Myocardial Blood Flow: Comparison of Oxygen-15-Water Bolus Injection, Slow Infusion and Oxygen-15-Carbon Dioxide Slow Inhalation

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This study investigates the most appropriate protocol for measuring regional myocardial blood flow (MBF) using ^{15}O-water in clinical applications. **Methods:** Regional MBF, perfusable tissue fraction (PTF) and arterial blood volume (V_a) were measured using ^{15}O-water and dynamic PET on five healthy volunteers based on previously published models. Calculated values were compared for the following three tracer administration protocols: ^{15}O-water bolus injection, ^{15}O-water slow (2 min) infusion and ^{15}O-carbon dioxide slow (2 min) inhalation. For the two slow administration protocols, the three parameters MBF, PTF and V_a were computed by fitting the model equations to the myocardial regional time-activity curve. For the bolus injection of ^{15}O-water, only two parameters, MBF and PTF, were fitted by using a fixed V_a value obtained by a carbon dioxide blood volume scan. **Results:** All protocols provided consistent MBF values, and the calculated values were homogeneous throughout the whole myocardial segments for all subjects. PTF values were also homogeneous and consistent in the anterior and lateral wall regions, but were significantly greater in the septum (~20%) when the slow ^{15}O-carbon dioxide inhalation protocol was used. MBF and PTF values obtained from the bolus injection protocol showed the smallest intersubject and interregional variations. The simulation study also showed that the magnitude of error was smallest when the bolus injection protocol was employed. **Conclusion:** The data suggest that the ^{15}O-water bolus injection protocol together with the two-parameter fitting procedure provides the most accurate results for MBF and PTF. However, it requires arterial cannulation and a separate carbon monoxide scan. For clinical studies, however, the ^{15}O-water infusion protocol would be a good alternative, providing MBF and PTF results with an acceptable degree of accuracy and without the need for arterial cannulation.

Key Words: PET; oxygen-15-water; myocardial blood flow; perfusable tissue fraction

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The use of ^{15}O-water in PET provides a noninvasive method for in vivo quantification of regional myocardial blood flow (MBF) (*1–4*). The technique to calculate regional MBF using a single-compartment approach intrinsically corrects for the systematic underestimation of the myocardial signal, which is due to cardiac wall motion and the small transmural thickness of the myocardial wall relative to the intrinsic spatial resolution of the PET scanner (*5,6*). This correction is based on the concept of perfusable tissue fraction (PTF) in describing the ^{15}O-water kinetics. PTF (originally called the tissue fraction (*1,7*)) is defined as the fractional mass of the tissue that is capable of rapidly exchanging water within a given region of interest (ROI), and corresponds to the discrepancy between the observed and the expected tissue densities (i.e., recovery coefficient).

The ^{15}O-water MBF method also included a correction for the spillover of blood radioactivity into the myocardial ROI, which is again due to the cardiac wall motion and the limited spatial resolution of PET. In the original procedure, this correction was made based on information provided by an ^{15}O-carbon monoxide scan (*1,8*). More recently, the method was improved by incorporating an additional arterial blood volume parameter (together with MBF and PTF) into the modeling process, circumventing the need for an additional ^{15}O-carbon monoxide scan (*2–4,7,9*). In addition, this method was extended to employ inhalation of gaseous ^{15}O-carbon dioxide instead of the intravenous ^{15}O-water injection (*4,8–11*). Since the ^{15}O in carbon dioxide is rapidly transferred to ^{15}O-water in the lung, this procedure is therefore equivalent to an intravenous ^{15}O-water infusion. These methods have been validated independently by several workers to provide quantitative MBF values consistent with those obtained by the microsphere technique over a wide physiological range (*2–4*).

A limitation was expected when applying the ^{15}O-water MBF method to the septal region, because of the complexity of the spillover of blood radioactivity into this region. The current model does not take into account the fact that the time-activity curves are different for the right and left heart chambers, and therefore the spillover of blood radioactivity from the right ventricle causes a systematic error in

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the interventricular septum. To minimize the effects of the spillover from the right ventricle, a procedure was proposed for a bolus ^{15}O-water injection protocol, in which the early portion of the myocardial time-activity data (e.g., the first minute) was neglected in the fitting procedure (*1*). This procedure was successful and yielded MBF and PTF values which, in normal subjects, were not significantly different from those of the nonseptal regions. A drawback of this procedure is that it requires arterial cannulation for an independent measurement of the input function using an online beta detector because of the limited accuracy of conventional PET scanners in recording the extremely high counting rates following bolus administration of ^{15}O-water. To obtain the input function noninvasively from the left ventricular chamber in the PET images themselves, slow administration protocols (i.e., slow carbon dioxide inhalation or slow ^{15}O-water infusion) are preferred, especially when using conventional PET scanners that employ BGO detectors.

When using the slow ^{15}O-carbon dioxide inhalation protocol, it has been demonstrated that the obtained PTF values are significantly greater in the septum (~20%) as compared to nonseptal segments, while MBF values in the septum are not significantly different from other regions. This overestimation in PTF has been attributed to the spillover from the right chambers (*7–10*). However, the use of a slow ^{15}O-water infusion protocol can be expected to reduce this problem (*7,9–11*).

This study evaluates the effects of the spillover of radioactivity from right ventricular blood into the septal ROI in three ^{15}O-water MBF methods: bolus ^{15}O-water injection, slow ^{15}O-carbon dioxide inhalation and slow ^{15}O-water infusion. These protocols were investigated in terms of consistency of calculated parameters and their practicality for clinical applications. Strategies for ROI selection in the septum were also investigated.

METHODS

Subjects

Five healthy volunteers (four male and one female), 27–58 yr old (mean ± s.d.; 41 ± 14 yr), were included in this study. None of the subjects had any signs or symptoms of cardiac disease, and all had normal electrocardiograms and normal echocardiography, at rest and after the treadmill test. All subjects gave written informed consent to the protocol approved by the clinical PET research committee of the Research Institute for Brain and Blood Vessels-Akita.

PET Protocol

PET studies were performed using a Headtome-IV scanner (*12*) which allowed seven planes of data acquisition in an axial field of view (FOV) of 7.8 cm. All emission data were reconstructed using the filtered backprojection method. A Butterworth filter with a low cutoff frequency was used, resulting in an in-plane spatial resolution of 10 mm FWHM at the center of the FOV. The axial resolution was 9.0 mm at the center of the FOV.

All subjects laid supine on the scanner bed with their arms out of the FOV. Electrocardiograms, for measurement of heart rate, and blood pressure (by automatic arm-cuff sphygmomanometer), were monitored throughout the study. Following a transmission scan for attenuation correction, the blood pool was imaged using inhalation of ^{15}O-carbon monoxide. The ^{15}O-carbon monoxide inhalation lasted for 1 min (a total supply of approximately 3.7 GBq), and a 4-min single-frame emission acquisition was initiated at 3 min after the end of ^{15}O-carbon monoxide inhalation. Arterial blood samples were taken every minute during the scan, and the ^{15}O-carbon monoxide concentration in the whole blood was measured using a NaI well counter cross-calibrated against the PET scanner.

After a 15-min interval to allow for ^{15}O radioactivity decay to a background level, a dynamic scan was obtained following a bolus injection of ^{15}O-water (555 MBq) into the antecubital vein. Injection of ^{15}O-water in 5 ml saline was given after an additional injection of nonradioactive saline (20 ml) to flush the radioactivity in the tube. The scan sequence was 6 × 5 sec, 6 × 15 sec, and 8 × 30 sec. The total scan time was 6 min.

Approximately 20 min after this scan, ^{15}O-carbon dioxide gas was inhaled for 2 min (3–5 MBq/ml at a flow rate of 500 ml/min); a second dynamic scan over 6 min was started at the same time as the start of ^{15}O-carbon dioxide delivery. The scan sequence was the same as that used for the ^{15}O-water injection scan. Twenty minutes later, another dynamic scan was initiated during a slow infusion of ^{15}O-water. The ^{15}O-water infusion lasted for 2 min (constant rate of 2.5 ml/min, total infused dose 1.48 GBq). PET imaging was initiated when the radioactivity appeared in the FOV (right ventricular chamber). The ^{15}O-water infusion was followed by an additional constant infusion of nonradioactive saline for 2 min.

A catheter was placed in the radial artery. During the bolus ^{15}O-water injection, arterial blood was continuously withdrawn (withdrawal rate: 5 ml/min), and the arterial input function was monitored using a beta probe.

Input Function

For the slow ^{15}O-carbon dioxide inhalation and the slow ^{15}O-water infusion studies, the arterial input function was obtained from the left ventricular time-activity curve using a previously validated method (*13*). Here, the limited recovery of the left ventricular ROI and the spillover from the myocardial signals were corrected. In the ^{15}O-water bolus study, the beta probe curve was used as the input function. The delay and dispersion occurring in the tube system (delay <1 sec, dispersion time constant <0.5 sec) and those in the radial artery were corrected using a previously reported method (*14,15*).

Regions of Interest

ROIs were selected manually on the left ventricular chamber and three myocardial segments; namely the septum, the anterior wall and the lateral wall (Fig. 1). In the septal region, two kinds of ROIs were drawn, one by tracing the whole septum and the other by tracing the half adjacent to the left ventricular chamber. These selections were performed on two mid-ventricular slices and the data were analyzed independently for each slice. The number of pixels selected in ROIs (pixel size = 2 × 2 mm^2) were 220–250 for the left ventricle, 250–300 for the whole septum, 150–200 for the half septum, 300–350 for the anterior wall and 300–400 for the lateral wall.

Fitting Procedure

Based on previous works (*1,4,7,10,11,13*), the myocardial time-activity curve, $R(t)$, was expressed as:

$$R(t) = \alpha \cdot Ci(t) + V_a \cdot a(t), \quad \text{Eq. 1}$$

where $Ci(t)$ is the net tissue time-activity curve which can be expressed according to the single-tissue compartment model (*16*) as:

$$Ci(t) = f \cdot a(t) \otimes e^{-f/p \cdot t}, \quad \text{Eq. 2}$$

where $\otimes$ denotes the convolution operation, $a(t)$ the arterial input function, f and α the regional MBF and PTF, respectively, p the myocardial-to-blood partition coefficient of water and V_a the arterial blood volume (spillover from cardiac chamber).

In the ^{15}O-carbon dioxide slow inhalation and the ^{15}O-water slow infusion studies, three parameters f, α and V_a were fitted to Equation 1 based on a previously validated procedure (*4*). For the ^{15}O-water bolus injection study, the two parameters f and α were fitted using a fixed value of V_a which was measured from the ^{15}O-carbon monoxide blood pool scan (*1,7*). Because of the limited accuracy of the PET scanner at high counting rates in the bolus injection study, the early portion of the time activity data was neglected as proposed previously (*1*).

Statistical Test

All data were presented as mean ± s.d. Comparisons of multiple data sets were performed using a one-way ANOVA, and $p < 0.05$ was considered statistically significant. Specific differences were identified by either a paired or an unpaired Student's t-test corrected for multiple comparisons with Bonferroni inequality adjustment.

Simulation

A simulation study was carried out to estimate errors in the septum due to inappropriate modeling for the spillover from the right ventricle. The septal time-activity curves, $R_{Sep}(t)$, were simulated as:

$$R_{Sep}(t) = \alpha \cdot C_i(t) + V_{LV} \cdot LV(t) + V_{RV} \cdot RV(t), \quad \text{Eq. 3}$$

where V_{LV} and V_{RV} are the fractional volume of the spillover from the left ventricle and the right ventricle and $LV(t)$ and $RV(t)$ are the time-activity curves in the left- and right ventricular chambers.

Using typical left ventricular and right ventricular time-activity curves, Equation 1 was simulated for the three tracer administration protocols for various ratios $V_{RV}/(V_{LV} + V_{RV})$ under the condition: $V_{LV} + V_{RV} = 0.4$ ml/ml. The input function was defined from the left ventricular time-activity curves for each administration protocol. In addition, the following values were assumed:

$$\alpha = 0.6 \text{ g/ml}$$

$$f = 1.0 \text{ ml/min/g}$$

$$p = 0.91 \text{ ml/g}. \quad \text{Eq. 4}$$

Then, MBF (f), PTF (α) and the arterial blood volume (V_a) were fitted as described above. For the bolus-injection curves, V_a was set equal to 0.4 ml/ml ($V_{LV} + V_{RV}$) and the two parameters f and α were fitted. Finally, errors in the calculated values of f, α and V_a were estimated as a function of the ratio $V_{RV}/(V_{LV} + V_{RV})$ for all protocols.

Another set of simulation studies was performed to view effects of overestimation in the arterial blood volume V_a in the two-parameter fitting procedure. The overestimation may be introduced in the V_a value, if measured directly from a ^{15}O-carbon monoxide scan, because the carbon monoxide scan would provide the total blood volume that includes the arterial and venous blood volume in the myocardium (see Discussion). First, the myocardial ROI concentration curves were simulated using Equation 1 for each of the three administration protocols using the arterial input functions obtained from typical studies. In this simulation, a fixed V_a value of 0.20 ml/ml was assumed. The constants α, f and p were assumed to be as in Equation 4. Second, the parameters f and α were fitted by assuming various values for V_a. Errors in the calculated values of f and α were expressed as a function of percent overestimation in the V_a value. For the ^{15}O-water bolus injection procedure, fitting was performed according to two procedures: in one procedure, all time-activity data were equally weighted and fitted to the model equation (the same as the slow administration protocols), and in another procedure, the early portion of the time-activity data was neglected in the fitting, as was done in the human data analysis for the bolus injection study (*1*).

RESULTS

Figure 2 shows serial PET images of a mid-ventricular slice obtained from a typical volunteer following bolus ^{15}O-water injection, slow ^{15}O-water infusion and slow ^{15}O-carbon dioxide inhalation. It can be seen that in the bolus and slow ^{15}O-water administration protocols, the radioactivity appeared in the right ventricular chamber first, diffused into the lung and to the left ventricular chamber, and then to the whole heart, including the myocardium. In contrast, in the ^{15}O-carbon dioxide inhalation protocol, the tracer appeared first in the left ventricular chamber, and then diffused into the myocardium. In the latter case the radioactivity concentration in the right ventricular chamber was lower than that in the left ventricular chamber throughout the scan period. The peak-counting rate (including random coincidence events) at the mid-ventricular slice was 70–90 kcps for the bolus injection study, and 20–30 kcps for the slow administration protocols. The maximum dead time correction factor was 1.5–2.0 for the bolus injection study, and 1.1–1.2 for the slow administration protocols. The total coincidence counts (corrected for randoms) acquired during the 6 min scan period was ~1.5 mega counts, and 2–3 mega counts, corresponding to the bolus and the slow administration procedures.

Typical time-activity curves observed in the left and the right ventricle regions for the three administration protocols are shown in Figure 3 for comparison. These curves were used in the simulation study. Figure 4 shows typical fits of the myocardial time-activity curves for the three administration protocols.

Heart rate and blood pressure were constant in all studies during the entire scan period. Table 1 summarizes results of the various analyses performed on the five normal subjects. No significant difference was observed in MBF values among the three protocols. In addition, no significant difference was observed among the segments. PTF values were also homogeneous (no significant difference) among all myocardial regions except for the septum. In this region, when measured by the carbon dioxide inhalation

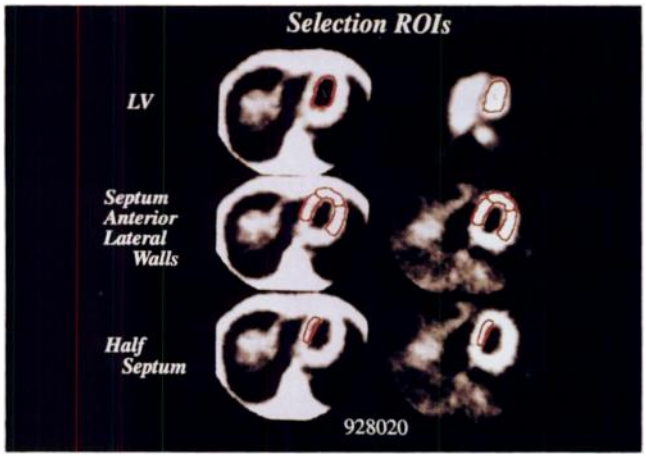

FIGURE 1. Selection of ROIs on the left ventricular chamber and three myocardial segments (septum, anterior wall and lateral wall). The left ventricular ROI was placed on the extravascular density image (top left) and the blood-pool image (top right). The three myocardial ROIs were placed by tracing the extravascular density (middle left) and the ^{15}O-water washout images (middle right). An ROI was also selected on the septum by tracing half the septum on the left ventricular side guided by the extravascular density (bottom left) and ^{15}O-water washout images (bottom right). These ROI selections were performed on two PET image slices in each study, yielding ten datasets from five studies for each tracer administration protocol. These data were analyzed independently (each left ventricular curve defined for the same tomographic slice as the myocardial data).

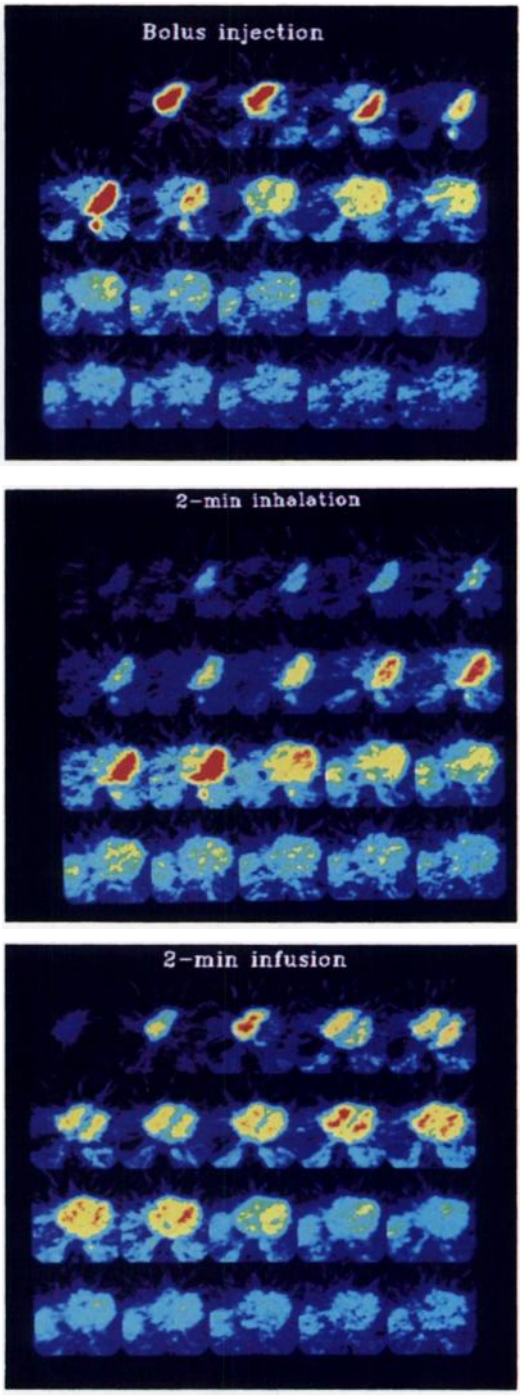

FIGURE 2. Serial PET images of the mid-ventricular slice obtained from a typical study following administration of ^{15}O-water with three different administration protocols: intravenous bolus injection of ^{15}O-water (top), continuous (slow) inhalation of gaseous ^{15}O-carbon dioxide for a period of 2 min (middle), and continuous (slow) intravenous infusion of ^{15}O-water for a period of 2 min (bottom). The scan sequence was 6–5 sec, 6–15 sec and 8–30 sec. Sequential images are ordered from left to right, and top to bottom.

protocol, the calculated PTF values were significantly greater than other regions ($p < 0.001$). The ^{15}O-carbon dioxide inhalation protocol indicated significantly greater PTF values in the septum than the other protocols ($p < 0.001$). A significant difference was also observed in PTF values between the whole septal and half septal regions ($p < 0.01$) for the ^{15}O-carbon dioxide inhalation protocol, whereas MBF values were not different in this protocol.

The total blood volume (V_B) measured by the carbon monoxide PET scan was significantly greater in the septum ($p < 0.001$) compared with the anterior and the lateral wall regions (Table 1). The arterial blood volume (V_a) in the anterior and the lateral wall regions measured by the slow carbon dioxide inhalation and the slow ^{15}O-water infusion protocols were found to be significantly smaller than the total blood volume measured by the ^{15}O-carbon monoxide scan. The arterial blood volume in the septum measured by the slow ^{15}O-carbon dioxide inhalation was also found to be smaller than the total blood volume by a factor of two. No significant difference was observed between the arterial blood volume and the total blood volume in the septum when measured by the slow ^{15}O-water infusion.

Figure 5 shows results of the first simulation study, demonstrating effects of spillover from the right ventricular chamber at three MBF conditions; f = 0.5 (Fig. 5A), f = 1.0 (Fig. 5B) and f = 2.0 ml/min/g (Fig. 5C). At each MBF condition, results are shown for the three tracer administration protocols with different fitting procedures. The increase in the ratio $V_{RV}/(V_{LV} + V_{RV})$ corresponds to an increase of the spillover component from the right ventricle. The bolus injection protocol with two-parameter fitting (in which the early portion of the data was neglected)

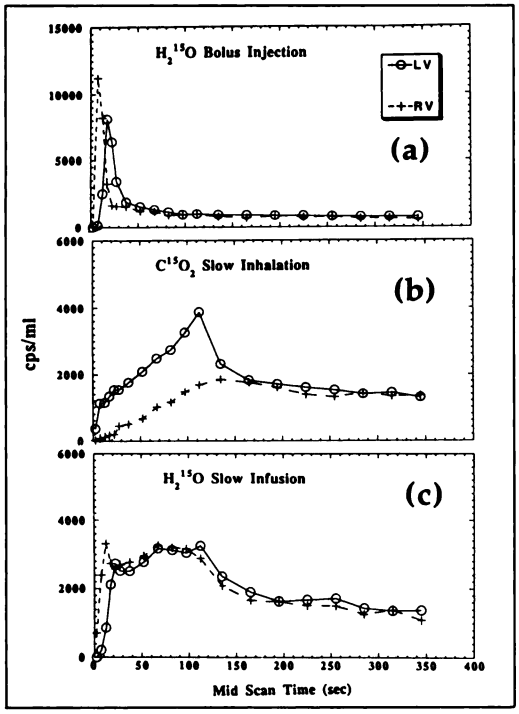

FIGURE 3. Representative time-activity curves obtained from ROIs in the left (open circles) and in the right ventricles (pluses). These data were recorded for 6 min following (a) the intravenous bolus injection of ^{15}O-water; (b) the slow (2 min) inhalation of gaseous carbon dioxide; and (c) the slow (2 min) infusion of ^{15}O-water. The data were already corrected for the radioactivity decay of ^{15}O (half-life = 123 sec). The curves of this particular study were used in the simulation study (see also Fig. 5).

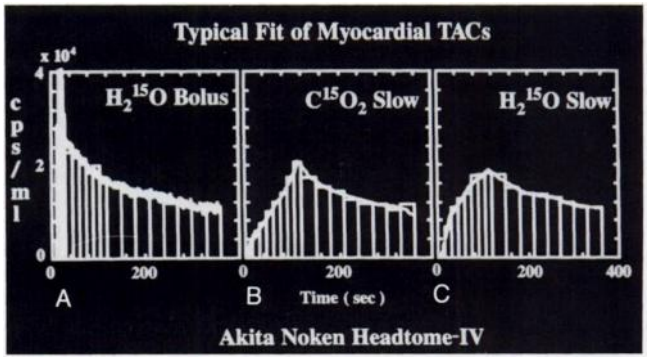

FIGURE 4. Examples of the fit of the model equation to the myocardial time-activity curves obtained from a typical volunteer study using three different tracer administration protocols: (A) the intravenous bolus injection of ^{15}O-water, (B) the slow (2 min) inhalation of gaseous carbon dioxide, and (C) the slow (2 min) constant infusion of ^{15}O-water. Histograms correspond to measured myocardial time-activity curves. Solid lines denote the best fits to the model equations. All the data were already corrected for radioactivity decay of ^{15}O. For the ^{15}O-water bolus injection two parameters (MBF and PTF) were fitted using a blood volume value measured by the carbon monoxide scan. For the slow administration protocols (^{15}O-carbon dioxide slow inhalation and ^{15}O-water slow infusion), three parameters (MBF, PTF and the arterial blood volume) were fitted (see also methods).

provided the smallest errors in the calculated MBF and PTF values. Errors were small in MBF with the slow ^{15}O-carbon dioxide inhalation protocol, but a relatively large error (overestimation) was introduced in PTF, e.g.,

TABLE 1

Summary of Regional Myocardial Blood Flow (MBF), Perfusable Tissue Fraction (PTF), Arterial Blood Volume (V_a) and the Total Blood Volume (V_B) Obtained from Five Volunteers

Protocol	Myocardial segment			
	Whole septal	Half septal	Whole anterior	Whole lateral
^{15}O-water bolus				
MBF [ml/min/g]	0.85 ± 0.13	0.86 ± 0.14	0.87 ± 0.17	0.85 ± 0.12
PTF [g/ml]	0.55 ± 0.08	0.57 ± 0.04	0.52 ± 0.04	0.50 ± 0.07
^{15}O-carbon dioxide slow				
MBF [ml/min/g]	0.81 ± 0.16	0.91 ± 0.22	0.94 ± 0.18	0.97 ± 0.24
PTF [g/ml]	0.69 ± 0.07†	0.63 ± 0.08†	0.53 ± 0.06	0.50 ± 0.07
V_a [ml/ml]	0.24 ± 0.05§	0.38 ± 0.06§	0.18 ± 0.03‡	0.25 ± 0.03‡
^{15}O-water slow				
MBF [ml/min/g]	0.76 ± 0.14	0.85 ± 0.18	0.89 ± 0.15	0.81 ± 0.17
PTF [g/ml]	0.48 ± 0.04	0.55 ± 0.05	0.52 ± 0.03	0.50 ± 0.06
V_a [ml/ml]	0.55 ± 0.11*	0.52 ± 0.13*	0.22 ± 0.04§	0.26 ± 0.05§
^{15}O-carbon monoxide				
V_B [ml/ml]	0.55 ± 0.10*	0.56 ± 0.08*	0.28 ± 0.05	0.29 ± 0.03

MBF, PTF and V_a were calculated by fitting the dynamic PET data for ^{15}O-water bolus injection, ^{15}O-carbon dioxide slow inhalation and ^{15}O-water slow infusion. V_B was calculated from a ^{15}O-carbon monoxide inhalation static PET scan. ROIs were placed on two slices in each study, yielding 10 datasets. The four myocardial regions corresponded to the whole septal segment, half the septal segment, the whole anterior wall segment, and the whole lateral segment. These data together with the left-ventricular time-activity curve for the same tomographic slice were analyzed independently. ROI selections are shown in Figure 1.

*$p < 0.001$ vs. the anterior and lateral regions.

†$p < 0.001$ vs. all other ROIs and all other protocols by Student's t-test, n = 10 (5 subjects × 2 slices).

‡$p < 0.01$ vs. V_B measured by the ^{15}O-carbon monoxide scan.

§$p < 0.001$ vs. V_B measured by the ^{15}O-carbon monoxide scan.

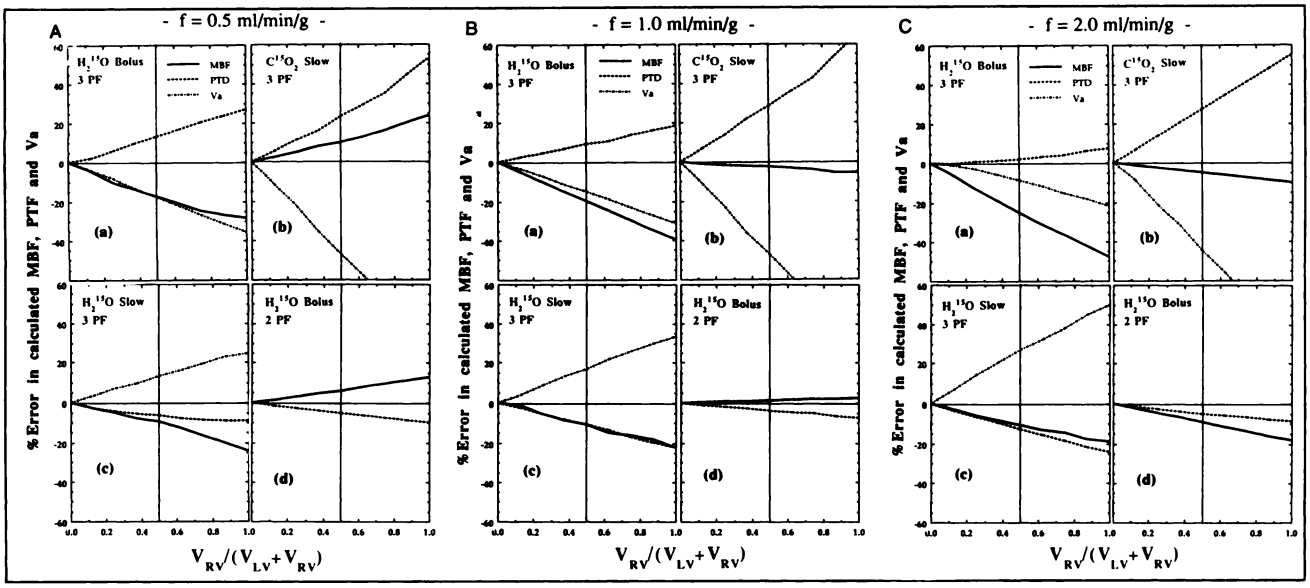

FIGURE 5. Results of the simulation study demonstrate the effects of inappropriate modeling in the septal region due to spillover from the right ventricle at a flow condition of f = 0.5 ml/min/g (A), at a flow condition of f = 1.0 ml/min/g (B), and at a high flow condition of f = 2.0 ml/min/g (C). Results are shown for three tracer administration protocols with three-parameter fitting (3 PF) of MBF, PTF and the arterial blood volume (V_a); i.e., (A) bolus injection of ^{15}O-water, (B) the slow carbon dioxide inhalation and (C) the slow infusion of ^{15}O-water. Results are also shown for the bolus injection of ^{15}O-water with two-parameter fitting (2 PF) of MBF and PTF (D). Abscissa denotes the right ventricle component, i.e., $V_{RV}/(V_{LV} + V_{RV})$, where V_{LV} and V_{RV} are the fractional volume of the left and the right ventricles, and $V_{LV} + V_{RV} = 0.4$ ml/ml was assumed. Systematic error increases in the calculated parameters as the right ventricle component increases in all protocols. Bolus injection protocol with the two parameter fitting (shown in D) provides the smallest errors in calculated MBF and PTF values. Note that the early portion of the myocardial time-activity data was neglected in the fitting in the ^{15}O-water bolus injection protocol.

20% for $V_{RV}/(V_{LV} + V_{RV}) = 0.5$. Errors in PTF were smaller in the slow ^{15}O-water infusion protocol than the slow carbon dioxide inhalation protocol (underestimation of approximately 8% for $V_{RV}/(V_{LV} + V_{RV}) = 0.5$). The error was also small in MBF with the slow ^{15}O-water infusion protocol, but slightly larger than the slow ^{15}O-carbon dioxide inhalation protocol (e.g., underestimation of approximately 10% for $V_{RV}/(V_{LV} + V_{RV}) = 0.5$).

Figure 6 shows results of the second simulation study, demonstrating effects of overestimation in the arterial blood volume (V_a) on errors in the calculated MBF and PTF values for the two-parameter fitting procedure. When fitting was performed using equally weighted time-activity data, both MBF and PTF were found to be underestimated for an overestimated V_a value (A, B, C). An overestimation of 30% in V_a caused an underestimation in MBF of approximately 20%. Neglecting the early portion of the time-activity data (first minute) in the fitting for the bolus injection protocol (D) was found to produce only small errors in both MBF and PTF (overestimation of V_a by 30% corresponded to errors in MBF and PTF of ~5%).

DISCUSSION

It was demonstrated that the three protocols compared in this study yielded consistent MBF values which were not significantly different from each other. In addition, the calculated MBF values were homogeneous throughout the left ventricular myocardial wall and no significant differences were observed between the three myocardial segments. These findings suggest that all tracer administration protocols are practically identical for quantitative measurement of regional MBF using ^{15}O-water and PET, and that the conventional single-compartment model (*2–4,7,13*) can be applied to MBF measurement even in the interventricular septal region.

A relatively small but systematic error can, however, be introduced in the septum due to the spillover from the right ventricular chamber, particularly in the PTF estimates. The magnitude of this error was found to be slightly dependent on the tracer administration protocol and on the fitting procedure (Fig. 5) and, therefore, an optimization of the protocol would be suggested to minimize the error.

The previously proposed procedure (*1*) was found to minimize the effects of the spillover from the right ventricular blood radioactivity in the septum. In this procedure, the bolus injection protocol and two-parameter fitting were employed, and the data taken at the early portion were neglected in the fitting process. As shown in Table 1, the inter-regional differences of both MBF and PTF are the smallest with this procedure. The simulation study (Fig. 5) also demonstrated that errors due to the spillover from the right ventricle were the smallest using this procedure. A drawback of this method is the requirement of continuous arterial blood sampling and a separate PET measurement of the blood volume using carbon monoxide. Noninvasive determination of the arterial input function from the left ventricular time-activity curve of the PET images themselves, which would be preferable for clinical use, is diffi-

cult to achieve with the bolus injection protocol due to the limited accuracy of a conventional PET scanner at high counting rates.

Calculated PTF values were found to be significantly greater in the septum (20%–30%) than other regions when the ^{15}O-carbon dioxide inhalation protocol was employed. The septal PTF values obtained by using the ^{15}O-carbon dioxide inhalation protocol were found to be significantly greater than those obtained from other protocols by 20%–30%. The simulation study predicted spillover from the right ventricle chamber and caused the overestimation of PTF (e.g., an overestimation of PTF by 20% for $V_{LV} = V_{RV}$ at f = 1.0 ml/min/g). This can be explained by the right ventricular radioactivity curve being equal to the average of whole-body tissues (i.e., mixed venous blood). The spillover from the right ventricular chamber is equivalent to the inclusion with tissues of low perfusion in the ^{15}O-carbon dioxide inhalation study.

Previous articles (*7,10,11*) proposed the use of PTF and/or an index derived from PTF (perfusable tissue index, PTI) for assessment of myocardial viability in patients with both acute and chronic myocardial infarction. However, the ^{15}O-carbon dioxide slow inhalation protocol was shown to provide these indices with a limited accuracy in the interventricular septal region, although the MBF values are not affected by the spillover from the right ventricle. An alternative protocol using intravenous administration of ^{15}O-water should be suggested for PTF (and PTI) determination.

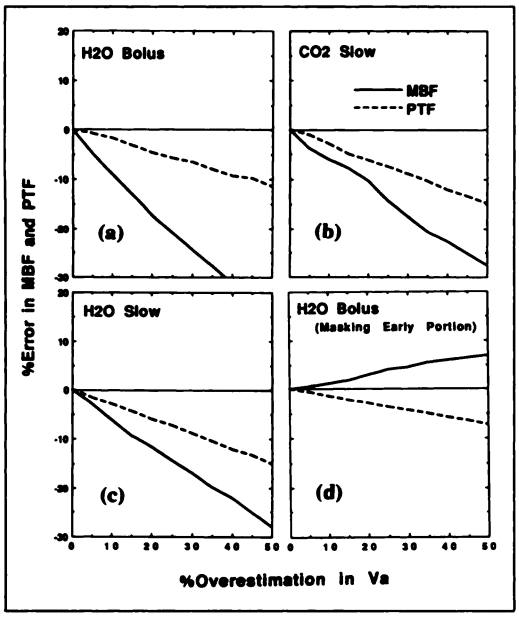

FIGURE 6. Results of the simulation study demonstrate the effects of overestimation in the arterial blood volume (V_a) on the calculated MBF and PTF values for the two-parameter fitting procedure (fitting MBF and PTF with an assumed V_a of 0.20 ml/ml). Percent errors in MBF and PTF were plotted as a function of % overestimation in V_a for three tracer administration protocols: (A) ^{15}O-water bolus injection; (B) CO_2 slow inhalation; and (C) ^{15}O-water slow infusion. In these fitting procedures, all time-activity data were equally weighted and fitted to the model equation. Errors were also evaluated for a previously proposed procedure (D), in which the early portion of the time-activity data were neglected from the fitting process (masking early portion).

The ^{15}O-water slow infusion protocol would be the method of choice for practical measurement of both MBF and PTF within an acceptable accuracy. A small systematic error may be caused in the septal region. However, the magnitude of this error was found to be relatively small, and was practically negligible as shown in Table 1. The errors in MBF and PTF in the septum can be further reduced by selecting the ROI slightly shifted to the left ventricular side from the middle of the septum as proposed by Hutchins et al (*17*). For instance, selection of only the half of the septal region adjacent to the left ventricular side $\{V_{RV}/(V_{LV} + V_{RV}) < 0.5\}$ is expected to reduce the error.

One advantage of using the ^{15}O-water slow infusion protocol is the smaller radiation dose to the patient as compared to the ^{15}O-carbon dioxide slow inhalation protocol, particularly in the trachea and in the lung. However, the use of an automatic infusion system would be recommended to reduce the radiation to the technologists in this protocol.

The observed arterial blood volume (V_a) in the anterior and the lateral wall regions was consistent between the slow ^{15}O-carbon dioxide inhalation and slow ^{15}O-water infusion protocols. However, it was shown that the arterial blood volume obtained by both methods was slightly smaller than the total blood volume directly measured by the ^{15}O-carbon monoxide scan (see Table 1). This observation has been explained previously (*7*) by the venous blood volume in the myocardial tissue (~0.1 ml/g of the myocardium (*18*)). Since the venous radioactivity concentration is equal to the regional tissue radioactivity concentration, the arterial blood volume fitted by the kinetic analysis excludes this venous volume fraction, while the total blood volume measured by the ^{15}O-carbon monoxide scan includes it.

The arterial blood volume in the septum obtained with the ^{15}O-carbon dioxide inhalation study was approximately half of that of the total blood volume measured by the ^{15}O-carbon monoxide scan. This is due to the fact that the ^{15}O-water concentration in the right ventricle is equal to an average of the whole-body tissue concentrations and, therefore, spillover from the right ventricle is equivalent to the inclusion of low-perfusion tissue but not arterial blood volume. It should be noted that the arterial blood volume in the septum measured with the slow ^{15}O-water infusion protocol was almost the same as the total blood volume measured with the ^{15}O-carbon monoxide scan. This is consistent with the fact that the blood radioactivity concentration is almost equal between the left and right ventricular chambers throughout the whole scan period.

CONCLUSION

Using a conventional ^{15}O-water MBF kinetic model, all protocols yielded consistent and homogeneous MBF val-

ues throughout the left ventricular wall, including the septum, the anterior wall and the lateral wall regions. However, PTF was systematically overestimated in the septum with the ^{15}O-carbon dioxide inhalation protocol; this can be attributed to an incomplete model of spillover from the right ventricular chamber. The present study suggests that the bolus ^{15}O-water injection protocol is the method of choice if arterial cannulation is acceptable, providing the most statistically stable MBF and PTF values with minimum systematic errors. For clinical applications, the ^{15}O-water slow infusion protocol is recommended, although small systematic errors can occur. Selection of the ROI slightly shifted to the left ventricle side would be recommended, providing noninvasive quantification of regional MBF and PTF without arterial cannulation. The ^{15}O-carbon dioxide slow inhalation protocol may be used for the MBF measurement alone, but a further improvement of the model is required for determination of PTF in the septum when using this protocol.

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