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ORIGINAL PAPER

Myocardial perfusion abnormality in the area of ventricular septum-free wall junction and cardiovascular events in nonobstructive hypertrophic cardiomyopathy

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Abstract Myocardial perfusion abnormality in the left ventricle is known to be prognostic in patients with hypertrophic cardiomyopathy (HCM). Magnetic resonance imaging and necropsy studies on HCM hearts revealed myocardial lesions predominating in the area of ventricular septum-free wall junction. We assessed perfusion abnormality in this area and correlated it with the prognosis of HCM patients. We performed exercise Tc-99m tetrofosmin myocardial scintigraphy in 55 patients with nonobstructive HCM. Perfusion abnormalities were semiquantified using a 5-point scoring system in small areas of anterior junctions of basal, mid, and apical short axis views in addition to a conventional 17-segment model. All patients were prospectively followed for sudden death, cardiovascular death and hospitalization for heart failure or stroke associated with atrial fibrillation. Cardiovascular events occurred in 10 patients during an average follow-up period of 5.7 years. Stress and rest scores from anterior junction, and conventional summed stress score were significantly higher in patients with cardiovascular events than without (all $P < 0.05$). Anterior junction stress score of >2 produced a sensitivity of 50% and a specificity of 98% for cardiovascular events and was an independent predictor (hazard ratio 8.33; 95% confidence interval, 1.61–43.5; $P = 0.01$), with rest scores producing similar values, which were higher than summed stress score of >8 (5.68; 1.23–26.3; $P = 0.03$). The absence of myocardial perfusion abnormality in the narrow area of anterior junction differentiated HCM patients with low-risk.

Keywords Hypertrophic cardiomyopathy · Myocardial perfusion · Scintigraphy · Area of junction · Cardiovascular events · Fibrosis

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Introduction

Patients with hypertrophic cardiomyopathy (HCM) often develop myocardial perfusion abnormalities in multiple segments of the left ventricle (LV), which has been demonstrated by stress myocardial scintigraphy in more than half of HCM patients with no epicardial coronary artery disease [1–4]. Regional myocardial perfusion abnormality as assessed by stress scintigraphy was associated with decreased survival rates in children and adult patients with HCM [3, 4]. Diffuse

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subendocardial perfusion abnormality of the LV myocardium with no coronary lesions has also been detected clinically as transient LV cavity dilation on stress myocardial scintigraphy in approximately one-third to half of HCM patients, without knowledge of its prognostic significance [1, 2, 5–7].

Midway between the base and apex of the LV, latitudinal muscle fibers in the midwall layer run circularly and continuously through the ventricular septum and LV free wall and longitudinal or oblique fibers predominate in the layers on both sides [8, 9]. Necropsy study on HCM hearts clarified that the continuity of the LV midwall circular layer was destroyed by myocardial disarray and fibrosis in and near the area of ventricular septum-free wall junctions, in particular, to a high degree in patients who died at a young age [10]. Myocardial fibrosis and the abnormality of myocardial perfusion and fatty acid metabolism have been demonstrated to occur predominantly in this area by magnetic resonance imaging [11, 12] and myocardial scintigraphy [13], respectively.

Thus we assessed LV myocardial perfusion abnormality by stress scintigraphy in HCM patients based on three different categories as to the area of interest: first, areas of ventricular septum-free wall junctions, a new category; second, conventionally defined 17 segments; third, entire subendocardium. We then correlated the results with the prognosis by comparing the score of myocardial perfusion abnormality between 2 patient groups with or without cardiovascular events.

Methods

Study population

Of the total patients visiting Department of Cardiology at Matsushita Memorial Hospital in an outpatient setting from November 2001 to December 2003, 62 patients diagnosed consecutively as having nonobstructive HCM underwent exercise myocardial scintigraphy for initial risk assessment. Diagnosis of HCM was based on echocardiographic demonstration of LV end-diastolic thickness of $\geq$15 mm and LV end-diastolic diameter of $\leq$55 mm in the absence of any cardiac or systemic disorder that could cause hypertrophy, such as severe hypertension defined as systolic blood pressure $\geq$160 mm Hg or diastolic blood pressure $\geq$100 mm Hg at examinations or aortic stenosis defined as peak jet velocity >3.0 m/s or aortic valve area <1.5 cm^2. We excluded patients having any heart disease, in addition to HCM, which is possibly associated with significant impairment of cardiac function. Accordingly, following 5 patients with HCM were excluded: 2 having persistent atrial fibrillation, 2 having moderate or severe mitral regurgitation, and 1 having coronary stenosis with a diameter reduction of $\geq$50% on angiograms. We had excluded HCM patients having LV outflow obstruction with the peak jet velocity >3.0 m/s by continuous wave Doppler method under resting conditions in the supine position because hemodynamic instability during exercise testing suggested the presence of an increased risk.

Finally, this prospective study consisted of 57 patients with nonobstructive HCM (48 men and 9 women; 27–77 years of age, mean age 56 years); 49 patients had asymmetric septal hypertrophy, 5 had apical hypertrophy, and 3 had lateral hypertrophy. There was no patient with diffuse LV hypertrophy which was sometimes difficult to distinguish from hypertensive heart diseases. New York Heart Association class was I in 39 patients, II in 12, and III in 6 at the time when the exercise myocardial scintigraphy was performed. Episodes of syncope were observed in 2 patients and ventricular tachycardia defined as a short run of 3 or more premature ventricular beats, in 3 patients. Family history of sudden cardiac death or HCM was present in the first degree relatives of 8 or 11 patients, respectively. There were 2 HCM patients having severe LV hypertrophy of >30 mm. There were no patients treated with permanent mechanical devices, e.g., pacemaker or implantable cardioverter-defibrillators. Coronary heart disease was ruled out in 15 patients on the basis of coronary angiography and 30 patients on the basis of exercise scintigraphy; coronary heart disease was not examined in 10 patients because of absence of any chest symptoms or coronary risk factors consisting of hypertension, dyslipidemia, or diabetes mellitus; the remaining 2 patients had one or more coronary risk factor but did not undergo coronary assessment. Genetic analysis was not performed in the present patients. Informed consent for this study was obtained from all patients with HCM.

Stress scintigraphy

All patients underwent maximum symptom-limited exercise testing with myocardial scintigraphy. All medications, if any, were withdrawn at least five half-lives before exercise testing. The exercise workload began with 25 W and was increased by 25 W every 2 min using an electrically operated sitting bicycle ergometer under continuous monitoring with 12-lead electrocardiogram. Blood pressure was measured using an arm-cuff sphygmomanometry every 2 min or more frequently. The exercise testing was finished at the achievement of 85% of the maximal predicted heart rate, or due to physical exhaustion, ST-segment depression $\geq$0.2 mV or elevation $\geq$0.1 mV, systolic blood pressure $\geq$200 mm Hg, or significant arrhythmias causing hemodynamic instability. Every exercise-induced displacement of the ST-segment was measured at 0.08 s after J point over 3 consecutive beats. Positive ST-segment depression was defined as horizontal or down sloping depression $\geq$0.1 mV. Abnormal blood pressure response was defined as a failure for systolic blood pressure to rise by >25 mm Hg from the resting value during the whole exercise period [6].

Tc-99m tetrofosmin of 370 or 740 MBq was injected intravenously 1 min before the termination of exercise and 4 h later. Single photon emission computed tomograms were then obtained after stress and at rest each 30 min after the injections of tracer with a digital gamma camera equipped with a low-energy, high resolution, parallel-hole collimator (Starcam 3000XC/T, General Electric Medical Systems, Milwaukee, USA). The camera was rotated 180° from the 45° right anterior oblique position to 45° left posterior oblique position. Finally, 32 images were obtained on a matrix of 64 × 64 pixels by means of 30 s of exposure for each 5.6° interval, and reconstructed using a Hanning filter without correction for attenuation or scatter.

Image interpretation

On the short-axis images at the basal, mid, and apical LV levels, we visually semiquantified myocardial perfusion after stress and at rest separately in the area of anterior junction and area of posterior junction, a new category of myocardial segments (Fig. 1), using a standard 5-point scoring system (0 = normal uptake, 1 = mild reduction in tracer uptake, 2 = moderate reduction, 3 = severe reduction, 4 = absence of detectable tracer uptake). The anterior or posterior junction is the boundary made by the LV radius through the anterior or posterior edge of the right ventricle, dividing the ventricular septum and anterior or posterior segment of the LV free wall. We defined junction segment to be located between the 2 radii each making an angle of 30° with the junction line on opposite side. Finally, anterior junction score or posterior junction score, respectively, was the total of perfusion scores of the anterior or posterior junction segment from the three short axis slices (Fig. 2). Junction difference score was calculated from the stress and rest scores.

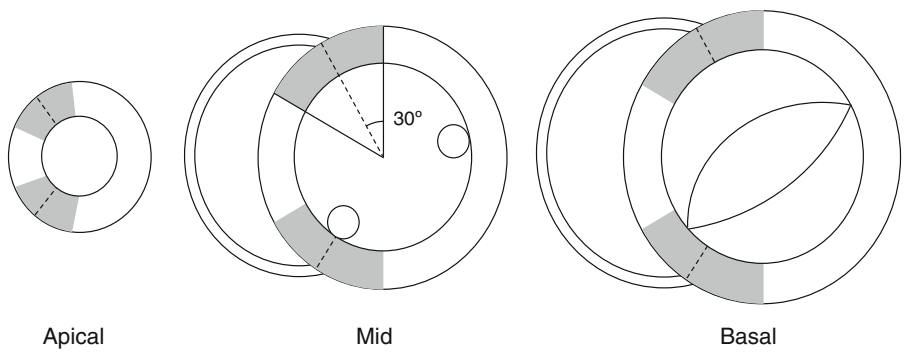

Fig. 1 Diagrams of anterior and posterior junction segments (*gray*) in 3 ventricular short axis views: apical slice, between papillary muscles and cavity ends; mid slice, at the level of papillary muscles; and basal slice, at the level of mitral valve tips. The anterior or posterior junction (*dotted line*) is the boundary made by a left ventricular radius through the anterior or posterior insertion of the right ventricle. We defined junction segment to be located between the 2 radii each making an angle of 30° with the junction line on opposite side

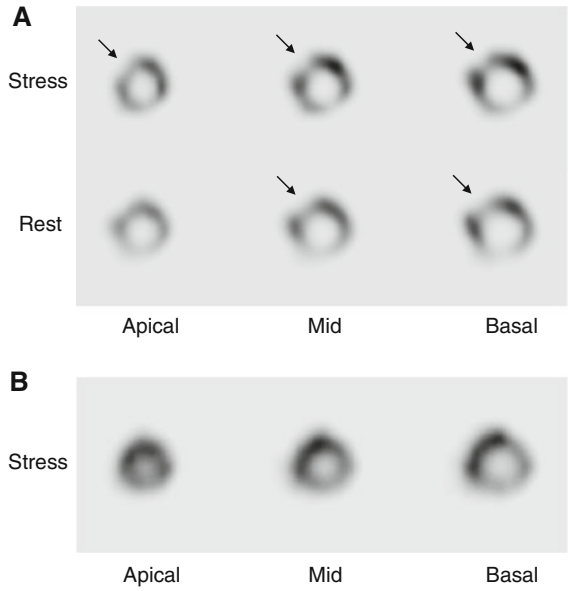

Fig. 2 **a** Short-axis stress and rest images of single photon emission computed tomograms at the apical, mid, and basal left ventricle in a 59-year-old man with anteroseptal hypertrophy. He had a history of mild hypertension but not diabetes mellitus nor dyslipidemia, and was not diagnosed as having coronary heart disease by coronary angiography. Note that accumulation of tracer is high in the ventricular septum and anterior wall with marked hypertrophy but is decreased in the area of anterior junction (*arrows*). Detection of tracer is reduced in the inferior wall probably because of partial volume effect and/or liver attenuation. Anterior junction stress score and rest score were calculated to be 4 and 3. He died of ventricular fibrillation 4.3 years after this recording. **b** Short-axis stress images in a 51-year-old man with anteroseptal hypertrophy, in the absence of a history of hypertension, diabetes mellitus, or dyslipidemia. Note high tracer accumulation in the hypertrophied regions without perfusion abnormality in the area of anterior junction; both stress score and rest score in anterior junction segment were calculated to be 0. This patient remained clinically stable over 8.0 years after this recording

Stress and rest images were also visually semi-quantified in a conventional 17-segment model of the LV, including one apex segment on vertical long-axis view and 16 segments on three short-axis views [14]. Basal and mid sections were divided into 6 segments (anterior, anteroseptal, inferoseptal, inferior, inferolateral, anterolateral) and apical section was divided into 4 segments (anterior, septal, inferior, lateral). Summed stress score and summed rest score were obtained from the 17 segments by the standard 5-point scoring system. Summed difference score was the sum of difference between stress score and rest score in each segment.

To assess diffuse subendocardial perfusion abnormality, we quantified transient LV cavity dilation using the software which we had produced previously [5, 15] and had modified certainly [7]. Briefly, the LV was divided into 15 short-axis slices and 100 radii were generated at 3.6° intervals from the center of each image. The area surrounded by the 100 points each displaying the maximum count on each radius was calculated automatically in the stress and rest images. Transient dilation index was defined as the stress to rest ratio in the sum of the 15 surface areas, and diffuse subendocardial perfusion abnormality was considered present if transient dilation index was >1.07, which cutoff point was determined on the basis of the index in control subjects who had no evidence of cardiac disease [7].

Echocardiography

All patients underwent transthoracic echocardiography with a wide-band sector transducer (SONOS 5500 and S4 probe, Philips Medical Systems, Best, The Netherlands). Conventional indexes measured were: LV end-diastolic diameter, LV fractional shortening, maximum wall thickness in the LV, left atrial end-systolic diameter, isovolumic relaxation time of the LV, the ratio of E to A wave velocity, and E wave deceleration time of the mitral valve. The average time interval from echocardiography to stress scintigraphy was 1.9 months (range 0 day to 5.6 months).

Magnetic resonance imaging

Of the 57 HCM patients enrolled and followed up, 6 patients underwent cardiac magnetic resonance after stress scintigraphy with an average time lapse of 2.1 months (range 0.1–6.0 months). All magnetic resonance images were acquired using a 1.5 Tesla imaging system (Signa HDx, General Electric Medical Systems, Milwaukee, USA). As in scintigraphic analysis above-described, three short-axis images at the basal, mid, and apical LV levels and a long-axis image of the apex segment were obtained under serial breath-holds using a 2-dimensional, spoiled, and segmented inversion recovery and gradient-echo sequence approximately 10 min after an intravenous injection of approximately 0.1 mmol/kg

gadopentatate dimeglumine (Magnevist, Schering AG, Berlin, Germany). Inversion time was selected using a standardized algorithm on the basis of myocardial, blood T1 values, heart-rate, time of imaging from contrast injection, and dose of contrast administered. The following scan parameters were employed: slice thickness 7 mm, field of view 360 mm × 360 mm, flip angle 20°, spatial resolution 1.6 mm × 2.3 mm, number of averages 2. Late gadolinium enhancement was considered present if myocardial areas with signal intensity above the average of apparently normal myocardium plus 2 standard deviations [12]. The site of late gadolinium enhancement was determined on the basis of 17-segment model of the LV [14] and in relation to the anterior and posterior junction segments as described in Fig. 1.

Follow-up

After the enrollment of patients into the present study, all semiquantitative data were visually interpreted by 2 experienced investigators blinded to patients' clinical information; disagreement in investigators were resolved by consensus. All patients were then prospectively followed for the occurrence of cardiovascular events defined as sudden death, cardiovascular death, and hospitalization due to heart failure or stroke associated with atrial fibrillation because these 3 modes of death were prevalent in patients with HCM [16]. Sudden death was a witnessed death within 1 h after the onset of symptoms or an unwitnessed death in a patient who was known to be alive and functioning normally 24 h before. The history of successfully resuscitated life-threatening arrhythmia was considered to have caused a cardiovascular death. Heart failure was the development of pulmonary edema requiring intravenous treatments (inotropic agents, vasodilators, or diuretics), mechanical ventilation, or circulatory supports. Stroke associated with atrial fibrillation was suspected when a patient had a sudden onset of neurologic symptoms persisting for ≥24 h or cerebral infarction confirmed by computed tomography and/or magnetic resonance imaging and when a patient had histories of atrial arrhythmia that may cause embolism. Patient information was obtained from available medical records and interviews with patients or their physicians.

Statistical analysis

Categorical variables were compared by Chi-square test or Fisher's exact test as appropriate. Continuous variables were expressed as mean ± standard deviation and compared using Student's *t* test. Scintigraphic variables were expressed as mean ± standard error and compared using Mann–Whitney *U* test. Spearman correlation coefficients were used to determine the correlations of scintigraphic variables. Receiver operator characteristics analysis was performed to determine optimal cutoff points. The event-free curves were compared by Kaplan–Meier analysis with the log-rank test statistic. Univariate and multivariate Cox proportional hazards regression analysis was performed to determine independent predictors of cardiovascular events. Scintigraphic variables that were associated with cardiovascular events with a P value <0.05 were further tested by univariate regression analysis, and those with a P value <0.05 on univariate analysis were included into a multivariate model. Intraobserver and interobserver reproducibility for anterior junction stress score were evaluated using mean absolute differences in the 15 HCM patients enrolled in the present study. Intraobserver variability was assessed twice by 1 investigator, and interobserver variability by 2 independent investigators. A P value <0.05 was considered statistically significant. Calculations were performed with commercially available software SPSS version 11.0 (SPSS Inc., Chicago, USA) and StatView 5.0 (SAS institute, Cary, USA).

Results

Exercise testing was performed without any complications in all HCM patients. The workload was achieved up to 85% of the maximum predicted heart rate in 39 patients with HCM but discontinued in 18 patients: 15 for physical exhaustion, 2 for systolic blood pressure ≥200 mm Hg and 1 for additional horizontal ST-segment depression ≥0.2 mV. Neither ST-segment elevation nor significant arrhythmia was observed. Of all, 23 patients showed positive ST-segment depression and 11 exhibited an abnormal blood pressure response.

Follow-up data were available in 55 patients with nonobstructive HCM except 2 who could not be

followed up. Cardiovascular events occurred in 10 patients during an average follow-up period of 5.7 years (range 0.4–7.3 years): 1 patient died suddenly, 1 died of ventricular fibrillation, and 1 died of stroke associated atrial fibrillation; 5 were hospitalized for heart failure and 2, for stroke. The 2 groups of HCM patients with or without cardiovascular events were well matched with respect to baseline characteristics and conventional echocardiographic measurements except that the patients with cardiovascular events were older and had a higher New York Heart Association functional class than those without (Table 1). The incidence of apical hypertrophy or lateral hypertrophy was similar between patients with and without cardiovascular events (10% vs. 9%, $P = 0.65$; 10% vs. 4%, $P = 0.46$). Comorbidities and medications at the time of enrollment did not differ significantly between the 2 groups: hypertension (40% vs. 29%, $P = 0.53$), dyslipidemia (60% vs. 30%, $P = 0.11$), diabetes mellitus (20% vs. 16%, $P = 0.76$); beta-blockers (30% vs. 4%, $P = 0.13$), calcium antagonists (30% vs. 22%, $P = 0.66$), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (30% vs. 18%, $P = 0.49$); none had taken amiodarone.

Anterior junction stress score (1.2 ± 0.5 vs. 0.3 ± 0.1, $P = 0.02$) and rest score (1.0 ± 0.3 vs. 0.3 ± 0.1, $P = 0.03$) but not difference score were significantly higher in patients with than in patients without cardiovascular events (Table 2). Posterior junction scores were similarly high after stress and at rest in patients with and without events. Summed stress score but not summed rest score of the 17 conventional segments was significantly higher in patients with cardiovascular events than in patients without (7.4 ± 1.7 vs. 4.4 ± 0.4, $P = 0.04$). Summed stress score was positively correlated with anterior junction stress score ($\rho = 0.43$, $P < 0.01$) and

Table 1 Baseline characteristics at the time of enrollment

	Cardiovascular events		*P*
	Present (n = 10)	Absent (n = 45)	
Age, years	63 ± 3	55 ± 11	<0.01
Men	8 (80%)	38 (84%)	0.80
Body mass index (kg/m^2)	25.2 ± 2.5	24.1 ± 2.8	0.23
NYHA functional classification			<0.01
I	4 (40%)	33 (74%)	
II	2 (20%)	10 (22%)	
III	4 (40%)	2 (4%)	
Syncope	1 (10%)	1 (2%)	0.33
Ventricular tachycardia	1 (10%)	2 (4%)	0.46
Family history of sudden death	2 (20%)	6 (13%)	0.45
Family history of HCM	1 (10%)	10 (22%)	0.35
Echocardiographic findings			
LV end-diastolic diameter (mm)	45 ± 7	46 ± 4	0.70
LV fractional shortening (%)	38 ± 6	39 ± 7	0.66
Maximum LV wall thickness (mm)	22 ± 6	19 ± 4	0.16
Left atrial diameter (mm)	40 ± 4	40 ± 6	0.84
LV isovolumic relaxation time (ms)	101 ± 24	88 ± 31	0.39
Mitral valve E/A ratio	1.0 ± 0.4	0.9 ± 0.4	0.72
Mitral valve deceleration time (ms)	253 ± 105	218 ± 60	0.39
Exercise testing			
≥85% of the maximal predicted heart rate	6 (60%)	31 (69%)	0.82
Maximum rate-pressure product	25,843 ± 5,809	27,660 ± 5,609	0.38
Positive ST-depression >0.1 mV	4 (40%)	19 (42%)	0.59
Abnormal blood pressure response	2 (20%)	9 (20%)	0.68

Data are mean ± standard deviation or number (%)

HCM hypertrophic cardiomyopathy, *LV* left ventricular, *NYHA* New York Heart Association

Table 2 Scintigraphic findings and cardiovascular events

	Cardiovascular events		*P*
	Present (n = 10)	Absent (n = 45)	
Perfusion in the area of junction			
Anterior junction stress score	1.2 ± 0.5	0.3 ± 0.1	0.02
Anterior junction rest score	1.0 ± 0.3	0.3 ± 0.1	0.03
Anterior junction difference score	0.2 ± 0.2	0.0 ± 0.1	0.25
Posterior junction stress score	1.3 ± 0.6	1.0 ± 0.2	0.78
Posterior junction rest score	1.0 ± 0.5	0.9 ± 0.2	0.57
Posterior junction difference score	0.3 ± 0.4	0.1 ± 0.2	0.62
Myocardial perfusion in conventional 17 segments			
Summed stress score	7.4 ± 1.7	4.4 ± 0.4	0.04
Summed rest score	4.7 ± 1.5	3.0 ± 0.3	0.40
Summed difference score	2.7 ± 1.1	1.4 ± 0.3	0.46
Subendocardial perfusion			
Transient dilation index	1.04 ± 0.01	1.06 ± 0.02	0.70
Incidence of diffuse subendocardial perfusion abnormality	5 (50%)	16 (36%)	0.40

Data are mean ± standard error or number (%)

anterior junction rest score ($\rho = 0.41$, $P < 0.01$). Transient dilation index or the incidence of diffuse subendocardial perfusion abnormality did not differ between patients with and without cardiovascular events.

Receiver operator characteristics curve for the detection of cardiovascular events showed that the area under the curve was larger in anterior junction stress score (0.84) and anterior junction rest score (0.85) than summed stress score (0.65) (Fig. 3). The optimal cutoff point for the detection of cardiovascular events was 2 for anterior junction stress score, 1 for anterior junction rest score, and 8 for summed stress score. These cutoff points were associated significantly with cardiovascular events on the basis of univariate analysis (Table 3). After adjustment for age, sex, and comorbidities (hypertension, dyslipidemia, and diabetes mellitus), anterior junction stress score >2 and summed stress score >8 were independent predictors of cardiovascular events (hazard ratio 8.33 and 5.68; 95% confidence interval, 1.61–43.5 and 1.23–26.3; $P = 0.01$ and $P = 0.03$) (Table 3).

Predictive values for cardiovascular events produced by anterior junction stress score >2 were: a sensitivity of 50%, a specificity of 98%, an accuracy of 89%, a positive predictive value of 83%, and a negative predictive value of 90%. Similar diagnostic values were obtained in anterior junction rest score >1: a sensitivity of 60%, a specificity of 93%, an accuracy of 87%, a positive predictive value of 67%, and a negative predictive value of 91%. Summed stress score >8 yielded a sensitivity of 40%, a specificity of 89%, an accuracy of 80%, a positive predictive value of 44%, and a negative predictive value of 87%. As shown in Fig. 4, a 5-year event-free rate in Kaplan–Meier analysis was significantly lower in patients with anterior junction stress score >2 (25% vs. 88%), anterior junction rest score >1 (40% vs. 88%), summed stress score of >8 (63% vs. 87%) but similar between patients with transient dilation index >1.07 and ≤1.07 (83% vs. 87%).

Of 57 HCM, 9 patients underwent myocardial scintigraphy twice in patients during the average follow-up period of 2.9 years (range 0.7–7.0 years); anterior junction stress score and summed stress score increased from 1.0 ± 0.4 to 2.7 ± 1.1 ($P = 0.06$) and from 5.9 ± 1.0 to 8.9 ± 3.7 ($P = 0.03$). In 3 patients with cardiovascular events, the 2 scores increased from 2.0 ± 1.0 to 5.0 ± 3.0 and from 6.3 ± 2.7 to 12.3 ± 1.3; in 6 patients without events, however, from 0.5 ± 0.2 to 1.5 ± 0.5 and from 5.7 ± 0.9 to 7.2 ± 1.2. Of the 3 patients with cardiovascular events, 1 had anterior junction stress score and summed stress score both below the cutoff point at the time of enrollment but the 2 scores increased from 1 to 2 and from 0 to 11 after 3.3 years follow-up.

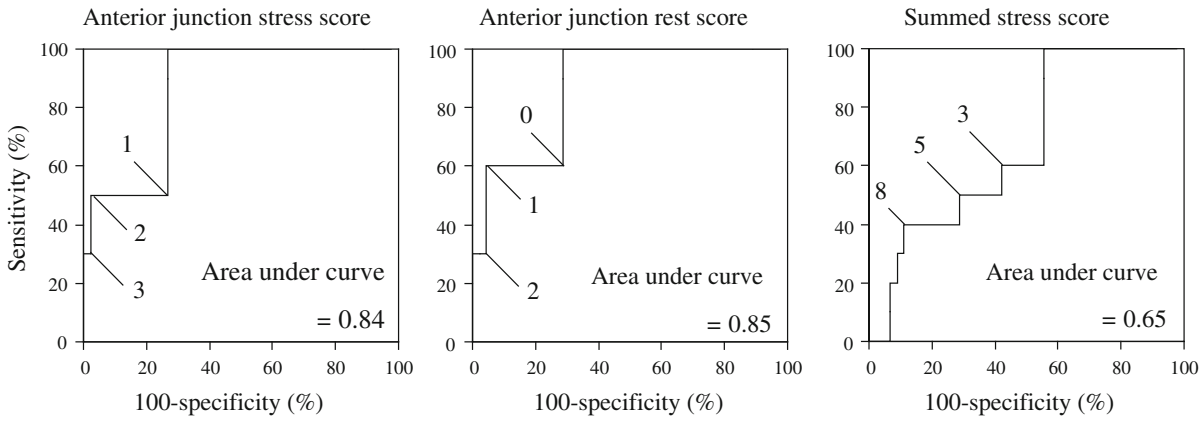

Fig. 3 Receiver operator characteristics curves for the detection of cardiovascular events showing that anterior junction stress score and anterior junction rest score are more prognostic than summed stress score

Table 3 Scintigraphic predictors of cardiovascular events

	Chi-square	Hazard ratio (95% CI)	*P*
Univariate analysis			
Anterior junction stress score >2	9.93	9.17 (2.31–35.7)	<0.01
Anterior junction rest score >1	6.79	6.13 (1.46–23.8)	<0.01
Summed stress score >8	4.29	5.12 (1.08–16.9)	0.04
Multivariate analysis[a]			
Anterior junction stress score >2	6.32	8.33 (1.61–43.5)	0.01
Summed stress score >8	4.97	5.68 (1.23–26.3)	0.03

CI confidence interval

[a] Anterior junction rest score was not tested by multivariate regression analysis because of the strong correlation with anterior junction stress score

Intraobserver and interobserver variability was small as to both anterior junction stress score (0.36 ± 0.57 and 0.18 ± 0.88) and summed stress score (0.81 ± 1.70 and 0.18 ± 1.57) in 15 HCM patients, not changing the 15 patients in their classification according to the cutoff point of either anterior junction stress score or summed stress score.

Of the 6 HCM patients undergoing stress scintigraphy and magnetic resonance imaging, 4 patients showed late gadolinium enhancement, in the anterior and posterior junction segments, and anteroseptal, anterior, inferoseptal, and inferior segments. The location of late gadolinium enhancement appeared to coincide well with that of scintigraphic perfusion defects; 3 of 4 patients had both late gadolinium enhancement and scintigraphic defects in the anterior and/or posterior junction segments.

Discussion

The present study aimed at clarifying the prognostic significance of scintigraphic myocardial perfusion abnormality in patients with HCM under 3 settings for the area of interest. Semi-quantification of scintigraphic defects focusing on a single narrow area of anterior junction both after stress and at rest produced significant prognostic values, which were more excellent than those obtained from the summation of stress scores from 17 segments conventionally organized. Stress score of anterior junction segment >2 or rest score of anterior junction >1 produced an excellent specificity for the occurrence of cardiovascular events (98 and 93%, respectively), implying that the absence of this abnormality is linked to a very low risk. On the other hand, diffuse subendocardial perfusion abnormality in the LV was similar in our patients with and without cardiovascular events although diffuse subendocardial perfusion abnormality has been reported to be associated with unfavorable hemodynamic changes, e.g., LV end-diastolic pressure elevation at rest [6] and during rapid atrial pacing [2].

Anterior junction scores after stress and at rest were significantly higher in patients with cardiovascular events than in patients without but difference score did not differ between the 2 patients groups. In general,

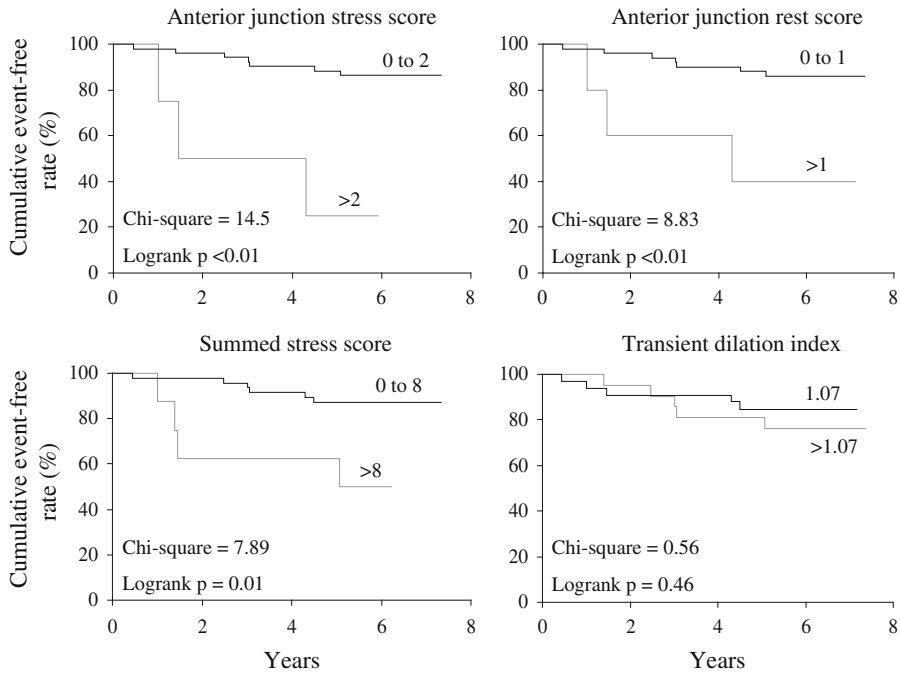

Fig. 4 Kaplan-Meier event-free rates showing that cardiovascular events are related to anterior junction stress score, anterior junction rest score, and summed stress score but not to transient dilation index

scores from the stress images represent extent and severity of myocardial perfusion abnormality reflecting myocardial fibrosis and ischemia after stress; scores from the rest images represent the extent of fibrosis; and the difference between stress score and rest score represents the extent and severity of inducible myocardial ischemia [17]. Thus, the present score of perfusion abnormality of the anterior junction segment in HCM patients with cardiovascular events was considered to be brought about, for the most part, by myocardial fibrosis. This view is supported by the previous study on the basis of magnetic resonance imaging in which myocardial scarring was predominantly located in the area of anterior junction in more than two-thirds of HCM patients [11, 12], and further by the autopsy study in which 36 of 47 HCM hearts had significant fibrosis or scar here [10].

Unlike the anterior junction score, the posterior junction score did not significantly differ between patients with and without cardiovascular events. Previous studies on HCM hearts have shown that areas of the anterior and posterior junctions were prevalently affected by myocardial fibrosis with a minimal preponderance in the area of anterior junction [10–12]. The present discrepancy between anterior and posterior junction scores may be explained by the partial volume effect [18, 19]. Tracer uptake may have been underestimated in the inferior segment that is not very hypertrophied in HCM hearts with asymmetric septal hypertrophy, thus making less conspicuous the difference in diminished perfusion of the adjacent posterior junction segment. The underestimation of tracer uptake in the inferior segment may also occur under the influence of hepatic activity to intake and accumulate the tracer, particularly in case that tetrofosmin was used [20]. Scintigraphic images obtained without attenuation correction might affect the discrepancy between anterior and posterior junction scores.

Recent prospective studies on HCM demonstrated that the presence of late gadolinium enhancement was associated with a hazard ratio of 8.6 for cardiac mortality in 220 HCM patients [21], and further that the risk of adverse events was proportional to increased amounts of fibrosis in 217 HCM patients [22] although the location of late gadolinium enhancement was not taken into account as the factor of poor prognosis in these studies. Rubinshtein et al. [23] retrospectively examined 424 patients with HCM and found that 56% of patients had late gadolinium enhancement, with its location most common in the area of junctions (73%). Furthermore, late gadolinium enhancement was observed in the area of junction in 6 of 8 patients who died suddenly or underwent

appropriate implantable cardioverter defibrillator discharges during the mean follow-up period of 43 months [23]. Similarly, our present scintigraphic assessment of perfusion abnormality focusing on the relatively narrow area of junction produced good predictive values for cardiovascular events, the location of perfusion abnormality well coinciding with that of late gadolinium enhancement.

The present myocardial perfusion abnormality in the anterior junction segment and the midwall destruction of the ventricular septum in our recent echocardiographic study on HCM [24] are considered to participate together in the destruction of the LV circular muscle layer running continuously through the midwall of the ventricular septum and LV free wall. In more than a dozen patients with HCM who were enrolled in both studies, scintigraphic perfusion abnormality in the anterior junction segment concurred almost always with a reduction of cyclic variation of integrated backscatter on ultrasonic tissue characterization (unpublished data). Late gadolinium-enhanced magnetic resonance imaging studies [11, 12] and a histologic case report with magnetic resonance [25] also clarified that the midwall layer of LV myocardium had the greatest amount of scarring which consistently involved the area of junction in HCM hearts. The importance of the unit of this muscle layer for the systolic and diastolic function of the LV has been suggested elsewhere [9, 13, 24, 26]. Previous animal studies [27, 28] suggested that these myocardial lesions destroying the continuity of the LV circular muscle layer resulted from abnormal myocardial architecture in the fetus, in which the midwall muscle layer of the ventricular septum was continuous with right ventricular free wall.

Study limitations

The present study was a single-center study and the size was not large enough to extrapolate the present result to a community-based population. We excluded HCM patients with persistent atrial fibrillation, mitral regurgitation or LV outflow obstruction. The relation of these pathophysiologic conditions to myocardial perfusion abnormality in the area of junction is obscure in HCM and their exclusion from the enrollment may have influenced its predictive value. We have not yet obtained necropsy findings in the present HCM patients to compare directly with scintigraphic score; the data should confirm our present results concerning prognosis in relation to myocardial fibrosis.

Conclusions

Myocardial perfusion abnormality was detected in the narrow area of anterior junction of ventricular septum and free walls by Tc-99m tetrofosmin scintigraphy in patients with nonobstructive HCM. Semi-quantification of the abnormality produced an excellent specificity for the occurrence of cardiovascular events; i.e., the absence of this abnormality was linked to a considerably low risk.

Conflict of interest None.

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