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Original article

Phenotypic overlap in hypertrophic cardiomyopathy: Apical hypertrophy, midventricular obstruction, and apical aneurysm

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ABSTRACT

Background: Within the diverse phenotypic spectrum of hypertrophic cardiomyopathy (HCM), subgroups of patients with apical hypertrophy (APH), midventricular obstruction (MVO), and apical aneurysm (APA) have emerged. While previous studies have suggested the existence of considerable overlap between APH, MVO, and APA, there are still many unanswered questions. Therefore, we attempted to clarify the relationship of the above three phenotypes of HCM with respect to prevalence, overlap, and outcomes.
Methods: Among the 544 study HCM patients (mean follow-up period: 11.6 ± 7.4 years), 170 with APH (31.3%), 51 with MVO (9.4%), and 24 with APA (4.4%) were examined.
Results: There was phenotypic overlap between APH and MVO in 17 patients, APH and APA in 14 patients, and MVO and APA in 14 patients. Furthermore, a combination of APH, MVO, and APA was observed in eight patients. Detailed analysis of the relationship between overlapping phenotypes and the prognosis showed that APA patients without a history of APH had an extremely poor outcome (probability of the combined endpoint of sudden death and potentially lethal arrhythmic events ≥50%). Conversely, APH patients without MVO had a strikingly good outcome (probability of the combined endpoint <5%). Other patients had an intermediate outcome (probability of the combined endpoint 10–40%).
Conclusions: Our results suggest that overlap between these three forms of HCM is substantial, and that detailed classification of the overlapping phenotypes is clinically meaningful.

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disease characterized by marked variability of the morphological features and natural history [1–6]. Within the diverse clinical and phenotypic spectrum of HCM, subgroups of patients characterized by left ventricular apical hypertrophy (APH), midventricular obstruction (MVO), and apical aneurysm (APA) have emerged [7–9]. APH is a specific variant of HCM, in which myocardial hypertrophy predominantly affects the left ventricular apical region, resulting in a spade-shaped left ventricular configuration and giant negative T-waves [7,10–14]. MVO is a relatively rare form of HCM that is characterized by a pressure gradient at the midventricular level and is unrelated to systolic anterior motion of the mitral valve, being caused by contact between the hypertrophic septum and a hypercontractile left ventricular free wall [9,15]. APA is a rare variant of HCM, in which there is a thin-walled dyskinetic or akinetic segment at the most distal portion of the chamber that has relatively wide communication with the left ventricular cavity [8]. While numerous previous case reports and studies have suggested the existence of considerable overlap between APH, MVO, and APA [8,9,12,13,16–23], the clinical courses of the above three forms of HCM seem to be heterogeneous. Our previous study and a report by Maron and colleagues have demonstrated a largely unfavorable clinical course for HCM patients with MVO and/or APA [8,9]. In contrast, APH patients typically have mild symptoms, and APH generally follows a more benign course with a lower mortality rate than other forms of HCM [7,14]. Accordingly, it is our impression that there are many unanswered questions about the overlap between these three phenotypes of HCM. Therefore, we attempted to clarify the relationship between APH, MVO, and APA in a relatively large HCM cohort, especially with respect to their prevalence, overlap, clinical course, and outcomes.

Methods

Patients

The study population included 544 patients with a clinical diagnosis of HCM who were enrolled from 1980 to 2008 at Tokyo

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Women's Medical University Hospital (Tokyo, Japan). The initial evaluation was defined as the first clinical assessment at which an echocardiogram diagnostic of HCM was obtained, while the most recent evaluation was performed in the clinic or by telephone interview. Some of these patients were included in a previous publication from our institution [9], but clinical follow-ups were updated from the time of completion of the study. This study was carried out according to the principles of the Declaration of Helsinki, and the study protocol was approved by our institutional ethics committee.

Definitions

The diagnosis of HCM was based on documentation by two-dimensional echocardiography of a hypertrophic, non-dilated left ventricle in the absence of any other cardiac and/or systemic disease that could cause similar hypertrophy [1,2].

Left ventricular MVO was diagnosed when both of the following criteria were satisfied: (1) the peak instantaneous midventricular gradient was estimated to be ≥30 mmHg; and (2) midcavitary obliteration was caused by contact of marked septal hypertrophy with a hypercontractile left ventricular free wall, rather than by systolic anterior motion of the anterior leaflet of the mitral valve [9,15,24].

The diagnostic criteria for APH included asymmetric left ventricular hypertrophy that was confined predominantly to the left ventricular apical region, along with an apical wall thickness ≥15 mm [7]. Left ventricular APA was defined as a thin-walled dyskinetic or akinetic segment at the most distal part of the chamber showing relatively wide communication with the left ventricular cavity [8]. Patients presenting with APH subsequently developing APA during the follow-up period were considered to have an overlap between APH and APA. In patients with APA, MVO was considered to be absent when the estimated peak instantaneous gradient was <30 mmHg. These patients were thus considered to have APA alone.

Documentation of atrial fibrillation was based on electrocardiograms recorded either after the onset of symptoms or during a routine medical examination in an asymptomatic patient [25]. Ambulatory electrocardiograms covering at least a 24-h period were reviewed in all patients to detect the occurrence of non-sustained ventricular tachycardia, which was defined as a minimum of three consecutive ventricular beats with a rate of ≥120 per minute [1,2].

The endpoint of this study was the combination of sudden death and potentially lethal arrhythmic events, in which unexpected death occurred in the absence of or within 1 h after the onset of symptoms in patients with a previously relatively stable or uneventful course, including those who were successfully resuscitated after cardiac arrest (ventricular fibrillation or ventricular tachycardia with pulseless collapse) and those with appropriate implantable defibrillator interventions [9].

Echocardiography

Echocardiographic studies were conducted using commercially available ultrasound equipment. Complete M-mode, two-dimensional, and Doppler studies were performed in the left lateral decubitus or supine position by the parasternal, apical, and subcostal approaches. Color Doppler and pulse-wave Doppler echocardiography were used to localize the site of left ventricular obstruction. The peak left ventricular gradient was quantified by continuous-wave Doppler echocardiography under resting conditions. MVO was defined by the detection of systolic apposition of the mid-left ventricular walls (and often the papillary muscles), with abnormally high velocities persisting through late systole and often with early diastolic paradoxical jet flow [26]. When an apical acoustic window was difficult to obtain, contrast-enhanced echocardiography (27 patients) and/or cardiovascular magnetic resonance (CMR) imaging (55 patients) was done to obtain adequate visualization of the left ventricular apex among 208 patients with APH and/or MVO and/or APA. Contrast-enhanced echocardiography was performed by intravenous injection of 300 mg/ml galactose–palmitic acid (Levovist, Schering, Berlin, Germany) at a rate of 5 ml/5 s.

Cardiovascular magnetic resonance imaging

All CMR studies were performed with a Magnetom Vision 1.5-T whole body imaging system (Siemens Medical Systems, Erlangen, Germany) from 2001 to July 2003, while a Gyroscan Intera (Philips Medical Systems, Best, The Netherlands) was used from July 2003 onward. Breath-holding electrocardiography-gated steady-state free precession cine images were acquired in 7–10 short-axis slices and in the 2- and 4-chamber long-axis views.

Statistical analysis

Analyses were performed with SAS system ver. 9.1 software (SAS Institute, Cary, NC, USA). Results are presented as the mean ± SD or as frequencies. One-way analysis of variance was used to compare values among the groups for continuous variables, and Kruskal–Wallis *H*-test was used for ordinal variables. A chi-square or Fisher exact test (when an expected value was <5) was used to compare nominally scaled variables. A two-tailed *p*-value of less than 0.05 was considered to indicate statistical significance.

Results

Prevalence, overlap, clinical course, and baseline characteristics

The 544 HCM patients (age at diagnosis: 50.7 ± 15.2 years, 63.6% men, follow-up period: 11.6 ± 7.4 years) included 170 patients with APH (31.3%), 51 patients with MVO (9.4%), and 24 patients with APA (4.4%). As shown in Fig. 1, the overlap between APH, MVO, and APA was observed in 208 HCM patients who had APH and/or MVO and/or APA. A flow diagram summarizing the clinical course of these 208 HCM patients is shown in Fig. 2. Of the 170 APH patients, 17 patients were complicated by MVO, and 8 of these 17 APH patients with MVO developed APA formation during the

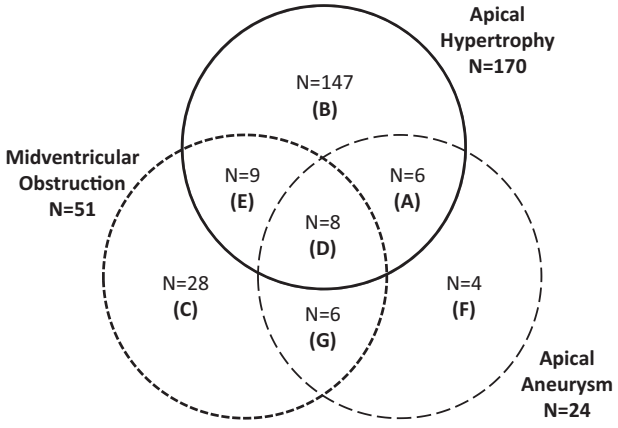

Fig. 1. Venn diagram of phenotypic overlap among APH, MVO, and APA in 208 HCM patients with APH and/or MVO and/or APA. There was overlap between APH and MVO in 17 patients (subsets D and E), APH and APA in 14 patients (subsets A and D), and MVO and APA in 14 patients (subsets D and G). Furthermore, the combination of APH, MVO, and APA was observed in eight patients (subset D). APA, apical aneurysm; APH, apical hypertrophy; HCM, hypertrophic cardiomyopathy; MVO, midventricular obstruction.