Can Serum Carnitine Levels Distinguish Hypertrophic Cardiomyopathy From Hypertensive Hearts?

Tomoki Nakamura, Hiroki Sugihara, Noriyuki Kinoshita, Satoshi Yoneyama, Akihiro Azuma, Masao Nakagawa

Abstract—Although echocardiography is a useful diagnostic tool in hypertrophic cardiomyopathy (HCM), it is sometimes difficult to differentiate it from hypertensive heart disease (HHD): some patients with HCM show symmetrical hypertrophy, whereas patients with HHD sometimes show asymmetrical septal hypertrophy. We used a radioiodinated long-chain fatty acid tracer to visualize the altered myocardial fatty acid metabolism of HCM and HHD. Carnitine is the essential substance for the β-oxidation of long-chain fatty acids. We recently reported that serum free carnitine levels in HCM were elevated and that they were significantly correlated with the severity of myocardial fatty acid metabolic disorder. Therefore, we investigated serum carnitine levels in patients with HCM and HHD, which can contribute to the differentiation of each other. We studied 56 patients with HCM and 20 patients with essential hypertension. Serum free carnitine levels were significantly higher in patients with HCM than those with HHD (HCM 52.5±9.5 nmol/mL, HHD 46.6±6.4 nmol/mL, $P<0.01$), but they showed no statistical difference between patients with HHD and normal subjects. Serum acylcarnitine levels were significantly lower in patients with HCM than those with HHD (HCM 10.1±4.0 nmol/mL, HHD 14.5±4.9 nmol/mL, $P<0.0005$), although they did not differ between patients with HHD and normal subjects. Scintigraphic analyses with a long-chain fatty acid analog revealed that myocardial tracer uptake was much reduced in patients with HCM compared with that in patients with HHD (quantitative analysis: HCM 2.11±0.12, HHD 2.22±0.17, $P<0.05$; semiquantitative analysis: HCM 13.6±6.3, HHD 2.0±1.5, $P<0.0001$). In conclusion, the differences in serum carnitine levels between HCM and HHD reflect altered myocardial fatty acid metabolic impairment, and the levels can help to distinguish these 2 diseases. **(*Hypertension*. 2000;36:215-219.)**

Key Words: fatty acids ■ hypertrophy, cardiac ■ cardiomyopathy ■ metabolism

Echocardiography provides useful morphological information for the diagnosis of hypertrophic cardiomyopathy (HCM), for which asymmetrical septal hypertrophy (ASH) is one of the characteristic findings.[1] However, hypertensive heart disease (HHD) is characterized by symmetrical (concentric) hypertrophy of the left ventricle. This diagnostic modality sometimes makes it difficult to distinguish HCM from HHD: 31% of patients with HCM are reported to show symmetrical hypertrophy,[2] whereas 4% to 47% of patients with HHD demonstrate ASH.[3–5] In particular, 70% of patients with HHD who have a diastolic blood pressure of ≥120 mm Hg had ASH.[6]

[^{123}I]-15-(*p*-Iodophenyl)-3-*R*,*S*-methylpentadecanoic acid (BMIPP) is a radioiodinated long-chain fatty acid analog that is used for the evaluation of cardiac fatty acid metabolism. Myocardial BMIPP scintigraphy demonstrated the differences in abnormal myocardial fatty acid metabolism between HCM and HHD, which permits differential diagnosis: impaired myocardial fatty acid metabolism is observed in 92% of patients with HCM, whereas only 8% of patients with HHD showed such an abnormality.[7] Carnitine is an essential substance for the β-oxidation of long-chain fatty acid metabolism. Our recent investigation disclosed that serum free carnitine levels are elevated and acylcarnitine levels are decreased in patients with HCM. Moreover, serum free carnitine levels significantly correlated with the severity of decreased BMIPP uptake, indicating that it is a good indicator of impaired myocardial fatty acid metabolism.[8] Therefore, the purpose of the present study was to investigate serum carnitine levels in patients with HCM and HHD, which can reflect differences in impaired myocardial fatty acid metabolism.

Methods

Study Patients

We examined 56 normotensive patients with HCM (42 men, 14 women; mean age 56±12 years), and 20 patients with essential hypertension (10 men, 10 women; mean age 60±11 years). HCM

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subgroups consisted of 36 patients with hypertrophic nonobstructive cardiomyopathy, 7 patients with hypertrophic obstructive cardiomyopathy, and 13 patients with apical hypertrophic cardiomyopathy (APH). The classification of hypertension was defined according to the 1993 World Health Organization/International Society of Hypertension criteria.[9] All hypertensive patients were classified as having moderate and severe hypertension before the initiation of antihypertensive treatment. Their extent of organ damage was stage II, which is showing only left ventricular hypertrophy. The diagnoses of HCM and HHD were based on echocardiographic, electrocardiographic, and myocardial scintigraphic studies. Patients who had coronary artery disease, congestive heart failure, diabetes mellitus, hepatorenal dysfunction, and elevated levels of nonesterified fatty acids were excluded from the study, because such conditions affect myocardial metabolism and the kinetics of BMIPP; in addition, carnitine is mainly synthesized in the liver and excreted in urine.[10–15]

The control group consisted of 80 normal healthy volunteers (40 men, 40 women; mean age 54±13 years) who were receiving no medications. All patients and volunteers signed informed consent forms before the study, and the study protocol was approved by the research council of our institution.

Echocardiographic Study

Echocardiography was performed in all patients with HCM or HHD and in 20 of 80 normal control subjects (11 men, 9 women). This study consisted of M-mode, 2-dimensional, and Doppler blood flow measurements made with a Hewlett-Packard Sonos 2500 ultrasound system. We evaluated the distribution of hypertrophy, wall thickness, cavity size, and wall motion from multiple windows. The morphology of the left ventricular apex was assessed from the apical view for the diagnosis of APH. We also determined the presence or absence of complete end-systolic cavity obliteration at the papillary muscle level in the short-axis view for the diagnosis of hypertrophic obstructive cardiomyopathy. Ventricular wall thickness and posterior wall thickness were measured at the level of the mitral valve tip. ASH was defined as a septal/posterior wall thickness ratio of ≥1.3.[16] The criteria of HHD were determined when left ventricular septal or posterior wall thickness was ≥13 mm.

Determination of Serum Carnitine Levels

Serum free carnitine and acylcarnitine levels were evaluated with the enzymatic cycling method, as reported previously.[8] A 10-mL blood sample was drawn from the antecubital vein of each patient at rest under fasting conditions. Blood samples were centrifuged at 3000*g* at 3°C for 10 minutes, and serum samples (4 mL) were stored at −70°C until assayed. Total and free carnitine assay kits and enzymes were purchased from Kainos Laboratories Co.

At 37°C, we incubated 1 mL of 100 mmol/L Tris-HCl buffer (pH 9.5), 5 mmol/L thio-NAD^+, 0.2 mmol/L NADH, and 100 kU/L carnitine dehydrogenase in a 10-mm path-length cuvette for 3 minutes. Then, the increasing rate of thio-NADH, which is proportional to the amount of L-carnitine, was measured from absorbance at 415 nm during a time interval of 1 to 6 minutes after the addition of 50 μL of the serum specimen or L-carnitine standard solution. For the determination of total carnitine, 1 kU/L acylcarnitine hydrolase was added to the above reagent, because acylcarnitine is hydrolyzed to L-carnitine by this acylcarnitine hydrolase. Acylcarnitine levels were calculated on the basis of the difference between total carnitine and free L-carnitine concentrations. The concentration of L-carnitine was calculated on the basis of a comparison with the rate obtained with a 50 μmol/L L-carnitine standard solution. We used a model UV-250 (Shimadzu Seisakusyo Co) spectrometer and a Cobas-Fara analyzer (Roche Co).

Scintigraphic Study

Myocardial BMIPP scintigraphy was performed in all of the patients with HCM or HHD and in 20 normal subjects who underwent echocardiography. A dose of 111 MBq BMIPP (Nihon Medi-Physics Co, Ltd) was administered intravenously at rest under fasting conditions. Anterior planar and single-photon emission computed tomography (SPECT) images were obtained 15 minutes later. We used a rotating digital scintillation camera (gamma-camera 901 A; Toshiba Co, Ltd) equipped with a collimator dedicated to ^{123}I with a 20% energy window centered on the 159-keV photon peak of ^{123}I. In the planar studies, each image was obtained for 5 minutes, and the data were stored on a 256×256 matrix. In the SPECT studies, a total of 30 projection images (40 s/frame) were acquired over 180° from the left posterior oblique 45° to the right anterior oblique 45°. The images were reconstructed with a Shepp-Logan filter without correction for attenuation.

Furthermore, within 2 weeks of the BMIPP scintigraphy, all patients with HHD underwent exercise/rest SPECT with ^{99m}Tc-tetrofosmin to exclude the complication of ischemic heart disease. The patients underwent bicycle exercise according to a standard multistage exercise protocol. At peak exercise, 370 MBq ^{99m}Tc-tetrofosmin (Nihon Medi-Physics Co, Ltd) was intravenously injected and the patients continued to exercise for an additional 90 seconds. SPECT data acquisition was performed 30 minutes later. Three hours after the first injection, 740 MBq ^{99m}Tc-tetrofosmin was injected for the rest SPECT images. The method of data acquisition was the same as that for BMIPP except for the collimator used.

Analysis of Scintigraphic Imaging

BMIPP imaging was analyzed quantitatively and semiquantitatively (qualitatively), as reported previously.[9,18] For quantitative analysis, we calculated the heart-to-mediastinum uptake ratio from the average scintillation counts. Regions of interest were assigned in the heart and mediastinum on the anterior planar image, and the average scintillation counts in each segment were calculated. For semiquantitative (qualitative) analysis, the left ventricular tomograms were divided into 17 segments; the short-axis slices were separated into 8 segments at the basal and midventricular levels. Vertical long-axis slices were used to evaluate the apical portion of 1 segment. Each segment was visually graded in a blinded manner by 2 experienced nuclear cardiologists with a 0 to 3 scale in which 0 indicates normal, 1 indicates mildly reduced uptake, 2 indicates moderately reduced uptake, and 3 indicates markedly reduced uptake or absent activity. Differences of opinion were resolved by consensus. The sum of each score was defined as total defect score, reflecting the severity of impaired myocardial fatty acid metabolism.

The ^{99m}Tc-tetrofosmin SPECT images of patients with HHD were also analyzed by the 2 nuclear cardiologists. Cases with exercise-induced or fixed myocardial-decreased tracer uptake were excluded from this study, because these findings highly suggest the presence of coronary artery disease.

Statistical Analysis

Data were expressed as mean±SD. One-way ANOVA with subsequent Scheffé's multiple range tests was used to compare the data among the 3 variables. Correlations between continuous variable data were determined with linear regression analysis. Statistical significance was defined at $P<0.05$.

Results

The clinical data for the patients with HCM or HHD and the normal control subjects are presented in Table 1.

Echocardiographic Findings

Morphological patterns of hypertrophy in HCM were asymmetrical in 36 of 56 (64.3%) patients, symmetrical in 7 of 56 (12.5%) patients, and distal ventricular in 13 of 56 (23.2%) patients. However, only 1 of 20 patients with HHD (5.0%) showed asymmetrical left ventricular hypertrophy, and 19 of 20 (95.0%) demonstrated symmetrical left ventricular hypertrophy. Ventricular septal wall thickness in patients with HCM was significantly greater than that in patients with HHD and in normal subjects, whereas posterior wall thickness in patients with HHD significantly exceeded that in

TABLE 1. Clinical Data for HCM and HHD Patients and Normal Subjects

	HCM Patients (n=56)	HHD Patients (n=20)	Normal Subjects (n=80)
Age, y	56±12	60±11	53±13
M/F	42/14	10/10	40/40
Systolic blood pressure, mm Hg	122±10‖	151±19‡	119±10
Diastolic blood pressure, mm Hg	72±910	88±11‡	72±7
Ventricular septal wall thickness, mm	19±5‡§	14±2*	9±1
Left ventricular posterior wall thickness, mm	12±3†§	14±1‡	9±1
Fractional shortening, %	43±8	41±9	40±5
Serum creatinine level, mg/dL	0.71±0.14	0.77±0.18	0.76±0.15

Values are expressed as mean±SD.
*$P<0.001$, †$P<0.0005$, ‡$P<0.0001$ vs normal subjects.
§$P<0.005$, ‖$P<0.0001$ vs HHD patients.

patients with HCM and normal subjects. Fractional shortening did not differ among the 3 groups (Table 1).

Serum Carnitine Levels

Serum free carnitine levels were significantly higher in patients with HCM (52.5±9.5 nmol/mL) than in patients with HHD (46.6±6.4 nmol/mL, $P<0.01$) and normal subjects (42.3±5.5 nmol/mL, $P<0.0001$), but they were not statistically different between patients with HHD and normal subjects. In contrast, serum acylcarnitine levels were significantly lower in patients with HCM (10.1±4.0 nmol/mL) than in patients with HHD (14.5±4.9 nmol/mL, $P<0.0005$) and normal subjects (13.2±3.9 nmol/mL, $P<0.0005$), although they showed no statistical difference between patients with HHD and normal subjects (Table 2).

BMIPP Scintigraphic Findings

Representative BMIPP scintigrams for patients with HCM and HHD are shown in Figure 1. Reduced myocardial BMIPP uptake is prominent in the anterior and posterior junctions of the hypertrophied ventricular septum in HCM, whereas it is scarcely seen in HHD. The heart-to-mediastinum uptake ratio of BMIPP was significantly lower in patients with HCM (2.11±0.12) than in patients with HHD (2.22±0.17, $P<0.05$) and normal subjects (2.33±0.16, $P<0.0001$). In addition, the ratio was significantly lower in patients with HHD than in normal subjects ($P<0.05$). The total defect score of BMIPP in patients with HCM (13.6±6.3) exceeded that in patients with HHD (2.0±1.5, $P<0.0001$) (Table 3).

TABLE 2. Serum Carnitine Levels for HCM and HHD Patients and Normal Subjects

	HCM Patients (n=56)	HHD Patients (n=20)	Normal Subjects (n=80)
Free carnitine, nmol/mL	52.5±9.5†‡	46.6±6.4	42.3±5.5
Acyl carnitine, nmol/mL	10.1±4.0*§	14.5±4.9	13.2±3.9

Values are expressed as mean±SD.
*$P<0.0005$, †$P<0.0001$ vs normal subjects.
‡$P<0.01$, 927$P<0.0005$ vs HHD patients.

Relationship Between Free Carnitine Levels and Analysis of BMIPP Imaging

Both quantitative (heart-to-mediastinum ratio) and semiquantitative (total defect score) analyses of BMIPP imaging were significantly correlated with free carnitine levels in HCM ($r=-0.422$, $P=0.0012$, and $r=0.633$, $P<0.0001$, respectively). However, these correlations were not statistically significant in HHD (Figures 2A and 2B).

Discussion

In most cases, the diagnosis of HCM still depends on echocardiographic results, because ASH and distal ventricular hypertrophy are the morphological features of HCM. However, this diagnostic modality sometimes makes it difficult to differentiate HCM from HHD. Shapiro et al[2] reported that the patterns of left ventricular hypertrophy in HCM are 31% symmetrical (concentric), 55% asymmetrical septal, and 14% distal ventricular. However, most patients with HHD show concentric hypertrophy, although 4% to 47% of patients with HHD demonstrate ASH.[3–5] In particular, 70% of patients with HHD who have a diastolic blood pressure of ≥120 mm Hg are reported to have ASH.[6] In the present study, 64.3% of patients with HCM had ASH, 12.5% had symmetrical hypertrophy, and 23.2% had distal hypertrophy, whereas only 5% of patients with HHD demonstrated ASH. Compared with the study by Shapiro et al,[2] the prevalence of distal hypertrophy in our patients with HCM was relatively high. This suggests that APH is fairly common in Japan.[18]

Approximately 70% of myocardial energy requirements are derived from the β-oxidation of nonesterified fatty acids at rest under normal aerobic conditions, where long-chain fatty acids are the major substrate for β-oxidation in the myocardium.[19,20] Carnitine is an essential substance that transports long-chain fatty acids into the mitochondria, where β-oxidation takes place. In addition, carnitine modulates the intramitochondrial CoA/acyl CoA ratio.[21] The myocardial concentration of carnitine is 80- to 140-fold higher than the plasma concentration.[22] Carnitine is not synthesized in the heart, and carnitine uptake into the myocardium occurs against a large concentration gradient from the bloodstream.

BMIPP is a radioiodinated long-chain fatty acid analog that is used for the evaluation of cardiac fatty acid metabolism. BMIPP is also suitable for the assessment of mitochondrial dysfunction[23] and myocardial ATP content.[24] The application of BMIPP scintigraphy in patients with HCM revealed impaired myocardial long-chain fatty acid metabolism in the hypertrophied myocardium, especially in the anterior and posterior junctions of the ventricular septum and left ventricular apex.[25] These segments correspond pathologically to myocardial disarray.[26] In addition, myocardial electron microscopic findings in patients with HCM disclosed mitochondrial damage, such as swelling of the mitochondria and disruption of cristae, in 14 of 15 patients.[27] These abnormalities were more marked in the hypertrophied ventricular septum than in the left ventricular free walls. As shown in Figure 1 and Table 3, the extent of reduced myocardial

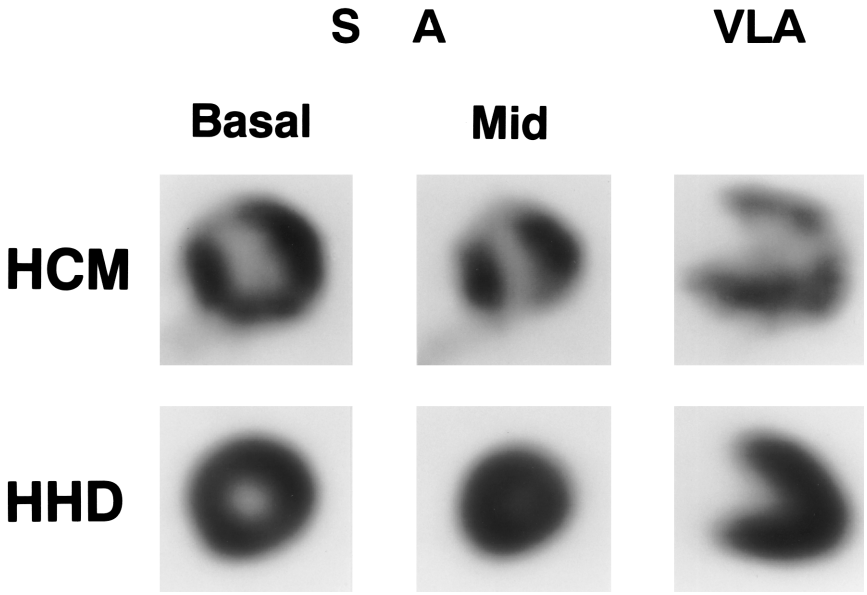

Figure 1. BMIPP imaging of patients with HCM and HHD showing symmetrical left-ventricular hypertrophy. Reduced myocardial BMIPP uptake is prominent in the anterior and posterior junctions of the ventricular septum in patients with HCM. In contrast, BMIPP distribution is uniform in the hypertrophied myocardium, and the decreased tracer uptake is scarcely seen in patients with HHD. SA indicates short-axis view; VLA, vertical long-axis view.

BMIPP uptake in HHD is mild compared with that in HCM. These findings suggest that impaired myocardial fatty acid metabolism is scarcely observed in HHD, although mitochondrial findings in humans were not reported.

In the experimental studies, myocardial BMIPP uptake was reduced in the ventricular septum, and serum carnitine levels were elevated in Bio 14.6 Syrian hamsters, representing a model for HCM.[28–30] In hypertensive rats, impaired myocardial fatty acid metabolism is seen in the endocardium and left ventricular free walls, even though coronary perfusion is normal.[31] Furthermore, myocardial energy production in hypertensive rats is decreased compared with that of normal control rats, but most of the mitochondrial structure is intact.[32] Serum free carnitine and acylcarnitine levels were higher in hypertensive rats than in normal control rats.[33]

We recently reported that serum free carnitine levels in patients with HCM were elevated, which might result from the reduced carnitine uptake into the myocardium or an efflux of myocardial free carnitine into the bloodstream due to the myocardial disarray.[8] In addition, free carnitine levels were significantly correlated with reduced myocardial BMIPP uptake (Figures 2A and 2B), indicating that the levels are sensitive indicators for the severity of impaired myocardial fatty acid metabolism.[8] However, serum free carnitine and acylcarnitine levels in patients with HHD were significantly lower and higher than those in patients with HCM, respectively. In addition, the levels did not show a statistical difference between patients with HHD and normal subjects, and no relationship was observed between free carnitine levels and BMIPP findings in patients with HHD (Figures 2A and 2B). These results may be because myocardial fatty acid metabolism in patients with HHD was so slightly affected that serum free carnitine levels did not correlate with reduced BMIPP uptake.

TABLE 3. Scintigraphic Data With BMIPP in HCM and HHD Patients and Normal Subjects

	HCM Patients (n=56)	HHD Patients (n=20)	Normal Subjects (n=20)
Heart/mediastinum ratio	2.11±0.12†‡	2.22±0.17*	2.33±0.16
Total defect score	13.6±6.3§	2.0±1.5	...

Values are expressed as mean±SD.
*$P<0.05$, †$P<0.0001$ vs normal subjects.
‡$P<0.05$, §$P<0.0001$ vs HHD patients.

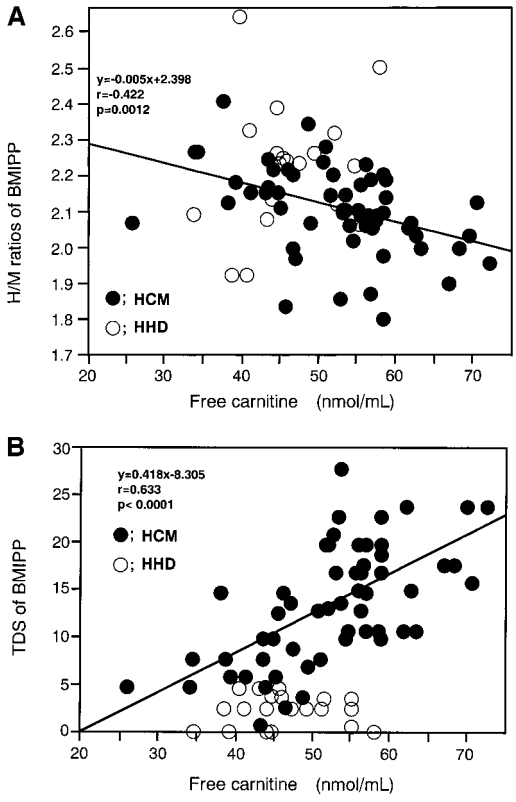

Figure 2. A, Relationships of serum free carnitine level with heart/mediastinum uptake ratios of BMIPP imaging. B, Relationships of serum free carnitine levels with total defect score of BMIPP imaging.

In addition to the conventional morphological diagnosis, the myocardial metabolic approach is essential to distinguish HCM from HHD. Serum carnitine levels reflect the differences in the severity of impaired myocardial fatty acid metabolism between HCM and HHD, which can contribute to the differential diagnosis.

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