^{13}N-ammonia and $H_2{}^{15}O$ 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. $H_2{}^{15}O$ is characterized by different kinetic properties as compared with $^{13}NH_3$, and ^{82}Rb. 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, $H_2{}^{15}O$ 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 $H_2{}^{15}O$ are of little diagnostic value. In recent years, however, improved techniques and parametric imaging by automated software packages, have generated qualitatively gradable $H_2{}^{15}O$ perfusion images comparable to $^{13}NH_3$, and ^{82}Rb. 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 ^{82}Rb and $^{13}NH_3$. 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 $H_2{}^{15}O$ PET study a significantly decreased subendocardial MBF was found in ischaemic myocardium.

Table 1. Characteristics of $H_2{}^{15}O$, $^{13}NH_3$, and ^{82}Rb for PET myocardial perfusion imaging.

	$H_2{}^{15}O$	$^{13}NH_3$	^{82}Rb	Comment
Half-life	123 sec	9,97 min	76 sec	Mandatory on-site production of the tracers given their short physical half-life

Production	Cyclotron	Cyclotron	Generator	Generator equipment have lower installation and maintenance costs
Kinetics	Freely diffusible, metabolically inert	Metabolically trapped in myocardium	Metabolically trapped in myocardium	Complete extraction from bloodpool into myocardial tissue renders $H_2{}^{15}O$ an ideal perfusion tracer
Mean positron range in tissue	1,1 mm	0,4 mm	2,8 mm	^{82}Rb 's higher tissue penetration depth limits the spatial resolution of the perfusion imaging
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 $mL \cdot min^{-1} \cdot g^{-1}$ 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 multidectector-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 conformation 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 laesions 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: $^{13}NH_3$, $H_2{}^{15}O$ 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 $H_2{}^{15}O$ 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:	$H_2{}^{15}O$
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-3 D 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:

$H_2{}^{15}O$: 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 anaelgesia 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 termporarily. 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 $H_2{}^{15}O$ -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 $H_2{}^{15}O$ 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 $H_2{}^{15}O$.
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 $mL \cdot min^{-1} \cdot g^{-1}$ 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 $H_2{}^{15}O$ PET hyperaemic MBF is ≤ 2,3 $ml \cdot min^{-1} \cdot g^{-1}$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

- Harms HJ, Knaapen P, de Haan S, Halbmeijer R, Lammertsma AA, Lubberink M. Automatic generation of absolute myocardial blood flow images using [15O]H2O and a clinical PET/CT scanner. European journal of nuclear medicine and molecular imaging. 2011;38(5):930-9.
- Harms HJ, Nesterov SV, Han C, et al. Comparison of clinical non-commercial tools for automated quantification of myocardial blood flow using oxygen-15-labelled water PET/CT. Eur Heart J Cardiovasc Imaging. 2014;15(4):431-41.
- Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis. Journal of the American College of Cardiology. 2012;60(18):1828-37.
- Parker MW, Iskandar A, Limone B, et al. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: a bivariate meta-analysis. Circulation Cardiovascular imaging. 2012;5(6):700-7.
- Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. Journal of the American College of Cardiology. 2012;59(19):1719-28.
- Danad I, Raijmakers PG, Knaapen P. Diagnosing coronary artery disease with hybrid PET/CT: It takes two to tango. J Nucl Cardiol. 2013;20(5):874-90.
- Danad I, Raijmakers PG, Harms HJ, et al. Impact of anatomical and functional severity of coronary atherosclerotic plaques on the transmural perfusion gradient: a [15O]H2O PET study. Eur Heart J. 2014;35(31):2094-105.
- Fiechter M, Ghadri JR, Gebhard C, et al. Diagnostic value of 13N-ammonia myocardial perfusion PET: added value of myocardial flow reserve. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2012;53(8):1230-4.

- Hajjiri MM, Leavitt MB, Zheng H, Spooner AE, Fischman AJ, Gewirtz H. Comparison of positron emission tomography measurement of adenosine-stimulated absolute myocardial blood flow versus relative myocardial tracer content for physiological assessment of coronary artery stenosis severity and location. JACC Cardiovascular imaging. 2009;2(6):751-8.
- Kajander SA, Joutsiniemi E, Saraste M, et al. Clinical value of absolute quantification of myocardial perfusion with (15)O-water in coronary artery disease. Circ Cardiovasc Imaging. 2011;4(6):678-84.
- Muzik O, Duvernoy C, Beanlands RS, et al. Assessment of diagnostic performance of quantitative flow measurements in normal subjects and patients with angiographically documented coronary artery disease by means of nitrogen-13 ammonia and positron emission tomography. Journal of the American College of Cardiology. 1998;31(3):534-40.
- Danad I, Raijmakers PG, Appelman YE, et al. Hybrid imaging using quantitative H215O PET and CT-based coronary angiography for the detection of coronary artery disease. J Nucl Med. 2013;54(1):55-63.
- Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol. 2013;62(18):1639-53.
- Danad I, Raijmakers PG, Appelman YE, et al. Coronary risk factors and myocardial blood flow in patients evaluated for coronary artery disease: a quantitative [15O]H2O PET/CT study. European journal of nuclear medicine and molecular imaging. 2012;39(1):102-12.
- Schindler TH, Cardenas J, Prior JO, et al. Relationship between increasing body weight, insulin resistance, inflammation, adipocytokine leptin, and coronary circulatory function. Journal of the American College of Cardiology. 2006;47(6):1188-95.
- Dorbala S, Di Carli MF, Beanlands RS, et al. Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry. Journal of the American College of Cardiology. 2013;61(2):176-84.
- Marwick TH, Shan K, Patel S, Go RT, Lauer MS. Incremental value of rubidium-82 positron emission tomography for prognostic assessment of known or suspected coronary artery disease. The American journal of cardiology. 1997;80(7):865-70.
- Ziadi MC, Dekemp RA, Williams KA, et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. Journal of the American College of Cardiology. 2011;58(7):740-8.
- Yoshinaga K, Chow BJ, Williams K, et al. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? Journal of the American College of Cardiology. 2006;48(5):1029-39.
- Schenker MP, Dorbala S, Hong EC, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. Circulation. 2008;117(13):1693-700.
- Herzog BA, Husmann L, Valenta I, et al. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. Journal of the American College of Cardiology. 2009;54(2):150-6.
- Farhad H, Dunet V, Bachelard K, Allenbach G, Kaufmann PA, Prior JO. Added prognostic value of myocardial blood flow quantitation in rubidium-82 positron emission tomography imaging. European heart journal cardiovascular Imaging. 2013.
- Fukushima K, Javadi MS, Higuchi T, et al. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical 82Rb PET perfusion imaging. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2011;52(5):726-32.

- Naya M, Murthy VL, Foster CR, et al. Prognostic interplay of coronary artery calcification and underlying vascular dysfunction in patients with suspected coronary artery disease. Journal of the American College of Cardiology. 2013;61(20):2098-106.
- Di Carli MF, Hachamovitch R. New technology for noninvasive evaluation of coronary artery disease. Circulation. 2007;115(11):1464-80.
- Schuijf JD, Wijns W, Jukema JW, et al. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. Journal of the American College of Cardiology. 2006;48(12):2508-14.
- Gaemperli O, Schepis T, Koepfli P, et al. Accuracy of 64-slice CT angiography for the detection of functionally relevant coronary stenoses as assessed with myocardial perfusion SPECT. European journal of nuclear medicine and molecular imaging. 2007;34(8):1162-71.
- Meijboom WB, Van Mieghem CA, van Pelt N, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. Journal of the American College of Cardiology. 2008;52(8):636-43.
- Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. Journal of the American College of Cardiology. 2010;55(25):2816-21.
- Kajander S, Joutsiniemi E, Saraste M, et al. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. Circulation. 2010;122(6):603-13.
- Groves AM, Speechly-Dick ME, Kayani I, et al. First experience of combined cardiac PET/64-detector CT angiography with invasive angiographic validation. European journal of nuclear medicine and molecular imaging. 2009;36(12):2027-33.
- Gaemperli O, Husmann L, Schepis T, et al. Coronary CT angiography and myocardial perfusion imaging to detect flow-limiting stenoses: a potential gatekeeper for coronary revascularization? European heart journal. 2009;30(23):2921-9.
- Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation. 1998;97(6):535-43.
- Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. The New England journal of medicine. 2007;356(15):1503-16.
- Group BDS, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. The New England journal of medicine. 2009;360(24):2503-15.
- Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation. 2008;117(10):1283-91.
- Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation. 2003;107(23):2900-7.
- Danad I, Raijmakers PG, Harms HJ, et al. Effect of cardiac hybrid (1)(5)O-water PET/CT imaging on downstream referral for invasive coronary angiography and revascularization rate. Eur Heart J Cardiovasc Imaging. 2014;15(2):170-9.
- 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

Cardiology and the Netherlands Heart Foundation. 2010;18(2):90-8.

- Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2006;13(1):24-33.
- Kaufmann PA, Camici PG. Myocardial blood flow measurement by PET: technical aspects and clinical applications. J Nucl Med. 2005;46(1):75-88.
- Beanlands RS, Youssef G. Diagnosis and prognosis of coronary artery disease: PET is superior to SPECT: Pro. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2010;17(4):683-95.
- Bengel FM, Higuchi T, Javadi MS, Lautamaki R. Cardiac positron emission tomography. Journal of the American College of Cardiology. 2009;54(1):1-15.
- Danad I, Uusitalo V, Kero T, et al. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H2O PET imaging. J Am Coll Cardiol. 2014;64(14):1464-75.