

EDITORIAL POINT OF VIEW

Quantification of Coronary Flow Reserve by ^{15}O -Water PET with ATP Stress; from a Practical Application Perspective

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Abstract

^{15}O -water has been considered to be a near-perfect and the most ideal myocardial blood flow (MBF) tracer because it is freely diffusible, metabolically inert, and independent of the myocardial metabolic state, which results in the highest extraction fraction. Absolute coronary flow reserve (CFR) is the ratio of MBF during maximal hyperemia in a coronary artery to MBF in the same artery under resting conditions and can be quantified noninvasively by positron emission tomography (PET). A growing body of literature is accumulating to show that the prognostic value of absolute MBF or CFR, which is quantified by cardiac PET.

ATP infusion protocol of 0.16 mg/kg/min for 5 minutes and its safety profile have been established in humans and it has been widely applied in many clinical and investigative studies including ^{15}O -water PET. With the use of the 3-min acquisition data, the regions of interest in the left ventricular chamber and myocardium could be set for all of the subjects. Six-min CFR data could be used to separate the CAD patients and controls. A 3-min, but not 2-min, scan with ^{15}O -water PET can be used for the quantitative evaluation of MBF and CFR. A shorter scan time will result in a reduction of body motion of patients, which may lead to the more precise quantification of MBF and CFR.

Keywords: ^{15}O -H₂O, ATP, Coronary flow reserve, PET

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Quantification of myocardial blood flow (MBF) from dynamic positron emission tomography (PET) is a well-established method. ^{15}O -labeled H₂O (^{15}O -water), ^{13}N -ammonia and ^{82}Rb are the PET tracers commonly used in the assessment of MBF. Among them, ^{15}O -water is a near-perfect and the most ideal MBF tracer because it is freely diffusible, metabolically inert, and independent of the myocardial metabolic state, which results in the highest extraction fraction. It has a short half-life of approximately 2 minutes and requires an expensive onsite cyclotron. A practical disadvantage of ^{15}O -water is its relatively poor image quality, since it fails to accumulate enough in the myocardium. Additionally, it is not covered by insurance, therefore mainly

used for research purposes. Japan Radioisotope Association recommended the continuous infusion of 120–480 MBq/min (or 2–8 MBq/kg/min) for ^{15}O -water with radiation exposure of $0.9\ \mu\text{Sv/MBq}$ (1), although there is no specific details of ^{15}O -water usage in the latest PET guidelines by the American Society of Nuclear Cardiology (2).

Absolute coronary flow reserve (CFR) is the ratio of MBF during maximal hyperemia in a coronary artery to MBF in the same artery under resting conditions (3). Absolute CFR can be quantified invasively using intracoronary Doppler-based technique or thermo-dilution flow measurements, as well as noninvasively by PET. A growing body of literature is accumulating to show the prognostic value of absolute MBF or CFR, which is quantified by cardiac PET. Briefly, an intact CFR, which has been reported as >2.5 with ^{15}O -water, is

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associated with a favorable prognosis. On the other hand, a reduced CFR leads to a worse prognosis either through a severe, focal abnormality with future risk of an acute coronary syndrome, or through a global flow reduction which is a marker for diffuse coronary artery disease (CAD) and its overall burden.

Maruo et al. demonstrate that estimated CFR value of 6-min acquisition data by ^{15}O -water PET was 4.16 ± 1.39 in healthy subjects, while it was 2.19 ± 0.92 in patients suspected of having CAD (4). These values are not significantly different to the CFR values of 3-min data and nearly coincide with those that have been reported so far.

Pharmacological stress with ATP for dynamic ^{15}O -water PET

For the pharmacological stress, they infused ATP into an antecubital vein and the PET scanning started at 3 min after the beginning of infusion. Once ATP is injected into the peripheral vein, it is rapidly hydrolyzed to adenosine diphosphate, followed by dephosphorylated AMP with a half-life of <20 seconds in plasma. In the animal study, most ATP (>95%) is finally degraded to adenosine on the way from a peripheral vein to the coronary sinus. Its degradation product, adenosine, can induce maximal coronary vasodilation through activation of the A2a receptors with a rapid onset of action and a very short plasma half-life (<2 seconds). Since ATP is a precursor of adenosine, it would be expected to have longer vasodilatory effects than adenosine. ATP infusion protocol of 0.16 mg/kg/min for 5 minutes and its safety profile have been established in humans (5-8). Although it is not covered by insurance, ATP stress is feasible and inexpensive (<10 dollars per study), therefore it has been widely applied in clinical and investigative studies (9,10).

Maruo et al. reported that there were no significant differences between the values of hemodynamics among the 2-min, 3-min and 6-min after the start of the scan, which are, in other words, among the 5-min, 6-min and 9-min after the start of ATP infusion, including the heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate pressure product (RPP). Those are substantially similar to the results achieved in the previous reports (5-8) and the maximal coronary vasodilation should be accomplished throughout their study period (Fig. 1).

Shorter scan time is feasible for quantitative ^{15}O -water PET

However, for analysis of the 2-min data, they found difficulties to set proper region of interest (ROI) on the left ventricular (LV) myocardium in 26.7% of the resting images and 13.3% of the stress images due to the poor quality of images. ^{15}O -water is intravenously injected in a slow-infusion

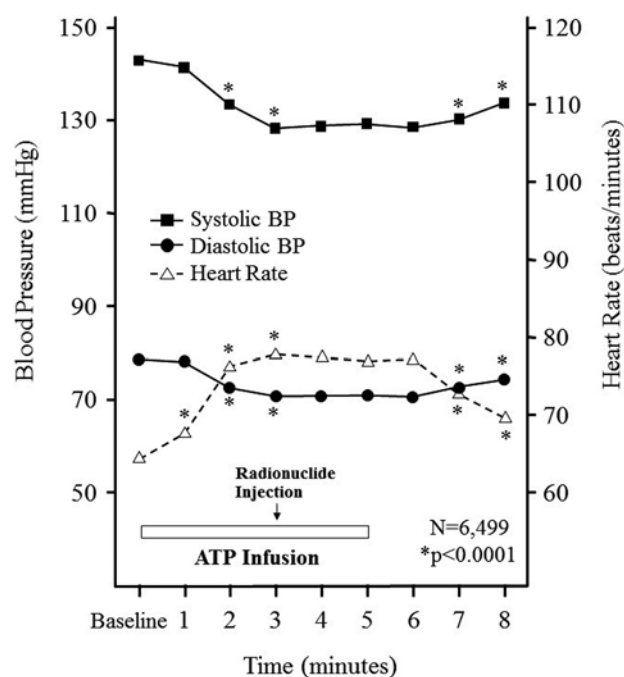


Fig. 1

The mean heart rate and blood pressure response at baseline, during, and after the 5-minute infusion protocol of ATP in 6,499 patients (6). Heart rate increased from the baseline of 64.3 ± 11.2 to the maximum of 81.8 ± 13.4 beats/min, while systolic blood pressure (BP) decreased from 142.4 ± 24.7 to 117.9 ± 19.2 mmHg and diastolic BP decreased from 78.5 ± 14.0 to 62.6 ± 11.1 mmHg. Hemodynamic effects of ATP infusion reach the plateau at 3 minute after the beginning of infusion and last 3 to 6 minutes.

*: significantly different to the prior time point.

manner for 2-min and there are some delay time to reach the accumulation level of high enough to draw ROIs over the whole LV myocardium. Thus, the low accumulation of whole LV due to the low MBF may be the cause of difficulties in the considerable number of patients.

Meanwhile, the 9-min infusion of ATP seems too long for patients to tolerate. Even with the use of standard 5-min ATP infusion protocol, patients often complain of a chest pain, flushing, headache, neck discomfort, and dyspnea. Moreover, a few patients have high-degree atrioventricular block or ST depression on ECG, which result in early termination of the infusion protocol (8). The body movements of patients can be a source of quantitative errors. Such movement may be problematic when scans are carried out for a relatively long period. Maruo et al. showed that the acquisition time of ^{15}O -water PET can be decreased from 6 to 3 min together with that the ATP infusion time can be decreased from 9 to 6 min. A shorter scan time will result in a reduction of body motion of patients, which may lead to the more precise quantification of MBF and CFR. Their innovation in ^{15}O -water PET will be of great help for many patients as well as physicians in the field.

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Conflicts of interest

None declared.

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