Heterogeneity of Myocardial Fluoro-18 2-Deoxyglucose Uptake in Patients With Apical Hypertrophic Cardiomyopathy

Nobuyuki Shiba, MD; Yutaka Kagaya, MD; Nobumasa Ishide, MD; Hiroki Otani, MD; Daiya Takeyama, MD; Yuriko Yamane, MD; Masanobu Chida, MD; Jun Ikeda, MD; Tatsuo Ido, Ph D*; Kunio Shirato, MD

We have shown that myocardial glucose metabolism is heterogeneous in patients with hypertrophic cardiomyopathy. It is not known, however, whether glucose metabolism is impaired in patients with apical hypertrophic cardiomyopathy, which is fairly common in Japan. We studied 7 patients with apical hypertrophic cardiomyopathy and 5 normal subjects using fluoro-18 2-deoxyglucose (FDG) and positron emission tomography (PET). We calculated regional FDG fractional uptake and the inter-regional coefficient of variation (CV) of FDG fractional uptake in the interventricular septal, anteroapical, and posterolateral regions. The regional FDG fractional uptake was similar in the 2 groups and among the 3 different segments within each group. However, the inter-regional CV of FDG fractional uptake was increased in the anteroapical wall segment of the patient group compared with the control group and also with the other 2 regions in the patient group. The results did not differ when we studied another 5 patients and 6 normal control subjects with a PET scanner with higher spatial resolution. These data suggest that myocardial glucose metabolism may be impaired in the anteroapical wall segment of patients with apical hypertrophic cardiomyopathy.


Key Words: Apical hypertrophic cardiomyopathy; Fluoro-18 2-deoxyglucose; Positron emission tomography; Myocardial glucose metabolism

Hypertrophic cardiomyopathy is characterized by a hypertrophic ventricle in the absence of other cardiac or systemic diseases that may cause cardiac hypertrophy! In a previous study2 we showed that myocardial glucose metabolism is heterogeneous in patients with this disease. Sakamoto et al3 and Yamaguchi et al4 described a subtype of hypertrophic cardiomyopathy, apical hypertrophic cardiomyopathy, that is fairly common in Japan and is characterized by ventricular hypertrophy confined to the apex and by an electrocardiographic pattern of ‘giant’ negative T waves. The myocardial metabolic characteristics of apical hypertrophic cardiomyopathy, however, have not been clarified. The purpose of this study was to investigate whether glucose metabolism is different in patients with apical hypertrophic cardiomyopathy and normal subjects using fluoro-18 2-deoxyglucose (FDG) and positron emission tomography (PET).

Methods

Seven patients with apical hypertrophic cardiomyopathy and 5 normal subjects were studied. The diagnosis of apical hypertrophic cardiomyopathy was based on myocardial hypertrophy confined to the apex demonstrated on both left ventriculography and 2-dimensional echocardiography. The main features of the patients are listed in Table 1. No patient suffered from diabetes mellitus, systemic hypertension, or hyperlipidemia. No patient was receiving treatment

(Received December 11, 1995; revised manuscript received May 30, 1996; accepted August 9, 1996)
First Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan, and *Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan
Mailing address: Kunio Shirato, MD, The First Department of Internal Medicine, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-77, Japan
Table 1 Clinical Characteristics of Patients With Apical Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>NYHA functional class</th>
<th>Blood pressure (mmHg)</th>
<th>Negative T in ECG (mV)</th>
<th>Echocardiographic findings</th>
<th>FS</th>
<th>Cardiac catheterization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IVS (mm)</td>
<td>LVPW (mm)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>51</td>
<td>Male</td>
<td>I</td>
<td>116/66</td>
<td>2.3</td>
<td>10</td>
<td>8</td>
<td>0.36</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>Female</td>
<td>I</td>
<td>110/70</td>
<td>2.5</td>
<td>8</td>
<td>10</td>
<td>0.41</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>Male</td>
<td>I</td>
<td>138/72</td>
<td>2.3</td>
<td>7</td>
<td>10</td>
<td>0.38</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Male</td>
<td>I</td>
<td>140/70</td>
<td>1.4</td>
<td>12</td>
<td>11</td>
<td>0.36</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>Male</td>
<td>II</td>
<td>115/75</td>
<td>1.2</td>
<td>9</td>
<td>12</td>
<td>0.41</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>Male</td>
<td>I</td>
<td>124/80</td>
<td>2.1</td>
<td>11</td>
<td>10</td>
<td>0.47</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>Male</td>
<td>I</td>
<td>134/86</td>
<td>2.1</td>
<td>9</td>
<td>11</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>51 (3)</td>
<td></td>
<td></td>
<td>126/74</td>
<td>2.0</td>
<td>(5)/(3)</td>
<td>(0.2)</td>
<td>(1) (0.02)</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; FS, fractional shortening; IVS, interventricular septum; LVEDP, left ventricular end-diastolic pressure; LVPW, left ventricular posterior wall; NYHA, New York Heart Association.

with beta blockers or calcium antagonists. The normal subjects comprised 5 healthy men with a normal electrocardiogram and echocardiogram. The purpose and nature of this study were approved by the Committee for Administration of Radioactive Substances of the Tohoku University School of Medicine. Written consent was obtained from all subjects before each study.

Echocardiography and Cardiac Catheterization

M-mode and 2-dimensional echocardiography were performed in all cases on the day of the tomographic study (SSH-65A and SSH-160A, Toshiba, Tokyo). Interventricular septal and posterior wall thickness were measured at the level of the mitral leaflet tips using the 2-dimensional left parastral image at end-diastole. Apical myocardial thickness was evaluated from the 2-dimensional apical 4-chamber view. Cardiac catheterization and selective coronary angiography were performed within 3 months of the PET study in 5 patients. In the case of patients 4 and 7, these studies were performed 4 and 8 years, respectively, before the PET study. In these 2 cases, the diagnosis of apical hypertrophic cardiomyopathy was confirmed by echocardiography on the day of the PET study, as with the other patients.

Histologic Study

Left ventricular endomyocardial biopsy was carried out in 5 patients during cardiac catheterization. The specimens were fixed in 10% formalin and dehydrated. Sections (6 μm) were stained with hematoxylin-eosin or with Masson trichrome. The histologic analyses were performed by a single observer without knowledge of the other data. The degrees of myocyte hypertrophy, interstitial fibrosis, and degenerative change in myocytes, such as vacuolization or deposition of lipofuscin, were semiquantitatively scored as follows: 0, normal; 1, mild; 2, moderate; 3, severe.

Radiopharmaceutical and Scanning Procedure

FDG is a glucose analog that traces the transmembraneous transport and hexokinase-mediated phosphorylation of glucose. The end product, FDG-6-phosphate, is trapped within the cell and enables visualization of the myocardial regional glucose flux. The imaging studies were performed using a single-slice PET scanner (ECAT II, CTI, Knoxville, Tennessee) 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. Acquired data were reconstructed in a matrix size of 100×100 pixels and transformed into MS-DOS file format for analysis by a personal computer. Each subject, after fasting for at least 6 h, was administered 50 g of glucose orally 1 h before 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, 148–296 MBq (4–8 mCi) of FDG dissolved in 6 ml of 0.9% NaCl solution was administered intravenously over 1 min. We performed serial arterial sampling until the end of scanning (every 20 sec up to 180 sec, and then 4, 5, 7, 10, 15, 20, 30, 45 and 65 min after the FDG injection). Four cross-sectional images of the left ventricle were obtained at 10-mm intervals by scanning over a period of 300 sec per plane 45–60 min after the FDG injection. We measured arterial plasma concentrations of glucose, insulin, and free fatty acids 3 times.
Table 2  Plasma Substrate Concentrations, PET Data, and Histological Findings

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Glucose (mmol/L)</th>
<th>Insulin (µIU/ml)</th>
<th>FFA (mmol/L)</th>
<th>inter-regional coefficient of variation of FDG fractional uptake (%)</th>
<th>Histological finding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IVS</td>
<td>Anteroapical</td>
</tr>
<tr>
<td>1</td>
<td>7.2</td>
<td>31</td>
<td>0.48</td>
<td>4.5</td>
<td>9.7</td>
</tr>
<tr>
<td>2</td>
<td>5.7</td>
<td>12</td>
<td>0.22</td>
<td>3.1</td>
<td>5.3</td>
</tr>
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<td>3</td>
<td>6.5</td>
<td>20</td>
<td>0.16</td>
<td>3.5</td>
<td>7.1</td>
</tr>
<tr>
<td>4</td>
<td>5.8</td>
<td>13</td>
<td>0.27</td>
<td>8.6</td>
<td>18.6</td>
</tr>
<tr>
<td>5</td>
<td>7.1</td>
<td>50</td>
<td>0.24</td>
<td>2.9</td>
<td>10.0</td>
</tr>
<tr>
<td>6</td>
<td>6.1</td>
<td>3</td>
<td>0.30</td>
<td>2.4</td>
<td>14.6</td>
</tr>
<tr>
<td>7</td>
<td>6.4</td>
<td>34</td>
<td>0.30</td>
<td>3.3</td>
<td>6.6</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>6.4</td>
<td>23</td>
<td>0.28*</td>
<td>4.0</td>
<td>10.3**</td>
</tr>
<tr>
<td></td>
<td>(0.2)</td>
<td>(6)</td>
<td>(0.04)</td>
<td>(0.8)</td>
<td>(1.8)</td>
</tr>
<tr>
<td>n1</td>
<td>6.2</td>
<td>34</td>
<td>0.67</td>
<td>2.6</td>
<td>3.5</td>
</tr>
<tr>
<td>n2</td>
<td>7.4</td>
<td>45</td>
<td>0.18</td>
<td>0.8</td>
<td>3.1</td>
</tr>
<tr>
<td>n3</td>
<td>6.3</td>
<td>13</td>
<td>0.32</td>
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<td>1.6</td>
</tr>
<tr>
<td>n4</td>
<td>5.7</td>
<td>12</td>
<td>0.67</td>
<td>6.6</td>
<td>5.1</td>
</tr>
<tr>
<td>n5</td>
<td>5.6</td>
<td>3</td>
<td>0.66</td>
<td>3.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>6.2</td>
<td>21</td>
<td>0.50</td>
<td>4.5</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>(0.3)</td>
<td>(8)</td>
<td>(0.10)</td>
<td>(1.5)</td>
<td>(0.6)</td>
</tr>
</tbody>
</table>

FDG, fluoro-18 2-deoxyglucose; FFA, free fatty acids; IVS, interventricular septum; NA, not applicable; PET, positron emission tomography; n1-n5, normal subjects. *p<0.05 vs normal subjects. **p<0.05 vs the other 2 regions.

during the tomographic study (0, 15, and 30 min after FDG injection) and these data were averaged.

It is possible that the measure of heterogeneity of FDG uptake depends on the spatial resolution of the PET scanner. We therefore studied additional 5 patients with apical hypertrophic cardiomyopathy and 6 normal subjects using a PET scanner, PT 931/04 (CTI), to determine if the findings obtained with a PET scanner with a relatively large full-width at half-maximum can also be obtained using one with a higher spatial resolution. The full-width at half-maximum of PT 931/04 is 7 mm, which is less than half of that of the ECAT II scanner. The study protocol was exactly the same as that using ECAT II.

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 define regional segments of the left ventricle. We carefully selected only 1 cross-sectional image at the mid-left ventricular level. We divided the left ventricular wall into 3 segments, namely interventricular septum, anteroapical wall, and posterolateral wall. Between 4 and 8 contiguous rectangular regions of interest were selected in each wall segment. Each region of interest was 0.73 cm² (9 pixels) in area. We calculated the FDG fractional uptake in each region of interest as described by Camici et al⁷ as follows:

\[
\text{FDG fractional uptake (\%) = } \left( \frac{C_{M(FDG)}}{C_{P(FDG)}} \right) \times 100
\]

where \(C_{M(FDG)}\) is the FDG radioactivity per pixel in the myocardium and \(C_{P(FDG)}\) is the integral of the plasma FDG radioactivity per gram from the time of the injection until the end of scanning. Regional FDG fractional uptake was defined as the mean FDG fractional uptake in all regions of interest of each wall segment. Furthermore, in each wall segment of each patient, we determined the inter-regional coefficient of variation (CV) (SD/mean × 100) of FDG fractional uptake in the regions of interest as a measure of the regional heterogeneity of myocardial glucose uptake. The plasma glucose concentration was measured by a modification of the glucose oxidase method⁸; the plasma insulin concentration was determined by radioimmunoassay⁹; and the plasma concentration of free fatty acids was measured by an enzymatic method¹⁰.

Data are presented as means±SEM. We used 2-way analysis of variance with repeated measures on 1 factor¹¹ to compare regional profiles of both regional FDG fractional uptake and the inter-regional CV of
FDG fractional uptake between the 2 groups. Differences in each wall segment within each group and between the 2 groups were analysed by Fisher's exact test. Other mean values between the 2 groups were compared by the unpaired Student's t test. A p value <0.05 was considered significant.

**Results**

The clinical characteristics and echocardiographic and cardiac catheterization data of the patient group studied using the ECAT II scanner are listed in Table 1. Blood pressure was not elevated in any patient. All patients had giant negative T waves in the standard 12-lead electrocardiogram. There was a significant age difference between patients and normal subjects (51±3 vs 31±3 years, p<0.01). The wall thickness of the interventricular septum and left ventricular posterior wall and left ventricular fractional shortening as determined by echocardiography were normal in all patients. Two-dimensional echocardiography demonstrated no hypertrophic myocardium, except at the apical region of the left ventricle. The wall thickness of the apical region was 15–21 mm. Cardiac catheterization and selective coronary angiography were performed in all patients. There was no pressure gradient in the left ventricular outflow tract, and no diameter stenosis greater than 50%. Left ventriculography showed the typical 'spade-like' configuration at end-diastole in all patients. The plasma concentra-
Fig 3. Transaxial PET image of fluoro-18 2-deoxyglucose uptake in the left ventricular wall of patient 5. Top left, interventricular septum; top right, anteroapical segment; bottom right, postero-lateral segment.

Fig 4. (A) Regional FDG fractional uptake in the 3 wall segments in the patient and control groups. (B) Inter-regional CV of FDG fractional uptake in the 3 wall segments in the patient and control groups. FDG, fluoro-18 2-deoxyglucose; NS, not significant. *p<0.05 vs normal subjects, A<0.05 vs the other 2 wall segments in the patient group (analysis of variance followed by Fisher's exact test). Values are means (SEM).

sections of glucose and insulin measured during the PET study was the same in patients and normal subjects. The plasma free fatty acid content, however, was significantly lower in the patients than in the normal subjects (Table 2).

Fig 1 shows a representative 12-lead electrocardiogram from a patient with apical hypertrophic cardiomyopathy. Left ventriculograms from the same patient are shown in Fig 2. Fig 3 shows a FDG PET image from the same patient. Fig 4A shows regional FDG fractional uptake in the 3 wall segments in the 2 groups. There was no significant difference in the profile of regional FDG fractional uptake between the patient group and the control group. Fig 4B and Table 2 show the inter-regional CVs of FDG fractional uptake in the 3 wall segments in the patient and control groups. The regional profile of inter-regional CV of FDG fractional uptake was different in the 2 groups (p<0.01). The inter-regional CV of FDG fractional uptake in the anteroapical wall was significantly higher in the patient group than in the control group. Furthermore, in the patient group, the inter-regional CV in the anteroapical wall increased significantly compared with the interventricular septum and pos-
terolateral wall. In the interventricular septum and posterolateral wall, both FDG fractional uptake and the inter-regional CV of FDG fractional uptake did not differ between the patient group and the normal subjects.

The histologic findings of biopsy samples taken from 5 patients are summarized in Table 2. No specimens showed ‘bizarre myocardial hypertrophy with disorganization’, the typical histologic findings of hypertrophic cardiomyopathy or small vessel lesions. Patient 2, whose inter-regional CV of FDG fractional uptake at anteroapical regions was the lowest among the 7 patients, showed almost normal histology. Patient 6, whose inter-regional CV at the same region was the highest among the 5 patients subjected to left ventricular endomyocardial biopsy, demonstrated the greatest histologic changes.

In the additional study with another 5 patients and 6 normal subjects using a PET scanner (PT931/04) with a higher spatial resolution, the inter-regional CV of FDG fractional uptake in the anteroapical wall of the patient group was significantly higher than that of the control group (13.1±1.5 vs 4.8±0.8, p<0.01). In both the interventricular septum and posterolateral wall, the inter-regional CV of FDG fractional uptake did not differ between the patient group and the normal control subjects (4.8±1.0 vs 4.0±1.5 and 7.4±1.8 vs 3.8±0.5, respectively). Furthermore, in the patient group, the inter-regional CV in the anteroapical wall increased significantly compared with those in the interventricular septum and posterolateral wall (p<0.05 for each comparison). Those data were consistent with those obtained using ECAT II scanner.

**Discussions**

We have demonstrated for the first time that FDG uptake in the anteroapical wall segment of the left ventricle in patients with apical hypertrophic cardiomyopathy is more heterogeneous than normal subjects. Furthermore, in these patients, the heterogeneity of FDG uptake is significantly higher in the anteroapical region than in the interventricular septum and posteriorlateral wall segment.

Apical hypertrophic cardiomyopathy was first reported in Japan and is characterized by left ventricular hypertrophy confined to the apex, electrocardiographic demonstration of giant negative T waves, and spade-shaped left ventriculograms. This disease category appears to be different from the hypertrophic cardiomyopathy with interventricular septal hypertrophy localized to the apex that was reported by Maron et al\(^{12}\) because both electrocardiographic and angiographic features differ from those of the apical hypertrophic cardiomyopathy commonly found in Japan\(^{3,4}\). As reported by Louie and Maron in 1987\(^{13}\), apical hypertrophic cardiomyopathy is likely to be very rare in western countries.

The mechanism of the increased heterogeneity of FDG uptake in the left ventricular anteroapical wall is unclear. Our patient no 2, whose inter-regional CV of FDG fractional uptake at anteroapical regions was lowest among the 7 patients, showed almost normal histologic findings. Patient 6, whose inter-regional CV in the same region was the highest among the 5 patients subjected to left ventricular endomyocardial biopsy, demonstrated the greatest histologic changes. The correlation between the total score of histologic findings and inter-regional CV of FDG fractional uptake at the anteroapical region was not significant, probably because of the small number of subjects studied. It is possible, however, that the heterogeneity of myocardial FDG uptake in the anteroapical segment demonstrated in our present study is due to the histologic changes, such as myocyte hypertrophy, fibrosis, and degeneration.

Several studies have shown that myocardial ischemia may play an important role in the pathophysiology of hypertrophic cardiomyopathy\(^{14-16}\). Camici et al\(^{17}\) demonstrated that the coronary vasodilatory reserve is diminished in patients with hypertrophic cardiomyopathy. Nienaber et al\(^{18}\) reported blood flow-glucose metabolism mismatches indicative of myocardial ischemia in patients with symptomatic hypertrophic cardiomyopathy. Although we did not measure the regional blood flow in our patient group, and almost all patients in the present study were asymptomatic, it is possible that the heterogeneity of regional FDG uptake was caused by regional ischemia.

In our previous study\(^2\), we found that the FDG fractional uptake in patients with hypertrophic cardiomyopathy was 5.4±0.4, and that the inter-regional CV of FDG fractional uptake was 9.4±0.9. Those values are very similar to those obtained in the anteroapical regions of patients with apical hypertrophic cardiomyopathy in the present study. We could not, therefore, differentiate apical hypertrophic cardiomyopathy from typical hypertrophic cardiomyopathy in terms of glucose metabolism using FDG and PET.

In our 5 patients subjected to left ventricular endomyocardial biopsy, we could not find any typical histologic findings of hypertrophic cardiomyopathy even though they showed the typical ‘spade-like’ left ventriculogram and giant negative T wave on the electrocardiogram. Sumino et al\(^{19}\) reported apical
FDG Uptake in Apical Hypertrophic Cardiomyopathy in a patient who died of non-cardiac disease. In that case, they found histologic changes that were very similar to those found in typical hypertrophic cardiomyopathy, including disarray of myocardial fibers and myocardial fibrosis near the apical region. On the other hand, Nakanishi et al. reported that only 3 out of 6 patients with apical hypertrophic cardiomyopathy showed typical histologic findings of cardiomyopathy. In 2 of those 3 patients, myocardial biopsy specimens were obtained during cardiac surgery instead of by endomyocardial biopsy. In the present study, we obtained only 2 or 3 small specimens from each patient by endomyocardial biopsy. Further study with a sufficient number of patients and specimens may be needed to determine whether apical hypertrophic cardiomyopathy is different from typical hypertrophic cardiomyopathy in terms of histologic findings.

It is possible that the measure of heterogeneity of FDG uptake depends on the spatial resolution of the PET scanner. We therefore studied a small number of additional patients and normal control subjects using a scanner with higher spatial resolution, and found that the results were very similar to those obtained using a scanner with a lower spatial resolution. These findings suggest that the difference of heterogeneity of FDG uptake between the patients with apical hypertrophic cardiomyopathy and normal control subjects does not depend on the spatial resolution of the PET scanner. As the spatial resolution of PET is limited, it is impossible to measure the radioactivity only in the apex of the left ventricle. It is not clear, therefore, whether the higher inter-regional CV of FDG fractional uptake in the anteroapical segment is due to the increased heterogeneity of glucose metabolism in the left ventricular anterior wall or the apex.

There was a significant age difference between the patient and control groups. Although it is possible that the greater heterogeneity of FDG uptake in the anteroapical wall segment can be explained by the higher age of the patient group, it is not likely because there was no correlation between inter-regional CV and age in the normal control subjects in the present study or in our preliminary study (data not shown). It is not certain why the plasma concentration of free fatty acids was lower in the patient group than in the normal subjects. It is not likely, however, that increased heterogeneity of FDG fractional uptake in the anteroapical segment is due to the lower plasma concentration of free fatty acids because the other 2 wall segments of the patient group showed heterogeneity of FDG uptake similar to those of normal control subjects.

Acknowledgments

We are grateful to Hikonojo Orihara, Ph D, Keizo Ishii, Ph D, Ren Iwata, Ph D, Toshihiro Takahashi, Ph D, and other members of the Cyclotron and Radioisotope Center, Tohoku University, for preparation of FDG. We thank Mr. Seiichi Watanuki and Shinya Seo for their invaluable assistance in the PET study. We also thank Mr. Brent Bell for reading the manuscript.

References


