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

^{15}O-labeled Water is the Best Myocardial Blood Flow Tracer for Precise MBF Quantification

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Abstract

Oxygen-15-labeled water (^{15}O-H_2O) is used as a radiopharmaceutical tracer with positron emission tomography (PET). Its short radioactive half-life permits consecutive rest and stress imaging acquisition while requiring an on-site cyclotron near a PET imaging system. ^{15}O-H_2O PET has the disadvantage of being less than ideal for visual assessment; however, its high extraction fraction allows for highly accurate quantification of myocardial blood flow (MBF). Therefore, ^{15}O-H_2O is considered to be a gold standard for MBF quantification. This is one of the great advantages of ^{15}O-H_2O PET over other PET myocardial perfusion imaging modalities. The purpose of this review is to provide the advantages and characteristics of ^{15}O-H_2O PET.

Keywords: Cardiac PET, Extraction fraction, Flow reserve, Myocardial blood flow, O-15-labeled water
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PET myocardial perfusion imaging (MPI) provides for accurate diagnosis and has prognostic value in patients with coronary artery disease (CAD). PET MPI also has significant advantages such as myocardial blood flow (MBF) estimation.

Oxygen-15-labeled water (^{15}O-H_2O) makes it possible to perform consecutive rest and stress data acquisition because of its short radioactive half-life (2.04 min). In addition, ^{15}O-H_2O PET can provide accurate quantification of MBF due to its high extraction fraction, leading to its being widely considered a non-invasive gold standard test for MBF measurement. In this review, we will address the characteristics and advantages of ^{15}O-H_2O.

Advantages of ^{15}O-H_2O

^{15}O-H_2O is metabolically inert and passes freely across cell membranes. It can therefore be distributed over vascular and extravascular spaces (1). Its distribution and clearance depend completely on the rate of blood flow. The tracer kinetics of ^{15}O-H_2O show the linear relationship between myocardial perfusion and first-pass extraction (1). Therefore, ^{15}O-H_2O is considered a standard for MBF measurement, remaining stable over a wide range of flow rates.

^{15}O-H_2O PET is used as a gold standard to estimate MBF and has been used as a standard against which to measure other newly developed MBF quantification tools such as PET tracers (2–4), single-photon emission computed tomography (SPECT) (5), cardiac magnetic resonance imaging (CMR) (6) and dynamic computed tomography (CT) (7).

Short physical half-life

The physical half-life of ^{15}O-H_2O is 2.04 min, which allows serial rest and stress PET data acquisition (Figure 1) (8). Using a current PET/CT scanner, the rest and stress clinical protocol can be completed within 30 minutes. This time frame is similar to that for Rubidium-82 (^{82}Rb)-PET/MPI data acquisition and this protocol should be quite suitable in clinical settings.

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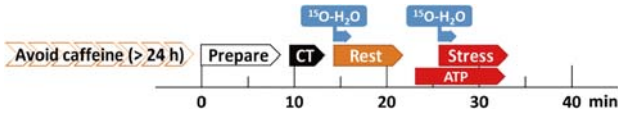

Figure 1 Protocol of ^{15}O-H_2O PET/CT scan.
^{15}O-H_2O has a short half-life allowing for multiple and serial scans. To quantify stress MBF, ^{15}O-H_2O should be injected when the myocardium reaches the hyperemia stage (2 to 3 min after the start of the pharmacological stimulation).

Disadvantages of ^{15}O-H_2O

^{15}O-H_2O requires an on-site cyclotron for tracer production, similar to the case with ^{13}N-ammonia (^{13}N-NH_3) PET. ^{15}O-H_2O is therefore available in a limited number of PET centers around the world.

An exercise imaging protocol is not feasible due to the short physical half-life.

^{15}O-H_2O is suboptimal for visual assessment given its low myocardial accumulation and the low myocardial-to-background count ratio. However, a group at Vrije Universiteit in Amsterdam introduced a method for generating a parametric perfusable tissue index, which is defined as the ratio between water-perfusable and anatomic tissue fractions and is used as a marker of myocardial viability in images from a single ^{15}O-H_2O PET/CT scan (9). This approach may add some clinical value to ^{15}O-H_2O PET/CT.

The average positron range, which is a potential limit for achievable PET spatial resolution, of ^{15}O is 4.14 mm, which is longer than that for ^{18}F (1.03 mm) or ^{13}N (2.53 mm) but shorter than that for ^{82}Rb (8.60 mm) (10).

^{15}O-H_2O is not approved by the US Food and Drug Administration (FDA) and Japanese Ministry of Health, Labour, and Welfare for clinical use, and its use is limited to clinical practice, primarily for measuring MBF in research settings.

Protocol of a ^{15}O-H_2O PET scan

Similar to the case for other PET MPIs, the standard protocol is rest and pharmacological stress data acquisition. Subjects should be instructed to abstain from caffeine-containing products for at least 24 h prior to the PET study for the pharmacological stress test (11). Currently, pharmacological stress agents using PET MPI include adenosine, adenosine triphosphate (ATP), dipyridamole, or regadenoson. At first, a transmission scan for PET or a low-dose CT scan at free breathing for PET/CT are obtained for attenuation and scatter correction. ^{15}O-H_2O (around 1480 MBq for PET and 740 MBq for PET/CT) is slowly administered intravenously with simultaneous 5 to 10 min list mode data acquisition at rest scan. Due to the short physical half-life of ^{15}O-H_2O, the stress study can be performed immediately after rest data acquisition. In our institution, pharmacological stress is induced by an intravenous injection of ATP (140 to 160 μg/kg/min) at 3 min before the emission scan to achieve maximal hyperemia. Once the effects of ATP are evident, ^{15}O-H_2O (a similar amount to that for the rest scan) is injected for stress data acquisition, followed by dynamic imaging for the same list mode data acquisition at rest. Slow infusion (100 to 120 sec) provides the perfusable tissue fraction values to obtain regional MBF (12) even in the 3-dimension (3D) data acquisition mode (13).

The total-body effective dose of radiation for a typical 3D ^{15}O-H_2O protocol was less than 3 mSv during PET/CT (14). In our institution, the total radiation dose from sequential rest and stress imaging is estimated to be about 3.0 mSv (less than 0.1 mSv for the scout, 0.7 mSv for the attenuation correction CT, and 1.1 mSv for each ^{15}O-H_2O PET scan / 500 MBq injection) (13).

Quantification of MBF and myocardial flow reserve (MFR)

PET/CT requires manual registration in coronal, sagittal, and transaxial views for accurate attenuation correction. Rest and stress PET/CT images are visually aligned for proper registration, and attention must be paid to ensure that the left ventricular myocardial activity on PET does not overlap with the lung parenchyma on CT (14). MBF derived from ^{15}O-H_2O PET was correlated closely with direct measurements of MBF in an open-chest dog model and concomitantly administered radiolabeled microsphere (15). Both rest and hyperemic MBF derived from ^{15}O-H_2O PET showed reliable reproducibility in normal control individuals (16). Even the 3D data acquisition MBF and MFR derived from ^{15}O-H_2O PET/CT can also be reliably reproduced in CAD patients (13).

Diagnostic value of CAD validated by clinical standard measurements

MFR derived by ^{15}O-H_2O was inversely correlated with percent coronary stenosis in patients with CAD (17). Danad et al. reported that quantitative MBF measurements acquired through ^{15}O-H_2O PET provided high diagnostic performance in 330 patients with CAD (18). Previous studies validating the usefulness of MBF measurements used quantitative coronary angiography (CAG) as a diagnostic standard. However, recently fractional flow reserve (FFR) measurement has become an important diagnostic parameter to determine the indication for coronary revascularization. This approach is the so-called physiology-based PCI (19). The study by Danad et al. evaluated the diagnostic accuracy of stress MBF and MFR with ^{15}O-H_2O PET based on a cut-off FFR value of 0.80. The main point of this study is to validate the clinical utility of ^{15}O-H_2O PET MBF measurement under the current standard of patient management approach in patients with CAD.

Data associated with this PET tracer is unique. In addition,

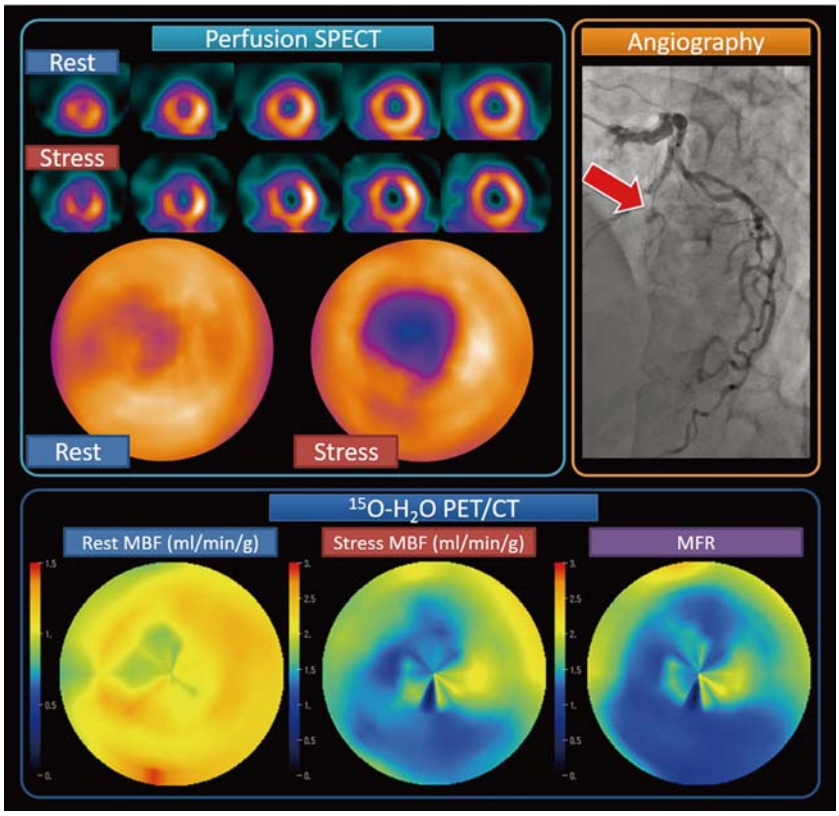

Figure 2 Representative case of coronary artery disease.
A woman in her 40s with type 1 diabetes mellitus was examined to rule out asymptomatic cardiovascular disease (CVD). ^{99m} Tc-tetrofosmin SPECT images at stress show the perfusion decrease in the mid to apical anterior and septal wall, which is improved at rest, indicating moderate ischemia in the left anterior descending artery (LAD) territory. Invasive CAG showed LAD coronary occlusion. ^{15}O-H_2O PET/CT reveals a decrease in myocardial blood flow (MBF) at stress and myocardial flow reserve (MFR) in the whole myocardium, including the LAD territory due to the microcirculatory disorder.

Table 1 Characteristics of ^{15}O-water

Parameter	
Production	cyclotron
Half-life (min)	2.04
Positron range (mm)	4.14
Scan duration (rest and stress) (min)	30
Effective dose (mSv/MBq)	0.0011
Extraction fraction (%)	100
Uptake mechanism	freely diffusible

the study by Danad et al. showed the diagnostic cut-off value of MFR as 2.5. Another possible cut-off value of MFR from a cardiac event prediction point of view was 2.0 with ^{82}Rb and ^{13}N-NH_3. Compared to these two PET MPI tracers, ^{15}O-H_2O has a higher cut-off value. This may be due to the high extraction fraction of ^{15}O-H_2O and may contribute to easier separation between physiologically abnormal population and a now significant population of patients with known or suspected CAD.

Microvascular dysfunction associated with coronary risk factors

Estimated MFR is influenced not only by coronary stenosis severity but also by coronary risk factors. Yoshinaga et al. reported that MFR in remote (no coronary stenosis) segments in patients with CAD was significantly lower than that in age-matched normal subjects (20). Risk factors such as diabetes, smoking, hypertension and dyslipidemia showed a lower MFR even in regions without severe coronary stenosis (21–23) (Figure 2).

Conclusion

What makes ^{15}O-H_2O PET attractive is its ability to accurately quantify MBF based on its high extraction fraction. A short physical half-life makes it possible to perform a short stress and rest data acquisition protocol and contributes to lowering radiation exposure. Although the availability of ^{15}O-H_2O is limited, we hope this excellent MBF measurement modality will be more widely available and will contribute to CAD patient management in the near future.

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Conflicts of interest

None of the authors has any conflict of interest.

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