

The New England Journal of Medicine

© Copyright, 2000, by the Massachusetts Medical Society

VOLUME 342

FEBRUARY 10, 2000

NUMBER 6



EFFICACY OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS FOR THE PREVENTION OF SUDDEN DEATH IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

BARRY J. MARON, M.D., WIN-KUANG SHEN, M.D., MARK S. LINK, M.D., ANDREW E. EPSTEIN, M.D.,
ADRIAN K. ALMQUIST, M.D., JAMES P. DAUBERT, M.D., GUST H. BARDY, M.D., STEFANO FAVALE, M.D.,
ROBERT F. REA, M.D., GIUSEPPE BORIANI, M.D., N.A. MARK ESTES III, M.D., AND PAOLO SPIRITO, M.D.*

ABSTRACT

Background Hypertrophic cardiomyopathy is a genetic disease associated with a risk of ventricular tachyarrhythmias and sudden death, especially in young patients.

Methods We conducted a retrospective multicenter study of the efficacy of implantable cardioverter-defibrillators in preventing sudden death in 128 patients with hypertrophic cardiomyopathy who were judged to be at high risk for sudden death.

Results At the time of the implantation of the defibrillator, the patients were 8 to 82 years old (mean [\pm SD], 40 ± 16), and 69 patients (54 percent) were less than 41 years old. The average follow-up period was 3.1 years. Defibrillators were activated appropriately in 29 patients (23 percent), by providing defibrillation shocks or antitachycardia pacing, with the restoration of sinus rhythm; the average age at the time of the intervention was 41 years. The rate of appropriate defibrillator discharge was 7 percent per year. A total of 32 patients (25 percent) had episodes of inappropriate discharges. In the group of 43 patients who received defibrillators for secondary prevention (after cardiac arrest or sustained ventricular tachycardia), the devices were activated appropriately in 19 patients (11 percent per year). Of 85 patients who had prophylactic implants because of risk factors (i.e., for primary prevention), 10 had appropriate interventions (5 percent per year). The interval between implantation and the first appropriate discharge was highly variable but was substantially prolonged (four to nine years) in six patients. In all 21 patients with stored electrographic data and appropriate interventions, the interventions were triggered by ventricular tachycardia or fibrillation.

Conclusions Ventricular tachycardia or fibrillation appears to be the principal mechanism of sudden death in patients with hypertrophic cardiomyopathy. In high-risk patients with hypertrophic cardiomyopathy, implantable defibrillators are highly effective in terminating such arrhythmias, indicating that these devices have a role in the primary and secondary prevention of sudden death. (N Engl J Med 2000;342:365-73.)

©2000, Massachusetts Medical Society.

HYPERTROPHIC cardiomyopathy is a genetically determined myocardial disease with a diverse natural history.¹⁻⁷ Since a subgroup of patients with hypertrophic cardiomyopathy are at high risk for sudden death, there has been considerable interest in risk stratification^{1,3,8-11} and appropriate preventive measures.^{3,11,12} There are few data supporting the efficacy of prophylactic treatment with amiodarone in patients with hypertrophic cardiomyopathy,¹³ and the frequent adverse consequences of long-term use of this drug limit its application for the prevention of sudden death in young patients with this disease.

The implantable cardioverter-defibrillator¹⁴ is widely accepted as a definitive treatment for the prevention of sudden death, principally in high-risk patients with ischemic heart disease.¹⁵⁻¹⁷ The superiority of the implantable defibrillator over antiarrhythmic-drug treatment has been documented in prospective, randomized trials.^{15,16} There are few data, however, on the efficacy of implantable cardioverter-defibrillators in patients with hypertrophic cardiomyopathy.^{12,18-20} We conducted a retrospective, multicenter study to determine the efficacy of defibrillators in a group of patients with hypertrophic cardiomyopathy who were considered to be at high risk for sudden death.

From the Minneapolis Heart Institute Foundation, Minneapolis (B.J.M., A.K.A.); the Mayo Clinic, Rochester, Minn. (W.-K.S., R.F.R.); New England Medical Center and Tufts University School of Medicine, Boston (M.S.L., N.A.M.E.); the University of Alabama at Birmingham, Birmingham (A.E.E.); University of Rochester Medical Center, Rochester, N.Y. (J.P.D.); University of Washington Medical Center, Seattle (G.H.B.); Università degli Studi di Bari, Bari, Italy (S.F.); Università di Bologna, Bologna, Italy (G.B.); and Ente Ospedaliero Ospedale Galliera, Genoa, Italy (P.S.). Address reprint requests to Dr. Maron at the Minneapolis Heart Institute Foundation, 920 E. 28th St., Suite 40, Minneapolis, MN 55407, or at gencvres@skypoint.com.

Other authors were Susan A. Casey, R.N., Minneapolis Heart Institute Foundation, Minneapolis; Marshall S. Stanton, M.D., Mayo Clinic, Rochester, Minn.; and Sandro Betocchi, M.D., Università Federico II, Naples, Italy.

*Participating centers and investigators are listed in the Appendix.

METHODS

Selection of Patients

Patients were recruited at 19 institutions in the United States and Italy. U.S. centers were invited to participate in the study because of their experience with the use of implantable defibrillators in patients with hypertrophic cardiomyopathy and because they routinely offered implantation of a defibrillator as a treatment option to patients judged to be at high risk (e.g., those with prior cardiac arrest or sustained ventricular tachycardia). In Italy, all major electrophysiology centers were invited to participate in the study. The participating centers enrolled an average of seven patients each, and eight institutions enrolled at least five patients.

The 128 patients enrolled in the study were the consecutive patients at each institution who met the following enrollment criteria: an unequivocal diagnosis of hypertrophic cardiomyopathy based on two-dimensional echocardiographic evidence of a hypertrophied and nondilated left ventricle in the absence of another cardiac or systemic disease that could have accounted for the hypertrophy^{7,21}; successful implantation of a cardioverter-defibrillator for the prevention of sudden death; and a follow-up period of at least three months after implantation of the defibrillator, with documentation of the clinical outcome as of September 1, 1998 (for 124 patients), the time of death (2 patients), or the removal of the device because of infection (2 patients). One patient with severe symptoms (who had survived cardiac arrest at the age of 16 years) died at the time of thoracotomy for implantation and is not included in the analysis.

Defibrillators

The defibrillators were implanted between December 1984 and June 1998; 101 patients (79 percent) underwent implantation after January 1, 1994. Implantation was performed through a thoracotomy with epicardial lead systems in 22 patients (17 percent) or transvenously in 106 (83 percent). Most of the devices were third-generation defibrillators with the capacity to provide antitachycardia and antibradycardia pacing and the potential for pectoral implantation; 95 (74 percent) of the devices had diagnostic memory and the ability to record and store electrocardiographic data, including intracardiac electrograms, for subsequent review.²²

Defibrillation thresholds were routinely tested to document suc-

cessful termination of ventricular tachyarrhythmias. Programmed antitachycardia pacing²³ was activated at the discretion of the investigator. Stored data were reviewed after all discharges.

Interpretation of Intracardiac Electrograms

Stored data were analyzed to classify the arrhythmias responsible for precipitating defibrillator discharges, according to the following definitions. Ventricular fibrillation or flutter was defined as regular or irregular tachycardia with regard to QRS or electrographic polarity, amplitude, morphology, and sequence, with a mean cycle length of 240 msec or less. Ventricular tachycardia was defined as regular (monomorphic) or irregular (polymorphic) tachycardia with regard to QRS or electrographic polarity, amplitude, and morphology, with a mean cycle length of more than 240 msec. Atrial flutter was defined as regular tachycardia with a ventricular cycle length of 350 to 450 msec and with no differences in electrographic morphology and polarity as compared with sinus rhythm. Atrial fibrillation was defined as irregular tachycardia with more than 60 msec between consecutive complexes and no differences in QRS morphology as compared with sinus rhythm. Sinus tachycardia was defined as regular tachycardia with a gradual acceleration identical to that recorded during sinus rhythm and a mean rate exceeding the programmed cutoff rate.

Classification of Discharges as Appropriate or Inappropriate

Defibrillator discharges that were considered appropriate included automatic defibrillation shocks or programmed antitachycardia overdrive pacing triggered by ventricular tachycardia or fibrillation and documented by stored intracardiac electrographic or cycle-length data. For events occurring in patients who had defibrillators without the capacity to store electrographic data, discharges were judged to be appropriate on the basis of clinical findings that strongly suggested the presence of ventricular arrhythmia (i.e., symptoms such as presyncope or syncope immediately before the discharge and the absence of these symptoms immediately afterward).

For patients with defibrillators that stored electrographic data, inappropriate discharges were defined as those triggered by a rapid ventricular rate exceeding the programmed threshold rate as a consequence of supraventricular tachycardia, exercise-related sinus tachycardia, or a malfunction of the device. For patients with de-

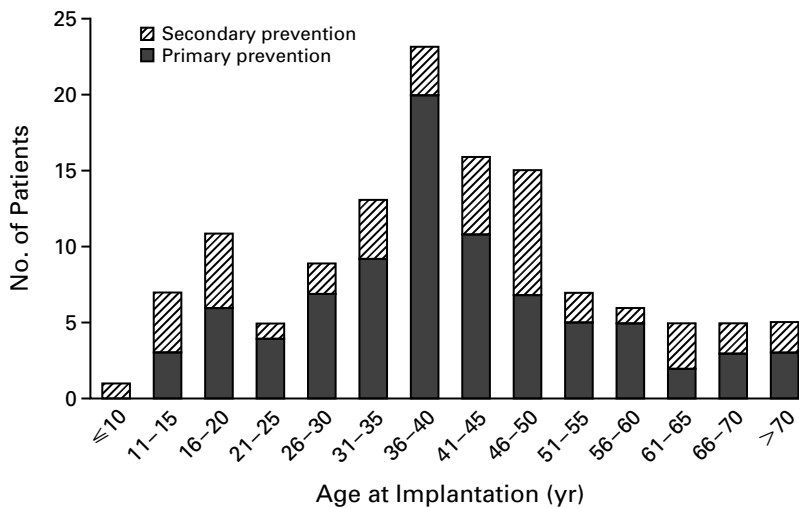


Figure 1. Age at the Time of Implantation of a Defibrillator in 128 Patients with Hypertrophic Cardiomyopathy Who Were Judged to Be at High Risk for Sudden Death.

The age distribution is shown according to whether the defibrillator was implanted for primary or secondary prevention.

fibrillators that did not store electrographic data, discharges were defined as inappropriate if they were not preceded by symptoms, if circumstances suggested the presence of sinus tachycardia due to emotional or physical stress, or if there was a malfunction of the device.

Each investigator initially classified a discharge as appropriate or inappropriate. For the group of 40 patients with discharges initially classified as appropriate, the stored electrographic data or clinical circumstances at the time of the discharge were subsequently reviewed independently by two of the investigators, who were experienced electrophysiologists.

The two independent reviews were concordant for 38 of the 40 patients (95 percent); for the other 2 patients, an agreement was reached. On the basis of these reviews, discharges were classified as appropriate in 29 patients and as inappropriate in 11 patients.

Statistical Analysis

Continuous data are expressed as means ±SD. Cumulative rates of appropriate discharges were estimated by the Kaplan-Meier method.²⁴

RESULTS

Characteristics of the Patients

At the time of implantation, the 128 patients were 8 to 82 years old (mean age, 40±16); 69 patients (54 percent) were less than 41 years old (Fig. 1) and 88 patients (69 percent) were male (Table 1). A total of 126 patients survived to the end of the follow-up period. Two patients (2 percent) with end-stage hypertrophic cardiomyopathy, systolic dysfunction, and refractory congestive heart failure died after defibrillator discharges failed to reverse ventricular tachyarrhythmias.²⁵

Two patients had an apical aneurysm associated with a midcavity obstruction,⁴ 12 had undergone prior septal myotomy-myectomy,^{1-4,7} and 6 had end-stage disease with severe systolic dysfunction and cavity dilatation.²⁶ The ejection fraction, estimated on the basis of echocardiography, was at least 55 percent in all the patients except the eight with end-stage disease or an aneurysm.

Reasons for Implantation of Defibrillators

In 43 patients (34 percent), with a mean age of 40±19 years, defibrillators were implanted for secondary prevention after either resuscitation from cardiac arrest (with documented ventricular fibrillation)²⁷ or sustained, spontaneous ventricular tachycardia. In the remaining 85 patients (66 percent), with a mean age of 40±15 years, defibrillators were implanted prophylactically for primary prevention of sudden death. The predominant clinical reasons for these prophylactic implantations, either alone or in combination, were syncope (in 41 patients), a family history of one or more sudden deaths due to hypertrophic cardiomyopathy (in 39), nonsustained ventricular tachycardia on Holter electrocardiographic monitoring (in 32), and a left-ventricular-wall thickness of at least 30 mm (in 10). In addition, 56 patients had inducible ventricular tachycardia or fibrillation during electrophysiologic testing.

TABLE 1. CLINICAL AND ECHOCARDIOGRAPHIC DATA ON 128 PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY WHO RECEIVED IMPLANTABLE CARIOVERTER-DEFIBRILLATORS.*

CHARACTERISTIC	VALUE
Mean age — yr	40±16
Male sex — no. (%)	88 (69)
NYHA class — no. (%)	
I	83 (65)
II	27 (21)
III or IV	18 (14)
Antiarrhythmic drugs — no.	
Amiodarone	
Before implantation	33
After implantation	22
Sotalol	
Before implantation	13
After implantation	11
Disopyramide	
Before implantation	7
After implantation	8
Maximal LV-wall thickness — mm†	
Mean	23±7
Range	14–60
LV end-diastolic cavity dimension — mm	
Mean	44±8
Range	23–61
Left atrial dimension — mm	
Mean	44±6
Range	26–62
LV outflow gradient — no. (%)	
≥30 mm Hg	23 (18)
<30 mm Hg‡	105 (82)
Electrophysiologic testing to induce VT or VF — no.	
Not inducible	12§
Inducible	79¶

*Data were documented at the time of implantation, unless otherwise indicated. Plus-minus values are means ±SD. NYHA denotes New York Heart Association, LV left-ventricular, VT ventricular tachycardia, and VF ventricular fibrillation.

†The analysis excluded 18 patients who had localized apical hypertrophy or who underwent echocardiographic studies after ventricular septal myotomy-myectomy was performed.

‡Included in this category were 94 patients in whom the gradient was zero. Twelve of the 105 patients were assessed after they had undergone myotomy-myectomy.

§In 4 of the 12 patients (33 percent), there was subsequently an appropriate defibrillator discharge.

¶In 19 of the 79 patients (24 percent), there was subsequently an appropriate defibrillator discharge.

Inappropriate Discharges

Of the 128 patients, 32 (25 percent) had one or more episodes of inappropriate discharges due to sinus tachycardia (in 13 patients), atrial fibrillation with a rapid ventricular rate (in 10), or lead dislodgment, disruption, or oversensing (in 9). Of these 32 patients, 13 had only 1 inappropriate discharge, and 19 had more than 1, including 5 patients who had 6 or more discharges (average, 2.6). In 7 of the 32 patients with inappropriate discharges, there was also at least one appropriate discharge.

Appropriate Discharges

Twenty-nine of the 128 patients (23 percent) had one or more appropriate discharges. Of these 29 pa-

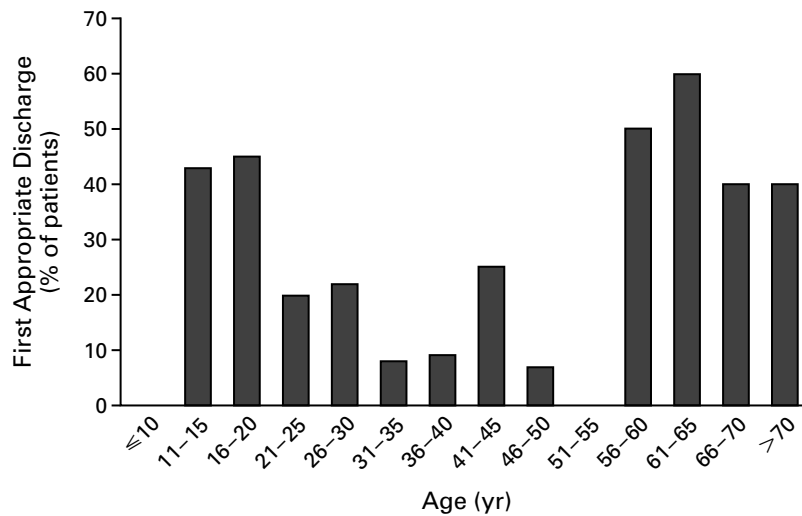


Figure 2. Age at the Time of the First Appropriate Defibrillator Discharge in 29 Patients.

The bar for each age category shows the number of patients with appropriate discharges expressed as a proportion of the patients who were in the same age category at the time that the defibrillator was implanted.

tients, 19 were in the group of 43 patients who had received defibrillators for secondary prevention (44 percent of the group), and 10 were in the group of 85 patients who had received defibrillators for primary prevention (12 percent of the group). Twenty-one of the 29 patients with appropriate discharges had defibrillators that stored electrographic data. The interventions were defibrillation shocks in 18 of these 21 patients and antitachycardia pacing in 3. Discharges in the other eight patients were considered to be appropriate on the basis of the clinical findings.

The age at which the first appropriate discharge occurred ranged from 11 to 83 years (mean, 41). Patients with appropriate discharges were most likely to be less than 31 years old or more than 55 years old (Fig. 2).

In the group of 10 patients who had appropriate discharges after implantation of defibrillators for primary prevention, the clinical reasons for implantation were as follows: syncope unassociated with sustained ventricular tachycardia or hemodynamic compromise in 5 patients (syncope on exertion in 2 and at rest in 3, with recurrent syncope in 2 of the 5), each with inducible ventricular tachycardia or fibrillation on electrophysiologic testing; nonsustained ventricular tachycardia in 2; massive left ventricular hypertrophy in 2; and a family history of sudden death in 1, with inducible ventricular arrhythmias in the patient. However, the 5 patients with syncope represented only 12 percent of the 41 patients in whom syncope was a major justification for prophylactic implantation of a defibrillator.

At the time of implantation, 26 of the 29 patients with appropriate discharges were asymptomatic or

had mild functional limitation (New York Heart Association class I or II), and 3 had severe symptoms (class III). Information about activity at the time of the first appropriate discharge was available for 28 patients; 25 were sedentary, asleep, or engaged in mild physical activity (e.g., walking or eating), and 3 were performing activities that involved physical exertion. Only 3 of 29 patients (10 percent) had left ventricular outflow obstruction (i.e., a gradient of at least 30 mm Hg). At the time of implantation, the cardiac rhythm was normal sinus in all the patients, but three had a history of atrial fibrillation.

Fifteen of the 29 patients with appropriate discharges (52 percent) received antiarrhythmic drugs (11 received amiodarone, 4 sotalol, and 2 disopyramide, alone or in combination) after implantation, as compared with 21 of the 99 patients (21 percent) with inappropriate discharges or none.

The interval between implantation of the defibrillator and the initial appropriate discharge²⁸ ranged from 2 weeks to 9 years (mean, 23 months) (Fig. 3). The interval was four or more years in six patients. Conversely, 12 patients had an initial appropriate discharge less than six months after implantation; in 9 of these 12 patients, there was at least one additional discharge (more than one year later in 6 patients).

Discharge Rates

With an average follow-up of 3.1 years after implantation, the rate of appropriate discharges for the overall study group was 7 percent per year. In the group of 43 patients with defibrillators implanted for secondary prevention, the rate of appropriate dis-

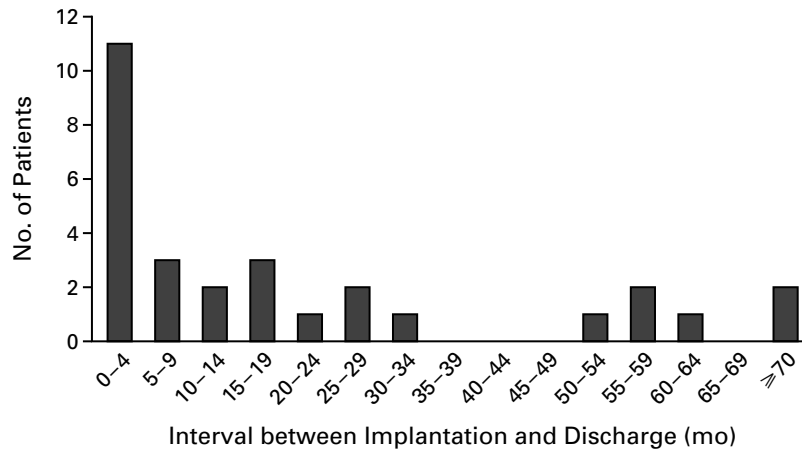


Figure 3. Interval between Implantation of the Defibrillator and the First Appropriate Discharge in 29 Patients.

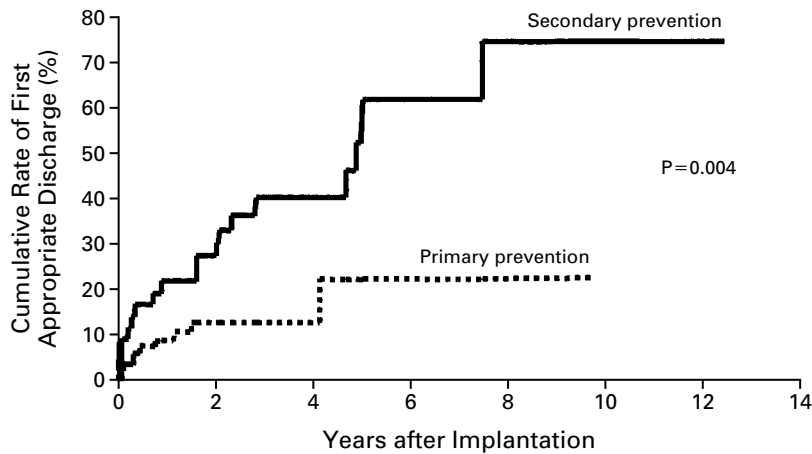


Figure 4. Estimated Cumulative Rates of First Appropriate Discharges, Calculated Separately for the 85 Patients with Defibrillators for Primary Prevention and the 43 Patients with Defibrillators for Secondary Prevention.

charges was 11 percent per year (mean follow-up period, 4.0 years). In the group of 85 patients with devices implanted for primary prevention, the estimated rate of appropriate discharges was 5 percent per year (mean follow-up period, 2.6 years). Cumulative rates of first appropriate discharges (Fig. 4) were significantly higher in the secondary-prevention group than in the primary-prevention group ($P=0.004$).

Multiple Discharges

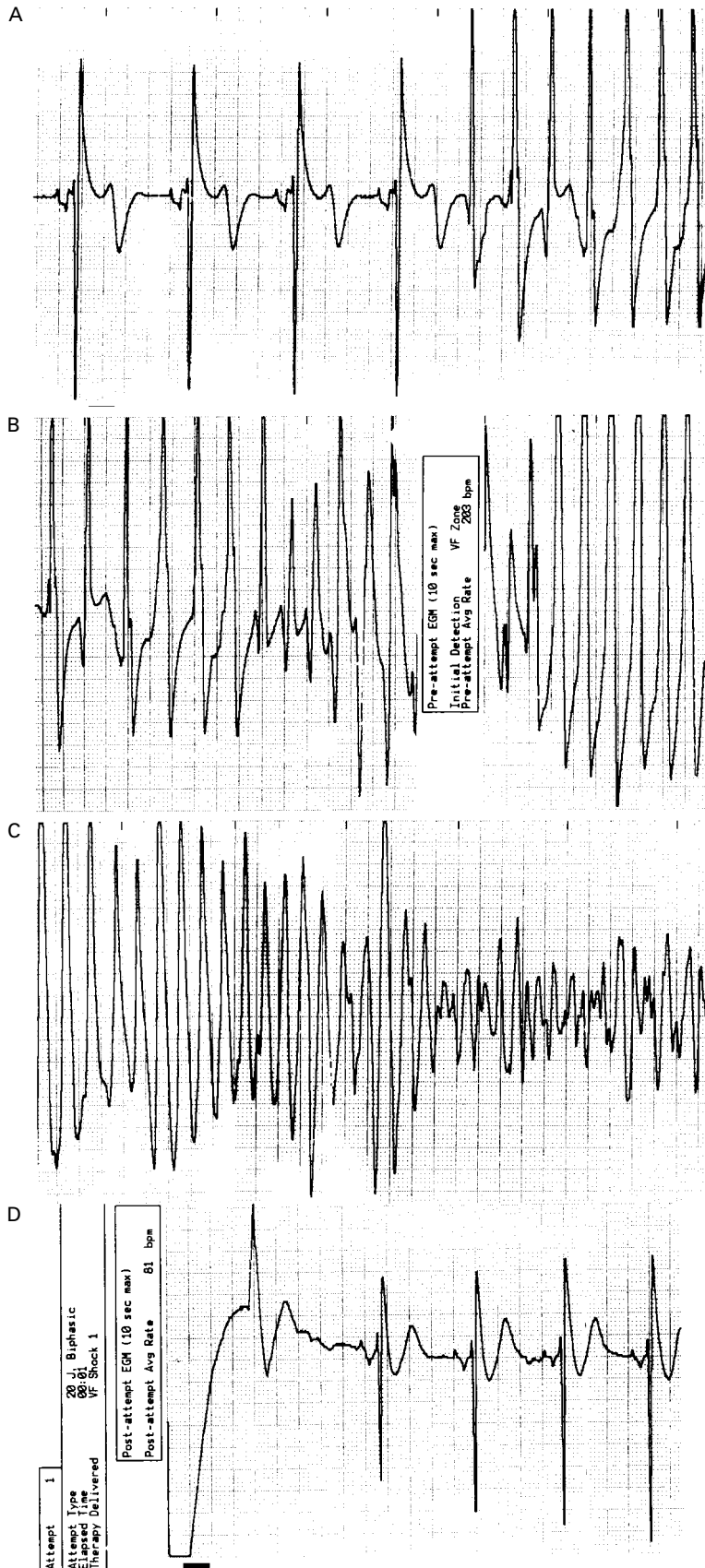
Of the 29 patients with appropriate discharges, 8 had a single defibrillation shock or cardioversion, and 12 had two to five interventions. Nine patients had more than five interventions, including six with clusters of multiple and consecutive appropriate discharges (three or more within 24 hours).²⁹

Triggering Events

Analysis of the stored electrographic data, which were available for 21 of the patients with appropriate discharges, showed that the intervention was triggered by ventricular tachycardia in 10 patients and by ventricular fibrillation in 9 patients, preceded by ventricular tachycardia in 3 of the 9 (Fig. 5). In two other patients, multiple discharges were preceded by either ventricular tachycardia or fibrillation.

Complications

Complications of defibrillator therapy occurred in 18 patients. These included lead malfunctions with fracture or disruption (in 12 patients, including 9 with inappropriate discharges), infection requiring removal of the defibrillator (in 2), and subclavian



thrombus, hemorrhage requiring thoracotomy, hematoma, and clinical depression in 1 patient each.

DISCUSSION

Sudden death has been recognized as a devastating consequence of hypertrophic cardiomyopathy since the initial description of the disease in 1958.³¹ Many authors have emphasized that sudden deaths frequently occur in young, asymptomatic patients, with reported annual mortality rates as high as 4 to 6 percent.³²⁻³⁶ Prevention of sudden death in patients with hypertrophic cardiomyopathy continues to be a major challenge.

The implantable cardioverter-defibrillator is clearly effective in terminating life-threatening ventricular arrhythmias in patients with coronary artery disease.¹⁴⁻¹⁷ Furthermore, the evolution of the implantable defibrillator from a device with epicardial leads that requires thoracotomy for implantation to a transvenous endocardial electrode system with pectoral implantation of the pulse generator has facilitated its clinical use. However, studies of defibrillators in small numbers of patients with hypertrophic cardiomyopathy have had mixed results,^{12,18-20} leaving the role of the implantable defibrillator in the management of this disease unresolved.³⁷ Indeed, in the joint recommendations of the American College of Cardiology and the American Heart Association, hypertrophic cardiomyopathy is not a standard indication for implantation of a defibrillator.³⁸

The results of our multicenter study establish an important role for implantable-defibrillator therapy in the prevention of sudden death in high-risk patients with hypertrophic cardiomyopathy. The defibrillator proved reliable in sensing and terminating life-threatening ventricular tachyarrhythmias. Appropriate discharges occurred in almost 25 percent of the 128 patients during an average follow-up period of three years. The annual discharge rate was 7 percent per year; furthermore, in about 70 percent of the patients

with appropriate discharges, there were multiple appropriate interventions. It should be emphasized, however, that the discharge rates in this study may have been influenced by the selection of patients and are most appropriately regarded as estimates. More than one third of the patients were taking amiodarone at the time of an appropriate discharge — a finding that highlights the superiority of the defibrillator in preventing sudden death.¹⁵

Discharges were most frequent in patients who had received defibrillators for secondary prevention of sudden death (i.e., those with prior cardiac arrest or spontaneous, sustained ventricular tachycardia). In over 40 percent of these patients, the defibrillator was activated on one or more occasions during a relatively short follow-up period. The frequent recurrence of potentially lethal ventricular tachyarrhythmias after cardiac arrest is consistent with reports on the clinical course of hypertrophic cardiomyopathy in the era before defibrillators were available.²⁷ Nevertheless, in our study, the implantable defibrillator did not provide complete protection against sudden death. The device failed to prevent death in two patients who had end-stage hypertrophic cardiomyopathy with severe systolic dysfunction and heart failure.²⁶

The rate of appropriate discharges was about 5 percent per year in the group of patients who had received defibrillators solely for primary prevention (i.e., those with one or more risk factors for sudden death). By extrapolating from this discharge rate, one could predict that within 10 years, almost 50 percent of the defibrillators prophylactically implanted in young patients would discharge and prevent sudden death. Also, the 5 percent annual discharge rate in our study is remarkably similar to the rates reported in selected high-risk patients with hypertrophic cardiomyopathy at tertiary referral centers.³²⁻³⁶

In the primary-prevention subgroup, the patients with appropriate discharges were most likely to have received a defibrillator because of syncope. However, our investigation was not designed to establish firm guidelines for prophylactic implantation of defibrillators in patients with hypertrophic cardiomyopathy, and one must be cautious in interpreting these findings, given our study design. The use of defibrillators for primary prevention in this retrospective study, although based on the generally accepted risk factors for sudden death in patients with hypertrophic cardiomyopathy,^{1,3} was not systematic or controlled and relied largely on the participating electrophysiologists' evaluation of the level of risk in their patients.

Since some patients with hypertrophic cardiomyopathy are at risk for sudden death over a long period, which may extend throughout midlife and thereafter,³⁹ the implantable defibrillator has the potential to prolong life substantially in such patients. In patients with coronary artery disease, defibrillators are implanted at a relatively advanced age (average, about

Figure 5. Stored Ventricular Electrogram from an Asymptomatic 35-Year-Old Man Who Received a Defibrillator Prophylactically Because of a Family History of Sudden Death Related to Hypertrophic Cardiomyopathy and Marked Ventricular Septal Thickness (31 mm).

The electrogram was obtained four years eight months after implantation of the defibrillator. The data were recorded at 1:20 a.m. while the patient was asleep. A continuous recording, at 25 mm per second, is shown in four panels, with the tracing recorded from left to right in each. After four beats of sinus rhythm, ventricular tachycardia begins abruptly, at a rate of 200 beats per minute (Panel A). The defibrillator senses ventricular tachycardia and charges (Panel B). Ventricular tachycardia deteriorates into ventricular fibrillation (Panel C). The defibrillator discharges appropriately (a 20-J shock denoted by the bar, Panel D) during ventricular fibrillation and restores sinus rhythm. Adapted from Maron et al.³⁰

65 years), whereas patients with hypertrophic cardiomyopathy who are at high risk for sudden death are often much younger and have few or no symptoms. Indeed, the average age of our patients at the time of implantation was 40 years (more than 25 percent were under the age of 31 years), and the average age at the time of the first appropriate defibrillator discharge was only 41 years. Despite our relatively short period of follow-up, in some cases, there was a particularly long interval between implantation and the first appropriate discharge, with a maximal interval of nine years; in 21 percent of the patients with appropriate discharges, the interval was at least four years. Thus, in patients with hypertrophic cardiomyopathy, the implanted defibrillator may remain dormant for a long period but eventually discharge appropriately. As a result, the decision to implant a cardioverter-defibrillator in a high-risk patient is likely to represent a lifelong preventive measure.

It has been difficult to identify the arrhythmias responsible for sudden death in patients with hypertrophic cardiomyopathy, largely because of the paucity of electrocardiographic recordings at the time of such events.⁴⁰ Considerable attention has been focused on primary ventricular tachyarrhythmias,^{33,34,40} but alternative mechanisms have been proposed.¹⁹ In our study, defibrillators in 21 patients recorded and stored electrographic data during appropriate discharges. In each instance, ventricular tachycardia or fibrillation was the rhythm that activated the device. These findings support the hypothesis that ventricular tachycardia or fibrillation is often the primary cause of sudden death in patients with hypertrophic cardiomyopathy, with the arrhythmia emanating largely from a substrate of electrical instability and distorted electrophysiologic transmission as a result of the characteristically disorganized arrangement of cardiac-muscle cells.⁴¹ The occurrence of bradycardia-mediated events could not be ruled out in our study population because of the backup pacing capacity in many of the devices.

Our data support the view that the implantable defibrillator can be a lifesaving device in patients with hypertrophic cardiomyopathy and support its use for both secondary and primary prevention. The defibrillator proved effective in terminating ventricular tachycardia or fibrillation despite the substantial increases in heart mass and wall thickness that are characteristic of this disease.^{1-4,6,21} However, it is also important to recognize that the implantable defibrillator is expensive, that its availability is still limited in many countries, that it may be associated with complications and may be activated inappropriately, and that it is not invariably effective. Although the rates of appropriate discharges in our patients with hypertrophic cardiomyopathy were lower than those reported in patients with ischemic heart disease,^{15,16} they are nevertheless substantial when viewed in the con-

text of a disease that frequently affects young patients without symptoms of congestive heart failure and with preserved systolic function. Given the protection afforded by an implantable defibrillator, such patients may survive for many decades, with normal or nearly normal life expectancy.

Since our study was retrospective and uncontrolled, with possible limitations related to the selection of patients, we wish to be cautious in drawing conclusions about the role of implantable defibrillators in the management of hypertrophic cardiomyopathy. We can reasonably conclude that the defibrillator was effective in preventing sudden death in a group of patients with hypertrophic cardiomyopathy who were considered to be at high risk. However, we did not compare the outcome in this group with that in a group of patients with hypertrophic cardiomyopathy and a similar clinical profile who were evaluated at the same centers but who did not receive defibrillators. It would be difficult to conduct prospective, randomized trials of the efficacy of defibrillators as compared with that of drug therapy in patients with hypertrophic cardiomyopathy because of ethical considerations, the relatively low prevalence of the disease in the general population,¹ and the relatively low event rate,^{1,3} as well as major practical limitations (e.g., the frequently long dormant period between implantation of the defibrillator and a first discharge).

Although selection bias could have influenced the precision of the estimated rates of appropriate discharges reported here, this factor does not obscure the basic message that the implantable cardioverter-defibrillator provides lifesaving protection by effectively terminating ventricular tachycardia or fibrillation in patients with hypertrophic cardiomyopathy who have few or no symptoms, many of whom are young. The use of a defibrillator is therefore warranted, for both primary and secondary prevention of sudden death, in high-risk patients with hypertrophic cardiomyopathy.

Funded in part by a grant from Medtronic, which manufactures implantable cardioverter-defibrillators.

We are indebted to Drs. Michel Mirowski and Morton M. Mower for their pioneering efforts, without which the clinical use of the implantable cardioverter-defibrillator would not have been possible, and to Dr. Cynthia De Souza, of Medtronic, Minneapolis, for statistical support.

APPENDIX

The following centers and investigators participated in the study: Mayo Clinic, Rochester, Minn. — W.-K. Shen, M.S. Stanton, and R.F. Rea; Azienda Ospedaliero S. Maria della Misericordia, Udine, Italy — A. Proclemer; Georgetown University Medical Center, Washington, D.C. — A.J. Solomon; Minneapolis Heart Institute Foundation, Minneapolis — A.K. Almquist, S.A. Casey, and B.J. Maron; New England Medical Center, Boston — M.S. Link and N.A.M. Estes III; North Shore University Hospital, Manhasset, N.Y. — M. Ovadia; Ospedale Civile, Asti, Italy — R. Massa; Ente Ospedaliero Ospedale Galliera, Genoa, Italy — P. Spirito and M. Berisso; Ospedale Maggiore della Carità, Novara, Italy — E. Occhetta; Ospedale Niguarda-Cá Granda, Milan, Italy — M. Lunati; Ospedale S. Filip-

po Neri, Rome — M. Santini and R. Ricci; Ospedale San Gerardo, Monza, Italy — A. Vincenti; St. Luke's-Roosevelt Hospital Center, New York — M.V. Sherrid and F. Ehler; Università degli Studi di Bari, Bari, Italy — S. Favale; Ospedale S. Orsola, Università di Bologna, Bologna, Italy — G. Boriani and C. Rapezzi; Università Federico II, Naples, Italy — S. Betocchi; Cattedra di Cardiologia, Università di Milano, Milan, Italy — P. Della Bella; University of Alabama at Birmingham, Birmingham — A.E. Epstein; De Paul Hospital, Norfolk, Va. — J.M. Herre; University of Rochester Medical Center, Rochester, N.Y. — J.P. Daubert; and the University of Washington Medical Center, Seattle — G.H. Bardy and J. Anderson.

REFERENCES

1. Maron BJ. Hypertrophic cardiomyopathy. *Lancet* 1997;350:127-33. [Erratum, *Lancet* 1997;350:1330.]
2. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy: clinical spectrum and treatment. *Circulation* 1995;92:1680-92.
3. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med* 1997;336:775-85.
4. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy: a review. *Prog Cardiovasc Dis* 1985;28:1-83.
5. Maron BJ, Moller JH, Seidman CE, et al. Impact of laboratory molecular diagnosis on contemporary diagnostic criteria for genetically transmitted cardiovascular diseases: hypertrophic cardiomyopathy, long-QT syndrome, and Marfan syndrome: a statement for healthcare professionals from the councils on clinical cardiology, cardiovascular disease in the young, and basic science, American Heart Association. *Circulation* 1998;98:1460-71.
6. Louie EK, Edwards LC III. Hypertrophic cardiomyopathy. *Prog Cardiovasc Dis* 1994;36:275-308.
7. Maron BJ, Bonow RO, Cannon RO III, Leon MB, Epstein SE. Hypertrophic cardiomyopathy: interrelations of clinical manifestations, pathophysiology, and therapy. *N Engl J Med* 1987;316:780-9, 844-52.
8. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation* 1997;96:2987-91.
9. Olivetto I, Maron BJ, Monteregeggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1999;33:2044-51.
10. Spirito P, Rapezzi C, Autore C, et al. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. *Circulation* 1994;90:2743-7.
11. McKenna WJ, Camm AJ. Sudden death in hypertrophic cardiomyopathy: assessment of patients at high risk. *Circulation* 1989;80:1489-92.
12. Primo J, Geelen P, Brugada J, et al. Hypertrophic cardiomyopathy: role of the implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1998;31:1081-5.
13. McKenna WJ, Oakley CM, Krikler DM, Goodwin JF. Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. *Br Heart J* 1985;53:412-6.
14. Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980;303:322-4.
15. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-83.
16. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933-40.
17. Zipes DP, Roberts D. Results of the international study of the implantable pacemaker cardioverter-defibrillator: a comparison of epicardial and endocardial lead systems. *Circulation* 1995;92:59-65.
18. Silka MJ, Kron J, Dunnigan A, Dick M II. Sudden cardiac death and the use of implantable cardioverter-defibrillators in pediatric patients. *Circulation* 1993;87:800-7.
19. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1999;33:1596-601.
20. Zhu D, Sun H, Hill R, Roberts R. The value of electrophysiology study and prophylactic implantation of cardioverter defibrillator in patients with hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol* 1998;21:299-302.
21. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995;26:1699-708.
22. Ruppel R, Schlüter CA, Boczor S, et al. Ventricular tachycardia during follow-up in patients resuscitated from ventricular fibrillation: experience from stored electrograms of implantable cardioverter-defibrillators. *J Am Coll Cardiol* 1998;32:1724-30.
23. Schaumann A, von zur Mühlen F, Herse B, Gonska B-D, Kreuzer H. Empirical versus tested antitachycardia pacing in implantable cardioverter defibrillators: a prospective study including 200 patients. *Circulation* 1998;97:66-74.
24. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
25. Pires LA, Lehmann MH, Steinman RT, Baga JJ, Schuger CD. Sudden death in implantable cardioverter-defibrillator recipients: clinical context, arrhythmic events and device responses. *J Am Coll Cardiol* 1999;33:24-32.
26. Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. *Am J Cardiol* 1998;81:1339-44.
27. Cecchi F, Maron BJ, Epstein SE. Long-term outcome of patients with hypertrophic cardiomyopathy successfully resuscitated after cardiac arrest. *J Am Coll Cardiol* 1989;13:1283-8.
28. Myerburg RJ, Luceri RM, Thurer R, et al. Time to first shock and clinical outcome in patients receiving an automatic implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1989;14:508-14.
29. Credner SC, Klingenberg T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. *J Am Coll Cardiol* 1998;32:1909-15.
30. Maron BJ, Casey SA, Almquist AK. Aborted sudden cardiac death in hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 1999;10:263.
31. Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958;20:1-8.
32. Shah PM, Adelman AG, Wigle ED, et al. The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy. *Circ Res* 1974;35:Suppl II:1179-II-195.
33. McKenna WJ, Deanfield JE. Hypertrophic cardiomyopathy: an important cause of sudden death. *Arch Dis Child* 1984;59:971-5.
34. McKenna W, Deanfield J, Faruqui A, England D, Oakley C, Goodwin J. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. *Am J Cardiol* 1981;47:532-8.
35. Fiddler GI, Tajik AJ, Weidman WH, McGoon DC, Ritter DG, Giuliani ER. Idiopathic hypertrophic subaortic stenosis in the young. *Am J Cardiol* 1978;42:793-9.
36. Maron BJ, Henry WL, Clark CE, Redwood DR, Roberts WC, Epstein SE. Asymmetric septal hypertrophy in childhood. *Circulation* 1976;53:9-19.
37. Borggrefe M, Breithardt G. Is the implantable defibrillator indicated in patients with hypertrophic cardiomyopathy and aborted sudden death? *J Am Coll Cardiol* 1998;31:1086-8.
38. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). *J Am Coll Cardiol* 1998;31:1175-209.
39. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Acippli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA* 1999;281:650-5. [Erratum, *JAMA* 1999;281:2288.]
40. Nicod P, Polikar R, Peterson KL. Hypertrophic cardiomyopathy and sudden death. *N Engl J Med* 1988;318:1255-7.
41. Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. *Circulation* 1979;59:689-706.