International Journal of Cardiology 167 (2013) 1737–1749

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Assessment of myocardial perfusion and viability by Positron Emission Tomography

Constantinos Anagnostopoulos [a,*], Alexandros Georgakopoulos [a], Nikoletta Pianou [a], Stephan G. Nekolla [b]

[a] Centre for Clinical Research, Biomedical Research Foundation of the Academy of Athens, Greece
[b] Nuklearmedizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universitaet Muenchen, Germany

ARTICLE INFO

Article history:
Received 5 July 2012
Received in revised form 30 October 2012
Accepted 4 December 2012
Available online 11 January 2013

Keywords:
Coronary artery disease
PET
Perfusion
Viability

ABSTRACT

An important evolution has taken place recently in the field of cardiovascular Positron Emission Tomography (PET) imaging. Being originally a highly versatile research tool that has contributed significantly to advance our understanding of cardiovascular physiology and pathophysiology, PET has gradually been incorporated into the clinical cardiac imaging portfolio contributing to diagnosis and management of patients investigated for coronary artery disease (CAD). PET myocardial perfusion imaging (MPI) has an average sensitivity and specificity around 90% for the detection of angiographically significant CAD and it is also a very accurate technique for prognostication of patients with suspected or known CAD. In clinical practice, Rubidium-82 (^{82}Rb) is the most widely used radiopharmaceutical for MPI that affords also accurate and reproducible quantification in absolute terms (ml/min/g) comparable to that obtained by cyclotron produced tracers such as Nitrogen-13 ammonia (^{13}N-ammonia) and Oxygen-15 labeled water (^{15}O-water). Quantification increases sensitivity for detection of multivessel CAD and it may also be helpful for detection of early stages of atherosclerosis or microvascular dysfunction. PET imaging combining perfusion with myocardial metabolism using ^{18}F-Fluorodeoxyglucose (^{18}F FDG), a glucose analog, is an accurate standard for assessment of myocardial hibernation and risk stratification of patients with left ventricular dysfunction of ischemic etiology. It is helpful for guiding management decisions regarding revascularization or medical treatment and predicting improvement of symptoms, exercise capacity and quality of life post-revascularization. The strengths of PET can be increased further with the introduction of hybrid scanners, which combine PET with computed tomography (PET/CT) or with magnetic resonance imaging (PET/MRI) offering integrated morphological, biological and physiological information and hence, comprehensive evaluation of the consequences of atherosclerosis in the coronary arteries and the myocardium.

1. Introduction

Positron Emission Tomography (PET) is a nuclear medicine modality, which for many years has been employed as a highly sophisticated research tool only in centers with access to cyclotron facilities. A shift in the use of PET imaging from the research to clinical setting has taken place recently, as a result of the greater availability of PET scanners (mainly to support cancer services) and the increasing documentation of PET's clinical efficacy. PET scanners are currently available in a hybrid form, combining PET with computed tomography (CT) or magnetic resonance imaging (MRI) offering a unique opportunity for a comprehensive noninvasive evaluation of the consequences of atherosclerosis both in the coronary arteries and the myocardium and translating advances in molecular imaging into humans. This review covers the current developments and future directions of PET imaging, emphasizing the role of PET on the assessment of myocardial perfusion and viability. It discusses the radiopharmaceuticals which are used for performance of clinical studies and also the stress tests and imaging protocols as well as the modality's usefulness in the evaluation of coronary artery disease (CAD), from its early detection to heart failure. Issues around cost effectiveness and comparisons with other imaging modalities are also discussed.

2. Assessment of myocardial perfusion

2.1. Selection of patients for PET myocardial perfusion imaging

Both the ACC/AHA/ASNC clinical guidelines and the position statement on advanced noninvasive [1] cardiac imaging produced jointly by the Canadian Cardiovascular and Imaging societies [2] recommend PET myocardial perfusion imaging (MPI) for diagnosis and/or risk stratification of CAD patients who have had nondiagnostic, noninvasive imaging tests, or when there is discrepancy between a test's results and clinical diagnosis (Class I and evidence level B). Patients with left bundle brunch block (LBBB) or ventricular pacing may also benefit from PET MPI (Class IIa for ACC/AHA/ASNC but Class I for the more recent Canadian joint position statement, level of evidence B for both). It should also be used as a first line examination in patients who may be prone to attenuation

* Corresponding author at: Centre for Clinical Research, Biomedical Research Foundation of the Academy of Athens, 4 Soranou Ephessiou Street, 11527, Athens, Greece. Tel.: +30 210 6597 126, +30 210 6597 067; fax: +30 210 6597 502.
E-mail address: cdanagnostopoulos@bioacademy.gr (C. Anagnostopoulos).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2012.12.009

artifacts (e.g. obese patients or women) that could lead to an equivocal result on another test (Class I and evidence level B, according to the Canadian joint position statement). PET MPI can be used as the initial test for the detection as well as the extent and location of myocardial ischemia (Class IIa for ACC/AHA/ASNC but Class I according to the Canadian joint position statement (level of evidence B)).

2.1.1. Principles of PET imaging

PET studies are based on the use of tracers labeled with isotope emitting positrons. Positrons travel a very short distance within matter. After absorption of their kinetic energy they undergo an annihilation reaction with an electron, the result of which is the creation of two gamma photons of 511 keV emitted in almost opposite directions. These are sensed by a ring of detectors and, if an event is sensed in opposing detectors at the same time, they are presumed to have come from annihilation somewhere along the line between the detectors. PET has better spatial resolution (4–7 mm) than single photon emission computed tomography (SPECT) (>10 mm), higher sensitivity, and ability to measure tracer distribution in absolute terms as a function of time [3,4]. Contemporary PET scanners are equipped also with CT capabilities and more recently with MRI, thus allowing a comprehensive functional and anatomical assessment of the cardiovascular system.

2.1.2. PET radiotracers

A number of positron emitting radiopharmaceuticals can be used as tracers of myocardial perfusion. The most common are Rubidium-82 (^{82}Rb), Nitrogen-13 ammonia (^{13}N-ammonia) and Oxygen-15 labeled water (^{15}O-water) (Table 1). ^{82}Rb is a potassium analog like thallium-201 and is the most widely used radiopharmaceutical in clinical practice for MPI with PET [5]. It has a very short physical half-life (76 s) but it is produced by a commercially available elution generator with a 4 to 5 week shelf life thus allowing performance of PET MPI studies in centers without access to cyclotron. After an intravenous injection, ^{82}Rb rapidly crosses the capillary membrane and is extracted from plasma by myocardial cells via the Na+/K+ ATPase pump, by an extraction which is similar to that of thallium-201 and lower to that of ^{13}N-ammonia and ^{15}O-water. ^{13}N-ammonia is also administered intravenously and has a physical half-life of 9.96 min. Once inside the myocyte, ^{13}N-ammonia is incorporated into the glutamine pool and becomes metabolically trapped. The main disadvantage of ^{13}N-ammonia is that it requires an on-site cyclotron and a radiochemistry synthesis capability as well. ^{15}O-water (also a cyclotron produced tracer) can be administered either intravenously or by inhalation of $^{15}CO_2$ with rapid transformation to water by carbonic anhydrase in the lungs. More recently, a novel myocardial perfusion imaging tracer has been developed (^{18}F-labeled Flurpiridaz). This agent is a structural analog of pyridaben and binds to mitochondrial complex 1 with high affinity [6]. It has a high first-pass extraction fraction of 94%, and is currently being evaluated in phase 1 and 2 clinical studies. Beyond the tracer kinetics that allow very accurate and reproducible quantification of myocardial perfusion, at least in the experimental setting, the 110-min half-life of ^{18}F is an additional benefit as it permits a radiopharmaceutical distribution as a single-unit dose on a daily basis.

Table 1
PET radiotracers used for cardiac imaging and their characteristics.

Radiotracer	Physical half life	Production	On site cyclotron
Rubidium-82	76 s	Strontium-82 generator	Not required
^{13}N-ammonia	9.96 min	Cyclotron	Required
^{15}O-water	2 min	Cyclotron	Required
^{18}F-Fluorodeoxyglucose	119 min	Cyclotron	Not required
^{18}F Flurpiridaz	119 min	Cyclotron	Not required

2.1.3. Quantification

In the clinical setting, PET is the gold standard for quantifying myocardial perfusion in absolute terms (ml/min/g) both at rest and stress. This is because PET has a high sensitivity and temporal resolution which allows fast dynamic imaging of tracer kinetics and extensively validated algorithms for accurate correction of photon attenuation. Global and regional myocardial perfusion is measured by compartmental (usually one or two tissue compartments) tracer kinetic models which are then combined with appropriate corrections for physical decay of the radioisotope, partial volume-related underestimation of the true myocardial tissue concentrations and spillover of radioactivity between the left ventricular blood pool and the myocardium. ^{15}O-water is the ideal tracer as it diffuses freely across plasma membranes and exhibits a linear relationship between uptake and flow at high flow rates. Mathematical modeling provides precise measurements of myocardial perfusion, although images of regional perfusion are difficult to obtain because of left ventricular (LV) blood pool activity. ^{13}N-ammonia also offers robust quantitative assessment of myocardial perfusion along with good quality images. This is due to a combination of high first-pass myocardial extraction fraction (EF), (above 80%), long biological half-life because of trapping of ^{13}N-ammonia in the myocardial cells in the form of ^{13}N-glutamine and relatively long physical half-life of the ^{13}N isotope [7]. Although only a small fraction of the tracer diffuses back into the intravascular space, its retention by the myocardium has a non-linear inverse relationship with blood flow [5]. ^{82}Rb exhibits a lower first-pass extraction and a more prominent nonlinear myocardial uptake than ^{13}N-ammonia with increasing blood flow that can lead to relatively lower myocardial contrast resolution images and underestimation of blood flow at high flow rates. However, with appropriate corrections for flow dependent changes in net tissue extraction, ^{82}Rb compares reasonably well with ^{13}N-ammonia [8] or ^{15}O-water in absolute measurements of myocardial perfusion and it is therefore an attractive option for hospitals without easy access to a cyclotron [9]. Irrespective of tracer used, quantification measurements are highly reproducible, as intra and interobserver analysis demonstrates, with correlation coefficient (r) values above 0.95 for the former regarding both rest and stress perfusion estimates and 0.87 for interobserver correlation [8,10,11].

2.1.4. Stress tests

Pharmacological stress is the preferred method of inducing hyperemia. Adenosine or dipyridamole is used and in case of contraindications to vasodilators, stress is performed with dobutamine. Novel pharmacological stressors have also been introduced recently targeting the adenosine A_{2A} receptors responsible for the coronary vasodilator effect of adenosine and minimizing the usual side effects of adenosine or dipyridamole. Exercise stress testing can also be performed when ^{13}N-ammonia is used as a perfusion tracer (because of the relatively long physical half life) but it is more challenging with ^{82}Rb, because of its very short physical half-life [3,4]. Finally, a cold pressor test (CPT) can also be performed where the patients immerse their left hand in ice water usually for 60 s and the tracer is injected while the test continues for another 60 s to permit trapping of tracer in the myocardium. CPT is used to assess the health of the vascular endothelium alone as opposed to the stress test performed with the vasodilators, which provides information on the vasomotor function that combines both the endothelial and the smooth muscle cell vasodilator function. CPT has a different action compared to vasodilators as it is based on sympathetic stimulation. Release of norepinephrine from stimulated sympathetic neurons activates a-adrenoceptors on the endothelium that mediate the release of nitric oxide. In the presence of an intact endothelium, this leads to a 30–65% increase in MBF compared to baseline levels. a-Adrenergic stimulation of vascular smooth muscle cells that causes vasoconstriction is normally counteracted, however if endothelial integrity is impaired, it prevails over the endothelium-derived vasodilatation [12–14]. In experienced hands, CPT is strongly reproducible (interobserver correlation, $r = 0.78$