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Solitary Papillary Muscle Hypertrophy as a Possible Form of Hypertrophic Cardiomyopathy

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Patients can present with hypertrophied papillary muscles in the left ventricle, even without hypertrophy in other segments, and they have electrocardiographic (ECG) abnormalities suggestive of hypertrophic cardiomyopathy (HCM). This study was performed to evaluate whether the solitary papillary muscle hypertrophy was related to HCM. By analyzing 6731 echocardiographic studies between 1990 and 1994, the incidence of patients with papillary muscle hypertrophy was retrospectively examined, as well as the ECG features and family history related to HCM in these patients. After the normal size of the anterolateral and posteromedial papillary muscles was obtained from echocardiographic studies in 40 healthy subjects (0.7±0.2 cm for each of the vertical and horizontal axis), papillary muscle hypertrophy was defined as follows: either the vertical or horizontal diameter of at least one of the 2 papillary muscles was more than 1.1 cm (mean + 2SD in the normal subjects). Using this definition, 29 patients with papillary muscle hypertrophy were identified, of whom 14 (48%) showed high voltage QRS complexes, 10 (34%) showed T wave inversion, and 6 (21%) showed abnormal Q waves. Ten patients (34%) had a family history of HCM. In 2 patients that were followed for 18 and 11 years, respectively, the voltages of the QRS complexes and inverted T waves progressed with the hypertrophy of the papillary muscle. These findings suggest that solitary papillary muscle hypertrophy is related to HCM and that papillary muscle hypertrophy is a newly identified subtype of or an early form of HCM. (*Jpn Circ J* 1998; **62:** 811–816)

Key Words: Hypertrophic cardiomyopathy; Papillary muscle hypertrophy

Electrocardiographic (ECG) and echocardiographic examinations are 2 major tools for the identification of patients with hypertrophic cardiomyopathy (HCM). In almost all patients with HCM, echocardiography is more valuable not only for the diagnosis of the disease but also for the localization and the quantification of the hypertrophy when left ventricular hypertrophy (LVH) and ST-T abnormalities with or without abnormal Q waves are present on ECG. It is well known that asymmetric septal hypertrophy is the most common feature[1] but many subgroups[2] or other forms of hypertrophy, such as apical[3,4] symmetric[5,6] or reversed posterior hypertrophy[7] have been reported in the literature.

In our daily practice, we occasionally encounter patients with ECG evidence of LVH that cannot be explained even with other invasive or noninvasive examinations. We recognized that in some of these patients, the papillary muscles of the left ventricle were hypertrophied on echocardiography, but no other hypertrophic segment could be detected. We also found this papillary muscle hypertrophy in the relatives of the patients with typical HCM in a family survey using echocardiography. Therefore, this present study was performed to examine whether solitary papillary muscle hypertrophy of the left ventricle is a new subtype of or an early form of HCM.

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Methods

Echocardiography

Two-dimensional echocardiographic observations were made via the transthoracic approach in the left lateral decubitus position with a 3.75 MHz transducer using a Toshiba SSH-140A or 160A apparatus (Toshiba Medical Co, Tokyo, Japan). When the visualization via the transthoracic approach was poor, echocardiographic evaluation was performed by the transesophageal approach with a 5 MHz transesophageal echocardiographic probe (Model PEF-507SB, Toshiba Medical Co) using the same apparatus.

Definition of Papillary Muscle Hypertrophy

At present, there are no data concerning the size of the papillary muscle in normal subjects. Therefore, we determined the normal size of the papillary muscle by conducting an echocardiographic study in 40 healthy volunteers (23 males and 17 females, age range, 15–77 years) who showed normal physical and ECG findings. From the parasternal view of the transverse section of the left ventricle, where the bases of the papillary muscles were clearly visualized as circles and the muscles probably had their maximum sizes, the horizontal and vertical diameters of the anterolateral and posteromedial papillary muscles were measured at end-diastole. The horizontal diameter was measured in parallel with a line drawn between the centers of the anterolateral and posteromedial papillary muscles, and the vertical diameter perpendicularly to it (Fig 1). In the 3 patients whose left ventricles were poorly visualized on the parasternal approach, the measurements were made similarly but using the transgastric short-axis view via the

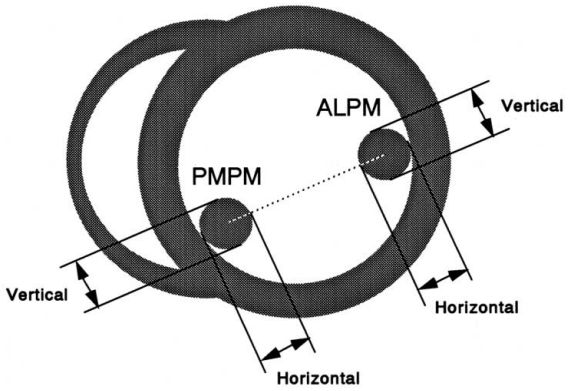

Fig 1. The schema of the left ventricle on the short-axis view. The horizontal diameter of the papillary muscle was measured in parallel with the line drawn between the center of the anterolateral and posteromedial papillary muscles (dot line); the vertical diameter was measured perpendicularly to it, at the end-diastolic phase. ALPM: anterolateral papillary muscle, PMPM: posteromedial papillary muscle.

transesophgeal approach. Papillary muscle hypertrophy was defined as measured data that exceeded 2SD above the mean value in these normal volunteers.

Study Population and ECG Definition

We examined the incidence of solitary papillary muscle hypertrophy by reviewing the reports of 6731 echocardiographic studies that had been performed from January 1990, when we identified the first patient with solitary papillary muscle hypertrophy in the left ventricle, to December 1994. Patients who had pressure or volume overload of the heart, typical features of HCM, or echocardiographic evidence of LVH (wall thickness ≥1.2 cm at any part of the left ventricle at end-diastole) had already been excluded. Among these 6731 echocardiograms, 117 had been performed in the family members of the patients with HCM for the purpose of surveying HCM and verifying papillary muscle hypertrophy.

If the duration of the Q waves was more than 0.04 sec or the depth was more than one-fourth of the height of the R wave, it was considered as abnormal[8] As the QRS voltage criteria, LVH was considered to be present when the sum of the depth of the S wave in V_1 and the height of the R wave in V_5 or V_6 was more than 3.5 mV. In patients under the age of 16 years, LVH was considered to be present when the R wave or S wave amplitudes in at least 2 leads (including V_1, V_2, V_5 or V_6) exceeded the 95% confidence limits stratified by age and sex[9] Negative T wave was defined as the depth of inversion by more than 0.1 mV in the T wave and the giant negative T wave of more than 1 mV[4]

Results

Diameter of the Papillary Muscle

The mean values of the horizontal and vertical diameters of the anterolateral and posteromedial papillary muscles obtained in the 40 normal subjects were within relatively narrow ranges (both muscles, 0.7±0.2 cm) (Table 1). Thus, papillary muscle hypertrophy was defined as at least 1 of the 2 papillary muscles being more than 1.1 cm in the horizontal or vertical diameter or in both.

Twenty-nine patients (17 males and 12 females; age range, 12–68 years) had papillary muscle hypertrophy according to the preceding definition. The mean values in each diameter of the 2 papillary muscles in the normal subjects and in the patients with papillary muscle hypertrophy are shown in Table 1. For individual patients with hypertrophy, the diameter of each papillary muscle, the ECG findings and the family history of HCM are indicated in Table 2. No significant differences between the diameters of the anterolateral and posteromedial papillary muscles were found in these patients.

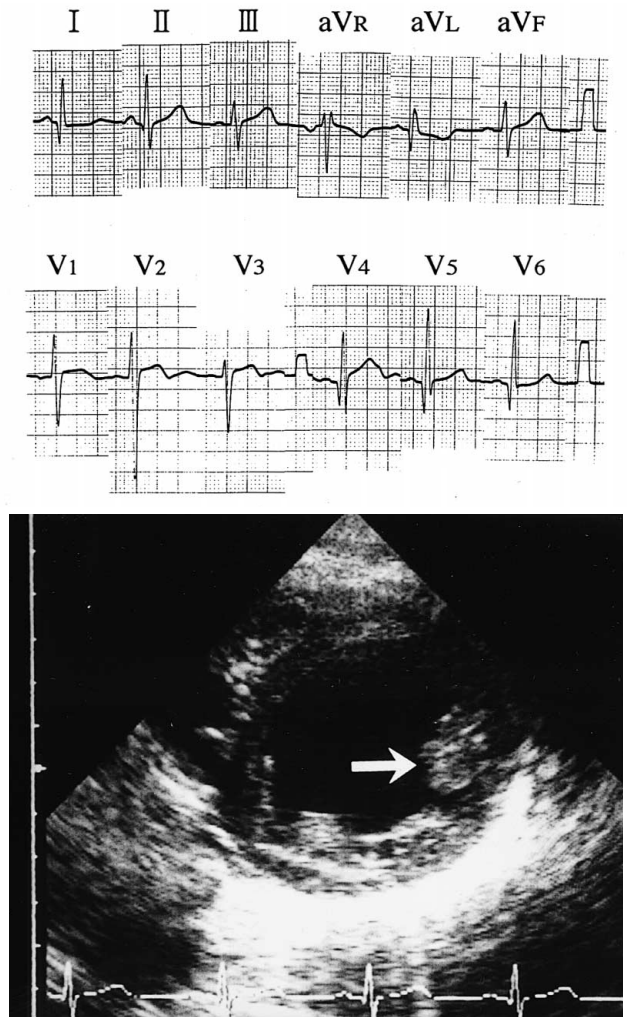

Fig 2. Electrocardiogram (A) and the echocardiogram in the transverse section of the left ventricle (B) in a representative patient with papillary muscle hypertrophy. This patient was a 12 year-old boy, who had been identified when the family members of his father, who had hypertrophic cardiomyopathy, were surveyed. Left ventricular hypertrophy can be seen with an abnormal Q wave in the lateral leads. The left ventricular echocardiogram shows that the anterolateral papillary muscle (arrow) is hypertrophied (1.2×1.3 cm in diameter).

ECG Findings (Tables 2,3)

Among these 29 patients, LVH was detected using voltage criteria in 14 (48%), T wave inversion was seen in 10 (34%), abnormal Q waves in 6 (21%), and frequent premature ventricular contractions (PVC) on the routine ECG in 4 (14%), but no ECG abnormalities were seen in 6 (21%). Among the 14 patients with LVH, 8 showed hypertrophy in the anterolateral papillary muscle, 2 in the

Table 1 The Horizontal and Vertical Diameters of the Anterolateral and Posteromedial Papillary Muscles in Patients with Papillary Muscle Hypertrophy and Control Subjects

	Diameter (cm)			
	ALPM		PMPM	
	H	V	H	V
PMH	1.1±0.2	1.2±0.3	1.0±0.3	1.0±0.4
Control	0.7±0.2	0.7±0.2	0.7±0.2	0.7±0.1

ALPM, anterolateral papillary muscle; PMPM, posteromedial papillary muscle; PMH, papillary muscle hypertrophy; H, horizontal diameter; V, vertical diameter; Data expressed as mean±standard deviation.

Table 3 Electrocardiographic Findings in 29 Patients with Papillary Muscle Hypertrophy

Electrocardiographic findings		n (%)
1. LVH		14 (48%)
2. Q wave	in II, III, aV_F	2 (7%)
	in I, aV_L, $V_{5,6}$	5 (17%)
3. T wave inversion	<1mV (max in V_4, V_5 or III)	6 (21%)
	≥1mV (max in V4 or V_5)	4 (14%)
1. + 2.		4 (14%)
1. + 3.		7 (24%)
2. + 3.		4 (14%)
1. + 2. + 3.		3 (10%)

LVH, left ventricular hypertrophy.

Table 2 The Diameters of the Papillary Muscles, Electrocardiographic Findings and Family Histories of the 29 Patients with Papillary Muscle Hypertrophy

Patient	Age/ Gender	Diameter (cm)				Wall thickness		ECG findings (mV)			Family history of HCM†
		ALPM		PMPM				Abnormal Q	SV_1+RV_5	Negative T	
		H	V	H	V	IVS	PW				
1	61/F	0.8	0.8	1.2	1.7	0.8	0.7	+	6.1	1.0 (V4)*	–
2	16M	1.2	1.0	0.6	0.6	1.1	1.1	–	4.5	–	–
3	23/M	1.2	0.7	1.2	0.8	0.7	1.0	+	2.4	–	1/1
4	45/M	1.2	1.2	1.2	0.9	0.7	0.8	–	5.4	–	1/1
5	19/F	0.9	1.2	1.2	1.1	0.9	0.9	+	6.8	0.6 (V4)	1/3
6	12/F	1.0	1.2	1.3	0.8	0.9	0.7	–	2.0	–	1/2
7	19/F	0.7	0.7	1.2	1.0	1.0	1.0	–	2.1	–	-
8	20/F	0.8	1.2	1.2	1.0	1.0	0.7	–	2.3	–	-
9	18/M	1.2	1.0	0.9	1.1	1.1	0.9	–	4.6	–	1/2
10	52/F	1.0	1.3	0.8	1.0	0.7	0.9				2/2
11	19/M	1.2	1.1	0.6	0.6	0.8	0.8	–	5.2	–	–
12	61/F	1.2	1.1	0.5	0.5	0.8	0.8	+	4.5	0.4 (V4)	–
13	15/M	1.4	1.1	0.9	0.8	0.7	0.8	–	3.8	–	–
14	12/M	1.2	1.3	1.1	1.1	0.9	0.9	+	4.2	–	1/3
15	15/M	0.9	1.3	0.8	0.8	0.7	0.9	–	2.4	–	–
16	15/M	0.9	1.2	1.0	0.7	0.9	0.8	–	3.7	–	–
17	60/F	1.2	1.9	0.8	1.4	0.9	0.8	–	4.9	1.0 (V4)	–
18	25/F	0.7	1.0	1.2	1.1	0.6	0.8	–	1.4	–	1/2
19	38/M	1.4	1.0	0.6	0.6	0.8	0.8	–	2.6	–	–
20	25/M	1.2	1.2	1.2	1.6	0.8	1.1	–	5.4	–	–
21	68/F	0.8	1.3	0.9	0.9	1.0	1.0	–	1.5	0.9 (V4)	–
22	19/F	0.9	1.2	0.5	0.5	0.9	1.0	–	1.9	–	–
23	57/M	1.0	1.0	1.4	1.3	1.0	1.0	–	1.2	0.3 (V4)	–
24	19/M	1.2	1.3	1.4	0.9	1.1	1.1	–	2.3	–	–
25	57/F	1.2	1.7	0.7	0.9	1.1	1.1	–	6.8	0.5 (V5)	0/3
26	18/M	1.8	1.5	0.9	0.9	0.6	0.7	–	4.8	–	–
27	52/F	0.9	1.0	1.6	1.5	1.0	0.9	–	4.1	1.1 (V5)	0/3
28	37/M	1.1	1.2	1.1	1.2	1.0	1.0	–	4.3	1.4 (V5)	1/2
29	35/M	1.4	1.3	1.6	1.9	1.0	0.9	+	2.5	0.1 (III)	1/1
	mean	1.1±0.2	1.2±0.3	1.0±0.3	1.0±0.4	0.9±0.2	0.9±0.1		3.7±1.7		
	total							6/29		10/29	10/29

**The lead in which maximum T wave inversion was seen; †Number of HCM patients / surveyed patients; (–), no family history by history taking; IVS, interventricular septum; PW, posterior wall; HCM, hypertrophic cardiomyopathy (other abbreviations as in Table 1).*

posteromedial muscle, and 4 in both. Among the 6 patients with abnormal Q waves, 2 showed hypertrophy in the anterolateral muscle, 1 in the posteromedial muscle, and 3 in both. Among the 10 patients with T wave inversion, only 4 patients showed giant negative T waves in leads V_4 or V_5. Five other patients showed small (<1.0 mV) T wave inversion in lead V_4 or V_5, and 1 in lead III. Therefore, it was suggested that ECG evidence of LVH more frequently coexisted with hypertrophy of the anterolateral papillary muscle than with that of the posteromedial muscle, although the difference was not significant. However, there was no relation between the leads showing abnormal Q wave or T wave inversion and the localization of the hypertrophy of the papillary muscles.

A Representative Case

The patient was a 12-year-old boy (Patient 14), who had been identified when the family of his father, who had HCM, were surveyed. His ECG trace revealed LVH and abnormal Q waves in the lateral leads and the anterolateral papillary muscle was hypertrophied (1.2×1.3 cm in diameter) on his left ventricular echocardiogram (Fig 2).

Follow-up Studies

Among these 29 patients, we could perform the follow up in only 9 because most of them were asymptomatic.

In a 61-year-old woman (Patient 1), who had had a good clinical course for 18 years following open mitral commissurotomy for mitral valve stenosis, the voltages of the QRS

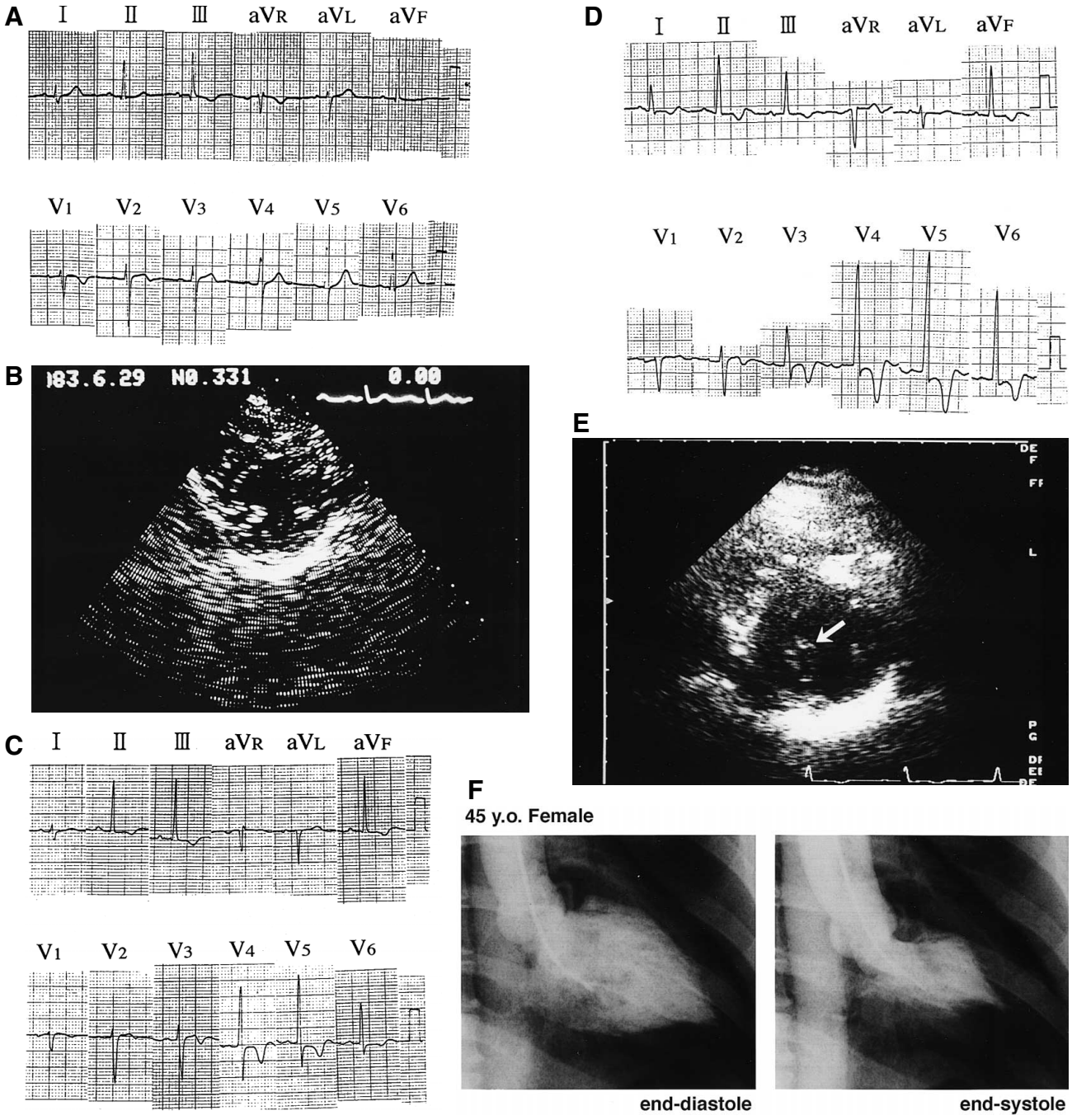

Fig 3. Electrocardiograms and echocardiograms obtained from a patient in whom their papillary muscle progressively hypertrophied during follow-up. In 1983, when the patient had consulted us for chest pain syndrome, both the electrocardiogram (A) and echocardiogram (B) were almost normal in appearance. In 1988, her electrocardiogram (C) revealed prolongation of the QRS complex and small inverted T waves when she returned with the same symptoms. Thereafter, the QRS voltage progressively increased with the appearance of giant negative T waves on electrocardiogram (D), and prominent hypertrophy of the posteromedial papillary muscle (arrow) (1.6×1.5 cm) developed in 1994 (E). Her left ventriculography was somewhat spade-like configulation in 1988 (F).

complexes and inverted T waves gradually increased in association with progressive hypertrophy of the papillary muscle.

A 52-year-old woman (patient 27), who had a normal ECG (Fig 3A) and echocardiogram (Fig 3B) on her first visit in 1983 for chest pain syndrome, showed some prolongation of the QRS duration and small T wave inversion on her ECG (Fig 3C) when she returned with similar symptoms in 1988. Furthermore, LVH with giant negative T waves had progressed on her ECG and the hypertrophy of the posteromedial papillary muscle gradually became more prominent on echocardiography during the next 6 years (Fig 3D, E). Her left ventriculography showed a somewhat spade-like configuration in 1988 (Fig 3F).

However, other 7 patients (2 were followed for 9 years and 5 for 5 years) had no clear alterations in clinical features during follow-up.

Family History (Table 2)

Among the 29 patients with papillary muscle hypertrophy, 10 (34%) had the clinical features of classical HCM in at least 1 first- to third-degree relative. Nine of these 10 patients had been identified during the echocardiographic examinations of the family members of patients with HCM (about 8% [9/117] of all family surveys). A 19-year-old female patient had been referred to us for further examination because of ECG evidence of LVH and abnormal Q waves; we found that her father had typical apical HCM.

Left Ventriculography and Histological Findings

Among the 29 patients, 5 had cardiac catheterization for elucidating the diagnosis of cardiomyopathy or coronary artery disease. However, we did not perform an invasive work-up because the remaining 24 had no clinical symptoms. The right anterior oblique view on left ventriculography indicated cavity obliteration with a negative shadow from the hypertrophied papillary muscle in end-systole but no spade-like configuration in end-diastole in 2 patients, a spade-like configuration in end-diastole in 2 and normal configuration in 1. Right ventricular endomyocardial biopsy perfomed in 4 patients showed mild hypertrophy and disarrangement of myocardial cells in 1 (Patient 25) but no histological findings suggestive of HCM in the other 3.

Reproducibility

The reproducibility in the measurement of the diameters of the papillary muscles was evaluated. The inter- and intraobserver variation of the data was quite small. The interobserver coefficients of the mean difference were 2% for the horizontal and 2.6% for the vertical diameter of the posteromedial papillary muscle and 1.4% for the horizontal and 3% for the vertical diameter of the anterolateral papillary muscle. The intraobserver coefficients of the mean difference were 2% for the horizontal and 1% for the vetrical diameter of the posteromedial papillary muscle and 1% for the horizontal and 1% for the vertical diameter of the anterolateral papillary muscle.

Discussion

Although HCM has traditionally been characterized as manifesting LVH of an unknown etiology,[10] there is considerable variability in the degree, pattern, and localization of the hypertrophy.[2] A typical morphological feature is disproportionate hypertrophy in the interventricular septum and anterolateral wall of the left ventricle.[1] However, a variant type with predominant hypertrophy in the apical segment of the left ventricle is also common in Japan.[3,4]

We identified 29 patients with solitary papillary muscle hypertrophy using our new echocardiographic definitions. Some of them had a few ECG abnormalities suggestive of HCM, and typical HCM was easily detected in their relatives. Two patients were followed up for more than 10 years under the tentative diagnosis of 'HCM without left ventricular wall hypertrophy' because of ECG evidence of LVH but no hypertrophy on echocardiography; their papillary muscles progressively became hypertrophied with the increment of the QRS voltages and T wave inversion. Therefore, our results may suggest a relation between papillary muscle hypertrophy and HCM, and that solitary papillary muscle hypertrophy is a newly identified subtype (papillary muscle hypertrophic cardiomyopathy) of or the initial stage of HCM.

As an initial case, we experienced a patient (patient 1 in Table 2), who indicated severe hypertrophy of posteromedial papillary muscle on an echocardiographic examination for a work-up of severe LVH. This patient did not reveal the progression of left ventricular wall in the apex during a follow-up study of 18 years. Furthermore, some family members in the patients with papillary muscle hypertrophy had various type of HCM: apical hypertrophy or asymmetrical septal hypertrophy. However, in these patients the electrocardiographic findings indicated by high left precordial voltage and inverted T wave were very similar to those of apical hypertrophy, but the left ventriculogram also revealed various configurations: spade shape, somewhat hypertrophied papillary muscle or normal configuration. Therefore, at present we consider that this entity is most similar to apical hypertrophy, but not simply an early stage of apical hypertrophy.

It is not clear which hypertrophied papillary muscle, the anterolateral or posteromedial, is related to the ECG changes of high voltage QRS complexes and inverted T waves. In our study, the high voltage QRS complexes seemed to be related to the hypertrophy of the anterolateral muscle, and the abnormal Q waves may be related to the hypertrophy of both muscles. Some investigators have suggested that hypertrophy of the papillary muscle, especially of the posteromedial muscle, might play an important role in the development of giant negative T waves.[11,12] In our study, 10 patients (34%) showed various T wave inversions and only 4 of them showed giant negative T waves, but the localization of the hypertrophied papillary muscles was not related to the presence of or lead location of the T wave inversion.

In the present study, 10 patients (34%) had a family history of HCM in a first- to third-degree relative. Some of them may have inherited HCM from family members more than one generation removed. It is now clear that the pattern of inheritance in HCM is autosomal dominant. However, more than 3 genes have been linked to the development of HCM[13–17] and many distinct mutations of a particular gene can cause HCM. Therefore, it is likely that there are subjects without phenotypic expression of the classic cardiac appearance even though they inherited the genotype for the disease.

At the present time, there are no data concerning the relationship between papillary muscle hypertrophy and HCM. Some investigators have noted a few cases with the diagnosis of HCM without hypertrophy at necropsy after sudden death,[18,19] but did not discuss the papillary muscle hypertrophy in their reports. Sudden death may occur in asymptomatic patients with HCM who were unaware that they had the disease. Therefore, we consider that solitary papillary muscle hypertrophy may carry clinically important implications for the screening of HCM.

Limitations

Because there are no data concerning the quantification of the papillary muscle size, we defined it by examining the size of the papillary muscles on the transverse view of the left ventricle with echocardiography. However, there is a limitation to defining papillary muscle hypertrophy only on the transverse view. Moreover, when the transverse view of the left ventricle does not reveal the maximum diameter of the papillary muscle, we may underestimate it, or conversely we may overestimate it when the papillary muscle

is oblique to the cross-section. Therefore, in further examinations we plan to consider another method of quantifying papillary muscle size, such as longitudinal, spatial or volumetric measurement.

Since 1990 when we recognized the first patient with papillary muscle hypertrophy without other hypertrophic segments in the left ventricle, we have paid attention to the papillary muscles in echocardiographic examinations. But in the family survey of HCM patients, we were particular in surveying their papillary muscles. So, there may be more of a bias in the evaluation of the papillary muscle hypertrophy in HCM families than in others.

On examining the family members of patients with papillary muscle hypertrophy, classical HCM is sometimes detected. At the present time, it has been reported that various genes are related to the genesis of hypertrophic cardiomyopathic process![3–17] Therefore, genetic evaluation is necessary to evaluate the relationship between papillary muscle hypertrophy and HCM. However, we have not performed such a study yet because at the present time it is impossible to survey all of the genes that are related to the genesis of HCM.

We could perform echocardiographic study in all 29 patients, but an invasive study was performed in only 5 because they had no clear clinical symptoms. So in most of the patients we could not elucidate the diagnosis of HCM invasively and histologically.

Conclusions

We found that patients with papillary muscle hypertrophy showed LVH on ECG with no apparent etiology; some of them had relatives with clinical features of HCM. Therefore, we consider that solitary papillary muscle hypertrophy may be a newly identified subtype of or an early form of HCM. To clarify the relation between this hypertrophy and HCM, it is necessary to follow these patients and examine the genetic disorder.

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