Clinical Characteristics and Outcome of Patients With High Defibrillation Thresholds
A Multicenter Study

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Background. Successful defibrillation by an implantable cardioverter-defibrillator (ICD) depends on its ability to deliver shocks that exceed the defibrillation threshold. This study was designed to identify clinical characteristics that may predict the finding of an elevated defibrillation threshold and to describe the outcome of patients with high defibrillation thresholds.

Methods and Results. The records of 1,946 patients from 12 centers were screened to identify 90 patients (4.6%) with a defibrillation threshold ≥25 J. Excluding three patients who received ICDs that delivered >30 J, there were 81 men and six women with a mean age of 59.5±10.1 years, a mean left ventricular ejection fraction of 0.32±0.14, and a 76% prevalence of coronary artery disease. Sixty-one patients (70%) were receiving antiarrhythmic drugs, and 45 (52%) were receiving amiodarone. Seventy-one patients (82%) received an ICD. Death occurred in 27 patients—19 of the 71 (27%) with an ICD (eight arrhythmic), and eight of the 16 (50%) without an ICD (four arrhythmic). Actuarial survival for all patients at 5 years was 67%. Actuarial survival rates at 2 years for patients with and without an ICD were 81% and 36%, respectively (p=0.0024). Actuarial survival at 5 years for the ICD patients was 73%; no patient without an ICD has lived longer than 32 months. Actuarial survival free of arrhythmic death in the ICD patients at 5 years was 84%. Although the only variable to predict survival was ICD implantation (p=0.003), it is entirely possible that in this retrospective analysis, clinical selection decisions to implant or not implant an ICD differentiated patients destined to have better or worse outcomes, respectively.

Conclusions. Antiarrhythmic drug use may be causally related to the finding of an elevated defibrillation threshold. When patients with high defibrillation thresholds receive an ICD, arrhythmic death remains an important risk (42% of deaths in these patients were arrhythmia related, with 16% actuarial incidence at 5 years). Vigorous testing to optimize patch location can potentially benefit patients by enhancing the margin of safety for effective defibrillation. (Circulation 1992;86:1206–1216)

KEY WORDS • cardiac arrest • defibrillation • implantable cardioverter-defibrillator • sudden death • ventricular fibrillation

Successful defibrillation by an implantable cardioverter-defibrillator (ICD) depends on its ability to deliver shocks that exceed the defibrillation threshold.1,2 Fortunately, finding a defibrillation threshold that exceeds ICD output capacity is an infrequent occurrence,3 although one series reported an incidence of 18%.4 Many factors are related to defibrillation energy requirements, and several factors have been related to and implicated as causes of elevated defibrillation thresholds including drug therapy5–35; underlying cardiac disease4,36,37; the size, configuration, and number of defibrillating leads2,38; the time that ventricular fibrillation persists before shock delivery16,39–41; ischemia and hypoxia42,43; the amplitude of the ventricular fibrillation waveform16,44; temperature45; heart weight16,46; body weight16,46; species46; the chronicity of lead implantation24,47; and the waveform2,48,49 and direction50 of the delivered shock. Because of the potential adverse consequences of an elevated defibrillation threshold,1,51,52 identifying patient characteristics that are predictive for this occurrence is important. To this end, a consortium was formed to pool a large collective experience and identify potential predictors of an elevated defibrillation threshold.

Methods

Patient Population

Data bases from 12 centers were screened to identify patients with defibrillation threshold ≥25 J. The charts of these patients were systematically reviewed, and the patient data were entered into a registry of predefined variables including age, sex, cardiac diagnosis, ejection fraction, presenting arrhythmia, New York Heart Asso-
association functional class, presence or absence of congestive heart failure, and antiarrhythmic drug treatment. In addition, concomitant surgery including coronary artery bypass grafting, valve replacement, left ventricular aneurysmectomy, ventricular tachycardia surgery, or any other procedure was noted. The location of defibrillator patch implantation was recorded as being intrapericardial or extrapericardial. The defibrillating lead configurations tested were tabulated. All patients had defibrillation thresholds that were \( \geq 25 \) J, and the actual defibrillation threshold was recorded as being \( \geq 25 \) J, \( \geq 30 \) J, \( \geq 35 \) J, \( 40 \) J, or \( >40 \) J. The patients evaluated were limited to those receiving an automatic implantable defibrillator (AID, Intec Systems, Inc., Pittsburgh, Pa.) or an automatic ICD (AICD, Cardiac Pacemakers, Inc., St. Paul, Minn.). All devices implanted had a maximum output capability of \( \leq 30 \) J, and any patient who received a custom device that delivered more than \( 30 \) J was excluded from the analysis. Follow-up data included whether a device was implanted at the initial operation or later, whether shocks were given, whether the shocks were appropriate by clinical criteria, and the final management of the patient, specifically, ICD therapy or drug therapy. The date of implantation, date of last follow-up, date of death if applicable, and cause of death were recorded.

**ICD Implantation Approaches and Methods for Defibrillation Threshold Testing**

Each center followed its own protocol for device implantation. All centers kept the patients normothermic during isolated ICD implantation by the standard approaches of left lateral thoracotomy, median sternotomy, subxiphoid incision, or subcostal incision. When concomitant cardiovascular surgery was performed, hypothermic cardiopulmonary bypass was used.

Whether defibrillation threshold testing was performed on or off cardiopulmonary bypass was determined at the discretion of the implanting physicians, as was the decision to implant the ICD in a one-stage or two-stage procedure or not at all. Because this study was retrospective and the operations were performed at multiple centers, a standardized method for defibrillation threshold testing was not used. Each center followed its own protocol for the entire implantation procedure and reported defibrillation thresholds according to their local criteria. Reproducibility of success or failure at a given energy level was not specified. Because the implantations spanned several years, not only defibrillation threshold testing protocols but also the equipment changed. Thus, in the early implantations, only the external cardioverter-defibrillator (Intec Systems, Inc., and Cardiac Pacemakers, Inc.) was used for testing. For later procedures, the ECD-II (Cardiac Pacemakers, Inc.), the HVS-02 (Ventritex, Inc., Sunnyvale, Calif.), and other intraoperative testing devices were used. The reported defibrillation thresholds were virtually always estimates rather than measured values of delivered energy.

**Comparison of Study Group to Other Studies**

The possible influences of age, sex, left ventricular ejection fraction, presence of coronary artery disease, and antiarrhythmic drug use (especially amiodarone) on the defibrillation threshold was assessed by comparing the study population to patients with ICDs in other clinical trials. The data were also compared with patients in phase I and II clinical trials for market approval of the Model 1600 Ventak-P conducted by the manufacturer (Cardiac Pacemakers, Inc.). In this study, data were recorded on the investigational implantation forms sent to the manufacturer at the time of ICD device implantation. Since underreporting may have biased the large volunteer registry (now including 18,970 patients) maintained by the manufacturer, we elected to use this clinical trial for comparison.

**Statistical Analysis**

Numerical values are presented as mean ± SD. Comparisons were made using \( t \) tests and \( \chi^2 \) tests where appropriate. Survival curves were estimated using the method of Kaplan and Meier. Comparisons of the survival curves were performed using Cox proportional hazards regression. This allowed for adjustment by other variables such as age, sex, and other clinical parameters. A value of \( p<0.05 \) was considered significant.

**Results**

**Study Population**

The 12 centers had data bases that included 1,946 patients. Of those patients, 90 (4.6%) were identified who had defibrillation thresholds \( \geq 25 \) J. Three patients were excluded because they received high-energy ICDs (all model 1555 AICDs, which deliver 35 J). Thus, there were 87 patients analyzed — 81 men and six women with a mean age of 59.5 ± 10.1 years (range, 29–83 years). Mean left ventricular ejection fraction was 0.32 ± 0.14 (range, 0.11–0.82), and the incidence of coronary artery disease was 76%. Descriptive characteristics are given in Table 1.

**Antiarrhythmic Drug Therapy**

At the time of initial defibrillation threshold testing, 61 (70%) of the study patients were receiving antiarrhythmic drugs. Therapy included class Ia drugs in six patients (quinidine in three and procainamide in three), class Ib drugs in five patients (mexiletine in two, lidocaine in one, and aprindine in two), class Ic drugs in three patients (encainide, flecainide, and propafenone in one patient each), and class I drug combinations in two patients (quinidine/mexiletine in one and lidocaine/mexiletine/brtylalum in one). Amiodarone was administered to 45 (52%) patients, alone in 31 patients and in combination with other antiarrhythmic drugs in 14 patients. When patients who were receiving amiodarone were compared with those who were not receiving the drug (Table 1), the former patients tended to be older, but there were no differences in sex, underlying cardiac disease, presenting arrhythmia, ejection fraction, or New York Heart Association functional class.

**Surgical Approach**

The surgical approach was left lateral thoracotomy in 57 of the 87 patients, median sternotomy in 18, subxiphoid approach in seven, a subcostal approach in three, and the use of previously implanted leads in two patients. The patches were placed intrapericardially in 46 patients, extrapericardially in 37 patients, and intrapericardially and extrapericardially in four patients.
Defibrillation Thresholds

All 87 patients had defibrillation thresholds $\geq$25 J. Details of the defibrillation thresholds separating patients who received and did not receive an ICD are given in Table 2. The table is constructed to define the thresholds as specifically as the data allow. Those without an ICD tended to have higher defibrillation thresholds than patients with an ICD ($p<0.001$).

Thirty-five patients had defibrillation thresholds measured at a subsequent procedure, usually at a second attempt at device implantation after healing of the leads implanted at the initial attempt or at pulse generator change (Table 3). Recognizing the inherent limitations of defining the defibrillation threshold as a point value and of its variability, a change in the defibrillation threshold was defined as a change of $\geq$5 J in threshold between the two tests. In 19 of the patients, the defibrillation threshold was lower than at the first attempt; in four patients, it was higher than at the first attempt; and in 12 patients, there was no change. In the 19 patients whose defibrillation threshold decreased, the defibrillation threshold was $\leq$20 J in only nine patients, and it remained $\geq$25 J in the other 10 patients, including three who still had defibrillation thresholds $\geq$30 J. Data regarding drug changes between the two tests and of the time between the two tests were not consistently available but are reported when possible.

Lead Configurations Tested

There were 128 lead configurations tested in the 87 patients. As many as five configurations were reported to have been tested in one patient. Two large patches were tested in 50 patients, a large patch and small patch in 38 patients, and two small patches in three patients. A large patch–vena caval spring configuration was tested in 19 patients, and a small patch–vena caval spring combination was tested in seven patients. Two patients had custom lead configurations evaluated, including one using two large patches and a small patch and a second using two large patches coupled to an endocardial lead with two springs (Endotak, Cardiac Pacemakers, Inc.). In most instances, the defibrillation configuration using spring-patch leads was a secondary attempt to find a lead configuration with a lower defibrillation threshold than was determined during dual-patch testing. In many instances, patches were moved once or more often so that more configurations (i.e., different positions using the same patches) were tested than were reported. Also, lead polarity was reversed in at least 11 patients, but this maneuver was not consistently reported.

Early Patient Management

Of the 87 patients, 71 (82%) received an ICD – 54 at the initial operation and 17 at a later operation. A comparison of patients with and without an ICD is given in Table 1. The only characteristic that distinguished the two groups was the more frequent use of antiarrhythmic drugs, amiodarone in particular, in patients who did not receive a device. Of the 16 patients not treated with an ICD, 12 were treated with drugs (amiodarone in eight, quinidine in two, tocainide in one, and not reported in one), one was transplanted, two died (one periopera-
<table>
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<th>FC</th>
<th>CHF</th>
<th>Antiarrhythmic drugs</th>
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<th>Late DFT (J)</th>
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<td>12 Days</td>
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EF, left ventricular ejection fraction; FC, functional class; CHF, congestive heart failure; DFT, defibrillation threshold; M, male; F, female; CAD, coronary artery disease; VT, ventricular tachycardia; AS, aortic stenosis; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; AVR, aortic valve replacement; CoA, coarctation of the aorta; CM, cardiomyopathy; VF, ventricular fibrillation; ICD, implantable cardioverter-defibrillator; NA, not available.
tively), and the ultimate therapy in one patient is unknown. Whether the patient received an ICD was at the discretion of the physician. Notably, 13 of the 16 patients without an ICD had a defibrillation threshold $\geq 35$ J (Table 2).

Late Follow-up

Of the 71 patients who received ICDs, 43 received shocks. The shock was deemed appropriate according to clinical criteria in 31 patients, inappropriate in nine patients, and indeterminate in three patients.

Death occurred in 27 (31%) of the 87 patients, 19 (27%) of the 71 patients with an ICD, and eight (50%) of the 16 patients without an ICD. The causes of death are given in Table 4 and were sudden or the result of a ventricular tachyarrhythmia in 12 (14%) patients—eight (11%) with an ICD and four (25%) without an ICD. The cause was congestive heart failure in seven (8%) patients (five [7%] with an ICD and two [13%] without an ICD), a nontachyarrhythmic but cardiac cause in five (6%) patients (four [6%] with an ICD [three myocardial infarction and one bradycardia with electromechanical dissociation], and one [6%] without an ICD [lead abrasion and bleeding perioperatively]), and three (3%) deaths were noncardiac (two [3%] with an ICD and one [6%] without an ICD). The actuarial probability of survival for all patients is presented in Figure 1. The cumulative probabilities for survival for all patients at 1, 2, 3, 4, and 5 years were 87%, 75%, 75%, 67%, and 67%, respectively.

A separate analysis was carried out for the 31 patients with an ICD who received appropriate shocks. Death was sudden or due to a ventricular tachyarrhythmia in six (19%) of these patients, congestive heart failure in two patients, and myocardial infarction and a noncardiac cause in one patient each. The details of the six arrhythmic deaths are as follows. One patient died due to refractory ventricular tachycardia and had defibrillation thresholds $> 25$ J on two different occasions. Interestingly, the defibrillation threshold in this patient was time dependent; it was $< 15$ J when the duration of ventricular fibrillation was $< 10$ seconds. The second patient died suddenly, and although no other details are available, this individual had had a defibrillation threshold of $30$ J on two separate occasions. The third patient also had a $30$ J defibrillation threshold, died without any witnesses, and device interrogation showed that only one shock had been delivered, presumably at the time of death. It is interesting that this individual also had high defibrillation thresholds when tested with a nonthoracotomy ICD system (Endotak, Cardiac Pacemakers, Inc.). The fourth patient had sudden death and a defibrillation threshold of $25$ J. The fifth patient who died suddenly was awaiting cardiac transplantation and had defibrillation thresholds of $30$ J both at implantation and at pulse generator change. The sixth patient had a $25$ J defibrillation threshold and class IV heart failure, was bed-ridden, and died during sleep. Thus, three of the six patients with sudden death or death due to a ventricular arrhythmia had a $30$ J defibrillation threshold.

Actuarial comparison of survival was also carried out for patients with and without an ICD (Figure 2). Median survival for the ICD group was $79.0$ months, and mean survival was $62.6 \pm 4.0$ months. Median survival for the group without ICDs was $18.6$ months, and mean survival $16.7 \pm 2.5$ months. At 1- and 2-year follow-up, the cumulative probabilities of survival were $89\%$ and $81\%$ for patients with an ICD, and $77\%$ and $36\%$ for those without an ICD, respectively. At 5-year follow-up for the patients with an ICD, the cumulative probability of survival was $73\%$, and for survival free of sudden or arrhythmic death, probability was $84\%$. No patient without an ICD has lived longer than 32 months. In a stepwise Cox regression, the only variable to predict survival was implantation of the ICD ($p=0.003$). No other variable added significance at the 5% level to the model given that the ICD variable was already in the model.

Comparison of High Defibrillation Threshold Patients With Patients in Other Studies

In the present study of patients with high defibrillation thresholds, 70% were receiving an antiarrhythmic drug, whereas in the other trials, the frequency of

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**TABLE 4. Kaplan-Meier Actuarial Mortality Rates**

<table>
<thead>
<tr>
<th>Mode of death</th>
<th>All patients</th>
<th>ICD patients</th>
<th>No ICD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths</td>
<td>27 (31%)</td>
<td>19 (27%)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Sudden/arrhythmic</td>
<td>12 (14%)</td>
<td>8 (11%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7 (8%)</td>
<td>5 (7%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Nonarrhythmic/cardiac</td>
<td>5 (6%)</td>
<td>4 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>3 (3%)</td>
<td>2 (3%)</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

ICD, implantable cardioverter-defibrillator.
antiarrhythmic drug usage ranged from 40% in the Ventak P clinical trial to 91% in the study of Fogoros et al (Table 5). However, with the exception of the Fogoros et al study, amiodarone use was recorded significantly more frequently in the present study (52% of patients) than in the other cited studies (range, 9%-54% to 45%; p<0.05 comparing each study with the present study). Although there were proportionately more men in the present study than in six of the eight other studies, there were no differences in mean ages, frequencies of coronary artery disease, or mean left ventricular ejection fractions observed in patients in the present study compared with those in the other trials. Unfortunately, the number of patients with high defibrillation thresholds was not consistently reported in the other trials for comparison. In fact, many are never reported since they do not receive devices.

**Discussion**

Results from this study show, first, that the clinical variables of age, incidence of coronary artery disease, and degree of myocardial dysfunction were similar in patients with defibrillation thresholds ≥25 J compared with those with defibrillation thresholds <25 J in other studies (Table 5). However, patients with high defibrillation thresholds were more frequently men receiving an antiarrhythmic drug, amiodarone in particular. The excess of men in the present study is not readily explainable. Second, although many patients in this study had devices implanted despite an elevated defibrillation threshold, 42% (eight of 19) of the deaths in those patients were sudden. Thus, even though the devices apparently were used successfully by some patients, effective therapy was not ensured.

Factors that affect the defibrillation threshold include drug therapy, underlying cardiac disease, size, configuration, and number of defibrillating leads; time that ventricular fibrillation persists before shock delivery; ischemia and hypoxia; amplitude of the ventricular fibrillation waveform; heart weight; body weight; species; chronicity of lead implantation, and waveform and direction of the delivered shock. In this study, complete data were available to assess the roles of drug therapy, underlying heart disease, and lead configurations.

**Role of Drugs on the Defibrillation Threshold**

The class Ib drugs have been shown to variably affect the defibrillation threshold, either increasing it or causing no change. The class Ic drugs have been associated with an increase of the defibrillation threshold. Although most data were derived from animal models, there is a case report showing that mexiletine also increases the defibrillation threshold. The class Ic drugs encainide, flecainide, propafenone, and racinam have all been shown to increase the defibrillation threshold. In addition, these agents also increase the pacing threshold. The latter drug/device interaction has implications in newer generation ICD devices that incorporate antitachycardia pacing and bradycardia pacing with cardioversion and defibrillation since both the defibrillation and pacing energy requirements may be changed by drug therapy. Finally, propranolol, a class II drug, and verapamil, a class IV drug, also have been shown to elevate the defibrillation threshold.

The apparent association between amiodarone therapy and high defibrillation thresholds warrants special mention. Amiodarone has previously been shown to increase the energy requirements for defibrillation. Amiodarone-induced refractoriness to cardioversion in a patient undergoing ICD implantation, which was reversible after the drug was stopped. Haberman et al showed in a dog model that amiodarone treatment increased the defibrillation threshold compared with control. Furthermore, they found that the effect was more pronounced the longer that ventricular fibrillation persisted. In contrast, Fain et al showed that in dogs, the defibrillation energy requirement was decreased by acute intravenous amiodarone therapy, whereas no effect was demonstrable with chronic oral administration. In a similar study, Frame showed that although intravenous amiodarone had no significant effect on the acute defibrillation threshold in dogs, chronic administration produced a dose-dependent increase in the defibrillation threshold. Only in the study of Huang et al was amiodarone not implicated in elevation of the defibrillation threshold. Information on amiodarone doses and levels is not available for the present study.

Kelly et al reported a series of 94 patients intended to receive an ICD of whom five (5%) could not be implanted because a defibrillation threshold of ≤25 J could not be achieved despite testing multiple defibrillating lead positions and configurations. All five of these patients were receiving amiodarone. One of these patients had a defibrillation threshold ≥40 J and died.

| TABLE 5. Comparison With Manufacturer's Data and Other Studies |
|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Present study  | Ventak P        | Huang et al     | Kelly et al     | Tchou et al     | Winkle et al    | Myerburg et al  | Fogoros et al   | Manolis et al   |
| No. in study    | 87             | 292             | 62              | 64              | 94              | 70              | 270             | 60              | 65             | 77             |
| Antiarrhythmic drug | 61 (70%)      | 116 (40%)*      | 42 (68%)*       | 44 (49%)*       | 28 (40%)*       | 186 (69%)*      | 37 (62%)*       | 59 (91%)*       | 52 (68%)*       |
| Amiodarone      | 45 (52%)       | 47 (16%)*       | 28 (45%)        | 16 (14%)        | 6 (9%)*         | 71 (26%)*       | 17 (29%)*       | 37 (57%)*       | 26 (34%)*       |
| Male (%)        | 93             | 79*             | 86              | 77*             | 73*             | 80*             | 82*             | 77*             | 87             |
| Age (years)     | 59.5±10.1      | 61.5±11.9*      | 60±12           | 58.6±12.7       | 59.7±11.8       | 58.2±11.9*      | 63.9±9.6*       | 60±10           | 60±12          |
| Coronary disease (%) | 76          | 78              | 81              | 65              | 76              | 78              | 85              | 83              | 78             |
| EF              | 0.32±0.14      | 0.34±0.14       | 0.37±0.17       | 0.33±0.15       | 0.37±0.15       | 0.34±0.15       | 0.33±0.13       | 0.36±0.14       | 0.35±0.16       |
| High DFT incidence (%) | 4.6         | NA              | 3.2†            | 5.3             | 0               | 2.6             | NR              | NR              | 1.3            |

EF, left ventricular ejection fraction; DFT, defibrillation threshold; NA, not available; NR, not reported.

*p≤0.05 compared with present study. tDFT >40 J in these patients.
perioperatively. After 6–10 weeks following amiodarone washout, the other four patients underwent repeat defibrillation threshold testing; three received devices since the defibrillation thresholds had decreased to ≤15 J, but the fourth patient had no change in the defibrillation threshold from >40 J and did not receive a device. In the study of Manolis et al., one of 78 patients (1%) did not receive an ICD due to a defibrillation threshold >40 J, and this patient was receiving amiodarone. Borbola et al reported that four patients not treated with amiodarone had defibrillation thresholds of 11.8±7.9 J compared with 12 patients receiving amiodarone who had defibrillation thresholds of 19.2±13.0 J (p<0.05).

In view of these previous data and despite the likelihood that amiodarone increases the defibrillation threshold, the actual contribution of amiodarone to the difficulty that was observed in defibrillating our patients is uncertain since many other patients who receive the drug have acceptable defibrillation thresholds. Unfortunately, the frequency of amiodarone use in the 1,856 patients with defibrillation thresholds <25 J from which the present study population was drawn is not available. Kelly et al found a 5.3% incidence of high defibrillation thresholds in a population where 14% were taking the drug. However, 100% of the patients with high defibrillation thresholds were taking amiodarone. On the other hand, Manolis and Borbola et al reported a 1.3% incidence (two patients; one on amiodarone) of elevated defibrillation thresholds in a population where 34% were taking the drug, and Tchou et al reported a 0% incidence of excessive defibrillation thresholds in 70 patients, of whom 9% were taking amiodarone. Thus, there may have been other factors that contributed to the high observed defibrillation thresholds, that may have biased intraoperative decisions, and that may in part account for the reported observations. For example, patients receiving amiodarone may have had more resistant arrhythmias, other cardiac physiological variables unaccounted for in the present analysis (e.g., ventricular volume, ventricular size, and heart weight), or pharmacological variables related to amiodarone itself including the duration of administration and dose intensity. These variables could not be assessed in our analysis.

Not all drugs adversely affect the defibrillation threshold. Both dl- and d-sotolol decrease defibrillation energy requirements in anesthetized dogs. Similarly, N-acetyl procainamide has also been shown to lower the defibrillation energy requirement by variable degrees. Several investigators have demonstrated that clofilium, an investigational antiarrhythmic drug with class III activity, decreased the defibrillation energy requirement in a variety of animal models. Bretylium has no effect on the defibrillation threshold.

Complete data were not available regarding the particular anesthetic agents used in the present study. However, where data are available, fentanyl was commonly used. Although Wang and Dorian have shown that the defibrillation energy requirements may differ among anesthetic agents, the defibrillation threshold with fentanyl was lower than that with pentobarbital or enflurane.

The mechanism for the alteration of the defibrillation by antiarrhythmic drugs is unclear. Echt et al provided some insight into the role of sodium channel blockade and the importance of the effect on action potential duration and QT interval. They summarized that sodium channel-blocking drugs that shorten action potential duration are associated with an increase in the defibrillation energy requirement (lidocaine, phenytoin, encainide, O-desethyl encainide), whereas drugs that prolong action potential duration either have no effect or decrease the defibrillation energy requirement (procainamide, 3-methoxy-O-desethyl encainide, bretylium, d-sotolol). These authors suggest that the effect of amiodarone on defibrillation is difficult to predict because the drug exhibits activity in all four antiarrhythmic classes.

Other Factors That Affect the Defibrillation Threshold

The spectrum of cardiac diseases in this study population is similar to that described in other studies (Table 5) and, therefore, does not explain the high defibrillation thresholds we observed. Troup et al have shown that larger defibrillation lead areas (two large patches, or one large and one small patch electrode) provide lower defibrillation thresholds than when smaller lead areas are used (two small patches, or a superior vena caval spring-patch lead system). In the present study, two large patch electrodes were tested in 52 patients, and a large-small patch configuration was tested in 41 patients. Thus, the use of small defibrillation electrode areas cannot be the only cause of the high defibrillation thresholds observed in the present study.

The role of ischemia on the defibrillation threshold is controversial. Although some studies indicate that ischemia does not affect the defibrillation threshold, many of these studies use animal models with normal hearts. Furthermore, the setting in which ventricular fibrillation occurs influences the defibrillation threshold. For example, the defibrillation threshold for ventricular fibrillation that occurs spontaneously and as a result of ischemia is higher than the defibrillation threshold for ventricular fibrillation that is induced during ischemia or without ischemia. Furthermore, as shown by Echt et al in dogs and by Winkle et al in humans, the defibrillation threshold increases when the duration of ventricular fibrillation increases. Faster tachycardias are more difficult to terminate. Geddes et al have shown a positive correlation between the defibrillation energy requirement and both body weight and species. Relevant to the situation where ICD implantation is carried out at the time of other cardiac surgery, cardiopulmonary bypass has been shown to influence the defibrillation threshold. Finally, cardiac size and acid-base disturbances have also been shown to adversely affect the defibrillation threshold. Pinski et al reported that a low ejection fraction correlates with high defibrillation thresholds. The ejection fraction in the present study, however, was not appreciably different from other reported experiences (Table 5).

Study Limitations

There are several limitations to the present study. First, the study was retrospective and may therefore incorporate important biases. This limitation may be especially important in the interpretation of the observations regarding
amiodarone therapy, as was addressed above. However, a prospective study would be difficult given that these patients are rare and accumulating such a large number would be difficult to do a second time, even in a multicenter study, because the present patients were seen over a decade of implantation experience.

Second, the precision and accuracy of the reported defibrillation thresholds were limited by the retrospective nature of the study, the varied defibrillation threshold-testing protocols, and different generations of testing equipment that were used. Other uncontrolled variables include duration of ventricular fibrillation, time between defibrillation threshold tests, and whether ventricular fibrillation, as opposed to polymorphic ventricular tachycardia, was tested. Although it is possible that there was underreporting of the number of lead configurations tested, this is a minor aspect. Nevertheless, even if the defibrillation thresholds were measured according to a prospectively defined protocol, the “defibrillation threshold” is not a precise number but rather a dose–response description of the probability of successful defibrillation at a particular level of delivered energy.14 Although our patients were more difficult to defibrillate than other patients who usually receive ICDs, the precise value of the defibrillation threshold, its reproducibility, and its relation to the probability of successful defibrillation at a particular energy are difficult to quantify.

Third, underreporting is always a potential in multicenter data base studies such as this.52 However, underreporting is unlikely to be the cause for our finding that antiarrhythmic drug use, especially amiodarone, is associated with high defibrillation thresholds since the prevalence of antiarrhythmic drug use, including amiodarone, in our patients does exceed that in most other previously reported series.53–56,58 Interestingly, in the one study in which amiodarone use was more frequent than in our study, patient entry was restricted to those with defibrillation thresholds ≤20 J,57 i.e., patients with high defibrillation thresholds were excluded.

Fourth, because several centers that were approached to include patients in the present study had no patients with a defibrillation threshold ≥25 J, the “denominator” of the proportion of patients undergoing ICD implantation with a defibrillation threshold exceeding this value will be underestimated in the present study. Although some series report an elevated defibrillation threshold in 2–3% of patients,3,8,55,58 in others the incidence is higher,4,53 and in some series of ICD therapy these patients are not reported since they never received a device.

Finally, comparison of actuarial curves obtained retrospectively with treatment decisions made in a nonrandomized manner is hazardous. Thus, because there were no predefined criteria for deciding who did or did not receive an ICD and although the actuarial data on Figure 2 may appear to imply that the poorer outcome in patients not receiving an ICD was causally related to their not receiving an ICD, the poorer outcome may instead be related to a higher preexisting risk of death. A reasonable hypothesis is that physicians refrained from implanting a defibrillator in patients with high defibrillation thresholds who they perceived as having less chance for benefit. Indeed, 13 of the 16 patients who did not receive a device had a defibrillation thresh-old ≥35 J, the maximum energy delivered by devices that were approved at the time these patients were studied. No patient in the present series received a device that delivered >30 J. Whether the difference in mortality between the groups with and without an ICD is related to the ICD itself or only in part to the ICD would require a prospective clinical trial.

Despite these limitations, this data base represents the largest number of patients with the problem of a high defibrillation threshold that has been so far reported. A particular strength of this series is that multiple centers have provided patients, thereby providing a cross-sectional appreciation of the magnitude of this problem in the clinical setting.

Reflections and Recommendations for Management

There is no evidence that the 87 patients described in this study are “less sick” than those previously reported since their mean age of about 60 years, mean ejection fraction of 0.32, and 76% incidence of coronary artery disease are very similar to virtually all other ICD study populations. Thus, to place our study population in perspective with previously reported studies is warranted and of interest despite the uncontrolled differences between series in patient selection, technical factors, and other unknown factors.

Of the patients with an ICD, 11% died suddenly or as a result of a ventricular arrhythmia. This mechanism of death accounts for 42% of the deaths in this group. Actuarial analysis indicates that at 5 years the cumulative probability of survival for our patients with high defibrillation thresholds was 73% and for survival free of sudden death, 84%. This 5-year 73% rate of overall survival is remarkably similar to the rate of 69% reported by Lehmann et al52 at 4-year follow-up, 74% reported by Winkle et al53 and by Fogoros et al57 at 5 year follow-up, and 79% reported by Nisam et al58 at 5-year follow-up. It is superior to the 5-year overall survival rate of <40% reported by Manolis et al,59 52% reported by Gross et al,60 62% reported by Kav et al61 and 64% reported in the Bilitch Registry.71 The 5-year 84% rate of survival free of sudden death in our patients is, however, lower than rates reported in all except one59 of the studies just cited: 91% at 1-year follow-up,56 92% at 3-year follow-up,58 88% at 4-year follow-up,52 and 87%,71 96%,55,56 and 97%70 at 5-year follow-up. Also, the extremely poor survival of patients with high defibrillation thresholds who did not receive an ICD is notable (36% at 2-year follow-up).

A definite explanation for why these patients with defibrillation thresholds ≥25 J who received ICDs did unexpectedly well in regard to overall survival is uncertain, but there are several possible explanations. First, many of the “appropriate” shocks that were delivered to these patients may have been for ventricular tachycardia rather than ventricular fibrillation. Because the cardioversion energy requirement is virtually always less than the defibrillation energy requirement,72 it is not unlikely that some successful therapy was given for rhythms that were easier to convert than ventricular fibrillation. The ICD does not store electrograms so the actual rhythm for which therapy was given cannot be determined. In the Cox analysis, the second most powerful predictor after “no ICD” versus “ICD” as a predictor for death was the clinical arrhythmia being ventricular fibrillation
(estimated coefficient ±SEM, \(-1.823 ± 1.027; p=0.076\)). This is compatible with the speculation that ventricular tachycardia can be converted in patients in whom defibrillation is not expected to be successful because of a high defibrillation threshold.

Second, it is possible that the acute high defibrillation threshold decreased with time following implantation. Grubb et al\(^7\) reported six patients in whom adequate defibrillation thresholds could be obtained after patch healing had occurred when retesting was performed 10–15 days after initial implantation.

Although many of our patients had devices implanted despite a high defibrillation threshold, we do not advocate abandonment of defibrillation threshold testing or a priori implantation of devices in patients with high defibrillation thresholds, noting that 42% of all deaths in these patients were sudden, and survival free of sudden death appears to be less than in the studies discussed.\(^{52,55,56,58,68,70,71}\) Even if it is true that many of our patients had successful treatment of ventricular tachycardia (as opposed to ventricular fibrillation), cardioversion of monomorphic ventricular tachycardia can be proarrhythmic, leading to ventricular fibrillation and cardiac arrest that requires defibrillation.\(^{72–74}\) Thus, effective defibrillation should always be established, and finding the lowest possible defibrillation threshold benefits patients by providing greater margins of safety by ensuring the ability to defibrillate.

Because antiarrhythmic drugs appear to be associated with elevated defibrillation thresholds,\(^5–35\) an increased chance for unsuccessful implantation should be considered if an antiarrhythmic drug, especially amiodarone (References 5–7, 9, 22–25, 53, 55, and 58 and the present study), is being given at the time of operation. Also, because antiarrhythmic drugs appear to be important factors influencing surgical success, further studies are in order to identify the mechanisms by which they alter the defibrillation threshold. Until the results are known of such studies, limiting the use of drugs that adversely affect the defibrillation threshold may be helpful. As new-generation devices are released that deliver biphasic, multidirectional, and sequential shocks, the probability of successful defibrillation will be increased.\(^{48–50,75}\) Nevertheless, the possibility that the defibrillation threshold will exceed the outputs of any pulse generator will remain, and testing still should not be omitted. This may become even more important as new-generation devices deliver antiarrhythmias pacing therapy for ventricular tachycardia pacing therapy for ventricular tachycardia so that the duration of ischemia will be increased, leading to increases in the defibrillation threshold beyond that observed when short durations of hemodynamically unstable arrhythmias were tested in the operating room.

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Appendix

High Defibrillation Threshold Investigators

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