Clinical Profiles of Hypertrophic Cardiomyopathy With Apical Phenotype
—— Comparison of Pure-Apical Form and Distal-Dominant Form ——

Toru Kubo, MD; Hiroaki Kitaoka, MD; Makoto Okawa, MD; Takayoshi Hirot, MD; Eri Hoshikawa, MD; Kayo Hayato, MD; Naohito Yamasaki, MD; Yoshihisa Matsumura, MD; Toshikazu Yabe, MD; Masanori Nishinaga, MD; Jun Takata, MD; Yoshinori L. Doi, MD

Background: Hypertrophic cardiomyopathy (HCM) with an apical phenotype, in which hypertrophy of the myocardium predominantly involves the apex of the left ventricle, is not uncommon in Japan, but its morphologic variations are not well recognized. The aim of this study was to investigate if these variations have different clinical characteristics although they are still confused to be the same.

Methods and Results: Patients with the apical phenotype were divided into 2 groups, the “pure-apical” form and the “distal-dominant” form, and their clinical profiles were compared. From the study cohort of 264 patients with HCM, 80 (30%) were classified as having the apical phenotype: 51 with the pure-apical form and 29 with the distal-dominant form. The age at diagnosis was approximately 60 years, and in both groups the majority were male. The distal-dominant group had a significantly larger left atrial diameter (43 vs 39 mm) and higher ratio of proven familial HCM (28 vs 6%), and were more symptomatic (New York Heart Association ≥3) at presentation (17 vs 0%). The event-free rate of cardiovascular events in patients with the distal-dominant form was significantly worse (log-rank P=0.012) than that in patients with the pure-apical form (follow-up period: ≈5 years).

Conclusions: The 2 phenotypes of apical HCM should be recognized and distinguished clinically. (Circ J 2009; 73: 2330–2336)

Key Words: Apex; Hypertrophic cardiomyopathy; Phenotypes

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with heterogeneous morphologic, functional, and clinical features, although left ventricular hypertrophy (LVH), particularly asymmetric septal hypertrophy (ASH), is the most characteristic feature.1–5 The apical phenotype of HCM, in which hypertrophy of the myocardium predominantly involves the apex of the left ventricle (LV), was originally reported in Japan as a subset of non-obstructive HCM characterized by a striking ECG pattern of giant negative T (GNT) waves associated with an angiographic “spade-shaped deformation of the LV cavity” at end-diastole.6–12 Detailed observation of the morphology by echocardiography has shown that the apical phenotype can be divided into a “pure-apical” form and a “distal-dominant” form (Figures 1a, b).13 Although those phenotypes are sometimes confused, they may have different clinical characteristics, so we investigated the clinical characteristics of HCM patients with the apical phenotype in the context of comparing the 2 forms.
The severity and distribution of the LVH were assessed in the parasternal short-axis plane at the level of the mitral valve and the papillary muscles. LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were measured from M-mode and 2-D images obtained from parasternal long-axis views, and fractional shortening \[(LVEDD - LVESD)/LVEDD \times 100\] was calculated. Mitral inflow velocities were determined using pulsed-wave Doppler with the sample volume positioned at the tips of the mitral leaflets in the 4-chamber view. Peak E-wave velocity \(E\), peak A-wave velocity \(A\) and E/A ratio were recorded. Tissue Doppler imaging was performed in the pulse-Doppler mode to allow for a spectral display and recording of mitral annulus velocities at the septal and lateral corners. The peak early diastolic (Ea) velocity was measured, and the E/Ea ratio as an index of LV diastolic dysfunction was calculated. The LV outflow tract (LVOT) gradient was calculated from the continuous-wave Doppler using the simplified Bernoulli equation.

Using the LV wall thickness assessed by echocardiography, we classified the patients into 3 morphologic patterns: (1) hypertrophy (≥15 mm) confined to the LV apex below the PM level (a) “Pure-apical” form (Figure 1a), (2) apical hypertrophy extending to the interventricular septum (IVS) without basal septal hypertrophy (b) “Distal-dominant” form (Figure 1b), and (3) typical HCM presenting as segmental or diffuse hypertrophy involving the basal portion of the LV (c) “Typical” form of HCM (Figure 1c).

Peripheral blood samples were collected for the measurement of plasma B-type natriuretic peptide (BNP) at the time of clinical evaluation.

Data on survival and the clinical status of patients were obtained during serial clinic visits or by direct communication with patients and their cardiologists for patients who were followed up at other institutions. For survival analysis, 3 types of cardiovascular death were defined: (1) sudden and unexpected death (including resuscitated cardiac arrest), in which collapse occurred in the absence of, or <1 h from, the onset of symptoms in patients who previously experienced a relatively stable or uneventful clinical course; (2) heart failure-related death, which was in the context of progressive cardiac decompensation ≥1 year before death; and (3) stroke-related death, which occurred as a result of probable or proven embolic stroke. Major morbid events included (1) hospitalization for heart failure, (2) stroke, and (3) sustained ventricular tachycardia (VT), defined as ≥30 consecutive ventricular beats or associated with hemodynamic instability.

Statistical Analysis
Statistical analysis was performed using SPSS (version 14.0) statistical software (SPSS Inc, Chicago, IL, USA). All data are expressed as mean±SD (range) or frequency (percentage). Differences in continuous variables were assessed using Student’s t-test. Pearson’s chi-square test was used for comparisons between non-continuous variables, and Fisher’s exact test was used when the expected frequency was lower than 5. Survival estimates were calculated by the Kaplan-Meier method and log-rank test. Statistical significance was defined as P≤0.05. The BNP level was subjected to logarithmic transformation for statistical analysis.
Baseline Echocardiography and Electrocardiography
From the study cohort of 264 patients, 80 (30%) were classified as having the apical phenotype (by definition, no patient demonstrating basal interventricular septal hypertrophy (≥15 mm)): 51 patients (19%) with the pure-apical form (Figure 2a) and 29 patients (11%) with the distal-dominant form (Figures 2b, c). The echocardiographic and electrocardiographic characteristics of these 2 groups at initial evaluation are summarized in Table 1. LV systolic function was preserved in all patients with the apical phenotype. In patients with the distal-dominant form, the left atrial diameter was larger and the E/Ea ratio was higher than in the patients with pure-apical form, although the LVEDD, LVESD, %FS, and E/A ratio were not different between the groups. None of the patients showed LVOT obstruction (pressure gradient at rest ≥30 mmHg). On the other hand, midventricular obstruction or apical obliteration was frequently seen in patients with the distal-dominant form. Half of the patients with both the pure-apical and distal-dominant forms showed GNT waves on ECG (defined as a depth ≥10 mm). There were no differences between the 2 groups in the frequency of nonsustained VT and pacemaker implantation.

Results
Baseline Echocardiography and Electrocardiography
From the study cohort of 264 patients, 80 (30%) were classified as having the apical phenotype (by definition, no patient demonstrating basal interventricular septal hypertrophy (≥15 mm)): 51 patients (19%) with the pure-apical form (Figure 2a) and 29 patients (11%) with the distal-dominant form (Figures 2b, c). The echocardiographic and electrocardiographic characteristics of these 2 groups at initial evaluation are summarized in Table 1. LV systolic function was preserved in all patients with the apical phenotype. In patients with the distal-dominant form, the left atrial diameter was larger and the E/Ea ratio was higher than in the patients with pure-apical form, although the LVEDD, LVESD, %FS, and E/A ratio were not different between the groups. None of the patients showed LVOT obstruction (pressure gradient at rest ≥30 mmHg). On the other hand, midventricular obstruction or apical obliteration was frequently seen in patients with the distal-dominant form. Half of the patients with both the pure-apical and distal-dominant forms showed GNT waves on ECG (defined as a depth ≥10 mm). There were no differences between the 2 groups in the frequency of nonsustained VT and pacemaker implantation.

Baseline Clinical Characteristics
The clinical characteristics of patients with the pure-apical and distal-dominant forms at presentation are summarized in Table 2. The age at diagnosis in the patients with each
Clinical Variations in Apical HCM

The majority (>80%) of the patients in both groups were male. The distal-dominant group had a significantly higher ratio of proven familial HCM with at least 1 relative who had an unequivocal diagnosis. All 3 patients with the pure-apical form and proven familial HCM were diagnosed at a relatively young age (ages at diagnosis: 29, 43 and 45 years, respectively). Although the reason for diagnosis was not different in the 2 groups, more patients with the distal-dominant form experienced significant dyspnea (New York Heart Association (NYHA) ≥3). Of the 5 patients with NYHA ≥3, all had a history of hospitalization for treatment of heart failure and 4 had paroxysmal or chronic atrial fibrillation (AF). One patient had severe mitral valve regurgitation because of mitral annular dilatation (left atrial diameter 80 mm) and coaptation loss of the mitral valve. He later underwent mitral annuloplasty (no findings of chordal rupture). The other 4 patients had heart failure symptoms because of diastolic dysfunction. At initial evaluation, the BNP level was significantly higher in patients with the distal-dominant form. None of the patients in either group underwent cardioverter-defibrillator implantation.

Clinical Course

The mean follow-up period in the pure-apical and distal-dominant groups was 5.4±5.1 and 4.3±4.9 years, respectively. No patient progressed to the dilated phase of HCM. There were no cardiovascular deaths among the 51 patients with the pure-apical form during the follow-up period (there were 4 non-cardiovascular deaths). On the other hand, 2 patients with the distal-dominant form died of cardiovascular death (sudden death in 1 patient and heart failure in the other). The patient who died suddenly had had AF since he was diagnosed as having apical hypertrophy and died suddenly at the age of 77 years while working as a fisherman. The patient who died of heart failure had a family history of sudden death (2 daughters) and her severe heart failure was considered to be caused by diastolic dysfunction. Cardiac amyloidosis was not detected and she died at the age of 73 years. There were additional cardiovascular events

| Table 2. Clinical Characteristics of Patients With “Pure-Apical” or “Distal-Dominant” Form of Hypertrophic Cardiomyopathy at Initial Evaluation |
|---------------------------------|-----------------|-----------------|--|
| “Pure-apical” form (n=51) | “Distal-dominant” form (n=29) | P value |
| Age, years | 61±13 (24–87) | 62±11 (30–80) | 0.668 |
| Male, n (%) | 42 (82%) | 24 (83%) | 0.963 |
| Age at diagnosis, years | 59±13 (24–87) | 60±11 (30–80) | 0.746 |
| Proven familial HCM, n (%) | 3 (6%) | 8 (28%) | 0.014 |
| Family history of sudden death, n (%) | 6 (12%) | 7 (24%) | 0.208 |
| Reason for diagnosis, n (%) | | | |
| Symptoms | 19 (37%) | 15 (52%) | 0.208 |
| Incidental findings | 32 (63%) | 14 (48%) | |
| Symptoms at presentation, n (%) | 27 (53%) | 20 (69%) | 0.162 |
| Palpitation | 3 (6%) | 6 (21%) | 0.065 |
| Syncope | 2 (4%) | 1 (3%) | 1.000 |
| Chest pain | 23 (45%) | 11 (38%) | 0.533 |
| NYHA class at presentation, n (%) | | | |
| I | 36 (71%) | 14 (48%) | 0.048 |
| II | 15 (29%) | 10 (35%) | 0.638 |
| III and IV | 0 (0%) | 5 (17%) | 0.005 |
| BNP, pg/ml | 104±120 (4–476) (n=27) | 300±242 (16–1,920) (n=20) | 0.013 |
| Hypertension, n (%) | 26 (51%) | 12 (41%) | 0.408 |
| Antihypertensive medications, n (%) | 18 (35%) | 10 (34%) | 1.000 |

Data are mean±SD (range) or number (%).
NYHA class, New York Heart Association class; BNP, plasma B-type natriuretic peptide.

Figure 3. Kaplan-Meier event-free survival. (a) Occurrence of cardiovascular death during follow-up. Log rank for trend P=0.044. (b) Occurrence of cardiovascular events during follow-up. Log rank for trend P=0.012. , Pure-apical form; ••••••, Distal-dominant form.
(major morbid events) in each group (stroke in 1 patient with the pure-apical form and hospitalization for heart failure in 2 patients with the distal-dominant form). The admissions of the latter 2 patients were basically because of diastolic dysfunction. Figure 3b shows that the event-free rate of cardiovascular events (cardiovascular deaths and major morbidity events) in patients with the distal-dominant form was significantly worse (log-rank P=0.012) than that in patients with the pure-apical form.

Paroxysmal or chronic AF was detected in 10 (20%) of the 51 patients with the pure-apical form: 5 presented with AF at the initial evaluation and the other 5 patients experienced AF during the follow-up period (incidence, 1.9%/year). Of the patients with the distal-dominant form, 8 had AF (28%): 4 already had AF at the initial evaluation and the other 4 patients experienced AF after the initial evaluation (incidence, 3.3%/year). Of the 5 patients who suffered from cardiovascular events, 4 already had AF.

Longitudinal Morphologic Changes

The hypertrophy had extended to the IVS in some patients. Hypertrophy progressed in 2 of the 29 patients with the distal-dominant form to the typical form. Hypertrophy also progressed in 7 of the 51 patients with the pure-apical form; 2 of them, who were relatively young (ages at diagnosis: 24 and 41 years, respectively), progressed to the typical form of HCM (1 patient was reported previously), although neither was confirmed to have familial HCM. The other 5 patients progressed to the distal-dominant form; 2 of them had familial HCM and were relatively young (ages at diagnosis: 29 and 45 years, respectively).

Discussion

HCM is a primary disease of cardiac muscle that is characterized by a hypertrophied, nondilated LV unassociated with other cardiac diseases. Morphologic expression regarding the site and extent of LVH can often be heterogeneous. There has been some controversy, and confusion, regarding the apical phenotype of HCM, in which hypertrophy of the myocardium predominantly involves the apex of the LV, because of the different diagnostic modalities used by investigators and the various morphologic presentations of apical hypertrophy. Even in the apical phenotype, there are several morphologic variations and terms, including the Japanese form, Western form, apical ASH, pure apical HCM, and mixed apical HCM. Although those variations may have different clinical characteristics, in daily clinical practice they are still confused as “just apical hypertrophy”. Therefore, we previously suggested the use of terms such as “pure form” (isolated apical hypertrophy, limited to the LV apex below the papillary muscle level: Figure 1a) and “mixed form” (apical hypertrophy, with coexistent hypertrophy of the distal/basal IVS: Figures 1b, c). Although the “mixed form” includes apical hypertrophy with coexistent hypertrophy of the distal IVS and occasionally the basal septum, now we divide the “mixed form” into 2 types and regard patients with hypertrophy of the basal IVS, even in cases demonstrating the greatest wall thickness in the apical segment, as part of the common disease spectrum of HCM (“typical” HCM: Figure 1c). Recently, Choi et al reported the phenotypic spectrum and clinical characteristics of apical HCM and they used the term “mixed type”, defined as presenting with hypertrophy of the IVS in which the hypertrophy was greatest in the apical segments, but did not extend to the basal segments (Figure 1b). Because they used the term “mixed type” (or “mixed form”) differently to our previous definition, here we use a new term “distal-dominant form” to indicate apical hypertrophy extending to the IVS without basal septal hypertrophy (Figure 1b).

In the present study, we focused on the apical phenotype (Figures 1a,b) and to the best of our knowledge this is the first report of the longitudinal clinical profiles of HCM patients with the apical phenotype from the viewpoint of comparing the pure-apical and distal-dominant forms.

Clinical Background

In the present study, the mean age of patients at diagnosis was approximately 60 years and the majority in both subtypes were male. Our data are in accordance with previously reported Japanese data for apical HCM. The prevalence of GNT waves on ECG, which has been reported as a characteristic hallmark of apical hypertrophy (the so-called “Japanese type”), was the same in patients with either the pure-apical or distal-dominant form. The presence of mild hypertension was also similarly seen in both subtypes. Therefore, it is difficult to distinguish these 2 groups by clinical background factors such as age, sex, and ECG features. A significant difference between the 2 groups was only seen in the prevalence of proven familial HCM. A family history of HCM was rare in patients with the pure-apical form (3 (6%) of 51 patients), whereas 28% of the patients with the distal-dominant form were confirmed as having familial HCM. We presume that many cases of the pure-apical form may not be caused by a single mutation that is transmitted with a Mendelian autosomal dominant pattern of inheritance. The age at diagnosis of HCM in these 3 patients with the pure-apical form and familial HCM was relatively young in the present cohort (<45 years old). The relatives of these 3 patients with the pure-apical form and an unequivocal diagnosis of HCM did not show apical hypertrophy, but rather the typical form of HCM (hypertrophy involving the basal portion of the LV).

Clinical Manifestations

Patients with the distal-dominant form were significantly more limited (NYHA ≥3) at presentation and were also more prone to have left atrial enlargement on echocardiography, presumably as a consequence of elevated filling pressure because of impaired LV relaxation. Although the number of the patients was limited in our study, the E/Ea ratio as an index of LV diastolic dysfunction and the BNP levels were significantly higher in patients with the distal-dominant form.

During the follow-up period, there were no HCM-related cardiovascular deaths among the 51 patients with the pure-apical form, whereas there were 2 such deaths among the 29 patients with the distal-dominant form. The frequency of cardiovascular events (cardiovascular deaths and major morbidity events) was significantly higher in patients with the distal-dominant form (1 sudden death, 1 heart failure-death, 2 hospitalizations for heart failure). HCM in the pure-apical form is generally associated with a benign clinical manifestation (only 1 stroke admission). On the other hand, patients with the distal-dominant form had a more symptomatic and worse clinical course, more closely resembling the clinical manifestation of patients with typical HCM. Among the previous investigations of apical HCM, Ericksson et al presented the largest number of patients (105) with apical HCM who were divided into those with the “pure form”
(isolated asymmetric apical hypertrophy) and those with the “mixed form” (with coexisting IVS hypertrophy), using morphologic criteria mainly based on echocardiography. They found no difference between those 2 subtypes with regard to long-term morbidity cardiovascular events. The difference in the results of their study and ours may be related to the different definitions of morbidities, the low prevalence of the “mixed form” in their cohort, and the fact that their study population was younger than ours.

However, despite the benign clinical manifestation, patients with the pure-apical form need to be followed up regularly because of the high incidence of AF. The incidence of AF was not low in either the pure-apical or distal-dominant groups compared with that in a whole HCM cohort reported by Olivotto et al (incidence, 2%/year), although our cohort of apical phenotype was older than theirs.26 The incidence of AF in our cohort was much higher than that in community-dwelling older people (the Kahoku Longitudinal Aging Study, data available upon request). Furthermore, the fact that 4 of 5 patients with the apical phenotype (pure-apical form and distal-dominant form) presented with AF before their cardiovascular events indicates that more careful management (including anticoagulation therapy) is needed for patients with AF. In whole cohort of HCM, AF is known as an important prognostic feature for cardiovascular mortality, stroke, and severe functional disability.26,27 The results of our study indicate that even in patients with the apical phenotype, in whom complications are considered infrequent, AF seems to be a key determinant of clinical deterioration.

From the longitudinal point of view, some patients with the apical phenotype, including both forms, showed progression and extension of hypertrophy. Although the incidence of familial HCM is relatively high in patients with the distal-dominant form compared with those with the pure-apical form, it is important to recognize young patients with the apical phenotype as the initial manifestation of typical HCM.

Study Limitations
The average follow-up period was about 5 years, and further studies on the outcome and prognosis in patients with the apical phenotype in terms of comparing the 2 forms are needed. Although we found a low frequency of proven familial HCM in the pure-apical form group, genetic screening was not performed in the present study. Several studies have shown that mutations in sarcomere genes, such as the cardiac troponin T, troponin I, cardiac actin, and essential myosin light chain genes, are associated with apical hypertrophy.28-34 Therefore, it is important to further perform mutation analysis to clarify the genetic difference between the pure-apical and distal-dominant forms.

Conclusions
It is better to clinically distinguish the phenotypes of HCM because patients with the distal-dominant form are significantly more symptomatic and have more cardiovascular events than do patients with the pure-apical form. However, AF is not uncommon in both groups, and careful management is needed once AF has occurred.

Acknowledgments
The study was supported by St Luke’s Life Science Institute.

Disclosures
None of the authors has a conflict of interest to disclose in connection with this manuscript.

References


