FFR in Left Main Disease

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Disclosure Statement of Financial Interest

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>
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<tr>
<td>Consulting Fees/Honoraria:</td>
<td>Medtronic</td>
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<tr>
<td>Major Stock Shareholder/Equity Interest:</td>
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<td>Royalty Income:</td>
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<td>Ownership/Founder:</td>
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<td>Salary:</td>
<td>NIH-R01 HL093475 (PI)</td>
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<td>Intellectual Property Rights:</td>
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<tr>
<td>Other Financial Benefit (minor stock options):</td>
<td>HeartFlow</td>
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LM FFR Overview:

- Physiologic versus anatomic information
- Limitations of IVUS for assessing Left Main (LM)
- Data supporting FFR assessment of LM
- Limitations/Practical Aspects of FFR of LM
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Factors impacting ischemic potential of a stenosis

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

Viscous + Separation

Variability of IVUS Assessment of the LM

- 73 patients with distal left main disease underwent IVUS pullback from the LAD and from the L Cx.

- The average MLA of the LM from the LAD pullback was 6.7 ±3.1 mm² and from the L Cx pullback was 6.8 ±3.3 mm²

- However, in ½ the patients the L Cx measurement was smaller and in 11% the difference was > 1 mm².

- In the other ½ of the patients the LAD measurement was smaller and in 16% the difference was > 1 mm².

Variability of IVUS Cutoff Values

3 Yr Follow-up in 214 Intermediate Left Mains Assessed by IVUS

Fassa et al. J Am Coll Cardiol 2005;45:204-211
Variability of IVUS Cutoff Values

55 patients with ambiguous left main disease

Variability of IVUS Cutoff Values

55 patients with 30-80% LM and FFR and IVUS

![Graph showing the relationship between MLA and FFR](image)

- **Sensitivity**: 89%
- **Specificity**: 83%
- **PPV**: 82%
- **NPV**: 89%
- **Accuracy**: 86%

**Cut-off = 4.8 mm²**

Variability of IVUS Cutoff Values

**6 mm² TOO SMALL?**
- 6 mm²
- 55% stenosis
- FFR = 0.60

**6 mm² SUFFICIENT?**
- 6 mm²
- 10% stenosis
- FFR = 0.90
LM FFR Overview:

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Is it safe to defer LM Rx based on FFR?

**FFR measured in 54 patients with equivocal left main**


- **FFR ≥ 0.75**
- **FFR < 0.75**

![Graph showing freedom from death](image)

- Freedom from Death
- p = NS
- Number at risk:
  - Years: 0, 1, 2, 3
  - Medical group: 24, 22, 15, 7
  - Surgical group: 30, 29, 21, 8

Is it safe to defer LM Rx based on FFR?

FFR measured in 54 patients with equivocal left main

Is it safe to defer LM Rx based on FFR?

55 patients with ambiguous left main disease

FFR and Intermediate Left Main

274 patients with LMCA

213 patients enrolled

26 patients with protected LMCA

10 patients with valvular disease

4 patients requiring surgery but treated medically

21 patients requiring surgery for other vessel disease

138 Nonsurgical group

2 patients lost in FU

136 patients included in the analysis

75 Surgical group

2 patients lost in FU

73 patients included in the analysis

FFR for Assessing LM Significance

Poor correlation between “eyeball” and FFR

FFR for Assessing LM Significance

Survival Rate

<table>
<thead>
<tr>
<th>No at risk</th>
<th>Months</th>
<th>FFR $\geq 0.80$</th>
<th>FFR $&lt; 0.80$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>136</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>103</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>72</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>52</td>
<td>30</td>
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<tr>
<td></td>
<td>48</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>26</td>
<td>10</td>
</tr>
</tbody>
</table>

p = 0.48

**MACE Rate**

- **No at risk**
  - FFR $\geq 0.80$: 136, 106, 77, 57, 42, 30
  - FFR $< 0.80$: 73, 56, 40, 29, 15, 10

### FFR for Assessing LM Significance

**Recent meta-analysis of 6 studies including 525 patients**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bech</td>
<td>0.401</td>
<td>0.016</td>
<td>10.301</td>
<td>-0.551</td>
<td>0.581</td>
</tr>
<tr>
<td>Jimenez-Navarro</td>
<td>0.278</td>
<td>0.031</td>
<td>2.497</td>
<td>-1.143</td>
<td>0.253</td>
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<tr>
<td>Legutko</td>
<td>0.161</td>
<td>0.007</td>
<td>3.590</td>
<td>-1.153</td>
<td>0.249</td>
</tr>
<tr>
<td>Lindstaedt</td>
<td>0.107</td>
<td>0.005</td>
<td>2.090</td>
<td>-1.474</td>
<td>0.140</td>
</tr>
<tr>
<td>Courtis</td>
<td>0.722</td>
<td>0.140</td>
<td>3.705</td>
<td>-0.391</td>
<td>0.696</td>
</tr>
<tr>
<td>Hamilos</td>
<td>0.678</td>
<td>0.242</td>
<td>1.899</td>
<td>-0.740</td>
<td>0.459</td>
</tr>
<tr>
<td></td>
<td>0.497</td>
<td>0.237</td>
<td>1.040</td>
<td>-1.856</td>
<td>0.063</td>
</tr>
</tbody>
</table>

**Cardiac death rate tended to lower when LM deferred based on FFR**

FFR for Assessing LM Significance

Recent meta-analysis of 6 studies including 525 patients

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<tr>
<td>Legutko</td>
<td>2.846</td>
<td>0.109</td>
<td>74.379</td>
<td>0.628</td>
<td>0.530</td>
</tr>
<tr>
<td>Lindstaedt</td>
<td>0.208</td>
<td>0.010</td>
<td>4.559</td>
<td>-0.997</td>
<td>0.319</td>
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<tr>
<td>Courtis</td>
<td>3.026</td>
<td>0.330</td>
<td>27.781</td>
<td>0.979</td>
<td>0.328</td>
</tr>
<tr>
<td>Hamilos</td>
<td>1.647</td>
<td>0.066</td>
<td>40.936</td>
<td>0.304</td>
<td>0.761</td>
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<tr>
<td></td>
<td>1.225</td>
<td>0.335</td>
<td>4.481</td>
<td>0.306</td>
<td>0.760</td>
</tr>
</tbody>
</table>

Revascularization Deferred

MI rate was similar between both groups

**FFR for Assessing LM Significance**

*Recent meta-analysis of 6 studies including 525 patients*

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<tr>
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<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bech</td>
<td>2.368</td>
<td>0.504</td>
<td>11.125</td>
<td>1.092</td>
<td>0.275</td>
</tr>
<tr>
<td>Jimenez-Navarro</td>
<td>2.027</td>
<td>0.087</td>
<td>47.429</td>
<td>0.439</td>
<td>0.660</td>
</tr>
<tr>
<td>Legutko</td>
<td>2.846</td>
<td>0.109</td>
<td>74.379</td>
<td>0.628</td>
<td>0.530</td>
</tr>
<tr>
<td>Lindstaedt</td>
<td>8.667</td>
<td>0.960</td>
<td>78.268</td>
<td>1.923</td>
<td>0.054</td>
</tr>
<tr>
<td>Courtis</td>
<td>15.639</td>
<td>0.892</td>
<td>274.209</td>
<td>1.882</td>
<td>0.060</td>
</tr>
<tr>
<td>Hamilos</td>
<td>2.494</td>
<td>0.807</td>
<td>7.704</td>
<td>1.588</td>
<td>0.112</td>
</tr>
<tr>
<td></td>
<td>3.238</td>
<td>1.513</td>
<td>6.931</td>
<td>3.026</td>
<td>0.002</td>
</tr>
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</table>

*Revascularization rate was higher when LM deferred based on FFR*

LM FFR Overview:

- Physiologic versus anatomic information
- Limitations of IVUS for assessing Left Main (LM)
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- Limitations/Practical Aspects of FFR of LM
FFR of Left Main

Pullback of Pressure Wire During Maximal Hyperemia

Across Mid LAD  Across LM
FFR of Left Main

Pullback of Pressure Wire During Maximal Hyperemia

Across Mid LAD
 Across LM

(98) Pa mean
(82) Pd mean
0.84 FFR
After rotational atherectomy and 2.5x28 mm DES, post-dilated to 3.0 mm
FFR of Left Main

FFR of Left Main = 0.72
(In absence of LAD lesion)

Proximal to LAD stent
Across LM
Effect of Tandem Lesions

Myocardium

0.84

0.64

Myocardium

0.72
Left Main Stem Stenoses are Rarely Isolated

The influence of a distal stenosis on the FFR of the LM depends on the extent to which hyperemic flow across the LM stenosis will be decreased by this distal lesion

• Severity
• Myocardial mass

Courtesy Bernard De Bruyne, MD, PhD
The influence of a distal stenosis on the FFR of the LM depends on the extent to which hyperemic flow across the LM stenosis will be decreased by this distal lesion.

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Left Main Stem Stenoses are Rarely Isolated

The influence of a distal stenosis on the FFR of the LM depends on the extent to which hyperemic flow across the LM stenosis will be decreased by this distal lesion

- Severity
- Myocardial mass

Courtesy Bernard De Bruyne, MD, PhD
Effect of Epicardial Lesions on FFR Assessment of Intermediate LM Disease

In Vitro Model

Effect of Epicardial Lesions on FFR Assessment of Intermediate LM Disease

In Vitro Model

Effect of Epicardial Lesions on FFR Assessment of Intermediate LM Disease

Animal Model

Effect of Epicardial Lesions on FFR Assessment of Intermediate LM Disease

*Animal Model*

Effect of Epicardial Lesions on FFR Assessment of Intermediate LM Disease

Animal Model

Mild Epicardial Disease
(FFR_{epicardial} 0.70-0.80)

Moderate Epicardial Disease
(FFR_{epicardial} 0.60-0.69)

0.76±0.04 vs 0.78±0.05, P<0.001

0.75±0.05 vs 0.78±0.05, P<0.001

Effect of Epicardial Lesions on FFR Assessment of Intermediate LM Disease

**Animal Model**

Severe Epicardial Disease

(\(\text{FFR}_{\text{epicardial}} 0.40-0.59\))

Complete Epicardial Occlusion

(\(\text{FFR}_{\text{epicardial}} < 0.40\))

Effect of Downstream Stenosis on LM FFR:

*Human Validation*
Variable Downstream LAD Disease

After balloon inflation, $\text{FFR}_{\text{epi}}$ decreases to 0.35

FFR of LM in nondiseased LCx

$\text{FFR}_{\text{true}} = 0.77 \quad \text{FFR}_{\text{app}} = 0.82$
Effect of Downstream Stenosis on LM FFR: Human Validation

91 paired measurements obtained in 24 patients

0.81±0.08 vs. 0.83±0.08, $P<0.001$

JACC CV Intervent 2015;8:398-403.
Effect of Downstream Stenosis on LM FFR: Human Validation

91 paired measurements obtained in 24 patients

When $\text{FFR}_{\text{app}} > 0.85$, $\text{FFR}_{\text{true}} > 0.80$ 100% of the time.

---

JACC CV Intervent 2015;8:398-403.
Pre Stent

Post Stent

FU @ 8 mo

Courtesy of Chang-Wook Nam, MD
FFR of “Jailed” Left Circumflex

29 patients with LM/LAD crossover stenting with FFR of “jailed” Cx

## FFR of “jailed” Circumflex

<table>
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<th>Mean 20 month follow-up</th>
<th>Defer group</th>
<th>PCI group</th>
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<tbody>
<tr>
<td></td>
<td>n = 24</td>
<td>n = 5</td>
</tr>
<tr>
<td>Death, n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial Infarction, n</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLR, n</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Stent Thrombosis, n</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total Events, n</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

FFR of “jailed” Circumflex

43 patients with cross-over LM to LAD PCI and post PCI FFR of L Cx

Practical Aspects of LM FFR:

- First measure FFR in the least diseased vessel, preferably the LAD, with a pullback
  - If FFR < 0.80, then revascularize
  - If FFR >0.85, then treat medically
  - If FFR between 0.80 and 0.85 and there is significant downstream epicardial disease in the other epicardial vessel, then can consider IVUS
Practical Aspects of LM FFR:

- Intravenous adenosine is the ideal hyperemic agent because it allows time to pull the guide catheter out of the ostium.
- A physiologic evaluation of left main disease, compared to an anatomic evaluation alone, is safe and appropriate, just as it is in non-left main CAD.
- Never forget the patient and the clinical scenario.