Fundamental Fallacies of FFR

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David L. Brown, MD, FACC
Professor of Medicine
@DavidLBrownMD
Disclosures

• None
  • I have no financial or intellectual conflicts of interest regarding the topic of today’s discussion
Fractional Flow Reserve

**Fractional Flow Reserve (FFR)**

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

where:
- \( P_d \) is the distal coronary pressure
- \( P_a \) is the proximal coronary pressure
Derivation of FFR

Angiography Bad --> Calibrate FFR to Stress Tests --> Stress Tests Calibrated Against Angiography

Exercise Stress Testing — Correlations among History of Angina, ST-Segment Response and Prevalence of Coronary-Artery Disease in the Coronary Artery Surgery Study (CASS)

Exercise echocardiography as a screening test for coronary artery disease and correlation with coronary arteriography

Myocardial Imaging with Thallium-201 at Rest and during Exercise

Comparison with Coronary Arteriography and Resting and Stress Electrocardiography

2019 ESC Chronic Coronary Syndromes Guidelines

**STEP 1:** Assess symptoms and perform clinical investigations
- Unstable angina? Follow ACS guidelines

**STEP 2:** Consider comorbidities and quality of life
- Revascularization futile
  - Medical therapy

**STEP 3:** Resting ECG, biochemistry, chest X-ray in selected patients, echocardiography at rest
- LVEF <50%
  - See section 4

**STEP 4:** Assess pre-test probability and clinical likelihood of CAD
- Cause of chest pain other than CAD?
  - Treat as appropriate or investigate other causes

**STEP 5:** Offer diagnostic testing
- Coronary CTA
  - Choice of the test based on clinical likelihood, patient characteristics and preference, availability, as well as local expertise
- Invasive angiography (with iFR/FFR)
  - Testing for ischaemia (imaging testing preferred)

**STEP 6:** Choose appropriate therapy based on symptoms and event risk

**Clinical likelihood of obstructive CAD**
- Very low
- Clinical likelihood of obstructive CAD
- Very high

Washington University in St. Louis • School of Medicine
Department of Medicine
Division of Cardiovascular Medicine
Four Fundamental Fallacies of FFR

1. Ischemia caused by an obstructive epicardial coronary stenosis is on the direct pathway to death/MI and should be a target of revascularization
2. The microvasculature is irrelevant in the assessment of coronary physiology and pathophysiology
3. FFR-guided PCI improves outcomes through targeted lesion selection (FAME)
4. FFR-guided PCI improves outcomes compared to OMT (FAME 2)
Fallacy 1: Ischemia caused by an obstructive epicardial coronary stenosis is on the direct pathway to death/MI and should be a target of revascularization
The Foundational Premise of FFR

• “In coronary artery disease, the most important factor related to outcome is the presence and extent of inducible ischemia.”

• “Functionally significant stenoses should be revascularized, if technically possible.”
Association of Ischemia with Cardiac Death

Association ≠ Causation

Ischemia vs. Atherosclerotic Burden in COURAGE

Ischemic burden:
OR 1.01 (0.98–1.03) P=0.54

Atherosclerotic burden:
OR 1.05 (1.02–1.08) P=0.002

J Am Coll Cardiol Intv 2014;7:195–201
PCI Does Not Reduce Death or MI in Patients with Ischemia

Fallacy 2: The microvasculature is irrelevant in the assessment of coronary physiology and pathophysiology
Focus on FFR Obscures the Critical Role of the Microvasculature

CFR = Coronary flow reserve

IMR = Index of microcirculatory resistance = \( \text{Pd} \times Tmn \)

JACC 2016; 67:1170-2
Impact of Coronary Microvascular Dysfunction on FFR - Worst Case Scenario

For a given epicardial disease severity, FFR increases with increasing HMR (MVD).

HMR = mean distal coronary pressure/mean distal flow velocity at maximum hyperemia.

Tim P van de Hoef et al. Heart 2014;100:951-959
RESEARCH CORRESPONDENCE

Coronary Microvascular Dysfunction Is Associated With Significant Plaque Burden and Diffuse Epicardial Atherosclerotic Disease

**TABLE 1** Patients and Vessels Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 77)</th>
<th>CNI (Abnormal HMR) (n = 30)</th>
<th>No CNI (Normal HMR) (n = 47)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>56 ± 10</td>
<td>60 ± 10</td>
<td>53 ± 10</td>
<td>0.003</td>
</tr>
<tr>
<td>Male</td>
<td>39 (51)</td>
<td>15 (50)</td>
<td>24 (51)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55 (71)</td>
<td>23 (77)</td>
<td>32 (68)</td>
<td>0.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (23)</td>
<td>12 (40)</td>
<td>6 (13)</td>
<td>0.012</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>59 (77)</td>
<td>22 (73)</td>
<td>37 (79)</td>
<td>0.59</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>163 ± 36</td>
<td>161 ± 33</td>
<td>164 ± 37</td>
<td>0.85</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>44 ± 12</td>
<td>44 ± 11</td>
<td>44 ± 13</td>
<td>0.96</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>95 ± 32</td>
<td>92 ± 35</td>
<td>98 ± 30</td>
<td>0.42</td>
</tr>
<tr>
<td>HMR</td>
<td>1.9 ± 0.7</td>
<td>2.62 ± 0.49</td>
<td>1.47 ± 0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFR</td>
<td>0.93 ± 0.06</td>
<td>0.94 ± 0.05</td>
<td>0.92 ± 0.07</td>
<td>0.13</td>
</tr>
<tr>
<td>EEM area, mm²</td>
<td>15.7 ± 4.3</td>
<td>16.2 ± 4.4</td>
<td>15.4 ± 4.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>9.7 ± 3.2</td>
<td>9.5 ± 3.2</td>
<td>9.8 ± 3.1</td>
<td>0.75</td>
</tr>
<tr>
<td>MUA, mm²</td>
<td>51 ± 2.4</td>
<td>4.7 ± 1.8</td>
<td>5.3 ± 2.8</td>
<td>0.76</td>
</tr>
<tr>
<td>Plaque area, mm²</td>
<td>6.9 ± 7.5</td>
<td>8.3 ± 10.7</td>
<td>6.0 ± 4.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Minimum PB%</td>
<td>18.8 ± 9.8</td>
<td>21.9 ± 9.8</td>
<td>16.8 ± 9.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Median PB%</td>
<td>37 ± 15.3</td>
<td>41.3 ± 13.0</td>
<td>34.3 ± 16.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Maximum PB%</td>
<td>61.3 ± 18.1</td>
<td>67.4 ± 15.3</td>
<td>57.5 ± 18.9</td>
<td>0.037</td>
</tr>
<tr>
<td>Percentage of IVUS frames with PB = 40%</td>
<td>41 ± 35</td>
<td>50.1 ± 34.3</td>
<td>34.2 ± 33.5</td>
<td>0.039</td>
</tr>
</tbody>
</table>

**J A C C : C a r d i o v a s c u l a r I n t e r v e n t i o n s  2 0 1 9 ; 1 2 : 1 5 1 6 – 2 0**
Fallacy 3: FFR-guided PCI improves outcomes through targeted lesion selection
In 37% of lesions, the FFR was greater than 0.80 and PCI was not performed.

Death or MI-no (%)  55(11.1)  37(7.3)  0.66 (0.44-0.98)

Critical Unanswered Question

Was the reduction in death/MI seen with FFR-guided PCI the result of avoidance of hemodynamically insignificant lesions or simply the result of putting in 37% fewer stents?
A BARI 2D Simulation: Random (as opposed to FFR-guided) Selection of Patients for Deferral of PCI
Fallacy 4: FFR-guided PCI improves outcomes compared to OMT
Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

<table>
<thead>
<tr>
<th>F/U</th>
<th>N</th>
<th>PCI</th>
<th>MT</th>
<th>P</th>
<th>PCI</th>
<th>MT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>213 days</td>
<td>NEJM</td>
<td>888</td>
<td>0.2</td>
<td>0.7</td>
<td>0.31</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>3 years</td>
<td>Circ</td>
<td>888</td>
<td>2.7</td>
<td>3.6</td>
<td>0.43</td>
<td>6.3</td>
<td>7.7</td>
</tr>
<tr>
<td>5 years</td>
<td>NEJM</td>
<td>784</td>
<td>5.1</td>
<td>5.2</td>
<td>0.98 (0.55-1.75)</td>
<td>8.1</td>
<td>12</td>
</tr>
</tbody>
</table>

What About the Urgent Revascularizations? ‘Faith Healing’ and ‘Subtraction Anxiety’ in FAME 2


Circulation: Cardiovascular Quality and Outcomes. 2018;11:e004665
Impact of Baseline FFR on Angina Relief in ORBITA

Circulation. 2018;138:1780–1792
Conclusions

• FFR, in isolation, is of no value in the evaluation of patients with suspected ischemia
• The ESC guidelines continue to promote an outdated paradigm for evaluation of suspected ischemia
• Ideally, the entire coronary vasculature should be assessed for a comprehensive understanding of the pathophysiology and preferred treatment of individual patients
Thank You!