Regulation of Coronary Blood Flow

… for the Interventionalists

Bernard De Bruyne
Cardiovascular Center Aalst
Belgium
1. About Pressure, flow, mass, resistance, etc, ...

2. Epicardial vs microvascular compartments

3. Flow-function relationship

4. Coronary autoregulation
Extravascular Compressive Forces

Pressure

Aorta

LV

ETP April 24-26, 2014
Extravascular Compressive Forces

Pressure

Aorta

LV

LAD FLOW

ETP April 24-26, 2014
Extravascular Compressive Forces

Pressure

Aorta
Coronary
LV

LAD FLOW

ETP April 24-26, 2014

www.cardio-aalst.be
Extravascular Compressive Forces

Pressure

Aorta

RV

LAD FLOW

RCA FLOW

ETP April 24-26, 2014
Coronary and myocardial flow are influenced but not regulated by compressive forces and wave mechanics.
Relation between Vessel Size and Myocardial Mass

Cross-Sectional Lumenal Area (cm²)

Regional Myocardial Mass (g)

Normals

CAD

www.cardio-aalst.be
About Pressure, Flow, Resistance, and Vessel Size

Distance from the ostium

% of value at the ostium

Diameter

Mass

Flow

Pressure

ETP April 24-26, 2014
About 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] (~M¹)</td>
<td>0.005</td>
<td>70</td>
<td>100,000</td>
</tr>
<tr>
<td>Heart Weight [kg] (~M¹)</td>
<td>3.3x10⁻⁵</td>
<td>0.46</td>
<td>660</td>
</tr>
<tr>
<td>Stroke Volume [ml] (~M¹)</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>1</td>
<td>0.16 (&lt;10 bpm)</td>
</tr>
<tr>
<td>Cardiac Output [L/min] (~M³/⁴)</td>
<td>0.003</td>
<td>5</td>
<td>1000</td>
</tr>
<tr>
<td>Radius of Aorta [cm] (~M³/⁸)</td>
<td>0.02</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Mean Aortic Velocity [cm/sec] (~M⁰)</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>Mean Aortic Pressure [mmHg] (~M⁰)</strong></td>
<td><strong>100</strong></td>
<td><strong>100</strong></td>
<td><strong>100</strong></td>
</tr>
<tr>
<td>Mean Aortic Reynold’s No. (~M³/⁸)</td>
<td>15</td>
<td>530</td>
<td>8080 (turbulent!)</td>
</tr>
<tr>
<td>Mean Aortic Shear Stress [dynes/cm²] (~M⁻³/⁸)</td>
<td>180</td>
<td>5</td>
<td>0.3</td>
</tr>
</tbody>
</table>
About Pressure, Flow, Resistance, and Vessel Size

Ref Diam (mm) vs. % Stenosis for an Cross Sectional Area of 4 mm²

< 4 mm² = significant stenosis?
Anatomy vs Physiology: the Chimeric Link

Statistical (mechanistic) relation but little clinical relation

ETP April 24-26, 2014
ABC of Coronary Physiology
For the Interventionalist

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

2. Epicardial vs microvascular compartments

3. Flow-function relationship

4. Coronary autoregulation
Two-Compartment Model of the Coronary Circulation

The coronary angiogram detects only 5% of the total coronary tree

ETP April 24-26, 2014
Two-Compartment Model of the Coronary Circulation

Epicardial Artery

Microvasculature

FFR

IMR

CFR

ETP April 24-26, 2014
Two-Compartment Model of the Coronary Circulation

Conductance Arteries

>500 µ

Resistance Arteries

<500 µ

Microvasculature

MACRO

MICRO

ETP April 24-26, 2014
Pressure and Flow Velocity in Normal Coronary Arteries

FFR = 0.98
CFR = 4.15
Conductance Arteries

>500 µ

Resistance Arteries

<500 µ

Focal Stenosis

Microvasculature

ETP April 24-26, 2014

www.cardio-aalst.be

MICRO MACRO
Conductance Arteries

>500 µ

Resistance Arteries

<500 µ

Microvasculature

Focal Stenosis

Diffuse Atherosclerosis

ETP April 24-26, 2014
Conductance Arteries

Resistance Arteries

>500 µ

<500 µ

Stent

Diffuse Atherosclerosis

MACRO

MICRO

EPT April 24-26, 2014

www.cardio-aalst.be
Conductance Arteries

>500 µ

Resistance Arteries

<500 µ

Microvasculature

Diffuse Atherosclerosis

MACRO

MICRO
Endothelial Control of Coronary Blood Flow

Blood Flow

Shear Stress

ACh

Bradykinine

Endothelin

Normal Endothelium

Vascular Smooth Muscle Cell

L-Arginine

eNOS

NO

PGI₂

EDHF

Guanyl Cyclase

cGMP

Dilatation

ETP April 24-26, 2014
Endothelial Control of Coronary Blood Flow

Blood Flow → Shear Stress → L-Arginine → NO → Guanylyl Cyclase → cGMP → Constriction

ACh, Bradykinine, Endothelion

Abnormal Endothelium

Vascular Smooth Muscle Cell

ETP April 24-26, 2014
Importance of Maximal Vasodilation

Epicardial
- = Conductance
- Arteries > 550 µ

Microvasculature
- = Resistance
- Arteries < 550 µ

Nitrates
- Vasospasm

Adenosine
- Autoregulation
Effect of Mental Stress on the Diameter of Coronary Arteries

ABC of Coronary Physiology
For the Interventionalist

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

2. Epicardial vs microvascular compartments

3. Flow-function relationship

4. Coronary autoregulation
Flow-Function Relationship

% Reduction in Subendocardial Flow

% Reduction in Subendocardial Function

Flow Function Relationship

S. Vatner Circ Res 1980;47:201
Flow-Function Relationship

LV Wall Thickening (% of control value)

Resting Coronary Flow (% of control value)

Arterial saturation = 98%
Cor sinus saturation = 20%
Flow-Function Relationship

LV Wall Thickening (% of control value)

Resting Coronary Flow (% of control value)

ETP April 24-26, 2014
Flow-Function Relationship

ETP April 24-26, 2014
ABC of Coronary Physiology
For the Interventionalist

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

2. Epicardial vs microvascular compartments

3. Flow-function relationship

4. Coronary autoregulation
The Control of Myocardial Blood Flow

**Neuro-humoral factors**
- Noradrenaline
- Adrenaline
- Acetylcholine

**Physical factors**
- Arterial Pressure
- Coronary pressure
- RAP, LVDP and $P_{f=0}$
- Systolic compression
- Diastolic compression

**Metabolic factors**
- adenosine
- $PO_2$
- $PCO_2, H^+, K^+$

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

**Endothelium**

- Neuro-humoral factors
- Physical factors
- Metabolic factors
- Endo- and paracrine factors

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

Multiple, interacting, cumulative, nonlinear mechanisms

Coronary Autoregulation

Adapted from D.J.G.M. Duncker
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) vs. Coronary Blood Flow (mL/min)

Rubio and Berne, Prog CV Disease 1975
Coronary Perfusion Pressure (mm Hg)

Coronary Blood Flow (mL/min)

Autoregulatory Range

Rubio and Berne, Prog CV Disease 1975

ETP April 24-26, 2014
Autoregulatory Range

Coronary Perfusion Pressure (mm Hg)

Coronary Blood Flow (mL/min)

Initial Pressure

Rubio and Berne, Prog CV Disease 1975
Flow, Pressure, and Resistance

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

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

% Control Flow

% Area Stenosis

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

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

\( F \) = Flow
\( \Delta P \) = Pressure difference
\( R_{\text{epi}} \) = Resistance of epicardial arteries
\( R_{\text{myo}} \) = Resistance of myocardial arteries

% Area Stenosis vs. % Control Flow graph
Flow, Pressure, and Resistance

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

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

\[ F = \frac{\Delta P}{R_{\text{epi}} + R_{\text{myo}}} \]
Flow, Pressure, and Resistance

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

- \( P_a \) and \( P_v \) represent pressure at the arterial and venous ends, respectively.
- \( R_{\text{epi}} \) and \( R_{\text{myo}} \) represent resistances to flow due to epicardial and myocardial tissue, respectively.

The graph shows the relationship between percent area stenosis and control flow, indicating a decrease in flow as the area stenosis increases.

K. Lance Gould, 1974
• Proximal LAD stenosis (n = 26)
• Normal LV systolic function
• PET flow measurements (\textsuperscript{15}O-labeled water) at rest
Pressure-Flow Relationship During Maximal Vasodilation

Hyperemic Coronary Perfusion Pressure ( % of normal )

Hyperemic Coronary Blood Flow (% of Normal)

ETP April 24-26, 2014
People who wish to treat patients with CAD without coronary physiology must settle for a suboptimal treatment.
Fractional Flow Reserve

$$\text{FFR} = \text{ratio of hyperemic flow in the stenotic vessel to hyperemic flow in the same vessel but in the absence of the stenosis}$$

$$\text{FFR} = \text{extent to which (\%)} \text{ maximal myocardial flow is limited by the epicardial stenosis}$$

During maximal hyperemia (i.e. during maximal transstenotic flow)

$$\text{FFR} = \frac{Q_{\text{max}}^S}{Q_{\text{max}}^N} = \frac{P_d}{P_a}$$
Fractional Flow Reserve

$FFR = \frac{\text{ratio of hyperemic flow in the stenotic vessel to hyperemic flow in the same vessel but in the absence of the stenosis}}{\text{Maximal myocardial flow is limited by the epicardial stenosis}}$

$FFR = \frac{Q_s^{\text{max}}}{Q_N^{\text{max}}}$

$FFR = \frac{P_d}{P_a}$

(at hyperemia)
Fractional Flow Reserve is the ratio of maximal myocardial flow in the stenotic territory to normal maximal myocardial flow.

**Definition**

\[
FFR = \frac{Q_s^{\text{max}}}{Q_N^{\text{max}}}
\]

\[
= \frac{(P_d - P_v) / R_s}{(P_a - P_v) / R_N}
\]

- **Hyperemia** \(R_s = R_N\)
- \(P_v \ll P_a\) and \(P_d\)

\[
FFR = \frac{P_d}{P_a}
\]

ETP April 24-26, 2014
Pressure-Flow Relationship During Maximal Vasodilation

Hyperemic Coronary Perfusion Pressure ( % of normal )

Hyperemic Coronary Blood Flow ( % of Normal )

P_a = 100
P_d = 100
P_v = 0
Q_{max}^N

P_a = 100
P_d = 70
P_v = 0
Q_{max}^S

ETP April 24-26, 2014

www.cardio-aalst.be
Pressure-Flow Relationship During Maximal Vasodilation

Hyperemic Coronary Blood Flow (% of Normal)

Hyperemic Coronary Perfusion Pressure (% of normal)
Non-Linearity of the Pressure-Resistance Relationship?

Diameter normalized to the passive diameter at 100 mm Hg

Pressure (mm Hg)

Non-Linearity of the Pressure-Resistance Relationship?

Diameter Normalized to the Passive Diameter at 100 mm Hg

Pressure (mm Hg)

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

Diameter Normalized to the Passive Diameter at 100 mm Hg

Adapted from Spaan, J. A.E. et al. Circulation 2006
The relation between $P_d/P_a$ and $Q_s/Q_N$ is LINEAR during HYPEREMIA.
The relation between $P_d/P_a$ and $Q_S/Q_N$ is LINEAR during HYPEREMIA

- 22 Patients with an isolated proximal LAD stenosis
- $H_2^{15}O$ PET maximal flow in LAD vs normal territories
- FFR within 24 hours
**FFR: Physiologic Meaning**

During maximal hyperemia (i.e. during maximal transstenotic flow)

\[ FFR = \frac{Q_s^{max}}{Q_n^{max}} = \frac{P_d}{P_a} \]

**FFR has a well defined physiologic meaning**
(in sharp contrast to other indices like the \( \Delta P \), resting \( P_d/P_a \), iFR, FFR\(_{diast} \))
Pressure-Flow Relationship
During Maximal Vasodilation

Hyperemic Coronary Perfusion Pressure
(% of normal)

Hyperemic Coronary Blood Flow
(% of Normal)

Hyperemic Coronary Perfusion Pressure
(% of normal)
People who wish to treat patients with CAD without coronary physiology must settle for a suboptimal treatment