Quantitative PET/CT Measures of Coronary Flow Reserve with Existing and Novel Tracers
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<table>
<thead>
<tr>
<th>Tracer</th>
<th>Abbreviation</th>
<th>Physical Halflife</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen-15 Water</td>
<td>$H_2^{15}O$</td>
<td>2.4 min</td>
</tr>
<tr>
<td>Nitrogen-13 Ammonia</td>
<td>$^{13}\text{NH}_4^+$</td>
<td>9.8 min</td>
</tr>
<tr>
<td>Rubidium-82 Chloride</td>
<td>$^{82}\text{Rb}^+$</td>
<td>78 sec</td>
</tr>
</tbody>
</table>
Quantification of Myocardial Blood Flow (MBF) by PET Imaging: Technical and Methodological Aspects

(Saraste A et al. JNC 2012)
PET Myocardial Perfusion Imaging

N-13 Ammonia  Rubidium=82  O=15 Water

(Schindler TH et al. JACC Img 2010)
Advantages and disadvantages of Positron-Emitting Tracers

Oxygen-15 Water

Advantages:

- net-tracer uptake perfectly correlates with myocardial blood flow also in the high range of coronary flows (“no roll-off phenomenon”)

  ⇒ in principle, perfectly suited for MBF quantification

- short physical half-life (2.4 minutes)

  ⇒ Measurements can be repeated at short intervals of 10 to 15 minutes.
Disadvantages:

- 15O-water distributes into the water spaces of myocardium and blood pool.

  ⇒ necessitates a subtraction of the blood pool from the 15O water images (blood pool imaging: 15O water or 11C-labeled red blood cells).

- Subtraction of the blood pool from the 15O-water images, rapid clearance of 15O-water and its short half-life (2.4 min).

  ⇒ Statistically low-count images of the myocardium.
Advantages:

- selectively retained by the myocardial cells and physical half-life of 9.8 min
  ⇒ statistically high count 13N-ammonia images of the myocardium
- retention of N-13 ammonia by myocardial cells
  ⇒ affords the application of a 2-compartment model to reliably quantify MBF in ml/g/min
Disadvantages:

- relatively long physical half-life of approximately 9.8 min.
  \[ \text{\Rightarrow necessitates longer time intervals (\approx 45 minutes) between repeat assessments of MBF.} \]

- non-linear net-tracer uptake in particular in the higher coronary flow range ("roll-off phenomenon").
  \[ \text{\Rightarrow 2 - compartment tracer kinetic model to quantify MBF in ml/g/min needs to compensate for the "roll-off phenomenon."} \]
Advantages:

- ultra - short physical half-life of 82-Rb ($\approx 76$ seconds)
  
  $\Rightarrow$ serial investigations of myocardial perfusion at short time intervals (i.e. 10 minutes)

- retention of 82-Rb by myocardial cells
  
  $\Rightarrow$ statistically high count 82-Rb images of the myocardium and MBF quantification

- On-site cyclotron is not necessary (82-Sr / 82-Rb generator)
Disadvantages:

- ultra - short physical half-life of 82-Rb (≈ 76 seconds)
  ⇒ injection of relatively a relatively high dose of 82-Rb necessary for statistically high count 82-Rb images.

- non-linear net-tracer uptake in particular in the higher coronary flow range (“roll-off phenomenon”).
  ⇒ 1- or 2 - compartment tracer kinetic model to quantify MBF in ml/g/min needs to compensate for the “roll-off phenomenon.

⇒ High patient volume needed (cost/effectivness). (82-Sr / 82-Rb generator function ≈ 4 weeks).
Novel PET tracer: Flurpiridaz F18 (BMS-747258-02) PET

Stress-induced perfusion defect anterior and antero-septo-apical: comparison to 99mTc-SPECT

(Maddahi J et al. JNC 2012)
Advantages:

- relatively long physical half-life of \( \approx 110 \) min.
  \( \Rightarrow \) Flurpiridaz exhibits high resolution and extraction characteristics similar to N-13 ammonia

- Less non-linear net-tracer uptake in particular in the higher coronary flow range ("roll-off phenomenon") than N-13 ammonia and 82 Rubium.
  \( \Rightarrow \) Myocardial blood flow quantification.

- Cyclotron independent!
Flurpiridaz F18

Disadvantages:

- relatively long physical half-life of ≈ 110 min.
  \[ \Rightarrow \] 2-days protocol or 1 day protocol with 3x higher dose injection for second perfusion measurement.

  \[ \Rightarrow \] Radiotracer correction for myocardial blood flow quantification of second exam is necessary.
Protocols for Clinical Cardiac PET/CT

- ECG-gated imaging
- Multiframe or dynamic imaging
- List-mode imaging

(Di Carli MF J Nucl Med 2007; 48:783)
CTAC: CT-based attenuation correction
• Most common clinical approach
• Scan duration:
  82-Rb ~ 5 min and N-13 ammonia ~ 20 min
• Gated frames ~ 8-16

• Disadvantage: no quantification of myocardial blood flow (MBF) and, thus, myocardial flow reserve (MFR)
Multiframe or Dynamic Imaging

- Radionuclide Injection
  - CT-scout
  - CTAC
  - Dynamic rest emission
  - Gated rest emission
  - Prescan delay
  - Dynamic stress emission
  - pharm stress
  - Dynamic stress emission
  - CTAC
Multiframe or Dynamic Imaging

- Imaging begins with bolus injection of 82-Rb (7-8 min) or N-13 ammonia (20min)
- **Advantage:** MBF and, thus, MFR quantification!

- **Disadvantage:** separate 82-Rb injection to obtain ECG-gated images for the assessment of cardiac function
List-Mode Imaging

Radionuclide Injection

CT-scout  CTAC  Dynamic rest emission  Gated rest emission
(N-13 ammonia ~4 min)  (~15 min)

Radionuclide Injection

pharm stress  Dynamic stress emission  Gated stress emission  CTAC
(N-13 ammonia ~4 min)  (~15 min)
List-Mode Imaging

Ideal approach!
⇒ single radiotracer injection and image acquisition!

• Multiple image reconstruction (summed, ECG-gated, and multiframe or dynamic)
⇒ allows the examinations of
  - myocardial perfusion (static image after 20 min)
  - MFR (dynamic frames ~ 4 min)
  - cardiac function
N-13 Ammonia PET in a 58 Old Asymptomatic Diabetic Patient

(Schindler TH et al, JACC Cardiovasc Imaging 2010)
Compartment Models for Tracers of MBF Estimates in ml/g/min

Serially Acquired Images of a Bolus Transit of N-13 Ammonia

2-Compartment Model for N-13 Ammonia

(Schelbert HR et al., Circulation 1981)
Through fitting of the time activity curves with the operational equation formulated by the 2-compartment tracer kinetic model, estimates of MBF in ml/g/min are obtained.
Myocardial Flow Reserve (MFR) = Vasodilator Capacity of the Coronary Circulation

\[ MFR = \frac{MBF \text{ during hyperemia}}{MBF \text{ at rest}} \]

(a) Increasing age and microvascular dysfunction due to cardiovascular risk factors hyperemic MBF↓ ⇒ MFR ↓

(b) Resting MBF dependent on metabolic demand (or myocardial workload) !: e.g. heart rate ↑ and/ or arterial blood pressure ↑⇒ resting MBF↑ ⇒ MFR ↓

(MBF=myocardial blood flow as determined with PET)
Added Value of MFR in the Identification of Flow-Limiting Lesions

Coronary Angiography

Three vessel disease

LAD: 100% stenosis
LCX: 85% stenosis
RCA: 50% stenosis

(Schindler TH. JACC Cardiovasc Imaging 2010)
Coronary Angiography Unmasking Multivessel Disease

Left Coronary Tree
- LAD: 100%
- LCx: >80%
- rMFR: 1.20

Right Coronary Tree
- 50%
- rMFR: 1.35
Coronary Revascularization

1) Re-opening of the chronic LAD occlusion with stent deployment?

2) PCI of LAD and LCx with stenting?

3) CABG of all three main territories?
PET: Is myocardial flow quantification a clinical reality?

⇒ List of different software packages which are commercially available.

⇒ Keep in mind: FDA-Approval!

Saraste A. JNC 2012 (review)
Imaging Protocol of 82 Rb PET/CT or PET Myocardial Perfusion Imaging

Yoshinaga K et al. Journal of Cardiology 2010
Dipyridamole stress and rest 82Rb PET/CT images in a 56 year old obese (BMI≈33kg/m2) patient

In obese individuals and women:

Sensitivity: 95%
Specifity: 90%

Optimal attenuation correction with CT!

(Di Carli MF Circulation 2007)
Anterolateral Perfusion Defect on Stress-Rest 82-Rb PET?

(Di Carli MF J Nucl Med 2007)
Incorrect attenuation coefficients during tomographic reconstruction to area of LV myocardium overlying lung field on CT transmission scan

Up to 40% Misalignment possible! (Gould KL et al. J Nucl Med 2007)
Correct Transmission-Emission Alignment
Normal 82-Rb Myocardial Perfusion study

(Di Carli MF J Nucl Med 2007)
Gated Rest-Stress 82-Rb Myocardial Perfusion PET

Multivessel CAD with stenoses > 70 %
Unmasked with gated PET

⇒ Gated PET at “Peak Stress“ !

(Dorbala S. J Nucl Med 2007)
Extent of Angiographic CAD and Delta Change in LVEF as determined by gated 82-Rb PET

(Dorbala S. J Nucl Med 2007)
Coronary Vasodilator Capacity related to Stenosis


(DiCarli MF et al. Circulation 1995)
Stress-Induce Myocardial Ischemia, invasively-determined Coronary Flow Reserve (CVR) and Fractional Flow Reserve (FFR)

TABLE 2. Stress Testing and Directly Measured Coronary Blood Physiology

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Ischemic Test</th>
<th>CVR</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PV+</th>
<th>PV−</th>
<th>Accuracy</th>
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<tr>
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<td>Adeno/dipy MIBI</td>
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<td>82</td>
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<td>100</td>
<td>77</td>
<td>89</td>
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<td>Joye</td>
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<td>30</td>
<td>Exercise thallium</td>
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<td>92</td>
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<td>92</td>
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<tr>
<td>Danzi</td>
<td>32</td>
<td>30</td>
<td>Dipy echo</td>
<td>&lt;2.0</td>
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<td>84</td>
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<tr>
<td>Schulman</td>
<td>31</td>
<td>35</td>
<td>Exercise ECG</td>
<td>&lt;2.0</td>
<td>95</td>
<td>71</td>
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FVR

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Ischemic Test</th>
<th>CVR</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PV+</th>
<th>PV−</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Pijls</td>
<td>13</td>
<td>45</td>
<td>4-Test standard</td>
<td>&lt;0.75</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>88</td>
<td>93</td>
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<tr>
<td>De Bruyne</td>
<td>25</td>
<td>60</td>
<td>Exercise ECG</td>
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<td>Bartunek</td>
<td>33</td>
<td>37</td>
<td>Dobu/exercise echo</td>
<td>&lt;0.68</td>
<td>95</td>
<td>90</td>
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</table>

Adeno indicates adenosine; dipy, diprydamole; MIBI, sestamibi scan; dobu, dobutamine; PV+/PV−, predictive value positive/negative; and echo, echocardiogram.

(Kern MJ. Circulation 2000)
Added Diagnostic Value of MFR

- Stress-induced myocardial perfusion defect commonly signifies the «culprit lesion» in multivessel CAD disease.

- Adding regional MFR (<1.7) may also unmask flow-limiting downstream effects of lesions with intermediate severity (>70% diameter stenosis). (Thresholds still matter of ongoing research!)

- Keep in mind: Reductions of MFR are related to increases in epicardial and microcirculatory resistance and, thus, non-specific!

- In this case, however, adding regional MFR translated a functional 1-vessel to a three vessel disease and the patient was referred to CABG.
Integration of PET Perfusion Imaging and MFR

Stress-rest Myocardial Perfusion PET

- Normal Perfusion
  - MBF Quantification
    - MFR >2.5
    - MFR 2.0-2.5
    - MFR <2.0
- Abnormal Perfusion
  - Coronary Angiography: Epicardial Lesions 50-70% Stenosis

Coronary Circulatory Function

- Normal
- Borderline
- Abnormal

Preventive Medical Intervention
- -
- +
- ++

MBF Quantification

- MFR >2.5
- MFR 2.0-2.5
- MFR <2.0

Revascularization
- -
- +
- ++

(Schindler TH et al. JACC Cardiovasc Imaging 2010)
• 62 year old type 2 diabetic patient.

• The patient was referred for N-13 ammonia PET/CT stress-rest perfusion imaging as pre-operative risk stratification (bioprosthese for abdominal aneurysm).

• N-13 ammonia PET/CT perfusion imaging was performed with dipyridamole-induced hyperemic flow increases.
N-13 ammonia PET/CT Perfusion Images

Short Axis

Stress
Rest

Vertical Long Axis

Stress
Rest

Horizontal Long Axis

Stress
Rest
Left Coronary Angiography and Regional MFR

- LAD: 60-70% stenosis
- Marginal branch of the LCx: 100%
- RCA: lesion <50% (not shown)

<table>
<thead>
<tr>
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<th>PET-determined MBF (ml/g/min)</th>
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<tbody>
<tr>
<td></td>
<td>rest</td>
<td>stress</td>
<td>MFR</td>
</tr>
<tr>
<td>LAD:</td>
<td>1.00</td>
<td>1.77</td>
<td>1.77</td>
</tr>
<tr>
<td>LCX:</td>
<td>1.07</td>
<td>1.32</td>
<td>1.23</td>
</tr>
<tr>
<td>RCA:</td>
<td>0.91</td>
<td>1.95</td>
<td>2.14</td>
</tr>
</tbody>
</table>

Clinical decision: PTCA and stent employment of the proximal LAD stenosis in view of abnormally reduced MFR.
• Stress-induced regional perfusion defect identifies «culprit lesion» in multivessel CAD disease. In this patient infero-lateral perfusion defect due to occlusion of Marginal branch of LCx.

• Abnormally-reduced MFR in the LAD territory gave an argument for PTCA and stent employment of the proximal LAD stenosis of intermediate range.

• Conceptually, preventive medical care with statine and/or ACE-Inhibitors could have improved coronary microcirculatory dysfunction leading to a normalization the MFR! This again could have avoided the coronary intervention.

⇒ Reductions of MFR are related to increases in epicardial and microcirculatory resistance and, thus, **non-specific!**
Myocardial Perfusion, Flow Reserve and Prognosis

(Herzog B et al, J Am Coll Cardiol 2009;54:150)
Myocardial Perfusion, Flow Reserve and Prognosis

Prediction of MACE by CFR

Prediction of Cardiac Death by CFR

(P<0.05)

(Herzog B et al, J Am Coll Cardiol 2009;54:150)
Myocardial Flow Reserve by PET and Outcomes in Ischemia

(Ziadi C. et al. JACC 2011)
Annualized Cardiac Mortality by Tertiles of MFR and Categories of Myocardial Ischemia

(Murthy VL et al. Circulation 2011)
Risk Reclassification by adding MFR

Pre-CFR Risk
- Low (1100): 16% (16%) 84% (84%)
- Intermediate (898): 17% (17%) 34% (34%
- High (785): 49% (49%) 3% (3%)

Post-CFR Risk
- Low (927): 0.2% (0.2%) 1.7% (1.7%)
- Intermediate (445): 0.2% (0.2%) 2.3% (2.3%)
- High (149): 0.0% (0.0%) 4.4% (4.4%)
- Low (22): 0.0% (0.0%) 3.4% (3.4%)
- Intermediate (89): 0.0% (0.0%) 10.5% (10.5%)

(Murthy VL et al. Circulation 2011)
Integrative Index of Vascular Health!

Hypercholesterolemia / Dyslipidemia

Arterial Hypertension
Smoking

Postmenopause
Insulin resistance

Genetic Susceptibility!

Coronary Circulatory Dysfunction

Diabetes Mellitus

Cardiovascular Risk Stratification?
HMG-CoA Reductase Inhibitors and Regional Myocardial Blood Flow

Improvement in coronary vasodilator capacity and/or collateral flow after follow-up.

(Schelbert HR: Atlas Nuclear Cardiology)
Vasomotor Function, Medical Intervention and Outcome

(Kitta J et al, J Am Coll Cardiol 2009)
Myocardial Perfusion or Flow Reserve with PET/CT

- Reflect Alterations in Coronary Circulatory Function Associated Early Atherosclerosis
- Contain Predictive Information on Future Coronary Events
- Contribute to Identify and Characterize CAD in Multivessel Disease.
- Allow Monitoring of Beneficial Effects of Therapeutic Risk Factor Modification that may Improve the Long-Term Cardiovascular Outcome
Conclusions

The aim of image-guided and individualized cardiovascular therapy may be attained in the near future by PET technology.