A trial for the quantification of regional myocardial blood flow with continuous infusion of Tc-99m MIBI and dynamic SPECT

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We propose a new method to quantify regional myocardial blood flow (rMBF) by continuous infusion of Tc-99m MIBI and dynamic SPECT.

Methods: Five patients with old myocardial infarction were studied. During continuous infusion of MIBI (approximately 740 MBq) with a syringe pump in 10 min, dynamic SPECT scan was performed every minute and lasted 20 min after the start of infusion to identify myocardial uptake of MIBI. Input function was obtained from the radioactivity in the left ventricle (LV) in dynamic SPECT images. Spillover fraction between LV and myocardium (M) was corrected with phantom data. The influx constant (Ku) was calculated by Patlak plot graphical analysis, and compared with rMBF measured by PET (F) with N-13 ammonia based on Patlak plot analysis with correction for the extraction fraction. To correct the limited first-pass extraction of MIBI, linearization correction by means of the permeability-surface area (PS) product value was also applied. Results: Spillover fractions of MIBI were 0.169 ± 0.056 from LV to M, and 0.042 ± 0.021 from M to LV. Ku was well correlated with F ($Ku = 0.057 + 0.220F$, $r = 0.83$, $p < 0.01$) and the slope and correlation were improved after linearizaiton ($F_{MIBI} = -0.131 + 0.858F$, $r = 0.94$, $p < 0.01$). Conclusion: The proposed method has the potential to be a clinically feasible tool for quantitative measurement of rMBF.

Key words: continuous infusion, dynamic SPECT, graphical plot, myocardial blood flow, quantification

INTRODUCTION

QUANTIFICATION of regional myocardial blood flow (rMBF) can still only be performed by positron emission tomography (PET) in human studies.

Maddahi[1] reported that there are some problems in the quantification of rMBF with SPECT such as limited temporal resolution, attenuation correction, spillover, and partial volume effect.

The myocardial perfusion agent, technetium-99m hexakis 2-methoxybutyl isonitrile (MIBI) is rapidly distributed and is retained in the myocardium for a long time after intravenous administration and is rapidly cleared from the blood.[2] But because of its faster kinetics, to obtain the arterial input function from dynamic tomographic images as performed in myocardial PET study with N-13 ammonia is difficult when a bolus injection is used.

We previously introduced a new method for the quantification of regional cerebral blood flow with technetium-99m ethyl cysteinate dimer (ECD) using continuous infusion and dynamic SPECT.[3] ECD is distributed rapidly in the brain, and its clearance from blood is fast,[4] which characteristics are similar to those of MIBI.

The objective of this study is to investigate the possibility of quantification of rMBF by continuous infusion of MIBI and dynamic SPECT.

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MATERIALS AND METHODS

We examined 5 patients with old myocardial infarction (54–71 years old). MIBI was diluted with saline (approximately 740 MBq/20 m*l*), and continuously infused with a mechanical syringe pump for 10 minutes at the rate of 2 m*l*/min. A triple-head rotating SPECT camera (GCA9300A/HG, Toshiba, Tokyo, Japan) equipped with low-energy, high-resolution, parallel-hole collimators was used for the acquisition of dynamic SPECT imaging. The spatial resolution was 8 mm full width at half maximum (FWHM) in the center of the field of view. Dynamic data acquisition was performed in 128 × 128 matrices. The camera rotation of 120° around the body in 1-min covered 360° projections. Data acquisition started 1 minute before the start of infusion and altogether 21 frames of every 1-min data were acquired. Acquired dynamic data were reconstructed under the following conditions: pre-filter, Butterworth filter; cut-off frequency, 0.15; order, 8; reconstruction filter, Ramp filter. Neither attenuation correction nor scatter correction was performed. Contiguous 2 frame images were averaged because the gamma camera performed clockwise and counter-clockwise rotation in turn, which causes asymmetrical uptake of MIBI in myocardium, and generated 20 sets of averaged images. The second to tenth frames were used for graphical analysis in the first 10 frames as the first frame contains less activity, and the last 10 frames were used for identification of the myocardium.

As a reference data, rMBF was measured with N-13 ammonia (NH_3) and a whole-body PET scanner, ADVANCE (GE-YMS, Tokyo, Japan). After transmission scan, approximately 740 MBq of NH_3 was injected intravenously over 30 seconds, and dynamic scan was performed (10 sec × 12 frames, 1 min × 8 frames). rMBF was calculated by patlak plot graphical analysis (7–12 frame) with correction of the extraction.[5] These 2 studies were performed within 2 weeks in the same patient.

Phantom study

In this study, as the radioactivity in the left ventricle (LV) is kept high and that of the myocardium (M) increases gradually during continuous infusion, spillover between LV and myocardium could not be negligible. To correct the spillover of the radioactivity between the LV and M, phantom study was performed. We use a myocardial phantom in this study (RH-2, Kyoto Kagaku Co. Ltd., Kyoto, Japan) in this study. At first, to obtain background activity (BKG), both chambers were filled with saline and a scan was performed. Data acquisition time was 15 minutes and reconstruction parameters were the same as for a clinical study. For the assessment of the spillover from M to LV, the M chamber was filled with 1.4 MBq/m*l* of Tc-99m solution (Tc) and the LV chamber was filled with saline. A scan was performed every 6 hours for 24 hours. For evaluation of the spillover from LV to M, the LV chamber was filled with 7 MBq/m*l* of Tc, and the M chamber was filled with saline. The scan also lasted 24 hours. In the reconstructed image, regions of interest (ROIs) (3 × 3 pixels in size) were placed on the center of the LV chamber, anterior and lateral walls and septum of the M chamber. The spillover fraction (Sf) was calculated with following equation;

$$Sf = \frac{\text{Counts in saline chamber} - \text{BKG}}{\text{Counts in Tc chamber}} \quad (1)$$

Data analysis

Graphical analysis with measured input function

We selected the transaxial-slices on PET images that were closest to the corresponding SPECT images by visual inspection. ROIs (3 × 3 pixels in size) were manually placed on the anterior wall, infarcted area, and in the center of the LV in the mid-ventricular image. The Gjedde-Patlak graphical plot method was used for data analysis.[6,7] The method was expressed as follows;

$$\frac{Cm(t)}{Ca(t)} = Ku \cdot \frac{\int_0^\tau Ca(\tau)d\tau}{Ca(t)} + Vn \quad (2)$$

where Cm(t) is the tissue activity in the myocardium, Ca(t) is the arterial input function obtained from LV, Ku is the influx constant (m*l*/min/1 g myocardium), and Vn (m*l*/m*l*) is the initial distribution volume. Ku was expressed as the product of E by F_{MIBI}, where E is the first-pass extraction of the tracer, and F_{MIBI} is rMBF (m*l*/min/1 g myocardium) measured by MIBI. In this study, Cm(t) means the true radioactivity of myocardium after spillover correction. The procedure of correction is set out in the results section.

Correction of extraction

To overcome low extraction of MIBI, the linearization correction method was applied. Leppo et al.[8] reported the permeability-surface area (PS) product of MIBI as 0.44 m*l*/g/min, and using this value, E was calculated in each region with the following equation;

$$E = 1 - \exp^{(-PS/F)} \quad (3)$$

where F is rMBF measured by PET, and PS is 0.44 m*l*/g/min.

In each region, Ku was divided by calculated E, and F_{MIBI} was obtained. Both Ku and F_{MIBI} were compared with F.

RESULTS

In the phantom study, Sf was calculated as follows; 0.042 ± 0.021 M to LV, and 0.169 ± 0.056 LV to M. These values demonstrated no significant difference in any ROI position.

In clinical studies, the radioactivitiy of both LV and myocardium affected by spillover into each other and to

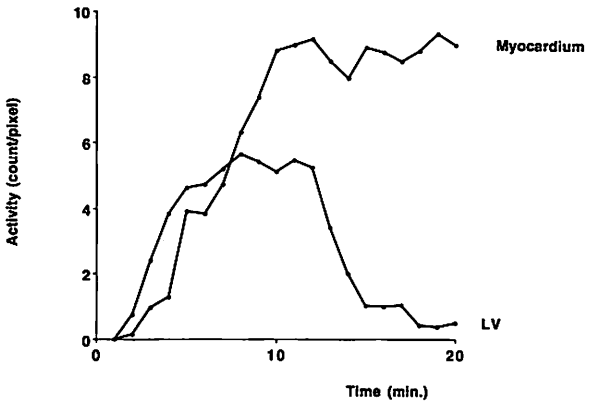

Fig. 1 Representative time-activity curve in left ventricle (LV) and myocardium. LV and Myocardium means the Ca(t) and Cm(t) in Gjedde-Patlak graphical analysis.

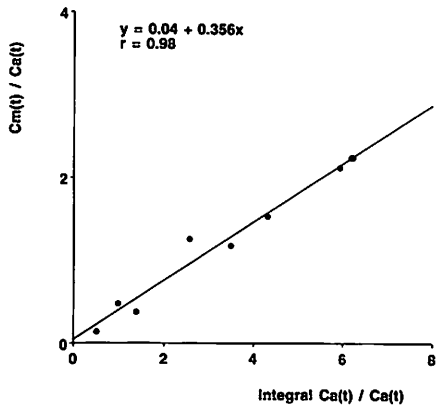

Fig. 2 Representative plotting of graphical analysis. The second to tenth frame data shown as the plot in this graph were used for the analysis.

obtain both true radioactivities is impossible, and therefore, we only corrected the myocardial radioactivity which is more affected by spillover. We found the true radioactivity of myocardium as subtracting seventeen percent of LV radioactivity from the that of myocardium. Figure 1 shows an example of the time-activity curve. Activity in myocardium increased linearly during continuous infusion. In contrast, activity in the left ventricle reached a plateau 8 min after the start of infusion and rapid clearance from blood after the end of infusion was also observed. In the graphical analysis, an excellent linear relationship was demonstrated (Fig. 2). This means that MIBI has characteristics suitable for graphical analysis during continuous infusion.

Figure 3 shows the relationship between Ku and rMBF, demonstrating a excellent correlation (Ku = 0.056 + 0.220 F, r = 0.83, $p < 0.01$).

Figure 4 shows the relationship between F and F_{MIBI}. The slope was improved after correction of extraction ($F_{MIBI} = -0.131 + 0.857F$, r = 0.94, $p < 0.01$).

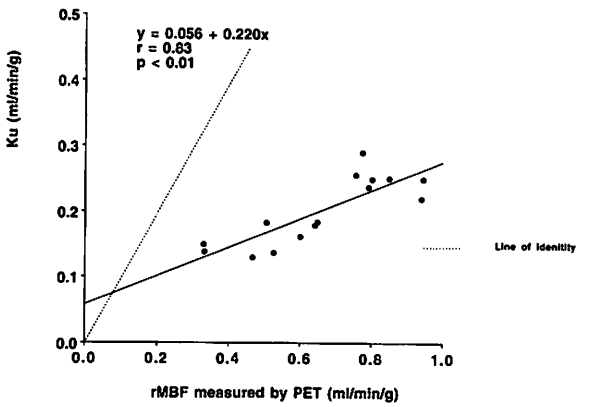

Fig. 3 Comparison of Ku and F. Excellent relationship was observed between Ku and F, but Ku was significantly lower than F.

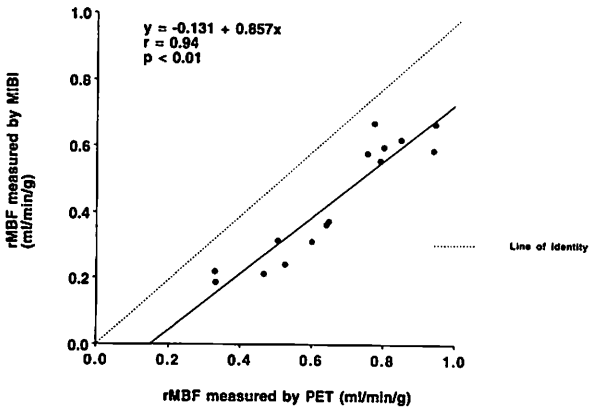

Fig. 4 Relationship between F_{MIBI} and F. The slope was improved with correction of extraction.

DISCUSSION

In the previous SPECT study, the assessment of rMBF was limited by qualitative or semi-quantitative analysis. The greatest disadvantage of such an analysis is that an abnormal hyperperfused area and globally hypoperfused area cannot be detected because these images are normalized with the maximal value in each image. It was therefore necessary to obtain the absolute value for rMBF with SPECT.

Although Maddahi et al.[1] listed some problems mentioned in the introduction, at first we tried to overcome the problem of temporal resolution by means of continuous infusion with the SPECT machine which is available now.

For quantification of rMBF with SPECT, the major problem is how to obtain the input function non-invasively. In brain PET and SPECT studies, because input function cannot be obtained from tomographic images, we performed at least one-point arterial blood sampling in the former study.[3] In contrast, in myocardial PET studies, input function was usually obtained from the left atrium

(LA) because spillover could be negligible. But in this study, identification of the LA was impossible and we obtained input function from the LV and performed spillover correction. In the phantom study, spillover from myocardium to the LV was about 4%, which was much less than the spillover from the LV to the myocardium and the center of the LV is the place least affected by the spillover, so that the positions of ROIs are thought to be appropriate even though a comparison with arterial blood sampling data is required.

Continuous infusion is suitable for dynamic SPECT as the changes in tissue activity can be accurately measured and input function from the LV can be obtained easily even though a bolus injection is inappropriate as MIBI is distributes in the myocardium rapidly, and the time resolution of SPECT was limited to obtain these change. We selected 1-min data acquisition per frame to obtain a sufficient signal to noise ratio.

In the physiological range, initial uptake of MIBI is related to myocardial blood flow[9] in experimental studies. Because our results showed a significant correlation between Ku and F, this method seemed to be appropriate for the quantification of rMBF.

But there was a problem in that Ku was significantly lower than F. We have to determine what causes this underestimation. Leppo et al.[8] reported that extraction of MIBI was 0.38 ± 0.09 which was significantly lower than that of Tl-201 (0.73 ± 0.10) and this might result in a smaller slope. We therefore tried to correct the extraction with the PS model. After correction, a negative intercept was appeared even though the slope was improved. This might be caused by a partial volume effect and even the positive intercept before correction might be underestimated. In myocardial PET studies, intravenous administration of dipyridamole increases rMBF to about 4 times that at rest.[10] So the myocardium is not thought to be a tissue which readily causes underestimation of blood flow. In our proposed method, graphical analysis demonstrated excellent linear relationship and this implies that MIBI has favorable characteristics for this analysis. We cannot say if significant underestimation is caused by this method or not until a more sophisticated method is proposed for the quantification of rMBF with SPECT. In summary, the reason for underestimation is thought to be the lower extraction of MIBI.

In this method, because scatter and attenuation correction were not performed as we did not have an appropriate technique, ROIs were placed on the anterior wall where the effect of attenuation might be less than in other areas such as the septum and inferior wall. Because considerable high accumulation in the liver and gall bladder might inhibit the assessment of the adjacent myocardium, such regions were not included in this study.

We also did not perform correction of the partial volume effect with recovery coefficients as the infarcted area was included in this study and the thickness of the myocardium is not uniform. If the partial volume effect was corrected, the true radioactivity of the myocardium would be increased and the graphical analysis slope would be higher. Appropriate correction of partial volume effect will therefore be required for accurate quantification.

This proposed method still involves several problems as Maddahi[1] indicated, but at least the problem of limited temporal resolution could be overcome with the assistance of data on spillover correction in a phantom study. We think this is the limit of quantification of rMBF with SPECT clinically available now.

We are confident that this method which we propose has the potential to be very useful in the quantification of rMBF, even though several improvements will be required.

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