Noninvasive Assessment of Coronary Flow Physiology
PET and CT

Daniel S. Berman, MD
Director, Cardiac Imaging
Cedars-Sinai Heart Institute
Professor of Medicine and Imaging
Cedars-Sinai Medical Center

HCNM
Vail
2016
DISCLOSURE

Daniel S. Berman, M.D.
declares the following relationships:

Royalties: Cedars-Sinai Medical Center
Assessment of Coronary Flow Physiology by PET and CT

• General Considerations

• CT
  – Plaque
  – Perfusion
  – FFRct

• PET
  – Perfusion
  – Coronary flow reserve
Limitations of Percent Stenosis in CAD

- Percent stenosis inaccurate in assessing coronary blood flow across plaque
- Multiple factors (e.g., friction, turbulence, length) contribute to loss of pressure/flow across stenosis
- Particularly important with eccentric or irregular stenosis
- Does not assess microvascular disease
  - Important in the changing manifestations of coronary vascular disease

Source: Pijls N et al NEJM 1996 1703-08
PCI Did Not Reduce Death or MI

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Therapy</td>
<td>1138</td>
<td>1017</td>
<td>959</td>
<td>834</td>
<td>638</td>
<td>408</td>
<td>192</td>
<td>30</td>
</tr>
<tr>
<td>PCI</td>
<td>1149</td>
<td>1013</td>
<td>952</td>
<td>833</td>
<td>637</td>
<td>417</td>
<td>200</td>
<td>35</td>
</tr>
</tbody>
</table>

Optimal Medical Therapy (OMT)

PCI + OMT

Hazard ratio: 1.05
95% CI (0.87-1.27)
P = 0.62

Boden et al NEJM 2007
A Survival, Revascularization vs. Medical Therapy

Revascularization

Medical therapy

P = 0.97

No. at Risk: 2368, 2296, 2247, 2197, 1892, 1196

Multicenter RCT in 1,000 pts undergoing DES-stenting for multivessel CAD in 20 US and Europe.

- **30 days**
  - Survival Free of MACE: 97.1% for FFR-guided PCI, 97.4% for Anglo-guided PCI

- **90 days**
  - Survival Free of MACE: 96.2% for FFR-guided PCI, 96.5% for Anglo-guided PCI

- **180 days**
  - Survival Free of MACE: 95.4% for FFR-guided PCI, 95.7% for Anglo-guided PCI

- **360 days**
  - Survival Free of MACE: 94.6% for FFR-guided PCI, 95.0% for Anglo-guided PCI

- **p=0.02**

MACE=Death, MI, CABG, or repeat PCI.
**Fractional Flow Reserve vs. Angiography for Multivessel Evaluation (FAME) Trial**

- FFR-guided PCI: reduces PCI; improves survival free of death or MI compared to angiographically guided PCI.

Multicenter RCT in 1,000 pts undergoing DES-stenting for multivessel CAD in 20 US and Europe.

- 30 days: 2.9% MI, 90 days: 3.8%, 180 days: 4.9%, 360 days: 5.3%

Survival Free of MACE


MACE=Death, MI, CABG, or repeat PCI.
Obstructive CAD identified by invasive coronary angiography correlates poorly with FFR

Tonino et al. JACC 2010;55:2816-21 (FAME)

Park et al. JACC Interv 2012; 5:1029 –36

* Dattilo, et al. JACC 2012
Predicting Benefit from Revascularization in SIHD

- Invasive anatomic strategy: not-proven effective
  - Invasive physiologic strategy: add
- Opportunity for noninvasive physiologic strategies:
  - Better define patients who benefit from revascularization
    - ISCHEMIA trial
  - Define flow
    - Detect/assess microvascular disease
    - Add to FFR in predicting benefit from revascularization
At present there is no technique that enables direct visualisation of the coronary microcirculation in humans *in vivo*
Relating FFR and MFR
Physiologic Assessment of the Coronary Circulation

Epicardial vessels

Small vessels

FFR

CFR

M. Di Carli
Physiologic Assessment of the Coronary Circulation

Epicardial vessels

Small vessels

FFR

CFR

M. Di Carli
Invasive Fractional Flow Reserve (FFR) and Coronary Flow Reserve (CFR) Complementary Information

**Fractional Flow Reserve (FFR)**

\[ \text{FFR} = \frac{\text{Distal coronary (Pd)}}{\text{Proximal coronary (Pa)}} \]

**Coronary Flow Reserve (CFR)**

\[ \text{CFR} = \frac{\text{Hyperemic flow}}{\text{Baseline flow}} \]

Pa = Aortic pressure

Pd = Distal pressure

Baseline

Hyperemia
FFR/CFR Relationship: ~40% discordance

Assessment of Coronary Flow Physiology by PET and CT

• General Considerations
• CT
  – Plaque
  – Perfusion
  – FFRct
• PET
  – Perfusion
  – Coronary flow reserve
“What should I do about it?"

**Level of risk**

- **Very Low**
- **Low**
- **Borderline**
- **Can’t tell**
- **Medium**
- **High**

**Assure**

**Prevent**

**+ Stress imaging or FFRct**

**+ Cath**
APFs on CCTA Predict Ischemia

Shmilovich, Cheng, et al., Atherosclerosis 2011
51 patients with coronary CTA and rest-stress $^{13}$N-ammonia PET

Ischemia automatically derived from PET. Plaque analysis by Autoplaq

Dey et al Circulation Cardiovascular Imaging, 2015
Collaboration with Dr. Erick Alexanderson, Mexico City
Prediction of impaired MFR by coronary CTA (per-vessel)  

153 vessels

True positive rate

False positive rate

Composite Score 0.83 (0.79-0.91)

Stenosis 0.66 (0.57-0.76)

p = 0.005*

Dey et al Circulation Cardiovascular Imaging, in press
CT Perfusion: CORE320: Prediction of SPECT/ICA Ischemia

64-year-old male with chest pain

Rochitte C E et al. Eur Heart J 2014
Non-Invasive FFR_{CT}

- From typically acquired rest CCTA
- Computational fluid dynamics
  - Stenosis
  - Vessel volume after lesion
  - Myocardial mass distal to lesion
- No additional acquisition, radiation
- No modification to imaging protocols
- No administration of medications

**FFR\textsubscript{CT} for Lesion-Specific Ischemia**

**Case 1**
- **CT**: LAD stenosis
- **ICA and FFR**: FFR 0.65 = Lesion-specific ischemia
- **FFR\textsubscript{CT}**: FFR\textsubscript{CT} 0.62 = Lesion-specific ischemia

**Case 2**
- **CT**: RCA stenosis
- **ICA and FFR**: FFR 0.86 = No ischemia
- **FFR\textsubscript{CT}**: FFR\textsubscript{CT} 0.87 = No ischemia
NXTPer-Vessel: $\text{FFR}_{\text{CT}}$ vs. FFR and ICA

$\text{FFR}_{\text{CT}}$ diagnostic accuracy superior to both CT and ICA stenosis

Norgaard et al JACC 2014
Workstation-Based Calculation of CTA-Based FFR for Intermediate Stenosis
Sensitivity and Specificity for FFR ≤ 0.8

- 90 patients with 50-90% stenosis on coronary CTA
- 6 pts excluded
- ICA with FFR

FFRct

Strengths:
– Promising initial validation
– Single examination
– Lesion specific ischemia
– Pre-procedural planning
– Meets needs of interventional cardiologist:
  • which patient / lesion / type of revascularization
– May reduce unnecessary PCI

Limitations:
– High cost ($1500); delay
– Artifacts lead to exclusions
Assessment of Coronary Flow Physiology by PET and CT

• General Considerations
• CT
  – Plaque
  – Perfusion
  – FFRct
• PET
  – Perfusion
  – Coronary flow reserve
PET/CT Cameras

GE

Siemens

Philips
Multicenter Rb-82 PET Prognosis Registry: Mortality vs % Myocardial Hypoperfusion

N=7,786; 593 deaths

Dorbala...Shaw JACC 2013
Cumulative Cardiac Mortality Rates by % Abnormal Stress Myocardium with Rb-82 PET

Women (n=2,904); 54 deaths

Men (n=3,133); 115 deaths

Model $X^2=47$, $p<0.0001$.  
Model $X^2=71$, $p<0.0001$.  

Kay...Shaw JACC 2013
Coronary Flow Reserve by Rb-82 PET

Source: Bengel et al JACC 2009
Physiologic Assessment of the Coronary Circulation

Epicardial vessels

Small vessels

FFR

CFR
Absolute MBF Assessment With Rb-82 PET Prognostic Value Over Regional Perfusion

Accuracy and Reproducibility of Absolute $^{82}$Rb MBF Quantification

$^{82}$Rb vs $^{13}$N-ammonia MBF at rest and during peak stress

$y = 0.717x + 0.313$

$R^2 = 0.857$

Reproducibility of $^{82}$Rb MBF in repeated PET studies

$y = 0.983x$

$R^2 = 0.889$

El Fakhri et al, J Nucl Med 2009
Distribution of CV Risk by Coronary Flow Reserve

Annualized Cardiac Mortality (%/yr) vs. Coronary Flow Reserve

N=2783, CD=137

Coronary Flow Reserve (CFR) Predicts Mortality Independent of Perfusion Defects

<table>
<thead>
<tr>
<th>Tertile</th>
<th>≥10%</th>
<th>1-9%</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Tertile</td>
<td>2.4%</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>(n)</td>
<td>(119)</td>
<td>(195)</td>
<td>(614)</td>
</tr>
<tr>
<td>Middle Tertile</td>
<td>4.4%</td>
<td>4.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>(n)</td>
<td>(217)</td>
<td>(202)</td>
<td>(509)</td>
</tr>
<tr>
<td>Lower Tertile</td>
<td>10.2%</td>
<td>6.0%</td>
<td>3.6%</td>
</tr>
<tr>
<td>(n)</td>
<td>(416)</td>
<td>(190)</td>
<td>(321)</td>
</tr>
</tbody>
</table>

N = 2,783
CD = 137

P < 0.0001


Coronary Flow Reserve (CFR) Predicts Mortality Independent of Perfusion Defects
Coronary Flow Reserve (CFR) Predicts MACE Independent of Perfusion Defects

N=704; F/U: 1.1 years
MACE: ACD, MI (n=71)

Ziadi et al, JACC 2011
Preserved CFR by PET Effectively Excludes High-risk CAD

N=290; High risk: LM ≥50% , 2 v CAD including proximal LAD or 3 v CAD ≥ 70%

Naya…Di Carli et al JNM 2014
CFR is Associated with Cardiac Events Independently of Stenosis and Modifies the Effect of Early Revascularization

329 patients referred for ICA after PET; median f/u 3.1 year for CV death or HF
CFR and CAD prognostic index (ICA): independent predictors
Significant interaction (p=0.039) between CRF and early CABG but not PCI

Taqueti et al, Circulation 2015
## Coronary Microvascular Dysfunction Clinical Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>CMD w/o obstructive CAD (e.g., smoking, HTN, hyperlipidemia, and diabetes, “syndrome X”)</td>
</tr>
<tr>
<td>Type 2</td>
<td>CMD in the presence of myocardial diseases (e.g., HCM, DCM, hypertensive heart disease)</td>
</tr>
<tr>
<td>Type 3</td>
<td>CMD in the presence of obstructive CAD</td>
</tr>
<tr>
<td>Type 4</td>
<td>Iatrogenic CMD (e.g., distal embolization during PCI)</td>
</tr>
</tbody>
</table>

## Coronary Microvascular Dysfunction Clinical Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>CMD w/o obstructive CAD (e.g., smoking, HTN, hyperlipidemia, and diabetes, “syndrome X”)</td>
</tr>
<tr>
<td>Type 2</td>
<td>CMD in the presence of myocardial diseases (e.g., HCM, DCM, hypertensive heart disease)</td>
</tr>
<tr>
<td>Type 3</td>
<td>CMD in the presence of obstructive CAD</td>
</tr>
<tr>
<td>Type 4</td>
<td>Iatrogenic CMD (e.g., distal embolization during PCI)</td>
</tr>
</tbody>
</table>

CFR Differentiates Risk of Cardiac Death in Diabetics

Annualized Cardiac Mortality

- CAD+/DM+ (N=606): 2.9%, P=0.07
- CAD+/DM- (N=569): 2.0%, P=0.33
- CAD-/DM+ CFR ≤1.6 (N=227): 2.8%, P=0.005
- CAD-/DM+ CFR >1.6 (N=339): 0.3%, P=0.65
- CAD-/DM- Nl MPI/EF (N=682): 0.5%

P=0.015
N=2423 (935 with DM)
CD=122

*Adjusted for Duke score, ischemia + scar, rest LVEF and early revascularization

CFR Differentiates Risk of Cardiac Death in Diabetics

- CAD+/DM+ (N=606) 2.9% (P=0.07)
- CAD+/DM- (N=569) 2.0% (P=0.33)
- CAD-/DM+ CFR ≤1.6 (N=227) 2.8% (P=0.005)
- CAD-/DM+ CFR >1.6 (N=339) 0.3% (P=0.65)
- CAD-/DM- NI MPI/EF (N=682) 0.5%

*Adjusted for Duke score, ischemia + scar, rest LVEF and early revascularization

Abnormal CFR in Patients with No Perfusion Defects Predictive of MACE: Both Sexes

N=1218 (405 men, 813 women)
*No known CAD; no visual perfusion defect

MACE: 75 (death:32; CD:12; MI: 27; Late rev: 10; HF admission: 27)
Abnormal CFR in Patients with No Perfusion Defects Predictive of MACE: CAC 0

- 404 (307 women/97 men) no CAC: 48% W/44% men

Murthy et al Circulation 2014
Interaction of Impaired CFR and Cardiomyocyte Injury* on Prognosis in Patients without Overt CAD

n=761: Suspected CAD with serial troponin; F/U: 2.8 years for CV death, MI, late revascularization Excluded: known heart disease, EF<40%
* Elevated serum troponin

Taqueti, et al Circulation 2015
Clinical Value of PET Flow Quantitation

• Adds prognostic value over all other assessments: both sexes
• Increased accuracy compared to relative perfusion measurement for detecting high-risk CAD
  • Normal study rules out high risk CAD
  • No flow increase allows detection of absence of vasodilator response (caffeine)
• Likely better predictor than FFR regarding symptomatic improvement with revascularization
• Assesses microvascular dysfunction and associated prognosis
  • Independent risk from coronary atherosclerosis (CAC 0)
Different parameters to assess physiological significance

**Fractional Flow Reserve (FFR)**

\[ FFR = \frac{\text{Distal pressure (hyp)}}{\text{Aortic pressure (hyp)}} \]

**Coronary Flow Reserve (CFR)**

\[ CFR = \frac{\text{Hyperemic flow}}{\text{Baseline flow}} \]

\[ \text{Pa} = \text{Aortic pressure} \]
\[ \text{Pd} = \text{Distal pressure} \]
FFR/CFR Relationship: ~40% discordance

FFR/CFR Relationship: ~40% discordance

Diffuse epicardial or high risk CAD; Define anatomy

FFR/CFR Relationship: ~40% discordance

Abnormal FFR
- Normal flow
- Low risk
- Not source of pain
- Revasc not needed

Diffuse epicardial or high risk CAD;
Define anatomy

Discordant FFR and CFR in the cath lab
Frequency and Prognostic Importance

40-70% stenosis; PCI deferred
83% of discordance was FFR≤0.80 (low) and CFR≥2.0 (normal)
Low FFR with normal CFR: Sufficient flow for metabolic demands; benign

The primary objective of the DEFINE FLOW study is to determine the prognostic value of combined FFR and CFR measurements to predict the 24-month rate of MACE.
Noninvasive Assessment of Coronary Physiology
Potential Clinical Algorithm

- Lower risk: start with CCTA
  - Borderline add FFRct or perfusion
- Higher risk: start with perfusion/CFR
  - If abnormal, define anatomy/FFR
- Data not yet in:
  - If start with perfusion, may miss atherosclerosis (CAC helps)
  - If start with CTA: may miss microvascular disease
WHY FEEL HELPLESS ABOUT YOUR CORONARY ARTERY DISEASE?

TRY

HIGH TECH ROTO-ROOTER!

• No better than cheap heart meds
• Accounts for 10% of recent increase in Medicare spending
• Proven useless unless you’re in the middle of a heart attack or have severe ischemia on stress test
• Chance of heart attack or stroke right there on the operating table

SPECIAL:
Only $20,000 - $200,000
Act now, and Medicare (your tax dollars) or your insurance company will pick up most of the tab!

WAY EASIER THAN EXERCISING OR CHANGING YOUR DIET!

GET THAT FEELING OF DOING SOMETHING:
The 21st Century’s Answer to Leeches

by Carolyn Thomas ♥ @HeartSisters
• Thank you very much
Challenging Case – False Positive or “Collateral Flow”? Difficult to interpret cases- 67 year old asymptomatic male
Myocardial Flow Reserve 3.20 (normal >2) vs FFRCT of 0.65 ("normal" >0.80)

MFR = MBF hyperemia/MBF rest

Nuclear Results:
- Rubidium (Same day) gated PET [stress/rest rubidium (Supine)]
- Technical quality: excellent
- Myocardial Perfusion: Total perfusion defect 0% myocardium (0% reversible, 0% fixed)
  - no perfusion abnormalities.
  - LV enlargement: yes; Visual TID: no; TID Ratio 1.03
- Myocardial Function:
  - LVEF
  - Rest: 55% 76 ml/m2
  - Post Stress: 58% 83 ml/m2
- Resting and regadenoson stress gated PET revealed no wall motion abnormalities.

Conclusion: Clinical Response Nonischemic  Perfusion Normal
ECG Response Nonischemic  Function Normal

These test results indicate a low (<10%) likelihood for the presence of hemodynamically significant coronary artery disease.
The left ventricle is enlarged.
Stress flow 2.19 ml/gm/min. Rest flow 0.69 ml/gm/min. The myocardial flow reserve of 3.20 is normal (> 2.0) (J Am Coll Cardiol 2011;58:740-8).

MFR is related to epicardial and microcirculatory changes
Clinical Judgments Prevails
CFR in Prognosis and Therapy

CFR preserved?

No

- High-risk Angiographic CAD Present
  - OMT +/- Revasc

- High-risk Angiographic CAD Absent
  - OMT

Yes

- High-risk Angiographic CAD Unlikely

Prognosis:
- POOR
  - High-risk Angiographic CAD Present
  - High-risk Angiographic CAD Absent

Therapy:
- OMT +/- Revasc
- OMT

What is OMT?
Which Revasc Strategy?

Courtesy of Dr. V. Taqueti
Proposed Pathophysiologic Link Between Abnormal Coronary Flow Reserve, Ischemia/Injury, and Clinical Outcomes

Coronary Risk Factors → Reduced CFR → Microvascular ischemia → Low level myocardial injury/fibrosis → Obstructive CAD magnifies this process → Heart failure/MACE → Chest pain/dyspnea → Diastolic dysfunction → Coronary Risk Factors

Global Coronary Flow Reserve Is Associated With Adverse Cardiovascular Events Independently of Luminal Angiographic Severity and Modifies the Effect of Early Revascularization

Viviany R. Taqueti, MD, MPH; Rory Hachamovitch, MD, MS; Venkatesh L. Murthy, MD, PhD; Masanao Naya, MD, PhD; Courtney R. Foster, MS; Jon Hainer, BS; Sharmila Dorbala, MD, MPH; Ron Blankstein, MD; Marcelo F. Di Carli, MD
Distribution of Global Coronary Flow Reserve by Luminal Angiographic Severity


*Extent and severity of CAD
Strengths:
- Lesion specific pressure drop
- Randomized trial data suggestive of benefit in guiding revascularization decisions in SIHD
- Decreases unnecessary revascularization and reduces the number of stents used

Limitations:
- Not a measure of ischemia
- May have pressure drop in presence of preserved flow
- Flow, not pressure drop, determines ischemia
- May be falsely negative in presence of severe microvascular disease
Advantages of Quantitative PET/MRI

- Non-invasive quantification of *regional* stress flow and CFR to define physiologic severity to guide management

- Non-invasive quantification of *global* stress flow and CFR to define physiologic severity of diffuse high risk CAD and microvascular dysfunction

- Established low flow *ischemic threshold* for angina & ECGΔ

- Coronary flow controls ischemia, NOT pressure.

- Extensive literature documents PET predictive power and potential outcomes with PET directed intervention.
**FFR: How it works**

FFR: Derived during invasive angiography from the ratio of mean distal coronary-artery pressure to aortic pressure during maximal vasodilation.

Pressure-monitoring guidewire advanced through femoral artery and positioned distal to stenosis.

Adenosine infused to induce maximal coronary blood flow, this corresponds to minimal distal coronary pressure.

Source: [http://professional.sjm.com/products/vas/intravascular-diagnostics-imaging/ffr/pressurewire-certus#how-it-works](http://professional.sjm.com/products/vas/intravascular-diagnostics-imaging/ffr/pressurewire-certus#how-it-works)
Figure 1. Typical example of physiological assessment of an atheromatous lesion in the mid right coronary artery, using a pressure wire. Simultaneous aortic pressure (Pa) and distal coronary pressure (Pd) recordings during maximal hyperaemia as induced by intracoronary adenosine. Fractional flow reserve (FFR) is 0.69, meaning that the stenosis is haemodynamically significant. MLD – minimum lumen diameter.
Percent Diameter Stenosis (QCA) versus FFR, N = 4089

Toth et al. European Heart Journal 2014
FFR is valid only for moderate stenosis on angiogram. It is not a stand alone metric of severity w/o angiogram stenosis.

Mild anatomic stenosis Low FFR

Severe % DS High FFR

35% discordance

Toth et al. European Heart Journal 2014
Advantages of Quant MBF

- Extent and severity of CAD
- Balanced decrease in blood flow
- Microvascular disease
- Diffuse disease
FFR vs CFR: Relationship to Ischemia

• Differences between FFR and CFR
  – Pressure drop across a given coronary stenosis is determined by the magnitude of coronary flow
  – Low coronary flow may exist with normal FFR
  – High coronary flow may exist with an abnormal FFR

• Discordance between FFR and flow: 30-40% of cases

• Inadequate flow—not pressure drop—determines myocardial function and symptoms

• FFR is not a gold standard for ischemia

Noninvasive Evaluation with Quantitative Stress Myocardial Perfusion Imaging

- If normal,
  - Preventive therapy
- If abnormal
  - Mildly abnormal: consider CCTA
  - Moderate/severe perfusion defect: cath/FFR
Distinguishing Stable from Active Atherosclerosis
Identifying the Vulnerable Patient

Fibroatheroma: Stable Plaque
TCFA with Cap Rupture

Narula & Willerson, JACC (ed) Narula & Virmani, 1999
Distinguishing Stable from Active Atherosclerosis
Identifying the Vulnerable Patient

Current paradigm: Revascularize when: stenosis and ischemia
Potential paradigm: Revascularize the lesion likely to rupture

Narula & Willerson, JACC (ed) Narula & Virmani, 1999
F-18 Sodium Fluoride PET Identifies Ruptured and High-Risk Coronary Plaques

- 40 AMI
  - 93% uptake in culprit plaque at ICA

- 40 Stable angina
  - 45% uptake in plaques with high risk features (IVUS)

Joshi…Newby
Lancet 2013
F-18 Sodium Fluoride PET Identifies Ruptured and High-Risk Coronary Plaques

- 40 AMI
  - 93% uptake in culprit plaque at ICA

- 40 Stable angina
  - 45% uptake in plaques with high risk features (IVUS)

Fluride F-18: Potential to alter treatment paradigm in SIHD

Joshi…Newby
Lancet 2013
CT and PET Assessment of Coronary Flow Physiology

• CT
  – Plaque
  – Perfusion
  – FFRct

• PET
  – CFR
    • Gold standard for ischemia
    • Diffuse disease
    • Complementary to FFR
  – Molecular imaging

• SPECT
  – Potential for CFR
Landmark analysis incorrectly discounts procedure-related events during 0–7 days.

**FAME 2**

0 to 2 years for PCI vs Med

- Death from any cause: \( P = 0.58 \)
- Cardiac deaths: \( P = 0.99 \)
- Myocardial infarction: \( P = 0.56 \)
- Death or MI: \( P = 0.35 \)
- Later urgent PCI: \( P = 0.001 \)

\[ 0–7 \text{ days}: \text{Hazard ratio, 9.01 (95\% CI, 1.13–72.0)} \]

\[ 8 \text{ days to 2 yr}: \text{Hazard ratio, 0.56 (95\% CI, 0.32–0.97)} \]

\( P \) for interaction = 0.002

FAME 2

0 to 2 years for PCI vs Med
Death from any cause  P = 0.58
Cardiac deaths  P = 0.99
Myocardial infarction  P = 0.56
Death or MI  P = 0.35
Later urgent PCI  P = 0.001

Landmark analysis incorrectly discounts procedure related events during 0 – 7 days.

FFR-guided PCI: compared to angiographically guided PCI
• improves survival free of death/MI
• Fewer stents
• Unproven whether superior to medical therapy alone

Revascularization Decisions in Patients with Stable Angina and Intermediate Lesions: International Survey of 495 Interventionalists

- 495 interventionalists evaluating intermediate coronary stenoses;
- Asked to make decisions to achieve best clinical practice without financial constraints

Toth, et al: Circ CVI 2014
Revascularization Decisions in Patients with Stable Angina and Intermediate Lesions: International Survey of 495 Interventionalists

Conclusion: Even in idealized setting, despite guideline recommendations, visual estimation dominate treatment decisions for intermediate stenoses

Toth, et al: Circ CVI 2014
Problems with ICA/FFR-Based Strategy for all patients with a intermediate to high likelihood of CAD

- **Overuse of ICA:**
  - High rates of non-obstructive CAD
  - Risks: vascular access, MI, death
  - Occulo-stenotic reflex

- **FFR**
  - Only applied in small proportion of patients; operator choice
  - “High guideline thresholds” (0.8): not shown to benefit
  - No assessment of diffuse/microvascular disease
  - No accounting for size of hypoperfused zone
  - Unnecessary revascularization
  - Overestimation of likelihood of true ischemia (symptoms)
  - Reduced but still overused PCI
Advantages of Quantitative PET/MRI

- Non-invasive quantification of *regional* stress flow and CFR to define physiologic severity to guide management

- Non-invasive quantification of *global* stress flow and CFR to define physiologic severity of diffuse high risk CAD and microvascular dysfunction

- Established low flow *ischemic threshold* for angina & ECGΔ

- Coronary flow controls ischemia, NOT pressure.

- Extensive literature documents PET predictive power and potential outcomes with PET directed intervention.
Fractional Flow Reserve vs. Angiography for Multivessel Evaluation (FAME) Trial

Multicenter RCT in 1,000 pts undergoing DES-stenting for multivessel CAD in 20 US and Europe

Survival Free of MACE

30 days 2.9%
90 days 9%
180 days 14%
360 days 17%

p=0.02

FFR-guided PCI improves survival free of death or MI compared to angiographically guided PCI; predicts symptomatic relief

MACE=Death, MI, CABG, or repeat PCI.

FAME 2: Primary Outcomes

PCI+MT vs. MT: HR 0.32 (0.19-0.53); p<0.001
PCI+MT vs. Registry: HR 1.29 (0.49-3.39); p=0.61
MT vs. Registry: HR 4.32 (1.75-10.7); p<0.001

Primary endpoint

• Composite of all-cause death, MI, unplanned hospitalization with urgent revasc
Disadvantages of FFR

Invasive measurement at coronary angiogram.

Uses Adenosine stress in cath lab.

FFR is valid only for moderate stenosis on angiogram. It is not a stand alone metric of severity w/o angiogram stenosis.

Fails to account for diffuse CAD incurring high risk.

Coronary flow controls ischemic dysfunction, NOT pressure.

Derived relative flow reserve not absolute flow or CFR.

FFR guided PCI in randomized trials failed to reduce MI/death
FFR Guided Revascularization Problems with Evidence

- Arbitrary binary thresholds for FFR studied in randomized trials are guiding decisions*
- FAME 2 data: No benefit regarding MI/death; 9x risk of death or MI within 7 days of PCI*
- Reduced flow—not reduced pressure—causes ischemia
  - Stenosis with no or mild flow reduction (sub-ischemic) may reduce FFR with no symptomatic benefit from PCI (CFR above ischemic threshold)
- High risk diffuse CAD may reduce/eliminate potential benefit of PCI for individual stenoses

Modified from Gould and Johnson Circ CV Imaging 2015

* Initially validated ischemia threshold: 0.65
Comparison of observed Ob-CAD prevalence in MEN to probability calculated in the Diamond-Forrester Classification

- Nonanginal Chest Pain
- Atypical Angina
- Typical Angina

Age (years)
Prevalence (%)
Disadvantages of Direct Cath and FFR

- Most patients do not have obstructive CAD
- FFR infrequently used; up to subjective judgment of operator
- Fails to account for diffuse CAD incurring risk
- Coronary flow controls ischemia dysfunction: not pressure
Advantages of Quantitative PET

Noninvasive quantification of global stress flow and CFR to define physiologic severity of diffuse high risk CAD and microvascular disease

Coronary flow controls ischemic dysfunction, not pressure
Extensive literature documents PET predictive power and potential outcomes with PET directed intervention
Based Strategy for all patients with an intermediate to high likelihood of CAD

- Overuse of ICA
  - High rates of non-obstructive CAD
  - Risks: vascular access, MI, death
- FFR
  - Only applied in a small proportion of patients
  - Possibility of false positive FFR
  - Possibility of a false negative
    - Missing risk of diffuse/microvascular disease
  - No accounting for size of hypoperfused zone
  - Guideline-thresholds for FFR: too high
  - Unnecessary revascularization
  - Overestimation of likelihood of true ischemia (symptoms)
  - Reduced but still overused PCI
Why can FFR be right?

- Optimal cut-point for ischemia during exercise: 0.66 (ECG and objective signs/symptoms of ischemia)
- Drastically lower than 0.8
- In FAME II: Dominant effect of PCI over MT was in FFR <0.65
- Optimal prognostic threshold 0.68
- Solitary 0.80 cut-off value not supported by trials

Van de Hoef, et al EHJ 2015
FFR Interventionalist Quote (HN)

- It’s not significant now, but it will be
- “0.75 is a better threshold: but if we dropped to this, we would lose half of our business”
- “Only FFR the lesions that are the ones you don’t want to stent”
- “0.75 and you have a ticket to ride”
### Secondary Endpoint:
Catheterization Without Obstructive CAD ≤90 days

<table>
<thead>
<tr>
<th></th>
<th>CTA (n=4996)</th>
<th>Functional (n=5007)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive catheterization without obstructive CAD — N (%)</td>
<td>170 (3.4)</td>
<td>213 (4.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>Invasive catheterization</td>
<td>609 (12.2%)</td>
<td>406 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>With obstructive CAD (% of caths)</td>
<td>439 (72.1%)</td>
<td>193 (47.5%)</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>311 (6.2%)</td>
<td>158 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>72</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

Douglas et al NEJM 2015
15-NH3 vs 99mTc for MBF Measurement

Nikolla et al; JNC 2014
Anger Camera MBF (Symbia)

Symbia
10 sec acq
10 mCi MIBI

Hsu et al
EJNMB 2014
Anger Camera MBF (Symbia)

Symbia
10 sec acq
10 mCi MIBI

Hsu et al
EJNMB 2014
72 year old DM Woman with CP

- General Considerations
- Noninvasive evaluation
  - Stress testing
  - Coronary CTA
  - CFR vs FFR
  - Molecular imaging
Coronary Flow Is More Important Than Coronary Pressure

• FAME II
  – 60% with abnormal FFR did not require intervention up to 2 years later
  – 10% with normal FFR had MACE within 2 years
  – FFR guided PCI might limited the number of events compared with angiography guided PCI, however should not be considered gold standard

Van de Hoef, et al EHJ 2015
Why can FFR be right?

• Optimal cut-point for ischemia during exercise: 0.66 (ECG and objective signs/symptoms of ischemia

• Drastically lower than 0.8

• In FAME II: Dominant effect of PCI over MT was in FFR <0.65

• Optimal prognostic threshold 0.68

• Solitary 0.80 cut-off value not supported by trials

Van de Hoef, et al EHJ 2015
Why can FFR be right?

• Optimal cut-point for ischemia during exercise: 0.66 (ECG and objective signs/symptoms of ischemia
• Drastically lower than 0.8
• In FAME II: Dominant effect of PCI over MT was in FFR <0.65
• Optimal prognostic threshold 0.68
• Solitary 0.80 cut-off value not supported by trials

Van de Hoef, et al EHJ 2015
Microvascular disease: diagnostic blond spot in FFR guided strategies

- Could be normal in patients with increased microvascular resistance, even in presence of critical stenosis
- Combination of epicardiac and microvascular disease that dictates inability to meet demand
Coronary Flow Assessment

- PET or MRI: quantitative in ml/gram/min and regional flow reserved
- Difficult measurement to make in the cath lab: technically more demanding
  Prone to measurement error

Paramount prognostic relevance in SIHD
Discordance between FFR and CFR

• CFR: ability to identify ischemia producing coronary stenoses AND prognostic value
• FFR: epicardial domain
• CFR: both epicardial and microvasculature
• 30-40% of vessels with equivocal angiographic severity have FFR and CFR discordance

Van de Hoef, et al EHJ 2015
Effects of Sex on Coronary Microvascular Dysfunction (CMD) and Cardiac Outcomes

Figure S4: Cumulative Incidence of MACE by Gender and Coronary Flow Reserve for CAC=0 Subgroup

P=0.01 (CFR)
P=0.59 (gender)

Murthy et al Circulation 2014
Effects of Sex on Coronary Microvascular Dysfunction (CMD) and Cardiac Outcomes

Figure S6: Cumulative Incidence of MACE by Gender and Coronary Flow Reserve for CAC>100 Subgroup

P=0.38 (CFR)
P=0.71 (gender)

<table>
<thead>
<tr>
<th></th>
<th>Female CFR&lt;2.0</th>
<th>Male CFR&lt;2.0</th>
<th>Female CFR≥2.0</th>
<th>Male CFR≥2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>100</td>
<td>59</td>
<td>59</td>
<td>50</td>
</tr>
<tr>
<td>Years 0</td>
<td>71</td>
<td>31</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Years 1</td>
<td>38</td>
<td>15</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td>Years 2</td>
<td>12</td>
<td>7</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Years 3</td>
<td></td>
<td></td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

Murthy et al Circulation 2014
Prognostic Interplay of Coronary Artery Calcification and Underlying Vascular Dysfunction in Patients With Suspected Coronary Artery Disease

Masanao Naya, MD, PhD,* Venkatesh L. Murthy, MD, PhD,*† Courtney R. Foster, Mariya Gaber, MS,‡ Josh Klein, BA,‡ Jon Hainer, BS,‡ Sharmila Dorbala, MD,*‡ Ron Blankstein, MD,* Marcelo F. Di Carli, MD*‡

Boston, Massachusetts; and Ann Arbor, Michigan
Prognosis of CACS and Abnormal Flow Reserve

• 901 consecutive symptomatic patients with normal Rb-82 PET having CFR and CAC scan
• CFR decreasing with increasing CAC
• 57 MACE over 1.53 years (CD, NFMI, >90 day revasc), rehosp for CHF
• MACE rates higher with CRF <2 (p<0.001), but only borderline associated with CAC (p=0.09)
• MACE increased with low CFR even without CAC
• CFR improved model fit, risk discrimination and reclassification over clinical risk, whereas CAC did so only modestly
• Conclusion: In symptomatic patients with normal MPI, global CFR but not CAC provides significant incremental risk stratification over clinical risk score for prediction of MACE

Naya et al JACC 2013
Novel approach to SIHD: Put Flow First

- Comprehensive assessment of both obstructive and non-obstructive disease
- If normal, need no more
- If abnormal, need to define FFR/anatomy
Novel approach to SIHD: Put Flow First

- Coronary flow: fundamentally more important (in producing ischemia) than pressure
- FFR: pressure-derived estimate of flow impairment from which it was derived
- FFR with standard cut-points: suboptimal performance in guiding PCI
- “It is no longer tenable to delay the introduction of more comprehensive diagnostic strategies that aim to directly identify perfusion impairment for clinical decision making

Van de Hoef, et al EHJ 2015
Integrating MBF/MBFR Estimates into Clinical Reports

1. No increase in myocardial blood flow
2. Severely reduced increase in myocardial blood flow
3. Normal increase in myocardial blood flow
Question 1:

Which of the following parameters are reliable indicators that your patient has had an adequate stress when tested using dipyridamole/adenosine/regadenoson?

1. Increase in heart rate
2. Decrease in systolic blood pressure
3. Both an increase in heart rate and a decrease in systolic BP
4. Symptoms such as chest pain or dyspnea
5. All of the above
6. None of the above
Changes in HR and BP Do Not Identify Adenosine-Responders

Mishra et al. JACC 45: 553-558, 2005

348 pts without known CAD
N13-Ammonia
6-minute Adenosine study

Peak Myocardial Blood Flow (ml/min/gm)

Change in HR (beats/min)

Change in MAP (mmHg)

R = 0.10, P = 0.06

R = 0.04, P = 0.44

Mishra et al. JACC 45: 553-558, 2005
Non-Responders to Adenosine and Dipyridamole

Adenosine

- 25 pts with near nl coronaries
- IV adenosine (140 ug/kg/min)
- CF measured with intracoronary doppler
- Maximal hyperemia = 84%
- Near maximal hyperemia = 92%
- 8% failed to develop significant hyperemia

Adenosine reduces but does not totally overcome neurally-mediated sympathetic coronary arterial vasoconstriction

Wilson et al, Circ 1990; 82: 1595-1606
Non-Responders to Adenosine and Dipyridamole

- Rb-82 PET measurements of MBF in 50 normals
- All pts had low CAD risk & a normal high-level TMET
- Intravenous dipyridamole (0.56 mg/kg)
- Employed 3 different flow software programs
- By all 3 programs, 3/49 subjects (6%) had no flow augmentation

Sunderland et al, J Nucl Cardiol 2015 (On-line First)
CASE #1

Stress LVEF 60%; Rest LVEF 60%
Re-tested one-week later off caffeine for 24 hours
Interrelation of Coronary Calcification, Ischemia and Outcomes in Patients with Intermediate-High Lk of CAD

![Graphs showing the relationship between CAC score and serious events in nonischemic and ischemic patients.](Image)

**Source:** Schenker et al, Circulation. 2008;117:1693-1700
Annualized MACE by Extent of Coronary Calcification and Flow Reserve

901 patients with normal Rb-81 PET

Naya et al JACC 2013
Benefit of Noninvasive evaluation with a intermediate to high likelihood of CAD

• Effectively detects high risk patient
• Reduces use/risk of ICA/revascularization:
  – High rates of non-obstructive CAD
  – Risks: Dissection, hematoma, fistula, aneurysm, thrombus, MI, death
• If CAC added, allows for treatment of subclinical atherosclerosis
• If PET flow, adds microvascular disease
• Reduces unnecessary revascularization
Problems with ICA/FFR-Based Strategy for all patients with a intermediate to high likelihood of CAD

• Overuse of ICA:
  – High rates of non-obstructive CAD
  – Risks: vascular access, MI, death

• FFR
  – only applied in small proportion of patients
  – Possibility of false positive FFR
  – Possibility of a false negative
    • Missing risk of diffuse/microvascular disease
  – No accounting for size of hypoperfused zone
  – Guideline-thresholds for FFR: too high
  – unnecessary revascularization
  – Overestimation of likelihood of true ischemia (symptoms)
  – Reduced but still overused PCI
**Autoplaq: Automated method for quantitative plaque characterization**

- % Diameter Stenosis
- % Area Stenosis
- NCP, CP, total plaque volume/burden
- Low-density NCP plaque volume/burden
- % NCP/Total plaque Volume
- % Aggregate plaque volume
- Remodeling index
- Contrast density difference
- Minimum luminal area, lesion length

Quantitative plaque measurement

Plaque components by automated software

- Non-calcified
- Low-density
- Calcified

Volume (mm$^3$)

Burden (%) = \frac{\text{plaque volume}}{\text{vessel volume}}

Dey et al JCCT 2009, Dey et al JCCT 2014
Dey et al Radiology 2010
Quantitative plaque measurement

Remodeling Index = Maximum / proximal vessel area in lesion

Contrast density difference = Maximum difference in mean lumen HU/ area in lesion

Hell et al EJR 2015, Dey et al JCCT 2014
15-NH3 vs 99mTc for MBF Measurement

Nikolla et al; JNC 2014
Anger Camera MBF (Symbia)

Symbia
10 sec acq
10 mCi MIBI

Hsu et al
EJNMB 2014
Anger Camera MBF (Symbia)

Symbia
10 sec acq
10 mCi MIBI

Hsu et al
EJNMB 2014
Quantitative PET CFR

• Non-invasive quantification of global stress flow and CFR to define physiologic severity of focal CAD, 
  diffuse high risk CAD and microvascular disease.

• Coronary flow controls ischemic dysfunction, NOT pressure.

• Extensive literature documents PET predictive power and potential outcomes with PET directed 
  intervention.
Discordance between FFR and CFR

- CFR: ability to identify ischemia producing coronary stenoses AND prognostic value
- FFR: epicardial domain
- CFR: both epicardial and mycrovasculature
- 30-40% of vessels with equivocal angiographic severity have FFR and CFR discordance

Van de Hoef, et al EHJ 2015
CT Perfusion: Logistics

- 12 Lead EKG
- Adenosine Infusion pump
- Double-Head Injector

- 12 Lead EKG pre and post study
- Continuous BP and EKG monitoring
- 2 I.V. Lines (contrast and adenosine infusion)
Stress Perfusion Scan Modes

Static perfusion
Single dataset “single” phase

Dynamic perfusion

Altern. table position

Full coverage

Kurata, JCircJ 2005
Blankstein, JACC 2009

Hattori, JCircJ 1998 (EBCT)
Bamberg, Eur Radiol 2010 (DSCT)

George, Circ CV Img 2009

Courtesy of J Min
Computational fluid dynamics, is a branch of fluid mechanics that uses numerical analysis and algorithms to solve and analyze problems that involve fluid flows. Computers are used to perform the calculations required to simulate the interaction of liquids and gases with surfaces defined by boundary conditions using high-speed supercomputers.
Assessment of Coronary Flow Physiology by PET and CT

CCTA: Plaque, perfusion, FFRct

- All add to stenosis assessment
- Plaque
  - Little added effort
- Perfusion
  - Requires additional scan
- FFRct
  - Initial data promising
Strengths:
- Gold standard for ischemia
- Allows detection of diffuse hypoperfusion
  - Identifies diffuse high risk CAD and microvascular disease.
- Incremental prognostic information
- Normal study rules out high risk CAD
- Useful to detect inadequate vasodilation (caffeine)

Weaknesses in guiding decision for ICA
- Affected by diffuse atherosclerosis without stenosis, endothelial dysfunction, and microvascular disease