13N-ammonia and H2 15O PET/CT of Myocardial Perfusion

P. Raijmakers, VUmc Amsterdam

1. Introduction

Coronary artery disease (CAD) is a major cause of death in the modern world. The diagnosis of CAD is mainly focused on the detection of obstructive epicardial coronary stenosis. Positron emission tomography (PET) is widely accepted as a diagnostic technique which can be used to assess myocardial perfusion. Three PET tracers have been validated (Table 1) for assessing myocardial perfusion. H2 15O is characterized by different kinetic properties as compared with 13NH3, and 82Rb. The latter tracers become metabolically trapped while cleared from the intravascular compartment, yielding excellent qualitatively gradable imaging due to high tissue-to-background ratios. In contrast, H2 15O is a freely diffusible, metabolically inert tracer that promptly reaches equilibrium between blood and tissue, thus is not accumulated in the myocardium. As a consequence, direct radiotracer distribution images of H2 15O are of little diagnostic value. In recent years, however, improved techniques and parametric imaging by automated software packages, have generated qualitatively gradable H2 15O perfusion images comparable to 13NH3, and 82Rb. Meta-analyses comparing myocardial PET to SPECT and cardiovascular magnetic resonance imaging (CMR), demonstrate that MPI with PET yields the highest diagnostic accuracy. The majority of clinical studies on the diagnostic accuracy of detection of obstructive CAD have been conducted with static uptake images of 82Rb and 13NH3. Weighted sensitivity, specificity, NPV, and PPV were 91, 86, 81, and 93%, respectively. Furthermore, cardiac PET imaging can potentially be used to study subendocardial perfusion. Myocardial ischaemia occurs principally in the subendocardial layer, whereas conventional myocardial perfusion imaging provides no information on the transmural myocardial blood flow (MBF). In a recent H2 15O PET study a significantly decreased subendocardial MBF was found in ischaemic myocardium.

Table 1. Characteristics of H2 15O, 13NH3, and 82Rb for PET myocardial perfusion imaging.

<table>
<thead>
<tr>
<th></th>
<th>H2 15O</th>
<th>13NH3</th>
<th>82Rb</th>
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<tbody>
<tr>
<td>Half-life</td>
<td>123 sec</td>
<td>9.97 min</td>
<td>76 sec</td>
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Mandatory on-site production of the tracers given their short physical half-life.
**Production**

<table>
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<tr>
<th>Cyclotron</th>
<th>Cyclotron</th>
<th>Generator</th>
</tr>
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<tbody>
<tr>
<td>Equipment have lower installation and maintenance costs</td>
<td></td>
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</table>

**Kinetics**

<table>
<thead>
<tr>
<th>Freely diffusible, metabolically inert</th>
<th>Metabolically trapped in myocardium</th>
<th>Metabolically trapped in myocardium</th>
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<tr>
<td>Complete extraction from bloodpool into myocardial tissue renders H$_2^{15}$O an ideal perfusion tracer</td>
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**Mean positron range in tissue**

<table>
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<tr>
<th>1,1 mm</th>
<th>0,4 mm</th>
<th>2,8 mm</th>
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<tr>
<td>$^{82}\text{Rb}$'s higher tissue penetration depth limits the spatial resolution of the perfusion imaging</td>
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**Dose**

| 0,00093 mSv/MBQ | 0,002 mSv/MBq | 0,0034 mSv/MBq |

Quantification of myocardial perfusion with PET

Dynamic PET acquisition protocols allows quantification of stress and rest myocardial blood flow (MBF in units of mL·min$^{-1}$·g$^{-1}$ and calculation of coronary flow reserve (CFR). Literature suggests that quantitative analysis is superior to static uptake image evaluation. Furthermore, hyperaemic MBF assessment seems to outperform CFR for the diagnosis of obstructive CAD, which may result in stress only protocols. Thresholds for what should be considered pathological hyperaemic MBF or CFR are unfortunately not uniform. MBF is related to age, sex, and cardiovascular risk profile. Perfusion thresholds will be tracer specific and may require correction for individual patient characteristics. Ongoing studies are targeted to addressing these issues. Use of a single cut-off may be a simplification of the underlying pathophysiology, as MBF is determined by the combination of epicardial coronary flow and microvascular vasomotor function. In terms of prognosis, the quantitative nature of PET has shown incremental value. The extent and severity of (reversible) perfusion defects diagnosed with PET holds strong prognostic information beyond traditional cardiovascular risk factors. Of particular interest is the fact that apparently normal perfusion images with a homogenous tracer distribution can be reclassified based on diffusely abnormal hyperaemic MBF or CFR. Several studies have revealed that this subset of patients is at increased risk for future cardiac events.
Coronary computed tomography angiography (CCTA)

CCTA is a promising tool for non-invasive evaluation of coronary anatomy. Pooled analysis of the currently available literature demonstrates a high sensitivity (96%) and negative predictive value (NPV, 94%), rendering it a clinically useful tool to rule out obstructive coronary stenosis. However, despite its non-invasive nature and high sensitivity, CCTA is not able to determine the haemodynamic relevance for a given epicardial coronary stenosis. Indeed, several studies have clearly demonstrated the disconcordancy between the anatomical and functional aspects of coronary atherosclerosis, emphasizing the role of myocardial perfusion imaging (MPI) in the non-invasive evaluation of CAD. In recent years there has been a fast evolution of the hybrid imaging technique, incorporating multidetector-row CT with PET detector techniques.

Hybrid Cardiac PET/CT

Hybrid cardiac PET/CT imaging enables the near simultaneous evaluation of coronary anatomy and (quantitative) myocardial perfusion in a single scanning session, which can be performed within 30-60 min. Although the number of diagnostic studies on the accuracy of hybrid cardiac PET/CCTA is small, they demonstrate an improved diagnostic performance as compared with either imaging modality alone. Three studies have evaluated the diagnostic value of hybrid PET/CCTA over stand-alone CCTA and PET MPI. Hybrid imaging is shown to be particularly useful for enhancing specificity and PPV of CCTA, although significant rises in these parameters can also be observed when compared to PET alone.

The hybrid cardiac PET/CT imaging results, generally categorize patients into one of four groups. The first category represents patients with a normal CCTA and a normal MBF/CFR, confirming a normal coronary circulation. Secondly, a normal CCTA combined with a decreased MBF and/or CRF represents coronary microvascular dysfunction. Hence, a completely normal CCTA can rule out epicardial atherosclerotic disease, but may need confirmation of normal hyperaemic MBF and CFR to rule out coronary microvascular dysfunction.

An abnormal CCTA, compatible with obstructive CAD, warrants confirmation with perfusion imaging to determine its actual haemodynamic relevance and MPI should act as a gatekeeper for further invasive testing. A third group, representing patients with an abnormal CCTA and a decreased MBF, may benefit from revascularization. Not only the presence of ischaemia, but also the extent of the jeopardized area is important. Revascularization in patients with mild to moderate ischaemic burden (i.e. <10% of the myocardium) does not alter outcome, yet alleviate symptoms. Satisfactorily medically controlled anginal symptoms therefore justify a conservative approach and a potentially hazardous invasive procedure should be deferred. Drug refractory angina and/or large ischaemic burden, seems to warrant revascularisation. This topic is, however, still a matter of debate and further studies are needed. Lastly, patients with an abnormal CCTA and a normal MBF may benefit from optimal medical treatment.

With the implementation of cardiac hybrid PET/CT protocols, a more pragmatic referral of patients to the catheterisation laboratory may be achieved, thus minimising the need for invasive diagnostic procedures.

2. Methodology

This review is based on available scientific literature on the subject.
3. Indications

Hybrid PET/CT:
Evaluation of patients with an intermediate likelihood of CAD, for diagnosis of CAD, including location and severity of CAD and extent of ischaemic area.

Additional indications

Myocardial Perfusion PET:
- Assessment of regional perfusion in the presence of obstructive coronary artery disease

Absolute contraindications for adenosine stress myocardial perfusion imaging with PET:
- Unstable angina/acute coronary syndrome,
- Severe bronchospasms
- Second or third-degree heart block or sick sinus syndrome, without a pacemaker
- Symptomatic aortic stenosis and hypertrophic obstructive cardiomyopathy
- Systolic blood pressure <90 mmHg
- Cerebral ischaemia
- Persantin/dipyridamol use in the 24 h before adenosine stress test

Relative contraindications to vasodilator stress tests are:
- Severe sinus bradycardia (heart rate <40/min)
- Severe atherosclerotic lesions of extracranial artery

4. Relation to other diagnostic procedures

Several techniques can be used to evaluate CAD, including CCTA, cardiac MRI, myocardial SPECT and stress echocardiography. Owing to the quantitative nature, routine use of attenuation correction, higher spatial resolution, shorter study protocols, and lower radiation exposure, cardiac PET surpasses SPECT MPI both in terms of diagnostic accuracy and patient convenience. However, comprehensive ‘head to head’ studies comparing diagnostic accuracy of imaging techniques regarding the detection of CAD and abnormal MBF are scarce. More clinical research is needed regarding efficient diagnostic strategies for detection of obstructive CAD. Furthermore, there are three PET perfusion tracers available for myocardial perfusion imaging: $^{13}$NH$_3$, H$_2$O and $^{82}$Rb. These are all short-lived tracers that require on-site production. $^{82}$Rb has the advantage of being generator produced, avoiding the need for an on-site cyclotron. However, $^{82}$Rb’s longer positron range and lower count statistics due to the ultra-short half-life (76 sec) compromise image resolution (see also table 1 for comparison of the PET tracers).

5. Medical information necessary for planning

- Information which should be available prior to planning of the procedure:
- Indication for diagnostic cardiac PET and/or CT
- Body mass
- Ability to lie still for approximately 45 min (in case of H$_2$O PET/CT procedure)
- Presence of metallic implants
- Renal function
- Allergy to iodinated contrast agents
- Heart rhythm
- (cardiac) medication (interaction with adenosine, preparation before adenosine PET, rhythm control during CCTA)
- contra indications for beta-blocker use
- pulmonary function including presence of COPD/asthma
- clinical instability (recent myocardial infarction, decompensated heart failure, hypotension)
- informed consent

6. Radiopharmaceutical
   Tracer: $\text{H}_2\text{O}^{15}$O
   Activity: 370 MBq (for PET detection in 3 dimensional mode)
   (dose depends upon characteristics of PET imaging system, above mentioned dose is for 3D mode)
   Administration: Intravenous injection, bolus

   Alternatively:
   Tracer: $^{13}$N-ammonia
   Activity: 370-925 MBq (dose depends upon characteristics of PET system, e.g. 2D-3D mode, crystal)
   Administration: Intravenous injection, bolus or <30 sec of infusion

7. Radiation safety
   Pregnancy is a contraindication for cardiac PET/CT procedure
   Lactation:
   Due to the short half time of $^{15}$O /$^{13}$N-ammonia only a short interruption of lactation is required
   Radiation exposure:
   $\text{H}_2\text{O}^{15}$O: 0,00093 mSv/MBq
   $^{13}$N-ammonia: 0,0034 mSv/MBq

8. Patient preparation/essentials for procedure
   - Refrain from intake of products containing caffeine or xanthine 24 h prior to the scan. This includes beverages such as cola, coffee, tea, energy drinks, foods such as chocolate and medication including analgesia containing caffeine.
   - Dipyridamol/ Persantin should be stopped 24 h prior to adenosine infusion.
   - Cardiac medication which may interfere with the stress test (eg adenosine) should be stopped temporarily. The decision to interrupt cardiac medication should be left to the referring physician. Interruption should ideally be five pharmacological half-lives of relevant drug. This applies for nitrates, but may also apply for beta-blockers and calcium antagonists.
   - Severe COPD: consider an alternative stress test.
   - The patient should be haemodynamically stable for >48 h prior to the stress test.
   - Additional preparation: ECG monitoring, blood pressure monitoring

9. Acquisition and processing
   Rest/ stress myocardial $\text{H}_2\text{O}^{15}$O-PET/CT imaging protocol:
   - Scout CT for patient positioning
- Two min after starting the intravenous adenosine infusion 140 µg. kg⁻¹. min⁻¹: 370 MBq of H₂¹⁵O injection as a 5 mL (0.8 mL.s⁻¹) bolus, immediately followed by a 35 ml saline flush (2 ml. s⁻¹).

A 6-min PET scan starts simultaneously with the administration of H₂¹⁵O. This dynamic scan sequence is immediately followed by a respiration-averaged low dose CT scan (LD-CT) to correct for attenuation (55 mAs; rotation time, 1.5 sec; pitch, 0.825; collimation, 16 ∙ 0.625; acquiring 20 cm in 37 sec) during normal breathing. The adenosine infusion is terminated after the LD-CT.

After an interval of 10 min, to allow for decay of radioactivity and washout of adenosine, an identical rest PET sequence can be performed under resting conditions. There is evidence supporting stress MBF only protocols, therefore the rest MBF PET study is optional.

Image reconstruction: 3D row action maximum likelihood algorithm of 22 frames (1x10, 8x5, x 10,x15, 3x20, 2x30, and 2x60 seconds), including all appropriate corrections. Parametric MBF images are generated and quantitative analysis can be performed using specifically developed software, Cardiac VUer. Other software packages such as Carimas are available, and yield comparable quantitative results. MBF is expressed in mL· min⁻¹ ·g⁻¹ of perfusable myocardium and is analysed according to the 17-segment model of the American Heart Association (AHA). Subsequently, MBF is calculated for each of the three vascular territories (right coronary artery [RCA], left anterior descending artery [LAD], and circumflex artery [CX]). The coronary flow reserve (CFR) is defined as the ratio between stress (hyperaemic) and rest (baseline) MBF.

10. Interpretation

The image analysis is performed on both global left ventricular uptake and on a per-vessel basis. Additionally, a semi-quantitative approach can be used. Myocardial perfusion PET images are divided into 17 segments (AHA model), and each segment is scored using a 5 point scale ranging from 0 (normal perfusion), 1 (mildly reduced perfusion), 2 (moderately reduced perfusion), 3 (severely reduced perfusion), to 4 (absent perfusion). This yields a summed perfusion score for both stress and rest myocardial perfusion images.

After gated acquisition, LV parameters including LV volumes and EF can be used for the overall interpretation. Quantitative analysis adds information to static uptake image grading. Reported thresholds of what should be considered pathologically decreased stress MBF or CFR are not consistent. Hence, different thresholds should be used for the different PET tracers. The optimal cut-off value for detecting flow-limiting stenosis of coronary arteries by means of H₂¹⁵O PET hyperaemic MBF is ≤ 2.3 ml.min⁻¹.g⁻¹ and that for CFR is ≤ 2.5.

In addition, hyperaemic MBF assessment seems to outperform CFR in the diagnosis of obstructive CAD, enabling stress only PET protocols offering a further reduction of PET imaging time.

The hybrid cardiac PET/CT imaging results generally categorise patients into one of four groups:

1. patients with a normal CCTA and normal MBF/CFR, confirming normal coronary circulation.
2. patients with a normal CCTA combined with decreased MBF and/or CRF, indicating coronary microvascular dysfunction
3. patients with an abnormal CCTA and decreased MBF/CFR, indicating vessels with significant stenosis of the coronary arteries.
4. patients with an abnormal CCTA and normal MBF, indicating vessel(s) with non-significant stenosis of coronary arteries.

11. Report
Patient-specific information
• Relevant history, current medication
• Indication for the study
• Type of study (radiopharmaceuticals, acquisition protocol, type of metabolic preparation), haemodynamics and ECG
• Image description (visual, semi-quantitative, quantitative evaluation)
• Quantitative data, including rest MBF, stress MBF, Coronary Flow Reserve, preferably for the three coronary territories (LAD, RCA and CX)
• For hybrid PET/CCTA: correlation between MBF and the main findings of the CCTA (e.g. location of significant coronary obstructive disease and downstream MBF)
• For gated acquisition: LV volumes, EF and wall motion abnormalities
• Conclusion

12. Literature


• Knaapen P, de Haan S, Hoekstra OS, et al. Cardiac PET-CT: advanced hybrid imaging for the detection of coronary artery disease. Netherlands heart journal : monthly journal of the Netherlands Society of
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