO}_2$
- $\text{PCO}_2, \text{H}^+, \text{K}^+$

Physical factors
- Arterial Pressure
- Coronary pressure
- RAP, LVDP and Pf=0
- Systolic compression
- Diastolic compression

Endo- and paracrine factors
- Angiotensine II
- Histamine
- Bradykinine

Adapted from D.J.G.M. Duncker
Extravascular Compressive Forces

Aorta

LV

Pressure

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Extravascular Compressive Forces

Pressure

Aorta

LV

LAD FLOW
Extravascular Compressive Forces

Pressure

LAD FLOW

Aorta
Coronary
LV
Extravascular Compressive Forces

Pressure

Aorta

RV

LAD FLOW

RCA FLOW

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Extravascular Compressive Forces

Pressure

Aorta

RV

LAD FLOW

RCA FLOW

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Extravascular Compressive Forces

Pressure

- Aorta
- RV

LAD FLOW

RCA FLOW

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Extravascular Compressive Forces

Pressure

- Aorta
- RV

LAD FLOW

- Green line (increasing and decreasing)

RCA FLOW

- Purple line (increasing and decreasing)
Relation between Vessel Size and Myocardial Mass

- **Normals**
- **CAD**

Cross-Sectional Lumenal Area (cm²) vs. Regional Myocardial Mass (g)

- Regional Myocardial Mass (g) range: 0 to 500
- Cross-Sectional Lumenal Area (cm²) range: 0 to 0.3

Source: C. Seiler et al, Circulation 1992

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Pressure, Flow, Resistance, and Vessel Size

% of value at the ostium

Distance from the ostium

100

Diameter

Mass

Flow

Pressure

BASE

APEX

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Pressure, Flow, Resistance, and Vessel Size

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Control of MBF

Pressure, Flow, Resistance, and Vessel Size

<table>
<thead>
<tr>
<th></th>
<th>Tree Shrew</th>
<th>Human</th>
<th>Blue Whale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass [kg]</td>
<td>0.005</td>
<td>70</td>
<td>100,000</td>
</tr>
<tr>
<td>Heart Weight [kg] (~M^1)</td>
<td>3.3x10^{-5}</td>
<td>0.46</td>
<td>660</td>
</tr>
<tr>
<td>Stroke Volume [ml] (~M^1)</td>
<td>0.0033</td>
<td>46</td>
<td>66,000</td>
</tr>
<tr>
<td>Heart Rate [s^{-1}] (~M^{-1/4})</td>
<td>11 (&gt;600 bpm)</td>
<td>0.16 (&lt;10 bpm)</td>
<td></td>
</tr>
<tr>
<td>Cardiac Output [L/min] (~M^{3/4})</td>
<td>0.003</td>
<td>5</td>
<td>1000</td>
</tr>
<tr>
<td>Radius of Aorta [cm] (~M^{3/8})</td>
<td>0.02</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Mean Aortic Velocity [cm/sec] (~M^0)</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Mean Aortic Pressure [mmHg] (~M^0)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mean Aortic Reynold’s No. (~M^{3/8})</td>
<td>15</td>
<td>530</td>
<td>8080 (turbulent!)</td>
</tr>
<tr>
<td>Mean Aortic Shear Stress [dynes/cm^2] (~M^{-3/8})</td>
<td>180</td>
<td>5</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Pressure, Flow, Resistance, and Vessel Size

Ref Diam (mm)

% Stenosis for an Cross Sectional Area of 4 mm²

< 4 mm² = significant stenosis?
Pressure, Flow, Resistance, and Vessel Size

Relationship between CSA by IVUS and FFR

- $r = 0.320$
- $P < 0.0001$

Waksman R et al JACC 2013
Angiographic Definition of “CAD”

Diagnostic Accuracy
- 60%
- 66%

N = 4089 Stenoses

Toth G, Hamilos M et al  Submitted 2013
Function trumps anatomy
ABC of Coronary Physiology
For the Interventionalist

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Two-Compartment Model of the Coronary Circulation

The coronary angiogram detects only 5% of the total coronary tree.
Two-Compartment Model of the Coronary Circulation

Conductance Arteries

Resistance Arteries

>500 µ

<500 µ Microvasculature

$P_a$

100

MACRO

MICRO

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Two-Compartment Model of the Coronary Circulation

Adenosine

FFR = 0.98

CFR = 4.15

1h05'15 +5 s +10 s +15 s +3 s +35 s +4 s +30 s +35 s +40 s +45 s
Conductance Arteries

Resistance Arteries

>500 µ

<500 µ

Microvasculature

Focal Stenosis

$P_a$

100

MACRO

MICRO

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Conductance Arteries

Resistance Arteries

>500 µ

<500 µ

Microvasculature

Stent

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Conductance Arteries

Resistance Arteries

>500 µ

<500 µ

Focal Stenosis

Diffuse Atherosclerosis

Microvasculature

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Conductance Arteries

Resistance Arteries

$>500 \mu$m

$<500 \mu$m

Microvasculature

Stent

Diffuse Atherosclerosis

MACRO

MICRO

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Endothelial Control of Coronary Blood Flow

- Normal Endothelium
- Blood Flow
- Shear Stress
- ACh
- Bradykinine
- L-Arginine
- NO
- cGMP
- Guanyl Cyclase
- Endothelin
- EDHF
- PGI₂

Dilatation

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Endothelial Control of Coronary Blood Flow

Blood Flow → Shear Stress → L-Arginine → Guanylyl cyclase → cGMP → Constriction

ACh → Bradykinine → Endothelin

Abnormal Endothelium

Vascular Smooth Muscle Cell

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Importance of Maximal Vasodilation

**Epicardial**
- = Conductance
- Arteries > 550 µ

**Microvasculature**
- = Resistance
- Arteries < 550 µ

Nitrates → **Vasospasm**
Adenosine → **Autoregulation**
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**Endo- and paracrine factors**

**Physical factors**

*Adapted from D.J.G.M. Duncker*
The Control of Myocardial Blood Flow

Multiple, interacting, cumulative, nonlinear mechanisms

Coronary Autoregulation

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**Endo- and paracrine factors**

*Adapted from D.J.G.M. Duncker*
Maximal hyperemia is easier to get than true resting conditions
Autoregulation

The ability of the heart of maintaining flow constant in case of change of perfusion pressure without the intervention of any other external mechanism
Coronary Autoregulation

Coronary Perfusion Pressure (mm Hg)

Coronary Blood Flow (mL/min)
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Autoregulatory Range

Coronary Perfusion Pressure (mm Hg)

Coronary Blood Flow (mL/min)

Initial Pressure

Rubio and Berne, Prog CV Disease 1975

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Autoregulatory Range

Coronary Perfusion Pressure (mm Hg)

Coronary Blood Flow (mL/min)

Rubio and Berne, Prog CV Disease 1975
Autoregulation

- Proximal LAD stenosis (n = 26)
- Normal LV systolic function
- PET flow measurements (\(^{15}\text{O}\)-labeled water) at rest
Flow, Pressure, and Resistance

\[ F = \frac{\Delta P}{R_{\text{epi}} + R_{\text{myo}}} \]

\( F \) = Flow

\( \Delta P \) = Pressure difference

\( R_{\text{epi}} \) = Epimyocardial resistance

\( R_{\text{myo}} \) = Myocardial resistance

\( P_a \) = Aortic pressure

\( P_v \) = Venous pressure

% Area Stenosis

K. Lance Gould, 1974
Flow, Pressure, and Resistance

\[ F = \frac{\Delta P}{R_{epi} + R_{myo}} \]

\( F \) = Flow, \( \Delta P \) = Pressure difference, \( R_{epi} \) = Resistance epi, \( R_{myo} \) = Resistance myo

% Area Stenosis

K. Lance Gould, 1974

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Flow, Pressure, and Resistance

\[ F = \frac{\Delta P}{R_{epi} + R_{myo}} \]

- \( P_a \)
- \( P_v \)
- \( R_{epi} \)
- \( R_{myo} \)

Graph: % Area Stenosis vs. % Control Flow

K. Lance Gould, 1974
Flow, Pressure, and Resistance

\[ F = \frac{\Delta P}{R_{\text{epi}} + R_{\text{myo}}} \]

% Area Stenosis

0 25 50 75 100

% Control Flow

0 25 50 75 100
Flow, Pressure, and Resistance

\[ F = \frac{\Delta P}{R_{\text{epi}} + R_{\text{myo}}} \]

where:
- \( F \) is the flow
- \( \Delta P \) is the pressure drop
- \( R_{\text{epi}} \) is the resistance of the epicardial layer
- \( R_{\text{myo}} \) is the resistance of the myocardium

K. Lance Gould, 1974
Autoregulation

- Proximal LAD stenosis (n = 26)
- Normal LV systolic function
- PET flow measurements ($^{15}$O-labeled water) at rest
**Fractional Flow Reserve**

**FFR** = ratio of hyperemic flow in the stenotic vessel to hyperemic flow in the same vessel but in the absence of the stenosis

**FFR** = extent to which (%) maximal myocardial flow is limited by the epicardial stenosis

During maximal hyperemia (i.e. during maximal transstenotic flow, when the relationship between pressure flow is linear)
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Pressure-Flow Relationship During Maximal Vasodilation

\[
\frac{Q_{\text{N, max}}}{Q_{\text{S, max}}}
\]

\[
P_a = 100 \quad P_d = 100 \quad P_v = 0
\]

\[
P_a = 100 \quad P_d = 70 \quad P_v = 0
\]

Hyperemic Coronary Perfusion Pressure (% of normal) vs. Hyperemic Coronary Blood Flow (% of Normal)

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Non-Linearity of the Pressure-Resistance Relationship

Diameter normalized to the passive diameter at 100 mm Hg

Pressure (mm Hg)

Diameter Normalized to the Passive Diameter at 100 mm Hg

Non-Linearity of the Pressure-Resistance Relationship?

Adapted from Spaan, J. A.E. et al. Circulation 2006
Non-Linearity of the Pressure-Resistance Relationship?

Adapted from Spaan, J. A.E. et al. Circulation 2006
Pressure-Flow Relationship During Maximal Vasodilation

Hyperemic Coronary Blood Flow (% of Normal)

Hyperemic Coronary Perfusion Pressure (% of normal)
Conclusions

The control of myocardial blood flow is amazingly complicated. This complexity is ‘due’ to the importance of constantly matching oxygen demand

When performing ‘coronary physiology’ in the cath lab a thorough understanding of the basic mechanisms is mandatory
Conclusions