Within the past 12 months, I or my spouse/partner have had a financial interest /arrangement or affiliation with the organization(s) listed below

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/ Research Support:</td>
<td>St. Jude Medical/Medtronic</td>
</tr>
<tr>
<td>Grant/ Research Support:</td>
<td>NIH-R01 HL093475 (PI)</td>
</tr>
<tr>
<td>Consulting Fees/Honoraria:</td>
<td>Medtronic</td>
</tr>
<tr>
<td>Major Stock Shareholder/Equity Interest:</td>
<td></td>
</tr>
<tr>
<td>Royalty Income:</td>
<td></td>
</tr>
<tr>
<td>Ownership/Founder:</td>
<td></td>
</tr>
<tr>
<td>Salary:</td>
<td>NIH-R01 HL093475 (PI)</td>
</tr>
<tr>
<td>Intellectual Property Rights:</td>
<td></td>
</tr>
<tr>
<td>Other Financial Benefit (minor stock options):</td>
<td>HeartFlow</td>
</tr>
</tbody>
</table>
Outline:

- Coronary Anatomy
- Myocardial Mass and Coronary Flow
- Coronary Resistance
- Pathophysiology of Atherosclerosis
Coronary Circulation:

Two Compartment Model

Epicardial Vessel

Microvasculature
Coronary Circulation:

Three Compartment Model

- >0.5 mm
- 0.1-0.5 mm
- <0.1 mm

Sympathetic Innervation
Endothelium-Dependent Shear Stress

Metabolic Milieu
Autoregulation
Myogenic Control

Coronary Circulation:

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

Courtesy of Bernard De Bruyne, MD, PhD
Determinants of a Pressure Gradient

\[ \Delta P = f_1\left(\frac{1}{A_s^2}, l, \dot{Q}\right) + f_2\left(\frac{1}{A_s^2}, \frac{1}{A_n^2}, \dot{Q}^2\right) \]

Viscous + Separation

The pressure gradient across a stenosis is related to the flow across the stenosis.

Relationship between pressure drop and flow across two different stenoses, A and B.
Relation Between Vessel Size and Perfusion Area

Cross-Sectional Area (≈ Flow) and Myocardial Mass

Disconnect between Anatomy and Physiology
Disconnect between Anatomy and Physiology
Disconnect between Anatomy and Physiology

50% Stenosis       FFR=0.85

Myocardium

Collaterals

50% Stenosis

FFR=0.73

Collateral-Supplied Myocardium

Vessel-Supplied Myocardium

...During Maximal Hyperemia
Disconnect between Anatomy and Physiology
Disconnect between Anatomy and Physiology

FFR of Circumflex = 0.94
Disconnect between Anatomy and Physiology
Disconnected between Anatomy and Physiology

- 90% Stenosis  FFR=0.65
  - 90% Stenosis  FFR=0.94

CABG  SVG

Myocardium

SVG-Supplied Myocardium

Vessel-Supplied Myocardium

...During Maximal Hyperemia
Disconnect between Anatomy and Physiology
Disconnect between Anatomy and Physiology

FFR of Left Circumflex
Disconnect between Anatomy and Physiology

DS=75%    FFR=0.70

Normal Myocardium

Identical CSA
4 mm²

Normal Myocardium

DS=75%    FFR=0.94

Scar
Outline:

- Coronary Anatomy
- Myocardial Mass and Coronary Flow
- Coronary Resistance
- Pathophysiology of Atherosclerosis
**Coronary Artery Resistance:**

- There is little if any resistance in the normal epicardial artery; most of the resistance occurs in the microvasculature, at the level of the arteriole (100-300 um)

---

Epicardial Coronary Pressure: 
*Pressure, Flow, Resistance and Vessel Size*

**Diagram:**
- **BASE** to **APEX**
- **Distance from the ostium**
- **Pressure**
- **Diameter**
- **Mass**
- **Flow**

**Graphic Description:**
- Graph showing the decrease in pressure, diameter, mass, and flow from the base to the apex of the heart.

**Legend:**
- 100% of value at the ostium

**Source:** Courtesy of Bernard De Bruyne
Fractional Flow Reserve (FFR)

Maximum flow down a vessel in the presence of a stenosis…

…compared to the maximum flow in the hypothetical absence of the stenosis

Pijls and De Bruyne, Coronary Pressure
Derivation of FFR

- $\text{FFR} = \frac{\text{Coronary Flow (Stenosis)}}{\text{Coronary Flow (Normal)}}$

- Coronary Flow $= \frac{\text{Pressure}}{\text{Resistance}}$

- \text{at maximal hyperemia} Coronary Flow $\approx$ Pressure
Derivation of FFR

- FFR = \( \frac{\text{Coronary Pressure (Stenosis)}}{\text{Coronary Pressure (Normal)}} \)

- Coronary Flow = \( \frac{\text{Pressure}}{\text{Resistance}} \)

- *at maximal hyperemia* Coronary Flow \( \approx \) Pressure
At maximum vasodilation

Adapted from: Pijls and De Bruyne, Coronary Pressure
At maximum vasodilation

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

Adapted from: Pijls and De Bruyne, Coronary Pressure
Outline:

- Coronary Anatomy
- Myocardial Mass and Coronary Flow
- Coronary Resistance
- Pathophysiology of Atherosclerosis
Determinants of Myocardial Flow

- Epicardial Coronary Flow
  - Functional Impairments → **Ach Testing**
    - Endothelial dysfunction (Variant Angina, CAD)
  - Structural Impairments → **FFR**
    - Obstructive coronary stenosis (CAD)

- Microvascular Flow
  - Functional Impairments → **Ach Testing**
    - Endothelial dysfunction (DM, dyslipidemia)
  - Structural Impairments → **IMR**
    - Atherosclerosis, fibrosis, decreased vessel density (MI)
Determinants of Myocardial Flow

**Endothelial (Dys)Function**

Adapted from J Nuc Cardiol 2010;17:545-54.
Endothelial Dysfunction:

After Acetylcholine

After Nitroglycerin
Mild Lesions Cause Most MIs

Smoking Gun Theory
Angiographically Normal or Mild Coronary Plaque as a Cause of Myocardial Infarction

Jason C. Kovacic, MD, PhD; Valentin Fuster, MD, PhD

of this disease. Thanks to a series of pivotal observations, we now appreciate that MI rarely arises because of progressive vessel narrowing that culminates in a critical flow-limiting stenosis. Rather, it is now understood that an atherosclerotic MI, when in 1988 we showed with Ambrose et al\(^3\) that MI frequently develops from previously nonsevere lesions. In a

Circulation 2012;126:2918-20.
**Do Mild Stenoses Cause Most MIs?**

*Serial Angiographic (Retrospective) Studies in Patients with MI and a Prior Coronary Angiogram*

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Delay Angio -MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrose et al, <em>JACC</em> 1988</td>
<td>23</td>
<td>1 month to 7 years</td>
</tr>
<tr>
<td>Little et al, <em>Circulation</em> 1988</td>
<td>42</td>
<td>4 days to 6.3 years</td>
</tr>
<tr>
<td>Giroud et al, <em>AJC</em> 1992</td>
<td>92</td>
<td>1 month to 11 years</td>
</tr>
<tr>
<td>Moise et al, <em>AJC</em> 1984</td>
<td>116</td>
<td>39 months</td>
</tr>
<tr>
<td>Webster et al, <em>JACC</em> 1990 abstr</td>
<td>30</td>
<td>55 months</td>
</tr>
<tr>
<td>Hackett et al, <em>AJC</em> 1989</td>
<td>10</td>
<td>21 months</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>313</strong></td>
<td><strong>A few days to 11 years</strong></td>
</tr>
</tbody>
</table>
Repetitive episodes of plaque rupture/erosion and healing lead to an increasingly severe stenosis and a greater chance for AMI.
Healing of Non-Culprit Ruptured Plaques

28 non-culprit ruptured plaques without significant stenosis were identified by IVUS at time of ACS and treated medically without events out to 2 years.

Do Mild Stenoses Cause Most MIs?

In 164 patients who died of AMI had 184 vessels with plaque rupture. The mean diameter stenosis by pre-existing atherosclerotic plaque was 91%.

<table>
<thead>
<tr>
<th>Coronary Artery</th>
<th>No. (%)</th>
<th>% Stenosis by Atheroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>79 (43)</td>
<td>90.5 ±5.8</td>
</tr>
<tr>
<td>LCx</td>
<td>38 (21)</td>
<td>90.7 ±6.1</td>
</tr>
<tr>
<td>RCA</td>
<td>67 (36)</td>
<td>90.4 ±7.5</td>
</tr>
</tbody>
</table>

Lesion Severity and ACS

Likelihood of lesion subsequently causing ACS in the COURAGE Trial

Do Mild Stenoses Cause Most MIs?

*Distribution of blood alcohol content levels in drivers involved in fatal drunk driving accidents*
Lesion Severity and Vulnerability

472 patients with chest pain and suspicion of ACS randomized to CTA arm of ROMICAT II trial underwent evaluation of stenosis severity and plaque vulnerability, based on CTA, and this was correlated with diagnosis of ACS.

Lesion Severity and Vulnerability

IVUS and OCT performed in all three arteries in 255 subjects and identified 643 plaques.

Fibrous cap thickness was thinnest in the most severe lesions, and remodeling index and plaque burden was greatest.

Lesion Severity and Plaque Vulnerability

**IVUS and OCT performed in all three arteries in 255 subjects and 643 plaques identified**

Tian, et al. J Am Coll Cardiol 2014;64:672-80
IVUS and OCT performed in all three arteries in 255 subjects and 643 plaques identified

Tian, et al. J Am Coll Cardiol 2014;64:672-80
Lesion Severity and Plaque Vulnerability

IVUS and OCT performed in all three arteries in 255 subjects and 643 plaques identified

Tian, et al. J Am Coll Cardiol 2014;64:672-80
Lesion Severity and Plaque Vulnerability

*IVUS and OCT performed in all three arteries in 255 subjects and 643 plaques identified*

Tian, et al. J Am Coll Cardiol 2014;64:672-80
Why does FFR work?

**Does Ischemia Lead to Plaque Vulnerability?**

Low shear stress down-regulates vasoprotective factors and up-regulates inflammatory, oxidative stress, and thrombogenic factors

Ischemia and “vulnerability”

*Increased production of TNF-α correlates with fractional flow reserve measured in 70 patients referred for PCI*

Adapted from Versteeg, et al. Heart 2008;94:770
Joining Anatomy and Morphology

Lesion Severity
Myocardia Ischemia
Plaque Vulnerability

Cardiac Events
Detecting Myocardial Ischemia in the Cath Lab:

Epicardial Vessel

Microvasculature
Detecting Myocardial Ischemia in the Cath Lab:

Epicardial Vessel

Microvasculature

FFR
Detecting Myocardial Ischemia in the Cath Lab: