Detection of Impaired Fatty Acid Metabolism and Dyskinesis in Hypertrophic Cardiomyopathy with Iodine-123-BMIPP

Tomoaki Nakata, Shigemichi Tanaka, Shiho Hamagami, Kenjiro Miyamoto, Katsumi Oh-hori and Osamu Iimura
Second Department of Internal Medicine, Sapporo Medical University School of Medicine; and Hokkaido Circulation Hospital, Sapporo, Japan

Metabolic imaging using ^{123}I-labeled 15- (p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) and Fourier phase analysis of gated blood-pool data were performed in a 60-yr-old woman with idiopathic hypertrophic cardiomyopathy. Dyskinetic wall motion was identified as a markedly delayed phase angle in the left ventricular apex, which was well perfused but highly hypertrophied like other ventricular segments. Fatty acid imaging, however, clearly demonstrated highly reduced activities in the apex, although there were no abnormalities in regional systolic function or in ^{201}Tl uptake in other hypertrophied regions. Contrast left ventriculography revealed a midventricular collapse of the left ventricle at end-systole due to markedly hypertrophied ventricular walls and dyskinesis at the apex. Thus, dyskinetic wall motion in the apex closely correlated not only with cardiac hypertrophy but also with impaired fatty acid uptake. These findings were unrelated to the myocardial perfusion state per se. Fatty acid imaging using BMIPP may contribute to the detection of myocyte degeneration not visible using conventional imaging modalities. It may also provide etiological information on regional dysfunction in hypertrophic cardiomyopathy.

Key Words: fatty acid metabolism; dual-isotope imaging; iodine-123-BMIPP; hypertrophic cardiomyopathy; dyskinesis

J Nucl Med 1996; 37:1679–1681

Metabolic imaging with a beta-methyl-branched fatty acid has demonstrated that myocardial fatty acid metabolism is impaired in patients with idiopathic hypertrophic cardiomyopathy (HCM) (*1-5*). However, the metabolic abnormality is not necessarily related to cardiac dysfunction and the pathophysiological implications are not clear. Although the etiology of idiopathic cardiomyopathy is still unknown and the prognosis in HCM is relatively good, lethal arrhythmias, congestive heart failure or sudden cardiac death is not unusual. In addition, there is no effective clinical tool for determining prophylactic strategies or those patients with HCM showing such deteriorative clinical outcome.

Radionuclide imaging of myocardial metabolism is one of the most promising approaches for revealing the pathogenesis of the disease process. Radioiodinated 15- (p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) is a recently developed beta-methyl-branched fatty acid which has several advantages compared to the straight-chain fatty acid analog, iodophenyl pentadecanoic acid (IPPA) (*6*): greater myocardial retention, lower liver uptake, appropriate dosimetry and kinetics for SPECT scanning with high image quality (*7,8*) and possible dual-isotope imaging with ^{201}Tl. Myocardial retention of BMIPP is relatively long because of subcellular distribution mainly in a triglyceride fraction and partially in mitochondrial and microsomal fractions without being oxidized in mitochondria.

Received Jun. 5, 1995; revision accepted Aug. 18, 1995.
For correspondence or reprints contact: Tomoaki Nakata, Second Department of Internal Medicine, School of Medicine, Sapporo Medical University, Sapporo 060, Japan.

In this report, we discuss the pathophysiological implications of abnormal fatty acid metabolism in a patient with HCM.

CASE REPORT

A 60-yr-old woman was admitted for further evaluation of syncope and dyspnea on effort. Her past history revealed that she had suffered from anterior chest discomfort for 8 yr and the symptom had gradually progressed. Physical examinations of the heart and chest were negative. Laboratory examinations indicated no systemic or hormonal disorders. A resting electrocardiogram revealed high voltage in the left precordial leads and depression of the ST-segment in leads II, III, aVF and V3-6. However, the duration and axis of the QRS complex were normal; 100 msec and +60, respectively, and there was no evidence for conduction disturbance of both ventricles. Two-dimensional and Doppler echocardiography identified markedly hypertrophied left ventricular walls with wall thicknesses of 16–20 mm. Left ventricular hypertrophy was concentric and there was neither systolic anterior movement of the mitral valve nor asymmetric septal hypertrophy. Radionuclide ventriculography using 740 MBq of ^{99m}Tc-labeled human serum albumin clearly demonstrated markedly reduced cavity size of the left ventricle due to severe myocardial hypertrophy (Fig. 1). Furthermore, the functional image and histogram of phase angles, derived from Fourier analysis with first-order harmonics, delineated highly asynchronized left ventricular wall motion. In particular, the phase angle at the apex was considerably delayed (Fig. 1), despite a slightly reduced left ventricular ejection fraction of 47%.

Dual-energy planar and tomographic imaging with ^{201}Tl (111 MBq) and [^{123}I]BMIPP (111MBq) were performed at rest after the patient had fasted for 12 hr. Based on the results of preliminary cardiac phantom experiments in our nuclear medicine laboratory, simultaneous dual-isotope acquisition was set for two energy windows: the 159-keV photopeak of ^{123}I with a 26% window and the 75-keV photopeak of ^{201}Tl with a 16% window. On ^{201}Tl scans, the left ventricular walls were normally perfused but markedly hypertrophied in all segments. In contrast, BMIPP uptake was definitely reduced only in the anteroapical segment (Fig. 2). Contrast left ventriculography demonstrated an apparently small left ventricular cavity due to severe left ventricular hypertrophy, midventricular collapse of the left ventricle at end-systole and dyskinetic wall motion at the left ventricular apex (Fig. 3). Endomyocardial biopsy revealed hypertrophied cardiac cells, disarray, bizarre nuclei, disorganization of myofilaments and interstitial fibrosis (Fig. 4).

DISCUSSION

Myocardial fatty acid metabolism is highly impaired in patients with HCM, despite the lack of systolic dysfunction or a perfusion abnormality (*1-5*). We have previously demonstrated that the metabolic abnormality detected by ^{201}Tl and BMIPP images occurs in normally perfused and contracting

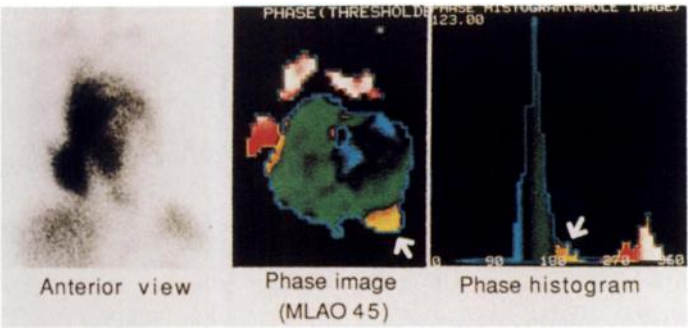

FIGURE 1. Radionuclide ventriculograms from the left anterior oblique view (left), a functional image of the phase angle (middle) and a histogram of left ventricular phase angles (right). Note reduced cavity size of the left ventricle and markedly delayed phase angle at the apex (white arrows).

myocardium in HCM patients (*5*). Similarly, inhomogeneously reduced fatty acid uptake at rest has been described using positron CT studies in human cardiomyopathy and cardiac hypertrophy (*9-12*). These findings suggest that metabolic alterations exist in cardiomyopathy cells before a myocardial perfusion abnormality, cardiac enlargement, systolic dysfunction or loss of myocytes as observed in end-stage HCM. However, because HCM is different from coronary artery disease (*13-15*), the lack of correlation between cardiac dysfunction and impaired fatty acid metabolism makes the pathophysiological role of metabolic abnormalities in HCM inconclusive. The etiological and prognostic implications of a BMIPP abnormality in a HCM patient without left ventricular dysfunction should be investigated in future studies.

Although left ventricular dilatation and serious ventricular arrhythmias were not present, this patient was symptomatic and global function was slightly reduced, suggesting that the patient was at a moderate stage of HCM. Nonetheless, apparently dyskinetic wall motion was observed only at the hypertrophied apical region. This region showed some metabolic abnormality,

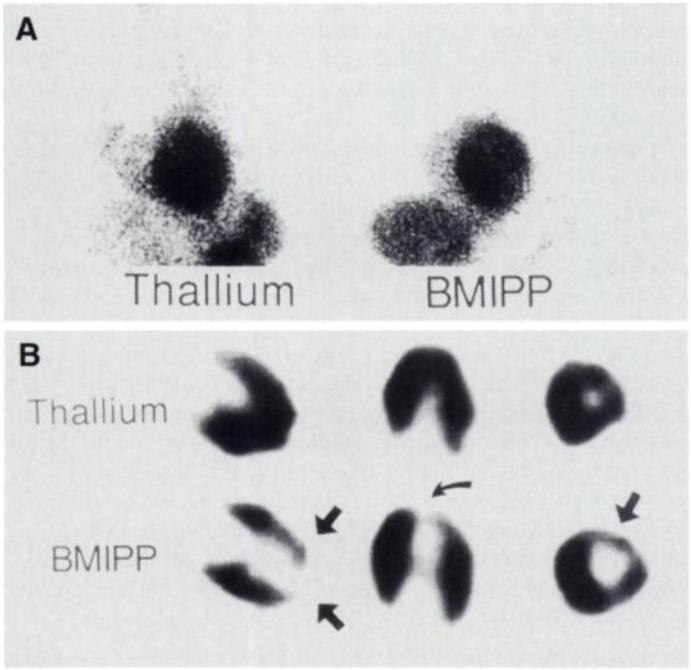

FIGURE 2. Planar (A) and tomographic (B) scintigrams of ^{201}Tl and BMIPP. Definitely reduced BMIPP uptake is seen at the left ventricular apex (large white arrow), which is more clearly visible in the vertical long-axis, horizontal long-axis and short-axis tomograms (small black arrows in lower panel). There is no perfusion abnormality, but the left ventricular walls are markedly hypertrophied on the ^{201}Tl scans.

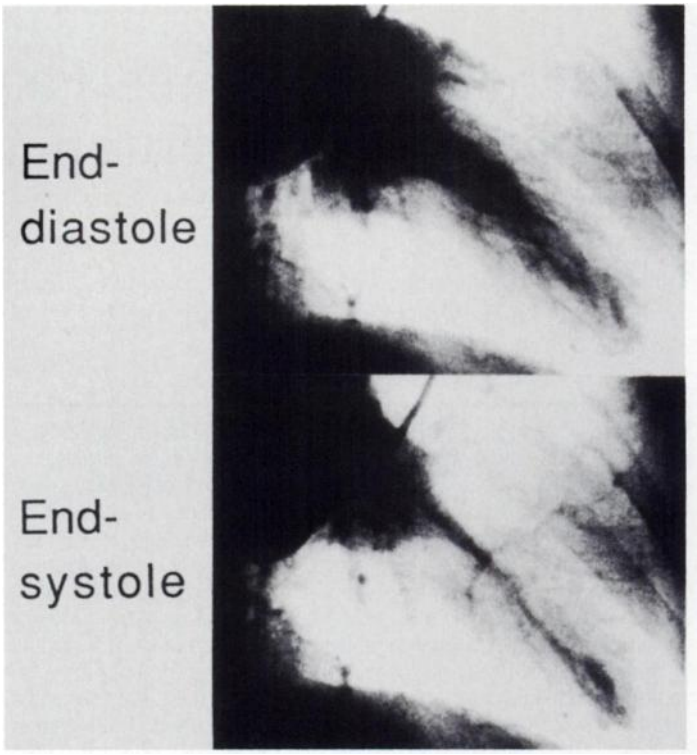

FIGURE 3. Contrast left ventriculograms during end-diastole (upper panel) and end-systole (lower panel) from the 30° right anterior oblique view. Highly hypertrophied left ventricular walls reduce the cavity size, and dyskinetic wall motion and midventricular collapse are observed during end-systole at the apex.

but myocardial perfusion was normal. A regional wall motion abnormality is unusual in HCM when myocardial perfusion is maintained and before cardiac enlargement or severe systolic dysfunction is manifested, even if severe myocardial hypertrophy exists. Dyskinetic wall motion is often observed in a necrotic or scarred region which is scintigraphically identified as a perfusion defect in patients with myocardial infarction or dilated cardiomyopathy.

Although the mechanisms of the metabolic and functional abnormalities in the left ventricular apex are not clear, several hypotheses can be offered. First, impaired fatty acid metabolism in myocardium which has myocardial viability and normal ^{201}Tl perfusion suggests that depressed aerobic energy production by beta-oxidation of fatty acid results in regional wall motion abnormality. Fujibayashi et al. (*16*) have demonstrated a linear correlation between BMIPP activity and intracellular ATP level. This finding suggests that BMIPP uptake is affected by energy (ATP) and fatty acid metabolism in the myocardium and that a decreased intracellular ATP level, probably due to mitochondrial dysfunction, may be responsible for reduced BMIPP activity and cardiac dysfunction. However, in hereditary cardiomyopathy hamster hearts, left ventricular contractility and ATP levels were maintained at normal values (*17*), despite reduced fatty acid metabolism (*12*). The explanation of the difference in these findings is unclear but the maintenance of tissue ATP levels and contractility may be a result of compensation of other energy production systems in the cardiomyopathy animal model. Nonetheless, this possibility in humans remains to be investigated.

Second, severe left ventricular hypertrophy and collapse of the left ventricular cavity in the midventricular region possibly increased wall stress and left ventricular end-diastolic pressure. This would lead to augmentation of myocardial stiffness and energy demand at the apex which may, in turn, lead to

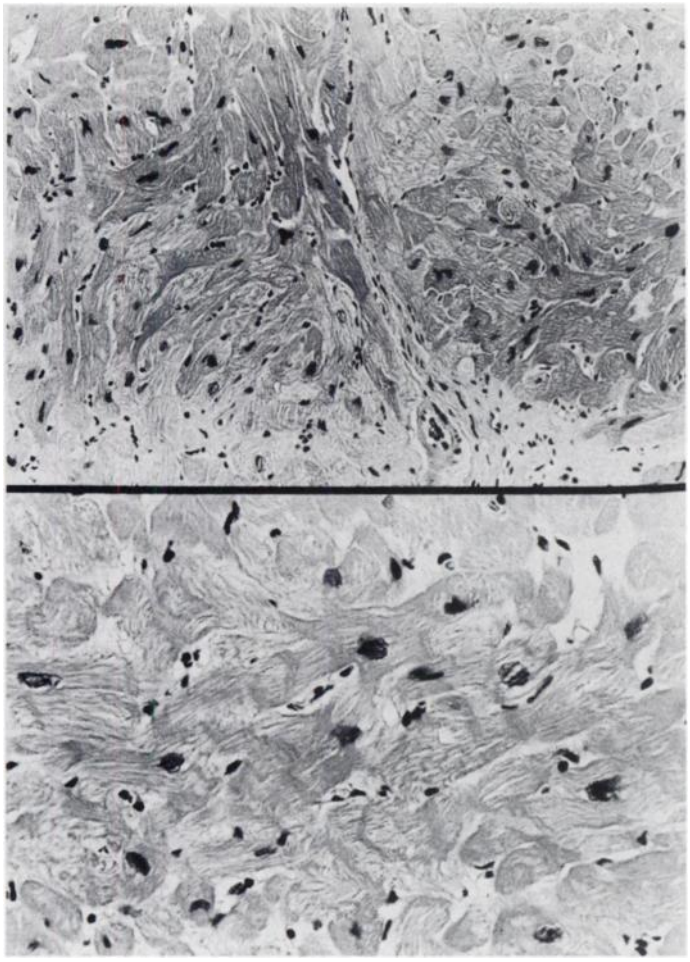

FIGURE 4. H&E stained histopathology of endomyocardial biopsy shows disarray, bizarre nuclei, disorganization of myofilaments and interstitial fibrosis in addition to hypertrophied myocytes (upper panel, 240×; lower panel, 470×).

derangements of myocardial fatty acid metabolism and regional wall motion. In our patient, in addition to left ventricular hypertrophy, mechanical stress at the apex due to midventricular collapse may have exacerbated metabolic derangement or an imbalance of energy production and demand in cardiomyopathic myocytes.

Third, hypertrophied myocardium exhibits limited coronary flow reserve and leads to exercise-induced myocardial ischemia (*18,19*). Wolfe et al. (*20*) reported heterogeneously reduced fatty acid ([^{123}I]IPPA) activities due to exercise-induced myocardial ischemia in hypertensive hearts. In contrast, IPPA distributions at rest were homogeneous. In an exercise study, however, it may not be possible to determine the mechanism of abnormal fatty acid uptake. Intracellular fatty acid metabolism which is depressed due to myocardial ischemia may be indistinguishable from limited myocardial delivery of the fatty acid analog.

Our patient did not have a perfusion abnormality, except for the severe cardiac hypertrophy depicted on the resting ^{201}Tl scan. An exercise-stress study was not performed. Even though coronary flow reserve is limited in hypertrophied myocardium, it is unlikely that myocardial ischemia or reduced delivery of the tracer to myocytes due to limited coronary flow is involved in the mechanism underlying abnormal BMIPP uptake at rest.

In our patient, the markedly delayed phase angle at the left ventricular apex strongly suggested dyskinetic wall motion. Phase abnormality is also observed when a conduction system is disturbed. However, this possibility is unlikely in this patient because the delayed phase angle was highly localized at the left ventricular apex where dyskinetic wall motion was determined by contrast left ventriculography and the electrocardiogram provided no evidence for conduction abnormalities responsible for the phase shifts.

Regional wall motion analysis by Fourier analysis and dual-isotope imaging with ^{201}Tl and BMIPP demonstrated the close correlation between impaired fatty acid metabolism and dyskinetic wall motion in hypertrophied, but well perfused, myocardium. These imaging techniques may contribute to the assessment of inherent subcellular alterations in HCM that cannot be detected by conventional techniques. However, more studies are needed to determine the etiological and prognostic implications of perfusion-metabolism mismatch in HCM patients before the manifestation of cardiac enlargement, dysfunction, heart failure or sudden cardiac death.

ACKNOWLEDGMENTS

We thank Naomi M. Anderson, PhD, Calgary, Canada, for editorial assistance.

REFERENCES

1. Kurata C, Tawarahara K, Taguchi T, et al. Myocardial emission tomography with iodine-123- labeled beta-methyl branched fatty acid in patients with hypertrophic cardiomyopathy. *J Nucl Med* 1992;33:6–13.
2. Torizuka K, Yonekura Y, Nishimura T, et al. Phase 3 study of methyl-p-(^{123}I)-iodophenyl pentadecanoic acid, a myocardial imaging agent for evaluating fatty acid metabolism—a multicenter trial. *Jpn J Nucl Med* 1992;29:413–433.
3. Shimonagata T, Nishimura T, Uehara T, et al. Discrepancies between myocardial perfusion and free fatty acid metabolism in patients with hypertrophic cardiomyopathy. *Nucl Med Commun* 1993;14:1005–1013.
4. Takeishi Y, Chiba J, Abe S, et al. Heterogeneous myocardial distribution of iodine-123-15- (p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) in patients with hypertrophic cardiomyopathy. *Eur J Nucl Med* 1992;19:775–782.
5. Kobayashi H, Nakata T, Han S, et al. Fatty acid metabolism and perfusion abnormalities in hypertrophied myocardium assessed by dual tracer tomography using thallium-201 and iodine-123-beta-methylpentadecanoic acid. *J Cardiol* 1994;24:35–43.
6. Reske SN, Sauer W, Machulla HJ, Knust J, Winkler C. Metabolism of 15(p-^{123}I-iodophenyl-)pentadecanoic acid in heart muscle and noncardiac tissues. *Eur J Nucl Med* 1985;10:228–234.
7. Goodmann MM, Kirsch G, Knapp FF Jr. Synthesis and evaluation of radioiodinated terminal p-iodophenyl-substituted alpha- and beta-methyl branched fatty acids. *J Med Chem* 1984;27:390–397.
8. Knapp FF Jr, Ambrose KR, Goodmann MM. New radioiodinated methyl-branched fatty acids for cardiac studies. *Eur J Nucl Med* 1986;12:S39–S44.
9. Geltman EM, Smith JL, Beecher D, et al. Altered regional myocardial metabolism in congestive cardiomyopathy detected by positron tomography. *Am J Med* 1983;74:773–785.
10. Grover-McKay M, Schwaiger M, Krivokapich J, et al. Regional myocardial blood flow and metabolism at rest in mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1989;13:17–24.
11. Sochor H, Shelbert HR, Schwaiger M, et al. Studies of fatty acid metabolism with positron emission tomography in patients with cardiomyopathy. *Eur J Nucl Med* 1986;12:S66–S69.
12. Kurata C, Kobayashi A, Yamazaki N. Dual autoradiographic study with thallium-201 and radioiodinated fatty acid in cardiomyopathy hamsters. *J Nucl Med* 1989;30:80–87.
13. Tamaki N, Kawamoto M, Yonekura Y, et al. Regional metabolic abnormality in relation to perfusion and wall motion in patients with myocardial infarction: assessment with emission tomography using an iodinated branched fatty acid analog. *J Nucl Med* 1992;33:659–667.
14. Uehara T, Nishimura T, Kumita S, et al. Diagnostic utility of myocardial imaging using ^{123}I-labeled beta-methyl iodophenyl pentadecanoic acid in ischemic heart disease. *Jpn J Nucl Med* 1992;29:347–358.
15. Hase, Nakata T, Yonekura S, et al. Correlation of regional wall motion and fatty acid metabolism in coronary artery disease, hypertension, and hypertrophic cardiomyopathy: assessment by dual-isotope SPECT with thallium-201 and iodine-123-methyl fatty acid analog. *Jpn J Nucl Med* 1993;30:529–539.
16. Fujibayashi Y, Yonekura Y, Takemura Y, et al. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analog, iodine-125-15-(p-iodophenyl)-3(R,S) methyl pentadecanoic acid (BMIPP), in relation to ATP concentration. *J Nucl Med* 1990;31:1818–1822.
17. Whitmer JT. L-Carnitine treatment improves cardiac performance and restores high-energy phosphate pools in cardiomyopathic syrian hamster. *Circ Res* 1987;61:396–408.
18. O'Gara PT, Bonow RO, Maron BJ, et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with ^{201}Tl emission computed tomography. *Circulation* 1987;76:1214–1223.
19. Von Dohlen TW, Prisant LM, Frank MJ. Significance of positive or negative ^{201}Tl scintigraphy in hypertrophic cardiomyopathy. *Am J Cardiol* 1989;64:498–503.
20. Wolfe CL, Kennedy PL, Kulkarni PV, et al. Iodine-123-phenylpentadecanoic acid myocardial scintigraphy in patients with left ventricular hypertrophy: alterations in left ventricular distribution and utilization. *Am Heart J* 1990;119:1338–1347.