Functional assessment (invasive) of Coronary Circulation

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Potential conflicts of interest

- Consulting fees and honoraria on my behalf go to the Cardiovascular Research Center Aalst

- Contracted Research between the Cardiovascular Research Center Aalst and the following pharmaceutical and device companies:
  
  Ablynx, Astra Zeneca, BMS, Eli Lilly, GSK, Therabel, Abbott Vascular, Biotronik, Boston Scientific, Cordis J&J, Edwards, Medtronic, Orbus Neich, St Jude, Terumo

- Ownership Interest: Cardiovascular Research Center Aalst is co-founder of Cardio³BioSciences, a start-up company focusing on cell-based regenerative cardiovascular therapies
Why do we need functional assessment?
Event Rates after a Negative Functional Stress Testing  
Myocardial Perfusion Imaging or Stress Echocardiography

<table>
<thead>
<tr>
<th>Exercise Imaging Modality</th>
<th>n</th>
<th>Mean Follow-Up (Months)</th>
<th>Summary Event Rate After Negative Test (%) (95% CI)</th>
<th>Negative Predictive Value (%) (95% CI)</th>
<th>Annualized Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2,900</td>
<td>32</td>
<td>1.03 (0.70–1.48)</td>
<td>99.0 (98.5–99.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Women</td>
<td>1,443</td>
<td>32</td>
<td>0.69 (0.33–1.27)</td>
<td>99.3 (98.7–99.7)</td>
<td>0.33</td>
</tr>
<tr>
<td>Men</td>
<td>1,457</td>
<td>20</td>
<td>1.37 (0.84–2.12)</td>
<td>98.6 (97.9–99.2)</td>
<td>0.82</td>
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<tr>
<td>Echo</td>
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<tr>
<td>All</td>
<td>5,946</td>
<td>37.6</td>
<td>3.23 (2.70–3.82)</td>
<td>96.8 (96.2–97.3)</td>
<td>1.03</td>
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<tr>
<td>Women</td>
<td>2,547</td>
<td>37.6</td>
<td>2.34 (1.71–3.13)</td>
<td>97.7 (96.9–98.3)</td>
<td>0.75</td>
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<tr>
<td>Men</td>
<td>3,399</td>
<td>37.6</td>
<td>3.90 (3.12–4.81)</td>
<td>96.1 (95.2–96.9)</td>
<td>1.24</td>
</tr>
</tbody>
</table>

Myocardial Perfusion Imaging  
Stress Echocardiography
Annual risk of Cardiac Death and Myocardial Infarction

Metanalysis of SPECT MPI studies in nearly 70K patients

- Normal: 0.6%
- Abnormal: 5.9%

8-10 x higher risk for abnormal compared to normal
Extent of Functional Assessment abnormality and Cardiovascular Event Rate

- 314 patients with CAD
- After either PCI+OMT or OMT
- Myocardial perfusion imaging prior and again 6 months after treatment

SWISSI II Trial

201 patients with silent ischemia after a myocardial infarction
10 Year-Follow-Up

P Erne et al, JAMA 2007
Freedom from Chest-pain

Ischemic lesions (FFR < 0.75) treated by stenting

Pijls NH et al. JACC 1997
Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI) *

Authors/Task Force Members: William Wijns (Chairperson) (Belgium) *, Philippe Kolh

In summary, documentation of ischaemia using functional testing is strongly recommended before elective invasive procedures, preferably using non-invasive testing before invasive angiography
Frequency of stress tests to document ischemia prior to elective CAG+PCI

55.5% No stress testing
45.5% Stress testing

23887 Medicare patients undergoing elective CAG+PCI in 2004

GA Lin et al. JAMA 2008

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Referral to CAG after the initial consultation

Countries with Low Rate of CAG
- Positive Exercise Test
- Female Gender

Countries with High Rate of CAG
- Positive Exercise Test
- Female Gender
- Invasive Centre
- Symptom duration > 6 months
Frequency of Stress Testing to Document Ischemia Prior to Elective CAG+PCI

23887 Medicare patients undergoing *elective* CAG+PCI in 2004

G.A. Lin et al JAMA 2008
Functional assessment of coronary circulation

Technician: 
Test ind: 

DOB: 
ACCOUNT #: 

Referred by: 
ADMITTED: 
Unconfirmed 
EKG #: 

150 Hz 25.0 mm/s 10.0 mm/mV

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Clinical conditions in which non-invasive testing is difficult to interpret

1. During and after acute myocardial infarction
2. Obesity, bundle branch block, …
3. “Intermediate lesion”
4. Left main stenosis
5. Multivessel disease
6. …
Diagnostic accuracy of ECG-gated SPECT MPI in patients 3-vessel disease

Angiographic vessel disease defined as:
- ≥ 50% DS of LM
- ≥ 70% DS of LAD and LCX or RCA
How to proceed?
It is not the question *IF* stenting is indicated, but *WHERE* and *HOW MANY*
2D and 3D QCA

Diameter stenosis = 53%

LAO 43, CAUD 20
DS 53%, 14.0 mm
Pro 2.7 mm, 2.7 mm
Dis 2.7 mm, 2.6 mm
Bending Angle: 13

Diameter stenosis = 53%

QAngio XA 3D

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Courtesy of Shengxian Tu
Low-to-intermediate Risk

COURAGE
W.E. Boden et al NEJM 2007

Intermediate-to-high Risk

SYNTAX
F.W. Mohr et al Lancet 2013
Relationship between %DS and coronary flow

\[ y = 3.7 - 1.0 \times 10^{-2}x + 2.4 \times 10^{-4}x^2 - 6.0 \times 10^{-6}x^3 \]

\[ r = 0.89 \]

\[ \frac{\text{SQ DEV}}{\text{DEV}} = 0.345 \]

\[ y = 1.0 - 1.9 \times 10^{-2}x + 6.2 \times 10^{-4}x^2 - 5.2 \times 10^{-6}x^3 \]

\[ r = 0.84 \]

\[ \frac{\text{SQ DEV}}{\text{DEV}} = 0.021 \]
Relationship between %DS and coronary flow

Functional assessment of coronary circulation

KL Gould et al. Am J Cardiol 1974
Relationship between %DS and coronary flow

Hyperemic

Resting

KL Gould et al. Am J Cardiol 1974
Anatomy vs Physiology: the Chimeric Link

Statistical (mechanistic) relation but little clinical relation
Fractional Flow Reserve

**FFR =** ratio of hyperemic flow in the stenotic vessel to hyperemic flow in the same vessel but in the absence of the stenosis

**FFR =** extent to which (%) maximal myocardial flow is limited by the epicardial stenosis

During maximal hyperemia (i.e. during maximal transstenotic flow)

\[
FFR = \frac{Q^S_{\text{max}}}{Q^N_{\text{max}}} = \frac{P_d}{P_a}
\]
The relation between $P_d/P_a$ and $Q_S/Q_N$ is LINEAR during HYPEREMIA
The relation between $P_d/P_a$ and $Q_S/Q_N$ is **LINEAR during HYPEREMIA**

- 22 Patients with an isolated proximal LAD stenosis
- $H_2^{15}O$ PET maximal flow in LAD vs normal territories
- FFR within 24 hours
Validation of FFR in Humans (Step 1)

Proper validation of any index needs **2 steps:**

1. Searching for the threshold value in a selected population (sens, specif, NPV, PPV, ROC analysis)

2. Prospective validation in a population with unknown characteristics

Pijls et al, Circulation 1995
De Bruyne, Circulation 1996
Functional assessment of coronary circulation

Testing of FFR versus True Gold Standard

Creating a gold standard by Prospective Multitesting Sequential Bayesian Approach:

- Exerc testing = electrical index of ischemia
- MIBISpect = perfusion index of ischemia
- Dobutrex Echo = contractile index of ischemia

- reversal from positive before to negative after intervention, proves true positivity before and true negativity after test

Diagnostic accuracy of FFR =

\[
\left[\left(1-0.75\right) \times \left(1-0.8\right) \times (1-0.8)\right]^{-1} = 99\%
\]

3 unclassifiable patients (no intervention)

\[\rightarrow\] worst case scenario for FFR \[\rightarrow\] 93%

Pijls et al, NEJM 1996

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Threshold value of FFR to detect significant stenosis in humans

FFR

non-signif. 0.80 0.75 stenosis significant

FFR is the only functional index which has ever been validated versus a true gold standard. (Prospective multi-testing Bayesian methodology)

ALL studies ever performed in a wide variety of clinical & angiographic conditions, found threshold between 0.75 and 0.80

Diagnostic accuracy > 93%

Oldroyd et al, Circulation 2010
Clinical Outcome

- In stable patients with single vessel disease, stenting functionally non-significant stenoses does not improve clinical outcome as compared to deferring these stenoses to optimal medical treatment → → DEFER trial
DEFER: Clinical Outcome at 5 Years

Rate of Death/MI after 5 years

P = 0.002
P = 0.003
P = 0.21

DEFER: FFR \geq 0.75
PERFORM: FFR < 0.75

0 5 10 15 20

%
Clinical Outcome

- In stable patients with single vessel disease, stenting functionally non-significant stenosis does not improve clinical outcome as compared to deferring these stenoses to optimal medical treatment \(\Rightarrow\) \(\Rightarrow\) DEFER trial

- In patients with multivessel disease, an FFR-guided PCI strategy improves clinical outcome as compared with an Angio-guided strategy \(\Rightarrow\) \(\Rightarrow\) FAME trial
FAME trial

ABSOLUTE DIFFERENCE IN MACE-FREE SURVIVAL

Survival Free from Major Adverse Cardiac Events

Days since Randomization

1 month 2.9%  6 months 4.9%  12 months 5.1%

FFR-guided

Angio-guided

P Tonino et al NEJM 2009
FAME trial

ABSOLUTE DIFFERENCE IN MACE-FREE SURVIVAL

Survival Free from Major Adverse Cardiac Events

Days since Randomization

1 month 2.9%
6 months 4.9%
12 months 5.1%
24 months 4.7%

FFR-guided
Angio-guided
Clinical Outcome

- In stable patients with single vessel disease, stenting functionally non-significant stenosis does not improve clinical outcome as compared to deferring these stenoses to optimal medical treatment. ➔ ➔ DEFER trial

- In patients with multivessel disease, an FFR-guided PCI strategy improves clinical outcome as compared with an Angio-guided strategy. ➔ ➔ FAME trial

- In stable patients with at least one functional significant stenosis, FFR-guided PCI plus MT is associated with better clinical outcome as compared with MT alone. ➔ ➔ FAME 2 trial
FAME 2 TRIAL
Primary End Point

- PCI+MT vs. MT: HR 0.32 (0.19-0.53, p<0.0001)
- 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<0.0001)

Cumulative incidence (%)

Months after randomization

No. at risk
- OMT: 441, 414, 370, 322, 283, 253, 220, 192, 162, 127, 100, 70, 37
- PCI+OMT: 447, 414, 388, 351, 308, 277, 243, 212, 175, 155, 117, 92, 53
- Registry: 166, 156, 145, 133, 117, 106, 93, 74, 64, 52, 41, 25, 13

B De Bruyne et al NEJM 2012
FAME 2: 607 Patients on Medical Therapy
(1027 lesions, Median FU= 191 days)

Actual FFR value predicts the natural history of stenoses in patients with stable coronary disease

Barbato E for the FAME2 investigators ESC 2013
Take-home messages

- Evidences of a beneficial clinical outcome with FFR-guided revascularization strategy in different angiographic settings:
  - Isolated equivocal left main stenosis (n=230+51)
    - Hamilos, Circ 2009/Lindstaedt, Am Heart J 2006
  - Isolated prox left anterior descending artery (n=730)
    - Muller, JACC Cardiovasc Intv 2011
  - Small vessel disease (n=717)
    - Puymirat, Circ Cardiovasc Interv 2012
  - By-pass grafts (n=223)
    - Di Serafino, Am Heart J 2013
  - Bifurcations (n=91+75)
    - Koo, EHJ 2008/Kumsars, Eurointv 2012
  - Serial stenoses (n=131)
    - Kim, JACC Cardiovasc Intv 2012
  - Drug Eluting Stent Restenosis (n=49)
    - Nam, Am J Cardiol 2011
  - Post-stenting (BMS and DES) (n=750+80)
    - Pijls NHJ, Circ 2002/Nam, Am J Cardiol 2011
  - All comers, contemporary practice (n=7358)
    - Li J, EHJ 2013

>10000 patients
Level of Evidence of FFR

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

Class of Recommendation: I

Level of Evidence: A
New Diagnostic Strategies

• RIPCORD study

• French registry

• POST-IT
French registry

1075 consecutive patients undergoing diagnostic CAG

Change of Revascularization Strategy in 43% of the patients

E. Van Belle et al Circulation 2013
New Therapeutic Strategies

• CABG registry

• GRAFFITI trial

• FAME 3 trial
Functional assessment of coronary circulation

Angio-guided  
n=429

FFR-guided  
n=198

Toth G. et al. Circulation 2013
Clinical endpoints @ 36 months

MACE-free survival

- FFR-guided
- Angio-guided

$p = 0.908$

TVR-free survival

$p = 0.378$

MI-free survival

$p = 0.780$

Overall survival

$p = 0.137$
CCS II-IV @ 36 months

Baseline:
- ANGIO: 377 [88%], p=1.000
- FFR: 174 [88%], OR=1.000, 95% C.I. 0.597 to 1.675; p=1.000

Follow-up:
- ANGIO: 201 [47%], p<0.001
- FFR: 62 [31%], OR=1.948, 95% C.I. 1.362 to 2.786; p<0.001
GRAFFITI trial: GRaft Patency After FFR-guided vs Angio-guided CABG: a randomized clinical Trial

Hypothesis

FFR-guided CABG is associated with a lower rate of 1-year graft occlusion

PI: Emanuele Barbato MD, PhD
Cardiovascular Center Aalst, Belgium
GRAFFITI trial: GRaft Patency After FFR-guided vs Angio-guided CABG: a randomized clinical Trial

200 Patient with MVD
Significant LAD / LM lesion (FFR <0.80) / Angio >69%
AND at least one more stenosis (Angio 30-90%)

FFR measurements

FFR blinded HEART TEAM consultation
(Surgeons will be asked to identify by visual estimation the target vessels to be revascularized, number of anastomosis and grafts)

FFR-GUIDED CABG
(ie surgeons unblinded to FFR values)

ANGIO-GUIDED CABG
(ie surgeons blinded to FFR values)

12-mo GRAFT PATENCY (CCTA and/or CA)
FAME 3: A Comparison of FFR-guided PCI and CABG in Patients with Multivessel Coronary Artery Disease

Hypothesis:
FFR-guided PCI in MVD will result in similar outcomes to CABG

Design:
- Noninferiority design
- Clinically relevant difference of 5%

PI’s:
- Fearon WF (PI)
- Pijls NHJ (Co-PI)
- De Bruyne B (Co-PI)

All Comers with 3 VD (not involving LM)

Amenable to PCI/CABG and meet inclusion criteria
No exclusion criteria met and patient consents

Heart team identifies lesions for PCI/CABG
and then patient is randomized

FFR-Guided PCI with DES
Stent all lesions with FFR < 0.80
(n=750)

Perform CABG based on coronary angiogram
(n=750)

One Year follow-up for MACCE
(1 month, 3 and 5 year follow-up)

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Functional assessment of coronary circulation

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Can we obtain the same results but simplifying the technique?
• Adenosine-free pressure derived coronary functional indexes:
  • bSR (Piek)
  • iFR (Davies)
  • iFG (Indolfi)
  • Pd/Pa (Mammhas)

• Non-invasive FFR:
  • $\text{FFR}_{\text{CT}}$
Accepted Manuscript

Multicenter Core Laboratory Comparison of the Instantaneous Wave-Free Ratio and Resting $P_d/P_a$ with Fractional Flow Reserve: The RESOLVE Study

Allen Jeremias, MD, M Asrress, MA, BM BCH
Bernard De Bruyne, MD Justin E.
Davies, MBBA Javier

Davies, MBBA Javier Escaned,

MD Jan J. Piek, MD Nico H. Pijls,
Correlation between Pd/Pa and iFR

\[ R^2 = 0.95 \]
\[ \text{Pd}/\text{Pa} = 0.32 + 0.67 \text{iFR} \]
Moderate diagnostic accuracy

Figure 2

<table>
<thead>
<tr>
<th></th>
<th>iFR</th>
<th>$P_d/P_a$ for $FFR \leq 0.8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC [95% CI]</td>
<td>0.81 [0.79, 0.83]</td>
<td>0.82 [0.80, 0.84]</td>
</tr>
<tr>
<td>Cut-off Value</td>
<td>0.90</td>
<td>0.92</td>
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</tbody>
</table>
Adenosine-free pressure derived coronary functional indexes:

- bSR (Piek)
- iFR (Davies)
- iFG (Indolfi)
- Pd/Pa (Mammhas)

Non-invasive FFR:

- $\text{FFR}_{\text{CT}}$
1. Coronary flow meets myocardial demand at rest
2. Resistance of microcirculatory vascular bed at rest is inversely proportional to size of feeding vessel
3. Microcirculation has a predictable response to adenosine

Computational Flow Dynamics

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Functional assessment of coronary circulation

Case 1
LAD stenosis

CT

FFR $0.62$
= Lesion-specific ischemia

ICA and FFR

FFR $0.65$
= Lesion-specific ischemia

Case 2
RCA stenosis

CT

FFR $0.87$
= No ischemia

ICA and FFR

FFR $0.86$
= No ischemia

1. Min et al. JAMA 2012;308:1237-1245

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Diagnostic Accuracy of FFR\textsubscript{CT} : DeFacto

**Per-Patient**

- FFR\textsubscript{CT} 0.81 (95% CI 0.75, 0.86)
- CT 0.68 (95% CI 0.62, 0.74)

**Before/After Stenting**

- AUC
  - FFR\textsubscript{CT} 0.81 (95% CI 0.75, 0.86)
  - CT 0.68 (95% CI 0.62, 0.74)

**Diagnostic accuracy ≈ 80%**

Min JK et al JAMA 2012

Kim KH et al JACC Cv Intv 2014
FFR is the gold standard to assess ischemia

100% accuracy – “The Holy Grail”

- FFR (Hyperemia) ≥93%
- Resting Indexes + FFR$_{CT}$ (Resting Pd/Pa, iFR) 80%
- Angio 70%

Functional assessment of coronary circulation

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Two-Compartment Model of the Coronary Circulation

The coronary angiogram detects only 5% of the total coronary tree.
Two-Compartment Model of the Coronary Circulation

Epicardial Artery

Microvasculature

FFR

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Two-Compartment Model of the Coronary Circulation

Epicardial Artery

Microvasculature

FFR

CFR
Two-Compartment Model of the Coronary Circulation

Epicardial Artery

Microvasculature

FFR

IMR

CFR

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Features of IMR

- Specific for the microvasculature
- Quantitative and reproducible
- Predictive of outcomes
- Independent from changes in heart rate, blood pressure and contractility (Ng, Circulation 2006)
Coronary Thermodilution Principle

**Temperature**

- $T_{mn}$ (hyper)
- $T_{mn}$ (rest)

**Time**

Functional assessment of coronary circulation

Coronary Thermodilution

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Derivation of IMR

- Resistance = Δ Pressure / Flow

- $1 / \text{Tmn} @ \text{Flow}$

- $\text{IMR} = \text{Distal Pressure} / (1 / \text{Tmn})$

- $\text{IMR} = \text{Distal Pressure} \times \text{Tmn at maximal hyperemia}$

Note: Must incorporate coronary wedge pressure to account for collateral flow if significant epicardial stenosis is present
Clinical use of IMR

- Assessment of myocardial perfusion in STEMI patients
- Predictive of left ventricular remodeling after primary PCI
Assessment of myocardial perfusion in STEMI patients

41 STEMI pts randomized either to pPCI plus IC STPK or pPCI alone

Sezer M, NEJM 2007
Predictive value after primary PCI

29 STEMI patients undergoing pPCI and IMR assessment

Acute setting

3 months after

Fearon W, JACC 2008
Clinical use of IMR

- Assessment of myocardial perfusion in STEMI patients
- Predictive value after primary PCI
- Assessment of microvascular damage after elective PCI
Assessment of microvascular damage after elective PCI

- 50 patients randomized to conventional stenting with predilatation versus direct stenting
- IMR measured after PCI and correlated with troponin release

Cuisset T, JACC 2008
Clinical use of IMR

- Assessment of myocardial perfusion in STEMI patients
- Predictive value after primary PCI
- Assessment of microvascular damage after elective PCI
- Assessment of pharmacologic strategies to prevent microvascular damage after elective PCI
Assessment of pharmacologic strategies to prevent microvascular damage after elective PCI

ProMicro trial

Mangiacapra & Barbato, JACC 2013
Conclusions

• Functional assessment of the coronary circulation enables the identification of the patients at increased risk of cardiovascular events

• With equivocal or absent objective evidence of vessel-related ischemia, FFR measurement is recommended to guide revascularization

• The latter when adopted eventually translates into an improved clinical outcome of the patients