Risk of Sudden Death and Outcome in Patients With Hypertrophic Cardiomyopathy With Benign Presentation and Without Risk Factors

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Patients with hypertrophic cardiomyopathy (HC) are reported to have a mortality rate of about 1.0% per year, and those patients without sudden death risk factors and with no or mild symptoms are generally considered to have a benign clinical presentation. However, the risk of sudden death and the outcome in this latter subgroup have not been investigated systematically and remain unresolved. We assessed the risk of sudden death and outcome in 653 consecutive patients with HC without risk factors and with no or mild symptoms. Over a median follow-up of 5.3 years, 35 patients (5.4%) died of HC-related causes. Mean age at death was 46 ± 20 years in patients who died suddenly and 66 ± 15 and 72 ± 9 years, respectively, in patients who died of heart failure or stroke. Event rate was 0.6% per year for sudden death, 0.2% per year for heart failure death, and 0.1% per year for stroke-related death. Sudden death risk was independently and inversely related to age, and risk of heart failure or stroke death was directly related to age ($p = 0.020$). At 10 years after the initial evaluation, sudden death risk was 5.9%, with sudden death rate being the lowest (0.3% per year) in patients with normal left atrial dimension (≤40 mm). In conclusion, in patients with HC without conventional risk factors and with no or mild symptoms, the risk of sudden death was not negligible, with an event rate of 0.6% per year. Heart failure and stroke-related death were less common and largely confined to older patients. These results underscore the need for a more accurate assessment of the sudden death risk in patients with HC. **(Am J Cardiol 2014;113:1550−1555)**

Sudden and unexpected cardiac death continues to be the most devastating complication in the natural history of hypertrophic cardiomyopathy (HC).[1,2] In recent years, evidence has emerged regarding the effectiveness of the implantable cardioverter-defibrillator (ICD) in preventing sudden death in high-risk patients with HC.[3,4] Therefore, increasing attention has been directed toward risk stratification in those patients with HC who have conventional risk markers for sudden death and who could benefit from ICD therapy.[5−9] However, the long-term clinical outcome in patients with HC without risk factors and benign clinical presentation has not been systematically investigated. This is highly relevant when considering that HC has a prevalence of 1 in 500 in the general population[10] and that about 50% of patients with HC have no markers for high-risk status.[5−9] Therefore, we have investigated the risk for sudden death and overall clinical outcome in a consecutive cohort of patients without risk factors for sudden death and with no or mild symptoms, who were selected from a large multicenter international HC population.

Methods

From January 1990 to March 2009, a total of 2,037 consecutive patients with HC were evaluated at 6 HC centers. Of these 2,037 patients, 668 (33%) were selected for the present investigation, based on the following clinical profiles at initial evaluation: (1) absence of each of the 4 conventional major sudden death risk factors; (2) no or only mild symptoms (New York Heart Association [NYHA] functional classes I or II); (3) absence of history of atrial fibrillation (AF); (4) no previous surgical myectomy, alcohol septal ablation, or ICD implant; (5) absence of systolic dysfunction (left ventricular [LV] ejection fraction <50% at rest); and (6) age ≥10 and ≤75 years at initial evaluation.

From October 2009 to August 2010, follow-up information was updated either by clinic visit or telephone contact in 653 of the 668 patients (98%) initially selected for the study. In 8 of the remaining 15 patients, the vital status could be ascertained from the National Registry Office.

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See page 1555 for disclosure information.

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0002-9149/14/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2014.01.435

Table 1
Clinical characteristics in 653 patients with hypertrophic cardiomyopathy and without risk factors at initial evaluation

Variable	Patients (n = 653)
Age (yrs)	
Median (range)	46 (10–75)
Mean ± SD	44.4 ± 16.8
Male sex	461 (70.6)
LV outflow obstruction	168 (25.7)
Maximal LV wall thickness (mm)	
Median (range)	18 (8–29)
Mean ± SD	19.0 ± 3.9
LV end-diastolic cavity dimension (mm*)	
Median (range)	45 (17–67)
Mean ± SD	44.1 ± 6.7
LA dimension (mm†)	
Median (range)	42 (20–67)
Mean ± SD	41.9 ± 6.7
Treatment	
None	227 (34.8)
β Blockers	317 (49.9)
Calcium antagonists	117 (18.4)
Amiodarone	11 (1.7)
Diuretics	55 (8.7)

Data are presented as n (%), unless otherwise specified.
* Available in 646 patients.
† Available in 650 patients.

Each patient was alive as of December 2010. However, these 8 patients were not included in the final study population because we did not know whether some of these patients had had ICD interventions, had survived a cardiac arrest, or had progressed to severe heart failure or AF. Therefore, the final study cohort comprised 653 patients with HC. A minimum follow-up of 6 months was achieved in all surviving patients in the study cohort. Diagnosis of HC was based on previously reported criteria.[5,8] LV outflow tract obstruction due to systolic anterior motion of the mitral valve was defined using standard criteria, as reported in previous studies.[5,8,11] The baseline clinical characteristics assessed in the study include the clinical features traditionally used in investigations on the natural history of HC.[5,8,11] In particular, continuous variables such as LV wall thickness and left atrial (LA) dimension were categorized based on standard criteria used in previous investigations.[5,8,11] Conventional markers for increased risk of sudden death include (1) family history of premature HC-related sudden death (aged <50 years), (2) massive LV hypertrophy (maximum wall thickness ≥30 mm), (3) ≥1 run of nonsustained ventricular tachycardia at a rate of ≥120 beats/min on 24-hour ambulatory (Holter) electrocardiographic monitoring and documented before or up to 6 months after initial clinical evaluation, and (4) previous unexplained syncope judged inconsistent with neurally mediated origin.[1,2,5–8]

Sudden death was defined as instantaneous and unexpected natural death, or an aborted cardiac arrest with documented ventricular fibrillation (VF), in patients previously in stable clinical condition.[5] In patients implanted with an ICD during follow-up, appropriate device interventions triggered by VF were considered as sudden death equivalent.[8] Death secondary to heart failure was defined as occurring in the context of long-standing symptoms of heart failure with severe clinical deterioration.[12] Death was defined as secondary to stroke when judged to be a direct consequence of an embolic event related to HC.[11,12]

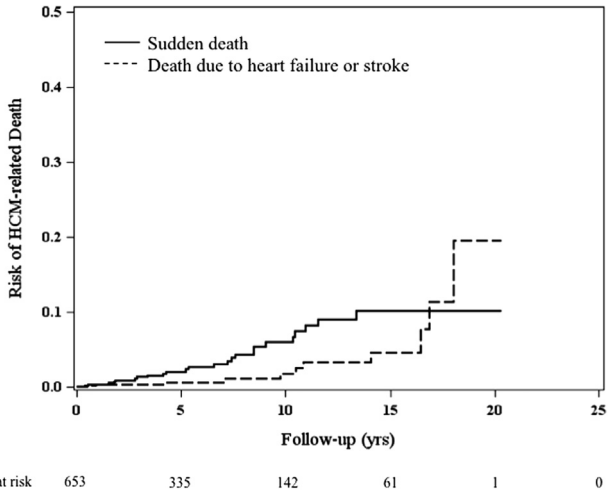

Figure 1. Incidence of sudden death and death due to heart failure (HF) or stroke. Ten years after initial evaluation, cumulative risk of sudden death was 5.9% and cumulative risk of death due to HF or stroke was 1.7%. HCM = hypertrophic cardiomyopathy.

Observation times of surviving patients without unfavorable events (progression to severe heart failure or AF) were censored at the date of the most recent follow-up. Median follow-up time was calculated according to the reverse Kaplan-Meier method. Cumulative risks of events were computed using the Kaplan-Meier method. To assess the role of clinical and echocardiographic features as predictors of outcome, a set of univariate and multivariate Cox proportional hazard models were fitted to the data. Progression to NYHA functional class III to IV and development of AF were treated as time-dependent covariates when evaluated as potential risk factors. All reported p values were 2-sided. No adjustment for multiple tests was performed. Analyses were done (by LB) using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

At initial evaluation, the 653 study patients were aged 10 to 75 years (mean 44 ± 17, median 46); 461 (71%) were men. Baseline clinical characteristics of the patient cohort are summarized in Table 1. The median duration of follow-up in the study population was 5.3 years, interquartile range 2.6 to 9.9. During follow-up, 47 of the 653 study patients (7.2%) died, 35 (5.4%) from HC-related causes, including 24 (3.7%) sudden death, 7 (1.1%) from heart failure, and 4 (0.6%) from embolic stroke. The remaining 12 patients (1.8%) died from non-HC causes.

The rate of sudden death was 0.6% per year, heart failure death 0.2% per year, and stroke-related death 0.1% per year, and total HC-related death was 0.8%/year. Ten years after the initial evaluation, the cumulative sudden death risk was 5.9% (95% confidence interval [CI] 3.7 to 9.5), and the cumulative risk of heart failure or stroke-related death was 1.7% (95% CI 0.6 to 4.6; Figure 1). At time of death, mean