Annals of Nuclear Cardiology Vol. 5 No. 1 73–76

REVIEW ARTICLE－DEBATE ARTICLES: WHICH PET FLOW TRACER IS THE BEST FOR MBF QUANTIFICATION?

A New Era of Myocardial Perfusion Imaging: ^{18}F PET Tracer

Mitsuru Hirano, PhD[1)], Rudolf A. Werner, MD[2), 3)] and Takahiro Higuchi, MD, PhD[1), 2), 3)]

Received: March 1, 2018/Revised manuscript received: March 28, 2018/Accepted: April 4, 2018
J-STAGE advance published: July 31, 2018

Abstract

Myocardial perfusion imaging (MPI) using advanced PET technology is increasingly used for non-invasive detection and evaluation of coronary artery disease (CAD), but is still limited for clinical use. Recently, ^{18}F labeled PET perfusion tracers have been actively developed as a novel class of PET MPI agents to overcome the disadvantages of conventional PET MPI tracers (^{15}O-labelled water, ^{13}N-ammonia, and ^{82}Rb chloride). This review summarizes the advantages and the feasibility of recent developed ^{18}F labeled tracers in clinical practice.
Keywords: ^{18}F-Flurpiridaz, ^{18}F labeled tracer, Coronary artery disease (CAD), Myocardial perfusion imaging (MPI), PET
Ann Nucl Cardiol 2019; 5 (1): 73–76

Currently, single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) remains the mainstay of risk stratification of coronary artery disease (CAD). The most frequently employed radiotracers for SPECT MPI are ^{201}Tl, ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin. PET MPI is becoming an increasingly attractive alternative for clinical routine application. In principle, PET has a higher count sensitivity and higher temporal and spatial resolution than SPECT (1). ^{15}O-labelled water, ^{13}N-ammonia, and ^{82}Rb chloride are available for clinical use, but the routine clinical use of PET MPI is still limited, particularly due to the short half-life of conventional PET MPI tracers. The drawbacks of short half-life radiotracers inherit the requirement of either a cost-intensive generator or an onsite cyclotron for production. Furthermore, due to short half-lives, these tracers are only suitable for use in conjunction with pharmacologic stress, but not with physical exercise stress. Recently, ^{18}F labeled PET perfusion tracers has been actively developed as a new class of PET MPI agent to overcome these disadvantages. The longer half-life of ^{18}F, compared with other radionuclides (110 min for ^{18}F, 76 sec for ^{82}Rb chloride, 2.1 min for ^{15}O-labelled water, 10 min for ^{13}N-ammonia), may open avenues to make the tracer available as a unit dose from regional cyclotron centers and allow the use in conjunction with treadmill exercise testing. The short positron range of ^{18}F (1.03 mm for ^{18}F, 8.6 mm for ^{82}Rb chloride, 4.14 mm for ^{15}O-labelled water, 2.53 mm for ^{13}N-ammonia) would result in considerably high spatial resolution.

Delivery of ^{18}F labeled tracers from regional centers

The radiotracers ^{15}O-labelled water, ^{13}N-ammonia, and ^{82}Rb chloride are clinically established for PET MPI. Because of a cyclotron dependency of ^{15}O-labelled water and ^{13}N-ammonia, their clinical use for PET MPI is limited to a few centers with on-site cyclotron (Figure 1a). This limitation could be overcome by the increasing use of ^{82}Rb chloride as it can be eluted from a commercially available ^{82}Strontium generator (Figure 1b). However, the generator is expensive and must be replaced every month, limiting the use of ^{82}Rb chloride to large centers that have the volume of referrals to justify the cost (2). On the other hand, ^{18}F tracers with longer radioactive half-lives can be distributed by a central cyclotron facility in a manner similar to ^{18}F-fluoro-2-deoxy-D-glucose (FDG), allowing for the ordering of only the needed dosages per day (Figure 1c) (3).

doi: 10.17996/anc.18-00056

1) Department of Bio Medical Imaging, National Cardiovascular and Cerebral Research Center, Suita, Osaka, Japan
2) Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany
3) Comprehensive Heart Failure Center, University Hospital Würzburg, Würzburg, Germany

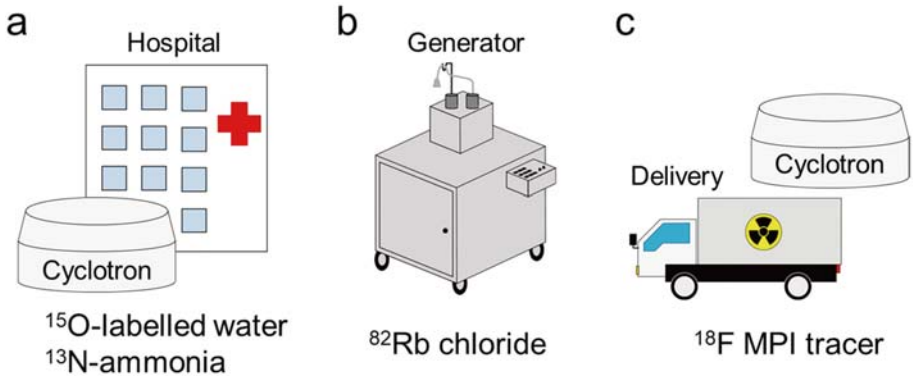

Figure 1 Schematic figure of required equipment for MPI tracers.

Physical exercise stress PET MPI

Rest and stress MPI is the most accurate test available for diagnosing CAD in patients who may be at risk for a heart attack at an early time of disease on-set. Rest and stress MPI have a proven risk-stratification capability and are sensitive to even the modest changes in coronary blood flow. Exercise is a safe physiologic stress, and exercise testing permits correlation of symptoms with exertion, measurement of exercise capacity and functional status, and assessment of efficacy of medical therapy (4). However, due to the short half-lives of current PET MPI tracers, stress imaging is only feasible in conjunction with pharmacologic stress. The half-life of ^{13}N-ammonia (10 min) is longer than those of ^{15}O-labelled water (2.1 min) and ^{82}Rb chloride (76 sec) and can be used in conjunction with supine bicycle exercise or treadmill exercise, but this approach is not practical for routine clinical use (5). Owing to the long half-life of ^{18}F, ^{18}F PET MPI tracer would be compatible with imaging protocols using exercise as well as pharmacologic stress. Actually, ^{18}F-Flurpiridaz (^{18}F-BMS-747158-02), which is the most promising ^{18}F labeled tracer for MPI (6, 7), was used in conjunction with treadmill exercise in the previous clinical trials, and the feasibility of ^{18}F-Flurpiridaz in rest and treadmill exercise has been demonstrated (8). It is known that a very high target-to-background ratio is noted when ^{18}F-Flurpiridaz is injected at peak treadmill exercise. From the relationship between rest-stress contamination and dosing, it was determined that for a same-day rest-exercise protocol, a minimum dose ratio of 3.0 was needed, with a 60 min waiting time between the 2 injections. For an optimum same-day rest-adenosine stress protocol, on the other hand, a dose ratio of 3 with a 30 min waiting time between the 2 injections was required (5). In a pig model, single-scan method which provides quantitative rest-adenosine stress blood flow in less than 15 min was also suggested. A two-injection, single-scan protocol was used in which an adenosine infusion was started 4 min after the first injection of ^{18}F-Flurpiridaz and followed either 3 or 6 min later by a second radiotracer injection (9).

The highest spatial resolution

The short positron range of ^{18}F (1.03 mm) would result in the highest spatial resolution (3,5). ^{15}O-labelled water has a 4.14 mm positron range resulting in an intermediate image resolution. The positron range of ^{13}N-ammonia is 2.53 mm resulting in an intermediate-high image resolution. Due to the high energy of positrons emitted during the decay of ^{82}Rb chloride (positron range, 8.6 mm) and lower count rates as a result of the ultra-short half-life (76 sec), the spatial resolution of ^{82}Rb chloride is lower than those of other PET MPI tracers (10). As shown in Figure 2, the induced ^{18}F-Flurpiridaz uptake defect corresponds precisely to the defect in ^{13}N-ammonia images. Images obtained using ^{18}F-Flurpiridaz demonstrated improved contrast and higher resolution resulting in better delineation of induced lesions, despite a higher injected dose of ^{13}N-ammonia (57 MBq) versus ^{18}F-Flurpiridaz (37 MBq) (11).

^{18}F-Flurpiridaz as one of the most promising ^{18}F PET MPI tracers and currently investigated in a Phase 3 trial in the United States

^{18}F labeled PET perfusion tracers, can be divided into two categories: analogues of mitochondrial complex-1 (MC-1) inhibitors and lipophilic cations. Current research progress in development of MPI tracers has been well reviewed by Mou and Zhang (2017) (12). Especially, ^{18}F-Flurpiridaz (^{18}F-BMS-747158-02), which is one of analogues of MC-1 inhibitors, is the most promising ^{18}F labeled tracer for MPI and the first of two Phase 3 trials have been completed (6, 7). ^{18}F-Flurpiridaz was rapidly taken up into neonatal rat cardiomyocytes, and the half-time of washout was greater than 120 min, which can be considered as promising properties for perfusion imaging (13). The first-pass extraction fraction of ^{18}F-Flurpiridaz by the myocardium is very high (>90% in isolated rat hearts perfused with the Langendorff method) and blood flow-independent, an important characteristic for stress myocardial blood flow (MBF) measurements (14). Furthermore, higher myocardial extraction facilitates detection of milder perfusion defects

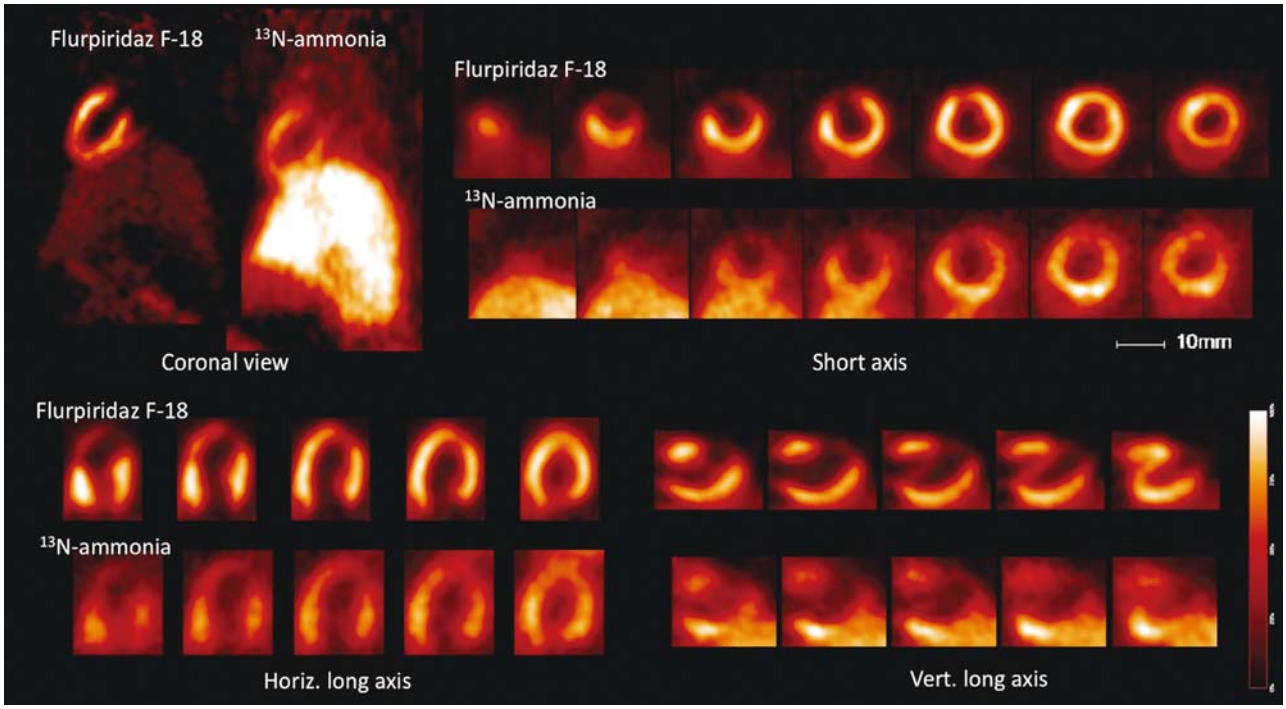

Figure 2 Coronal view, Short axis, Horizontal long axis, Vertical long axis images of a rat heart 1 week after coronary occlusion using ^{18}F-Flurpiridaz PET and ^{13}N-ammonia PET.

Table 1 Characteristics of various cardiac PET perfusion tracers

	^{18}F-Flurpiridaz	^{15}O-water	^{13}N-ammonia	^{82}Rb chloride
Half life	110 min	2.1 min	10 min	76 sec
Positron range	1.03 mm	4.14 mm	2.53 mm	8.6 mm
Production	Regional cyclotron	On-site cyclotron	On-site or nearby cyclotron	Generator
Image resolution	Highest	Intermediate	Intermediate-high	Lowest
Myocardial extraction fraction	>90%	100%	80%	65%
Treadmill exercise Imaging	Feasible	Not feasible	Feasible but not practical	Not feasible

(15). Absolute quantitation of MBF is important and is currently gaing ground in clinical practice (16). The elevated extraction fraction of ^{18}F-Flurpiridaz at different flow rates makes it an optimal candidate for absolute MBF quantitation (5). In a rat biodistribution study, heart-to-lung and heart-to-liver ratios of ^{18}F-Flurpiridaz were significantly higher than that of ^{99m}Tc-sestamibi SPECT (17). In a pig model, ^{18}F-Flurpiridaz showed higher activity ratios between myocardium and blood, liver, and lungs compared with ^{13}N-ammonia (18). In a Phase II clinical trial, ^{18}F-Flurpiridaz had a higher diagnostic accuracy for evaluating multi-coronary artery stenosis, compared with SPECT MPI agents ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, and ^{201}Tl (19). In a previous Phase 3 clinical trial, ^{18}F-Flurpiridaz showed also a significant reduction in radiation exposure compared with SPECT. Of note, ^{18}F-Flurpiridaz showed statistically superior sensitivity, specificity, accuracy, diagnostic confidence, and image quality compared with SPECT in obese subjects (6, 12). Consequently, ^{18}F-Flurpiridaz has entered Phase 3 multicenter clinical trials: A currently ongoing international study to evaluate the diagnostic efficacy of ^{18}F-Flurpiridaz injection PET MPI in the detection of CAD will be completed in August 2020 (ClinicalTrials.gov Identifier: NCT03354273).

Future perspective

^{18}F labeled PET MPI tracers offer several advantages due to their underlying physical properties (^{18}F radioisotope) (Table 1). The use of PET MPI was mostly limited to large hospital due to the requirement for either onsite or very nearby cyclotrons as well as costly generators. However, similar to the successful commercialisation of ^{18}F-FDG, ^{18}F labeled PET MPI tracers can be produced in regional centers for dose-by-dose delivery to multiple PET sites. In addition to that, they may be also injected during exercise stress with enough time to move the patient to the camera after successfully performing the stress protocol (10). Moreover, ^{18}F-Flurpiridaz

has also shown promising results in both preclinical examinations and clinical trials. Apart from that, other novel ^{18}F labeled MPI tracers have been recently introduced (12). Hence, given their promising physical and imaging properties, ^{18}F labeled MPI tracers might increase the acceptance of cardiac PET as a routine diagnostic tool.

Acknowledgments

None.

Sources of funding

None.

Conflicts of interest

None.

Abbreviation and Acronyms
CAD: coronary artery disease
MPI: myocardial perfusion imaging
FDG: ^{18}F-fluoro-2-deoxy-D-glucose
MC-1: mitochondrial complex-1
MBF: myocardial blood flow

Reprint requests and correspondence:
Takahiro Higuchi, MD, PhD
Department of Bio Medical Imaging, National Cardiovascular and Cerebral Research Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan
E-mail: thiguchi@me.com

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