Rise in Chronic Defibrillation Thresholds in Nonthoracotomy Implantable Defibrillator

Ferdinand J. Venditti, Jr, MD; David T. Martin, MBBS; George Vassolas, MD; Susan Bowen, RN

Background  To establish the chronic stability of defibrillation thresholds (DFTs) in a transvenous cardioverter/defibrillator (TCD) system, we studied 37 consecutive patients with TCD systems implanted for >6 months.

Methods and Results  DFT was measured by a step-down method at implant and 2 and 6 months later. The mean ejection fraction was 34.5 ± 14.3%. Coronary artery disease with previous myocardial infarction was present in 31 patients. The mean DFT rose from 13.3 ± 4.3 J at implant to 16.5 ± 4.7 J at 2 months (P < .001) and 17.6 ± 5.4 J at 6 months (P < .0001). ANOVA revealed a statistically significant rise in DFT over time (P < .0005). At 2 months, 25 patients had a rise in DFT, and 14 had a rise ≥ 5 J. The observed rise at 2 months persisted in 19 patients. A chronic rise, defined as ≥ 5 J rise at 6 months, occurred in 17 patients. Univariate analysis of clinical as well as implant variables revealed no predictors of a rise in DFT in this group.

Conclusions  We conclude that there is a significant rise in DFT at 2 and 6 months in this TCD system. Although the chronic threshold remained well within the available energy range of the pulse generator, this observation has important implications for implantation guidelines, programming, and future pulse generator development for TCD patients. (Circulation. 1994;89:216-223.)

Key Words  • defibrillation • arrhythmia

Implantable cardioverter/defibrillator (ICD) therapy has had a significant impact on sudden-death–free survival in patients with life-threatening ventricular arrhythmias.1-5 The currently approved systems require implantation via a thoracotomy, a median sternotomy, or a subcostal approach.5 These approaches carry significant perioperative risk. Operative mortality has been reported to be as high as 5%, with significant morbidity in 8% to 10% of patients.1-5

Several manufacturers have developed nonthoracotomy lead systems to reduce the risks of implantation.6-8 These systems incorporate transvenous and subcutaneous electrodes in the lead system for shock delivery. Initial experience has been encouraging.9,10

Although not rigorously evaluated, the chronic defibrillation threshold (DFT) in epicardial patch systems seems to be stable. In several studies, when repeat measurements were performed at the time of generator change, DFT did not rise if antiarrhythmic drug therapy had not been altered.11,12 The chronic stability of DFTs in transvenous cardioverter/defibrillator (TCD) systems currently in clinical trials in the United States has not been evaluated. Given the early experience with implantable transvenous cardioversion leads, in which a modest rise in energy requirements over time was noted in some patients,13 we decided to evaluate chronic DFTs in a series of patients undergoing TCD implantation.

Methods

Seventy-five patients requiring ICD therapy were prospectively entered into a protocol evaluating the efficacy and safety of the Endotak lead system (Cardiac Pacemakers Inc [CPI], St Paul, Minn) between May 1991 and December 1992. In addition to the manufacturer’s protocol, all patients gave written informed consent for this study designed to prospectively determine chronic DFT. The protocol was approved by the Human Studies Committee of the Lahey Clinic and was a substudy of the phase 2 clinical evaluation of this transvenous lead system being conducted at our institution.

Patients presenting with sustained ventricular tachycardia, ventricular fibrillation, or syncope with inducible sustained monomorphic ventricular tachycardia were candidates for this protocol. Patients requiring concomitant coronary revascularization were excluded. All patients underwent preoperative invasive electrophysiological testing and cardiac catheterization. In addition, Holter monitoring, echocardiography, and exercise testing were used where appropriate. Ejection fraction was calculated from left ventriculography or two-dimensional echocardiography. Patients with inducible ventricular arrhythmias were demonstrated to be refractory to several antiarrhythmic agents before implantation.

When leads were available from the manufacturer, this protocol was offered to all patients requiring ICD therapy; therefore, this series is unbiased by physician selection. All patients offered this device agreed to undergo attempted implantation. The subgroup of patients with successful TCD system implantation with programmable ICD generators were enrolled in the chronic DFT protocol.

Sixty-six patients (88%) had DFTs meeting the implant criteria and received a full system. At the time this article was written, 19 patients had not yet had their system for 6 months, 6 patients had nonprogrammable devices implanted (Ventak 1555, CPI, St Paul, Minn), 2 patients refused 6-month testing, 1 patient died before completing the protocol, and 1 patient had an infection that necessitated system removal. Therefore, 37 patients had their implants for >6 months and underwent all the required testing for the chronic DFT study.

Description of the Device

The Endotak lead system is composed of a tripolar, tined, transvenous lead, a Y connector, and a subcutaneous patch.
The 100-cm transvenous lead is capable of bipolar sensing (distal tip cathode versus distal spring anode) and defibrillation (distal spring cathode versus proximal spring anode) in a single lead (Fig 1). The subcutaneous patch and Y connector allow for the flexibility of multiple pathways to enhance the likelihood of successful defibrillation with the system during implant testing.

**Lead Configurations**

Three defibrillation electrodes allow multiple configurations for the delivery of energy (Fig 2). With two electrodes made electrically common (anode) by use of the Y connector, bidirectional shocks may be delivered in two configurations (configurations 1 and 2). With only two electrodes, unidirectional shocks can be applied in two configurations (configurations 3 and 4). Multiple configurations were tested in most patients (n=29) in an effort to minimize the DFT. The initial 27 patients had two configurations assigned at random as part of the manufacturer’s protocol.

**DFT Testing**

All testing at the time of implantation was done under general anesthesia. Induction was with fentanyl in 17 patients. Thirty-four patients received halothane for maintenance of anesthesia either alone (n=15) or in combination with fentanyl (n=12), propofol (n=2), or both (n=2). Two patients received propofol alone, and 1 received fentanyl alone.

Patients underwent a step-down testing scheme in the operating room after placement of the lead system (Fig 3). All testing was done in the automatic sensing mode of an external cardioverter/defibrillator (ECD 2, CPI, St Paul, Minn). Ventricular tachycardia was usually initiated with alternating current via the shocking or sensing electrodes. DFT testing was started at 20 J, and energy was decreased on successive attempts until a failure of defibrillation occurred. The following energy settings were used in order: 20, 15, 10, 8, 5, 4, 3, and 2 J. The time to shock delivery and impedance were recorded for all episodes. The lowest successful energy was identified as the DFT. All patients had a true DFT defined (ie, at least one unsuccessful shock was delivered).

If the patient’s condition permitted, two additional attempted conversions were performed at the DFT to determine the frequency of success at that energy level. Implant decisions were based on the step-down–determined DFT regardless of the outcome of these additional tests. DFTs of 20 or 25 J required three consecutive conversions at that energy level for implantation of the transvenous system.

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**Fig 1.** Top, Posteroanterior chest x-ray of an implanted Endotak lead and subcutaneous patch. Bottom, Schematic drawing of an Endotak transvenous lead. MS/D indicates morphology-sensing/defibrillating; RS, rate-sensing.
A similar scheme was used at 2 and 6 months with a programmable ICD (Ventak-P, CPI, St Paul, Minn). This allowed programming to the following shock energies: 20, 17, 14, 12, 10, 8, 6, and 4 J. All follow-up testing was done on an outpatient basis in the electrophysiology laboratory. Propofol (0.5 to 3.0 mg/kg via continuous intravenous infusion) or Brevitol (0.5 to 3 mg/kg) was used for anesthesia. Ventricular fibrillation was initiated with alternating current via a percutaneous pacing catheter with the ICD generator in the "electrophysiology testing mode" (which blinds the generator so as to permit arrhythmia induction). Care was taken to ensure that the catheter was far (>4 cm) from the endocardial lead to avoid shunting of energy during shock delivery. Testing began at 20 J and was decreased to the next available setting (except 12 J, which was rarely used) after successful defibrillation. The lowest successful energy was identified as the DFT. If 20 J was unsuccessful, the energy level was increased on successive attempts to 23, 26, and 30 J as necessary until successful conversion occurred. Again, if the patient’s condition allowed, two additional attempted conversions were performed at the identified DFT to assess the frequency of success at that energy level.

All patients had posteroanterior and lateral chest radiography performed before discharge and at each DFT reassessment. Lead position was examined in all postoperative films for evidence of dislodgment, and blinded measurements of cardiothoracic ratio were made to define any relation between heart size and DFT.

Multiple clinical and implant variables were collected at the time of implantation and evaluated to determine whether a rise in DFT could be predicted (Table 1).

**Statistics**

Multiple-treatment ANOVA was used to determine the effect of time on the variance in DFT measurements. Two-tailed paired t testing was used to locate significant differences where appropriate. Statistical significance was taken to be \( P < 0.05 \).

Because the energy levels tested at implantation and during follow-up were not always identical, energy levels were bracketed, and a second analysis was performed. This analysis assumed no difference between energies in the same bracket (Table 2). Also, since additional, smaller steps were necessary at the 2- and 6-month tests to define a DFT (usually one extra step to get to 10 J), a third analysis was performed with DFTs being rounded down (Table 3) and hence normalized for the number of steps during testing.

**Results**

The mean age in our group was 65±12 years in the 32 men and 5 women in this study. The mean ejection fraction in the study group was 34±14.3%, compared with 34±12% for the entire group (\( P = \text{NS} \)). The presenting arrhythmia was sustained monomorphic ventricu-
ular tachycardia in 57%, out-of-hospital cardiac arrest in 34%, and syncope with inducible sustained monomorphic ventricular tachycardia in 9%. Coronary artery disease was present with previous documented myocardial infarction in 86% (n=31). A mean of 2.6±1.6 antiarrhythmic agents were unsuccessful at controlling ventricular tachycardia or ventricular fibrillation before implantation in the 33 patients who underwent serial drug testing.

To determine the DFT at the time of implantation, ventricular fibrillation was induced 10±4 times, and 15±9 shocks delivered 352±277 J via the lead system. Impedance measured with the pulse generator was 47±7.7 Ω. The mean duration of ventricular fibrillation before shock delivery for testing in the configuration that was ultimately implanted was 11.3±2.5 seconds.

Configuration 3 was the most common configuration used, with 71% of patients implanted in this fashion (Fig 4). A mean of 2.5 configurations were tested in this group (only 8 patients had single-configuration testing). Reverse polarity (distal electrode as anode) was used in 7 patients (19%) when adequate DFTs could not be obtained with standard polarity in multiple configurations.

Follow-up Testing

ANOVA revealed a significant rise in DFT over time (P<.0005). The mean DFT rose significantly at 2 and 6 months, from 13.3±4.3 J at implantation to 16.5±4.7 J (P<.001) and 17.6±5.4 J (P<.0001), respectively (Fig 5). Therefore, the mean 6-month rise in DFT was 4.3 J (26%) for the entire group. However, there was no significant difference between 2 and 6 months (P>.20).

There was a statistically significant rise in the duration of ventricular fibrillation before delivery of the shock at both 2 and 6 months compared with implantation (Fig 6), but the absolute difference was <2 seconds. Impedance measured with the pulse generator did not rise from implantation at the 2- and 6-month tests (47, 46, and 47 Ω, respectively).

Repetitive testing at the identified DFT was performed in 33 patients at least once. The cumulative rates of successful defibrillation at the determined DFT at implant, 2 months, and 6 months were 76%, 74%, and 84%, respectively (P=NS).

Twenty-five patients (68%) had a rise in DFT at 2 months, with 14 having a rise ≥5 J. Nineteen patients (51%) continued to have an elevated DFT at 6 months, with 17 patients having a rise in DFT ≥5 J. Therefore, a majority of patients demonstrated a rise.

Since energy levels that could be tested at implantation and at 2 and 6 months were not always identical, DFTs were bracketed, and the analysis was repeated.

### Table 2. Bracketed Energy Levels

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<tr>
<th>Measured Energy, J</th>
<th>Bracketed Energy, J</th>
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<td>23</td>
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### Table 3. Rounded-Down Energy Levels

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<th>Measured Energy, J</th>
<th>Rounded Energy, J</th>
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This manipulation assumes that there is no difference between some individual energies (ie, 14, 15, and 17 J are considered identical) and resulted in a lower mean DFT at 2 and 6 months compared with the unbracketed data. Despite this conservative approach, a significant difference remains between implantation and 2 months as well as implantation and 6 months (Table 4).

A third analysis was performed to account for the added steps required to get to a DFT given the smaller steps required with the generator during chronic testing compared with the ECD at implantation. Again, this even more conservative approach to analysis still yielded a significant difference over time in DFTs (Table 4).

Nine patients (26%) were initially on antiarrhythmic drugs for their ventricular or atrial arrhythmias. Drug regimens were changed in four patients between implantation and follow-up testing. One each was started on amiodarone, quinidine sulfate, and procainamide. One additional patient had quinidine gluconate discontinued before 2-month testing. Exclusion of these patients from the analysis had no impact on the statistical significance of the DFT results (Fig 7).

Clinical Follow-up

The lead appearances were unchanged in later x-rays compared with immediate postoperative films in all patients (ie, no lead dislodgments). In addition, there was no change over time in the blindly measured cardiothoracic ratio, suggesting no overt deterioration in the clinical status of these patients. Linear regression disclosed no relation between the cardiothoracic ratio and DFT ($r=.08$).

All patients have been followed by one of the investigators every 2 months. Eleven patients (30%) have received 46 appropriate shocks associated with symptoms of their arrhythmia or with ECG documentation of ventricular arrhythmia in a median follow-up of 11 months. There have been no sudden cardiac deaths or failure of ICD conversion in this group. One patient died 1 year after implantation of intractable ischemia and heart failure with the ICD generator inactive. She had received two appropriate shocks.

Predictors of Rise in DFT

Multiple clinical variables were evaluated in univariate fashion to determine predictors of a rise in DFT over time (Table 1). None of these variables correlated with a chronic rise in the DFT.

Discussion

ICD therapy has had a significant impact on survival in patients with drug-refractory ventricular arrhythmias.1-5 Widespread use of the less invasive TCD systems should further increase the benefit by reducing the risks of implantation. However, the long-term reliability of TCD systems has not yet been established. Therefore, initial reduction in implant mortality could be offset by inferior long-term results if efficacy is less than that already demonstrated for epicardial patch systems.

Our data suggest that there is a substantial increase in the measured DFT over the first several months after lead implantation, raising the question of long-term system efficacy. The lack of a further statistically significant rise after 2 months suggests that the early DFT elevation is an acute phenomenon. However, there is a small upward trend in DFT between 2 and 6 months that warrants further observation.

A change in energy requirements for arrhythmia termination has been seen previously with chronically

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### Table 4. Measured, Bracketed, and Rounded Defibrillation Thresholds

<table>
<thead>
<tr>
<th></th>
<th>Implantation, J</th>
<th>2 Months, J</th>
<th>6 Months, J</th>
<th>P</th>
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<tr>
<td>Measured</td>
<td>13.3±4.3</td>
<td>16.5±4.7</td>
<td>17.5±5.4</td>
<td>.0005</td>
</tr>
<tr>
<td>Bracketed</td>
<td>13.3±4.3</td>
<td>15.8±3.9</td>
<td>16.8±4.7</td>
<td>.003</td>
</tr>
<tr>
<td>Rounded</td>
<td>13.3±4.3</td>
<td>14.9±5.7</td>
<td>16.8±6.0</td>
<td>.03</td>
</tr>
</tbody>
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Fig 6. Bar graph showing a statistically significant difference from time of initiation of tachycardia to conversion (Duration VF) by the delivered shock over time ($P<.006$ from implantation to 2 months; $P=.04$ from implantation to 6 months; $P=.46$ between 2 and 6 months). The absolute difference, however, was less than 2 seconds between time periods.

Fig 7. Bar graph showing that, excluding those patients with antiarrhythmic drug (AAD) changes, 33 patients without alteration in their antiarrhythmic drug regimen demonstrated a similar rise over time in defibrillation threshold. $P<.003$ from implantation to 2 months; $P=.001$ from implantation to 6 months; $P=.41$ between 2 and 6 months.
implanted devices. Miles and coworkers\textsuperscript{13} reported on an early experience with a transvenous lead system that demonstrated a modest rise in cardioversion energy requirements for ventricular tachycardia in some patients. Of the 11 patients treated chronically with that system, 4 developed a 0.3- to 1.5-J rise in energy required for reproducible cardioversion (100\% to 300\% rise from implantation). This was a small series, and lead design changes have occurred since this preliminary report.

In a more recent preliminary report with a different TCD system, early postimplantation DFT rose significantly and remained elevated at 6 and 12 weeks after implantation.\textsuperscript{14} In another report, in 13 patients, DFTs rose early after implantation but returned to preimplantation levels 4 to 6 weeks later.\textsuperscript{15} These preliminary reports involved a different system from that investigated in our report, were very small series, and evaluated the DFT much earlier in the postoperative period.

In a small series evaluating this same lead system, 2 of 10 patients with stable lead positions had a 5- to 10-J rise in DFT \textgreater 2 months after implantation, and 8 patients had no change.\textsuperscript{16} All of these patients received a totally transvenous system and represented a subgroup of patients selected from the total group implanted by the authors.

Finally, in a preliminary report using this system in an animal model, a 36\% rise in effective energy for conversion was noted at 38 days after implantation.\textsuperscript{17} A lead maturation process is suggested by the investigators to explain the noted rise.

Defibrillation energy requirements depend on many factors, including the shock waveform,\textsuperscript{18} size and shape of the electrodes,\textsuperscript{19} cardiac mass encompassed in the defibrillation field,\textsuperscript{20} duration of ventricular fibrillation,\textsuperscript{21,22} concomitant antiarrhythmic drug therapy,\textsuperscript{23-27} and underlying cardiac disease.\textsuperscript{28} Therefore, an elevation in DFT may be due to perturbations in any of these parameters.

Although the type of cardiac disease did not change in these patients, progression of the underlying disease could explain a rise in DFT over time if the progression altered the cardiac mass within the defibrillation field. Chest x-rays at the time of repeat DFT measurement demonstrated no change in the lead position or increase in cardiac size as determined by the cardiothoracic ratio. This strongly suggests that no gross deterioration in cardiac size occurred over the 6-month interval. Although minor changes in cardiac size could not be excluded by the gross measurement of the cardiothoracic ratio, it seems unlikely that minor changes would adversely affect DFT.

In one report of ventricular fibrillation duration affecting shock energy efficacy, the difference in time to shock delivery was 10 seconds (5- and 15-second delivery times tested).\textsuperscript{21} A difference in percent successful conversion was noted only at lower energies. Other investigators have reported no difference with duration of ventricular fibrillation before shock delivery up to 90 seconds.\textsuperscript{22} Although the duration of ventricular fibrillation before shock delivery in this series was different between the testing periods, the amount was <2 seconds and would not be expected to affect DFT measurement to the degree observed.

Antiarrhythmic agents in some instances have been shown to alter energy requirements for defibrillation.\textsuperscript{23-27} Patients with drug regimen alterations in our series were excluded from the analysis, and the rise in DFT was still apparent.

Altered energy requirements for defibrillation have been demonstrated in animal models for some anesthetic agents, although results seem inconsistent.\textsuperscript{26-30} Univariate analysis failed to demonstrate a relation between type of anesthetic agent used and measured DFT, making this an unlikely explanation for the observed rise in DFT.

Obviously, the size and shape of the electrodes were not altered, although it is possible that a “virtual electrode” akin to that seen in pacing is operative.\textsuperscript{31} In pacing, the electrode/tissue interface forms the virtual electrode. This “electrode” size changes with time in relation to edema and scar formation. The change in size influences the pacing threshold, since pacing threshold varies as an inverse function of electrode surface area.

Given the size of these endocardial leads and the voltage gradient generated, local myocardial damage and scarring might be expected. If scarring were to occur in an irregular fashion, resulting in uneven voltage gradients, this might alter observed defibrillation efficacy.\textsuperscript{32} Alternatively, extensive myocardial scarring from the electrode might result in altered myocardial conductivity and more shunting of current through the blood away from the myocardium.\textsuperscript{33}

In one case report, endocardial scarring was noted at postmortem in a patient who had received multiple shocks during 7 months of follow-up.\textsuperscript{34} This scarring extended interstitially into the midportion of the ventricular wall. Although this case report suggests that a histological change in the electrode/tissue interface develops over time, a resultant effect on defibrillation efficacy remains speculative.

Limitations

Potential limitations of this study relate primarily to the methodology of DFT measurement.

Mechanisms of fibrillation and defibrillation are highly complex and controversial. There is consensus that defibrillation is a stochastic process, and therefore, a categorical defibrillation “threshold” cannot exist. Indeed, it is generally agreed that defibrillation efficacy may best be seen as a probability density function with a sigmoid curve describing the relation between success and energy.\textsuperscript{35,36}

Previous reports have used variations of the nonlinear function

$$y = e^z(1-e^z)$$

to describe the dose-response relationship between energy (x) and percent success (y). The efficacy of defibrillation as described by the slope and position of this curve is affected by multiple interventions.

Generation of the large number of data points necessary to develop a dose-response curve entails many inductions and terminations of ventricular fibrillation. As a methodology, this is feasible in animal models but poses problems in clinical research on defibrillation. A number of investigators have tried to relate more con-
cise methods of determining defibrillation efficacy to the dose-response curve.37-39 This work has suggested that measurement of DFTs by the step-down technique, as used in this series, typically results in establishing the 50% to 60% success range (E$_{50}$ to E$_{60}$) of the dose-response curve. This technique appears to be highly reproducible and, counterintuitively, it has been demonstrated that repeat simple step-down measurements are more reliable than repeated E$_{50}$ determinations.39

Although the methodology of assessing defibrillation efficacy used in this study was a simple step-down technique rather than the creation of a dose-response curve, the mean success rates at the measured DFT at each time are similar (76%, 74%, and 84%). Therefore, there is ample reason to believe that the data are reliable.

Conclusions

Two factors are critical in guaranteeing the reliability of ICD therapy: sensing and defibrillation. Without both elements, an ICD system will not function properly, and inappropriate or no therapy may result in a lethal outcome. This is the first detailed report of elevation of chronic defibrillation thresholds by use of a transvenous lead system. It remains unknown whether this phenomenon is specific to this lead system or whether (as seems more likely) this rise in DFT is common to all methods of transvenous defibrillation. The major impact of these findings lies in the implications for implantation guidelines, device programming, and future generator development.

If pectoral implantation is to become a reality, it will be essential to reduce pulse generator volume. This may entail a reduction in maximal energy deliverable and thus have important safety margin implications for transvenous systems. Alternate shock waveforms may eliminate this concern by reducing defibrillation energy requirements.18 Postimplantation programming changes need to take into account the possible rise in DFT to avoid problems with defibrillation efficacy. All of the elevations in DFT observed in this study were within the usually accepted safety range for pulse generators capable of delivering 30 or 34 J. However, great care was taken to ensure that a configuration with a ≥ 10-J safety margin at the time of implantation was found. This frequently required detailed testing to determine the correct configuration for each patient. To avoid efficacy problems related to the DFT rise reported here, similar care needs to be taken by physicians doing implantations in the future.

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