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Myocardial glucose metabolism in patients with hypertrophic cardiomyopathy: Assessment by F-18-FDG PET study

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In an investigation of myocardial metabolic abnormalities in hypertrophic myocardium, the myocardial glucose metabolism was evaluated with F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) in 32 patients with hypertrophic cardiomyopathy, and the results were compared with those in 9 patients with hypertensive heart disease. F-18-FDG PET study was performed in the fasting and glucose-loading states. The myocardial regional %dose uptake was calculated quantitatively. The average regional %dose uptake in the fasting state in the patients with asymmetric septal hypertrophy and dilated-phase hypertrophic cardiomyopathy was significantly higher than that in the patients with hypertensive heart disease ($0.75 \pm 0.34\%$, $0.65 \pm 0.25\%$, and $0.43 \pm 0.22\%$/100 g myocardium, respectively). In contrast, the average %dose uptake in the glucose-loading state in the patients with asymmetric septal hypertrophy and dilated-phase hypertrophic cardiomyopathy was not significantly different from that in patients with hypertensive heart disease ($1.17 \pm 0.49\%$, $0.80 \pm 0.44\%$ and $0.99 \pm 0.45\%$, respectively). The patients with apical hypertrophy had also low %dose uptake in the fasting state ($0.38 \pm 0.21\%$) as in the hypertensive heart disease patients, so that the characteristics of asymmetric septal hypertrophy and dilated-phase hypertrophic cardiomyopathy are considered to be high FDG uptake throughout the myocardium in the fasting state. Patients with apical hypertrophy are considered to belong to other disease categories metabolically. F-18-FDG PET study is useful in the evaluation of the pathophysiologic diagnosis of patients with hypertrophic cardiomyopathy.

Key words: hypertrophic cardiomyopathy, positron emission tomography, glucose metabolism, F-18-FDG (fluorodeoxyglucose)

INTRODUCTION

HYPERTROPHIC CARDIOMYOPATHY (HCM) is defined as a disease in which idiopathic myocardial hypertrophy is present. Although most patients with HCM have asymmetric septal hypertrophy (ASH), some patients have apical hypertrophy.[1–5] Furthermore, recent studies have revealed another type of HCM known as dilated-phase HCM, in which myocardial integrity and left ventricular function deteriorate progressively.[6–9] HCM is histologically diagnosed by observation of characteristic disarray of myocardial filaments, and clinically diagnosed based on the morphological observation of characteristic ASH or systolic forward motion of the mitral valve and the absence of any known causes of myocardial hypertrophy such as hypertension.[10–12] Thus, while the morphological classification and characteristics have been well studied, the cause, pathophysiology and myocardial metabolism have not yet been clarified.

To identify and characterize hypertrophic myocardium in HCM, we evaluated the myocardial glucose metabolism by F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) in patients with HCM and

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compared the results with those in patients with hypertensive heart disease (HHD).

MATERIALS AND METHODS

Patient selection

We evaluated 32 patients with HCM and, for comparison, 9 patients with HHD. Of the 32 patients with HCM, 17 showed ASH, 6 apical hypertrophy, and 9 dilated-phase HCM. All patients underwent echocardiography, and 28 of them also underwent cardiac catheterization. No patients had diabetes mellitus. There were 24 males and 8 females. Their mean age was 54.5 ± 11.4 years old. For comparison, 9 patients with HHD were also evaluated. There were 6 males and 3 females. Their mean age was 51.3 ± 10.7 years old. No patients had diabetes mellitus. The protocol was approved by the hospital ethical committee. Written informed consent was obtained from all patients before they entered the study.

Definition of HCM

HCM was defined as the demonstration by echocardiography or left ventriculography, or myocardial biopsy of asymmetrically hypertrophied, nondilated left ventricle in the absence of another cardiovascular or systemic disease that could produce left ventricular hypertrophy. Asymmetric septal hypertrophy was considered to be present if the end-diastolic thickness of the septum was at least 15 mm and its ratio to that of the left ventricular posterior wall at least 1.3.[1,11,12] If the echocardiographic apical long-axis or four-chamber view demonstrated apical hypertrophy and a characteristic spade-like configuration was demonstrated in the left ventriculograms, apical hypertrophy was considered to be present.[4,5]

Dilated-phase HCM was defined as that phase representing an evolution from the typical asymmetrically hypertrophied and nondilated left ventricle to cavity enlargement or impaired systolic function, or any combination of these abnormalities, and associated with clinical evidence of progressive congestive heart failure in the absence of hemodynamically significant coronary artery disease.[6-9]

F-18-FDG PET study: Data acquisition

Tl-201 myocardial scintigraphy (planar anterior and SPECT imaging) was performed first to clarify myocardial perfusion and myocardial viability status, and for heart localization. After more than 5 hours fasting, transmission scanning was performed for 10 minutes, after which about 185 MBq of F-18-FDG was injected intravenously. Forty minutes later, static emission scanning was performed for 12 minutes as the FDG fasting imaging. Thereafter, 75 grams of glucose was given orally, and another 185 MBq of F-18-FDG was injected 30 minutes later. Forty minutes later, the static emission scanning was performed again as the glucose-loading imaging. The blood concentration of glucose, insulin, free fatty acid and lactate was evaluated in samples obtained before and 70 minutes after glucose intake. The PET scan was performed with a Headtome IV (Shimadzu Co. Ltd. Kyoto, Japan).

F-18-FDG PET study: Data analysis

The myocardial uptake of F-18-FDG was evaluated visually and quantitatively. In the quantitative analysis, the %dose uptake value in the center slice of myocardial cross-sectional images was obtained by the region of interest (ROI) method. A round ROI was set on each center slice in the septal, antero-apical, antero-lateral and postero-lateral regions. The %dose uptake for each slice was calculated as the ROI count divided by the injected dose, with cross-calibration factor and decay corrections. This method has been validated by Tamaki et al.[13] The formula used for the %dose uptake calculation was as follows:

$$\%\text{dose uptake (fasting)} = ((x/k)/(y \times 0.76 \times 1000)) \times 100\ (\%)$$

$$\%\text{dose uptake (glucose loading)} = ((X - 0.59x/k)/(Y \times 0.76 \times 1000)) \times 100\ (\%)$$

where x and X are the ROI count in the fasting and glucose-loading states (cps/100 m*l*), respectively, y and Y the injected dose in the fasting and glucose-loading conditions (mCi), respectively, k the calibration factor (8634.59 ± 251.33 cps/μCi), 0.76 the decay correction value in 40 minutes, and 0.59 the decay correction value in 70 minutes. With this method, the first F-18-FDG uptake can be subtracted from the second F-18-FDG uptake and it was supposed that the first F-18-FDG uptake did not change before glucose loading.

As the wall thickness is not uniform in HCM patients, the myocardial radioactivity does not accord with the myocardial FDG accumulation due to the partial volume effect (PVE). To correct for PVE, the regression curve between the recovery coefficient and wall thickness was obtained in an experiment with a heart phantom with changeable wall thickness. Thus, the corrected %dose uptake was calculated from the regression curve and the wall thickness value was obtained by echocardiography.

Echocardiography

Each subject underwent two-dimensional echocardiography at the time of the F-18-FDG PET study. From the echocardiographic data, the interventricular septum thickness and the posterolateral wall thickness were determined. From the left ventricular end-diastolic dimension (LVDd) and the left ventricular end-systolic dimension (LVDs), fractional shortening (%FS) was calculated with the following equation:

$$\%FS = \{(LVDd - LVDs)/LVDd\} \times 100\ (\%)$$

The %FS was regarded as an indicator of the severity of cardiac dysfunction. The calculation of each of these parameters was based on the standards prepared by the American Society of Echocardiography.

Statistic analysis

Mean values with standard deviation are given. The data were analyzed with Student's t-tests for paired and unpaired data. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the echocardiographic findings. The septal wall was significantly thicker than the lateral wall in the patients with ASH type HCM and dilated-phase HCM. Myocardial contractility was noticeably depressed in the patients with dilated-phase HCM. Table 2 shows the results of blood sampling. In the fasting state, the mean blood glucose concentration was less than 100 mg/dl in all subgroups of patients with HCM, but was slightly higher than that in the HHD group in all subgroups except the ASH-type HCM. The mean blood insulin concentration was within the normal range (5–10 μU/ml), while the mean blood free fatty acid (FFA) concentration varied greatly but was more than 500 μEq/l. At seventy minutes after glucose-loading, the blood glucose concentration in the HCM patients was slightly increased, but the blood insulin concentration was slightly decreased compared to the corresponding value in the HHD patients. The blood FFA concentration in the glucose loading state was decreased to less than half of that in the fasting state in almost all subgroups of patients, which was considered to be a normal response.

The mean overall %dose uptake per 100 g of myocardium in each subgroup is shown in Figure 1. The overall %dose uptake in the fasting state in the HCM patients in the ASH and dilated-phase HCM subgroups was 0.75 ± 0.34% and 0.65 ± 0.25%, respectively, and each was significantly higher than that in the HHD patients (0.43 ± 0.22%). The %dose uptake in the patients with apical hypertrophy was not significantly different from that in the HHD patients (0.38 ± 0.21% and 0.43 ± 0.22%). The %dose uptake value in the glucose-loading state in the ASH, dilated-phase and apical hypertrophy subgroups was 1.17 ± 0.49%, 0.80 ± 0.44% and 0.71 ± 0.43%, respectively, and was not significantly different from that in the HHD group (0.99 ± 0.45%).

The %dose uptake of the septal myocardium in the fasting state in the ASH, dilated-phase HCM was 0.85 ± 0.37% and 0.61 ± 0.22%, respectively, and each was significantly higher than that in HHD (0.36 ± 0.16%). The value in the patients with apical hypertrophy (0.40 ± 0.22%) was not significantly different from that in the HHD patients. Both the overall and septal wall %dose uptake in the glucose-loading state showed an increase to more than twice that in the fasting state in the HHD patients. The %dose uptake in the glucose-loading state in the ASH, dilated-phase and apical hypertrophy subgroups showed no significant difference from that in the HHD patients (Fig. 2).

The %dose uptake of the lateral myocardium in the fasting state in the ASH subgroup (0.69 ± 0.32%) was significantly higher than that in the HHD group (0.49 ±

Table 1 Echocardiographic findings

		Wall thickness (mm)		
		Septum	Lateral	%FS
HCM (ASH)	17	19.7 ± 3.9	12.3 ± 3.1	45.0 ± 6.3
(D-HCM)	9	15.7 ± 4.1	11.7 ± 3.0	26.6 ± 10.6
(Apical)	6	13.0 ± 4.4	11.3 ± 2.3	36.3 ± 6.8
HHD	9	14.8 ± 3.8	13.3 ± 3.3	40.6 ± 10.3

HCM = hypertrophic cardiomyopathy, ASH = asymmetric hypertrophy, D-HCM = dilated-phase hypertrophic cardiomyopathy, Apical = apical hypertrophy, HHD = hypertensive heart disease, %FS = % fractional shortening

Table 2 Blood concentration of glucose, insulin, free fatty acid and lactate in (a) fasting and (b) glucose loading state

(a) fasting state

	Glucose (mg/dl)	Insulin (μU/ml)	FFA (mEq/l)	Lactate (mg/dl)
HCM (ASH)	87.5 ± 13.1	5.1 ± 2.5	750 ± 347	8.3 ± 1.6
(D-HCM)	94.9 ± 9.4	7.9 ± 6.9	675 ± 347	—
(Aspical)	95.8 ± 4.8	9.7 ± 7.2	643 ± 351	7.7 ± 2.7
HHD	88.0 ± 8.5	6.8 ± 2.4	806 ± 364	9.0 ± 2.5

(b) 70 min after glucose loading

	Glucose (mg/dl)	Insulin (μU/ml)	FFA (μEq/l)	Lactate (mg/dl)
HCM (ASH)	180 ± 40	38.8 ± 29.1	279 ± 255	14.4 ± 4.6
(D-HCM)	215 ± 43	49.0 ± 39.0	337 ± 280	—
(Aspical)	197 ± 32	81.2 ± 28.8	248 ± 87	18.4 ± 2.7
HHD	157 ± 32	69.0 ± 29.4	427 ± 215	11.6 ± 3.3

FFA = free fatty acid

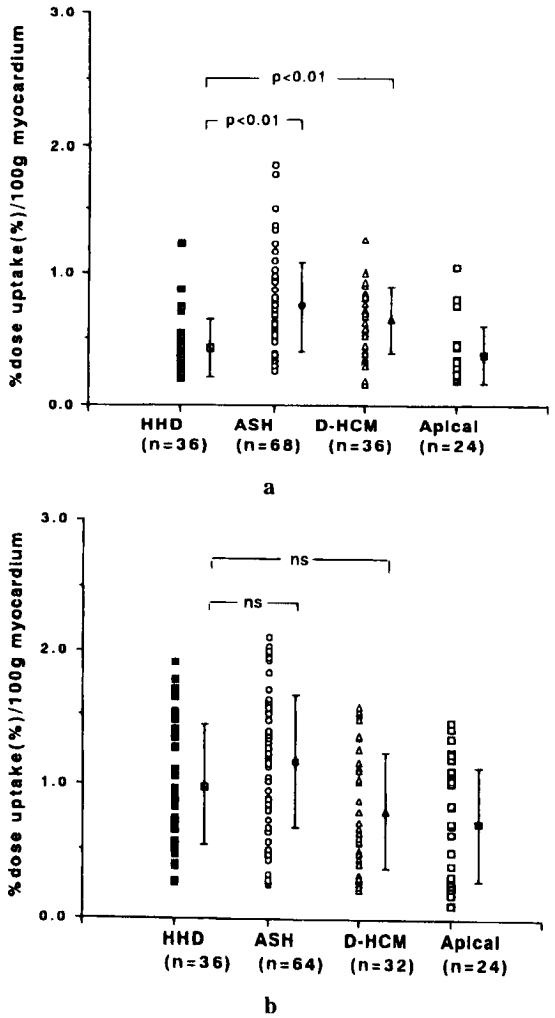

Fig. 1 Overall percent dose uptake values in the myocardium in (a) fasting and (b) glucose-loading state.

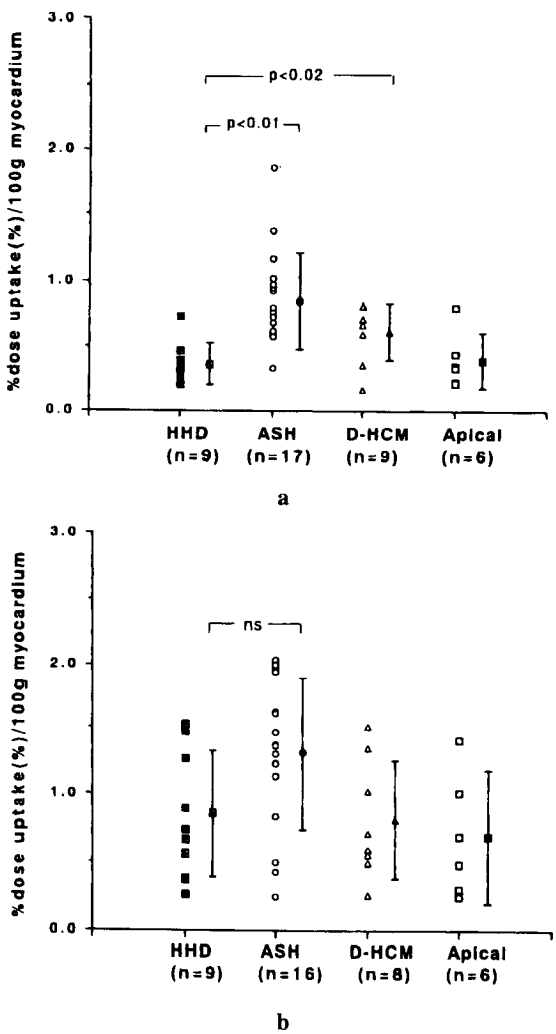

Fig. 2 Percent dose uptake value of the septal myocardium in (a) fasting and (b) glucose-loading state.

0.14%), but those in the dilated-phase HCM (0.71±0.35%) were slightly but not significantly higher than in the HHD patients, and that in the apical hypertrophy type (0.46 ± 0.30%) was almost the same as that in the HHD group. The %dose uptake in the glucose-loading state (1.10 ± 0.43%) was increased to more than twice that in the fasting state in the HHD patients (Fig. 3).

Case presentation

Case 1: The 57-year-old female patient had been diagnosed with hypertension 12 years previously. Echocardiography examination revealed concentric myocardial hypertrophy, the septal and lateral wall thickness was 13 and 11 mm, respectively, and %fractional shortening was 47%. Tl-201 myocardial scintigraphy disclosed generalized myocardial thickening and no perfusion defect. F-18-FDG myocardial images revealed little accumulation in the fasting state (%dose uptake, 0.29%/100 g myocardium), but the accumulation in glucose-loading state was noticeably increased (%dose uptake, 1.34%/100 g) (Fig. 4). The blood concentrations of glucose, insulin and free fatty acid in this patient were 80 mg/dl, 6.9 μU/ml and 428 μEq/l, in the fasting state, and 150 mg/dl, 99 μU/ml and 73 μEq/l, respectively, in the glucose-loading state. These data were within the normal range.

Case 2: This 51-year-old man with ASH-type HCM had shown no symptoms and had no family or past medical history of hypertension, but ECG abnormalities, including left ventricular hypertrophy and inverted T wave in precordial leads, had been noted at an annual screening examination. Echocardiography disclosed ASH, the thickness of the septal and lateral walls was 28 mm and 16 mm, respectively. The left ventricular dimension at end-diastole (LVDd) and end-systole (LVDs) was 47 mm and 20 mm, respectively, and %fractional shortening was 57%. Contrast left ventriculography revealed a left ventricular ejection fraction (LVEF) of 61%, and examination of the right ventricular biopsy specimen disalignment of the myocardium. Tl-201 myocardial images disclosed left ventricular thickening, especially of the septal wall.

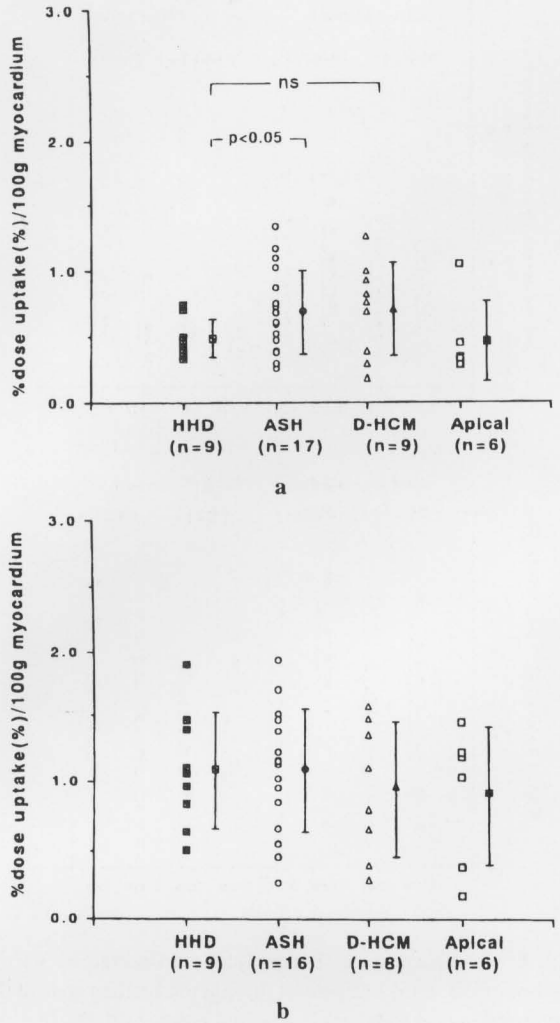

Fig. 3 Percent dose uptake value of the lateral myocardium in (a) fasting and (b) glucose-loading state.

The F-18-FDG myocardial accumulation in the fasting state was noticeably increased (average %dose uptake, 1.02%/100 g), but that in glucose-loading state was within normal range (average %dose uptake, 1.23%/100 g) (Fig. 5). The blood concentration of glucose and insulin was 75 mg/d*l* and 9.3 μU/m*l*, respectively, in the fasting state, and 144 mg/d*l* and 42 μU/m*l*, respectively, in the glucose-loading state. These data were within the normal range.

Case 3: This 60-year-old woman presented at the hospital with congestive heart failure. Her younger brother suffered from obstructive HCM, and aortic valvular disease had been identified in her elder sister. Echocardiography revealed ASH (the septal and lateral wall thickness was 18 mm and 13 mm, respectively), SAM and generalized reduced wall motion (LVDd, LVDs and %FS were 58 mm, 47 mm and 19%, respectively). Contrast left ventriculography and coronary arteriography revealed akinesis in the septal and anterior walls and reduced LV function (LVEF = 38%) but no coronary artery stenosis. These data indicated dilated-phase HCM. Tl-201 myocardial scintigraphy disclosed antero-septal hypo-perfusion and apical perfusion defect. The F-18-FDG images in the fasting state revealed septal hypo-uptake and no apical uptake (the %dose uptake of the septal and lateral myocardium was 0.18 and 0.24%/100 g, respectively). The antero-lateral and postero-lateral walls showed high uptake even in the fasting state (the %dose uptake values were 0.30 and 0.38%/100 g, respectively). The F-18-FDG myocardial images in the glucose-loading state disclosed almost the same distribution as in the fasting state (Fig. 6). The blood concentration of glucose and insulin was within the normal range (88 mg/d*l* and 6.8 μU/m*l*, respectively).

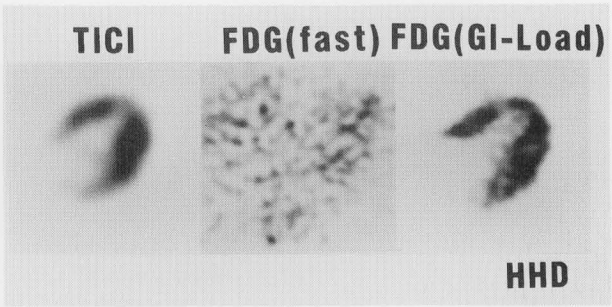

Fig. 4 F-18-FDG fasting images in a 47-year-old female with HHD reveal little uptake, while the glucose-loading images reveal normal uptake in the myocardium.

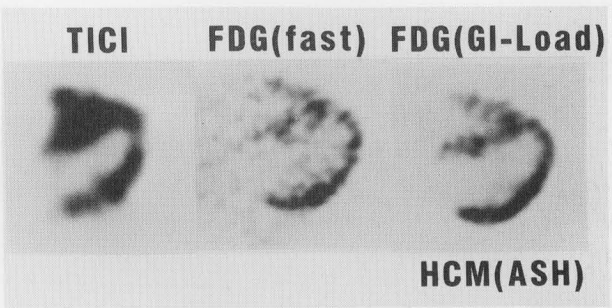

Fig. 5 F-18-FDG fasting images in a 51-year-old man with ASH-type HCM, disclose generalized uptake, and the glucose-loading images normal uptake in the myocardium.

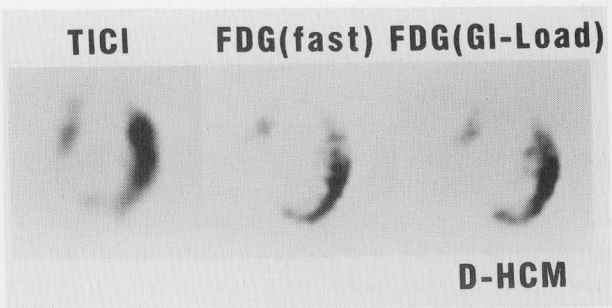

Fig. 6 Both fasting and glucose-loading F-18-FDG images in a 60-year-old woman with dilated phase HCM demonstrate antero-septal and apical uptake defect.

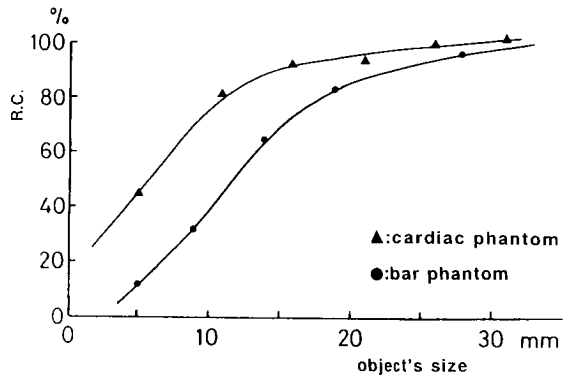

Fig. 7 Comparison of recovery coefficient curves between cardiac phantom and bar phantom.

DISCUSSION

Although HCM is characterized by idiopathic left ventricular hypertrophy, there are some variations in its morphology and clinical prognosis. The prognosis is generally good, but sudden death or progressive congestive heart failure occurs in some patients.[14–17] Although ASH is the typical configuration of HCM, apical hypertrophy or dilated-phase HCM are also reported.[4–9] The diagnosis is verified by histological observation of myocardial disalignment, but myocardial biopsy is a limited method with limitations because of its invasive character and the small size of the specimen obtained. The clinical diagnosis is difficult when the myocardial hypertrophy is atypical or concomitant hypertension is present. These variations suggest that HCM may be a combination of several different diseases. Recent reports suggest that not only hypertrophic but also non-hypertrophic portions have some abnormalities in diastolic function or histology.[18–20] Thus, the analysis of myocardial metabolism in HCM is thought to be important in clarifying the pathophysiology of this disease.

Recent reports by Grover-McKay[21] and Nienabar[22] et al., indicated the possibility of myocardial ischemia in patients with symptomatic HCM based on the F-18-FDG and N-13-NH_3 PET study. They noted a decrease in N-13-NH_3 uptake and intact F-18-FDG uptake in the area of myocardial hypertrophy. Kagaya et al.,[23] reported that young patients with HCM showed more inhomogeneous F-18-FDG myocardial uptake than middle-aged or elderly patients with HCM.

The recent development of I-123-BMIPP has facilitated the estimation of myocardial fatty acid metabolism. Shimonagata et al.,[24] reported that the hypertrophic portions of the myocardium in HCM patients show increased Tl-201 uptake and decreased I-123-BMIPP uptake. Therefore they speculated that the myocardial fatty acid metabolism was decreased in the hypertrophic portions in HCM. Kurata et al.,[26] reported that the decrease in I-123-BMIPP uptake preceded the decrease in Tl-201 uptake in histologically damaged myocardium in a syrian hamster cardiomyopathy model. Therefore, in the areas of viable myocardium, i.e., with normal Tl-201 uptake, with reduced fatty acid metabolism, i.e., reduced I-123-BMIPP uptake, glucose metabolism is thought to increase and compensate for the reduced myocardial energy production.[24–28]

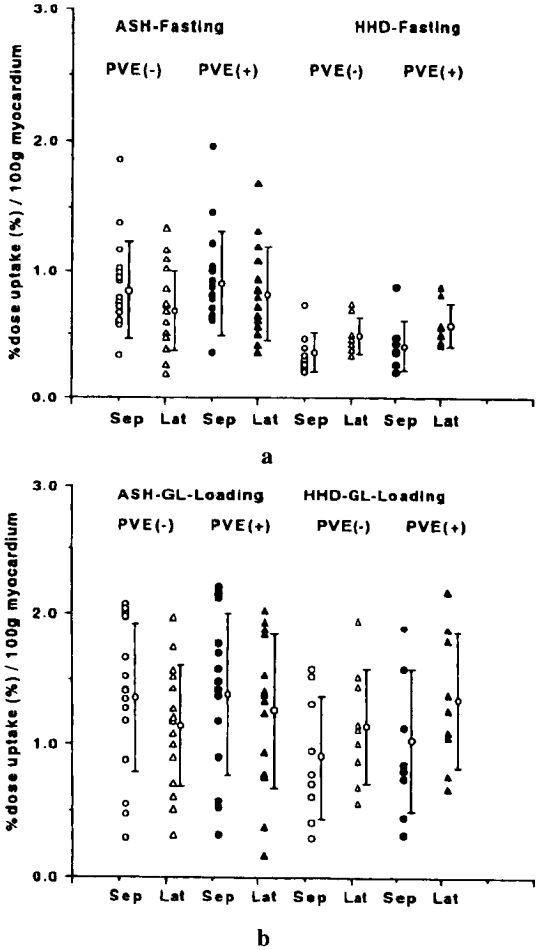

Fig. 8 Comparison of %dose uptake corrected by partial volume effect in (a) fasting and (b) glucose loading state at the septal and lateral walls. PVE = partial volume effect

Our study revealed that the myocardial glucose metabolism in the fasting state in HCM was noticeably increased in the hypertrophic portions, and slightly increased even in the non-hypertrophic areas. These patterns are thought to be characteristic of HCM and useful in diagnosis and clarification of the pathophysiology of HCM. The blood concentrations of glucose, insulin and free fatty acid in the fasting state were within the normal range, and the hypothesis that an extrinsic stimulation causes the high myocardial intake of F-18-FDG was denied, although the substrate concentration might effect F-18-FDG uptake in these patients. The cause of this high uptake is thought to be the intrinsic character of the

myocardium in HCM. Although a few individuals have noticeable F-18-FDG uptake in the fasting state without any obvious cause such as a high blood insulin level, we found a significant difference between HCM and HHD patients in F-18-FDG uptake in the fasting state in this study, which was thought to be an important phenomenon, but, in some case of HHD, we found slightly high F-18-FDG uptake, so that it is also possible that HHD patients have abnormal glucose metabolism. In this study we could not evaluate normal volunteers. Further investigation will be needed to evaluate HHD patients in comparison with normal volunteers.

We classified HCM into 3 subtypes. The patients with the ASH type, the most typical HCM, had marked F-18-FDG myocardial uptake in the fasting state, which was similar to that in the HHD patients in the glucose-loading state. This suggests that the myocardium in this type of HCM has the specific character of glucose utilization predominantly in the fasting state, with intact viability. Most patients with dilated-phase HCM had ASH and increased F-18-FDG uptake in the fasting state, but decreased F-18-FDG and Tl-201 uptake in the apical area, which suggests myocardial fibrosis in this area. The patients with apical HCM had almost the same uptake of F-18-FDG as the HHD patients in both the fasting and glucose-loading states, suggesting that the metabolism of patients with this type of HCM is normal and that apical HCM is not typical of HCM.

A rise in glucose utilization by the myocardium in the fasting state is thought to indicate myocardial ischemia in coronary artery disease. It is therefore reasonable to speculate that the cause of increased F-18-FDG accumulation in the fasting state in HCM is myocardial ischemia. There are some reports that myocardial ischemia has an important relationship to the hypertrophic area in HCM. Tl-201 exercise myocardial scintigraphy sometimes reveals filling-in in these areas.[29–31] There are reports of histological evidence of wall thickening of coronary arterioles, and small vessel disease is speculated in HCM.[32–35] Recent PET studies in which F-18-FDG (myocardial glucose metabolism) and N-13-NH_3 (myocardial perfusion) were evaluated simultaneously in symptomatic HCM patients revealed decreased myocardial perfusion and normal or increased myocardial glucose utilization in the hypertrophic areas of the myocardium, suggesting myocardial ischemia in these areas.[21,22,28,36] In our studies, most patients were asymptomatic, and the increased F-18-FDG uptake was observed in not only hypertrophic but also non-hypertrophic areas. These data suggest that the increase in myocardial F-18-FDG accumulation in the fasting state is not only an indicator of myocardial ischemia but also of alteration of the primary metabolic substrate from fatty acids to glucose.[32–37]

Heterogeneous uptake of F-18-FDG has been reported in young patients with HCM, suggesting myocardial damage.[23] Most of our clinical subjects were over 40 years old, and we therefore could not analyze the relationship of age to F-18-FDG uptake.

We used the %dose uptake as a quantitative parameter of myocardial F-18-FDG accumulation. Tamaki et al.[13] reported a high correlation between %dose uptake and the myocardial glucose metabolic rate. In addition, with this method, the first F-18-FDG uptake can be subtracted from the second F-18-FDG uptake so that we could obtain accurate values for F-18-FDG uptake in both the fasting and glucose-loading states even on the same day.

In ASH-type HCM, the correction of the partial volume effect (PVE) is important in obtaining accurate F-18-FDG uptake values because of the difference between the thicknesses of the septal and laterals walls.[38] In this study, the coefficient of recovery of PVE was calculated based on the results of experiments in a myocardial phantom with changeable wall thickness. The results thus obtained are more accurately applied in practice than those obtained in conventional experiments with a bar phantom. Thus we calculated the PVE corrected %dose uptake with the recovery coefficient obtained from the phantom experiments and the wall thickness measured by echocardiography (Fig. 7). The effect of PVE correction is shown in Figure 8. In HHD, the %dose uptake in the fasting state in the lateral wall was higher than that in the septal wall, and the PVE corrected %dose uptake showed the same results because the thicknesses of the septal and lateral walls were almost the same and the recovery coefficients were also the same. In contrast, the %dose uptake in the hypertrophic septal wall was higher than that in the lateral wall in ASH-type HCM, but the PVE corrected %dose uptake in the hypertrophic septal wall was as high as that in the lateral wall. The %dose uptake in the hypertrophic septal wall appeared to be higher than that in the lateral wall but after correction, it was almost as high as that in the lateral wall. Nonetheless, the PVE corrected %dose uptake of the septal and lateral walls in ASH-type HCM was significantly higher than that in HHD. Other causes such as the myocardium itself and small coronary arterial involvement might be considered in addition to the PVE.

In conclusion, HCM is characterized by F-18-FDG accumulation in the fasting state in not only the hypertrophic area but also throughout the myocardium, although the uptake in the septal wall is significantly increased, but that in the lateral wall is not, compared to that in HHD patients. F-18-FDG PET study is therefore useful in the pathophysiological diagnosis of HCM.

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