ORIGINAL ARTICLE

Feasibility of Quantifying Myocardial Blood Flow with a Shorter Acquisition Time Using ^{15}O-H_2O PET

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Abstract

***Purpose*: The quantification of coronary flow reserve (CFR) calculated as the ratio of the myocardial blood flow (MBF) during adenosine triphosphate (ATP) stress to MBF at rest is a useful method for evaluating the functional severity of coronary artery disease (CAD) using ^{15}O-H_2O positron emission tomography (PET). The shorter acquisition time may reduce dyspnea and other side effects of ATP stress and may also reduce the effect of body movements during data acquisition. However, the impact of the shorter data acquisition time on the accuracy of MBF quantification has not been studied. In this retrospective study, we evaluated the accuracy of the MBF and CFR values obtained with shorter scan times using ^{15}O-H_2O PET.**

***Methods*: Thirty patients suspected of having CAD (22 males, 8 females; age 56.5±8.8 yrs) and 17 healthy controls (17 males; age 27.7±6.2 yrs) underwent PET during rest and PET with ATP stress dynamic ^{15}O-H_2O. The MBF was estimated with a one-tissue compartment model analysis. MBF and CFR values were calculated using the first 2-min and 3-min PET data of ^{15}O-H_2O as shorter data acquisitions. These data were compared to the standard 6-min PET acquisition data.**

***Results*: With the use of the 3-min data, the regions of interest (ROIs) in the left ventricular (LV) chamber and myocardium could be set for all of the subjects. The intraclass correlation coefficients (ICCs) between the 3-min data and 6-min data of the rest MBF, stress MBF and CFR were 0.869, 0.870, and 0.819 in the patients, and 0.912, 0.910, and 0.930 in the controls. The 3-min CFR data showed a significant difference between the patients and controls (2.22±1.02 vs. 4.02±1.50, $p<0.01$), as did the 6-min data (2.19±0.92 vs. 4.16±1.39, $p<0.01$). However, the CFR based on 2-min data did not show a significant difference (1.96±1.66 vs. 2.73±1.03, $p=0.088$). Using a receiver operating characteristic (ROC) analysis, we observed that both the 3-min and 6-min CFR data could be used to separate the CAD patients and controls.**

***Conclusions*: A 3-min, but not 2-min, scan with ^{15}O-H_2O PET can be used for the quantitative evaluation of MBF and CFR.**

Keywords: ^{15}O-H_2O, Myocardial blood flow, Pharmacological stress, Positron emission tomography, Shorter acquisition time

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The quantification by positron emission tomography (PET) of myocardial blood flow (MBF) and coronary flow reserve (CFR), the latter of which is calculated as the ratio of the MBF during stress to the MBF at rest, is a useful method for evaluating the functional severity of known or suspected coronary artery disease (CAD) (1-4). These estimations provide valuable information for the diagnosis and monitoring of CAD, especially in multivessel disease with balanced ischemia on qualitative images (5). The use of PET MBF data is also useful for detecting endothelial dysfunction even in preclinical disease (6-9) and for assessing the risk of atherosclerosis (10,11).

^{15}O-labeled water (^{15}O-H_2O), ^{13}N-ammonia and ^{82}rubidium are the PET tracers commonly used in the assessment of MBF (12-14). ^{15} O-H_2O is known an ideal PET tracer for the quantification of MBF because of the high extraction fraction it provides (15). However, ^{15}O-H_2O has limited image quality because it is an inert, freely diffusible tracer (16).

PET stress studies are usually performed under pharmacological stress. Adenosine triphosphate (ATP) is administered intravenously from 2 or 3 minutes before the start of the scan to the end of the dynamic data acquisition (17). These agents have side effects such as dyspnea, palpitations and flushing. These side effects may also cause significant patient body motion during stress data acquisition, which reduces the data quality. Therefore, a shorter acquisition time may reduce the side effects and may reduce the number of body movements by the patient during the data acquisition. However, it is not clear whether a shorter acquisition time is sufficient to obtain an accurate region of interest (ROI) on the myocardium and accurate MBF quantification data. The purpose of the present study was to assess the possibility of quantifying MBF and CFR with a shorter ^{15}O-H_2O PET scan time.

Methods

Subjects

We reviewed the cases of 30 patients suspected of having CAD (22 males, 8 females; 56.5±8.8 years old) and 17 healthy controls (17 males; 27.7±6.2 years old) who underwent resting and ATP stress dynamic ^{15}O-H_2O PET scans between September 2001 and September 2009 at our institution (Table 1). They were instructed to abstain from caffeine-containing beverages for at least 24 h before the scans. All of 30 patients underwent coronary angiography, and coronary artery stenosis was considered significant when there was a reduction of ＞50% in the diameter of the main branch (18). All 17 healthy subjects had normal laboratory test results and no symptoms or history of cardiovascular disease. The potential risks of the study were explained to all of the subjects before they gave their voluntary consent to participate. The Ethics Committee of Hokkaido University Hospital approved the study protocol.

Table 1 The characteristics of the 30 CAD patients and healthy controls

	Healthy controls	CAD patients	p-value
Age (years old)	27.7±6.2	56.5±8.8	＜0.05
Gender (male/ female)	17/0	22/8	＜0.05
BMI (kg/ m^2)	22.0±2.8	24.8±2.6	＜0.05
Smoker (n)	0	17	＜0.05
HT (n)	0	10	＜0.05
HL (n)	0	16	＜0.05
DM (n)	0	9	＜0.05
LVEF	−	59.8±16.8	

BMI: body mass index; HT: hypertension; HL: hyperlipidemia; DM: diabetes mellitus; LVEF: left ventricular ejection fraction calculated by echocardiography

Study protocol

One observer (A.M.) who did not know the information of the participants analyzed all of the acquired data. We estimated the MBF values at rest and under pharmacological stress and the CFR values using the first 2-min ($MBF_{2\text{-min}}$, $CFR_{2\text{-min}}$) and 3-min ($MBF_{3\text{-min}}$, $CFR_{3\text{-min}}$) ^{15}O-H_2O PET data, and then we compared these values with the data obtained in the 6-min PET scans ($MBF_{6\text{-min}}$, $CFR_{6\text{-min}}$) as the gold standard (12,19) (Fig. 1). We compared the estimated CFR values of the patients and controls using a receiver operating characteristic (ROC) analysis to estimate the cutoff levels and diagnostic accuracies for each scan time.

PET imaging acquisition

PET data acquisition was performed using a whole-body scanner (ECAT/ EXACT HR＋; Siemens/ CTI, Asahi-Siemens Medical Technologies, Tokyo). Transmission scans were obtained with an external ^{68}Ge/ ^{68}Ga source. Subsequently, 1,500 MB of ^{15}O-H_2O was infused into an antecubital vein as a slow (2-min) infusion. A 24-frame dynamic PET scan consisting of 18×10 sz and 6×30 s frames was acquired for 6 min. After allowing 10 min for tracer decay, another dynamic scan using ^{15}O-H_2O was acquired with 0.16 mg/ kg/min of ATP, starting 3 min before the beginning of emission scanning (Fig. 2). The total administration time for the ATP was 9 min. The heart rate and blood pressure were recorded before and every minute during ATP infusion. All emissions and transmissions were acquired in the 2-dimensional (2D) mode, and attenuation-corrected radioactivity images were reconstructed using filtered back-projection with a Hann filter of 4-mm full-width at half-maximum.

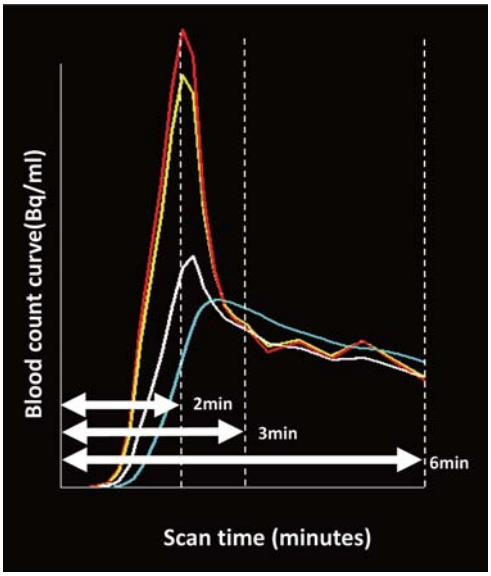


Fig. 1 Measured blood count curve
The dynamic curves obtained by ^{15}O-H_2O PET. The red line indicates the true arterial count (Ca (t)), the yellow line shows the measured left ventricular dynamic data (LV curve), the blue line shows the measured myocardial blood count (r (t)), and the white line shows the true myocardial blood count (Ct (t)). MBF was estimated from 2-min, 3-min, and 6-min data.

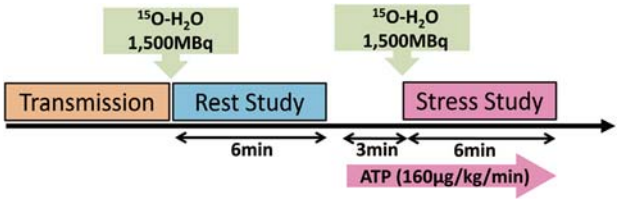


Fig. 2 Scan protocol
Time schedule of the ^{15}O-H_2O PET. After the transmission, 1,500 MB of ^{15}O-H_2O was infused for the scan at rest. After allowing a further 10 min for decay, another dynamic scan was acquired with 0.16 mg/kg/min of ATP, starting 3 min before the beginning of emission scanning.

Analysis of ^{15}O-H_2O

The MBF values obtained using ^{15}O-H_2O PET were measured as described previously (12). Briefly, ROIs were drawn over the whole LV myocardium and within the LV cavity to project onto the dynamic ^{15}O-H_2O images. Early-phase short-axial ^{15}O-H_2O images were calculated by summing the first 2-min dynamic images. Short-axial ^{15}O-H_2O washout images were generated by subtracting the LV cavity image of the frame with maximum counts from the whole LV image of the last frame. When the ^{15}O-H_2O washout images were superimposed on a transmission image and analyzed with a semiautomated edge-detection routine, a whole myocardial ROI was determined. The LV cavity ROI was determined as the area for which the count was 85% of the blood volume concentration in the LV cavity images (20).

We used the dedicated software (12) to extract a 3D region enclosing the whole myocardial wall. Arterial and myocardial tissue activity curves were derived with spillover correction, and were fitted to a single-tissue-compartment tracer kinetic model to calculate the MBF at rest and under ATP stress (12). MBF was calculated from the time activity curve by a single compartment model using the Powell method. Global LV and 3-coronary-regional MBFs were also calculated and validated as described in the previous study (12).

Statistical analysis

Data are expressed as the mean ± SD. The correlation between MBF and CFR values was assessed using linear regression analyses and Bland-Altman plots. Pearson's correlation coefficients and intraclass correlation coefficients (ICCs) were used to evaluate the concordance between the MBF and CFR values obtained at each acquisition time. To evaluate the variability of the estimates, we used independent t-tests to examine the differences in parameters, including age, body mass index (BMI), MBF, CFR and other variables. For both analyses, p-values <0.05 were considered significant. JMP ver. 11 (SAS Institute, Cary, NC) was used for all data analyses.

Results

Characteristics of the controls and the CAD patients

There were significant differences in age, gender, BMI, history of smoking, hypertension (HT), hyperlipidemia (HL), and diabetes mellitus (DM) between the healthy controls and the patients suspected of having CAD (Table 1). With regard to the patients, 10 had one-vessel disease, 10 had two-vessel disease, and 3 had three-vessel disease. Seven patients had no significant coronary stenosis. The left ventricular ejection fraction (LVEF) estimated by echocardiography was 59.8 ± 16.8% in the patients. Six of the patients showed impaired LVEF (<50%).

Hemodynamic data at the scan

The hemodynamic data of the participants are provided in Table 2. The hemodynamic data under stress, including the heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate pressure product (RPP), were significantly higher than those obtained at rest. There were no significant differences between the values of hemodynamics among the 2-min, 3-min and 6-min data, including SBP, DBP, HR, and RPP ($p=0.90$, 0.89, 0.23, 0.59 for all subjects by analysis of variance, respectively (21)).

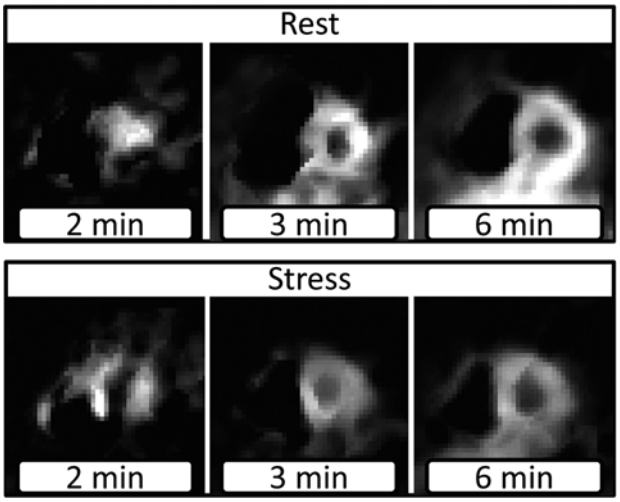
Setting of the ROI

For the analyses of the 3-min and 6-min data, ROIs could be set to the LV myocardium region in both the rest and stress

Table 2 Hemodynamic data at $^{15}O-H_2O$ scan

		Rest	2-min	3-min	Stress (ATP)
Healthy	HR	56.5 ± 3.5	68.9 ± 11.2	72.1 ± 10.9	81.2 ± 9.1
controls	SBP	105.4 ± 12.8	100.5 ± 12.1	100.4 ± 12.4	102.5 ± 13.4
	DBP	54.6 ± 14.3	50.1 ± 9.7	49.3 ± 12.2	50.3 ± 11.2
	RPP	5941.3 ± 728.1	6971.1 ± 1624.5	7281.1 ± 1621.5	8351.2 ± 1568.7
Patients	HR	61.6 ± 11.2	71.5 ± 12.4	73.6 ± 12.7	74.0 ± 13.2
	SBP	122.4 ± 20.6	115.6 ± 18.9	115.9 ± 17.6	126.5 ± 24.5
	DBP	63.6 ± 11.2	60.6 ± 11.4	60.0 ± 9.4	62.2 ± 14.0
	RPP	7550.1 ± 2100.0	8217.4 ± 1843.5	8538.0 ± 1800.3	9352.5 ± 2407.9

Hemodynamics data before injection (Rest), and at 2-min (5-min after injection) and 3-min (6-min after injection) after the start of the scan, and the HR-peak (Stress). HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; RPP: rate pressure product.
*Significantly higher than Rest ($p < 0.05$).



Rest and stress short axial ^{15}O-water washout images.
They were generated by subtracting max count images from last frame images.
2min, 3min, 6min last frame is 12th frame,20th frame, and 24th frame.

Fig. 3 Short axis images
Representative $^{15}O-H_2O$ PET images at each scan. Short-axis images from the 2-min (A), 3-min (B), and 6-min (C) data are displayed. For the 2-min image, the left ventricle (LV) could not be separated from the cardiac pool. In contrast, the 3-min image was enough to set the ROI on the LV.

examinations in all study subjects. However, for analysis of the 2-min data, the resting data of eight patients (26.7%) and the stress data of four patients (13.3%) could not be used to set proper ROIs. Therefore, these were excluded from further consideration of the MBF and CFR. In the control group, there was no subject for whom the ROI could not be set using the 2-min, 3-min, or 6-min data. A representative set of $^{15}O-H_2O$ PET images at each scan is presented in Fig. 3.

MBF and CFR values

The estimated MBF and CFR values for each scan time are given in Table 3. For the controls, there were no significant differences between the 3-min data (rest MBF=1.13 ± 0.25 mL/ min/ g, stress MBF=4.37 ± 1.35 mL/ min/ g, CFR=4.02 ± 1.50) and the 6-min data (rest MBF=1.14 ± 0.24 mL/ min/ g, stress MBF=4.58 ± 1. 27 mL/min/ g, CFR=4. 16 ± 1. 39). However, the rest $MBF_{2\text{-min}}$, stress $MBF_{2\text{-min}}$ values (2.86 ± 1.45 mL/ min/ g, 7.01 ± 2.06 mL/ min/ g, respectively) were significantly higher than those from the 6-min data, and the $CFR_{2\text{-min}}$ value (2.78 ± 1.15) was significantly lower than those from the 6-min data.

In the patient group, the rest and stress MBF and CFR values were not significantly different between the 3-min data analysis (1. 21 ± 0. 47 mL/ min/ g, 2. 41 ± 0. 94 mL/ min/ g, 2.22 ± 1.02, respectively) and the 6-min data analysis (1.20 ± 0.51 mL/ min/ g, 2.38 ± 0.96 mL/ min/ g, 2.19 ± 0.92, respectively). However, the $MBF_{2\text{-min}}$ values (rest: 2.97 ± 1.73 mL/ min/ g; stress: 4. 09 ± 1. 90 mL/ min/ g) were significantly higher and the $CFR_{2\text{-min}}$ values (1.96 ± 1.66) were significantly lower than those from the 6-min data, as was also observed for the healthy controls.

Correlation of the MBF and CFR values between shorter acquisition and 6-min data

For the patients, the MBF and CFR values showed no significant difference between the 3-min and 6-min data. The 3-min values demonstrated close relationships with the $MBF_{6\text{-min}}$ and $CFR_{6\text{-min}}$ (R values=0.92, 0.82; $p < 0.0001$, $p < 0.0001$, respectively) (Fig. 4). However, the $MBF_{2\text{-min}}$ and $CFR_{2\text{-min}}$ data were significantly different from the $MBF_{6\text{-min}}$ and $CFR_{6\text{-min}}$ data, and they showed a poor relationship to the $MBF_{6\text{-min}}$ and $CFR_{6\text{-min}}$ values (R=0.19, 0.16; p=0.19, 0.47) (Fig. 5).

For the CAD patients, the ICCs of the rest MBF, stress MBF, and CFR values obtained from the 2-min and 6-min plots were -0.05, 0.05, and 0.14, respectively, which were lower than those from the 3-min and 6-min plots (0.87, 0.87, and 0.82, respectively).

For the controls, the ICCs of the rest MBF, stress MBF, and CFR between the 2-min and 6-min plots were -0.03, 0.20, and

Table 3 Estimated MBF and CFR values

		2-min	3-min	6-min
Healthy controls (n = 17)	Rest MBF (mL/min/g)	2.86 ± 1.45	1.13 ± 0.25	1.14 ± 0.24
	Stress MBF (mL/min/g)	7.01 ± 2.06	4.37 ± 1.35	4.58 ± 1.27
	CFR	2.78 ± 1.15	4.02 ± 1.50	4.16 ± 1.39
Patients (n = 30 for 3-min and 6-min)				
	Rest MBF (mL/min/g)	2.97 ± 1.73*	1.21 ± 0.47	1.20 ± 0.51
	Stress MBF (mL/min/g)	4.09 ± 1.90**	2.41 ± 0.94	2.38 ± 0.96
	CFR	1.96 ± 1.66*	2.22 ± 1.02	2.19 ± 0.92

MBF: myocardial blood flow; CFR: coronary flow reserve.
*n = 22, **n = 26 because the ROIs could not be set for some of the patients.
The 6-min data are standard, and the 2-min values are significantly different from the 6-min values.

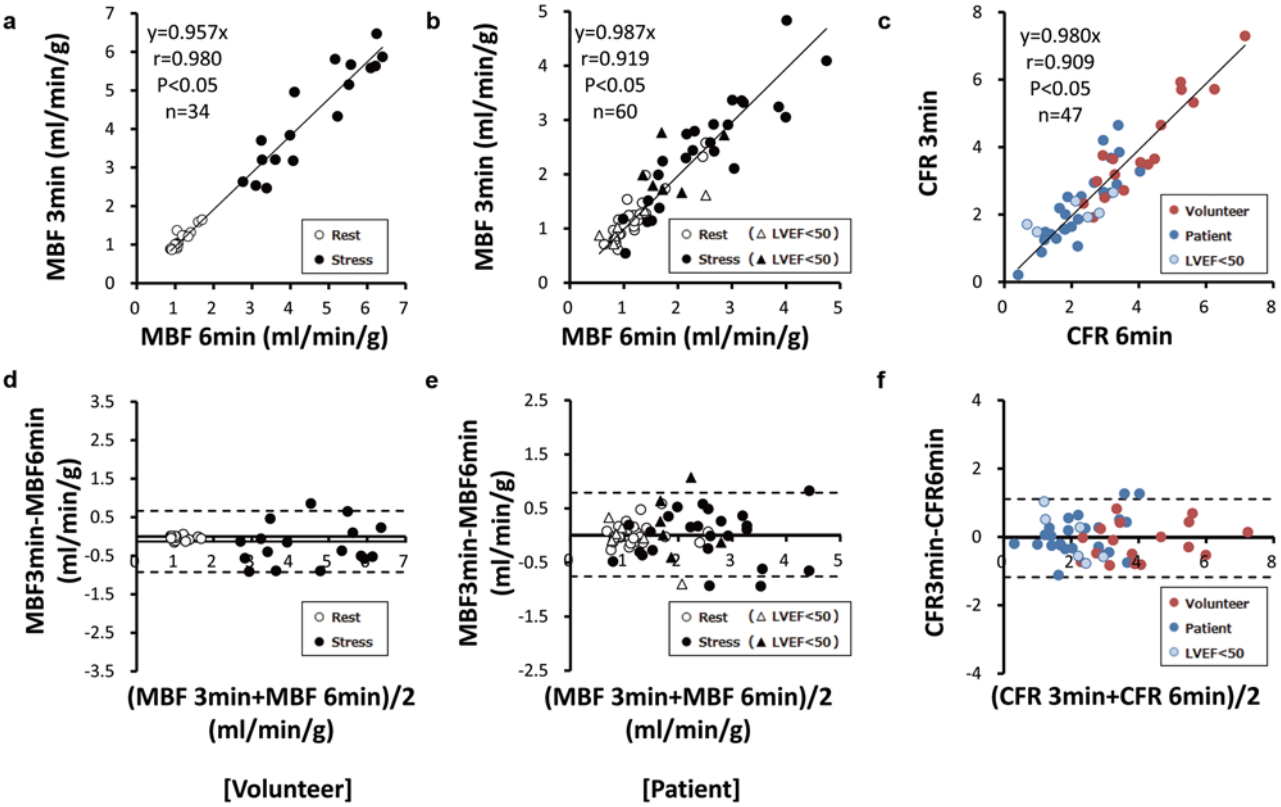


Fig. 4 3min whole MBF and CFR
Relationship between the 3−min and 6−min acquisition data. The MBF (a, b) and CFR (c) values showed significant correlations between the 3−min and 6−min acquisition data for both the controls and the patients, even in those whose left ventricular ejection fraction (LVEF) was lower than 50% (n=6). The Bland−Altman plots showed that the correlation between MBF (d, e) and CFR (f) calculated from 3−min and 6−min acquisition data was relatively stable (d−f).

0.21, respectively, which were also lower than those from the 3-min and 6-min plots (0.91, 0.91, and 0.93). The Bland-Altman plots of the MBF and CFR values were more stable between the 3-min and 6-min data compared to those from the 2-min and 6-min data (Figs. 4, 5).

Comparison of the CFR values between the controls and patients

The CFR values obtained from the 2-min (p=0.088), 3-min (p＜0.0001), and 6-min (p＜0.0001) data of the healthy controls were significantly higher than those of the patients (Table 3).

Discussion

Our results indicate that a 3-min scan of ^{15}O-H_2O PET can be used for the quantitative evaluation of MBF and CFR, whereas a 2-min scan was too short to estimate the MBF and CFR.

The quantification of stress MBF or CFR by PET is increasingly used for the diagnosis of CAD (22). For pharmacological stress, adenosine or ATP is usually adminis-

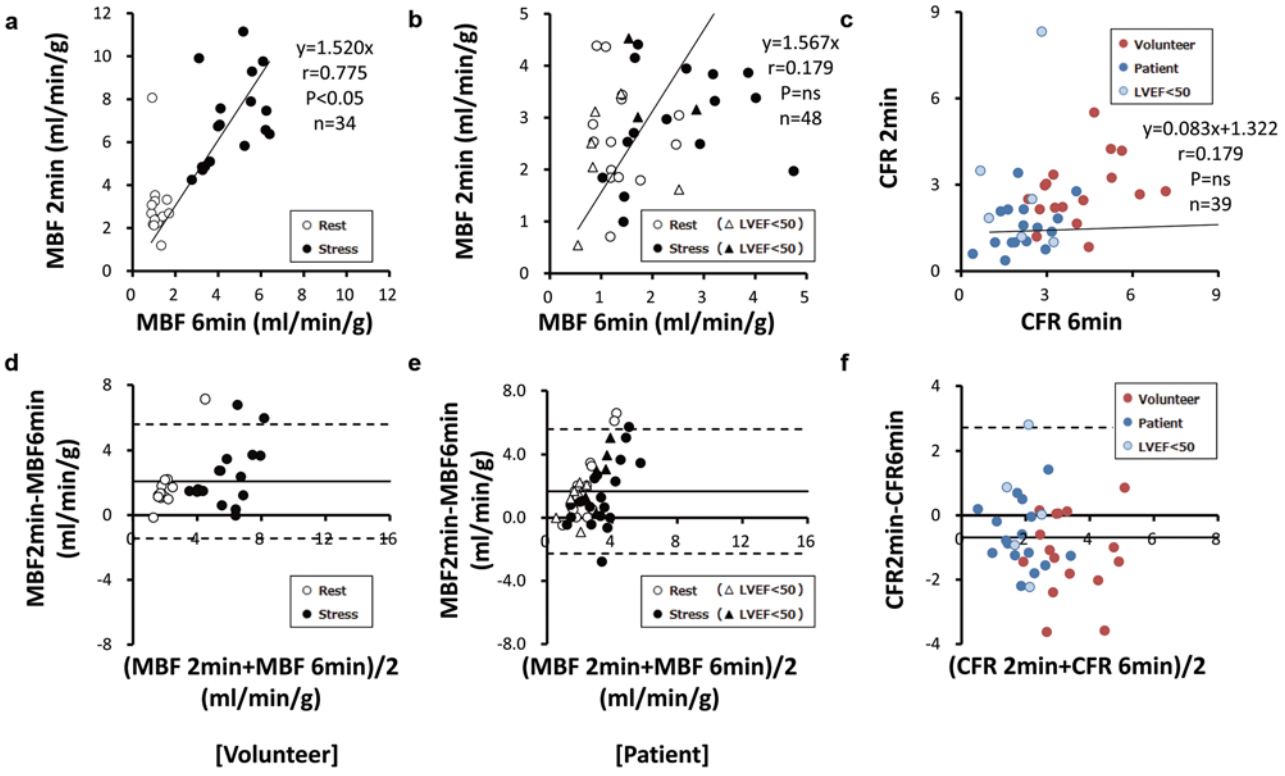


Fig. 5 2min whole MBF and CFR

Relationship between the 2-min and 6-min acquisition data. The MBF values of the healthy controls showed a slightly positive correlation (a). The MBF (b) and CFR (c) values of the patients showed poor correlations between the 2-min and 6-min acquisition data. In both the controls and patients, the Bland-Altman plots showed considerable variations, and the MBF values showed a positive correlation between the 2-min and 6-min acquisition data.

tered intravenously from 2 or 3 minutes before the start of a scan to the end of the scan. The reported scan times of ^{15}O-H_2O PET were over 4-min and 40-sec (23) to 6-min (24,25). In fact, our institution adopted the 6-min scan and the 9-min ATP infusion as a standard method (26,27). The side effects of the pharmacological stress could be lessened if the acquisition time were decreased. In addition, a shorter scan time could lead to a reduction in the effect of body movement, which has been considered an important source of errors when quantifying the MBF (28).

Among the several PET perfusion tracers, ^{15}O-H_2O is considered an ideal PET tracer for the quantification of MBF because it is metabolically inert, freely diffusible, and independent of the myocardial metabolic state (29). However, we found that it was challenging to set the ROI of the myocardium due to the limited image quality provided by ^{15}O-H_2O, especially using the shorter-time data. In fact, in the examinations of eight patients (26.7%) in the rest study and four patients (13.3%) in the stress study, it was difficult to set the ROI of the LV in the 2-min data acquisition. The difficulty or impossibility of setting an ROI is thought to be causally related to the low MBF, which in turn might lead to the delay of peak flow time. In fact, there was no subject among our 17 controls for whom the ROI could not be set, and among them, the resting MBF values were significantly lower than those of the patients for whom the ROI could be set. On the other hand, for the 3-min data acquisition, there was no subject for whom the ROI of the LV could not be set. The Bland-Altman plot comparing the MBF_{2min} and MBF_{6min} showed a positive correlation, and thus the estimated MBF_{2min} could be overestimated. One of the reasons for the overestimation may be the shortness of the dynamic data. The MBF value from shorter acquisition time may have been obtained from only a part of the LV tissue curve influenced by the steep peek of the LV cavity curve. In other words, it may be that only in-flow was dominant, while out-flow was underestimated. Therefore, the calculated MBF might have been overestimated.

The CFR values of our control subjects were significantly higher than those of the patients, even without significant stenosis. In this study, the patients were older and showed higher rates of DM, HT, HL, and smoking compared to the controls, and these are risk factors for low CFR (18,30,31). Second, we did not consider the coronary artery stenosis in the distal part, minor branches or collateral flow in the occluded vessels. It might be difficult to consider the effects from these factors, because there are variations in the anatomy of coronary arteries. In addition, stenosis in the distal part or minor branches may generally have little influence on the

MBF and CFR.

Study limitations

The present study had methodological limitations. First, the sample size was relatively small. However, even the smaller sample sizes used in previous physiological studies were found to have sufficient power to validate the methods (14,32). Finally, all of our data were taken by a PET scanner, and we discuss only 2D data acquisition. Current PET/CT scanners offer only a 3-dimensional (3D) data acquisition mode. This mode can reduce the patients' radiation exposure because of the lower injection dose of ^{15}O-H_2O. However, scatter and random gamma rays are increased due to the exclusion of the septa, which may cause deterioration in the image quality and increase the variability. Therefore, 2D data acquisition has been the standard approach for MBF quantification with ^{15}O-H_2O. In studies using PET/CT with 3D data acquisition (24,33,34), utility similar to that of 2D data acquisition was confirmed. For further evaluation, we plan to test the results of the present study by using PET/CT with 3D data acquisition.

Conclusions

A 3-min (i.e., shorter than the standard 6-min) scan by ^{15}O-H_2O PET can be used for the quantitative evaluation of MBF and CFR. The shorter scan time could lead to reductions in both the side effects from the pharmacological stress and the effect of body movement.

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Conflicts of interest

The authors declare that they have no conflicts of interest to report.

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