Familial Hypertrophic Cardiomyopathy With Triphasic Transmitral Flow Velocity

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Abstract

We describe a family in which five members had hypertrophic cardiomyopathy (HCM) with a similar distribution of left ventricular (LV) hypertrophy and LV filling pattern. All five family members had myocardial hypertrophy localized between the anterior LV wall and ventricular septum, in addition to having a triphasic transmitral flow (TMF) velocity pattern with a mid-diastolic wave. The HCM patients with this TMF velocity pattern exhibit decreased LV compliance and delayed LV relaxation, suggesting that the features of diastolic failure may be specific. Thus, these findings may provide an important clue to elucidating the relationship between the pathophysiology and mode of inheritance in patients with HCM. (J Echocardiogr 2006; 4: 37-42)

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Figure 1

Pedigree of a family showing mode of inheritance of hypertrophic cardiomyopathy. ■, hypertrophic cardiomyopathy (males); ●, hypertrophic cardiomyopathy (females); slashed symbols, dead; *, sudden death.
case 2) was diagnosed as having HCM based on the results of a family study, including routine echocardiography. In addition, the proband’s father and uncle died suddenly from unknown heart diseases. Case 1 had three children (case 3, a 23-year-old female; case 4, a 22-year-old male; and case 5, a 20-year-old female). Based on a family study performed 10 years ago, all of these children were diagnosed with HCM. The family profiles suggested that HCM in this family occurred as the result of autosomal dominant inheritance.

Table 1 shows LV wall thicknesses obtained by M-mode echocardiography, TMF velocity variables acquired by the pulsed Doppler method, and atrial systolic parameters obtained by apexcardiogram in the five patients with HCM. All the patients had no previous medication use. Clinical and echocardiographic features of these patients are described below.

**Case 1**

At the age of 42, the patient initially consulted our hospital for further examination of a heart murmur, although she did not complain of any apparent subjective symptoms. An electrocardiogram (EKG) showed sinus rhythm, and findings of LV hypertrophy accompanied by slight ST depressions in leads V5, 6 were observed. At the age of 49, the degree of LV hypertrophy had increased compared to that at initial examination, and increased ST depression and inverted T waves were observed in leads V5, 6. Furthermore, the patient experienced episodes of syncope, and a Holter electrocardiogram recording confirmed the occurrence of nonsustained ventricular tachycardia. In this patient, cardiac catheterization at the time of initial examination showed an LV end-diastolic pressure of 15 mm Hg, and the ratio of an amplitude of the atrial systolic wave to the total reflection obtained by apexcardiogram (A/H) increased from 19% at the time of initial examination to 26% at the age of 49.

Two-dimensional (2D) echocardiography demonstrated myocardial hypertrophy localized between the
anterior LV wall and ventricular septum (Figure 2, top). Because mid-diastolic waves were observed in TMF velocity patterns, the overall patterns were triphasic. However, the deceleration time of the early diastolic TMF velocity was normal, and the peak atrial systolic TMF velocity was not accentuated (Figure 2, bottom).

Case 2
The patient initially consulted our hospital at the age of 57, although no apparent findings of LV hypertrophy were detected on the EKG. However, 2D echocardiography demonstrated myocardial hypertrophy localized between the anterior LV wall and ventricular septum (Figure 3, top). Compared to case 1, this patient showed a trace mid-diastolic wave in the TMF velocity pattern, in addition to a compensatory increase in the peak atrial systolic velocities (Figure 3, bottom).

Case 3
An EKG demonstrated a trend toward right axis deviation since the initial consultation at the age of 13. However, the right axis deviation became more marked at the age of 17, although there were no findings of LV hypertrophy. In addition, the A/H on apexcardiogram was increased from 11% at the time of initial examination to 22% during the course of HCM.

Two-dimensional echocardiography at the time of initial examination demonstrated myocardial hypertrophy localized between the anterior LV wall and anterior ventricular septum, and the degree of ventricular septal hypertrophy increased gradually during the course of HCM (17 → 24 → 30 mm). Furthermore, LV hypertrophy also was observed in the posterior ventricular septum (Figure 4, top). As in cases 1 and 2, the patient showed triphasic TMF velocity patterns with mid-diastolic waves (Figure 4, bottom).

Case 4
Initial EKG at the age of 12 did not show any evidence of LV hypertrophy, and no apparent EKG changes were observed during a follow-up study. However, the patient noted palpitations starting at the age of 16, and multifocal ventricular premature beats were detected by Holter electrocardiography. The A/H on apexcardiogram increased from 12% at the time of initial examination to 20% at the age of 19. Initial 2D echocardiography acquired at age 12 demonstrated myocardial hypertrophy localized between the anterior LV wall and ventricular septum, and the degree of ventricular septal hypertrophy increased.
from 16 mm to 22 mm during the course of HCM. Moreover, the thickness of the posterior septum increased to 24 mm by the age of 16. At the age of 19, the thickness of the ventricular septum increased further to 26 mm (Figure 5, top). As in cases 1, 2, and 3, the patient showed triphasic TMF velocity patterns with mid-diastolic waves (Figure 5, bottom).

Case 5

Although the EKG showed a trend toward right axis deviation during the course of HCM, there were no findings of LV hypertrophy or arrhythmia. In addition, the A/H on apexcardiogram was increased from 17% at the time of initial examination at the age of 10 to 23% at the age of 16.

Initial 2D echocardiography at the age of 10 did not show any apparent LV hypertrophy. However, 2D echocardiography at the age of 16 demonstrated myocardial hypertrophy between the anterior LV wall and ventricular septum. The ventricular septal thickness increased from 18 mm at the age of 10 to 20 mm at the age of 18 (Figure 6, top). As in cases 1, 2, 3, and 4, the patient also showed triphasic TMF velocity patterns with mid-diastolic waves (Figure 6, bottom).

Discussion

It has been reported that HCM frequently develops within a family as the result of autosomal dominant inheritance [6]. Maron et al [1] evaluated the mode of inheritance in 70 families with HCM, and have reported that approximately 40% of familial HCM were caused by autosomal dominant inheritance. They also noted that only 22% of first-degree relatives of proband were genetically affected. Compared to nonfamilial HCM, the degree of ventricular septal hypertrophy increases rapidly during the course of familial HCM [7, 8], and the frequencies of sudden death, progression to heart failure, and cerebral thrombosis are higher in familial HCM [9, 10].

Although two elder sisters of the first patient (case 1) in this family were not investigated in detail, the 2D echocardiographic findings from her elder brother (case 2) and three children (cases 3, 4, and 5) were apparently consistent with the pathologic entity of HCM. These findings strongly suggest that HCM in this family was caused by autosomal dominant inheritance between the two generations. Furthermore, the degree of LV hypertrophy rapidly and markedly
increased over a relatively short period of time, and the father and an uncle of the first patient died suddenly from unknown heart diseases. Based on these findings, the clinical features of this family may sufficiently reflect the characteristics of familial HCM.

Family studies of HCM have demonstrated that the distribution of LV hypertrophy varies even in first-degree relatives, and only 30% of HCM patients exhibit similar patterns of LV hypertrophy [1]. For example, it has been reported that two patterns of asymmetrical septal hypertrophy and symmetrical LV hypertrophy appeared in one family with familial HCM [11]. Clinically, however, it was very interesting that the site of LV hypertrophy in this family was localized between the anterior LV wall and ventricular septum, and all family members showed a very similar distribution of LV hypertrophy.

The TMF velocity during sinus rhythm generally exhibits biphasic patterns consisting of early diastolic and atrial systolic waves (E and A, respectively), and young normal subjects usually show an E/A > 1. However, in HCM patients LV diastolic dysfunction caused by LV hypertrophy decreases the E/A ratio (< 1) frequently and prolongs the deceleration time for the early diastolic TMF velocity, both of which reflect LV relaxation abnormalities [3].

It has been reported that TMF velocity does not always exhibit a relaxation failure pattern (E/A < 1) depending on the severity of myocardial disarray and/or fibrosis in patients with HCM [2-4]. For example, there are no abnormalities in LV diastolic function in some young patients with a normal TMF velocity pattern (E/A > 1), although a similar pattern (pseudonormalized pattern) is observed in patients with markedly elevated LV end-diastolic pressures [3, 4].

Moreover, a mid-diastolic wave is observed between the E and A waves in few patients with HCM [3, 5, 12, 13]. Keren et al [14] described that mid-diastolic wave is produced by the re-establishment of a positive transmitral pressure gradient after rapid LV filling in healthy subjects. On the other hand, some studies [12, 15] reported the prominent mid-diastolic wave as a result of markedly prolonged relaxation that lowers LV diastolic pressure during mid-diastole in patients with HCM. In addition, Mishiro et al [16] and Oki et al [17] suggested that nonsmooth and delayed relaxation is observed in patients with asynchronous relaxation, such as dilated hearts with left bundle branch block or HCM.

In HCM patients showing marked mid-diastolic waves, the isometric relaxation time and time constant of the LV pressure decay during isovolumic diastole (tau) determined by LV pressure curve is markedly prolonged, and LV pressure following rapid filling gradually decreases [3, 5, 12]. Therefore, compared to those patients showing a relaxation failure pattern for the TMF velocity, HCM patients with a mid-diastolic wave are characterized by markedly delayed LV relaxation and decreased LV compliance during end-diastole.

All five members of this family apparently had mid-diastolic waves, four of whom had an increased A wave ratio on apexcardiogram, except for case 2, indicating a compensatory increase in the peak atrial systolic TMF velocity. Therefore, in addition to LV relaxation failure, LV compliance may be decreased in HCM patients with mid-diastolic waves, and the LV diastolic dysfunction may be more severe in such HCM patients than in those with decreased E waves and a compensatory increase in the A wave of the TMF velocity patterns.

Mid-diastolic waves are rarely recorded in patients with HCM. In addition, it is interesting that triphasic TMF velocity patterns with mid-diastolic waves were observed in all five members of this family. Similar patterns of LV hypertrophy and TMF velocity observed in these family members may be very important in considering genetic contributions to LV myocardial diastolic characteristics.

References