RESEARCH LETTER

Long-term mortality and risk factor analysis in hypertrophic cardiomyopathy patients with implantable cardioverter-defibrillators

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Introduction Hypertrophic cardiomyopathy (HCM) is a common disorder with the reported prevalence between 1:200 and 1:500.[1,2] Clinical manifestations, etiology, and disease course vary significantly between patients.[3,4] The annual mortality rate of HCM patients is estimated at 0.5%–1%.[3,5] Numerous data have shown a decline in mortality in HCM individuals over the past few decades.[3] Sudden cardiac death (SCD), heart failure, and thromboembolism are the main causes of death in this population.[3,5] Broad use of implantable cardioverter-defibrillator (ICD) therapy modifies the natural history of the disease. Therefore, cases with progression to the end-stage heart failure could become more frequent.[3] According to the literature overviews, the progression rate to end-stage HCM varies from 2.4% to 15.7%.[6] Modern studies show that end-stage heart failure is responsible for 60% of HCM-related deaths.[3] In this study, we present a long-term follow-up of 104 HCM individuals implanted with ICDs, with particular attention given to mortality and risk factors evaluated during an initial assessment. Our secondary objective was to evaluate the possible relationship between HCM Risk-SCD and all-cause or cardiovascular mortality. We wanted to verify, whether the patients with high HCM Risk-SCD, who had the ICD implanted, showed poor prognosis and high progression rate to end-stage heart failure after reduction of SCD risk through the ICD implantation.

Patients and methods A group of 104 consecutive patients with HCM, who had the ICD implantation performed in a single center between 1996 and 2006, were enrolled in the study.[7] Data were collected retrospectively between 1996 and 2019. The diagnosis of HCM was established based on valid 2014 European Society of Cardiology guidelines. Neither athletes nor individuals with metabolic / infiltrative diseases or syndromes were enrolled in the study.

Analyses were performed for the following risk factors: age at the time of implantation, unexplained syncope, family history of SCD, atrial fibrillation (AF), decreased left ventricular ejection fraction (LVEF) below 50%, nonsustained ventricular tachycardia, maximal left ventricular wall thickness, abnormal exercise blood pressure response, left ventricular outflow tract obstruction, increased left atrial (LA) diameter above 40 mm. HCM Risk-SCD was estimated using the HCM Risk-SCD Calculator V2 (doc2do.com).

The causes of death were determined through an analysis of the available medical history. To classify a particular case as the end-stage heart failure death, we verified the clinical context of each event, symptoms, echocardiography, and biochemical markers. When available data were nonconclusive, the cause of death was determined as unknown.

This study was approved by the institutional Ethics Committee (Approval No. IK-NPIA-0021-66/1653/17), and all procedures in the study were in accordance with the 1964 Declaration of Helsinki.

Statistical analysis Statistical analysis was performed with the SAS 9.4 package. Data are presented as a mean (SD) or median and interquartile range (age, follow-up, and HCM Risk-SCD) for continuous variables, and as numbers and percentage for categorical variables. To evaluate differences between the 2 groups, the χ^2 test or Fisher exact test and the *t* or Mann–Whitney test were used. The association of all the examined variables listed in TABLE 1 with the outcome

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(overall mortality and cardiovascular mortality) was assessed with the Cox proportional hazard model using univariable and backward multivariable procedures. A significance of 0.05 was required for a variable to stay in the multivariable model. Hazard ratios and 95% CIs were computed. A test for nonproportionality of hazards based on Schoenfeld residuals did not reveal significant violations of the proportionality assumptions. Probability of survival was estimated with Kaplan–Meier method. Homogeneity of the compared curves was assessed with the log-rank test. Two-sided *P* values above 0.05 were considered significant.

Results At the initial presentation there were 24 patients (23.1%) below the age of 20, and 35 (33.6%) between 20 and 40 years. The median age was 35.6 (26–47) years. Of those, 26 patients (25%) were implanted for secondary and 78 (75%) for primary SCD prevention. The median follow-up was 14.3 (13.0–16.4) years (range, 6.5–21 years). During the follow-up, 20 deaths (19.2%) were reported, including 13 (65%) due to cardiovascular causes. The leading cause of death in the analyzed population was advanced heart failure (8 cases; 40%). Further 3 cases (15%) were associated with heart transplantation complications. One person died due to ardiac tamponade during transvenous lead extraction procedure. Throughout the follow-up period, there was only a single incident of SCD. The SCD was determined as a cause of death in this case after a post mortem analysis of the arrhythmic episodes registered by the ICD. In 6 cases, the exact cause of death remained unknown. Colon cancer was confirmed as a cause of death in a single patient.

The summarized analysis of risk factors and their association with the end points is presented in TABLE 1. Multivariable analysis showed that LVEF and LA diameter were the independent risk factors for the cardiovascular and all-cause mortality in HCM patients with ICDs. Heterogeneity of Kaplan–Meier curves was demonstrated for the group of patients with LVEF below 50% and LVEF above 50% (log rank tests for all-cause mortality and cardiovascular mortality <0.001), and LA equal or below 39 for women and equal or below 41 for men vs above 39 for women and above 41 for men (all-cause mortality $P = 0.04$, cardiovascular mortality $P = 0.04$).

The relationship between age at initial presentation or AF and all-cause mortality was only proved in univariable analyses. A significant relationship between HCM Risk-SCD and the cardiovascular or all-cause mortality in HCM patients with ICDs was not proved.

Discussion The study analyzed HCM patients with ICDs. The young age of the study cohort, with the majority of patients below 40, and long follow-up period, allowed us to reliably assess the impact of modern clinical strategies on the prognosis of high-risk HCM patients. In our study, the estimated 1-, 3-, 5-, and 10-year survival rate (with 95% CI in brackets) were 100.0%, 97.1% (94.0%–100%), 96.2% (92.5%–99.9%), and 86.6% (79.8%–93.2%), respectively. A meta-analysis performed by Liu et al[8] showed lower pooled 1-, 3-, 5- and 10-year survival rates of 98.0% (97.4%–98.6%), 94.3% (93.1%–95.6%), 82.2% (75.2%–89.2%), and 75.0% (71.1%–78.9%), respectively. The observed discrepancies between the survival rates may be associated with the time when the studies were conducted and certain baseline characteristics of the populations. Furthermore, all of our patients underwent ICD implantation procedure that minimizes the risk of SCD.[2,7,8] The prevalence of SCDs in HCM populations differs between studies. For example, Weissler-Snir et al[9] estimated annual incidence rate of 0.31 per 1000 HCM patient-years for SCD death, while Songsirisuk et al[10] reported SCD events in 7% of their cohort. Contrary to these examples, we analyzed only HCM individuals with ICDs, and observed only a single case of SCD (0.96% of the analyzed population, and 7.7% of the HCM-related deaths). The lack of analysis of ICD interventions is the limitation of this study. Our observations showed that LVEF and LA diameter were the independent risk factors for the cardiovascular and all-cause mortality in HCM patients with ICDs. Decreased LVEF is widely known as an important factor of adverse prognosis in HCM individuals.[11] The predictive value of LA enlargement in HCM group is also broadly documented.[12,13] Moreover, increased LA diameter is the independent risk factor for the onset of AF and the occurrence of SCD in HCM patients.[13] Univariate analyses indicated that in HCM patients with ICDs, the AF and age at initial presentation correlated with all-cause mortality. Several studies indicated a higher prevalence of SCD in younger patients. The literature shows that a significant reduction in fatal arrhythmias through ICDs, and a high progression rate to end-stage HCM, which is strongly phenotype and genotype dependent, made age at the initial presentation not correlate with the HCM-related deaths in this group.[3] On the other hand, the older patients have a higher incidence of comorbidities and this could be an explanation for the significant role of age at initial presentation in the assessment of all-cause mortality risk.

We also wanted to assess whether high HCM Risk-SCD corresponded with cardiovascular and all-cause mortality in HCM patients with ICDs. We were fully aware that HCM Risk-SCD was created to calculate a 5-year risk of SCD in the HCM patients with no prior ventricular fibrillation or sustained ventricular tachycardia, and that our cohort baseline characteristics and outcomes differed from the population used to develop the HCM Risk-SCD.[7,8,13] However, this statistical model takes into account risk factors such as LA diameter and left ventricular outflow tract obstruction, which are associated with heart failure and HCM-related mortality.[14,15] Our statistical

TABLE 1 Risk factors for all-cause and cardiovascular mortality. Uni- and multivariable analysis

Risk factor	Cardiovascular mortality					All-cause mortality				
	Univariable analysis									
	Deceased (n = 13)	Other (n = 91)	*P* value	HR (95% CI)	*P* value	Deceased (n = 20)	Other (n = 84)	*P* value	HR (95% CI)	*P* value
Age at initial presentation, y, median (IQR)	44.1 (27.5–48.9)	34.6 (20.0–46.3)	0.31	1.02 (0.99–1.05)	0.24	44.8 (30.1–52.4)	33.4 (19.9–45.8)	0.04	1.03 (1.01–1.06)	0.02
Male sex, n (%)	6 (46.1)	42 (46.1)	1.00	1.00 (0.34–2.99)	1.00	9 (45.0)	39 (46.4)	0.91	0.95 (0.39–2.29)	0.91
LVEF, %, mean (SD)	50.3 (16.8)	64.9 (8.3)	0.01	0.91 (0.87–0.95)	<0.001	53.9 (15.4)	64.8 (8.2)	<0.001	0.92 (0.88–0.95)	<0.001
LA diameter, mm, mean (SD)	47.3 (6.1)	40.7 (6.6)	0.004	1.14 (1.04–1.25)	0.005	46.4 (6.6)	40.5 (6.5)	0.003	1.12 (1.04–1.22)	0.003
MWT, mm, mean (SD)	24.6 (9.1)	25.0 (8.2)	0.87	0.99 (0.93–1.06)	0.87	23.0 (8.0)	25.4 (8.3)	0.25	0.97 (0.91–1.03)	0.26
IVS >30 mm, n (%)	5 (38.5)	26 (28.6)	0.52	1.51 (0.49–4.62)	0.48	5 (25.0)	26 (30.9)	0.60	0.79 (0.29–2.19)	0.65
Significant LVOTO >30 mm Hg, n (%)	3/11 (27.3)	34/91 (37.4)	0.52	0.60 (0.21–1.71)	0.32	5/17 (29.4)	32/77 (41.6)	0.35	0.60 (0.21–1.71)	0.32
Secondary prevention, n (%)	3 (23.1)	23 (25.3)	1.00	0.84 (0.23–3.07)	0.79	4 (20.0)	22 (26.2)	0.57	0.72 (0.24–2.16)	0.55
AF, n (%)	6 (46.1)	25 (27.4)	0.20	2.07 (0.70–6.16)	0.2	10 (50)	21 (25)	0.03	2.46 (1.02–5.92)	0.047
nsVT, n (%)	9 (69.2)	59 (64.8)	1.00	1.21 (0.37–3.92)	0.75	13 (65.0)	55 (65.5)	0.97	0.98 (0.39–2.46)	0.97
Unexplained syncope, n (%)	7 (53.9)	50 (55.0)	0.94	0.90 (0.30–2.68)	0.85	10 (50.0)	47 (55.9)	0.63	0.77 (0.32–1.86)	0.57
aBPRE[a], n (%)	3 (23.1)	34 (37.4)	0.57	Ref	–	4 (20.0)	7 (8.3)	0.31	Ref	–
aBPRE+, n (%)	8 (61.5)	48 (52.7)		1.69 (0.45–6.37)	0.44	10 (50.0)	46 (54.8)		1.07 (0.39–2.95)	0.9
Not performed, n (%)	2 (15.4)	9 (9.9)		2.50 (0.42–14.95)	0.32	4 (20.0)	7 (8.3)		2.49 (0.70–8.81)	0.16
Family history of HCM, n (%)	10 (76.9)	56 (61.5)	0.37	1.95 (0.54–7.09)	0.28	14 (70.0)	52 (61.9)	0.5	1.40 (0.54–3.64)	0.49
Family history of SCD, n (%)	7 (53.8)	43 (47.2)	0.66	1.23 (0.41–3.67)	0.71	10 (50.0)	40 (47.6)	0.85	1.08 (0.45–2.60)	0.86
HCM Risk-SCD value, %, median (IQR)	7.6 (5.9–10.7)	7.0 (5.4–10.3)	0.89	1.01 (0.91–1.21)	0.89	6.2 (4.5–8.2)	7.7 (5.5–10.5)	0.3	0.96 (0.84–1.09)	0.49

Risk factor	Multivariable analysis			
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LVEF	0.917 (0.864–0.973)	0.004	0.921 (0.875–0.970)	0.002
LA	1.115 (1.014–1.227)	0.02	1.106 (1.023–1.195)	0.009

P value below 0.05 was considered significant.

a aBPRE was defined as a fall of >20 mm Hg or an increase of <20 mm Hg in systolic blood pressure during exercise.

Abbreviations: aBPRE, abnormal exercise blood pressure response; AF, atrial fibrillation; HR, hazard ratio; IVS, intraventricular septum; IQR, interquartile range; LA, left atrium; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MWT, maximum left ventricular wall thickness; nsVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death

analysis showed no relationship between HCM Risk-SCD and incidence of the assumed end points.

In conclusion, LVEF and LA diameter are prognostic factors associated with mortality in HCM patients with ICDs and may be useful in determining the subpopulation with poorer prognosis.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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