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Effect of regional myocardial perfusion abnormalities on regional myocardial early diastolic function in patients with hypertrophic cardiomyopathy

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Summary. Nonuniform hypertrophy of the left ventricle is an important factor in regional diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM). However, the effect of myocardial perfusion abnormalities on regional diastolic dysfunction has not been established in patients with HCM. We investigated the relationship between regional myocardial perfusion abnormalities and regional early diastolic function in 31 patients with HCM and 8 control patients. Short-axis images of the left ventricle recorded by cine magnetic resonance imaging were divided into ten blocks. The time-to-peak-wall-thickness-thinning rate (TPWR) and the wall thickness were measured in each block. Of the 310 blocks from the patients with HCM, 242 (78%) showed normal thallium-201 uptake (group 1), 40 (13%) showed slightly decreased uptake (group 2), and 28 (9%) showed markedly decreased uptake (group 3). There was no difference in the regional wall thickness among the three groups. The TPWR was longer in patients with HCM than in control patients. It was significantly longer in group 3 (190 ± 45 ms) than in group 1 (167 ± 36 ms) and group 2 (160 ± 31 ms). ($P < 0.01$). The linear regression slope of the relationship between the TPWR and the regional wall thickness was significantly steeper in group 3 than in groups 1 and 2 ($P < 0.05$). In conclusion, abnormalities in regional myocardial perfusion, in addition to regional hypertrophy, contributed to the regional early diastolic dysfunction in patients with HCM.

Key words: Hypertrophic cardiomyopathy—Myocardial perfusion abnormality—Early diastolic function—Magnetic resonance imaging

Introduction

Nonuniformity of regional left ventricular diastolic dysfunction, as well as global left ventricular diastolic dysfunction, are characteristic of patients with hypertrophic cardiomyopathy (HCM) [1–5]. The degree of regional left ventricular hypertrophy is important in the nonuniformity of regional diastolic dysfunction in patients with HCM [6–8]. Echocardiogrpahic assessment of regional left ventricular wall motion has been used to assess the relationship between regional left ventricular hypertrophy and regional diastolic function [6, 7]. However, this relationship between regional diastolic function and regional hypertrophy has been determined only for the basal septum and the basal posterior wall of the left ventricle in patients with HCM, since regional left ventricular wall motion at every site of the left ventricle cannot be measured precisely by echocardiography [6, 7]. Cine magnetic resonance imaging (MRI) with high spatial resolution can be used to analyze global and regional systolic and early diastolic function [8–11] because it clearly delineates the endocardial and epicardial margins of the entire left ventricle.

Regional myocardial fibrosis and myocardial ischemia contribute to regional ventricular dysfunction in patients with myocardial infarction [12–14]. Myocardial fibrosis and myocardial perfusion abnormalities, in addition to regional myocardial hypertrophy, are also characteristic morphological findings in patients with HCM [2, 3]. However, the effects of myocardial fibrosis and myocardial perfusion abnormalities on regional

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diastolic dysfunction have not been clarified. We therefore evaluated the relationship between regional myocardial perfusion abnormalities, detected by thallium-201 myocardial scintigraphy, and regional left ventricular early diastolic function, assessed by cine MRI.

Methods

Subjects

We studied 31 patients with HCM (23 men and 8 women; mean age, 54 ± 12 years; range, 24–70 years). The diagnosis of HCM was based on echocardiographic evidence of focal or diffuse hypertrophied (maximal wall thickness ≥15 mm), nondilated left ventricle, without an identifiable cause. Left ventricular ejection fraction in patients with HCM ranged from 55% to 86% (mean, 74 ± 10%) by M-mode echocardiography. Twenty-three of the 31 patients (74%) had asymmetrical septal hypertrophy (septal-to-free wall ratio >1.3). None of the 31 patients with HCM had an intraventricular pressure gradient above 30 mmHg, as determined by cardiac catheterization or echocardiography. All patients were in normal sinus rhythm, and had no associated cardiac, coronary, or pulmonary disease, including atrioventricular block and left bundle-branch block. Symptoms included dyspnea in 11 patients, chest pain in 7 patients, and syncope and/or palpitations in 6 patients. Drug treatment included calcium-channel blockers in 12 patients, beta-blockers in 16 patients, and amiodarone in 3 patients. We discontinued the cardiac medication in all patients, 24 h before the study, to exclude the major effect of the medication and in consideration of the their safety.

The age-matched control group consisted of eight patients (six men and two women; mean age 53 years; range, 29–72 years) who underwent echocardiography and cardiac catheterization to evaluate atypical chest pain. Their echocardiographic and catheterization findings were normal.

Cine MRI

Cine MRI was performed using a gradient echo sequence (repetition time, 50 ms; echo time, 12 ms; flip angle, 30°) at a magnetic field strength of 1.5 Tesla (Magnetom H15; Siemens AG, Erlangen, Germany). Images with a 192 × 256 pixel size were obtained with the use of four signal averages. First, we obtained an image of the left ventricle in the frontal plane (Fig. 1a). In this plane, the horizontal long-axis plane was obtained from the line extending from the point of the apex to the midpoint of the base (Fig. 1b). The vertical long-axis plane was then defined from the line extending from the point of the apex to the midpoint of the mitral valve (Fig. 1c). Finally, short-axis images were oriented perpendicular to the vertical long-axis plane. Electrocardiogram-triggered images were acquired in these true short-axis planes at the basal and apical sides of the heart. We obtained 15–18 cine MRI frames per cardiac cycle, depending on the heart rate. Cine MRI images were analyzed, independently, by two observers, as previously described [8], and the mean values were used for analysis. The endocardium and epicardium of the left ventricle in the frame images for one cardiac cycle were digitized and input into an image-analyzer computer (Mipron; Kontron Elektronik, München, Germany). The images for one cardiac cycle were superimposed by the center-of-gravity method. The

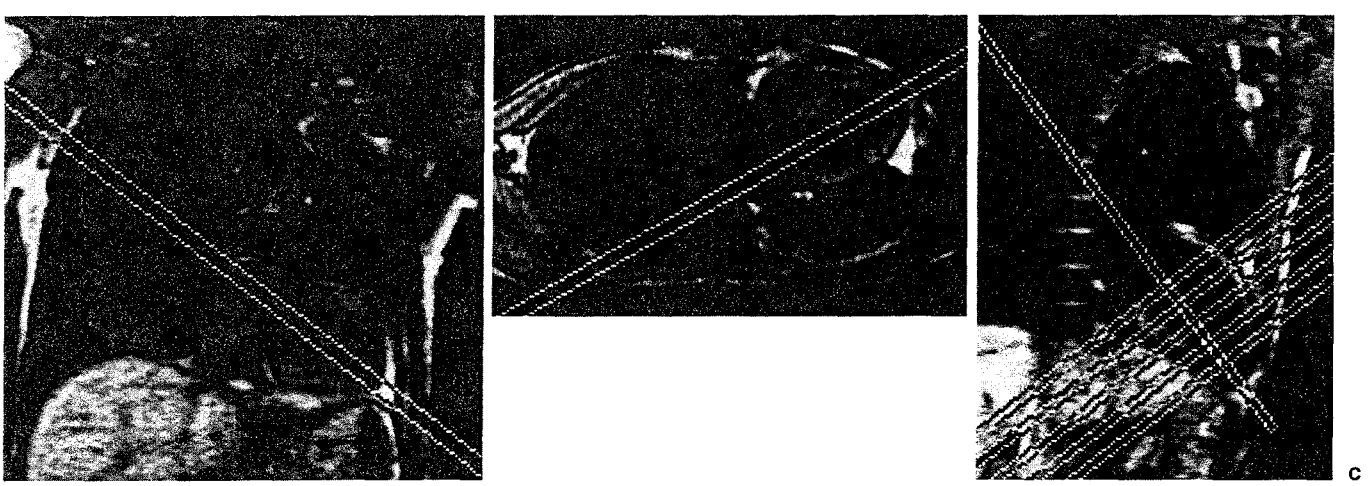

Fig. 1a–c. Method for determining left ventricular short-axis image. **a** Left ventricle in the frontal plane; **b** left ventricle in the provisional four chamber plane; **c** left ventricle in the true long-axis plane

endocardium and epicardium of a single-frame image were divided into 100 segments, beginning from the anterior interventricular sulcus. The wall thickness and the radius (the distance from the center to the endocardium) were measured in each segment, and the measurements obtained in 20 segments in each of five blocks, (anterior septum, posterior septum, inferior wall, lateral wall, and anterior wall), were averaged to estimate regional function in each block. The regional wall-thickness-time curve and radius-time curve for each block were then calculated with fourth degree fast Fourier transformation; in addition, the first derivative curves were also calculated. The nadir of the radius-time curve was used to define end-systole. Two parameters were measured in each block: the end-diastolic wall thickness and the time-to-peak wall-thickness-thinning rate (TPWR), which represents the time interval between end-systole and the peak value of the first derivative curve of the wall-thickness-time curve (Fig. 2).

Thallium-201 myocardial perfusion imaging

Thallium-201 myocardial perfusion imaging was performed, using a single photon emission computed tomographic (SPECT) gamma camera (GCA-901A/HG; Toshiba, Tokyo, Japan) equipped with a low-energy general purpose collimator. Imaging was initiated within 10 min of intravenous injection of 74 MBq of thallium-201 at rest. We obtained 36 projections, using a 128 × 128 matrix for 30 s each, in a 180° arc that extended from the 45° right anterior oblique projection to the left posterior oblique projection. Each block of SPECT im-

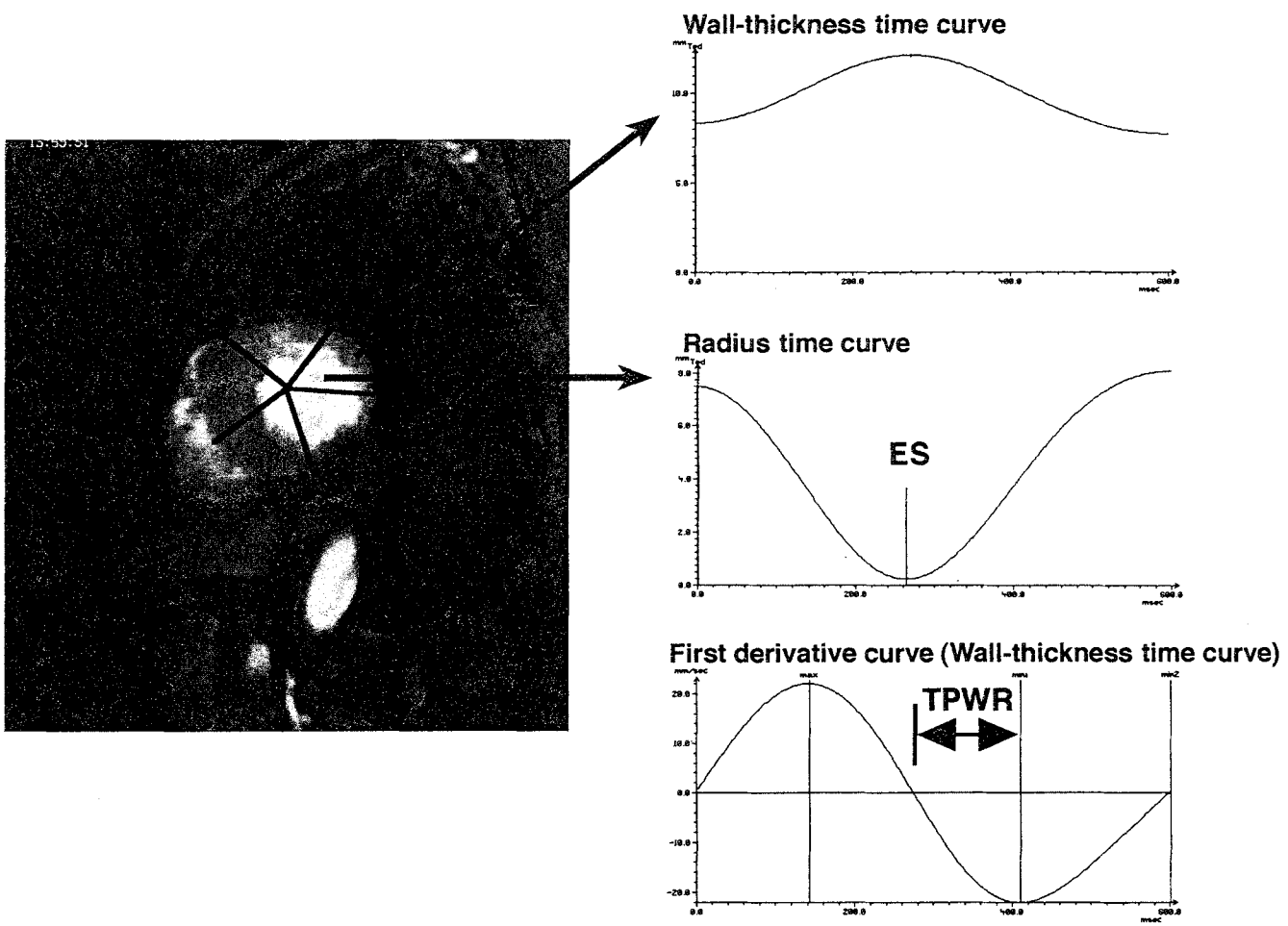

Fig. 2. *Left panel* showing basal short-axis planar image from cine magnetic resonance imaging at end-diastole in a patient with hypertrophic cardiomyopathy. He had asymmetric septal hypertrophy (septal-to-free wall ratio, 1.9). The left ventricular wall and cavity are divided into five blocks by the *black lines*. The *curves* on the *right* are, from *top to bottom*, the regional wall-thickness—time curve, the regional radius—time curve, and the first derivative curve for the regional wall-thickness—time curve for the lateral block of the image shown in the *left panel*. Time-to-peak wall-thickness-thinning rate (*TPWR*) represents the time interval between end-systole (*ES*) and the peak value in the first derivative curve for the wall-thickness time curve

ages in the basal and apical sides corresponding to cine MRI images was interpreted visually and divided into three groups by three independent observers, based on the regional myocardial thallium uptake: group 1, normal uptake; group 2, slightly decreased uptake; group 3, markedly decreased uptake. Thallium-201 SPECT and cine MRI were performed within a 2-week period.

Statistical analysis

Values are expressed as means ± SD. Differences in mean values among groups were examined by analysis of variance (ANOVA) and Scheffe's test. Linear regression analysis with the least-squares method was used to examine the relationship between regional wall thickness and TPWR, and differences in the regression slope among groups were evaluated by analysis of covariance (ANCOVA). A probability level of $P < 0.05$ was considered to be statistically significant.

Results

Hemodynamics and wall thickness

At the time of cine MRI, the heart rate did not differ between the control group and the patients with HCM (control, 63 ± 10 bpm; HCM, 60 ± 8 bpm), nor did the blood pressure (control, 125 ± 14/74 ± 9 mmHg; HCM, 123 ± 16/72 ± 9 mmHg). At the time of thallium-201 myocardial imaging, the heart rate and blood pressure values in patients with HCM did not differ when compared to the values obtained at the time of cine MRI (heart rate, 63 ± 7 bpm; blood pressure, 121 ± 16/71 ± 12 mmHg). The maximal wall thickness in the HCM group ranged from 16 to 34 mm (mean, 24 ± 6 mm) and was significantly greater in the HCM group than in the control group (10 ± 1 mm) ($P < 0.0001$). The regional wall thickness in all blocks was significantly greater in HCM patients than in the control group (control group, 8 ± 1 mm; group 1, 16 ± 6 mm; group 2, 15 ± 5 mm; group 3, 14 ± 5 mm) ($P < 0.0001$). However, there was no difference in the regional wall thickness among the HCM groups (Fig. 3).

Thallium-201 myocardial perfusion images

Based on thallium-201 SPECT myocardial images, 242 (78%) of the 310 blocks from the 31 patients with HCM were classified as group 1, 40 (13%) as group 2, and 28 (9%) as group 3. Six of the 31 patients (19%) exhibited a markedly decreased uptake.

Early diastolic function

The TPWR was significantly shorter in the control group than in the HCM groups (control group, 142 ± 19 ms; group 1, 167 ± 36 ms; group 2, 160 ± 31 ms; group 3, 190 ± 45 ms; control versus group 1 and group 3, $P < 0.0001$; control versus group 2, $P < 0.05$) (Fig. 4). The TPWR was significantly longer in group 3 than in

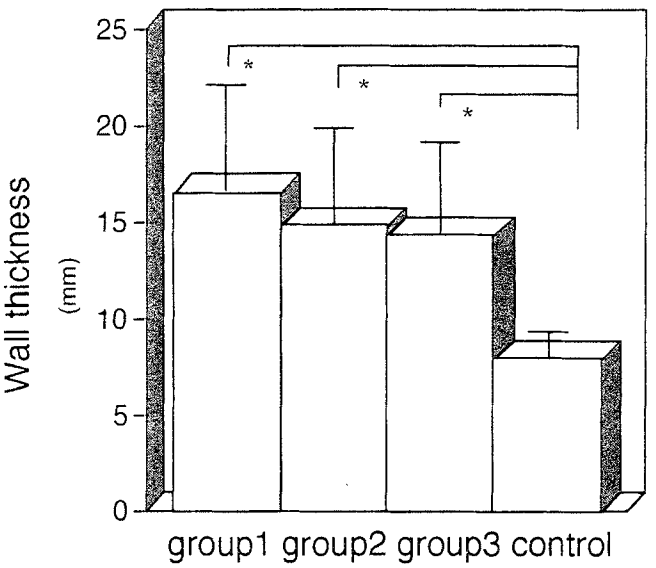

Fig. 3. Regional end-diastolic wall thickness in three groups with hypertrophic cardiomyopathy and the control group. *Group 1*, Normal thallium uptake; *group 2*, slightly decreased thallium uptake; *group 3*, markedly decreased thallium uptake. *$P < 0.0001$

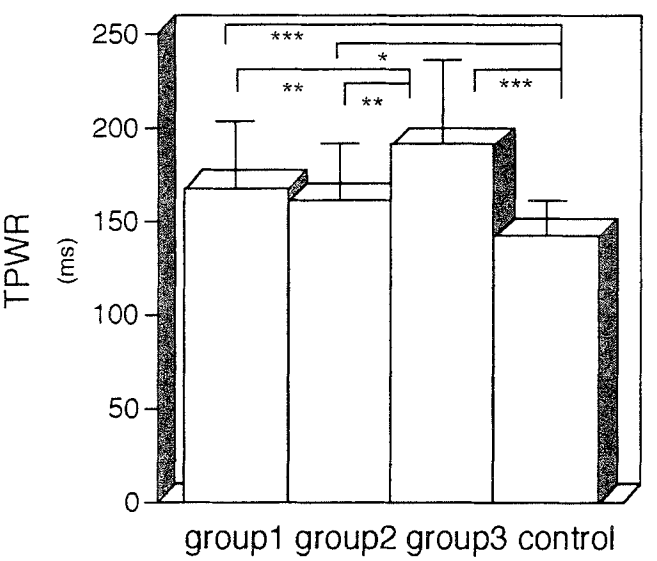

Fig. 4. Regional time-to-peak wall-thickness-thinning rate (*TPWR*) in three groups with hypertrophic cardiomyopathy and the control group. *Group 1*, Normal thallium uptake; *group 2*, slightly decreased thallium uptake; *group 3*, markedly decreased thallium uptake. *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$

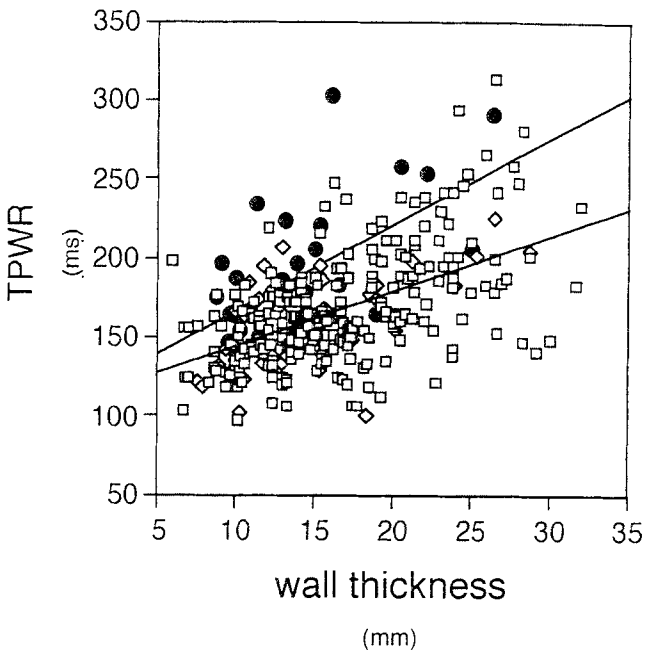

Fig. 5. Plots showing the relationship between regional wall thickness (WT) and time-to-peak wall-thickness-thinning rate (*TPWR*) in groups 1 (*squares*), 2 (*diamonds*), and 3 (*dots*). There are significant linear correlations among the three groups; the linear regression slope was significantly steeper in group 3 than in groups 1 and 2 ($P < 0.05$). Group 1, WT = 3.5 × TPWR + 110; $r = 0.53$; $P < 0.0001$. Group 2, WT = 3.5 × TPWR + 109; $r = 0.58$; $P = 0.0001$. Group 3, WT = 5.5 × TPWR + 112; $r = 0.58$; $P = 0.013$

groups 1 and 2 ($P < 0.01$). The TPWR showed a significant linear correlation with the regional wall thickness in all three groups. The linear regression slope was significantly steeper in group 3 than in groups 1 and 2 ($P < 0.05$) (Fig. 5).

Discussion

There was no variation in the regional wall thickness, regardless of the degree of thallium-201 uptake, among patients with HCM. The TPWR was significantly longer in patients with HCM than in the control group and was longer in patients with markedly decreased uptake than in patients with normal or slightly decreased uptake. The TPWR was linearly correlated with the regional wall thickness in patients with HCM, and the regression slope was steepest in patients with markedly decreased uptake.

Concentric ventricular hypertrophy is an important determinant of diastolic dysfunction in patients with essential hypertension and aortic stenosis [15]. Nonuniform ventricular hypetrophy and impaired diastolic function are characteristic of HCM [1–5, 16, 17]. The relationship between the degree of regional hypertrophy and regional diastolic dysfunction has been investigated with echocardiography [6, 7] and MRI [8] in patients with HCM. However, this relationship has been evaluated only in the basal interventricular septum and the basal posterior wall, which can be visualized by M-mode echocardiography, since echocardiography cannot precisely measure regional left ventricular wall motion at every site of the entire left ventricle [6, 7]. Nonuniform hypertrophy has been observed at various sites in patients with HCM [16, 17]. MRI clearly delineates the endocardial and epicardial margins of the entire left ventricle. Thus, MRI may be more useful than echocardiography for evaluation of the relationship between the regional wall thickness and diastolic function at every site of the left ventricle.

The rapid filling rate or the time-to-peak rapid filling have been used as parameters of global left ventricular early diastolic function in most previous studies [18–20]. We used the TPWR as a parameter of regional early diastolic function in the present study. Only a few previous studies on regional early diastolic function have used indices dissimilar to the TPWR, such as the rate of posterior wall diastolic thinning [7, 8]. The time-to-peak filling, which represents global early diastolic function, ranged from 180–190 ± 56–85 ms in HCM patients and from 136–160 ± 23–40 ms in normal subjects in previous studies [18–20]. As the TPWR in the present study was 160–190 ± 31–45 ms in HCM patients and 142 ± 19 ms in the control group, the range of TPWR was similar to the reported range of time-to-peak filling values. Thus, TPWR is considered to be a reliable parameter of regional early diastolic function, although it is not strictly equivalent to the time-to-peak filling.

Myocardial fibrosis, loss of myocardial contractile elements, myocardial perfusion abnormalities and changes in geometry cause early diastolic dysfunction to increase inappropriate spatial and temporal nonuniform distribution of loading and inactivation [12–14, 21–24]. Myocardial perfusion abnormalities have been detected by thallium-201 scintigraphy in patients with HCM [25–27]. Nagata et al. [27] observed marked myocardial fibrosis in patients with HCM who showed hypoperfusion or perfusion defects on thallium-201 scintigraphy. Thus, it is important to clarify the effect of myocardial perfusion abnormalities suggestive of myocardial fibrosis on the regional diastolic function. We assessed myocardial perfusion abnormalities by resting thallium-201 scintigraphy. Markedly decreased myocardial thallium uptake was considered to represent massive myocardial fibrosis, and slightly decreased uptake was considered to represent a small degree of myocardial fibrosis.

The TPWR is influenced by the rates of isovolumic relaxation and early left ventricular filling [28]. Multiple factors such as hypertrophy, asynchrony, abnormal loading, ischemia, and abnormal Ca^{2+} flux may be responsible for the isovolumic relaxation. A significant linear correlation between the TPWR and regional wall thickness in patients with HCM has been reported [8]. On the other hand, early left ventricular filling is affected not only by active relaxation but also by passive filling characteristics. Myocardial fibrosis could be responsible for the passive filling characteristics. Therefore, the TPWR can estimate the influence of hypertrophy and myocardial fibrosis on early diastolic function. Patients with HCM who exhibited a markedly decreased myocardial thallium uptake (group 3) showed a greater prolongation of the TPWR than patients with only a slightly decreased (group 2) or normal uptake (group 1). The linear regression slope of the relationship between the TPWR and regional wall thickness was significantly steeper in group 3 than in groups 1 or 2. Patients in group 3 had massive myocardial fibrosis, so passive filling characteristics, in addition to relaxation, affect the TPWR.

Regional uptake on thallium-201 myocardial perfusion imaging was evaluated relatively compared to a normal uptake site. Thus, the thallium uptake in relatively thin wall thickness without myocardial fibrosis was underestimated, because patients with HCM had heterogeneous hypertrophy. A large overlap between group 1 and group 2 in the relationship between the TPWR and wall thickness may have occurred because of the relative underestimation of the thallium uptake.

The present results suggest that the degrees of regional myocardial fibrosis and regional hypertrophy are important factors in the regional early diastolic dysfunction in patients with HCM. O'Gara et al. [25] reported that fixed or only partially reversible defects suggestive of myocardial scar and/or severe ischemia in patients with HCM occurred primarily in patients with impaired systolic performance, and that symptomatic patients with HCM had a significantly higher incidence of fixed or partially reversible defects. Thus, in addition to evaluation of systolic function and clinical symptoms, thallium-201 scintigraphy is useful for assessing regional early diastolic dysfunction.

In conclusion, regional myocardial perfusion abnormality, in additional to regional hypertrophy, contributed to regional early diastolic dysfunction in patients with HCM.

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