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Original article

Prognostic difference between paroxysmal and non-paroxysmal atrial fibrillation in patients with hypertrophic cardiomyopathy

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ABSTRACT

Background: The association of atrial fibrillation (AF) with sudden death and the difference in prognostic significance between paroxysmal and non-paroxysmal AF remains unclear in patients with hypertrophic cardiomyopathy (HCM). Our aim was to investigate the clinical significance of AF, and to assess the prognostic difference between paroxysmal and non-paroxysmal AF in HCM patients.
Methods: The study included 430 HCM patients. Documentation of AF was based on electrocardiograms obtained either after the acute onset of symptoms or fortuitously during routine examination of asymptomatic patients.
Results: AF was detected in 120 patients (27.9%). In the patients with AF, syncope and non-sustained ventricular tachycardia were more frequent and the left atrial dimension was larger. Multivariate analysis showed that AF was an independent determinant of the outcome, including the risk of HCM-related death (adjusted hazard ratio 3.57, $p < 0.001$) and sudden death (adjusted hazard ratio 2.61, $p = 0.038$). When patients with AF were divided into subgroups with paroxysmal AF ($n = 75$) or non-paroxysmal AF ($n = 45$), only paroxysmal AF was identified as an independent determinant of the outcome, including the risk of HCM-related death (adjusted hazard ratio 5.24, $p < 0.001$) and sudden death (adjusted hazard ratio 4.67, $p = 0.002$).
Conclusions: AF is a common supraventricular arrhythmia in HCM and has an adverse influence on the prognosis. In addition, each type of AF had a different clinical impact, with paroxysmal AF being a significant independent determinant of an adverse outcome, including sudden death.

Introduction

Hypertrophic cardiomyopathy (HCM) is a unique cardiovascular disease with a diverse clinical course [1–7]. Atrial fibrillation (AF) is an important arrhythmia that is associated with systemic thromboembolism, heart failure, and death in patients with HCM [8–12]. Previous clinical cohort studies have shown that AF is associated with a substantial increase in the overall risk of HCM-related death, but not sudden death [8,13]. On the other hand, there have been several reports of AF triggering life-threatening ventricular arrhythmias [14–20]. It thus remains controversial whether AF is associated with sudden death in patients with HCM. In addition, few studies have assessed the difference in clinical impact between the subsets of AF (paroxysmal or non-paroxysmal).

Therefore, in the present study, we investigated the clinical significance of AF in HCM patients who were diagnosed and followed at our hospital, as well as the prognostic impact of paroxysmal AF vs. non-paroxysmal AF.

Methods

Study patients

The study population included 430 patients with a clinical diagnosis of HCM who were enrolled consecutively from 1980 to 2003 at Tokyo Women's Medical University Hospital (Tokyo, Japan). Initial evaluation was defined as the first clinical assessment during which an echocardiographic diagnosis of HCM was made. The most recent evaluation was ascertained on review at the clinic or by telephone interview. Patients who had suffered from non-fatal cardiac arrest or resuscitated cardiac arrest at the time of referral to our hospital were excluded. This study was carried out according to the principles of the Helsinki Declaration, and the protocol was approved by the ethics committee of our hospital.

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Definitions

The diagnosis of HCM was based on echocardiographic identification of severe hypertrophy of the left ventricle in the absence of another systemic or cardiac disease that was capable of producing similar hypertrophy [10,11]. Left ventricular outflow tract obstruction was defined as systolic obstruction (a gradient ≥30 mm Hg on continuous-wave Doppler echocardiography) of the left ventricular outflow tract at rest [10,11].

End-stage HCM was defined by the detection of left ventricular ejection fraction <50% at rest, reflecting global systolic dysfunction, on two-dimensional echocardiography without a history of surgical or ablative septal reduction therapy during the follow-up period [4].

Documentation of AF was based on electrocardiograms obtained either after the acute onset of symptoms or fortuitously during routine examination of patients without symptoms [8]. AF was defined as paroxysmal when it was self-terminating within 7 days, or when sinus rhythm was successfully restored by electrical or pharmacologic cardioversion within 48 h [21]. AF was defined as non-paroxysmal when it progressed to persistent (sustained AF beyond 7 days or successfully restored by electrical or pharmacologic cardioversion after 48 h of AF), longstanding-persistent (continuous AF of greater than 12 months' duration), and permanent (AF for which a decision has been made not to restore or maintain sinus rhythm by any means) in this analysis [21]. Patients whose AF evolved from paroxysmal to non-paroxysmal during follow-up were classified into the non-paroxysmal AF group.

In all patients, ambulatory electrocardiograms covering at least 24 h were reviewed for the detection of non-sustained ventricular tachycardia, which was defined as a minimum of three consecutive ventricular beats at a rate ≥120/min [10,11].

For survival analysis, the following 3 modes of HCM-related death were defined [22]: (1) sudden and unexpected death, which meant collapse in the absence or <1 h after the onset of symptoms in a patient who had previously been relatively stable (including resuscitated cardiac arrest); (2) heart failure-related death, which was defined as occurring after progressive cardiac decompensation for >1 year before death, particularly if complicated by pulmonary edema or evolution to end-stage HCM; and (3) stroke-related death, which was defined as death from ischemic stroke.

The following four clinical features were defined as established major primary prevention risk factors for sudden death on the basis of previous reports [10,11]: (1) a family history of sudden death; (2) severe left ventricular hypertrophy (left ventricular wall thickness in any myocardial segment ≥30 mm on two-dimensional echocardiography); (3) non-sustained ventricular tachycardia (three or more consecutive ventricular beats at a rate ≥120/min); and (4) unexplained syncope. Abnormal exercise blood pressure was excluded from the analysis because exercise tests were not performed in all study HCM patients.

Echocardiography

Echocardiographic studies were performed with commercially available equipment. Complete two-dimensional, M-mode, and Doppler studies were done in the left lateral decubitus position or the supine position, using the standard parasternal, apical, and subcostal views. The M-mode left atrial end-systolic dimension was measured in the parasternal long-axis view. The severity and distribution of left ventricular hypertrophy were assessed in the short-axis view by dividing the left ventricular wall into four segments (anterior septum, posterior septum, anterolateral wall, and posterior wall) at the level of the mitral valve and also at the papillary muscles. Maximal left ventricular wall thickness was defined as the greatest thickness in any single segment. Left ventricular outflow tract obstruction was quantified by continuous-wave Doppler echocardiography under resting conditions.

Statistical analysis

Analyses were performed with SAS system ver. 9.1 software (SAS Institute, Cary, NC, USA). Data are expressed as the mean ± standard deviation or as frequencies. Student's *t*-test was used to compare continuous variables, while the chi-squared test or Fisher's exact test (when the expected value was <5) were used to compare discrete variables between patients with or without AF and patients with paroxysmal AF or non-paroxysmal AF. The probability of HCM-related death and sudden death was estimated by the Kaplan–Meier method, after which the log-rank test was used to compare survival curves. Cox proportional-hazards regression analysis was used to calculate hazard ratios and 95% confidence intervals for the relation between AF and survival. A *p*-value <0.05 was considered statistically significant in all analyses.

Results

Baseline characteristics of the HCM patients with and without AF

Among the 430 patients enrolled with HCM, AF was documented in 120 patients and its prevalence was 27.9%. The baseline characteristics of the patients with and without AF are shown in Table 1. Onset of AF was detected at ages from 21 to 84 years (average: 56 ± 13 years). There were no significant differences with respect to gender, family history of sudden death, or maximum left ventricular wall thickness between the patients with and without AF. The patients with AF were older than those without AF, but the difference was not significant. In the AF group, syncope was more frequent, non-sustained ventricular tachycardia was documented more often, and the left atrial dimension was larger than in the group without AF. In contrast, left ventricular outflow tract obstruction was significantly more frequent among patients without AF.

Outcome in patients with or without AF

Among the 120 patients with AF, 22 (18%) died of causes related to HCM during a mean follow-up period of 12.1 ± 7.3 years, including 16 patients (13%) with sudden death, 4 (3.3%) who died of heart

Table 1
Clinical features of HCM patients with or without AF.

	Patients with AF	Patients without AF	*p* value
Number of patients, *n* (%)	120 (27.9)	310 (72.1)	
Age at diagnosis (years)	52.4 ± 13.0	49.7 ± 15.1	0.089
Male, *n* (%)	86 (71.7)	199 (64.2)	0.175
Duration of follow-up (years)	12.1 ± 7.3	10.7 ± 7.3	0.083
Family history of sudden death, *n* (%)	16 (13.3)	27 (8.7)	0.210
Syncope, *n* (%)	35 (29.2)	31 (10.0)	<0.001
Non-sustained ventricular tachycardia, *n* (%)	70 (58.3)	102 (32.9)	<0.001
Echocardiographic findings			
Outflow tract gradient ≥30 mm Hg, *n* (%)	17 (14.2)	85 (27.4)	0.006
Maximum wall thickness (mm)	19.9 ± 4.1	19.4 ± 4.1	0.264
Left atrial dimension (mm)	41.8 ± 8.7	35.1 ± 6.4	<0.001

Values with ± represent the mean ± SD. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy.