Impaired myocardial accumulation of 15-(p-iodophenyl)-9-(R,S)-methylpentadecanoic acid in a patient with hypertrophic cardiomyopathy and exercise-induced ischemia due to vasospasm

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We encountered a patient with hypertrophic cardiomyopathy complicated with exercise-induced myocardial ischemia. Exercise-stress ^{99m}Tc-tetrofosmin imaging demonstrated reversible ischemia in the lateral wall, whereas resting fatty acid imaging with a new beta-methyl branched fatty acid analogue, I-123-15-(p-iodophenyl)-9-(R,S)-methylpentadecanoic acid (^{123}I-9-MPA), showed impaired uptake and accelerated washout kinetics in the inferoapical and posteroseptal walls but not in the ischemia-related region. These findings suggest that the metabolic derangement is closely related to cardiomyopathy per se rather than exercise-induced myocardial ischemia in this patient with hypertrophic cardiomyopathy and a spastic coronary lesion so that myocardial perfusion and ^{123}I-9-MPA imagings may contribute to clarifying the etiological background of impaired myocardial fatty acid metabolism.

Key words: hypertrophic cardiomyopathy, exercise-stress, fatty acid imaging, coronary vasospasm

INTRODUCTION

IN HYPERTROPHIC CARDIOMYOPATHY (HCM), effort-related or atypical chest pain is often observed and reversible ischemia has been demonstrated by perfusion imaging.[1–3] In addition, impaired fatty acid metabolism was also recently demonstrated in HCM patients by means of scintigraphic techniques.[4–7] Although the precise mechanisms behind these abnormalities have not been fully determined, limited coronary flow reserve (ischemia) due to small vessel disease, coronary spasm, or complicated coronary sclerosis as well as an increase in myocardial wall stress and oxygen consumption may be involved.[1–6] We encountered a patient with HCM who had exercise-induced perfusion abnormality and impaired uptake of a novel methyl-branched fatty acid analogue, I-123-15-(p-iodophenyl)-9-(R,S)-methylpentadecanoic acid (^{123}I-9-MPA).[8–10] ^{123}I-9-MPA is a branched fatty acid analogue for myocardial imaging, and this tracer has been designed to be beta-oxidized three times in cardiomyocyte relatively rapidly and then to be washed out from the myocardium by introducing a methyl branch in the ninth carbon location of the fatty acid chain (Fig. 1). The present report discussed the clinical implications of perfusional and metabolic abnormalities located in different regions which were detected by the new fatty acid imaging and perfusion scintigraphy in a cardiomyopathy patient.

CASE REPORT

A 66-year-old man was admitted for evaluation of exercise-induced chest pain. His chest pain improved spontaneously within several minutes at rest, and sublingual administration of nitroglycerine was very effective. He habitually smoked but had no history of hypertension, hyperlipidemia, or hyperglycemia. Despite treatment with

a calcium channel-blocker (diltiazem 120 mg per day), his chest pain had not been completely controlled. Physical examination showed no abnormal findings. Severe left ventricular hypertrophy was suggested by a high voltage ($SV1 + RV5 = 6.9$ mV), ST-segment depression, and T-wave inversion in leads I, II, III, aV_F, and V_2 to V_6 on a 12-lead electrocardiogram (Fig. 2). Two-dimensional echocardiography showed profound and heterogenous left ventricular hypertrophy; interventricular septal wall thickness was 15 mm, posterior wall thickness 12 mm, and apical wall thickness 21 mm, but neither wall motion abnormality nor left ventricular out-flow tract obstruction was detected (Fig. 3). Endomyocardial biopsy revealed hypertrophied cardiomyocytes, interstitial fibrosis, and mild disarray. There was no identifiable causes of cardiac hypertrophy. From these findings, the diagnosis of idiopathic hypertrophic cardiomyopathy was established. The patient underwent a symptom-limited ergometer exercise test with ^{99m}Tc-tetrofosmin single photon emission computed tomography (SPECT) on a one-day protocol with an exercise-rest sequence. Fifteen minutes after the administration of ^{99m}Tc-tetrofosmin (296 MBq), exercise

SPECT data were obtained at 8-degree increments for 45 seconds per increment during a 360-degree rotation with a 3-head gamma camera and a low-energy, high-resolution parallel-hole collimator (GCA9300A/DI, Toshiba, Japan). One hundred and eighty minutes after the exercise-stress test, ^{99m}Tc-tetrofosmin of 740 MBq was injected intravenously and, 30 minutes later, rest SPECT data were acquired in the same way. After transaxial reconstruction with a filtered back-projection algorithm and a Butterworth and Ramp filter, short-axis, vertical long-axis, and horizontal long-axis tomograms were reconstructed. Reversible perfusion abnormality was demonstrated in the lateral wall with chest pain and rest perfusion imaging revealed a somewhat hypertrophied left ventricle (Fig. 4). Cardiac fatty acid imaging with ^{123}I-9-MPA of 160 MBq (provided by Daiichi Radioisotope
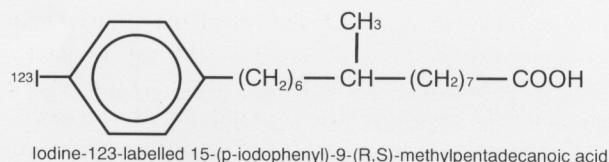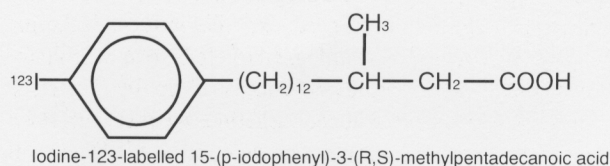

Iodine-123-labelled 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid

Iodine-123-labelled 15-(p-iodophenyl)-9-(R,S)-methylpentadecanoic acid

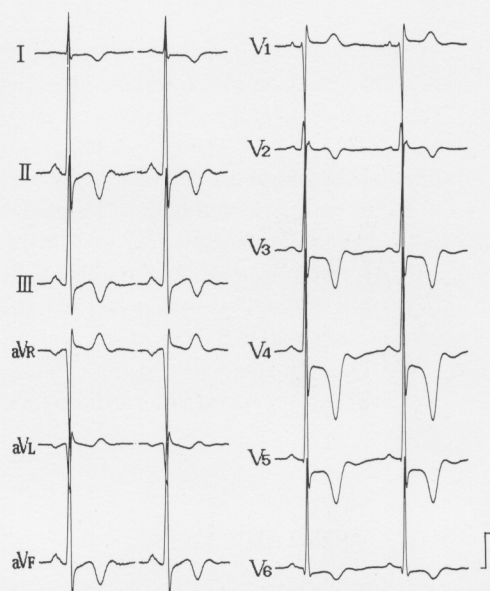**Fig. 1** Chemical structures of ^{123}I-BMIPP (upper) and ^{123}I-9-MPA (lower).

Fig. 2 Electrocardiogram on admission showing high voltages, ST-segment depression, and T-wave inversion in leads, I, II, III, aV_F, V_{2-6}.
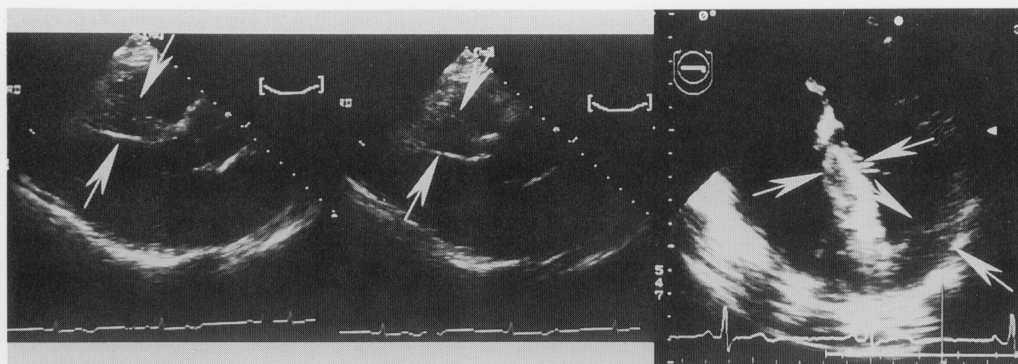

Fig. 3 Transthoracic (left panel; diastole phase, and mid panel; systole phase) and transesophageal (right panel) echocardiograms showing myocardium hypertrophy, particularly in the anteroseptal and apical walls.

Fig. 4 Exercise-stress ^{99m}Tc-tetrofosmin myocardial tomograms showing a reversible perfusion abnormality in the lateral wall (arrows) and severe left ventricular hypertrophy particularly in the apex and mid-ventricle.
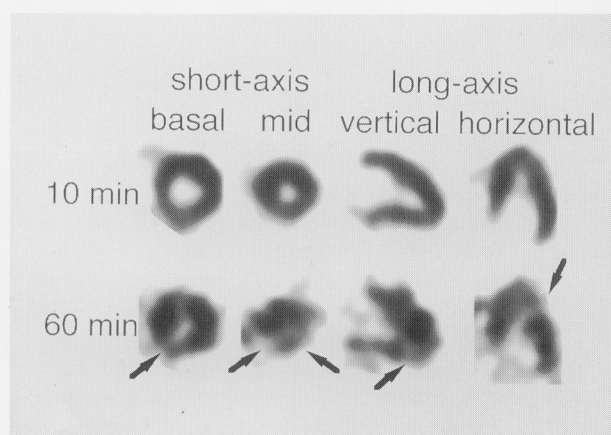

Fig. 5 Compared to early imaging (10-min, upper panels), delayed (60-min) ^{123}I-9-MPA tomograms (lower panels) show reduced uptakes of ^{123}I-9-MPA in the inferior, inferoapical, and posteroseptal segments (arrows), but not in the lateral wall which showed reversible ischemia on perfusion imaging, indicating accelerated washout kinetics of ^{123}I-9-MPA in these areas.

Laboratory, Tokyo, Japan) was performed 10 and 60 minutes after injection by the same imaging method as that used in perfusion imaging. Compared to the early (10-min) images, reduced uptakes of ^{123}I-9-MPA were observed in the inferior, inferoapical and posteroseptal segments, but not in the lateral wall on the delayed (60-min) images, indicating an apparently accelerated washout kinetics of ^{123}I-9-MPA from the myocardium in these areas (Fig. 5). Coronary arteriography revealed a 90% luminal narrowing of the circumflex coronary artery which improved to a less than 50% narrowing after sublingual administration of nitroglycerine. The coronary findings were anatomically identical to the reversible perfusion abnormality detected by stress perfusion imaging, and no other coronary lesion was detected. Contrast left ventriculography demonstrated marked hypertrophy of the left ventricle at the apex and mid-ventricle. No left ventricular dilatation, asynergy or an intra-ventricular pressure gradient was detected.

DISCUSSION

Reversible ischemia has been demonstrated by means of ^{201}Tl scintigraphy with an exercise- or hyperventilation-stress test in approximately 25% of patients with variant angina but no significant coronary stenosis.[11] In the present case, complete fill-in in the lateral wall was detected by exercise-stress ^{99m}Tc-tetrofosmin myocardial scintigraphy. Although reversible myocardial ischemia is demonstrated in HCM patients by exercise-stress ^{201}Tl scintigraphy,[1–3,12] the localization of reversible perfusion abnormality in the present patient corresponded to spontaneously induced circumflex artery vasospasm which improved immediately after nitroglycerin administration without significant residual stenosis, and no other spastic or stenosis lesion was found. In addition, hypertrophic myocardium was observed not only in the lateral wall but also in apex on the echocardiogram and myocardial scintigram. Therefore, in this case, exercise-induced ischemia associated with vasospasm[13] is likely to be responsible for chest pain and reversible perfusion abnormality on effort, although vasospasm-induced ischemia together with chest pain, significant ST-segment change, or both[14,15] was not confirmed on catheter examination with acetylcholine infusion. ^{123}I-9-MPA imaging showed no definite abnormality in fatty acid uptake in the region where reversible ischemia was identified. On the other hand, the new fatty acid imaging demonstrated accelerated washout kinetics of ^{123}I-9-MPA and more profound reduction in the uptake in markedly hypertrophied myocardium which showed no reversible ischemia on exercise-stress perfusion imaging. These findings strongly suggest that not only sarcolemmal uptake but also an intracellular retention mechanism of the long-chain free fatty acid analogue, ^{123}I-9-MPA, is impaired and that the mechanism of impaired fatty acid metabolism originates in the pathogenesis of HCM per se rather than in reversible myocardial ischemia which can be induced by exercise-stress and coronary artery spasm in the present case. Nevertheless, myocardial ischemia could impair myocardial fatty acid uptake in 40 to 48% of patients with angina pectoris[16–18] probably dependent upon the severity of myocardial ischemia.

As previously demonstrated,[4–6] impaired fatty acid uptake detected by 15-(p-iodophenyl)-3-(R,S)-methyl-pentadecanoic acid (BMIPP) imaging is observed in hypertrophied but normally perfused, contracting myocardium in HCM patients. Similarly, inhomogeneous reduction of fatty acid uptake has been described when using positron imaging in human cardiomyopathy and

cardiac hypertrophy,[19-21] but the etiological and clinical implications of impaired fatty acid metabolism in HCM have not been established. Although myocardial ischemia is observed in some HCM patients and the pathophysiologic significance has been demonstrated,[1-3] involvement of reversible perfusion abnormality in impaired myocardial fatty acid metabolism has not been clarified in these studies. In the present case, scintigraphically-identifiable reversible ischemia is unlikely to be related to depressed beta-oxidation of fatty acids leading to impaired ^{123}I-9-MPA metabolism. Nevertheless, increased wall stress (oxygen consumption) due to severe left ventricular hypertrophy and collapse of microvasculature which possibly provoke myocardial ischemia might be responsible for metabolic impairment at a myocyte level because limited coronary flow reserve in hypertrophied myocardium cannot be necessarily detected precisely by exercise-stress perfusion imaging. As Fujibayashi et al.[22] have demonstrated, long-chain fatty acid metabolism is affected by intracellular energy content (ATP level) and the energy production system in mitochondria. Several experimental investigations have described functional derangement of sarcolemma in cardiomyopathic hearts[23-26]: a defect in calcium handling which causes calcium overload leading to metabolic alterations or a defect in membrane transport of carnitine from the blood into the myocardial cells (a carrier-mediated process requiring metabolic energy)[27] which results in lower intracellular carnitine levels. Altered membrane integrity or carnitine-mediated processes may be associated with decreased uptake and impaired retention of long-chain fatty acids. In addition, decreased long chain acylcarnitine has been reported in both dilated and HCM hamster hearts.[28] Therefore, metabolic changes might occur in cardiomyopathy cells prior to or independent of stress-induced ischemia or myocardial perfusion abnormality so that several mechanisms, such as a depressed energy production system, mitochondrial dysfunction, and altered sarcolemmal or intracellular systems for transport and storage of long-chain fatty acids, may be responsible for impaired fatty acid metabolism in the present cardiomyopathy patient. Although the prognostic implications of impaired fatty acid metabolism in HCM remain to be established,[29] cardiac ^{123}I-9-MPA imaging could contribute to determining the pathophysiological role of myocardial fatty acid metabolism in hypertrophic cardiomyopathy and reversible ischemia.

SUMMARY

Myocardial perfusion and fatty acid metabolism were assessed in a hypertrophic cardiomyopathy patient with exercise-induced ischemia by using SPECT imagings with ^{99m}Tc-tetrofosmin and a new fatty acid tracer, I-123-15-(p-iodophenyl)-9-(R,S)-methylpentadecanoic acid (^{123}I-9-MPA). Exercise-induced coronary spasm was likely to be involved in reversible ischemia and chest pain, but abnormal ^{123}I-9-MPA kinetics, that is, mildly reduced initial uptake and accelerated release of ^{123}I-9-MPA leading to more profound reduction in ^{123}I-9-MPA, was observed in regions different from those showing signs of exercise-related ischemia. These findings strongly suggest that impaired myocardial fatty acid metabolism is not due to inducible myocardial ischemia but closely related to hypertrophic cardiomyopathy per se. Thus, combined assessments with ^{99m}Tc-tetrofosmin and ^{123}I-9-MPA imagings may contribute to clarifying the etiological backgrounds of impaired myocardial fatty acid metabolism in patients with hypertrophic cardiomyopathy and reversible ischemia.

ACKNOWLEDGMENTS

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