FFR Should be done in All Intermediate Lesions

Intracoronary Physiology *Beyond* Angiography

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Managing Stable CHDisease

Symptomatic 76 Female

42 Asymptomatic Male, Strong +ve F/Hx of CAD; neg MPI, Abnormal MSCT/Revascularization?

54% DS QCA
Most untreated plaques which become symptomatic have a large plaque burden which are detectable by IVUS but not by angiography. 

**PROSPECT Study**

68 male, non culprit STEMI

Non culprit lesion/RCA STEMI
A proposed shift in paradigm puts myocardial ischemia at the center of our approach; Critical Coronary stenosis as one of many contributors to myocardial ischemia.
Coronary Heart Disease: Integrating Structure & Function

- Pathology: Atherosclerosis
- Physiology: Ischemia - The Link to Mortality
2-yr Kaplan-Meier (KM) risk of ischemic stroke in the territory of the symptomatic carotid artery according to degree of carotid stenosis & angiographic appearance of the plaque surface in patients randomized to medical treatment only.

Rothwell P M et al. Stroke. 2000;31:615-621
Global Chi-Square Values
Incremental risk prediction beyond computed tomographic (CT) stenosis ≥50% when adding spotty calcification (SC); SC and low attenuation plaque (LAP); SC, LAP, and positive arterial remodeling (PR); SC, LAP, PR & % aggregate plaque volume (%APV).
FFR: Pressure/Not A Direct flow measurement

\[ \frac{P_d}{P_p} @ \text{Equalized Resistance} \]  
(Maximal dilatation)

\[ F_d = \frac{P_d}{R_d} \]  
\[ F_p = \frac{P_p}{R_p} \]

Lesions produce energy loss by friction, separation, turbulence.
Energy is taken out as heat and pressure loss:
Friction loss
Loss of distal pressure is related to blood flow

Microvessels
LVH
Flow @ Scarred area
Which Lesions Need FFR?

1329 lesions in the FFR-guided arm

FAME

~65%

~20%

~3%

FFR

50 - 70%

71 - 90%

91 - 100%

Need FFR

Discord

Stenosis classification by angiography

Tonino et al JACC 2009
Scatter plot showing relationship between angiographic stenosis grade and fractional flow reserve (FFR) readings for all measurements.

FFR resulted in a change in the number of vessels deemed significant and in need of revascularization in 32% of patients: important implications for routine clinical practice,

Managing Stable Disease

Symptomatic
76 Female

Non culprit lesion in a STEMI

FFR: 0.86
CFR?

FFR = 0.84
54% DS QCA

42 Asymptomatic Male, Strong +ve F Hx of CAD; neg MPI, Abnormal MSCT

54% DS QCA

68 male, non culprit STEMI

FFR=0.71

FFR=0.84
Stable CAD: Prognosis Beyond Angiographic Anatomy
Changing Paradigms

- Ischemia Fundamental mechanism & Target linking Atherosclerosis@ clinical events
- Physiologic assessment, FFR, sensitive and reproducible tool to assess “ischemia” beyond angiography
- Inducible Ischemia a predictor of high risk if not treated with revascularization

- Inducible Ischemia surrogate of plaque destabilization: Biologic Considerations!
- Evidence: Use of FFR in guiding selection of patients & lesions for treatment results in avoiding unnecessary procedures, reducing medical costs, & improving patient's clinical outcomes.
Discordance Between Ischemia & Stenosis, PINSS & NIPSS: Are We Ready for New Vocabulary?*

(1) Progressive Atherosclerosis

- Increase in isoprostanes
- Decrease in SOD

NADPH Oxidase

- Increase in O$_2^-$
- Decrease in nitric oxide

- Increase in lysoPC

- Increase in Lp-PLA2

(2) Inflammation

Detactable MPI or FFR-Verified ISCHEMIA

Endothelial Dysfunction

- Decrease in vasodilation
- Increase in vasoconstriction
Association of Coronary Stenosis and Plaque Morphology With Fractional Flow Reserve and Outcomes.

**IMPORTANCE:**
Obstructive coronary lesions with reduced luminal dimensions may result in abnormal regional myocardial blood flow as assessed by stress-induced myocardial perfusion imaging or a significant fall in distal perfusion pressure with hyperemia-induced vasodilatation (fractional flow reserve \[FFR\] ≤0.80). An abnormal FFR has been demonstrated to identify high-risk lesions benefitting from percutaneous coronary intervention while safely allowing revascularization to be deferred in low-risk lesions, resulting in a decrease in the number of revascularization procedures as well as substantially reduced death and myocardial infarction. While FFR identifies hemodynamically significant lesions likely to produce ischemia-related symptoms, it remains less clear as to why it might predict the risk of acute coronary syndromes, which are usually due to plaque rupture and coronary thrombosis.

**OBSERVATIONS:**
Although the atherosclerotic plaques with large necrotic cores (independent of the degree of luminal stenosis) are known to be associated with vulnerability to ACS syndromes, emerging evidence also suggests that they may induce greater rates of ischemia & reduced FFR compared with non-lipid-rich plaques also independent of the degree of luminal narrowing. It is proposed that the presence of large necrotic cores within the neointima may be associated with the inability of the vessel to dilate & may predispose to ischemia & abnormal FFR.

Ahmadi A et al. JAMA Cardiol. 2016
FFR Integrates Anatomy & Biology?
Ischemic FFR: What Does it Mean?

- Low perfusion pressure - ischemia
- Passive lesion site collapse - ischemia
- ?? Inflammation/Surrogate of ACS (FAME II)
- Vasa-vasora gradient of pressure - plaque rupture
- Validated diagnostic & therapeutic implications: FAME, FAMEII, French Registry, Korean experience .....

ACC Middle East Conference 2016
The prognosis of “non-ischemic” stenosis (FFR > 0.75) is excellent, the risk of “non-significant” stenosis or plaque to cause death or AMI is < 1% per year, and not decreased by stenting.
Event-free survival is shown by Kaplan-Meier curves. At 2 years, 76% of the patients were free from angina in the angiography-guided group compared with 80% in the FFR-guided group (p = 0.1).
Trends in the outcomes of percutaneous coronary intervention with the routine incorporation of fractional flow reserve in real practice

2699 patients before
2398 patients after routine use of FFR
Trends In The Outcomes of Percutaneous Coronary Intervention With The Routine Incorporation of Fractional Flow Reserve In Real Practice

FFR successfully measured in 1267 patients (1551 lesions)

A: Primary endpoint

B: Death from any causes

C: Death or myocardial infarction

D: Repeat revascularization
FAME 2, The primary end point composite of death, MI, or urgent revascularization

Prognostic Value of Fractional Flow Reserve: Linking Physiologic Severity to Clinical Outcomes

FFR demonstrates a continuous and independent relationship with subsequent outcomes, modulated by medical therapy versus revascularization. Lesions with lower FFR values receive larger absolute benefits from revascularization.

Measurement of FFR immediately after stenting also shows an inverse gradient of risk, likely from residual diffuse disease..

Risk / Benefit Continuum of FFR
Five published reports, 15000 lesions
Why Should FFR Should Be Done In Intermediate Lesions?

- **FFR Not Just A number**, Integrates several key elements of physiology, flow & Biology > Angiographic definition of Lesions
- Discordance Between Ischemia & Stenosis (PINSS & NIPSS)
- Functional assessment > anatomy (@outcome/Cost)
- ...should use FFR more routinely to select stable coronary patients, lesions, for PCI.
- CFR/FFR<sub>CT</sub> / On line FFR ....
- Judgment, Limitations, pitfalls! (LVH, ACS, Vessel, Nonviable myocardium)
Thank You!
In patients with stable chest pain and planned invasive coronary angiography, care guided by CTA and selective FFRCT was associated with equivalent clinical outcomes and QOL, and lower costs, compared with usual care over 1-year follow-up.

(The PLATFORM Study: Prospective Longitudinal Trial of FFRct: Outcome and Resource Impacts [PLATFORM])
The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) ; Eur J Cardiothorac Surg 2010;38:S1-S52

FFR guided PCI is recommended for detection of ischemia related lesion(s) when objective evidence of vessel related ischemia is not available

<table>
<thead>
<tr>
<th>Procedure</th>
<th>I</th>
<th>A</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Manual catheter thrombus aspiration should be considered during PCI of the culprit lesion in STEMI.</td>
<td>IIA</td>
<td>A</td>
<td>[204–208]</td>
</tr>
<tr>
<td>For PCI of unstable lesions, i.v. abciximab should be considered for pharmacological treatment of no-reflow.</td>
<td>IIA</td>
<td>B</td>
<td>[55,209,212]</td>
</tr>
<tr>
<td>Drug-eluting balloons(^d) should be considered for the treatment of in-stent restenosis after prior BMS.</td>
<td>IIA</td>
<td>B</td>
<td>[174,175]</td>
</tr>
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<td>Proximal embolic protection may be considered for preparation before PCI of SVG disease.</td>
<td>IIB</td>
<td>B</td>
<td>[214]</td>
</tr>
<tr>
<td>For PCI of unstable lesions, intracoronary or i.v. adenosine may be considered for pharmacological treatment of no-reflow.</td>
<td>IIB</td>
<td>B</td>
<td>[209]</td>
</tr>
<tr>
<td>Tornus catheter may be used for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting.</td>
<td>IIB</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Cutting or scoring balloons may be considered for dilatation of in-stent restenosis, to avoid slipping-induced vessel trauma of adjacent segments.</td>
<td>IIB</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>IVUS-guided stent implantation may be considered for unprotected left main PCI.</td>
<td>IIB</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Mesh-based protection may be considered for PCI of highly thrombotic or SVG lesions.</td>
<td>IIB</td>
<td>C</td>
<td>–</td>
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<tr>
<td>For PCI of unstable lesions, intracoronary nitroprusside or other vasodilators may be considered for pharmacological treatment of no-reflow.</td>
<td>IIB</td>
<td>C</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^d\) Class of recommendation.
\(^d\) Level of evidence.
\(^d\) References.

\(^d\) Recommendation is only valid for specific devices with proven efficacy/safety profile, according to the respective lesion characteristics of the studies.

DAPT = dual antiplatelet therapy; DES = drug-eluting stent; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft.
Invasive FFR & Noninvasive CFR In The Evaluation of Ischemia: The Future?

Adjusted Annualized Event Rate (%)

CFR High/No Revasc (n=79) 6.04% p=0.32
CFR High/PCI (n=70) 3.83% p=0.22
CFR High/CABG (n=17) 2.16% p=0.48
CFR Low/No Revasc (n=57) 11.52% p=0.001
CFR Low/PCI (n=84) 7.38% p=0.006
CFR Low/CABG (n=22) 0.88% p=0.37

* Adjusted for pretest clinical score, LV ejection fraction, LV ischemia, and coronary artery disease prognostic index.
† CFR denotes coronary flow reserve: high (≥1.6), low (<1.6).
‡ Early revascularization strategy denotes revascularization with percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or neither (No Revasc), within 90 days of noninvasive imaging.

FFR<sub>CT</sub> & Shear Stress assessment
In symptomatic patients with suspected CAD who required noninvasive testing, a strategy of initial CTA, as compared with functional testing, did not improve clinical outcomes over a median follow-up of 2 years.
CENTRAL ILLUSTRATION: The Future of Coronary Physiology

Patient with acute coronary artery disease (CAD)
- Culprit lesion(s)
  - Coronary physiology may support deferring percutaneous coronary intervention (PCI) in NSTEMI patients and augmenting PCI in STEMI patients
  - Not ready for clinical practice
  - Need randomized controlled trial (RCT)

Patient with stable CAD
- Non-culprit lesion(s)
  - Coronary physiology quantifies risk of future events and magnitude of revascularization benefit, thereby personalizing risk/benefit decisions
  - Future RCT of revascularization for focal, severe lesions has best chance of identifying a benefit for hard outcomes of death and myocardial infarction
  - Angina with FFR≤0.8 responds better to revascularization than medication

Angiogram
- FFR tracing
  - Diffuse disease carries an equal risk to focal lesions
  - Global CFR quantifies the burden of diffuse CAD (CFR<1.5 has the highest risk)
  - Future RCT in diffuse disease must compare coronary artery bypass grafting versus medical therapy

Angiogram
- PET image
  - Can produce refractory angina despite FFR>0.8
  - Because many therapies can be tried empirically without much cost or side-effects, this subset needs an RCT of expensive or more risky treatments showing a marked improvement