Fractional Flow Reserve: 
_Basics, FAME 1, FAME 2_

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Stanford University Medical Center
Conflict of Interest

- Advisory Board for HeartFlow
- Research grant from St. Jude Medical
- Research and salary support from National Institutes of Health: 1 R01 HL093475 (PI)
Fractional Flow Reserve

Distal Pressure ($P_d$)

Proximal Pressure ($P_a$)

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

during maximal flow

$P_d / P_a = 60 / 100$

$\text{FFR} = 0.60$
Unique Aspects of FFR

- Clearly defined normal value
- Not affected by resting hemodynamics
- Relatively easy to perform

Adapted from: Pijls and De Bruyne, Coronary Pressure
Fractional Flow Reserve

Validation of FFR

$FFR < 0.75$ :  Sensitivity = 88%
Specificity = 100%

Safety of Deferring PCI Based on FFR

5 Year Cardiac Death and Acute MI rate in DEFER trial

FFR and the “Grey Zone”

FFR and the “Grey Zone”

FFR for decision-making in the cath lab

Based on the teaching file of Paul G. Yock MD, Stanford University.

Note: The specificity of this cut-off value is 100% and the sensitivity is 88%.

References:
Performing FFR:
Performing FFR:

1. IC NTG and IV heparin/bivalirudin
2. Equalize Pressures
Performing FFR

Wiring the Lesion

Consider disconnecting the wire from the interface connector.

Can use exchange catheter to more safely position pressure wire.
Performing FFR

Inducing Hyperemia
Intravenous Infusion (Preferably Central Line)

- Adenosine 140 µg/kg/min

Intracoronary Bolus

- Papaverine 12 mg 8 mg
- Adenosine 16 µg 12 µg ≥100 µg!
Performing FFR

Pressure Pullback

Focal LAD Lesion

Proximal Edge of LAD lesion

Distal LAD
Performing FFR

Pullback in Moderately and Diffusely Diseased LAD

Distal LAD Proximal LAD

Pa mean 0.75
Pd mean 0.54
FFR 0.75
Cursor 0.4
Reset
Performing FFR

Recognizing Drift

True Gradient

Drift
Why do we need FFR?

Nuclear perfusion scans performed in > 5000 patients

Frequency of Stress Testing to Document Ischemia Prior to Elective Percutaneous Coronary Intervention

Grace A. Lin, MD, MAS
R. Adams Dudley, MD, MBA
F. L. Lucas, PhD
David J. Malenka, MD
Eric Vittinghoff, PhD
Rita F. Redberg, MD, MSc

Context Guidelines call for documenting ischemia in patients with stable coronary artery disease prior to elective percutaneous coronary intervention (PCI).

Objective To determine the frequency and predictors of stress testing prior to elective PCI in a Medicare population.

Design, Setting, and Patients Retrospective, observational cohort study using claims data from a 20% random sample of 2004 Medicare fee-for-service beneficiaries aged 65 years or older who had an elective PCI (N=23 887).

Main Outcome Measures Percentage of patients who underwent stress testing within 90 days prior to elective PCI; variation in stress testing prior to PCI across 306 hospital referral regions; patient, physician, and hospital characteristics that predicted the appropriate use of stress testing prior to elective PCI.

Results In the United States, 44.5% (n=10 629) of patients underwent stress testing within the 90 days prior to elective PCI. There was wide regional variation among the hospital referral regions with stress test rates ranging from 22.1% to 70.6% (national mean, 44.5%; interquartile range, 39.0%-50.9%). Female sex (adjusted odds ratio [AOR], 0.91; 95% confidence interval [CI], 0.86-0.97), age of 85 years or older (AOR, 0.83; 95% CI, 0.72-0.95), a history of congestive heart failure (AOR, 0.85; 95% CI, 0.79-0.92), and prior cardiac catheterization (AOR, 0.45; 95% CI, 0.38-0.54) were associated with a decreased likelihood of prior stress testing. A history of chest pain (AOR, 1.28; 95% CI, 1.09-1.54) and black race (AOR, 1.26; 95% CI, 1.09-1.46) increased the likelihood of stress testing prior to PCI. Patients treated by physicians performing 150 or more PCIs per year were less likely to have stress testing prior to PCI (AOR, 0.84; 95% CI, 0.77-0.93). No hospital characteristics were associated with receipt of stress testing.

Conclusion The majority of Medicare patients with stable coronary artery disease do not have documentation of ischemia by noninvasive testing prior to elective PCI.

JAMA. 2008;300(15):1765-1773

www.jama.com
Limitation of Noninvasive Imaging

143 Patients with angiographically significant 3 vessel disease (> 70% diameter stenosis)

<table>
<thead>
<tr>
<th>Thallium Scan Finding</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Defect</td>
<td>18%</td>
</tr>
<tr>
<td>Single Vessel Pattern</td>
<td>36%</td>
</tr>
<tr>
<td>Two Vessel Pattern</td>
<td>36%</td>
</tr>
<tr>
<td>Three Vessel Pattern</td>
<td>10%</td>
</tr>
</tbody>
</table>

Limitation of Angiography

Comparison of QCA to FFR in over 3,000 lesions

(-) Ischemia

(+ ) Ischemia

Courtesy of Bernard De Bruyne, MD, PhD
Why FFR instead of IVUS?
MLA = 4.98 mm$^2$
FFR = 0.75

Resting vs. Hyperemia
...During Maximal Hyperemia
## IVUS Evaluation of Intermediate Lesions

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Threshold</th>
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<tbody>
<tr>
<td>Briguori, et al. (AJC 2001)</td>
<td>FFR MLA &lt; 4.0 mm²</td>
</tr>
<tr>
<td>Takagi, et al. (Circ 1999)</td>
<td>FFR MLA &lt; 3.0 mm²</td>
</tr>
<tr>
<td>Kang, et al. (Circ CVI 2011)</td>
<td>FFR MLA &lt; 2.4 mm²</td>
</tr>
</tbody>
</table>
Determinants of an Abnormal FFR

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

Viscous Separation

Why do we need FFR?

Fractional Flow Reserve versus Angiography for Multivessel Evaluation

Lesions warranting PCI identified

Randomized

PCI performed on indicated lesions only if FFR ≤ 0.80

FFR-Guided

Primary Endpoint

Composite of death, MI and repeat revasc. (MACE) at 1 year

Angio-Guided

PCI performed on indicated lesions

FAME-like Case Example:

- 46 year old diabetic woman with HTN and dyslipidemia presents to outside hospital with a NSTEMI.

- Cath reveals 3 vessel CAD and the patient is transferred to Stanford for CABG.

- Cardiac surgeon reviews angiogram and asks for a second opinion.
FFR of RCA = 0.87

Resting  Hyperemia
FFR of Ramus = 0.97

Hyperemia
Summary of Case

- Anatomic 3V CAD, functional 1V CAD
- Successfully treated with single stent
- 130 cc contrast, < 1 hour procedure
- Remains event free at > 12 months
<table>
<thead>
<tr>
<th></th>
<th>Angio-Guided n = 496</th>
<th>FFR-Guided n = 509</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Indicated lesions / patient</td>
<td>2.7±0.9</td>
<td>2.8±1.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Stents / patient</td>
<td>2.7 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Procedure time (min)</td>
<td>70 ± 44</td>
<td>71 ± 43</td>
<td>0.51</td>
</tr>
<tr>
<td>Contrast agent used (ml)</td>
<td>302 ± 127</td>
<td>272 ± 133</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Equipment cost (US $)</td>
<td>6007</td>
<td>5332</td>
<td>&lt;0.001</td>
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<tr>
<td>Length of hospital stay (days)</td>
<td>3.7 ± 3.5</td>
<td>3.4 ± 3.3</td>
<td>0.05</td>
</tr>
</tbody>
</table>
FAME Study: One Year Outcomes

- Death
  - Angio-Guided: 3%
  - FFR-Guided: 1.8%
  - p=0.02

- MI
  - Angio-Guided: 8.7%
  - FFR-Guided: 5.7%
  - p=0.04

- Repeat Revasc
  - Angio-Guided: 9.5%
  - FFR-Guided: 6.5%
  - p=0.02

- Death/MI
  - Angio-Guided: 11.1%
  - FFR-Guided: 7.3%
  - p=0.04

- MACE
  - Angio-Guided: 18.3%
  - FFR-Guided: 13.2%
  - p=0.02

FAME Study: Two Year Outcomes

Death/MI was significantly reduced from 12.9% to 8.4% (p=0.02)

Survival Free of MACE

FFR-Guided

Angio-Guided

730 days 4.5%

328 of the 1,005 patients in FAME had UA or NSTEMI

FFR-guided PCI saved >$2,000 per patient at one year compared to Angio-guided PCI.

What happens to deferred lesions?

513 Deferred Lesions in 509 FFR-Guided Patients

2 Years

31 Myocardial Infarctions

9 Late Myocardial Infarctions

1 Myocardial Infarction due to an Originally Deferred Lesion

22 Peri-procedural

8 Due to a New Lesion or Stent-Related

Only 1/513 or 0.2% of deferred lesions resulted in a late myocardial infarction

Pijls, et al. J Am Coll Cardiol 2010;56:177-84
Which Lesions Need FFR?

1329 lesions in the FFR-guided arm

Stenosis classification by angiography

Patients with angiographically 3VD (N=115), proportions per number of diseased vessels after assessment by FFR

Angiographic 3 Vessel Disease

SYNTAX Score

- Angiography-based scoring system aimed at determining coronary lesion complexity

- Because it is angiography-based, it is inherently limited by the accuracy of the coronary angiogram
Outcomes Based on Syntax Score

Worse outcomes with PCI vs CABG with higher SYNTAX score

Outcomes Based on Syntax Score

Similar outcomes with PCI vs CABG with lower SYNTAX score

Low SYNTAX Score 0-22

Cumulative Rate of Major Adverse Cardiovascular Events (%)

- PCI
- CABG

P = 0.71

Months since Randomization

# Impact of SYNTAX Score on PCI

**Recently published European guidelines for revascularization**

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<td>1VD or 2VD - non-proximal LAD</td>
<td>IIb C</td>
<td>I C</td>
<td>—</td>
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<tr>
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<td>I A</td>
<td>IIa B</td>
<td>30, 31, 50, 51</td>
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Can we enhance the SYNTAX Score?

- By incorporating FFR into the SYNTAX score, termed “Functional SYNTAX Score” (FSS), can we:
  - Convert high/medium risk SYNTAX score patients to a lower risk group?
  - Improve our risk stratification of patients with multivessel CAD undergoing PCI?
FSS Reclassifies > 30% of Cases

Without FFR

FSS Reclassifies > 30% of Cases

Without FFR

A

Low SS: 167 (34%)
Medium SS: 167 (34%)
High SS: 163 (32%)

With FFR

B

Low FSS: 290 (59%)
Medium FSS: 106 (21%)
High FSS: 101 (20%)

FSS Discriminates Risk for Death/MI

FSS Discriminates Risk for MACE

Effect of FSS in Multivessel CAD

- The mean FSS decreased by ~25% compared to the mean SS

- 43% of patients with a SS > 22 moved to an FSS < 22

FSS Case: “Mr. H.”

- 79 year old retired physicist with angina
- Risk factors include HTN and dyslipidemia
- Stress echo revealed anteroseptal and apical ischemia
- Referred for coronary angiography on September 10th, 2010…
How should we handle this case?

Recently published European guidelines for revascularization

Calculated SYNTAX score = 25.5

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FFR of RCA = 0.91
How should we handle this case?

Recently published European guidelines for revascularization

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Recalculated SYNTAX score after FFR = 18.5

Sept. 19th, 2010:

Dr. Fearon....this is from New Mexico. Yesterday we were walking around on the base of the Santa Fe ski area at over 10,300 feet. Not too strenuous but then not too much air there. Feeling great and just wanted to tell you and say thanks...
Implications of FAME

Death and MI in the COURAGE study

Survival Free of Death from Any Cause and Myocardial Infarction

Hazard ratio, 1.05; 95% CI (0.87–1.27); P=0.62

FAME 2

Stable patients scheduled for one-, two- or three vessel DES stenting

FFR in all indicated stenoses

- There is at least one Stenosis With FFR ≤ 0.80
- There is no Stenosis with an FFR ≤ 0.80

1:1 Randomization

PCI+OMT

OMT

Cohort A

Cohort B

Follow-up after 1, 6 months, 1, 2, 3, 4, and 5 years

Primary Endpoint: Death, MI, Urgent TVR at 2 years
DSMB Recommends St. Jude Medical's FAME II Clinical Trial Stop Enrollment

(RTTNews.com) - St. Jude Medical Inc. (STJ) announced that an interim analysis of the FAME II trial has found a highly statistically significant reduction in the need for hospital readmission and urgent revascularization when Fractional Flow Reserve or FFR-guided assessment was used to direct treatment in patients with coronary artery disease.

As a result of the positive interim analysis, the FAME II independent Data Safety Monitoring Board or DSMB has recommended investigators stop patient enrollment in this trial as the DSMB considers it unethical to continue to randomize patients to optimal medical therapy or OMT alone, St. Jude Medical said.

The DSMB recommended that St. Jude Medical stop patient enrollment in its FAME II trial due to increased patient risk of major adverse cardiac events (MACE) among patients randomized to OMT alone compared to patients randomized to OMT plus FFR-guided PCI.

The FAME II trial will continue following patients currently enrolled according to the trial protocol and will not enroll any new patients. The trial randomized 1,219 patients with stable coronary artery disease in 28 centers in Europe, the U.S. and Canada.
FFR Receives IA Recommendation

Criminal trial begins for Eastern Shore doctor accused of unnecessary stent procedures

Meanwhile, Towson doctor accused of similar infractions awaits word on whether he can keep his medical license

July 12, 2011 | By Tricia Bishop, The Baltimore Sun

While the Maryland Board of Physicians weighs professional charges against one cardiologist accused of placing heart stents into hundreds of patients who didn't need them, a federal jury in Baltimore is considering criminal charges against another.

The health care fraud trial of Dr. John R. McLean, who practiced at a hospital on the Eastern Shore before surrendering his medical privileges in 2007, opened Tuesday in Baltimore's U.S. District Court.
Take Home Messages:

- FFR is an invasive, vessel-specific, lesion-specific index for evaluating the ischemic potential of coronary artery disease.

- FFR-guided PCI improves outcomes and saves resources.

- FFR evaluation of patients with multivessel CAD may help guide decision regarding CABG or PCI