Approaches to Identify and Characterize Hypertrophic Myocardium

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Echocardiography and cardiac blood-pool scintigraphy have been used for morphological and functional evaluation of hypertrophic cardiomyopathy (HCM). Morphology, characterized by echocardiography, classifies HCM into asymmetric septal hypertrophy or diffuse hypertrophy according to interventricular septal thickness (IVS), left ventricular posterior wall thickness (LVPW) and the ratio of the two thicknesses (IVS-to-LVPW) (1–6). Functionally, cardiac blood-pool scintigraphy classifies HCM by using the peak filling rate (PFR) and the time to peak filling rate (TPFR). These indices of diastolic ventricular function are reduced, although left ventricular ejection fraction (LVEF) values may be normal or elevated (7–11). The cause of impaired diastolic function is a reduction in left ventricular relaxation due to myocardial hypertrophy. Verapamil, a Ca antagonist, was shown to improve left ventricular early diastolic function and exercise tolerance in HCM patients (12–14). Thus, echocardiography and cardiac blood-pool scintigraphy are useful for morphological and functional characterization of HCM patients.

Recently, a subtype of HCM associated with left ventricular dilatation and marked cardiac failure has been observed. These patients progress to a phase of dilated cardiomyopathy (DCM). Thus, cardiomyopathy has attracted attention because it suggests a relationship between cardiac hypertrophy and myocardial degeneration (15–18).

This review summarizes the utility of various imaging modalities to identify and characterize hypertrophic myocardium and intramural (small vessel) coronary artery disease, myocardial fibrosis and necrosis (19–21).

THALLIUM MYOCARDIAL SPECT

Angina can be induced in HCM patients by exercise even though the coronary arteries are angiographically normal. The cause of myocardial ischemia in these patients appears to be intramural, small vessel disease due to a relative decrease in the vascular bed as compared to cellular mass, an increase in extravascular compression on the vessels and limiting flow (19–21). For this reason, exercise myocardial scintigraphy is used to detect myocardial ischemia and reductions in coronary reserve in HCM. In 1980, Pitcher et al. (22) noted transient defects in 10 (43%), persistent defects in 4 and reverse redistribution in 3 of 23 HCM patients. Moreover, because angina occurred in 8 of the 10 patients (80%) with transient defects, they suggested a close relationship between angina and thallium redistribution in HCM. Following this work, reports on the usefulness of exercise myocardial scintigraphy in HCM patients have increased (23,24). Cannon et al. (25) showed that thallium redistribution in exercise myocardial (single-photon emission computed tomography) SPECT is an important marker of myocardial ischemia in HCM, and that this finding is more reliable than electrocardiography or coronary angiography. In addition, they speculated that enlargement of the cardiac cavities on immediate postexercise images is related to compression of subendocardial tissues causing myocardial ischemia. O’Gara (26) noted perfusion abnormalities in 41 of 72 (57%) HCM patients with exercise myocardial SPECT. Of these 41 patients, LVEF was 60% or higher in 24 (59%) who showed transient defects, but it was 50% or less in 4 of the 17 (24%) patients who showed persistent defects. Transient defects occurred at sites where wall thickness was moderately or severely increased, whereas persistent defects were observed primarily at sites where wall thickness was normal or only slightly increased. Thus, thallium perfusion abnormalities in HCM were observed frequently. During dipyridamole administration, focal zones of relatively decreased perfusion have also been reported in about half the patients, probably reflecting a reduction in coronary reserve function. Figure 1 shows a patient with HCM in whom the transient defect was clearly observed in the anteroseptal wall (hypertrophic myocardium) on exercise myocardial SPECT.

In rest myocardial scintigraphy, we noted perfusion defects in 9 of 10 (90%) patients with familial HCM (15,27). In these patients, as perfusion deteriorated, cardiomegaly
progressed, cardiac function was reduced and serum enzymes derived from the myocardium such as CPK and LDH increased. Myocardial biopsy demonstrated myocardial fiber disarray with fibrosis. Figure 2 shows rest myocardial scintigrams in two patients (sisters) with familial HCM. Dilatation of the cardiac cavities was more remarkable in the elder sister than the younger, but both showed myocardial hypertrophy and bizarre myocardial scintigrams with perfusion abnormalities. In 76 consecutive HCM patients at our institution, rest myocardial scintigraphy demonstrated focally decreased perfusion in 9 (13%). Over a mean follow-up period of 3 yr, these lesions extended and the outcome was poor (28).

Udelson et al. (29) carried out exercise myocardial SPECT in 29 asymptomatic or slightly symptomatic patients with HCM before and after administration of verapamil and observed that transient defects disappeared after administration of verapamil in 10 of 14 (71%) patients. From these findings, they pointed out that verapamil is useful for prevention of silent myocardial ischemia or alleviation of HCM symptoms in asymptomatic or slightly symptomatic patients. This effect is thought to derive from the direct action of the drug on small coronary artery vessels or from regional myocardial relaxation (29,30). Therefore, detection of perfusion abnormalities in HCM by thallium myocardial SPECT is important for the diagnosis and management of HCM patients.

**UFCT AND MRI**

UFCT (ultra-fast computed tomography) and MRI (magnetic resonance imaging) allow easy evaluation of myocardial thickening and estimation of cardiac volume as does echocardiography. MRI, in particular, is more useful than x-ray CT for detection of apical hypertrophic cardiomyopathy because of the greater freedom of the cross-section (31–33). UFCT, on the other hand, has a temporal resolution of less than 50 msec and produces clearer images than conventional x-ray CT (34–36). UFCT and MRI provide morphological information of the hypertrophic myocardium in its entirety, but they also allow detailed evaluation of myocardial tissue characterization by use of contrast media.

In patients with myocardial infarction, early defect and late enhancement have been reported by UFCT after administration of an iodine contrast medium (37). Also, Saito et al. (38) noted late enhancement in 21 of 48 (44%) segments in HCM patients. The myocardial wall was clearly thinned in patients who show late enhancement when compared to those who did not. They suggested that late enhancement reflects an abnormal myocardial architecture. In experimental canine myocardial infarction, late enhancement is known to correspond to myocardial vascularization and fibrotic scarring (39) which could not be detected clinically with conventional x-ray CT in beating hearts because of poor spatial and temporal resolution. UFCT may allow differential representation of myocardial tissue characterization not only in patients with myocardial infarction but also in those with HCM based on late enhancement, which may be caused by myocardial vascularization and fibrosis. Figure 3 shows a patient with HCM in whom late enhancement was observed by UFCT.

With ECG-gated MRI, the myocardial wall can be clearly visualized without contrast medium. In addition, high signal intensity in hypertrophic myocardium was observed in 12 of 32 (38%) patients with HCM and 5 of 30 (17%) patients with hypertensive heart disease, especially in T2-weighted images without contrast medium (40). This probably reflects changes in myocardial condition such as fibrosis. By using MRI contrast medium (Gd-DTPA) (41), marked contrast enhancement was observed 1–2 wk after

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**FIGURE 1.** Exercise thallium myocardial SPECT. Transient perfusion defect was demonstrated at anteroseptal wall in a patient with HCM. Ex = exercise and RD = redistribution.

**FIGURE 2.** Rest thallium myocardial imaging with familial HCM. Dilatation of the cardiac cavity was more remarkable in the elder sister than the younger, but both show bizarre myocardial scintigrams with myocardial hypertrophy and perfusion defects.
the onset of myocardial infarction (42). This contrast enhancement is considered to be due to abnormal washin and washout of Gd-DTPA and its retention in infarct areas, which leads to marked T1 shortening (43, 44). In the hypertrophied heart, marked contrast enhancement is also obtained with Gd-DTPA, primarily in the most hypertrophic myocardium. We observed the appearance of high-signal intensity areas in T1-weighted images after administration of Gd-DTPA in 10 of 16 (68%) HCM patients (45). Although the cause of this contrast enhancement is still not clear, it may be explained by differences in washin and washout of the contrast medium between hypertrophic and normal myocardium due to subendocardial ischemia, impaired coronary microcirculation and myocardial fibrosis, which together cause marked T1 shortening. Contrast enhancement was seen more often in patients with remarkable septal thickening. Figure 4 shows a patient with HCM in whom marked contrast enhancement was observed in the hypertrophied area with use of Gd-DTPA.

IODINE-123-MIBG MYOCARDIAL SPECT

Iodine-123-MIBG (metaiodobenzylguanidine) is an analogue of guanethidine and is known to show behavior similar to norepinephrine. This agent is taken up by myocardial sympathetic nerve terminals by the uptake-1 mechanism (46–49). In animal experiments and clinical applications, defects in 123I-MIBG SPECT in the acute phase of myocardial infarction are wider than in thallium SPECT, but similar size in the chronic phase, due to sympathetic denervation and reinnervation (50–53). The difference in 123I-MIBG and thallium defects is considered to represent denervated but viable myocardium in the acutely infarcted myocardium. In patients with DCM, the myocardium-to-mediastinum uptake ratio of 123I-MIBG predicted the onset of heart failure more accurately than LVEF in a large series of patients (54–55). In HCM, sympathetic nerve function can also be evaluated with 123I-MIBG on the basis of the degree of cardiac hypertrophy and catecholamine metabolism (56–59).

In a Japanese multi-institution study of 123I-MIBG SPECT in patients with HCM, the presence of lesions and regional changes in clearance on delayed images were reported (56). Nakajima et al. (57) performed 123I-MIBG myocardial SPECT in 29 HCM patients and observed a significant correlation between MIBG uptake rate per unit of blood flow and myocardial wall thickness determined in echocardiograms (r = −0.535). This tendency was notable in septal hypertrophy (IVS > 20 mm). MIBG clearance was markedly increased to 13.4% ± 8% when IVS thickness was greater than 20 mm. In contrast, clearance was 3.2% ± 4.7% when it was less than 20 mm. This increase in MIBG clearance may correspond to an increase in MIBG loss, or a decrease in its uptake by vesicles on delayed images, and is closely related to damage of the sympathetic nervous system in HCM (57–58). Myocardial SPECT imaging of neurotransmitters and their receptors may provide useful information not only in heart failure but also in cardiac hypertrophy in the near future.

INDIUM-111-ANTIMYOSIN FAB MYOCARDIAL SPECT

Indium-111-antimyosin Fab accumulates specifically at sites of myocardial necrosis. Imaging of myocardial necrosis with this radiopharmaceutical is useful for detecting the location and extent of acute myocardial infarction (60–62). Dual-isotope SPECT imaging with 111In-antimyosin Fab and thallium demonstrates the overlap of the two isotopes (both thallium and antimyosin positive) in some cases, thus allowing diagnosis of myocardium in which necrosis and ischemia are mixed (63, 64). Indium-111-antimyosin Fab myocardial SPECT has been applied to the diagnosis of acute myocarditis and rejection after heart transplantation (65, 66). Antimyosin localization provides diagnostic information different from myocardial biopsy, the technique usually employed to evaluate the severity of cardiac rejection (67, 68). Marked uptake of 111In-antimyosin Fab was observed in 8 of 10 (80%) patients with marked asymmetric hypertrophy in a Japanese multicenter trial of HCM patients (69). Moreover, we observed marked myocardial uptake of 111In-antimyosin Fab in all seven (100%) patients in the dilated phase of HCM, a transitional condition from HCM to DCM (70). Active myocardial damage may be
The washout of fatty acids, which accounts for 60%–70% of myocardial energy metabolism under anaerobic conditions, is inhibited. Therefore, in consideration of routine examinations primarily dependent on SPECT, radioiodinated free fatty acids are suitable for imaging myocardial metabolism.

There are straight-chain and branched-chain iodinated free fatty acids. The former include 123I-hexadecanoic acid (IHA) and 125I-iodophenyl pentadecanoic acid (IPPA). The washout of IHA is reported not to be different between HCM and normal subjects (72). The behavior of IPPA appears to reflect beta oxidation similar to that of 11C-palmitate, but it is not suitable for myocardial SPECT because of its rapid clearance from the myocardium (73). Iodine-123-methyliodophenyl pentadecanoic acid (BMIPP) is a branched-chain fatty acid in which a methyl group is attached to the three position. The methyl group in the 3 position precludes beta oxidation, which results in prolonged retention in the myocardium (74). In 40-wk-old spontaneously hypertensive rats, dual-isotope autoradiography using 125I-BMIPP and thallium revealed that fatty acid uptake was reduced before the occurrence of abnormalities in myocardial blood flow distribution (Fig. 6). In some cardiomyopathies, myocardial metabolism is impaired earlier than myocardial blood flow because ATP production is reduced by damage of myocardial cell membranes and mitochondrial dysfunction (75).

Recently, a Phase III clinical trial of 123I-BMIPP was completed in Japan. Interestingly, defects were observed in 56 of 70 (80%) patients with HCM in this trial (76). Kurata et al. performed 123I-BMIPP and thallium myocardial SPECT in 17 HCM patients and observed that uptake of 123I-BMIPP was markedly reduced in 10 patients who showed severe asymmetric hypertrophy and that subendocardial lesions were more extensive in 123I-BMIPP images than with thallium SPECT (77). Moreover, 123I-BMIPP uptake was reduced at sites that corresponded to hypertrophied areas where thallium uptake was increased. Iodine-123-BMIPP washout was accelerated on delayed images, and, for this reason, appeared further reduced (78). Figure 7 shows 123I-BMIPP and thallium myocardial SPECT images in HCM. With 123I-BMIPP myocardial SPECT, marked reductions in fatty acid utilization are observed at sites of myocardial hypertrophy. Also, segmental analysis in 16 HCM patients revealed reduction in BMIPP uptake in 51% of those who showed increases in thallium uptake and 20% of those who showed normal thallium uptake. This demonstrates abnormal fatty acid metabolism not only in hypertrophied areas but also in nonhypertrophied areas. Furthermore, because a close correlation was observed between 123I-BMIPP uptake and LVEF, 123I-BMIPP myocardial SPECT was useful in evaluating the severity of HCM. Thus, 123I-BMIPP uptake may be useful for the diagnosis of HCM as well as ischemic heart disease (79–82).

**FLUORINE-18-FDG AND 11C-PALMITATE MYOCARDIAL PET**

Evaluation of hypertrophic myocardium with myocardial PET using 18F-FDG and 11C-palmitate has not been
studied to the same degree as myocardial ischemia or infarction. Thus, the results are not consistent (77). Grover-Mckay et al. (83) conducted PET studies using \(^{18}\)F-FDG, \(^{12}\)NH\(_3\) and \(^{11}\)C-palmitate in 10 symptomatic HCM patients to examine myocardial ischemia in hypertrophic myocardium. They indicated that uptake of \(^{18}\)F-FDG was reduced in patients with moderate or severe asymmetric hypertrophy (mean IVS-to-LVPW ratio = 1.84 ± 0.4) when compared with those of \(^{11}\)C-palmitate or \(^{12}\)NH\(_3\). On the other hand, Kagaya et al. (84) studied \(^{18}\)F-FDG uptake in hypertrophic myocardium in 16 HCM patients and indicated that myocardial hypertrophy was severer in younger patients (40 yr old or less) and that \(^{18}\)F-FDG uptake by hypertrophic myocardium was inhomogenous in these patients by calculating inter-regional coefficients of variance of \(^{18}\)F-FDG uptake. We also performed \(^{18}\)F-FDG myocardial PET twice during fasting and after glucose loading in comparison to results from thallium myocardial SPECT. Fluorine-18-FDG uptake is increased not only in the hypertrophic but also in the nonhypertrophic area of HCM when compared with normal controls. Fluorine-18-FDG uptake shows a broad spectrum related to the severity of HCM (85). Thus, the uptake of \(^{18}\)F-FDG varies with severity of myocardial hypertrophy associated with fibrosis and necrosis. Figure 8 shows a \(^{18}\)F-FDG myocardial PET image of an HCM patient. The uptake of \(^{18}\)F-FDG was slightly increased in the hypertrophic area during fasting but was mild under glucose loading, which suggests a slight metabolic abnormality in the septal wall. On the other hand, \(^{18}\)F-FDG uptake in the lateral wall was impaired during glucose loading and myocardial damage was suspected when compared to the septal wall. With thallium myocardial SPECT, normal thallium uptake was observed at the site of septal hypertrophy, but perfusion at the lateral wall was reduced.

Carbon-11-palmitate studies performed by Sochor et al. (86) demonstrated inhomogenous uptake by hypertrophic myocardium and delayed clearance from the myocardium in a small number of patients. Grover-Mckay et al. observed that myocardial blood flow evaluated by \(^{12}\)NH\(_3\) and fatty acid uptake evaluated by \(^{11}\)C-palmitate were both reduced in hypertrophic myocardium (83). They indicated that fatty acid metabolism in such hypertrophic myocardium is thought to represent changes secondary to fibrosis rather than functional abnormalities. Therefore, further evaluation is needed to determine the clinical significance of abnormalities in myocardial energy metabolism in comparison with regional myocardial contraction and oxygen metabolism (\(^{11}\)C-acetate).

CONCLUSIONS

Table 1 summarizes the incidence of abnormalities in myocardial hypertrophy observed with various imaging modalities. The hypertrophic myocardium is shown to have a wide variety of pathologic conditions in myocardial blood flow, metabolism, necrosis and morphometry. Imaging of myocardial metabolism is still in the research phase, but it is expected to contribute to our understanding of the pathophysiology of hypertrophic myocardium.

![Figure 7](image7.png)  
**Figure 7.** Iodine-123-BMIPP and thallium myocardial SPECT. Iodine-123-BMIPP uptake was reduced in hypertrophic myocardium, but thallium perfusion was increased in this patient with HCM. In addition, \(^{201}\)TI-BMIPP uptake was further reduced on delayed images due to accelerated BMIPP washout from hypertrophied area.

![Figure 8](image8.png)  
**Figure 8.** Fluorine-FDG myocardial PET. Fluorine-18-FDG uptake in the septal wall was slightly increased during the fasting state but was mild under glucose loading. On the other hand, it was impaired during glucose loading in the lateral wall in this patient with HCM. With thallium myocardial SPECT, thallium uptake was observed at the site of septal hypertrophy, but myocardial perfusion of the lateral wall was reduced.
TABLE 1

Incidence of Abnormal Findings in Myocardial Hypertrophy

<table>
<thead>
<tr>
<th>Modality</th>
<th>Abnormal findings</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thallium (exercise/dipyridamole)</td>
<td>Transient defect</td>
<td>50%–80%</td>
</tr>
<tr>
<td>X-ray-CT (kodinated contrast media)</td>
<td>Late enhancement</td>
<td>40%</td>
</tr>
<tr>
<td>Gated MR (Gd-DTPA)</td>
<td>Contrast enhancement</td>
<td>60%</td>
</tr>
<tr>
<td>123I-MIBG</td>
<td>Hyper-washout</td>
<td>80%</td>
</tr>
<tr>
<td>111In-antimyosin Fab</td>
<td>Persistent uptake</td>
<td>80%</td>
</tr>
<tr>
<td>123I-EMIPP</td>
<td>Decreased uptake</td>
<td>?</td>
</tr>
<tr>
<td>18F-FDG</td>
<td>Decreased uptake</td>
<td>?</td>
</tr>
<tr>
<td>11C-painitrate</td>
<td>Decreased uptake</td>
<td>?</td>
</tr>
</tbody>
</table>

? = unclear due to small number.

REFERENCES


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