Abnormal Myocardial Free Fatty Acid Utilization Deteriorates With Morphological Changes in the Hypertensive Heart

Hiroyuki Nakayama, MD; Takakazu Morozumi, MD; Shinsuke Nanto, MD; Tsuyoshi Shimonagata, MD*; Tomoki Ohara, MD; Yuzuru Takano, MD**; Junichi Kotani, MD; Tetsuya Watanabe, MD; Masashi Fujita, MD; Mayu Nishio, MD; Hideo Kusuoka, MD†; Masatsugu Hori, MD††; Seiki Nagata, MD

The left ventricle's morphological adaptation to high blood pressure is classified into 4 patterns based on mass and wall thickness. The geometric changes caused by maladaptation to pressure overload possibly relate to progression of contractile dysfunction with abnormal energy metabolism. The present study assessed whether the geometric adaptation of the left ventricle (LV) to high blood pressure relates to changes in myocardial energy metabolism, especially free fatty acid (FFA) utilization. Thirty-five patients with essential hypertension underwent echocardiography and dual isotopes myocardial scintigraphy using iodine-123 labeled 15-p-iodophenyl-3-(R,S)-methylpentadecanoic acid (BMIPP, an analogue of a FFA) and thallium-201 (TI-201). Systolic (endocardial fractional shortening; %FS) and diastolic indices (the ratio of early to atrial filling waves; E/A) of LV function were also assessed. Quantitative myocardial BMIPP uptake was evaluated by the BMIPP/TI-201 myocardial uptake ratio (B/T). The subjects were divided into 4 groups based on LV mass and wall thickness: (1) concentric hypertrophy (CH), (2) eccentric hypertrophy (EH), (3) concentric remodeling (CR), and (4) normal geometry (N). The %FS was lower in the EH group than in the other groups. The mitral E/A ratio in the CH group was lowest. B/T was significantly decreased in the EH group compared with the N group (p<0.05). B/T correlated with the mitral E/A ratio significantly (p<0.05, r=0.42), whereas there was no relationship between %FS and B/T. These results indicate that the geometric changes occurring in hypertensive hearts strongly correlate with alternations in cardiac function and with abnormal myocardial FFA metabolism, and that the latter is associated with diastolic abnormality, but not with systolic function. *(Jpn Circ J 2001; 65: 783–787)*

**Key Words:** Energy metabolism; Free fatty acids; Hypertensive heart; Hypertrophy

In essential hypertension, changes in the morphology of the left ventricle (LV) are commonly observed, and are considered to be the result of adaptation to pressure overload. The changes have been classified into 4 geometric patterns based on the LV mass and wall thickness.1 These geometric changes are consistent with progression of heart failure in an experimental model;2 and furthermore, are considered to reflect the course of hypertensive heart failure.3,4 On the other hand, it has been speculated that a disorder of myocardial energetic metabolism relates to progression of heart failure.123I-15-p-iodophenyl-3-(R,S)-methylpentadecanoic acid (I-123 BMIPP) is a radioisotope used for assessment of myocardial free fatty acid (FFA) metabolism and abnormal myocardial uptake of BMIPP has been reported in patients with heart failure.13 However, it has not been clarified whether the pathophysiological adaptation of changing the LV morphology in hypertensive hearts is related to changes in myocardial FFA metabolism.

**Methods**

Thirty-five patients (21 men, 14 women; mean age: 61±11 years) who had a history of essential hypertension (blood pressure ≥160 mmHg at systole or 90 mmHg at diastole according to the WHO criteria) were enrolled. The patients were free of any symptoms of ischemic heart disease, valvular heart disease, or concomitant important diseases such as diabetes mellitus. Two patients with symptomatic congestive heart failure (New York Heart Association class II–III) who took some diuretics were included. The evaluations, including a detailed medical history, 12-lead ECG, urinalysis, and serum levels of urea nitrogen, creatinine, glucose, cholesterol, sodium, potassium and calcium, were performed in all subjects. An echocardiogram of adequate quality to assess LV morphologic characteristics was also obtained from all subjects. Patients who showed LV asymmetrical hypertrophy on the echocardiogram were excluded, as were patients with diabetes mellitus or renal failure. All patients in the study gave written informed consent.

Echocardiography was performed using an ultrasonic sector scanner with 2.5- and 3.75-MHz transducers (SONOLAYER SSH-160A Toshiba Co, Japan). Standard...
parasternal long- and short-axis views and apical 2- and 4-chamber views were obtained in all patients. M-mode echocardiograms were derived from the 2-dimensional images. All measurements were made at the onset of the QRS complex using the American Society of Echocardiography leading. Left ventricular mass index (LVMI) was calculated by the formula

\[
LVMI = \frac{(0.80 \times (LVDd + PWth + IVSth)^3 - LVDd^3)}{BSA} + 0.6
\]

where LVDd is LV end-diastolic internal dimension, PWth is posterior wall thickness, IVSth is intraventricular septum thickness, and BSA is the body surface area. Relative wall thickness (RWT) was calculated as the ratio of 2×(thickness of LV posterior wall/LV end-diastolic diameter). LV hypertrophy was diagnosed when LVMI was greater than 125 g/m² in both men and women. A normal limit for RWT was set at 0.45. The subjects were divided into 4 mutually exclusive groups on the basis of the LV geometry: (1) concentric hypertrophy group (CH group: LV hypertrophy and normal RWT), (2) eccentric hypertrophy (EH group: LV hypertrophy and increased RWT), (3) concentric remodeling group (CR group: normal LV mass and increased RWT), and (4) normal geometry (normal LV group: normal LV mass and normal RWT). LV endocardial fractional shortening (%FS) calculated by (end-diastolic diameter – end-systolic diameter)/end-diastolic diameter was used as an index of systolic function. The diastolic function of the LV was determined by Doppler mitral flow patterns, which were recorded from apical 2- or 4-chamber views by the 2.5-MHz transducer. The pulsed wave beam was positioned in a line parallel to the LV long axis with the sample volume at the level of the mitral annulus. The highest velocity pattern of LV diastolic filling during at least 4 cardiac cycles was recorded. Peak flow velocities of early filling wave and atrial filling wave were obtained, and the ratio of early to atrial filling waves (E/A) was calculated. Two investigators unaware of the classification of patients obtained the Doppler tracings.

To assess myocardial FFA metabolism, dual isotopes myocardial scintigraphy with I-123 BMIPP and thallium-201 (TI-201) was performed. After overnight fasting, 111MBq of I-123 BMIPP (Nihon Mediphysics Co, Nishinomiya, Japan) and 111MBq of TI-201 were injected intravenously. An anterior planar image was obtained at 20 min after the injection (preset time 300 s) using a gamma camera (Starcam-3000, GE Yokogawa Medical System, Tokyo, Japan) equipped with a general purpose collimator in the 159-keV and the 72-keV photo peaks with 10% window. Then, to quantify the myocardial uptake of I-123 BMIPP, a region of interest (ROI) of the whole heart was drawn on an anterior planar image, and the ratio of I-123 BMIPP accumulation to that of TI-201 in the ROI (B/T) was calculated. Therefore, the B/T is an index for cardiac BMIPP uptake corrected by myocardial perfusion. Attenuation and scatter correction were not performed.

**Results**

The characteristics of the subjects in each group obtained the Doppler tracings. There was no significant difference between the groups. CR, concentric remodeling group; CH, concentric hypertrophy group; EH, eccentric hypertrophy group.

The data are presented as mean ± SD. The statistical significance of differences between mean values was analyzed with the unpaired Student's t-test or one-way ANOVA. Correlation between 2 variables was examined using linear regression analysis. Probability (p) values less than 0.05 were considered to be statistically significant.

**Fig 1.** Mean percent fractional shortening (%FS) in each group. There was no significant difference between the groups. CR, concentric remodeling group; CH, concentric hypertrophy group; EH, eccentric hypertrophy group.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Normal LV (n=16)</th>
<th>Concentric remodeling (n=7)</th>
<th>Concentric hypertrophy (n=7)</th>
<th>Eccentric hypertrophy (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62±11</td>
<td>53±11</td>
<td>65±11</td>
<td>62±8</td>
</tr>
<tr>
<td>M/F</td>
<td>9/7</td>
<td>3/4</td>
<td>6/1</td>
<td>3/2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>148±28</td>
<td>146±28</td>
<td>140±21</td>
<td>146±12</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>82±13</td>
<td>88±13</td>
<td>84±10</td>
<td>85±9</td>
</tr>
<tr>
<td>LVMI (g/mm²)</td>
<td>96±19</td>
<td>97±18</td>
<td>165±27**</td>
<td>162±40**</td>
</tr>
<tr>
<td>RWT</td>
<td>0.38±0.05</td>
<td>0.55±0.06*</td>
<td>0.62±0.15**</td>
<td>0.39±0.03</td>
</tr>
<tr>
<td>Gender</td>
<td>M (57%)</td>
<td>2 (29%)</td>
<td>4 (57%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Medication</td>
<td>ACEI (38%)</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>5 (31%)</td>
<td>0</td>
<td>0</td>
<td>3 (60%)</td>
</tr>
</tbody>
</table>

LVMI, LV mass index; RWT, relative wall thickness; ACEI, angiotensin-converting enzyme inhibitor. **p<0.0001, *p<0.001 vs normal LV group.
was considered as pseudonormalization.

Myocardial uptake of I-123 BMIPP (B/T) did not differ between the normal LV group and the CR group. However, H/H in the CH and EH groups significantly decreased compared with that in the normal LV group (p<0.05 and p<0.01, Fig 3). Although there was no significant relationship between %FS and H/H (r=–0.012, p=0.945), B/T correlated significantly with mitral E/A ratio (r=0.42, p<0.05, Fig 4) and LVMI (r=–0.44, p<0.01, Fig 5). Myocardial BMIPP uptake increased with E/A, and decreased with LVMI.

Discussion

Relation of LV Geometric Patterns to Cardiac Performance

In our study, systolic and diastolic performance differed between the normal LV and concentric remodeling groups. In the CH group, diastolic performance decreased significantly, despite no difference in systolic function. In the EH group, systolic dysfunction was observed and the mitral E/A ratio showed pseudonormalization, indicating that cardiac performance was lower than the other 3 groups. Thus, cardiac performance varied according to the geometric pattern and the change in morphology resembled the course observed in the experimental heart failure model, so we considered it was associated with progression of the hypertensive heart failure.

Relation of LV Geometric Patterns to Free Fatty Acid Metabolism

I-123 BMIPP was developed to assess myocardial FFA metabolism because previous studies had revealed that myocardial BMIPP uptake is closely related to the triglyceride content and ATP level of myocardium and reflects myocardial energy production. In the present study, the CR group showed no significant difference in BMIPP uptake (B/T) compared with the normal LV group. As B/T reflects the FFA metabolism per unit myocardial perfusion, the results suggest that the myocardium that has been concentrically remodelled has appropriately adapted to pressure overload with respect to energy metabolism. Izzi et al assessed myocardial oxygen consumption and LV pressure–volume area in normal and hypertrophic canine hearts, and reported that the working efficiency of hypertrophic hearts was equivalent to normal hearts. Our results are compatible with their conclusion and we suggested that concentric remodeling does not provoke abnormal myocardial energetic metabolism. With CH, which was accompanied by an increase of LV mass and RWT, B/T decreased significantly compared with the normal LV and CR groups. Furthermore, B/T showed a negative correlation with LVMI in all groups. These results suggest that LV hypertrophy in any pattern is associated with attenuation of myocardial FFA metabolism. Goto et al assessed the relationship between myocardial oxygen consumption and the pressure–volume area in dogs with pacing-induced heart failure, and concluded that the main pathophysiological issue of the failing heart is suppression of excitation–contraction coupling for energy expenditure or disturbance. It is reported that the content of ATP and creatine phosphate had declined in a sample of endocardial biopsy obtained from patients with chronic congestive heart failure and Katz pointed out that a failing heart is in an energy starvation state.

Relation of Cardiac Performance to Free Fatty Acid Metabolism

In the present study, there was no significant correlation between systolic function and B/T. In idiopathic dilated...
cardiomyopathy, myocardial I-123 BMIPP uptake is significantly related to LV systolic function. In an experimental study using isolated LV papillary muscle, a relationship between myocardial contractility, estimated by isometric contraction, and myocardial energy, indicated by myosin ATPase activity, has been reported. A relationship between regional wall motion abnormality and a focal defect on a BMIPP image had been reported, although the close relationship between the I-123 BMIPP accumulation of the whole heart and cardiac performance has not been reported in human hypertrophic hearts. We used endocardial fractional shortening as a simple index of LV systolic function and there might be a significant relation between LV systolic function and B/T if we used a more sensitive marker.

In contrast to systolic function, a significant correlation was observed between FFA metabolism and diastolic performance. The diastolic performance of the heart is based on 2 major factors: active relaxation and passive LV stiffness. The main biological determinant of active relaxation is the intracellular concentration of ATP, which is necessary for the re-uptake of intracellular Ca by Ca2+-ATPase in the sarcoplasmic reticulum. Thus, it is reasonable that LV diastolic dysfunction correlated with myocardial I-123 BMIPP accumulation, because BMIPP uptake closely represents the intracellular ATP concentration of the myocardium. Left ventricular stiffness and compliance are other major factors of the diastolic properties and myocardial fibrosis may be associated with those. There is not a report about the relationship between LV stiffness and myocardial energy metabolism. The myocardium that is undergoing fibrosis or apoptosis may have decreased cell function and energy metabolism similar to that of idiopathic dilated cardiomyopathy, which shows remarkable myocardial fibrosis with a severe abnormality on I-123 BMIPP imaging.

Quantitative Estimation of Myocardial I-123 BMIPP Accumulation

The mechanism of mechanical stress-induced cardiac hypertrophy has gradually become clear and it is evident that the energy metabolism of the myocardium changes dynamically in that process. The changes in myocardial energy metabolism have a close relation with the pathophysiology of hypertensive hearts. I-123 BMIPP is a unique tracer that can express the changes in energy metabolism in the hypertensive heart, and so the results of the present study, which assessed the relationships between myocardial accumulation of I-123 BMIPP, LV remodeling and function, have important implications.

We used B/T as an indicator of cardiac uptake of I-123 BMIPP in dual isotope imaging after the simultaneous injection of the same quantity of I-123 BMIPP and thallium-201. This index is very simple and has excellent reproducibility and objectivity, which makes it suitable for a clinical examination. However, any indicator obtained from dual isotope image includes some cross-talk interference between the 2 radiopharmaceuticals, the greater part of which consists of Compton scatter. Scatter correction was not performed in the present study because the relevant software had not been installed and so although the influence of cross-talk interference was estimated as reduced when using B/T, this problem is a limitation to our study. It is thought that some drugs influence myocardial metabolism, particularly angiotensin-converting enzyme inhibitors (ACEI), which have been reported to improve fatty acid utilization in the hypertensive heart. Although there was no difference between the 4 groups in the use rate of ACEI, we cannot deny their influence on cardiac metabolism because of a small number of subjects in the study.

Conclusion

Our study shows that the geometric patterns of remodeling of the LV in hypertensive hearts are associated with alternations of cardiac function and abnormal myocardial FFA metabolism, as indicated by I-123 BMIPP scintigraphy. Furthermore, it revealed that the abnormal FFA metabolism is associated with diastolic performance, but not with systolic function. Although systolic and diastolic blood pressure were well controlled by treatment, B/T can detect progression of diastolic dysfunction.

References

18. Jung WI, Dietz GS: 131I nuclear magnetic resonance spectroscopy: A
noninvasive tool to monitor metabolic abnormalities in left ventricular hypertrophy in humans. Am J Cardiol 1999; 83: 19H–24H