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Hypertrophic Cardiomyopathy: Role of the Implantable Cardioverter-Defibrillator

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Objectives. **We report the occurrence of cardiac events during long-term follow-up in patients with hypertrophic cardiomyopathy (HCM) after cardioverter-defibrillator implantation.**

Background. **The identification of patients at high risk for sudden death and the prevention of recurrence of sudden death in HCM represents a difficult problem.**

Methods. **We retrospectively analyzed the occurrence of cardiac events during follow-up of 13 patients with HCM who received an implantable cardioverter-defibrillator (ICD) because of aborted sudden death (n = 10) or sustained ventricular tachycardia (n = 3) (group I). Findings were compared with those in 215 patients with an ICD and other structural heart disease or idiopathic ventricular fibrillation (group II).**

Results. **After a mean (±SD) follow-up period of 26 ± 18 months, 2 of 13 patients in group I received appropriate shocks. The calculated cumulative incidence of shocks was 21% in group I and 66% in group II after 40 months ($p < 0.05$). We observed a low incidence of recurrence of ventricular tachycardia/fibrillation during follow-up in patients with HCM. No deaths occurred.**

Conclusions. **Our data suggest that ventricular tachyarrhythmias may not always be the primary mechanism of syncope and sudden death in patients with HCM. The ICD seems to have a less important impact on prognosis in patients with HCM than in patients with other etiologies of aborted sudden death.**

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Hypertrophic cardiomyopathy (HCM) is characterized by a partial or global hypertrophy of the left ventricle not caused by known diseases or conditions (1). The disease is transmitted with an autosomal dominant pattern of inheritance. Different genes have been related to the disease, and one single gene may be related to different phenotypic expressions, which may partly explain the remarkable anatomopathologic and clinical heterogeneity of the disease (2,3).

The natural history of HCM is usually characterized by a slow progression of symptoms such as angina or dyspnea or the occurrence of syncope. In contrast, sudden death may occur abruptly, with a particularly high incidence in children and young adults (4). Most patients are asymptomatic or only mildly symptomatic before the first episode of aborted sudden death.

The role of the implantable cardioverter-defibrillator (ICD) in preventing sudden death in patients with HCM is unclear.

The present study sought to assess the role of the ICD in patients with HCM who survived a first episode of sudden death. The findings in this patient group were compared with the occurrence of events in two other groups: patients with an ICD and structural heart disease (other than HCM) and patients with idiopathic ventricular fibrillation (structurally normal heart).

Methods

Patients. *Group I.* We retrospectively studied 13 patients with HCM (group I) and an ICD (eight men, five women; mean [±SD] age 48 ± 13 years). Five patients (39%) had hypertrophic obstructive cardiomyopathy, and all but one had asymmetric left ventricular wall hypertrophy. The maximal thickness of the affected wall was 25 ± 2 mm. All patients had normal coronary arteries. One patient had a minor systolic bridging in the left anterior descending coronary artery (5). Mean left ventricular ejection fraction (LVEF) was 65 ± 12%, and only one patient had abnormal systolic function (LVEF 40%).

The indication for ICD therapy was resuscitated sudden death with documented ventricular fibrillation during the aborted episode in 10 patients (77%), recurrent syncope with inducible polymorphic ventricular tachycardia or ventricular fibrillation during electrophysiologic evaluation in 2 patients (15%) and multiple episodes of sustained monomorphic ventricular tachycardia in the remaining patient. Programmed electrical stimulation of the heart was performed in all patients

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Abbreviations and Acronyms

ECG = electrocardiogram
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction

and was positive in seven (54%). The clinical characteristics and main echocardiographic findings of the patients are shown in Table 1.

All patients underwent ICD implantation with a transvenous lead system, and no complications were seen in the early postoperative period, with the exception of an early lead displacement in one patient. Two patients underwent elective generator replacement because of battery exhaustion. No device-related problems occurred during a mean follow-up period of 26 ± 18 months. After ICD implantation, 11 patients received antiarrhythmic drugs (Table 2).

Group IIA. Another 196 patients were analyzed (163 with ischemic heart disease, 33 with dilated nonischemic cardiomyopathy; mean age 63 ± 9 years, 88% male). The indications for ICD implantation were aborted sudden death in 80 patients (41%), syncopal ventricular tachycardia in 67 (34%) and medically uncontrollable ventricular arrhythmias in 43 (22%). In 3% of patients a prophylactic ICD implantation was performed because of poor left ventricular function in combination with inducible ventricular arrhythmias during electrophysiologic study. The mean LVEF in group IIA was 36 ± 15%. The mean follow-up period after ICD implantation was 24 ± 21 months.

Group IIB. A third group of patients with idiopathic ventricular fibrillation were also analyzed. There were 19 patients (90% male, mean age 39 ± 14 years) with a structurally normal heart, normal LVEF (71 ± 10%), normal left and right ventricles and normal coronary arteries. Twelve patients had an ICD implanted because of aborted sudden death (63%). The other six patients (32%) had syncopal sustained polymorphic ventricular arrhythmias. The remaining patient was an asymptomatic young patient with a family history of sudden death and an electrocardiogram (ECG) showing right bundle branch block, persistent ST segment elevation and easily inducible ventricular fibrillation (6). The follow-up period was 39 ± 20 months.

Shock occurrence and appropriateness or inappropriateness of therapy was assessed by analyzing the intracardiac electrograms or the RR intervals, or both, at the time of shock. Ninety-two percent of the total ICD group and 100% of patients with HCM had devices with capability for electrogram storage or RR interval analysis.

Statistical analysis. Kaplan-Meier analysis was performed to predict the incidence of the first appropriate shock at any time for a group, and the log rank test was performed to compare the study group with the other patient groups. The Student *t* test, Fisher exact test and chi-square analysis were used to compare the different study groups, respectively, for continuous and noncontinuous variables. Results are presented as mean value ± SD; $p < 0.05$ was considered significant.

Results

During the follow-up period of 26 ± 18 months, only 2 of 13 patients with HCM received appropriate shocks because of two episodes of sustained monomorphic ventricular tachycardia in one patient and several episodes of sustained polymorphic ventricular tachycardia or ventricular fibrillation in another.

Table 1. Clinical Manifestations and Diagnostic Study Results in 13 Patients With Hypertrophic Cardiomyopathy

Pt No./Gender	Age (yr)	Sync	CA	Holter Monitoring	HOCM	Wall	LVEF (%)	PES
1/M	35	+	+	rare nsVT	Yes	IVS	75	−
2/F	47	+	+	VEB	No	IVS	70	−
3/M	60	−	−	sVT	No	IVS	50	+
4/M	33	−	+	VEB	Yes	IVS	71	−
5/F	49	−	+		No	Inf-Ap	55	−
6/F	60	+	+	nsVT	No	Con	80	−
7/M	48	−	+	sVT	No	IVS-Ap	78	+
8/M	54	+	−	nspmVT	Yes	IVS	60	+
9/M	52	−	+	nsVT	Yes	IVS	76	+
10/F	15	+	+	nsVT	No	IVS	60	+
11/M	45	−	+	nsVT	No	IVS	65	+
12/M	63	+	−	VEB	No	IVS-Dil	40	+
13/F	58	−	+	VEB	Yes	IVS	70	−

Ap = apex; CA = cardiac arrest; Con = concentric wall hypertrophy; Dil = left ventricular chamber dilation; F = female; HCOM = hypertrophic obstructive cardiomyopathy; Inf = inferior wall; IVS = interventricular septum; LVEF = left ventricular ejection fraction; M = male; ns = nonsustained; PES = programmed electrical stimulation; pm = polymorphic; Pt = patient; s = sustained; Sync = syncope; VEB = ventricular ectopic beats; VT = ventricular tachycardia; Wall = segment affected; +/− = positive/negative.

Table 2. Events During Follow-Up in Patients With an Implantable Cardioverter-Defibrillator and Hypertrophic Cardiomyopathy

Pt No.	ICD Model	DFT (J)	No. of Appropriate Shocks	Inappropriate Shocks	Therapy Before Implant	Therapy After Implant	Follow-Up (mo)
1	P2	10	—	No	Sot	Sot	30
2	JEW	15	10	No	No	Amio; Sot	15
3	PRx	20	2	Yes	DDD pacing	DDD pacing	58
4	P2	15	—	Yes	Amio	Met	65
5	JEW	10	—	No	Amio	Met	34
6	MIN HC	15	—	No	Vera	No	9
7	JEW	15	—	No	Amio	Amio	30
8	P2	5	—	No	Amio; Prop	Prop	42
9	MIN	5	—	No	Vera	Vera	16
10	PRx III	5	—	Yes	Amio	Amio; Vera	26
11	MINI	8	—	No	Aten	Sot; Nif	11
12	MINI II	5	—	No	Amio	Amio	8
13	MINI II	10	—	No	Amio; Vera	Aten	3

Amio = amiodarone; Aten = atenolol; DFT = defibrillation threshold test; ICD = implantable cardioverter-defibrillator; Implant = ICD implantation; JEW = Medtronic Jewel; Met = metoprolol; MIN = CPI Ventak Mini; Nif = Nifedipine; P2 = CPI Ventak P2; Prop = propanolol; PRx = CPI Ventak Prx; Pt = patient; Sot = sotalol; Vera = verapamil.

The second of these two patients had previously been resuscitated.

Group IIA patients were older than group I patients (63 ± 9 vs. 48 ± 13 years, $p < 0.001$), but there were no age differences between groups I and IIB (48 ± 13 vs. 38 ± 14 years, p = NS).

Group IIA patients also had a worse LVEF than group I patients (36 ± 14% vs. 65 ± 12%, $p < 0.001$). LVEF was comparable in groups I and IIB (65 ± 12% vs. 71 ± 10%, p = NS).

The calculated cumulative occurrence of appropriate shocks in patients with HCM (group I) was 21% at 47 months of follow-up, significantly different from the cumulative occurrence of the first shock of 65% at 47 months for patients with a structurally normal heart and ventricular fibrillation (group IIB). The cumulative occurrence of shocks in patients with structural heart disease (group IIA) was also significantly higher, with 68% at 47 months of follow-up. Figures 1 and 2 show the Kaplan-Meier curves for shock occurrence in the different groups.

We also analyzed the subgroup of patients with ICD implantation after aborted sudden death (10 patients in group I, 80 in group IIA, 12 in group IIB), and we constructed Kaplan-Meier curves for the occurrence of the first appropriate shock in each subgroup. As can be seen in Figure 3, the cumulative incidence of first shock in group IIA and IIB patients with aborted sudden death was, respectively, 62% and 67% versus only 11% in resuscitated group I patients at 40 months ($p < 0.05$).

Three patients with HCM (23%) had inappropriate shocks because of fast atrial arrhythmias, which was comparable to the incidence of inappropriate shocks in group IIB (21%, p = NS) but significantly higher than the occurrence of inappropriate therapy in group IIA (6%, $p < 0.05$).

No deaths occurred in the study group. The total mortality rate during follow-up was 11% (26 patients) and occurred exclusively in group IIA.

Discussion

Risk stratification in hypertrophic cardiomyopathy. The identification of individual patients with HCM at high risk for sudden death and prevention of recurrence represents an unsolved problem in clinical cardiology.

Several factors have limited our ability to accurately stratify this risk. The disease prevalence is low, although probably underestimated (0.2% in the general population), and most published reports come from tertiary referral centers, introducing important selection biases (3). Furthermore, HCM seems to be a collection of different disease entities sharing certain morphologic characteristics.

There are several characteristics that seem to be associated with a worse prognosis: young age at clinical presentation, a positive family history of sudden death (which is also associated with particular genetic mutations) and a history of (pre)syncope or resuscitated sudden death. The presence of exercise-induced hypotension and nonsustained ventricular tachycardia in Holter monitoring would predict a poor prognosis (3). However, all these prognostic indicators have a low sensitivity and positive predictive accuracy that can be improved somewhat by combining several factors. Also, the presence of inducible ventricular arrhythmias at programmed electrical stimulation of the heart has a varying predictive accuracy, depending on the aggressiveness of the stimulation protocol (7,8).

Value of ICD therapy. We studied a group of patients with HCM highly selected in terms of risk because they underwent ICD implantation after such symptoms as impaired conscious-

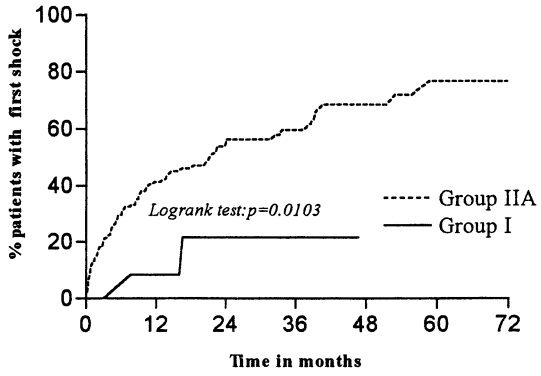


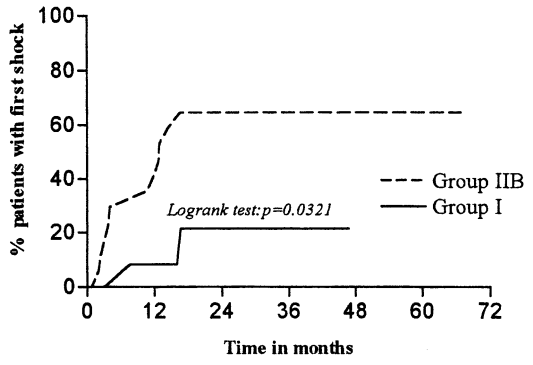
Figure 1. Cumulative occurrence of the first shock (Kaplan-Meier analysis) in patients with an ICD (group I) and patients with other forms of structural heart disease (group IIA). The cumulative occurrence of shocks was 68% in group IIA and 21% in group I after 47 months of follow-up.

ness, aborted sudden death or syncope. In an isolated case, symptomatic and sustained ventricular tachycardia in ambulatory ECG monitoring not suppressed by antiarrhythmic drug therapy was the indication for ICD implantation. Furthermore, ventricular fibrillation was documented during resuscitation in all patients, and in the two patients with syncope there were inducible ventricular tachycardias during programmed electrical stimulation of the heart.

We thus expected these patients to have the same benefit of ICD therapy as patients with ischemic heart disease and dilated cardiomyopathy (group IIA) or patients with an ICD and idiopathic ventricular fibrillation (group IIB). However, the number of patients with HCM who received shocks was only 2 of 13 after a mean follow-up of >2 years. We noted an important difference in cumulative occurrence of shocks in the different ICD groups, as well as in the subgroups with a history of aborted sudden death (Fig. 1 to 3)

These data suggest that ventricular arrhythmias may not always be the primary mechanism of syncope or sudden death in these patients. Although ventricular fibrillation was documented in all resuscitated patients, ventricular arrhythmias can be triggered by ischemia, outflow tract obstruction, arterial hypotension, diastolic dysfunction, proarrhythmic effects of antiarrhythmic drugs, sinus tachycardia during exercise or supraventricular tachyarrhythmias, such as atrial fibrillation (3–9).

Figure 2. Cumulative occurrence of the first shock (Kaplan-Meier analysis) in patients with HCM (group I) and patients with idiopathic ventricular tachycardia/ventricular fibrillation (group IIB). After 47 months of follow-up, the cumulative occurrence of first shock was 65% in group IIB and 21% in group I.



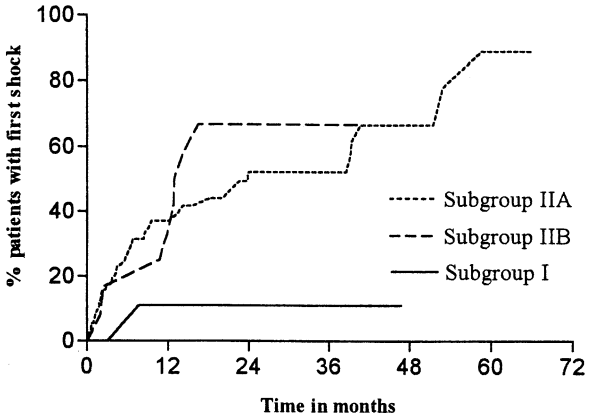


Figure 3. Cumulative occurrence of the first shock in patients with resuscitated sudden death (Kaplan-Meier analysis). The calculated cumulative occurrence of shocks was 62% in group IIA, 67% in group IIB and 11% in group I after 40 months of follow-up ($p = 0.0375$ for group I vs. group IIA and $p = 0.0372$ for group I vs. group IIB by log rank test). Groups I, IIA and IIB as in Figures 1 and 2.

Other mechanisms of syncope in HCM are known, such as bradyarrhythmias due to sinus node dysfunction or atrioventricular block or vasovagal mechanisms (10). Serious bradycardias were also documented in two of our patients before or after ICD implantation.

Because survival was 100% in our study group, we can speculate whether the "inappropriate shocks" for atrial fibrillation were sometimes perhaps "appropriate therapy" because it has been shown (4) that atrial fibrillation in patients with HCM can trigger malignant ventricular tachyarrhythmias. Also, antibradycardia pacing by the device could potentially have been life-saving in some patients.

Study limitations. There are several limitations that should be kept in mind when interpreting our findings. The study was a retrospective analysis, and although we evaluated a total of >200 patients with an ICD, this number is relatively small. However, to our knowledge there are no reports on the results of ICD therapy in larger groups of patients with HCM.

The analysis is confounded by the continuing use of antiarrhythmic drugs, but no significant difference in the use of these drugs before or after ICD implantation was noted.

Although the mean follow-up period exceeds 2 years, it is possible that with a longer follow-up period, a larger number of patients will have a recurrences. We therefore want to caution against interpreting the lower incidence of shocks in this cohort as evidence that ICD therapy is less indicated in patients with life-threatening ventricular tachyarrhythmias and HCM.

Conclusions. Our patients with HCM and sustained ventricular tachyarrhythmias had a lower incidence of recurrence

than did other patients with an ICD during a mean follow-up period of >2 years. These data suggest that ventricular arrhythmias may not always be the primary mechanism of syncope or sudden death in patients with HCM.

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