Tohoku J. Exp. Med., 1997, **182**, 125-138

Myocardial Glucose Metabolism is Different between Hypertrophic Cardiomyopathy and Hypertensive Heart Disease Associated with Asymmetrical Septal Hypertrophy

NOBUYUKI SHIBA, YUTAKA KAGAYA, NOBUMASA ISHIDE, DAIYA TAKEYAMA, YURIKO YAMANE, MASANOBU CHIDA, HIROKI OTANI, TATSUO IDO[1] and KUNIO SHIRATO

The First Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980-77, and [1]Cyclotron and Radioisotope Center, Tohoku University, Sendai 980-77

SHIBA, N., KAGAYA, Y., ISHIDE, N., TAKEYAMA, D., YAMANE, Y., CHIDA, M., OTANI, H., IDO, T. and SHIRATO, K. *Myocardial Glucose Metabolism is Different between Hypertrophic Cardiomyopathy and Hypertensive Heart Disease Associated with Asymmetrical Septal Hypertrophy.* Tohoku J. Exp. Med., 1997, **182** (2), 125-138 —— Myocardial glucose metabolism has been shown to be heterogeneous in patients with hypertrophic cardiomyopathy (HCM). We tested the hypothesis that myocardial glucose metabolism differs between patients with HCM and those with hypertensive heart disease (HHD) associated with asymmetrical septal hypertrophy. We studied 12 patients with HCM, 7 HHD patients associated with asymmetrical septal hypertrophy using ^{18}F 2-deoxyglucose (FDG) and positron emission tomography. We calculated % FDG fractional uptake in the interventricular septum and posterolateral wall. Heterogeneity of FDG uptake was evaluated by % interregional coefficient of variation of FDG fractional uptake in each wall segment. In both the interventricular septum and posterolateral wall, % FDG fractional uptake was not significantly different between the two groups. The % interregional coefficient of variation for both interventricular septum (10.6 ± 1.6 vs. 4.1 ± 0.5, $p < 0.01$) and posterolateral wall (5.9 ± 0.7 vs. 3.8 ± 0.5, $p < 0.05$) was significantly larger in patients with HCM than in HHD patients associated with asymmetrical septal hypertrophy. Echocardiography demonstrated that the degree of asymmetrical septal hypertrophy was similar between the two groups. These results suggest that myocardial glucose metabolism may be more heterogeneous in patients with HCM compared to HHD patients associated with asymmetrical septal hypertrophy, although the left ventricular shape is similar. The difference in the heterogeneity might have resulted from differences in the pathogeneses of the two diseases. ———— hypertrophic cardiomyopathy; hypertensive heart disease; glucose metabolism; positron emission tomography; ^{18}F 2-deoxyglucose

Received January 27, 1997; revision accepted for publication April 20, 1997.

Address for reprints: Kunio Shirato, M.D., Professor and Chairman, The First Department of Internal Medicine, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-77, Japan.

Hypertrophic cardiomyopathy (HCM) is characterized by a hypertrophic ventricle in the absence of other cardiac or systemic diseases known to cause ventricular hypertrophy. Asymmetrical septal hypertrophy, i.e., an interventricular septum that shows more severely increased wall thickness compared with the left ventricular free wall, has been considered a typical diagnostic sign of HCM (Teare 1958). However, several studies have reported that 4–18% of patients with left ventricular hypertrophy due to long-term systemic hypertension also show asymmetrical septal hypertrophy (Savage et al. 1979; Fujiwara et al. 1985; Shapiro et al. 1985). It is difficult, therefore, to distinguish HCM from hypertensive heart disease (HHD) associated with asymmetrical septal hypertrophy by cardiac shape alone.

In our previous study (Kagaya et al. 1992; Shiba et al. 1997), we have shown that myocardial ^{18}F 2-deoxyglucose (FDG) uptake in patients with HCM is heterogeneous, suggesting that not only a morphological change but also a metabolic abnormality are involved in this disease. It is not known, however, whether myocardial glucose metabolism in HHD with asymmetrical septal hypertrophy differs from that of HCM. To address this question, we studied myocardial glucose uptake in 12 patients with HCM and 7 patients with HHD associated with asymmetrical septal hypertrophy using positron emission tomography (PET) and a glucose analog, FDG.

Patients and Methods

Patients

The study group consisted of 19 patients referred to our hospital because of both abnormal electrocardiography and echocardiographic demonstration of asymmetrical septal hypertrophy. Twelve patients were diagnosed as having HCM because they had hypertrophic left ventricle as demonstrated by echocardiography, but without any cardiac or systemic disease known to cause ventricular hypertrophy. The other 7 patients were diagnosed as having HHD because they had definite histories of hypertension over ten years. None of the patients had diabetes mellitus. Medications for patients with HCM were calcium antagonists and/or beta blockers. Those for patients with HHD were calcium antagonists, beta blockers and/or diuretics. These medications were discontinued on the day of the tomographic study.

The purpose and nature of this study were approved by the committee for the administration of radioactive substances of the Tohoku University School of Medicine. We provided the details of this study to all subjects and written informed consent was obtained from all subjects before each study.

Echocardiography and cardiac catheterization

Two-dimensional echocardiographic studies were performed in all cases on the day of the PET study (SSH-65A or SSH-160A, Toshiba, Tokyo). Inter-

ventricular septal and posterolateral wall thickness were measured using the two-dimensional left parasternal image at end-diastole. Cardiac catheterization and selective coronary angiography were performed in 16 patients (10 patients in HCM group and 6 patients in HHD group). The peak-systolic pressure gradient in the left ventricular outflow tract was measured by continuous pressure recording using a 7 French-size fluid filled pig tail catheter while drawing the catheter out of the left ventricle to the aortic root.

Radiopharmaceutical and scanning procedure

FDG is a glucose analog that traces the transmembranous transport and hexokinase-mediated phosphorylation of glucose. The end product, FDG-6-phosphate, is effectively trapped within the cell and enables the visualization of regional myocardial glucose flux (Gallagher et al. 1977; Ratib et al. 1982).

The imaging studies were performed using a single-slice positron tomograph (ECAT II; CTI, Knoxville, TN, USA) with a spatial resolution of 17 mm full-width at half maximum in the transverse plane and a slice thickness of 17 mm full-width at half maximum. In two patients with HCM and three patients with HHD, we used another PET scanner, PT 931/04 (CTI), the full-width at half maximum of which is 7 mm. Acquired data were reconstructed in a matrix size of 100×100 pixels and transformed into an MS-DOS file format for analysis by a personal computer.

Each subject was administered 50 g of glucose orally one hour before the PET study. All medications were discontinued on the day of the tomographic study. We placed a catheter in the dorsal pedal or radial artery for arterial blood sampling. After a transmission scan for the attenuation correction, we administered intravenously 148 to 296 MBq of FDG dissolved in 6 ml of 0.9% sodium chloride solution for 1 minute. In the studies with the ECAT II scanner, four cross-sectional images of the left ventricle were acquired at 10 mm intervals by scanning over a period of 300 seconds per plane, 45 to 60 minutes after the FDG injection. In the studies with the 931/04 scanner, seven cross-sectional images of the left ventricle were obtained simultaneously by scanning over a period of 300 secconds, 45 minutes after the FDG injection. We performed serial arterial blood sampling until the end of scanning (every 20 seconds up to 180 seconds, and then 4, 5, 7, 10, 15, 20, 30, 45 and 65 minutes after the FDG injection). In one patient in the HHD group, arterial blood sampling was not performed because her peripheral arteries were severely sclerotic and winding (Case 6). We measured the arterial plasma concentrations of glucose, insulin and free fatty acids three times during the tomographic study (0, 15 and 30 minutes after FDG injection) and these data were averaged in each case.

Data analysis

The tomographic data were corrected for decay and attenuation, and were

displayed on the monitor of a personal computer (PC-9801DA, NEC, Tokyo) as 16-color transverse tomographic images to differentiate the left ventricular wall from the cardiac chamber and to define regional segments of the left ventricle. One cross-sectional image containing the mid-left ventricle and the largest mass of both the interventricular septum and left ventricular posterolateral wall was selected for analysis in each case. The posterolateral wall segment was defined as the basal two-thirds of the left ventricular free wall in the trans-axial image of the left ventricle. The interventricular septal region was defined as the basal two-thirds of the rightside of the left ventricular image. Four to eight contiguous rectangular regions of interest (ROIs) were selected in both the interventricular septum and left ventricular posterolateral wall. Each ROI consisted of 9 pixels. We calculated % FDG fractional uptake in each ROI as described by Camici et al. (1986), using the following equation:

$$\%\ \text{FDG fractional uptake} = (C_{M(FDG)} / {}_0\int^T C_{P(FDG)}dt) \times 100$$

where $C_{M(FDG)}$ is the FDG radioactivity per ROI in the myocardium; and ${}_0\int^T C_{P(FDG)}dt$ is the integral of the plasma FDG radioactivity per g from the time of the injection to the end of scanning. In each wall segment, mean % FDG fractional uptake was calculated by averaging the % FDG fractional uptake of the ROIs. Furthermore, in each wall segment, we determined % interregional coefficient of variation (SD/mean$\times$100) of % FDG fractional uptake in the ROIs as a measure of the regional heterogeneity of myocardial glucose uptake (Sochor et al. 1986). The plasma glucose concentration was measured by a modification (Trinder 1969) of the glucose oxidase method (Huggett and Nixon 1957); the plasma insulin concentration was determined by radioimmunoassay (Yalow and Berson 1960); and the plasma concentration of free fatty acids was measured by an enzymatic method (Mizuno et al. 1980).

Results are presented as mean$\pm$S.E.M. We used Student's t-test to compare variables between the HCM and HHD groups. A p value<0.05 was considered significant.

Results

Clinical characteristics in patients

The clinical characteristics of the two patient groups are listed in Tables 1 and 2. There was no significant difference in age between the two patient groups. Both systolic and diastolic blood pressure was significantly higher in the HHD group than in the HCM group. Case 4 in the HCM group is a brother of case 7 in the same group. The other 10 patients with HCM did not have a family history of HCM nor sudden cardiac death.

Echocardiographic data of the two patient groups are shown in Tables 1 and 2. There was no significant difference in the wall thickness of the interventricular septum or posterolateral wall between the two patient groups. Cardiac catheter-

TABLE 1. *Clinical characteristics and PET data in patients with hypertrophic cardiomyopathy*

Case No.	Age (years) & Gender	NYHA	Blood pressure (mmHg)	Echocardiography			PG (mmHg)	PET data			
				IVS (mm)	PL (mm)	IVS/PL		IVS%FU	IVS%CV	PL%FU	PL%CV
1	46 M	I	108/70	21	15	1.40	0	7.0	9.6	6.5	4.7
2	77 F	II	106/62	17	12	1.42	—	7.9	6.2	8.9	6.3
3	23 M	I	130/60	19	10	1.90	0	15.8	10.3	15.6	7.2
4	13 M	II	90/40	22	10	2.20	0	18.4	10.4	16.4	4.5
5	28 M	I	102/50	20	15	1.33	0	11.3	9.0	12.3	12.1
6	61 M	I	122/70	21	12	1.75	80	15.3	9.1	14.6	5.3
7	19 F	III	102/60	18	9	2.00	15	13.5	8.1	14.5	3.6
8	16 F	II	114/80	21	10	2.10	45	15.3	9.1	14.1	7.0
9	49 M	II	116/80	22	14	1.57	50	4.8	6.4	5.3	4.4
10	55 M	III	102/70	18	12	1.50	7	11.9	6.1	12.7	5.4
11	48 M	I	98/62	18	11	1.64	—	3.5	21.4	4.6	7.4
12	64 F	III	134/72	14	9	1.56	0	4.1	22.1	5.7	3.4
Mean	42		110/65	19	12	1.70		10.8	10.6	10.9	5.9
S.E.M.	6		4/3	1	1	0.08		1.5	1.6	1.3	0.7

Cases 1 to 10 were studied using ECAT II scanner, while cases 11 and 12 were studied using PT931/04 scanner. The blood pressure shown above was measured on the day of the PET study under no medications. PET, positron emission tomography; NYHA, New York Heart Association functional class; IVS, interventricular septum; PL, left ventricular posterolateral wall; PG, peak-systolic left ventricular outflow tract pressure gradient; %FU, %FDG fractional uptake; %CV, % interregional coefficient of variation in FDG fractional uptake; —, not measured.

TABLE 2. *Clinical characteristics and PET data in patients with hypertensive heart disease with asymmetrical septal hypertrophy*

Case No.	Age (years) & Gender	NYHA	Blood pressure (mmHg)	Echocardiography			PG (mmHg)	PET data			
				IVS (mm)	PL (mm)	IVS/PL		IVS%FU	IVS%CV	PL%FU	PL%CV
1	33 M	I	160/110	25	9	2.78	0	7.6	4.6	7.4	3.4
2	46 M	I	198/112	16	11	1.45	—	11.4	3.4	11.5	1.6
3	55 M	I	172/94	18	12	1.50	0	6.7	4.0	6.1	5.5
4	53 M	II	162/98	18	13	1.38	0	4.5	5.2	4.8	4.6
5	59 F	II	160/90	16	12	1.33	0	9.3	5.0	9.2	4.1
6	58 F	II	182/94	20	13	1.54	0	—	5.5	—	2.4
7	50 M	II	162/108	19	13	1.46	0	11.0	1.3	9.3	5.1
Mean	51		171/101	19	12	1.64		8.4	4.1	8.1	3.8
S.E.M.	3		5/3	1	1	0.19		1.1	0.5	1.0	0.5

Cases 1 to 4 were studied using ECAT II scanner, while cases 5 to 7 were studied using PT931/04 scanner. In case 6, arterial blood sampling was not performed because her peripheral arteries were severely sclerotic and winding. The blood pressure shown above was measured on the day of the PET study under no medications. Abbreviations are same as Table 1.

ization revealed the presence of a peak systolic pressure gradient in left ventricular outflow tract in 5 patients in the HCM group. Selective coronary angiography demonstrated no significant % diameter stenosis greater than 50% in any patient. Right ventricular endomyocardial biopsy was performed in only one patient from each patient group. The specimen of case 4 in the HCM group showed patchy focal fibrosis of myocardium and myocyte hypertrophy. The specimen of case 4 in the HHD group showed only marked myocyte hypertrophy.

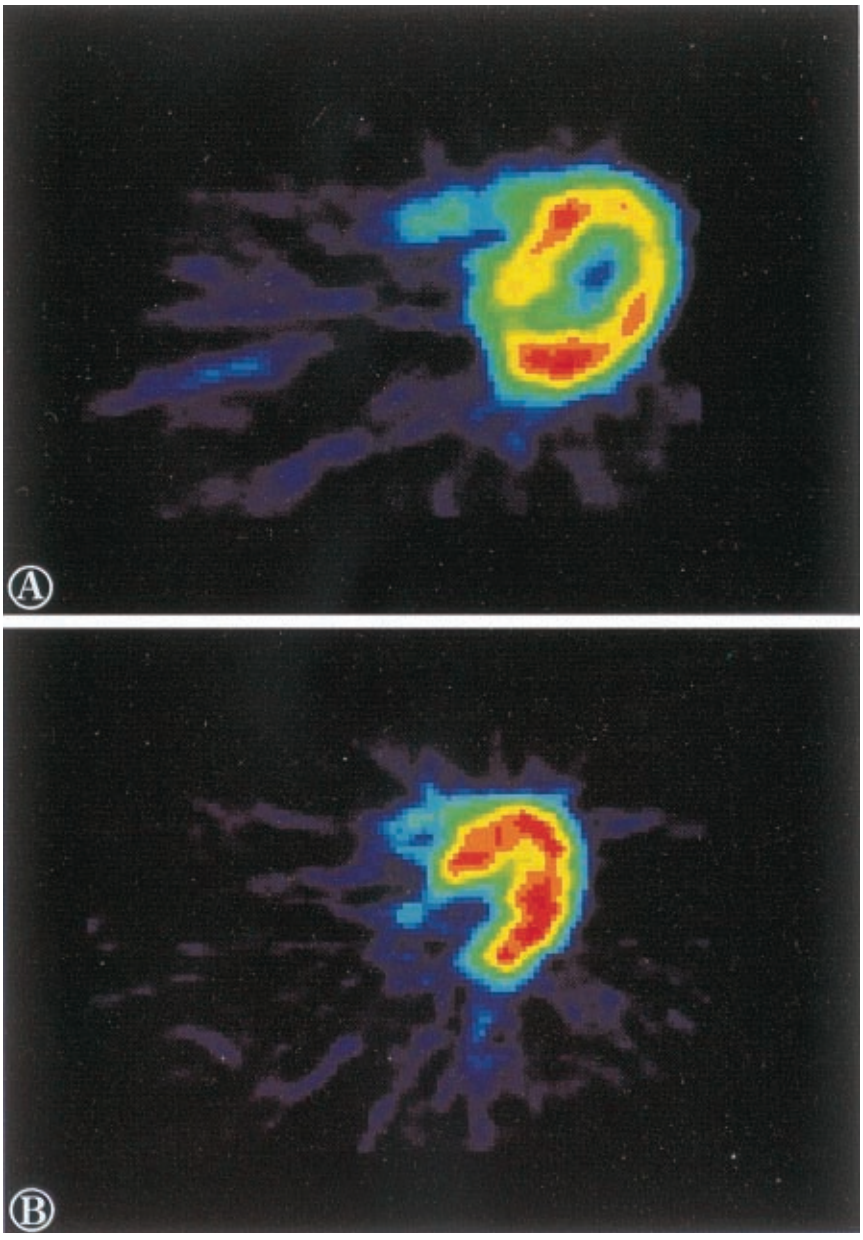

Fig. 1. Transaxial positron emission tomographic images of ^{18}F 2-deoxyglucose uptake in the left ventricular wall of patients with hypertrophic cardiomyopathy (A) and hypertensive heart disease associated with asymmetrical septal hypertrophy (B). In each cross-sectional image, the interventricular septum is in the upper left and posterolateral wall is in the lower right.

Myocardial FDG uptake

Fig. 1 (A) and 1 (B) show representative PET images of patients from the two patient groups. FDG uptake in both interventricular septum and left ventricular posterolateral wall was more heterogeneous in the patient with HCM (A) compared with the patient with HHD associated with asymmetrical septal hypertrophy (B).

PET data obtained from each patient from the two groups are summarized in Tables 1 and 2. In both the interventricular septum and posterolateral wall, % FDG fractional uptake was not significantly different between the two patient groups (Fig. 2). % Interregional coefficient of variation of FDG fractional uptake for both the interventricular septum and posterolateral wall was larger in the HCM group than in the HHD group (Fig. 3).

It is possible that the measure of heterogeneity of FDG uptake depends on the spatial resolution of the positron tomograph scanner. We therefore compared % interregional coefficient of variation of FDG fractional uptake obtained using the ECAT II scanner alone between the two patient groups. The % interregional coefficient of variation of FDG fractional uptake obtained with ECAT II for the interventricular septum was significantly larger in the HCM group than in the HHD group (11.2 ± 2.2 vs. 4.3 ± 0.6, cases 1 to 10 in the HCM group and cases 1 to 4 in the HHD group, $p < 0.05$). While that for the posterolateral wall tended to be higher in the HCM group than in the HHD group, the difference did not reach statistical significance (6.2 ± 1.3 vs. 4.2 ± 0.5).

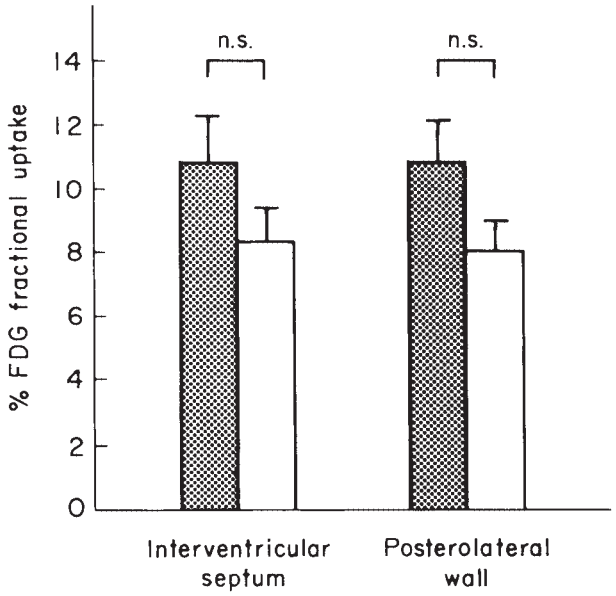

Fig. 2. % FDG fractional uptake in interventricular septum and left ventricular posterolateral wall in patients with hypertrophic cardiomyopathy (HCM, ▩) and those with hypertensive heart disease (HHD, □) associated with asymmetrical septal hypertrophy. FDG, ^{18}F 2-deoxyglucose.
n.s., not significant.

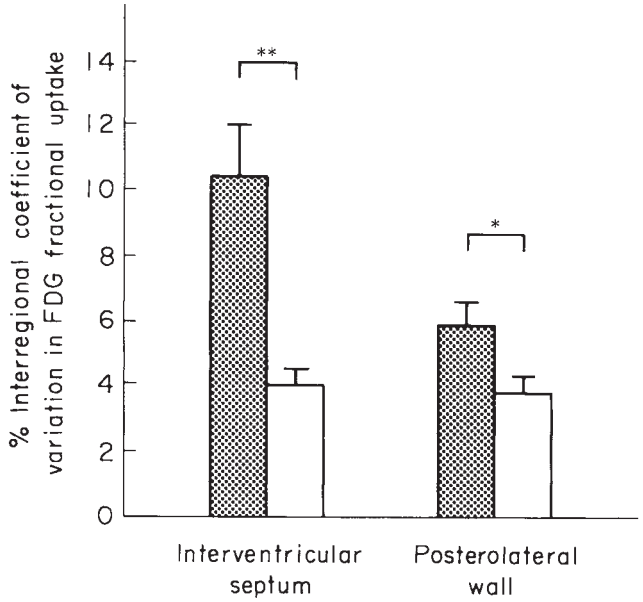

Fig. 3. % Interregional coefficient of variation in FDG fractional uptake in interventricular septum and left ventricular posterolateral wall in patients with hypertrophic cardiomyopathy (HCM, ▩) and those with hypertensive heart disease (HHD, □) associated with asymmetrical septal hypertrophy. FDG, ^{18}F 2-deoxyglucose. $*p<0.05$; $**p<0.01$.

The presence of a systolic pressure gradient in the left ventricular outflow tract in some patients of the HCM group might have been responsible for the larger % interregional coefficient of variation of FDG fractional uptake. We therefore compared those values between the HCM patients with and without a systolic pressure gradient in the left ventricular outflow tract, finding no significant difference for either the interventricular septum (7.8 ± 0.6 vs. 12.3 ± 2.5, with and without pressure gradient, respectively) or the posterolateral wall (5.1 ± 0.6 vs. 6.4 ± 1.6, with and without pressure gradient, respectively).

Plasma concentrations of glucose (123 ± 7 vs. 136 ± 8 mg/100 ml, HCM and HHD groups, respectively) and insulin (28 ± 8 vs. 25 ± 4 μU/liter, HCM and HHD groups, respectively) were not significantly different between the two patient groups. The plasma concentration of free fatty acids, however, was significantly higher in the HCM group than in the HHD group (1.1 ± 0.2 vs. 0.4 ± 0.1 mEq/liter, $p<0.05$).

Discussion

We found for the first time that myocardial FDG uptake is different between patients with HCM and those with HHD associated with asymmetrical septal hypertrophy. Although FDG fractional uptake in both the interventricular septum and left ventricular posterolateral wall was similar between the two patient groups, the % interregional coefficient of variation in both wall segments was larger in the HCM group than in the HHD group.

The mechanism for the difference in heterogeneity of FDG uptake between

the two patient groups is not clear. Glucose utilization is accelerated in myocardial ischemia (Opie 1976). Several earlier studies have suggested that myocardial ischemia plays an important role in the pathophysiology of HCM. Pasternac et al. (1982) and Cannon et al. (1985) demonstrated hemodynamic evidence of myocardial ischemia in patients with HCM. The increased heterogeneity of FDG fractional uptake in patients with HCM demonstrated in the present study might be partially explained by regional myocardial ischemia.

Histological examinations revealed myocardial fibrosis and scarring in patients with HCM (Maron et al. 1979; Olsen 1983; Tanaka et al. 1986). Right ventricular endomyocardial biopsy was performed in only one patient from each patient group in our present study. The specimen of case 4 in the HCM group showed patchy focal myocardial fibrosis and myocyte hypertrophy. The specimen of case 4 in the HHD group showed only marked myocyte hypertrophy. It is possible that the difference in myocardial fibrosis might partially explain the difference in the heterogeneity of FDG uptake. Further histological study with a larger number of patients, however, is needed to determine whether myocardial fibrosis predominantly contributes to the increased heterogeneity of myocardial FDG uptake in patients with HCM. Myocardial disarray, which is one of the common histological findings in patients with HCM, was not found in the patient with HCM. This may be due to the small sample number and/or the right ventricular, not left ventricular, endomyocardial biopsy. Although we still need further histological study, it is also possible that myocardial disarray contributes to the heterogeneity of FDG uptake.

A high plasma concentration of free fatty acids inhibits myocardial glucose utilization due to the predominance of free fatty acids as an energy source for myocardium (Wisneski et al. 1985). The reason why the plasma concentration of free fatty acids was significantly higher in the HCM group than in the HHD group in the present study is not clear. It is possible that sympathetic tone, which can increase the plasma concentration of free fatty acids (Opie 1988), was different between the two groups. It is unlikely, however, that the increased heterogeneity of myocardial FDG uptake in patients with HCM was caused by a higher plasma level of free fatty acids. This is because % FDG fractional uptake was similar between the two groups, suggesting that the effect of plasma free fatty acids on myocardial glucose uptake was similar in the present study.

The presence of a systolic pressure gradient in the left ventricular outflow tract in some patients of the HCM group might be responsible for the increased % interregional coefficient of variation of FDG fractional uptake in both the interventricular septum and posterolateral wall. This is because, in the HCM patients with a pressure gradient, only a part of the left ventricle is subjected to pressure overload which may increase myocardial glucose utilization (Kagaya et al. 1990) and may increase the heterogeneity of myocardial glucose metabolism. However, this would not be the case with the present study because % interregional

coefficient of variation of FDG fractional uptake was not significantly different between patients in the HCM group with and those without a pressure gradient.

HCM has been shown to be associated with mutations of the ß myosin heavy chain, troponin T, and a tropomyosin genes (Davies and Krikler 1994). Some mitochondrial encephalopathy due to mitochondrial gene mutation also has been reported to demonstrate hypertrophic cardiomyopathy (Hiruta et al. 1995). Although we did not investigate those gene mutations in the patients with HCM, such studies may suggest other possible mechanisms for the heterogeneity of myocardial glucose metabolism in those patients.

We did not correct regional myocardial FDG fractional uptake for regional wall thickness. It is unlikely, however, that the differences of % interregional coefficient of variation in FDG fractional uptake between the patient groups were due to the difference in the regional wall thickness, because the wall thickness of both the interventricular septum and posterolateral wall was similar between the two patient groups.

It is possible that the measure of heterogeneity of FDG uptake depends on the spatial resolution of the PET scanner. We therefore compared % interregional coefficient of variation of FDG fractional uptake obtained using an ECAT II scanner alone between the two patient groups. The % interregional coefficient of variation of FDG fractional uptake obtained using ECAT II for the interventricular septum was significantly increased in the HCM group compared with the HHD group. The difference in the % interregional coefficient of variation in FDG fractional uptake, therefore, cannot be explained by the difference in the spatial resolution of the two PET scanners. The % interregional coefficient of variation for the posterolateral wall tended to be higher in the HCM group than in the HHD group. The difference, however, did not reach statistical significance. This may be due to the fact that a relatively small number of patients with HHD were studied with the ECAT II.

The blood pressure measured just before the tomographic study in the HHD group was much higher than that in the HCM group. This was because medications were discontinued on the day of the study. It is not clear, therefore, whether the difference in the heterogeneity of glucose metabolism is in part due to the difference in the left ventricular pressure overloading between the two groups. It might be useful to study myocardial glucose metabolism in patients with HHD under medications.

Differential diagnosis between HCM and HHD with asymmetrical septal hypertrophy is sometimes difficult, especially in a case with borderline hypertension or an indistinct history of hypertension. Morphological findings, clinical characteristics and hemodynamic findings are not always sufficient for differential diagnosis. Evaluation of heterogeneity of myocardial glucose metabolism using PET and FDG may allow noninvasive differentiation between HCM and HHD associated with asymmetrical septal hypertrophy. Further study in patients with

borderline hypertension, however, is needed to determine if measurement of heterogeneity of myocardial glucose metabolism is useful for the differential diagnosis between HCM and HHD with asymmetrical septal hypertrophy and borderline hypertension.

As glucose and free fatty acids compete with each other as energy substrates for myocardium, it may be interesting to investigate HCM and HHD patients with asymmetrical septal hypertrophy with ^{123}I-β-methyl-iodophenyl pentadecanoic acid (^{123}I-BMIPP), a fatty acid analog, and single photon emission tomography. Kurata et al. (1992) reported the regional reduction of myocardial ^{123}I-BMIPP uptake, which was independent on regional perfusion determined by ^{201}Tl uptake in patients with HCM. However, the characteristics of ^{123}I-BMIPP uptake in HHD patients with asymmetrical septal hypertrophy are still unknown.

In conclusion, myocardial glucose metabolism may be more heterogeneous in patients with HCM compared with HHD patients associated with asymmetrical septal hypertrophy, although the left ventricular shape is similar. The difference in the heterogeneity between the two patient groups might be caused by differences in the pathogeneses of the two diseases.

Acknowledgments

We thank Dr. H. Orihara, Dr. K. Ishii, Dr. R. Iwata, and other members of the Cyclotron and Radioisotope Center, Tohoku University for the operation of the cyclotron and preparation of FDG. We are grateful to Mr. S. Watanuki and Mr. S. Seo for their invaluable support in the PET study. We also thank Mr. B. Bell for reading the manuscript.

References

1) Camici, P., Araujo, L.I., Spinks, T., Lammertsma, A.A., Kaski, J.C., Shea, M.J., Selwyn, A.P., Jones, T. & Maseri, A. (1986) Increased uptake of ^{18}F-fluorodeoxyglucose in postischemic myocardium of patients with exercise-induced angina. *Circulation*, **74**, 81–88.
2) Cannon, R.O., III, Rosing, D.R., Maron, B.J., Leon M.B., Bonow, R.O., Watson, R.M. & Epstein, S.E. (1985) Myocardial ischemia in patients with cardiomyopathy: Contribution of inadequate vasodilator reserve and elevated left ventricular filling pressure. *Circulation*, **71**, 234–243.
3) Davies, M.J. & Krikler, D.M. (1994) Genetic investigation and counselling of families with hypertrophic cardiomyopathy. *Br. Heart J.*, **72**, 99–101.
4) Fujiwara, S., Umemoto, M., Miyamoto, Y., Ota, A., Arita, M., Yokote, Y., Nakamura, Y., Ueno, Y., Nishio, I. & Masuyama, Y. (1985) The role of hypertension in apical hypertrophy. *J. Cardiogr.*, **6**, Suppl., 53–64. (in Japanese with English abstract)
5) Gallagher, B.M., Ansari, A., Atkins, H., Casella, V., Christman, D.R., Fowler, J.S., Ido, T., MacGregor, R.R., Som, P., Wan, C.N., Wolf, A.P., Kuhl, D.E. & Reivich, M. (1977) Radiopharmaceuticals XXVII. ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo: Tissue distribution and imaging studies in animals. *J. Nucl. Med.*, **18**, 990–996.
6) Hiruta, Y., Chin, K., Shitomi, K., Ichihara, T., Mochizuki, M., Adachi, K., Obayashi, T., Tanaka, M. & Ozawa, T. (1995) Mitochondrial encephalomyopathy with A to G

transition of mitochondrial transfer RNA (Leu(UUR)) 3,243 presenting hypertrophic cardiomyopathy. *Intern. Med.*, **34**, 670–673.
7) Huggett, A.S.G. & Nixon, D.A. (1957) Use of glucose oxidase, peroxidase, and O-dianisidine in determination of blood and urinary glucose. *Lancet*, **24**, 368–370.
8) Kagaya, Y., Kanno, Y., Takeyama, D., Ishide, N., Maruyama, Y., Takahashi, T., Ido, T. & Takishima, T. (1990) Effects of long-term pressure overload on regional myocardial glucose and free fatty acid uptake in rats. Quantitative autoradiographic study. *Circulation*, **81**, 1353–1361.
9) Kagaya, Y., Ishide, N., Takeyama, D., Kanno, Y., Yamane, Y., Shirato, K., Maruyama, Y., Itoh, M., Ido, T., Matsuzawa, T. & Takishima, T. (1992) Differences in myocardial fluoro-18 2-deoxyglucose uptake in young versus older patients with hypertrophic cardiomyopathy. *Am. J. Cardiol.*, **69**, 242–246.
10) Kurata, C., Tawarahara, K., Taguchi, T., Aoshima, S., Kobayashi, A., Yamazaki, N., Kawai, H. & Kaneko, M. (1992) Myocardial emission computed tomography with iodine-123-labeled beta-methyl-branched fatty acid in patients with hypertrophic cardiomyopathy. *J. Nucl. Med.*, **33**, 6–13.
11) Maron, B.J., Epstein, S.E. & Roberts, W.C. (1979) Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. *Am. J. Cardiol.*, **143**, 1086–1102.
12) Mizuno, K., Toyosato, M., Yabumoto, S., Tanimizu, I. & Hirakawa, H. (1980) A new enzymatic method for colorimetric determination of free fatty acids. *Anal. Biochem.*, **108**, 6–10.
13) Olsen, E.G.J. (1983) Anatomic and light microscopic characterization of hypertrophic obstructive and non-obstructive cardiomyopathy. *Eur. Heart J.*, **4**, Suppl. F, 1–8.
14) Opie, L.H. (1976) Effects of regional ischemia on metabolism of glucose and fatty acids: Relative rates of aerobic energy production during myocardial infarction and comparison with effects of anoxia. *Circ. Res.*, **38**, Suppl. I, I-52-I-74.
15) Opie, L.H. (1988) Sympathetic stimulation of ischemic myocardium: Role of plasma free fatty acids and potassium. *J. Cardiovasc. Pharmacol.*, **12**, Suppl. 1, S31–S38.
16) Pasternac, A., Noble, J., Streulens, Y., Elie, R., Henschke, C. & Bourassa, M.G. (1982) Pathophysiology of chest pain in patients with cardiomyopathies and normal coronary arteries. *Circulation*, **65**, 778–789.
17) Ratib, O., Phelps, M.E., Huang, S.C., Henze, E., Selin, C.E. & Shelbert, H.R. (1982) Positron tomography with deoxyglucose for estimating local myocardial glucose metabolism. *J. Nucl. Med.*, **23**, 577–586.
18) Savage, D.D., Drayer, J.I.M., Henry, W.L., Mathews, E.C., Ware, J.H., Gardin, J.M., Cohen, E.R., Epstein, S.E. & Laragh, J.H. (1979) Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. *Circulation*, **59**, 623–632.
19) Shapiro, L.M., Kleinebenne, A. & McKenna, W.J. (1985) The distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: Comparison to athletes and hypertensives. *Eur. Heart J.*, **6**, 967–74.
20) Shiba, N., Kagaya, Y., Ishide, N., Otani, H., Takeyama, D., Yamane, Y., Chida, M., Ido, T. & Shirato, K. (1997) Heterogeneity of myocardial fluoro-18 2-deoxyglucose uptake in patients with apical hypertrophic cardiomyopathy. *Jpn. Circ. J.*, **61**, 223–230.
21) Sochor, H., Shelbert, H.R., Schwaiger, M., Henze, E. & Phelps, M.E. (1986) Studies of fatty acid metabolism with positron emission tomography in patients with cardiomyopathy. *Eur. J. Nucl. Med.*, **12**, S66–S69.
22) Tanaka, M., Fujiwara, H., Onodera, T., Der-Jinn, W., Hamashima, Y. & Kawai, C. (1986) Quantitative analysis of myocardial fibrosis in normals, hypertensive hearts, and hypertrophic cardiomyopathy. *Br. Heart J.*, **55**, 575–581.
23) Teare, R.D. (1958) Asymmetrical hypertrophy of the heart in young adults. *Br.*

Heart J., **20**, 1-8.
24) Trinder, P. (1969) Determination of glucose using glucose oxidase with an alternative oxygen acceptor. *Ann. Clin. Biochem.*, **6**, 24-27.
25) Yalow R.S. & Berson, S.A. (1960) Immunoassay of endogenous plasma insulin in man. *J. Clin. Invest.*, **39**, 1157-1175.
26) Wisneski, J.A., Gerts, E.W., Neese, R.A., Gruenke, L.D., Morris, D.L. & Craig, J.C. (1985) Metabolic rate of extracted glucose in normal human myocardium. *J. Clin. Invest.*, **76**, 1819-1827.