Myocardial Blood Flow and Metabolism in Patients With Hypertrophic Cardiomyopathy — A Study With Carbon-11 Acetate and Positron Emission Tomography —

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The underlying pathophysiology of hypertrophic cardiomyopathy (HCM) is still unclear. Positron emission tomography is a suitable and promising technique for the detection of possible metabolic consequences of the disease. To assess regional myocardial blood flow and metabolism, 19 asymptomatic or only mildly symptomatic patients with HCM and 10 normal control subjects were studied using carbon-11 acetate and fluorine-18-labelled deoxyglucose (FDG) as tracers of myocardial blood flow (Ao), oxygen consumption (k), and exogenous glucose utilization. In the patients, regional Ao in the hypertrophied septum and apex (H) was similar to that in the nonhypertrophied free wall (N) ($91.3 \pm 3.9\%$ vs $92.9 \pm 3.1\%$; $p = \text{NS}$). However, the k values were significantly lower in H than in N (0.044 ± 0.012 vs $0.060 \pm 0.016/\text{min}$, $p < 0.0001$). The k value in N and normal control subjects (0.062 ± 0.013) was similar. Postprandial FDG uptake was lower in H than in N (70 ± 16 vs $91 \pm 7\%$; $p < 0.0001$) in 16 patients and slightly higher in 3 patients. Fasting FDG study showed increased FDG uptake in H in 3 out of 13 patients, suggesting a disorder of the myocardial microvascular circulation. A relative decrease in hypertrophied septal and apical oxidative metabolism and glucose utilization without any corresponding perfusion defect could reflect abnormal regional aerobic metabolism in the disproportionately thickened myocardium in patients with HCM. This suggests that a primary myocardial metabolic defect might be present in patients with HCM.

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Key Words: Carbon-11 acetate; Fluorine-18-labelled deoxyglucose; Oxidative metabolism; Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) has a wide spectrum of clinical and morphologic manifestations, and several hypotheses for its etiology have been proposed!^{1–9} In some previous studies ischemia has been detected in patients with HCM!^{10–14} In addition, positron emission tomography (PET) studies have recently shown that the coronary vasodilatory reserve is severely reduced in HCM patients with typical anginal chest pain!¹⁵ Conversely, other studies have found that the disproportionately thickened myocardium is not ischemic at rest, but is metabolically different from the normal myocardium, exhibiting markedly decreased metabolism with slightly de-

creased flow!¹⁶ Recent genetic analyses have shown that different missense mutations in the beta-cardiac myosin heavy-chain gene as well as in the alpha-tropomyosin and cardiac troponin T genes can cause HCM!^{8,9} However, little is known about the myocardial metabolic state and regional blood flow in patients with HCM. Positron imaging allows noninvasive study of myocardial metabolism, and is particularly promising for elucidating the causes and pathogenesis of cardiomyopathy. Furthermore, in view its ability to measure quantitatively influx and washout of specific biochemical substrates in vivo, cardiac PET provides insights into the biochemistry of HCM under physio-

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Table 1 Clinical Characteristics of the Study Patients

Patient	Diagnosis	Age (years) and sex	NYHA class	Family history	HR (beats/ min)	BP (mmHg)	RPP ($\times 0.01$)	Echocardiography			MRI		
								IVS (mm)	LVPW (mm)	FS (%)	Apical thickness (mm)	LVEDP (mmHg)	LVOT PG (mmg)
1	HNCM	66M	2	N	62	114/74	70.7	17	10	36	—	25	0
2	HNCM	52M	1	N	66	112/80	73.9	20	13	48	—	18	0
3	HOCM	18F	2	N	66	100/58	66.0	27	15	41	—	14	62
4	HOCM	35M	1	N	60	102/54	61.2	18	11	44	—	34	36
5	HNCM	63M	1	N	62	104/66	64.5	18	10	48	—	16	0
6	HNCM	51M	1	N	56	108/70	60.5	17	12	44	—	17	0
7	HOCM	54M	1	N	64	110/80	70.4	19	13	40	—	22	64
8	HNCM	55M	1	N	72	128/78	92.2	20	8	31	—	20	0
9	HNCM	61F	2	Y	70	104/70	71.4	20	12	38	—	23	22
10	HOCM	26F	2	Y	66	116/74	76.6	22	12	42	—	26	82
11	HOCM	34M	2	N	58	102/64	59.2	20	10	52	—	14	40
12	HNCM	45M	1	N	54	100/76	54.0	20	12	51	—	13	0
13	Apical	55M	1	N	58	136/90	78.9	12	11	45	32	22	0
14	Apical	65M	1	N	68	112/60	76.2	10	9	40	24	15	0
15	Apical	44M	1	Y	60	112/68	67.2	12	10	36	34	25	0
16	Apical	56M	1	Y	54	116/90	62.6	13	11	43	30	15	0
17	Apical	54M	1	N	64	120/68	76.8	10	9	40	32	16	0
18	Apical	67M	1	N	64	130/80	83.2	11	9	41	26	16	0
19	Apical	59M	1	N	52	116/78	60.3	12	10	41	30	14	0

HNCM, hypertrophic non-obstructive cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; Apical, apical hypertrophic cardiomyopathy; IVS, interventricular septum; LVPW, left ventricular posterior wall; LVOT, left ventricular outflow tract; LVEDP, left ventricular endodiastolic pressure; FS, fractional shortening; MRI, magnetic resonance imaging; —, no data.

logic conditions, thus aiding identification of defects in the underlying specific metabolism.

The aim of this study was to assess regional myocardial blood flow and potential alterations in regional oxidative metabolism and glucose metabolism in mildly symptomatic or asymptomatic patients with HCM using carbon-11 acetate and fluorine-18-labelled deoxyglucose (FDG) as tracers of myocardial blood flow, oxygen consumption, and exogenous glucose utilization. FDG studies were performed in both the postprandial and fasting state for comparison.

Methods

Patients and Normal Population

Nineteen patients with HCM (16 men and 3 women) were studied with C-11 acetate and FDG at rest 2 h after a meal. Thirteen of the 19 patients underwent an additional fasting FDG study. Demographic information, clinical and morphological data, as well as the hemodynamic data taken during the PET acquisition are summarized in Table 1. None of the patients suffered from a metabolic disorder or had a history of diabetes mellitus. Five patients presented clinical symptoms with mild exertional chest pain and palpita-

tion or dyspnea of New York Heart Association grade II, but the majority of subjects were asymptomatic in daily life and had good exercise tolerance. The values obtained from 10 normal control subjects (mean age 44 years) were used for comparison. Normal control subjects consisted of 6 volunteers and 4 subjects referred for atypical chest pain but who proved to be normal in every examination including cardiac catheterization, echocardiography, and stress tests.

There were 12 patients with asymmetric septal hypertrophy (ASH) and 7 patients with apical HCM. Their ages ranged from 18 to 67 years (mean 50). All patients met clinical, echocardiographic, and angiographic criteria for HCM with ASH and apical HCM.^{17–19} Septal thickness was increased in all patients with ASH (17–27 mm), with a mean value of 20 mm, compared with a myocardial thickness of 12 mm in the nonhypertrophied wall. In patients with apical HCM, apical thickness was assessed by magnetic resonance imaging (MRI) as accurate measurements were difficult to obtain by echocardiography alone. These values were used for partial volume correction in the later data analysis. In patients with ASH, echocardiographic measurements of end-diastolic and end-systolic septal and posterior wall thickness, which

were measured at the level of the tips of the mitral valve leaflets, were used to estimate differences in regional wall motion. All patients underwent cardiac catheterization and no definite coronary artery disease was found. Five patients had a left ventricular to aortic pressure gradient at rest and 1 had a provocative gradient using intravenous proterenol injection.

Tomographic Imaging Procedure

Each subject gave informed consent in writing after the investigative nature and possible risk of the study had been explained in detail. The study protocol was approved by the ethics committee and the radiopharmaceutical committee of Tokyo Metropolitan Institute of Gerontology. Carbon-11 acetate and FDG studies were performed in the postprandial state, with subjects being asked to eat a meal 2 h before examination. Thirteen of the 19 patients underwent an additional FDG study after a 6-h fast. Patients were requested to discontinue cardiac medication for at least 24 h.

Imaging was performed with a Headtome IV PET camera (Shimadzu, Kyoto), which provided 13-mm interval 7-slice tomographic images by reconstruction with Butterworth filter (cut-off frequency=8 mm), giving an effective image spatial resolution of 7.5 mm full-width half-maximum (FWHM)²⁰ An initial 8-min transmission scan was performed using a germanium-68 line source to be used later for photon attenuation correction after smoothing to suppress the statistical noise. A dynamic PET data acquisition was then initiated after intravenous injection of 450 MBq of carbon-11 acetate synthesized from [¹¹C]carbon dioxide²¹ Eighteen frames of dynamic PET data were collected over 20 min, consisting of 4 30-s frames, 10 1-min frames and 4 2-min frames. After the carbon-11 acetate study, 120 MBq of FDG was injected and the scan was performed for 12 min starting 45 min after injection. The FDG image was acquired in 6.5-mm interval 14-slice mode.

Data Analysis

Data analysis and image display were performed using an image data analysis system ('Dr View', Asahi Kasei, Tokyo) that runs on Titan 750 (Kubota, Tokyo Japan). The carbon-11 acetate data were analyzed using 2 methods: the region of interest (ROI) method, which provides quantitative estimates of Ao, k and FDG; and using parametric images, which provide a visual impression. ROIs were assigned to the posteroseptal, anteroseptal, apical, anterolateral, lateral, and posterolateral segments of the left ventricular wall. Time-activity curves were generated either pixelwise or from the ROIs over the serial images. The carbon-11

clearance rate (k : min^{-1}) was estimated from the clearance phase data points after the perfusion peak (starting 200–300 sec after injection in most cases to minimize spillover of blood pool activity), using the monoexponential curve-fitting method. The myocardial uptake of carbon-11 acetate (Ao) was calculated as the extrapolated value of the monoexponential fit at the peak time, to avoid the spillover from blood pool activity, and was used to assess regional difference in myocardial blood flow. In the ROI method, the Ao values were corrected for partial volume effect²² using the regional wall thickness measured by echocardiography or MRI and normalized to the highest myocardial value of the subject and expressed as percent Ao to allow comparison of the hypertrophied septum or apex and the nonhypertrophied free wall. In the pixelwise analysis, which takes into account high noise, the time-activity curve was fitted to the eighth order of a Chebishev polynomial to estimate the peak time, and parametric images of Ao and k were generated automatically. The parametric images of initial uptake (Ao) and clearance rate constant (k) were calculated and depicted as transaxial images, which permitted characterization of regional variations in perfusion and metabolism.

The FDG images were similarly analyzed using the ROIs and the values were also corrected for the partial volume effect. The corrected values were then normalized to the highest myocardial value found in the entire data set and expressed as a percentage of FDG uptake.

Statistical Analysis

The relative perfusion (percentage Ao value), oxidative metabolism (k value) and postprandial relative glucose metabolism (percentage FDG uptake) were compared in the posterolateral nonhypertrophied free wall and hypertrophied septum or apex in each subject using a paired t test.

Results

The transaxial images of Ao, k, and FDG, reflecting blood flow, oxidative metabolism, and glucose utilization, respectively, are shown in Fig 1 for representative cases. Regional blood flow was more homogeneous in younger patients (eg, patient A), whereas segmental perfusion defects in the hypertrophied septum were noted in elderly patients, as represented by patient C. Areas with obvious perfusion defects also showed greatly reduced oxidative metabolism and glucose utilization, suggesting the presence of myocardial fibrosis or scarring.

Fig 1. (A) Transaxial images of a 26-year-old female patient with ASH: Top: uptake image; middle: clearance image; bottom: FDG image. The perfusion is almost normal in all segments, whereas low clearance rate and glucose accumulation in the hypertrophied septum are apparent. Note the visual impression of the parametric images of uptake and clearance, which permitted characterization of the regional mismatch of perfusion and metabolism at a glance. (B) A 56-year-old male patient with ASH. The same type of perfusion-metabolism mismatches are obvious in the hypertrophied apex. (C) A 66-year-old male patient with ASH. This patient has a long clinical history including 25 years of follow-up since diagnosis and has reached old age without incurring important cardiac symptoms or clinical events. Compared with case A, extensive scar formation (white arrow) is noticeable in the hypertrophied septum. The area with normal blood flow shows a similar metabolic pattern to the above cases. (D) A 67-year-old male patient with apical HCM. A fasting study showed marked accumulation of FDG at the site of the hypertrophied apex. There is no evidence of a perfusion defect at the apex.

As indicated in Fig 2A and B, regional percentage A_o values in the hypertrophied segment in patients with HCM were similar to those in the nonhypertrophied left ventricular free wall. However, compared with the blood flow, the k values were significantly lower in the hypertrophied segment than in the nonhypertrophied free wall (0.044 ± 0.012 vs 0.060 ± 0.016 min^{-1} ; $p < 0.0001$) at a mean regional perfusion pressure of 8209 ± 1376 . The k value in the normal control subjects was 0.062 ± 0.013 min^{-1} at a mean regional perfusion pressure of 8514 ± 1562 and was not significantly different from the k values in the patients' nonhypertrophied free wall. In normal controls, percentage A_o was uniform. Fig 2C (left) shows that

postprandial FDG uptake as assessed by percent FDG uptake was lower in the hypertrophied segment than in the lateral free wall (70 ± 16 vs $91 \pm 7\%$; $p < 0.0001$), except in 3 patients with ASH. When these 3 patients were excluded, the mean FDG uptake in hypertrophied segment was 65% and the decrease in FDG was similar to the decrease in k values. The measurement of relative postprandial glucose metabolism revealed homogeneous FDG distribution in 9 out of 10 normal control subjects. One normal subject showed no FDG accumulation owing to low blood glucose level.

To determine whether ischemia is involved and to account for possible masking of the presence of

Fig 2. Comparison of regional myocardial blood flow (% Ao) (A), clearance rate constant (k) (B), and postprandial and fasting FDG uptake (C) in the hypertrophied septum or apex (H) and nonhypertrophied lateral free wall (N) in 19 subjects with HCM (closed circle; ASH, open circle; apical HCM). The percentage Ao in the hypertrophied segments was similar to that in the nonhypertrophied segments in each patient, whereas a significant decrease in the k values was observed in the hypertrophied segments. The postprandial FDG uptake was significantly reduced in hypertrophied septum and apex compared with the lateral free wall, except in 3 patients with ASH. During fasting, 3 patients showed a slightly increased FDG uptake in the hypertrophied segment. Open ovals represent myocardial FDG images taken under fasting conditions when no FDG accumulation has occurred.

any ischemia-induced flow-metabolism mismatch, 13 patients underwent an additional fasting FDG study (Fig 2C, right). Three fasting FDG patterns were detected: in type 1 (3 out of the 13 patients) FDG uptake was higher in the hypertrophied segments than in the nonhypertrophied segments; in type 2

(4 patients) FDG uptake was moderate in nonhypertrophied segments and reduced in hypertrophied segments, which were similar to postprandial images; in type 3 (6 patients) there was no FDG accumulation in the heart. One of the 3 type 1 patients had apical hypertrophy (Fig 1D) and the others had ASH. Two

Table 2 Plasma Substrate Concentrations Before and After PET Studies in the Postprandial and Fasting State

Patient no.	Glucose (mg/dl)		Insulin (μ U/ml)		Free fatty acid (mequiv./L) ($n=0.14\sim0.85$)	
	Before	After	Before	After	Before	After
1	98 (77)	78 (77)	81 (4.7)	57 (5.2)	0.22 (0.88)	0.11 (0.87)
2	86	91	7.9	4.9	0.24	0.39
3	82	79	5.8	5.7	0.12	0.79
4	93 (91)	102 (88)	5.3 (3.9)	6.6 (2.5)	0.09 (0.98)	0.38 (0.90)
5	123 (96)	125 (95)	24 (5.7)	17 (6.5)	0.34 (0.58)	0.28 (0.54)
6	93 (84)	85 (85)	23 (3.9)	16 (4.0)	0.21 (0.67)	0.30 (0.88)
7	109 (90)	113 (86)	5.1 (3.4)	9.0 (2.5)	0.06 (1.05)	0.08 (0.51)
8	103	99	8.0	6.2	0.19	0.15
9	113	124	12	16	0.46	0.23
10	87	93	5.0	4.6	0.19	0.11
11	144 (89)	100 (84)	15 (3.2)	2.8 (3.2)	0.06 (1.04)	0.11 (1.29)
12	92 (89)	91 (89)	5.8 (3.7)	5.0 (3.1)	0.34 (0.43)	0.68 (0.55)
13	141 (95)	109 (97)	11 (4.8)	21 (4.5)	0.40 (0.60)	0.36 (0.62)
14	125	115	31	48	0.25	0.25
15	126 (96)	118 (99)	9.5 (5.5)	8.2 (5.6)	0.08 (0.90)	0.06 (0.89)
16	147 (101)	165 (100)	24 (4.6)	20 (5.0)	0.08 (0.48)	0.07 (0.53)
17	88 (87)	89 (89)	8.2 (5.4)	11 (5.0)	0.21 (0.69)	0.20 (0.65)
18	98 (89)	86 (88)	14 (2.5)	14 (2.5)	0.21 (0.68)	0.24 (0.64)
19	127 (94)	126 (92)	28 (4.4)	30 (3.7)	0.31 (0.44)	0.28 (0.62)
Mean	109 (91)	104 (90)	17 (4.3)	16 (4.1)	0.21 (0.72)	0.27 (0.73)
SD($\pm$)	21 (6.1)	21 (6.5)	17 (1.0)	15 (1.3)	0.12 (0.02)	0.20 (0.01)

Fasting data are given in parentheses.

of the 3 patients who exhibited higher FDG uptake in hypertrophied segment than in nonhypertrophied segment in the postprandial state underwent a fasting FDG study; one was classified as type 1 and the other as type 3.

Five patients complained of mild symptoms such as chest pain or dyspnea. Four patients had a family history of HCM. However, there were no obvious differences in the studied parameters (Ao, k value and [18 F]FDG uptake) among the symptomatic group, asymptomatic group and the group with a family history of HCM. Table 2 summarizes the plasma levels of the major myocardial substrates, glucose, and free fatty acid and insulin, which were measured immediately before and after the PET study. There was no obvious correlation between FDG uptake and plasma glucose, insulin, or fatty acid levels.

Discussion

Evaluations of relative distributions as well as quantification of regional blood flow, metabolism, and exogenous glucose utilization with PET using carbon-11 acetate and [18 F]FDG revealed a disparity between blood flow and oxidative and glucose metabolism in asymptomatic or mildly symptomatic patients with

hypertrophic cardiomyopathy. Oxidative metabolism and glucose utilization in hypertrophied segments were significantly lower than in nonhypertrophied myocardial segments, whereas blood flow was uniform.

Oxidative Metabolism

Several interpretations can be offered to explain the lower oxidative metabolism in the hypertrophied septum and apex than in the lateral free wall. The regional mechanics showed hyperkinesia in the free wall, whereas the hypertrophied septum and apex exhibited normal or slightly decreased wall motion, possibly as a result of increased chamber stiffness²³⁻²⁶

Myocardial contractile work is a major determinant of myocardial oxygen consumption²⁷⁻³⁰. Thus, segmental differences in regional loading conditions or contractile function might lead to decreased oxygen consumption in hypertrophied segment. However, no previous study has directly compared regional work with oxidative metabolism using k values. One reason is the difficulty of evaluating regional wall motion in hypertrophic cardiomyopathy. Alternatively, there may be an abnormality in oxygen extraction, such as increased diffusion distances, or an abnormality in the regulation of blood flow in the disproportionately thickened myocardium.

Another interpretation of decreased oxygen consumption in hypertrophied portions is that hypertrophied segments in HCM are more severely affected by the myopathic process and might be metabolically different from normal myocardium. In this study, 7 patients with apical HCM showed the ASH pattern of images. Our previous study (not published) and several other reports^{17,31} have demonstrated the presence of bizarre myocardial hypertrophy with disorganization in hypertrophied apex in patients with apical hypertrophy. These pathological manifestations in apical HCM might explain their similarity to ASH on PET images. Furthermore, there are several reports of metabolic disparity between hypertrophied and nonhypertrophied segments in patients HCM, suggesting a still unknown primary metabolic defect in the disproportionately thick myocardium of these patients.^{14,16} In this study we found 3 patients with decreased oxidative metabolism in spite of high or nearly normal glucose uptakes. Thus, the decreased oxidative metabolism cannot be explained simply by decreased metabolic demand in these lower stressed and less contractile hypertrophied segments. These findings support the hypothesis of a primary metabolic defect in HCM rather than the 'reduced demand' theory.

Glucose Utilization

The postprandial FDG study revealed a reduction in FDG uptake in line with the reduction in oxidative metabolism in 16 of 19 patients. The relation between heterogeneous metabolic activity and regional wall motion was investigated by Perrone-Filardi et al³⁰ who concluded that altered regional glucose metabolism is associated with reduced wall motion of the same regions. In the 3 patients with ASH, however, glucose uptake was slightly higher in the septum than in the nonhypertrophied segment in spite of decreased oxidative metabolism (k value). Homogeneous regional perfusion makes it unlikely that regional differences in tracer delivery account for the heterogeneity of FDG activity. Therefore, we cannot conclude that reduced glucose metabolism is due to a reduction in oxidative metabolism, and other as yet unknown causes need to be considered. One cause of decreased glucose utilization could be regional changes in substrate selection due to a defect in an aerobic metabolic pathway at the cellular level, although little direct evidence of this is available.

As the postprandial FDG study may have masked any effect of ischemia, we performed an additional fasting study in 13 patients to obtain a better understanding of metabolism under different nutritional conditions, and in particular to determine the role of

ischemia. We found 3 patients who exhibited FDG accumulation at the site of hypertrophied myocardium, one with slightly increased FDG uptake in the postprandial state. Thus, in some patients, there may be ischemia of the microvascular circulation may be involved in the pathogenesis of HCM. However, the studies under fasting conditions show that ischemia is uncommon (3 of 13 patients) and does not appear to be a major pathogenic factor in our patient population. This is probably a heterogeneous process and thus accounts for the different patterns of glucose metabolism.

Comparison With Previous Study

The finding in this study that many patients show no evidence of obvious ischemia are consistent with a previous study by Perrone-Filardi et al³⁰ Grover-McKay et al¹⁶ reported a marked decrease in FDG uptake and slightly depressed myocardial perfusion in the hypertrophied septum compared with the lateral wall in mildly symptomatic patients. Furthermore, the accumulation of carbon-11 palmitate was also mildly depressed in the septum after correction for the partial volume effect, although the carbon-11 palmitate kinetics were relatively homogeneous. These metabolism-perfusion disparities are yet to be completely explained, but they appear unlikely to be caused by ischemia. Conversely, Nienaber et al¹⁴ found that blood flow was significantly lower in hypertrophied than in nonhypertrophied myocardium, whereas rates of glucose utilization were similar, suggesting the presence of ischemia in symptomatic HCM. Furthermore, they pointed out that the discrepancy between flow and glucose metabolism in hypertrophied myocardium was more prominent in younger patients. Kagaya et al³² also reported that the regional heterogeneity of [¹⁸F]deoxyglucose uptake is higher in young patients than in older subjects. These findings support the general notion that the development of HCM in young people might be the result of a different pathogenic process from that occurring in middle-aged or elderly patients³³⁻³⁹

Although our patients were of different ages, their patterns of glucose metabolism were similar. However, more heterogeneous perfusion defects were noted in the hypertrophied septum of elderly patients (Fig 1, patient C), and these areas did not take up glucose, which indicates myocardial scarring. We observed that younger patients had a lower oxidative metabolism in spite of a more homogeneous carbon-11 acetate uptake in hypertrophied segments. This suggests that scarring may occur in the long term preceded by abnormal myocardial metabolism. This finding was of interest in

identifying the natural course of HCM.

There are several possible explanations for the differences in the outcome observed between our study and previous reports. First, we have to take into consideration not only the disease types but also the duration of morbidity and the patient populations studied. Our study included only asymptomatic or mildly symptomatic patients, who may be experiencing pathologic processes that are different from those experienced by Nienaber's symptomatic patients. The long-term prognosis for middle-aged asymptomatic patients is reasonably favorable⁴⁰⁻⁴³ However, patients presenting moderate to severe symptoms have a relatively poor prognosis.³⁹ Secondly, we investigated regional myocardial blood flow and oxidative metabolism using carbon-11 acetate. To our knowledge, this is the first study to evaluate the pathogenesis of HCM using carbon-11 acetate. Carbon-11 acetate is a unique tracer that can be used to image both flow and metabolism simultaneously. The initial uptake of this tracer could be useful as an indirect index of regional myocardial perfusion. Furthermore, the carbon-11 clearance rate is insensitive to the partial volume effect. Thirdly, some previous studies were performed with subjects in the fasting state^{14,16} whether in other studies patients were administered a glucose load^{14,30,32} Glucose loading may be affected by sharp changes in plasma glucose and insulin levels over time, potentially limiting the quantitative evaluation and valid comparison of myocardial glucose utilization. Thus, our study was conducted under non-fasting metabolically stable conditions 2 h after meal to minimize temporal changes in metabolic conditions.

Study Limitations and Methodological Considerations

There are several potential methodological problems in determining the myocardial oxidative metabolism from carbon-11 acetate kinetics⁴⁴ Under conditions of increased physiologic stress, monoexponential curve fitting yields a significant underestimate of the true oxidative metabolism. However, as our study was performed at a low myocardial workload and under normal resting physiologic conditions, we adopted monoexponential fitting over the post-blood pool phase, which is clinically more useful and practical and is acceptably accurate in the resting state.⁴⁵

The initial uptake (Ao) was obtained by extrapolation of the fitted curve to avoid spillover in early phase. The Ao of carbon-11 acetate cannot be used as a direct index of regional myocardial blood flow because the input function varies from subject to subject. However, if the first-pass extraction fraction is uniform, inpatient comparison of regional

myocardial perfusion is valid. There has been no report of regional differences in extraction fraction in patients with HCM. Under resting conditions, the close correlation between net myocardial uptake of carbon-11 acetate and regional myocardial blood flow²⁷ suggests that the extraction fraction is not sufficiently variable to preclude its use for assessing myocardial flow. However, further studies are needed to establish the validation of carbon-11 acetate extraction for measurement of coronary blood flow under various conditions.

Basically we use echocardiographic measurements to correct the partial volume effect. In patients with apical HCM, apical thickness was measured from transaxial magnetic resonance images. Reorientation of transaxial images into short-axis images might allow more accurate spatial localization of anatomic segments of the left ventricle.⁴⁶ However, these correction methods have some limitations and might be inaccurate owing to the heterogeneous distribution of the myocardial hypertrophy in HCM. Furthermore, we have to consider the effects of cardiac wall motion. Sections of myocardium, especially in the free wall of patients with HCM, might move into and out of an ROI as the ventricle contracts and play a significant role in degrading quantitative data. This problem can be minimized using ECG-gated data acquisition.

Conclusions

Previous clinical observations suggested the presence of ischemia in the disproportionately thickened myocardium of patients with HCM. We found relative decreases in oxidative metabolism and glucose utilization without any corresponding perfusion defects in the hypertrophied septum and apex. This could indicate abnormal regional aerobic metabolism in the disproportionately thickened myocardium of patients with HCM independent of regional myocardial blood flow. This suggests that a primary unknown myocardial metabolic defect might be present in patients with HCM.

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