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Original article

Enlarged left atrium and sudden death risk in hypertrophic cardiomyopathy patients with or without atrial fibrillation

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ABSTRACT

Background: The relationships among enlarged left atrial dimension (LAD), the presence or absence of atrial fibrillation (AF), and sudden death risk in patients with hypertrophic cardiomyopathy (HCM) remain unclear. The aim of this study was to evaluate the impact of enlarged LAD on sudden death risk in HCM patients with or without documented AF.

Methods: This study included 564 HCM patients (follow-up period: 10.8 ± 7.4 years). LAD was measured from the parasternal long-axis view as the antero-posterior linear diameter at end-systole. Sudden death was defined as the combined endpoint of sudden cardiac death and potentially lethal arrhythmic events, and log-rank tests and Cox proportional hazards models were applied to evaluate the impact of LAD enlargement on the combined endpoint.

Results: The proportions of patients with sudden death and potentially lethal arrhythmic events were significantly higher among patients with enlarged LAD (≥48 mm, $N = 86$) compared with those without enlarged LAD (19.8% vs. 8.2%; $p = 0.002$). However, enlarged LAD was not identified as an independent determinant of sudden death risk in multivariate analysis of all study HCM patients [adjusted hazard ratio (HR): 1.83; 95% confidence interval (CI): 0.95–3.53; $p = 0.071$]. Among patients without documented AF during the follow-up periods, enlarged LAD was an independent determinant of sudden death risk (adjusted HR: 5.23; 95% CI: 2.17–12.58; $p < 0.001$), although there was no significant difference in sudden death risk between patients with and without enlarged LAD in patients with documented AF (adjusted HR: 0.77; 95% CI: 0.31–1.90; $p = 0.567$).

Conclusions: These results suggest that the relationship between LAD and outcome is influenced by the presence or absence of AF in HCM patients. It may thus be necessary to consider the need to prevent sudden death in LAD-enlarged HCM patients without documented AF.

Introduction

Hypertrophic cardiomyopathy (HCM) is a complex primary and genetic cardiac disease with heterogeneous clinical expression, characterized by a benign or stable clinical course over many years, progressive congestive heart failure symptoms requiring therapeutic intervention, and the possibility of systemic embolic events and sudden unexpected death [1–6].

Numerous previous studies have demonstrated that left atrial enlargement is a strong predictor of cardiovascular events such as stroke, coronary heart disease, and congestive heart failure in population-based and referral-based cohorts [7–10]. In patients with HCM, Nistri et al. reported that enlarged left atrial dimension (LAD) was independently associated with all-cause, cardiovascular, and heart failure-related death rates from a large Italian cohort [11]. In addition, an enlarged left atrium was a sensitive and specific parameter for the occurrence of atrial fibrillation (AF), and both left atrial enlargement and AF were independent markers of adverse outcome in HCM, particularly in relation to the identification of patients at risk of heart-failure-related death [11–14]. In contrast, their usefulness as clinical-risk markers for sudden unexpected death remains controversial, and the associations among left atrial enlargement, presence or absence of AF, and sudden death risk in patients with HCM remain unclear. We therefore evaluated the impact of enlarged LAD on sudden death risk in a relatively large cohort of HCM patients with or without documented AF.

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Methods

Patients

This retrospective study included 564 patients with clinically-diagnosed HCM who were enrolled consecutively from 1980 to 2009 at Tokyo Women's Medical University Hospital, Tokyo, Japan. The initial evaluation was taken as the first clinical assessment during which an echocardiographic diagnosis of HCM was made in our hospital, and the most recent evaluation was ascertained by review at the outpatient clinic or by telephone interview. The protocol was approved by the institutional review board of Tokyo Women's Medical University, and the study was carried out according to the principles of the Helsinki Declaration.

Hypertrophic cardiomyopathy

A diagnosis of HCM was based on two-dimensional echocardiographic evidence of left ventricular hypertrophy (wall thickness of at least 15 mm) in the absence of any other cardiac and/or systemic disease capable of producing similar hypertrophy [2,15]. The diagnostic criteria for apical hypertrophy included asymmetric left ventricular hypertrophy that was confined predominantly to the left ventricular apex with apical wall thickness ≥15 mm [16].

Left atrial dimension

The LAD was measured at initial evaluation in all study patients from the parasternal long-axis view as the antero-posterior linear diameter at end-systole, with two-dimensional echocardiographic guidance to position the cursor, as previously recommended [11,17]. On the basis of previously published data, LAD ≥48 mm was defined as enlargement of the left atrium in this study cohort [11].

Arrhythmias

Ambulatory electrocardiograms covering at least 24 h were reviewed to detect AF and non-sustained ventricular tachycardia at initial evaluation in all study patients. The presence of AF was documented either by 12-lead resting electrocardiogram or ambulatory electrocardiogram, obtained either after the acute onset of clinical symptoms or during routine medical examination in patients without symptoms, during the follow-up periods [14]. Non-sustained ventricular tachycardia was defined as a minimum of three consecutive ventricular extra-systoles at a rate of ≥120/min and lasting for <30 s [2].

Sudden death

Sudden death was defined in this study as the combination of sudden cardiac death and potentially lethal arrhythmic events, with unexpected death occurring in the absence of symptoms or within 1 h after the onset of symptoms in patients with a relatively stable or uneventful course, including patients successfully resuscitated after cardiac arrest (i.e. ventricular fibrillation or ventricular tachycardia with pulseless collapse) and appropriate implantable cardioverter-defibrillator interventions [18,19].

Major risk factors for sudden death

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

Echocardiography

Comprehensive echocardiographic studies were performed using commercially available ultrasound systems. Complete two-dimensional, M-mode, and Doppler studies were performed in the left lateral decubitus or supine position, from parasternal short- and long-axis views, apical four-chamber, two-chamber, and long-axis views, and subcostal views. A left ventricular intra-cavitary pressure gradient was considered to be present when the peak instantaneous gradient was estimated to be ≥30 mmHg at basal (resting) conditions, quantified by continuous-wave Doppler echocardiography at initial evaluation [15]. Left atrial volume was measured from an apical view by tracing the outline of the atrial endocardium at end-systole in 247 of 564 study patients.

Statistical analysis

Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA) software by an independent biostatistics and data center (STATZ Institute, Inc., Tokyo, Japan), and data are presented as the mean ± standard deviation (SD), as median with interquartile range, or as frequencies. Student's *t*-test was used to compare groups with normally-distributed continuous variables, and χ^2 or Fisher's exact tests (when an expected value was <5) were used to compare nominally-scaled variables. Cumulative probabilities of event curves were estimated using the Kaplan–Meier method and compared using log-rank tests. Univariate and multivariate Cox proportional hazards models were applied to evaluate the impact of LAD enlargement on the combined endpoint of sudden death and potentially lethal arrhythmic events. Two-tailed *p*-values <0.05 were considered to indicate statistical significance.

Results

Enlarged left atrium in study HCM patients

Baseline LAD in the 564 study participants (age at diagnosis: 50.7 ± 15.5 years; 63.3% men; follow-up period: 10.8 ± 7.4 years) was 38.6 ± 8.2 mm, and enlarged LAD (≥48 mm) was observed in 86 patients (15.2%). As for 247 study patients with left atrial volume measurements available, patients with enlarged LAD had a larger left atrial volume than those without enlarged LAD (117.9 ± 43.6 ml vs. 74.7 ± 32.9 ml, $p < 0.001$). The distribution of LAD in the study patients is shown in Fig. 1A. The distribution of LAD in HCM patients with and without AF is shown in Fig. 1B. Twenty-eight of the 86 patients with enlarged LAD (32.6%) and 38 of the 478 patients without enlarged LAD (8.0%) experienced episodes of progressive heart failure with an increase to ≥3 New York Heart Association functional class ($p < 0.001$). In addition, 19 of the 86 patients (22.1%) with enlarged LAD and 44 of 478 patients (9.2%) without enlarged LAD had ischemic embolic events ($p = 0.001$) during the follow-up periods.

Enlarged left atrium and sudden death risk

The distribution of LAD in HCM patients with sudden death and potentially lethal arrhythmic events is shown in Fig. 1C. Seventeen patients with enlarged LAD (19.8%) experienced sudden death and potentially lethal arrhythmic events, including 12 patients with sudden death, two with resuscitated cardiac arrest (one with

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