Coronary Microvascular Dysfunction: *Can we open the “Black Box”?*

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Disclosure Slide:

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  - St. Jude Medical
- Advisory Board
  - HeartFlow, Inc.
What is a “Black Box”? 

- A device, system or object which can be viewed in terms of its input, output and transfer characteristics without any knowledge of its internal workings. Its implementation is "opaque" (black).

Microvasculature

Wikipedia (April 2013)
What is the Microvasculature?

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

Courtesy of Bernard De Bruyne, MD, PhD
Why is it a “Black Box”? 

- Cannot image *in vivo* (~0.5 mm resolution of angiography)
- Animal models are not great representations
- Myocardial biopsy only includes <0.2 mm vessels and patchy
- Noninvasive imaging is challenging because of need to separate epicardial vessel and because of patchy nature (often no wall motion abnormality)
- Therefore, assessment of the microvasculature is primarily *functional* and not *anatomic*

What is the Microvasculature?

Two Compartment Model

Epicardial Vessel

Microvasculature
What is the Microvasculature?

**Three Compartment Model**

- **>0.5 mm**
  - Epicardial vessel
  - Sympathetic Innervation
  - Endothelium-Dependent Shear Stress

- **0.1-0.5 mm**
  - Prearterioles
  - Metabolic Milieu
  - Autoregulation
  - Myogenic Control

- **<0.1 mm**
  - Arterioles

What is the Microvasculature?

- **Conductive Arteries** (diameter >500 μm)
- **Prearterioles** (diameter 500–100 μm)
- **Arterioles** (diameter <100 μm)

**Drop in pressure from aorta to capillaries**

**Response to flow-dependent dilatation**

**Response to changes in intravascular pressure**

**Response to metabolites**

Determinants of Myocardial Flow

**Duncker DJ**

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

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

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

**Endothelium**

**Metabolic factors**
- Adenosine
- $PO_2$
- $PCO_2, H^+, K^+$
- Angiotensine II

**Endothelium**
- $\alpha_1\alpha_2$
- $\beta_1\beta_2$
- $\alpha_2$
- $A_2$
- $\beta_1\beta_2$
- $M$
- $M$
- $M$
- $NO\ PGI_2\ EDHF$
- $5-HT$
- $ET\ A$
- $ET\ B$
- $B_2$
- $H_1$
- $H_2$
- $NO\ PGI_2\ EDHF$
- $P_2$
- $P_2$
- $H_1$
- $B_2$
- $H_2$
- $NO\ PGI_2\ EDHF$
- $P_2$
- $P_2$
- $H_1$
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 pre-arteriole and arteriole.

Coronary microvascular dysfunction (CMD) is defined as abnormal coronary microvascular resistance (either arteriolar or pre-arteriolar) that is clinically evident as an inappropriate coronary blood flow response, impaired myocardial perfusion and/or myocardial ischemia that cannot be accounted for by abnormalities in the epicardial coronary arteries.

What is Microvascular Dysfunction?

- **Pathophysiology:**
  - **Structural**
    - Decreased lumen size
    - Decreased capillary number
  - **Functional**
    - Inappropriate vasoconstrictor response
    - Inadequate vasodilator response
    - Resulting from an intravascular issue (e.g., endothelial dysfunction) or extravascular issue (e.g., autonomic or humoral dysfunction)

Microvascular Dysfunction:

Classification

- Without myocardial/coronary disease
- With associated myocardial disease
- With associated epicardial disease
- Iatrogenic

Microvascular Dysfunction:

Classification

- Without myocardial/coronary disease
  - Smoking
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - Microvascular Angina/Syndrome X
- With associated myocardial disease
- With associated epicardial disease
- Iatrogenic

Syndrome X

- Introduced in the 1970s as an explanation for chest pain in patients without CAD
- Characterized by:
  - Exertional angina
  - Typical ST segment depression on exercise stress testing
  - Angiographically normal epicardial coronary arteries
  - No other explanation for microvascular dysfunction (e.g., HTN)

Microvascular Angina

- Introduced in the 1980s
- Characterized by:
  - Angina
  - No ST segment depression on exercise stress testing
  - Angiographically normal epicardial coronary arteries
  - Abnormal coronary blood flow response to vasodilatory stimuli (e.g., pacing, adenosine, dipyridamole)

Microvascular Dysfunction:

Classification

- Without myocardial/coronary disease
- With associated myocardial disease
  - Hypertrophic cardiomyopathy
  - Dilated cardiomyopathy
  - Infiltrative cardiomyopathies
- With associated epicardial disease
- Iatrogenic

Microvascular Dysfunction:

Classification

- Without myocardial/coronary disease
- With associated myocardial disease
- With associated epicardial disease
  - Acute Myocardial Infarction
  - Inappropriate pre-arteriole/arteriole vasoconstriction?
- Iatrogenic

50 women presenting with AMI and found to have “normal” appearing coronaries underwent IVUS followed by cardiac MR

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AMI and Normal Coronaries

50 women presenting with AMI and found to have “normal” appearing coronaries underwent IVUS followed by cardiac MR

50 Patients

42 IVUS

CMR not done*

8 Patients gave consent after angiography without IVUS**

LAD Plaque Rupture

# Microvascular Dysfunction and CAD

51 patients presenting with stable angina, abnormal stress test, or stabilized ACS and found to have no CAD had CFVR and IVUS performed to identify VH-TCFA.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency of TCFA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
</tr>
<tr>
<td>Age</td>
<td>0.30</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.04</td>
</tr>
<tr>
<td>HTN</td>
<td>0.02</td>
</tr>
<tr>
<td>DM</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.25</td>
</tr>
<tr>
<td>Log hs-CRP</td>
<td>-0.11</td>
</tr>
<tr>
<td>Impaired microvascular function (CFVR &lt; 2.0)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Microvascular Dysfunction:

Classification

- Without myocardial/coronary disease
- With associated myocardial disease
- With associated epicardial disease
- Iatrogenic
  - Plaque embolization related to PCI

Assessment of the Microvasculature

- Extremely challenging diagnosis
  - Heterogeneous patient population
  - Variety of pathogenetic mechanisms
  - Poor anatomic resolution
  - Potentially patchy nature of the disease
Assessment of the Microvasculature

Diagnostic Challenge

Epicardial CAD

Assessment of the Microvasculature

Diagnostic Challenge

A

Epicardial vessel

Prearterioles

Arterioles

Epi

Myocardium

Endo

Epicardial CAD

B

Conduit vessels

Flow distribution

Metabolic flow control

Epi

Myocardium

Endo

Microvascular Dysfunction

Assessment of the Microvasculature

- Extremely challenging diagnosis
  - Heterogeneous patient population
  - Variety of pathogenetic mechanisms
  - Poor anatomic resolution
  - Potentially patchy nature of the disease

- Therefore, assessment of the microvasculature is primarily *functional* and not *anatomic*
Evaluating the Microcirculation...  
...in the Cath Lab

TIMI Myocardial Perfusion Grade:
  Easy to obtain
  Specific for microvasculature
  Predictive of outcomes in large studies

Drawbacks:
  Qualitative
  Interobserver variability
  Not as useful in smaller studies
Doppler Wire Coronary Flow Reserve

CFR = \frac{\text{Hyperemic Flow}}{\text{Resting Flow}}
Coronary Wire-Based Assessment

**Coronary Flow Reserve**

- Not microvascular specific
- No clearly defined normal value
- Affected by resting hemodynamics

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Pijls NHJ and De Bruyne B, Coronary Pressure
Index of Microcirculatory Resistance

Epicardial Vessel

Microvasculature

FFR

IMR
Index of Microcirculatory Resistance

**Potential Advantages:**

- Readily available in the cath lab
- Specific for the microvasculature
- Quantitative and reproducible
- Predictive of outcomes
<table>
<thead>
<tr>
<th>Methods</th>
<th>Invasiveness</th>
<th>Parameters assessed</th>
<th>Tracers</th>
<th>Qualification</th>
<th>Current clinical usefulness</th>
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</thead>
<tbody>
<tr>
<td>PET scan</td>
<td>Non-invasive</td>
<td>Myocardial perfusion</td>
<td>Radioisotopes</td>
<td>Myocardial blood flow in ml/time/unit myocardial mass</td>
<td>Gold standard</td>
</tr>
<tr>
<td>SPECT</td>
<td>Non-invasive</td>
<td>Myocardial perfusion</td>
<td>Radioisotopes</td>
<td>None</td>
<td>For detection of myocardial ischaemia</td>
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<tr>
<td>MRI</td>
<td>Non-invasive</td>
<td>Myocardial perfusion</td>
<td>Contrast agent (gadolinium)</td>
<td>Myocardial blood flow in ml/time/unit myocardial mass</td>
<td>Moderate</td>
</tr>
<tr>
<td>CT scan</td>
<td>Non-invasive</td>
<td>Myocardial perfusion</td>
<td>Contrast agent (x-ray contrast)</td>
<td>Myocardial blood flow</td>
<td>Limited</td>
</tr>
<tr>
<td>Doppler echocardiography</td>
<td>Non-invasive</td>
<td>Coronary flow velocity</td>
<td>Echo contrast agents</td>
<td>CFR</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Myocardial contrast echocardiography</td>
<td>Non-invasive</td>
<td>Myocardial perfusion</td>
<td>Echo contrast agents</td>
<td>Perfusion defect size</td>
<td>Moderate</td>
</tr>
<tr>
<td>Myocardial contrast echocardiography (destruction replenishment imaging)</td>
<td>Non-invasive</td>
<td>Myocardial perfusion</td>
<td>Echo contrast agents</td>
<td>CFR, myocardial blood flow</td>
<td>Moderate</td>
</tr>
<tr>
<td>Doppler flow wire</td>
<td>Invasive</td>
<td>Coronary flow velocity</td>
<td>None</td>
<td>CFR</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Temperature and pressure sensor tripped coronary wire</td>
<td>Invasive</td>
<td>Intracoronary pressure and transit time</td>
<td>Saline</td>
<td>CFR, FFR, IMR</td>
<td>High</td>
</tr>
<tr>
<td>TIMI frame count and myocardial blush score</td>
<td>Invasive</td>
<td>Myocardial perfusion</td>
<td>Contrast (x-ray)</td>
<td>None</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Why is Microvascular Dysfunction Important?

- Up to 30% of patients continue to have angina despite successful coronary revascularization

- ~20% of patients with chest pain are found to have no angiographic apparent apparent CAD

- Microvascular dysfunction predicts adverse outcomes in a variety of clinical settings
Importance of Microvascular Dysfunction

Infarct-Free Survival based on Echo-Derived CFR in 394 Patients with Chest Pain and Normal Coronaries

189 women with chest pain and “normal” coronary arteries: % free of Death, MI, CVA, or CHF

Importance of the Microcirculation

2,423 patients undergoing PET-derived CFR

Importance of Microvascular Dysfunction

IMR measured at 1 year in 63 heart transplant recipients

% Free of Death, Graft Failure, CAV

Conclusions:

- The coronary microvasculature is an oft-ignored entity.
- The etiology of coronary microvascular dysfunction is complex and multifactorial.
- Microvascular dysfunction is associated with worse outcomes.
- The invasive assessment of microvascular function will likely play an increasingly important role in patient evaluation.