Survival After Cardiac Arrest or Sustained Ventricular Tachycardia in Patients With Hypertrophic Cardiomyopathy

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OBJECTIVES
The aim of this study was to evaluate the survival of patients with hypertrophic cardiomyopathy (HCM) after resuscitated ventricular fibrillation or syncopal sustained ventricular tachycardia (VT/VF) when treated with low dose amiodarone or implantable cardioverter defibrillators (ICDs).

BACKGROUND
Prospective data on clinical outcome in patients with HCM who survive a cardiac arrest are limited, but studies conducted before the widespread use of amiodarone and/or ICD therapy suggest that over a third die within seven years from sudden cardiac death or progressive heart failure.

METHODS
Sixteen HCM patients with a history of VT/VF (nine male, age at VT/VF 19 ± 8 years [range 10 to 36]) were studied. Syncopal sustained ventricular tachycardia/ventricular fibrillation occurred during or immediately after exertion in eight patients and was the initial presentation in eight. One patient had disabling neurologic deficit after VT/VF. Before VT/VF, two patients had angina, four had syncope and six had a family history of premature sudden cardiac death. After VT/VF all patients were in New York Heart Association class I or II, three had nonsustained VT during ambulatory electrocardiography and 11 had an abnormal exercise blood pressure response. After VT/VF eight patients were treated with low dose amiodarone and six received an ICD. Prophylactic therapy was declined by two patients.

RESULTS
Mean follow-up was 6.1 ± 4.0 years (range 0.5 to 14.5). Cumulative survival (death or ICD discharge) for the entire cohort was 59% at five years (95% confidence interval: 33% to 84%). Thirteen (81%) patients were alive at last follow-up. Two patients died suddenly while taking low dose amiodarone, and one died due to neurologic complications of his initial cardiac arrest. Three patients had one or more appropriate ICD discharges during follow-up; the times to first shock after ICD implantation were 23, 197 and 1,124 days.

CONCLUSIONS
This study shows that patients with HCM who survive an episode of VT/VF remain at risk for a recurrent event. Implantable cardioverter defibrillator therapy appears to offer the best potential benefit regarding outcome. (J Am Coll Cardiol 1999;33:1596–601) © 1999 by the American College of Cardiology

Hypertrophic cardiomyopathy (HCM) is a primary cardiac muscle disorder caused by mutations in genes encoding cardiac sarcomeric proteins (1). Sudden death, its most important complication, is reported to occur with an annual incidence of 2% to 4% in tertiary referral centers (2,3), and approximately 1% in predominantly regionally based populations (4–6). A relatively low annual event rate, and the fact that most patients with HCM fail to survive their first episode of ventricular fibrillation, mean that prospective studies of clinical outcome in patients who survive a cardiac arrest are scarce. The data that are available suggest that over a third of patients experience a further cardiac arrest or die from progressive heart failure within seven years when treated in a nonsystematic fashion (7). The aim of this study was to determine whether treatment with low dose amiodarone and/or implantable cardioverter defibrillators (ICDs) has improved clinical outcome in HCM patients who have survived a cardiac arrest or syncopal ventricular tachycardia.

METHODS

Patients. Sixteen patients (nine male) referred between 1988 and 1997 with a history of witnessed sudden cardiovascular collapse in association with documented ventricular
fibrillation or syncopal sustained ventricular tachycardia (VT/VF) requiring direct current cardioversion were studied. These patients were recruited from a larger series of 630 patients referred during the same period. Fourteen had a history of VT/VF before their first assessment at our institution, and one afterwards. The initial assessment of Patient 15 was performed at another hospital within the United Kingdom, but all his clinical data were reviewed by the authors, and other members of his family are under follow-up at our institution. To date, single amino acid substitutions in genes encoding sarcomeric protein mutations have been identified in six patients; beta-myosin heavy chain gene mutations in two patients (Arg719Trp and Arg453Cys) and cardiac troponin T mutations in four (Arg92Glu, Arg278Cys and Ile79Asn) (8–11). Three other patients have been screened for beta-myosin heavy chain and troponin T mutations with negative results. The results of genetic screening in the remaining seven patients are awaited.

Clinical evaluation. Two dimensional and M-mode echocardiography were performed using conventional techniques (12,13). Left ventricular wall thickness was recorded, where possible, at mitral valve and papillary muscle level in the anterior and posterior septum, and in the lateral and posterior left ventricular walls using short-axis two-dimensional images. Anterior and posterior wall thickness at the apex was measured in the four-chamber apical view. In 15 patients the diagnosis of HCM was based on the demonstration of a maximum left ventricular wall thickness greater than or equal to two standard deviations from the normal corrected for age and body surface area in the absence of any other cardiac or systemic cause of left ventricular hypertrophy (14). The remaining patient had nondiagnostic electrocardiographic and echocardiographic abnormalities, a family history of HCM and a troponin T mutation (Ile79Asn). Left ventricular outflow tract velocities were determined using continuous wave Doppler, and left ventricular outflow tract gradients were calculated using the modified Bernoulli equation.

All patients underwent 48-h ambulatory electrocardiographic monitoring while performing unrestricted daily activities using the Marquette (Marquette Electronics, Diagnostic Division, Milwaukee, Wisconsin) Holter recording system on two channels. Computer-assisted analysis was performed using the Marquette Series 8000 Laser Holter and Laser Holter XP system. Nonsustained ventricular tachycardia was defined as a run of three or more consecutive beats at a rate of 120 beats per minute or more.

Fourteen patients underwent symptom-limited maximal exercise testing using the Bruce or modified Bruce protocols, with simultaneous respiratory gas analysis by a dedicated metabolic cart (Marquette Electronics) and a mass spectrophotometric gas analyzer according to established methodology (15). Blood pressure was measured using a mercury sphygmomanometer and auscultation of the Korotkov sounds over the brachial artery at rest, every minute during exercise and every 15 s during the initial 5 min of the recovery period. Blood pressure responses were classified as normal, flat (i.e., a systolic blood pressure rise of less than 20 mm Hg above the resting value during the whole exercise period) or hypotensive (a continuous fall throughout exercise of >20 mm Hg from baseline or an initial increase in systolic blood pressure with a subsequent fall of >20 mm Hg compared with the peak pressure) (16).

Follow-up. Follow-up data were obtained at regular visits to our institution and/or by direct communication with the patients and their attending physicians.

RESULTS

Clinical presentation. Mean age at VT/VF was 19 ± 8 years (range 10 to 36). Syncopal sustained ventricular tachycardia/ventricular fibrillation occurred during or immediately after moderate to severe physical exertion in eight patients and was the initial presentation in eight patients. Before VT/VF, 4 (25%) patients had experienced syncope, and 2 (13%) had exertional chest pain. Six patients (38%) had a family history of hypertrophic cardiomyopathy and premature (<40 years) sudden death (Table 1). Following VT/VF 15 patients were in New York Heart Association functional class I and II. Patient 9 had disabling neurologic deficit after VT/VF and was confined to a wheelchair. Evaluation after VT/VF revealed that three patients (19%) had nonsustained VT during 48-h ambulatory electrocardiographic monitoring. One patient had seven runs; the remaining two patients had two runs each. The maximum number of beats in any run was five, and the maximum rate was 180 beats/min. Fourteen patients underwent symptom-limited exercise testing; 11 (79%) of the 14 had an abnormal blood pressure response.

Echocardiography. Follow-up echocardiograms performed at our institution were available in 10 of the 16 patients. The mean interval between the first and last echocardiogram was 4.7 ± 2.9 years (range 1.7 to 11.0). Mean left ventricular end-diastolic and end-systolic diameters, and maximal left ventricular wall thickness at initial echocardiogram were 45 ± 6 mm, 28 ± 5 mm and 20 ± 6 mm respectively. Three patients had resting left ventricular outflow tract gradients of more than 30 mm Hg, two more than 60 mm Hg. At last follow-up, mean left ventricular end-diastolic and end-systolic diameters, and
maximal left ventricular wall thickness were 49 ± 6 mm, 31 ± 6 mm and 18 ± 3 mm respectively (p = NS compared with first study). In five patients, there was a reduction of more than 15% in maximal left ventricular wall thickness. In three of these five patients, wall thinning was accompanied by a 10% increase in left ventricular end-diastolic and end-systolic cavity dimensions. In one of the five patients there was an increase in only end-systolic dimension. Changes in left ventricular dimensions were not associated with a change in functional class.

Treatment. The choice of treatment related to failure of low dose amiodarone therapy, availability of appropriate devices and individual patient preference. After VT/VF, eight patients were commenced on low dose amiodarone (200 to 300 mg daily). Six patients underwent implantation of an automatic cardioverter defibrillator. One patient who was taking low dose amiodarone at the time of his first cardiac arrest (Patient 11) received an ICD and discontinued the drug. Two patients declined any prophylactic therapy. No patient in this study underwent septal myotomy–myectomy, dual chamber pacemaker insertion or transcatheter alcohol ablation.

Survival. Mean follow-up from the first documented episode of VT/VF was 6.1 ± 4.0 years (range 0.5 to 14.5). Thirteen patients (81%) were alive at last follow-up. The five-year event-free survival (death or ICD discharge) was 59% (95% confidence interval: 33% to 84%) (Fig. 1). Two patients died while taking amiodarone; Patient 15 died suddenly three months after starting low dose amiodarone; Patient 10 died 1.6 years after VT/VF. Plasma levels before death were unavailable in both patients. Plasma levels in the remaining patients at last follow-up were 0.7 ± 0.4 mg/liter.

Patient 9 died due to neurologic complications of his initial cardiac arrest.

Of the six patients with ICDs, three (Patients 4, 8 and 11) had appropriate discharges for ventricular tachycardia or ventricular fibrillation. The times to first discharge after ICD implantation were 197, 1,124 and 23 days, respectively. Interrogation of the ICDs in two patients demonstrated several episodes of atrial fibrillation degenerating into polymorphic VT (Patient 11) and sinus tachycardia followed by ventricular tachycardia (Patient 4) (Fig. 2). Electrocardiographic recordings were unobtainable in the third patient but the recorded R-R intervals before the ICD discharge were most consistent with rapid VT degenerating into VF. One further patient (Patient 7) had a discharge for

Table 1. Baseline Clinical Characteristics, Genotype and Treatment After VT/VF

<table>
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<tr>
<th>Patient</th>
<th>Genotype</th>
<th>Age at VT/VF (yr)</th>
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<th>Exertional CP</th>
<th>NYHA</th>
<th>Syncope</th>
<th>Abn BP</th>
<th>NSVT</th>
<th>Amiodarone</th>
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Abn BP = abnormal exercise blood response; Arg = arginine; Asn = asparagine; CP = chest pain; Cys = cysteine; FHSD = family history of premature sudden death; Glu = Glutamine; ICD = implantable cardioverter defibrillator; Ile = isoleucine; MHC = beta-myosin heavy chain; nd = not done; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association functional classification; TNT = troponin T; Trp = tryptophan; VT/VF = syncopal sustained ventricular tachycardia or ventricular fibrillation.

Figure 1. Cumulative survival (Kaplan-Meier analysis) from initial episode of syncopal sustained ventricular tachycardia/ventricular fibrillation to death or first appropriate implantable cardioverter defibrillator discharge. The numbers in parentheses refer to the number of patients followed for any given time period.
previously undocumented atrioventricular nodal reentry tachycardia.

**DISCUSSION**

This study demonstrates that approximately 30% of patients with HCM and a history of cardiac arrest have a further event within six years of their first episode. It shows that ICD therapy is an effective prophylactic treatment in such patients, and that ICD therapy is probably superior to low dose amiodarone in this high risk cohort. The cumulative event-free survival of 59% at five years is very similar to that reported in the largest series published in the pre-ICD era by Cecchi et al. (7). However, there were a large number of heart failure deaths in the earlier series compared with none in this report. Patients in the earlier cohort differed from those in the present study in that they were older, had more severe hypertrophy and had a higher prevalence of left ventricular outflow tract obstruction (Table 2). These clinical and morphologic differences may explain the lack of progressive heart failure deaths in the present study, although the fact that some patients in our cohort did develop progressive wall thinning despite a maintained functional class suggests that progressive myocardial dysfunction may be a consequence of cardiac arrest in some patients.

**Markers of sudden death risk.** Several clinical features are associated with an increased risk of dying suddenly in patients with HCM (1,2,17–19). In the young, one of the most important is unexplained syncope (2), and this was a prominent symptom in a quarter of the patients in the present study. Syncope can be caused by supraventricular arrhythmia or self-terminating ventricular tachycardia, but in most individuals its cause is difficult to determine. Approximately 25% of patients with HCM have abnormal peripheral vascular responses in association with flat or hypotensive blood pressure profiles during exercise (16,19), and this may in some individuals predispose to syncope or presyncope. The mechanism of abnormal peripheral vascu-
lar responses remains uncertain, the most popular theory being a centrally mediated dilation of peripheral resistance vessels triggered by activation of ventricular mechanoreceptors (20). The importance of the abnormal vascular response has recently been underlined by the demonstration of an association with reduced survival in patients less than 40 years old (19), and it is of note that 11 of the 14 patients who were exercised in the present study had either flat or hypotensive blood pressure responses.

A family history of sudden death is another important risk factor in the young (2). Several “high risk” mutations in genes encoding a number of cardiac sarcomeric proteins are described, and the six patients who were genotyped in this study all had point mutations that are associated with a high incidence of premature sudden death (1,8–11).

In adult patients, nonsustained ventricular tachycardia during ambulatory electrocardiographic monitoring is associated with an increased risk of sudden death (17,18), but its significance in children and adolescents has been difficult to determine, as it occurs much less frequently. Recently presented data indicate that young patients with nonsustained VT may be at greater risk (21), and it is notable that the three patients in this study with nonsustained VT were less than 40 years old. Nevertheless, further prospective studies are required to examine the relation between specific characteristics of nonsustained ventricular tachycardia and survival.

Triggers for sudden cardiac death. As death in patients with hypertrophic cardiomyopathy is by its very nature unpredictable, the electrocardiographic events immediately preceding cardiac arrest are rarely recorded (22,23). The data storage facility of most modern ICDs now makes it possible to record such events, and device interrogation in patients who received shocks in the present study revealed that ventricular fibrillation was preceded by atrial fibrillation, sinus tachycardia and ventricular tachycardia. This observation is consistent with the hypothesis that ventricular fibrillation in patients with HCM and an appropriate arrhythmogenic substrate can be triggered by other tachyarrhythmias. The mechanism by which they do so is uncertain, but accessory pathways, myocardial ischemia and abnormal vascular responses may play a role in some patients (1).

Low dose amiodarone versus ICD. In the present study, similar numbers of patients were treated with low dose amiodarone and ICDs. The number of patients studied is too small to make definitive recommendations for therapy, but the fact that two patients had VT/VF while taking low dose amiodarone indicates that in the modern era, patients with hypertrophic cardiomyopathy who survive a cardiac arrest should be preferentially treated with an ICD. The event rate after cardiac arrest in this study is consistent with either flat or hypotensive blood pressure responses.

In a study of two consecutive age- and gender-matched populations with nonsustained ventricular tachycardia (29), patients treated with low dose amiodarone therapy had a significantly lower sudden death rate than patients treated with “conventional” antiarrhythmics (predominantly disopyramide). A later study (30) demonstrated increased mortality in patients treated with amiodarone, but the patients in this series had very severe functional limitation and were treated with much higher doses. Preliminary observational data from our own patient cohort recruited over 10 years suggest that low dose amiodarone therapy is associated with a substantial reduction in sudden death rates in patients with multiple risk factors (31).

Study limitations. The small size of the patient cohort in this study is an inevitable consequence of the fact that very few patients with HCM survive a cardiac arrest or syncopal ventricular tachycardia. Conclusions regarding therapy in this high risk cohort remain speculative, but in the context of the growing number of similar reports it seems reasonable to advocate ICD therapy in this high risk subset of patients.

Conclusions. This study shows that patients with HCM who survive an episode of VT/VF remain at risk for a recurrent event. Implantable cardioverter defibrillator therapy appears to offer the best potential benefit regarding outcome. The optimal treatment regimen for those patients who are at risk but have not yet experienced a catastrophic cardiac event requires further evaluation.

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