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Assessment of coronary vasodilator reserve by N-13 ammonia PET using the microsphere method and Patlak plot analysis

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Noninvasive quantification of regional myocardial blood flow (MBF) has been successfully achieved with N-13 ammonia. The microsphere method as a simple method for quantifying regional myocardial blood flow was reevaluated in comparison with Patlak graphical analysis. In addition coronary vasodilator reserve (CVR) was estimated by both methods. Methods: Dynamic N-13 ammonia PET studies were performed in 10 healthy volunteers and 10 patients with coronary artery disease at baseline and after dipyridamole infusion (0.56 mg/kg). MBF was estimated by the microsphere method at various times and by Patlak graphical analysis. In order to reduce the noise level in the microsphere method, MBF estimates were also performed after data in 10–40 seconds were averaged. Results: In the studies on normal subjects MBF (ml/min/g) determined by the microsphere method significantly differs from time to time. However, MBF determined by the modified microsphere method [with average (Extraction fraction) × MBF values obtained between 100 and 120 sec] linearly correlated well with MBF by Patlak graphical analysis ($r = 0.97$, slope = 0.98, intercept = 0.20). In the studies on patients with coronary artery disease a good agreement of the MBF estimates was also observed ($r = 0.97$, slope = 0.98, intercept = 0.22). In the studies on the normal subjects and patients with coronary artery disease, CVR obtained by the modified microsphere method after correcting the overestimated MBF values also correlated well with that by Patlak graphical analysis ($r = 0.90$, slope = 1.14, intercept = –0.15, and $r = 0.92$, slope = 0.82, intercept = 0.25, respectively). Conclusion: The modified microsphere method is a very simple and reliable approach for quantifying MBF with N-13 ammonia PET which is comparable to Patlak graphical analysis. It also makes possible CVR assessment as accurate as Patlak graphical analysis.

Key words: positron emission tomography, N-13 ammonia, myocardial blood flow, coronary vasodilator reserve

INTRODUCTION

NONINVASIVE QUANTIFICATION of regional myocardial blood flow (MBF) is one of the major goals in clinical cardiology. The evaluation of regional MBF under resting and stress conditions provides important clinical information. The high spatial and temporal resolution of PET imaging makes possible the definition of regional blood and tissue kinetics. Quantification of regional MBF by PET has therefore been investigated and successfully achieved with N-13 ammonia[1–12] and O-15 water.[13–15]

N-13 ammonia exhibits properties that to some extent resemble those of radioactive microspheres.[1] The microsphere method[16,17] was therefore introduced for quantification of MBF and validated,[7–9] but this method involves several problems. First, it is affected by the time of measurement after tracer injection.[7–9] Second, it inherently considers that the spillover fraction of radioactivities from the left ventricular chamber to the myocardium is

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zero and therefore overestimates MBF.[12] Third, it usually uses one single datum for static myocardial uptake which may contain significant noise.

In order to overcome these problems, two- or three-compartment model fitting was introduced and successfully applied to human studies.[2–4] This method requires sophisticated computer processing in order to translate scintigraphic information into absolute MBF measurements. A simpler method is therefore required, especially in the clinical settings. Choi et al. introduced Patlak graphical analysis for the quantification of regional MBF with N-13 ammonia PET and have shown that this is a simple and reliable method comparable to a compartment model fitting.[12]

This study was designed (1) to reevaluate the microsphere method by comparing Patlak graphical analysis and obtain a simpler method for the quantification of MBF, and (2) to evaluate coronary vasodilator reserve (CVR) by this method in clinical cases.

MATERIALS AND METHODS

We studied 10 normal healthy volunteers and 10 patients with coronary artery disease. The normal volunteers were 9 men and 1 woman who ranged in age from 26 to 52 years (average, 38.1 years old). They were selected because their history and physical examinations had shown them to be at low risk for coronary artery disease. All the patients had arteriographically documented coronary artery disease (6 men and 4 women with a mean age of 63.1, ranging from 48 to 77 years old). PET studies were performed at the baseline and again after dipyridamole induced myocardial hyperemia in each subject. Each subject gave written informed consent approved by the Kyoto University Ethical Study Committee.

The PET studies were performed with a whole-body PET camera (PCT 3600W, Hitachi Medical Co.; Tokyo, Japan). It provides 15 slices at 7 mm intervals simultaneously. The scanner has an effective resolution of 9 mm and an axial resolution of 7 mm at full width half maximum after reconstruction.[18] Each subject was positioned on the PET camera with the aid of an ultrasound technique. At the beginning of the PET study, a transmission scan was obtained for 20 minutes with a germanium-68/gallium-68 external source in order to correct photon attenuation.

Approximately 370 MBq (10 mCi) of N-13 ammonia was intravenously administered over a 30-sec period and the intravenous line was flushed with additional saline over a 30-sec interval. Serial dynamic PET scans (10 sec × 12 frames, 1 min × 8 frames) were initiated simultaneously with N-13 ammonia injection. The total acquisition time after the injection of N-13 ammonia was 10 min.

Approximately 100–120 minutes after the baseline study, dipyridamole (0.56 mg/kg) was infused intravenously over 4 min. The second injection of N-13 ammonia was started at 4 min after the end of the dipyridamole infusion and heart rate and blood pressure were stable. The dynamic positron emission tomographic image acquisition followed the same protocol as used in the baseline study.

N-13 ammonia static images were reconstructed from the last 8 frames (between 2 and 10 minutes postinjection).

Data Analysis

Twelve regions of interest (4 mm-wide) were drawn on the left ventricular myocardium of the static images (Fig. 1). Partial volume effects are corrected with a constant recovery coefficient of 0.78 assuming that myocardium is uniform and its thickness is 1 cm.[12] Small square regions of interest with an area of about 50 mm^2 were assigned to the left ventricular cavity.[19,20] These ROIs were copied onto the serially acquired transaxial dynamic image frames. In order to reduce the noise of the blood-pool activities, two regions of interest were drawn on the cavity of the mid-ventricular imaging planes and were averaged.[12] In order to calculate the true input function, Ca(t), the fraction of N-13 metabolites was subtracted on the basis of the previous reports.[20]

Calculation of MBF

Estimation of regional MBF by Patlak plot analysis. The two compartment mathematical model shown in Figure 2 was introduced for quantifying MBF by N-13 ammonia dynamic PET.[2,4,12] According to this model, the following equations were obtained,[2,12]

$$Q_i(t) = Q_1(t) + Q_2(t) + SP_{bt} \cdot AB(t) \qquad \text{Eq. 1}$$

$$\frac{dQ_1(t)}{dt} = -\frac{K_1 + MBF}{V} Q_1(t) + k_2 Q_2(t) + MBF^* C_a(t) \qquad \text{Eq. 2}$$

$$\frac{dQ_2(t)}{dt} = \frac{K_1}{V} Q_1(t) - k_2 Q_2(t). \qquad \text{Eq. 3}$$

Where AB(t) is N-13 radioactivity in arterial blood. The rate constant k_2 was assumed to be zero during the first 2 min after injection of the tracer due to relatively long clearance half-times of trapped N-13 activity.[1] At large t when $dQ_1(t)/dt$ was assumed to be zero, one can obtain the following Patlak equation:[12]

$$\frac{Q_i(t)}{C_a(t)} = K \frac{\int_0^t Ca(\tau)d\tau}{C_a(t)} + \frac{MBF^2 V}{(MBF + K_1)^2} + SP_{bt} \frac{AB(t)}{C_a(t)}. \qquad \text{Eq. 4}$$

K is expressed as follows:

$$K = MBF \frac{K_1}{K_1 + MBF}. \qquad \text{Eq. 5}$$

The extraction fraction (E) can be described as follows by equating it from the model fitting,

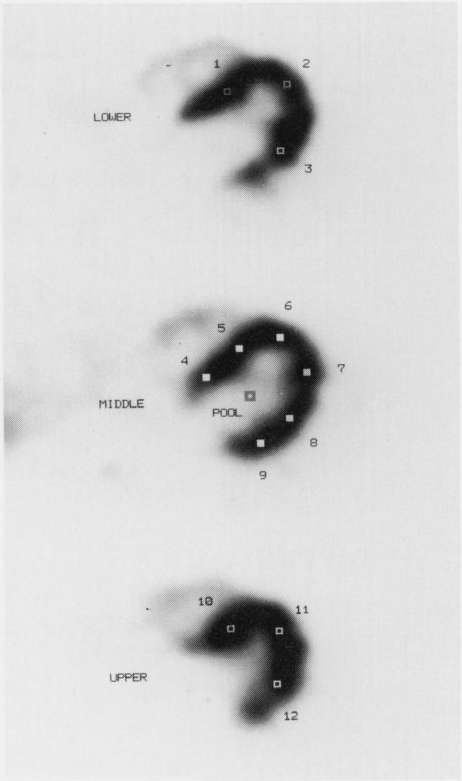


Fig. 1 Three trsansaxial images illustrate 12 ROI definition. Small ROI assigned to the left ventricular blood pool to derive arterial input functions is also illustrated.

$$E = \frac{K_1}{K_1 + MBF}. \qquad \text{Eq. 6}$$

The extraction fraction-flow relation experimentally determined in dogs was used in this model[1]

$$E = 1 - 0.607e^{(-1.25/MBF)}. \qquad \text{Eq. 7}$$

Therefore,

$$K = MBF[1 - 0.607e^{(-1.25/MBF)}]. \qquad \text{Eq. 8}$$

K was calculated by using myocardial tissue data recorded from 70 to 120 sec. AB(t)/Ca(t) is assumed to equal one for the time intervals used in analyzing the Patlak plot. Therefore, the intercept of Patlak Plot, $MBF^2V/(MBF + K_1)^2 + SP_{bt} \cdot AB(t)/Ca(t)$, can be simplified by using Equation 6 and Equation 7 to:

$$\frac{MBF^2V}{(MBF + K_1)^2} + SP_{bt}\frac{AB(t)}{C_a(t)} = 0.37Ve^{-(2.5/MBF)} + SP_{bt}. \qquad \text{Eq. 9}$$

The value for the intercept of the Patlak plot should be larger than SP_{bt}, and smaller than (0.22 m*l*/g + SP_{bt}) (when $V \approx 1.0$ m*l*/g and $MBF \approx 5$ m*l*/min/g) for MBF in the physiologic range. According to Choi's report the average for SP_{bt} estimated from a two compartment model fitting was 0.57 after the partial volume effect was corrected. Thus the intercept was constrained within the

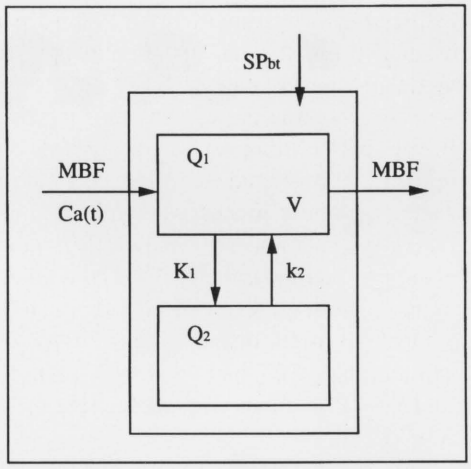


Fig. 2 Illustration of a two-compartment model which represents the kinetics of N-13 ammonia in the myocardium. Q_1 and Q_2 represent N-13 ammonia activities (counts/pixel/min) in free and trapped spaces, respectively. V (m*l*/g) is the distribution volume of free N-13 ammonia in the myocardium. K_1 (m*l*/min/g) and k_2 (/min) are forward and reverse rate constants, respectively. SP_{bt} is the spillover fraction of activity from myocardial blood pool to myocardial tissue ROI.

physiologically acceptable range for the results of the graphical analysis as Choi et al. reported.[12] MBF (m*l*/min/g) was estimated by using the relationship between MBF and K described in Equation 8.[12]

Estimation of regional MBF by the microsphere method. Partially extracted radiotracers have been used for measuring MBF in man by assuming that regional blood flow and extraction are coupled as in the following equation.[16,17]

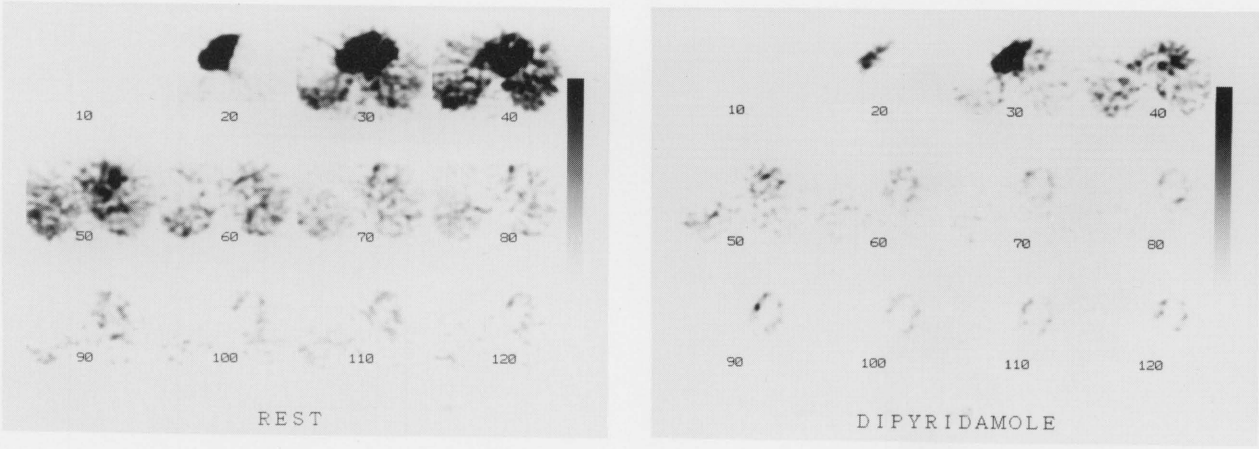
$$E \times MBF = \frac{C_T(t)}{g\int_0^t Ca(\tau)d\tau}. \qquad \text{Eq. 10}$$

Where E is the extraction fraction of N-13 ammonia. $C_T(t)$ represents tissue radioactivity. Ca(t) is the arterial input function obtained from the ROI drawn on the left ventricular cavity after correction for blood N-13 metabolites,[21] and g is the tissue gravity (1.08 g/m*l*).[10]

The Equation 10 assumes that there is no washout of the activity from the myocardium during the observation time. We calculated the E × MBF at various times (t = 70 to 240 sec) from the PET kinetic data according to Equation 10. Since the extraction fraction-flow relation is given in Equation 7, the following equation is obtained:

$$E \times MBF = MBF[1 - 0.607e^{(-1.25/MBF)}]. \qquad \text{Eq. 11}$$

Therefore MBF was estimated according to Equation 11. This method originally uses one single datum of static myocardial activity which may contain significant noise. In order to reduce the noise level, MBF was also estimated according to Equation 11 after averaging E × MBF values



A B

Fig. 3 Example of serial dynamic transaxial images of a normal subject from 0 to 120 sec at rest (A) and after pharmacological vasodilatation (B).

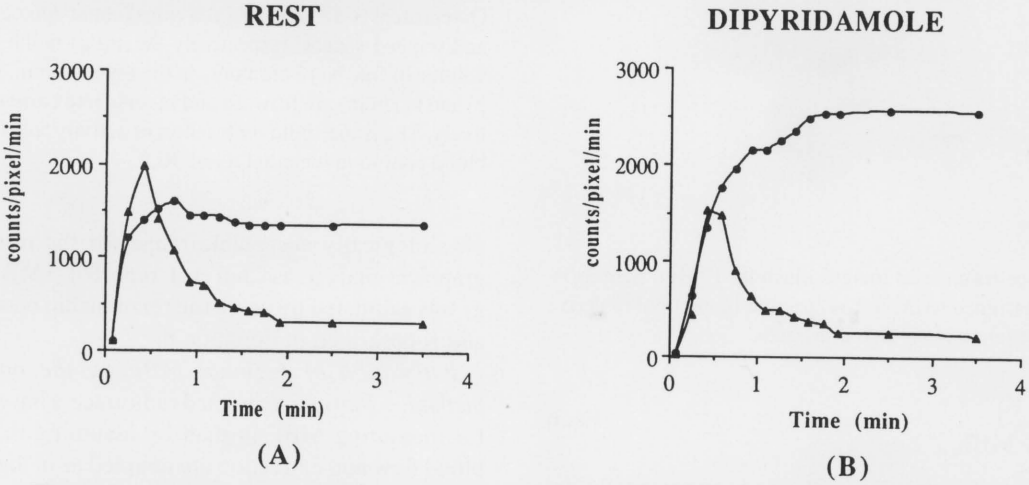


Fig. 4 Arterial input function (filled triangles) derived from ROI in the left ventricular cavity after correction for metabolites and a myocardial tissue time-activity curve after correction for the partial volume effect (filled circles) derived from a sectorial ROI in normal myocardium at rest (A) and after pharmacological vasodilatation (B).

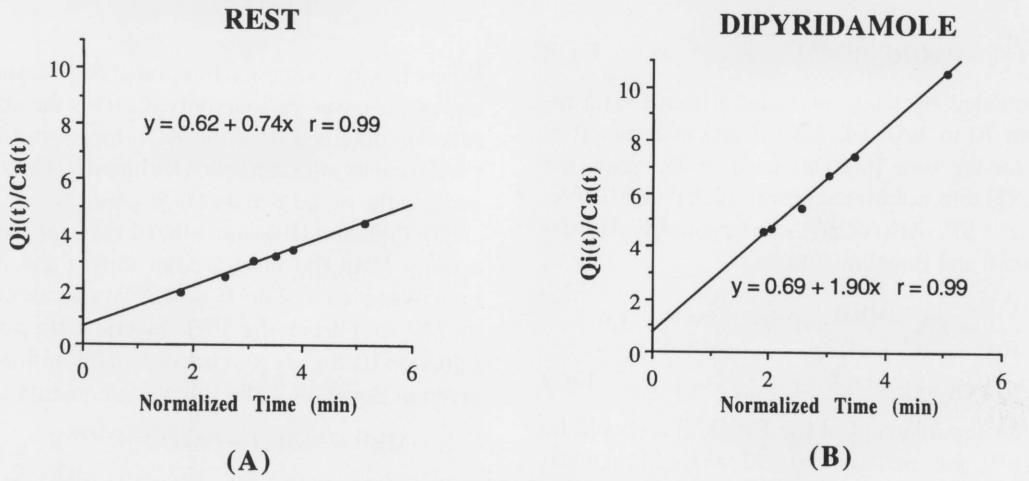


Fig. 5 The Patlak plot of normalized time ($\int_0^t C_a(\tau)dt/C_a(\tau)$) versus normalized counts ($Q_i(t)/C_a(t)$) for the same data set of Figure 4. Filled circles are data points, while the straight line is a linear fit to the data from 70–120 sec after tracer injection. In this case the linear regression lines and correlation coefficients for Patlak plot are $y = 0.62 + 0.74x$, r = 0.99 at rest (A), $y = 0.69 + 1.90x$, r = 0.99 after pharmacological vasodilatation (B).

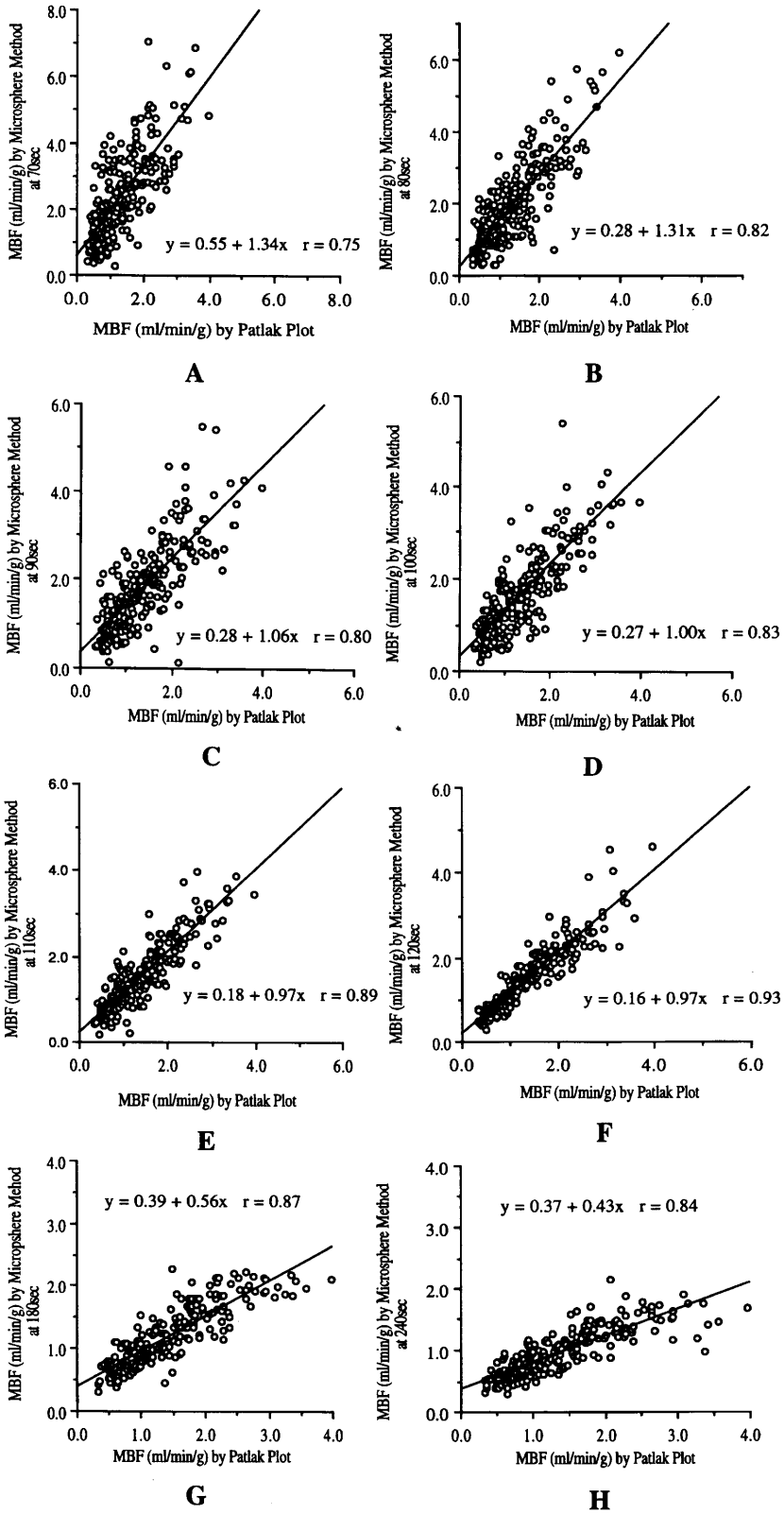


Fig. 6 Comparison of regional MBF in normal human volunteers estimated by Patlak graphical analysis (horizontal axis) and by the microsphere method (vertical axis). The microsphere method was applied to myocardial kinetic data at 70 sec (A), at 80 sec (B), at 90 sec (C), at 100 sec (D), at 110 sec (E), at 120 sec (F), at 180 sec (G), and at 240 sec (H). The linear regression lines and correlation coefficients for MBF estimates are $y = 0.55 + 1.34x$, $r = 0.75$ (A), $y = 0.28 + 1.31x$, $r = 0.82$ (B), $y = 0.32 + 1.06x$, $r = 0.80$ (C), $y = 0.27 + 1.00x$, $r = 0.83$ (D), $y = 0.18 + 0.97x$, $r = 0.89$ (E), $y = 0.16 + 0.97x$, $r = 0.93$ (F), $y = 0.39 + 0.56x$, $r = 0.87$ (G), and $y = 0.37 + 0.43x$, $r = 0.84$ (H).

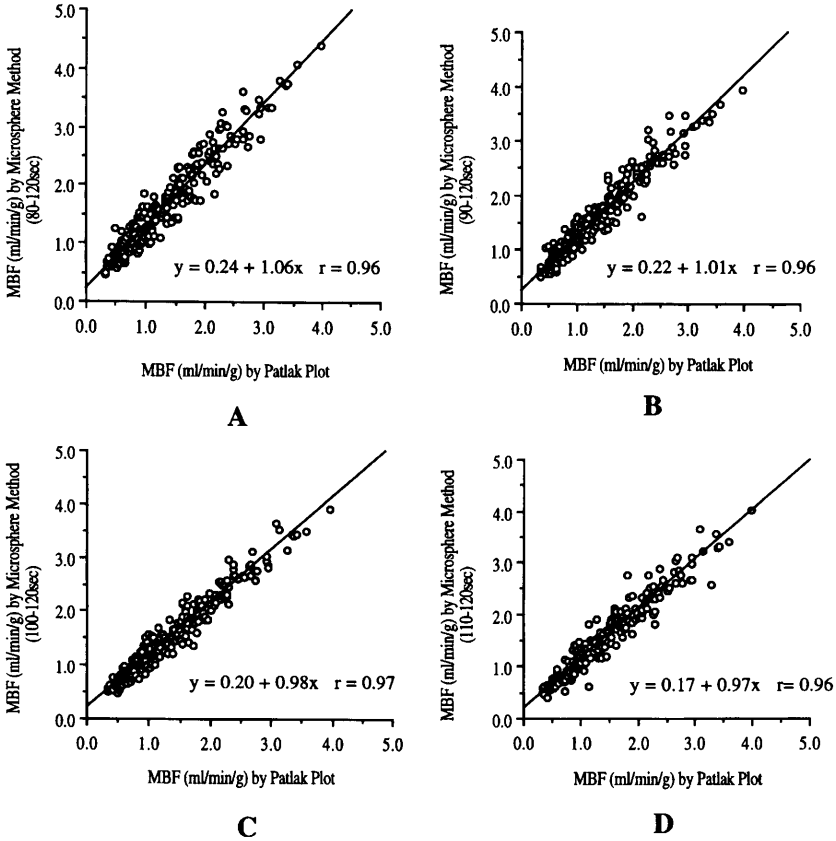


Fig. 7 Comparison of regional MBF in normal human volunteers estimated by Patlak graphical analysis (horizontal axis) and by the microsphere method (vertical axis). The microsphere method was performed after averaging E times MBF values between 80–120-sec (A), 90–120-sec (B),100–120-sec (C), and 110–120-sec (D). The linear regression lines and correlation coefficients for MBF estimates are $y = 0.24 + 1.06x$, r = 0.96 (A), $y = 0.22 + 1.01x$, r = 0.96 (B), $y = 0.20 + 0.98x$, r = 0.97 (C), $y = 0.17 + 0.98x$, r = 0.96 (D).

for various time intervals.

Estimation of coronary vasodilator reserve. The CVR was defined as the ratio of MBF during hyperemia to MBF at the baseline.

Statistical Analysis

CVR values are expressed as the mean ± s.d. The paired t-test was used to compare CVR in the microsphere method and the Patlak graphical analysis. A value of $p < 0.05$ was considered statistically significant.

RESULT

Figure 3 shows typical dynamic serial images of a normal subject from 0 to 120 sec at rest (A) and after pharmacological vasodilatation (B). These images contain significant noise because of 10-second scans. Figure 4 shows an arterial input function after correction for metabolites and one normal tissue time-activity curve after correction for the partial volume effect obtained from the normal subject at baseline (A) and after pharmacological vasodilatation (B). Figure 5 shows the Patlak plot for the same data set at rest (A) and after pharmacological vasodilatation (B) indicating the high quality (r = 0.99, in each case) of the linear fit.

Figure 6 shows a comparison of MBF estimates in 120 myocardial segments in the normal human studies generated with the microsphere method at various time points and with the Patlak graphical analysis. The MBF values estimated by the Patlak graphical analysis ranged to 0.38 to 4.00 (ml/min/g) in healthy volunteers. Some overestimation of MBF with a relatively low correlation coefficient (r = 0.75–0.82) was observed in the microsphere method applied when t was 70 to 90 sec (Fig. 6 A–C). On the other hand, the microsphere method applied when t was 180 to 240 sec underestimated MBF in hyperemic region (Fig. 6 G–H).

Figure 7 shows a comparison of estimates of regional MBF by the Patlak graphical analysis and by the microsphere method with averaging E × MBF at various interval. A high correlation of MBF estimates was observed in this approach. The best correlation (r = 0.97) was achieved when three E × MBF values between 100 to 120 sec were averaged. However mild overestimation of MBF was noted by this method (intercept = 0.20).

Figure 8 indicates a comparison of estimates in 120

segments in 10 baseline and 10 dipyridamole-induced hyperemic states in patients with coronary artery disease calculated by the Patlak graphical analysis and by the microsphere method with averaging three E × MBF between 100 and 120 sec. An excellent correlation of MBF estimates by these two methods (r = 0.97) was also observed over the wide range of blood flow levels. Some overestimation of MBF was also observed by this method (intercept = 0.22).

Mean overestimated values of MBF obtained by the modified microsphere method in normal volunteers and patients with coronary artery disease are considered to be 0.20 (ml/min/g) and 0.22 (ml/min/g) which are the intercept of the Figure 7C and Figure 8 because the slopes are nearly equal to 1.0. Therefore such overestimation is expected to be overcome simply by subtracting 0.20 (ml/min/g), mean overestimated values in normal volunteers, from MBF values obtained by this microsphere method. CVR assessed by this method and Patlak analysis were 2.75 ± 0.80 and 2.61 ± 0.74, respectively in normal subjects and did not show statistically significant difference. The relationship between CVR estimates by Patlak analysis and this method are shown in Figure 9. CVR estimates also correlated well with each other in normal subjects (A) and patients with coronary artery disease (B) ($y = -0.15 + 1.14x$, r = 0.90 and $y = 0.25 + 0.82x$, r = 0.92, respectively).

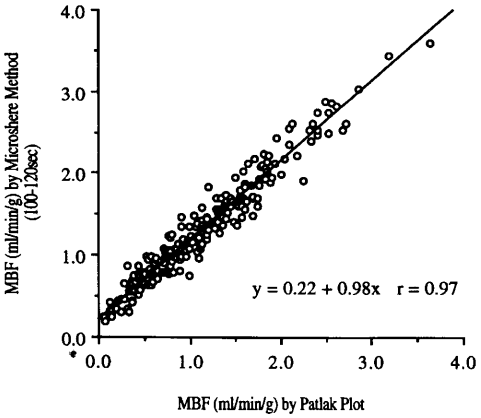


Fig. 8 Comparison of regional MBF in patients with coronary artery disease estimated by Patlak graphical analysis (horizontal axis) and by the microsphere method (vertical axis). The microsphere method was performed after averaging E times MBF values between 100–120-sec. The linear regression line and correlation coefficient for MBF estimates with the two methods are $y = 0.22 + 0.98x$, r = 0.97.

DISCUSSION

These data demonstrated that the MBF estimates obtained by the Patlak graphical analysis and by the microsphere method after averaging E × MBF values obtained between 100 and 120 sec (the modified microsphere method) linearly correlated well with each other with mild overestimation of MBF by this microsphere method. This excellent correlation indicates that the modified microsphere method is a reliable technique for quantifying MBF over a wide range of MBF.

In the present study the MBF estimates by the microsphere method were validated by comparing Patlak graphical analysis with the intercept constraint. These data

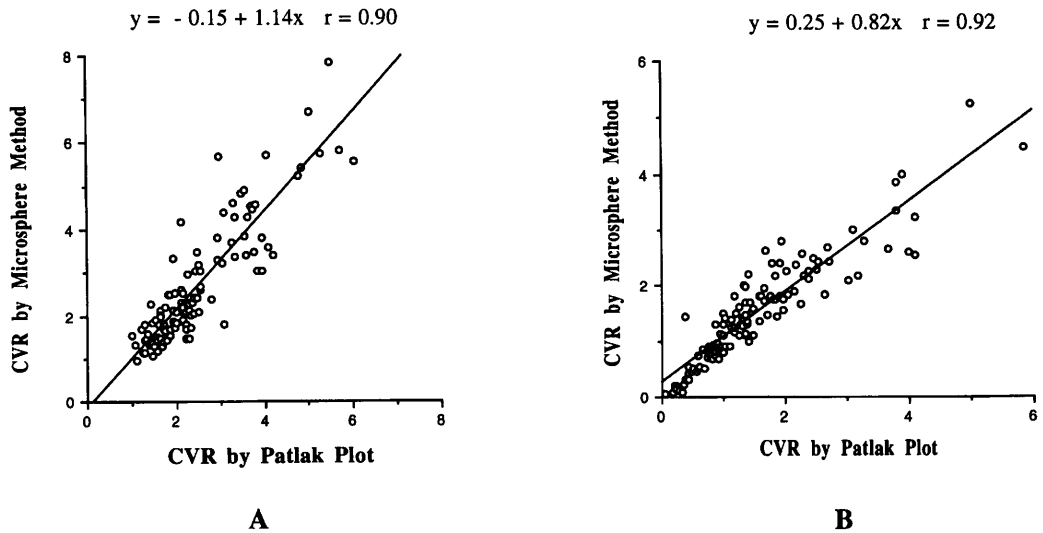


Fig. 9 Comparison of coronary vasodilator reserve (CVR) estimates by Patlak graphical analysis (horizontal axis) and by the microsphere method (vertical axis) in normal subjects (A) and in patients with coronary artery disease (B). The microsphere method was performed after averaging E times MBF values between 100–120-sec and then mean overestimation values, 0.20 ml/min/g, were subtracted from the obtained MBF. The linear regression lines and correlation coefficients for CVR estimates with the two methods are $y = -0.15 + 1.14x$, r = 0.90 (A) and $y = 0.25 + 0.82x$, r = 0.92 (B).

should be also compared with a well established two- or three-compartment model fit.[2-4] Recently Choi et al. reported that the MBF estimates by Patlak graphical analysis with the intercept constraint correlated well with those by the two-compartment model fitting[12] and therefore we have focused on the comparison of the modified microsphere method with the Patlak analysis rather than with the two compartment model fitting.

The microsphere method is affected by the time of measurement after tracer injection.[7-9] This may be partly due to the metabolite which did not contribute to input function. Rosenspire et al. showed the metabolic fate of the N-13 ammonia[21] and we used these data to correct the arterial input function.

Even though metabolites of N-13 ammonia were accurately corrected, MBF estimates obtained by this method change dramatically from time to time. At an earlier time such as 70-80 sec (Fig. 6 A–B) overestimation of MBF by the microsphere method was noted. This is caused by the high spillover from the left ventricular blood pool to myocardium and probably by the inadequate venous effluent of tracers. At a later time (180–240 sec) underestimation of MBF, particularly in the hyperemic myocardium, was noted (Fig. 6 G–H). This is mainly caused by some washout of the activities from the myocardium and the spillover from the myocardium to the blood pool. This suggests that Equation 2 cannot be applied to later kinetic data (later than 2 min after injection).

The microsphere method usually uses one single myocardial activity value which may contain significant noise. In fact, when one frame tissue value was used, the best correlation ($r = 0.93$) was observed at 120 sec but it may not be satisfactory for accurate quantification of MBF.

In order to reduce such a noise level in the microsphere method, MBF was assessed by averaging E×MBF values of various time intervals because, if accurately applied, E × MBF values should be constant. After averaging E × MBF values for various time intervals, MBF was estimated according to Equation 2. After averaging, a better correlation was obtained (Fig. 7 A–D). The best correlation ($r = 0.97$) of MBF estimates was observed when three E × MBF values between 100 and 120 sec were averaged (the modified microsphere method) (Fig. 7C). Such a good correlation was achieved mainly because the blood-pool activities became low in this time interval and the spillover from the blood pool to the myocardium was also decreased and stable.

The microsphere method assumes that the spillover fraction can be ignored. Therefore some overestimation of MBF is inevitable in this microsphere method using mean three E × MBF values between 100 and 120 sec (the modified microsphere method). Mean overestimated values in normal volunteers and patients with coronary artery disease are considered to be 0.20 (ml/min/g) and 0.22 (ml/min/g) which are the intercept of the Figure 7C and Figure 8 because the slopes are nearly equal to 1.0. Therefore such overestimation is expected to be overcome simply by subtracting 0.20 (ml/min/g), the mean overestimated value in normal volunteers, from MBF values obtained by the modified microsphere method.

Mean CVR assessed by the Patlak analysis and the modified microsphere method were 2.61 ± 0.74 and 2.75 ± 0.80, respectively, in normal subjects and did not differ significantly.

The good correlation of CVR estimates shown in Figure 6 indicates that the modified microsphere method adequately gives a reliable assessment of CVR in patients with coronary artery disease and will provide important clinical information.

The current approach offers several advantages over the techniques currently developed for measuring MBF.[2-4,11,12] This method needs only 3 tissue data from 100 to 120 sec. However a two-compartment model fitting requires at least 12 tissue time data from 0 to 120 sec after injection, and graphical analysis requires 6 tissue time data from 70 to 120 sec. The two-compartment model fitting needs nonlinear regression and sophisticated computer processing and it computationally takes much time for calculation. Patlak graphical analysis only requires a linear regression, but it finally requires the intercept constraint which is a little complicated. The present study also suggests that parametric images are easily generated by this microsphere method.

In order to apply the modified microsphere method for quantification of MBF, as mentioned before, it may require that the blood-pool activities become low and the k_2 is negligible. Therefore there is the possibility that this method may not be correctly applied to a patient with a severe left ventricular dysfunction or when the tracer is injected as a bolus.

In order to obtain input function, small ROIs (50 mm^2) were assigned to the left ventricular cavity in this study. It is possible that arterial input functions derived from the left ventricular blood pool can be contaminated by the spillover of activity from the myocardium to blood between 70 and 120 sec and MBF may be underestimated by Patlak analysis. But such a spillover fraction is considered to be negligible in humans by assigning small ROIs to the center of the cavity, as shown in Figure 1, because of the high spatial resolution of PET. In fact Choi et al. demonstrated that such underestimation of MBF by Patlak analysis was not observed in humans but was observed in dogs in comparison with the two-compartment model fitting.[12] The underestimation of MBF observed in dogs is probably due to their smaller ventricular cavity, but a small ROI in the left ventricular cavity increases the noise level of the arterial input function. In order to reduce such a noise level two ROIs were therefore drawn on the different mid-ventricular imaging planes and these time-activity curves were averaged as described before, according to the method reported by Choi.[12]

For accurate quantification of MBF, correction for the partial volume effect is necessary. But in this study such a correction was performed with a constant recovery coefficient assuming that myocardial wall thickness was 1 cm, because the main goal of this study was to compare the microsphere method and Patlak graphical analysis. We know that the recovery coefficients are not constant especially in the regions containing papillary muscles and infarcted regions. Therefore before obtaining MBF values according to Eq. 8 or Eq. 11, correction for the partial volume effect is essential after measuring wall thickness in such regions, but the effects of partial volume are the same in both the microsphere method and Patlak graphical analysis. The use of a constant recovery coefficient does not significantly influence the results of this investigation.

In conclusion, regional MBF estimates by the modified microsphere method correlate linearly well with those obtained by Patlak graphical analysis over a wide range of MBF. This method inherently overestimates MBF but this problem can be overcome simply by subtracting the mean overestimated value of 0.20 (ml/min/g). This method is simple and as reliable as Patlak graphical analysis for quantifying MBF. It also makes possible CVR assessment as accurate as Patlak graphical analysis.

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