Gross and Microscopic Pathological Changes Associated With Nonthoracotomy Implantable Defibrillator Leads

Andrew E. Epstein, MD; G. Neal Kay, MD; Vance J. Plumb, MD; Sharon M. Dailey, MD; Peter G. Anderson, DVM, PhD

Background—Although the effects of epicardial implantable cardioverter-defibrillator (ICD) leads on underlying cardiac tissue have been reported, the gross and microscopic changes associated with endocardial ICD leads are less well described. This study describes the gross and microscopic changes associated with endocardial ICD leads in humans.

Methods and Results—The hearts from 8 patients were examined. At the time of ICD implantation, the patients’ mean age was 47±11 years, and the left ventricular ejection fraction was 0.24±0.10. Four patients had ischemic heart disease, and 4 had dilated cardiomyopathy. Five hearts were examined after transplantation; 3, after death. The electrode-myocardial interfaces were characterized by intense endocardial fibrosis and were remarkably consistent. Each lead was encased by a ring of fibroelastic tissue, and there was fibrosis of the right ventricular myocardium adjacent to the leads. Fibrosis involved the tricuspid valve in 5 patients, and 1 had perforation of the valve by the lead. Microscopically, interstitial fibrosis was adjacent to each lead in the current path of ICD shocks. Acute cell injury was present only in the hearts that had received recent shocks.

Conclusions—The ICD electrode-myocardial interface is characterized by intense fibrosis. The fibrosis associated with endocardial ICD leads and the cumulative acute damage produced by defibrillation discharges may explain changes in the defibrillation and pacing thresholds and the difficulty of lead extraction that can be encountered with transvenous ICD systems. (Circulation. 1998;98:1517-1524.)

Key Words: arrhythmia ◄ death, sudden ◄ defibrillation ◄ fibrillation

Although the effects of epicardial defibrillator leads on underlying cardiac tissue have been reported in animals1–6 and humans,7–8 the gross and microscopic changes associated with endocardial implantable cardioverter-defibrillator (ICD) leads are less well described,9–14 especially in humans.15–17 Similarly, although the electrode-endocardial interface for transvenous pacing leads is well described,18–21 the interface for defibrillation leads has received little attention.15 In the case of endocardial pacing leads, there is a sequence of local events that follow implantation consisting of injury, acute inflammation, chronic inflammation, granulation tissue formation, foreign body reaction, and fibrosis.18–21 In the case of transvenous ICD leads, the electrical injury produced by shocks confounds the previously described sequence of events associated with the tissue response to an endocardial pacing lead. The morphological changes associated with transvenous ICD leads and the tissue injury and healing associated with ICD shocks may be responsible for the sequential progression of electrical phenomena that have been observed with these leads clinically, including elevation of the pacing threshold22 and changes in the defibrillation threshold.23–25 defibrillation lead system impedance,26 and electrogram.27–29 This article describes the gross and microscopic changes associated with nonthoracotomy ICD leads in humans.

Methods

Pathology Protocol

The hearts of 8 patients with transvenous ICD leads were examined in accordance with institutional guidelines. Photographs were taken of the gross anatomy, and the hearts were then sectioned to visualize the ICD lead and its interface with the endocardium. Thereafter, the hearts were fixed in formalin, and tissue sections were embedded in paraffin by use of standard histology techniques. These serial 5-µm sections were examined microscopically with hematoxylin and eosin stain, and Gomori’s aldehyde fuchsin trichrome stain was used to identify muscle, fibrous connective tissue, and elastic tissue. Gomori’s aldehyde fuchsin trichrome stain was used to identify muscle, fibrous connective tissue, and elastic tissue.

ICD Lead Systems

The ICD leads were manufactured by Cardiac Pacemakers, Inc (Endotak series) in 7 cases and Ventritex, Inc (TVL series) in 1 case. Each of these leads uses distal tip and spring electrodes in an integrated bipolar system for sensing, pacing, and defibrillation. The surface areas and lengths of the distal coils of these leads ranged from 295 to 470 mm² and 3.6 to 5.0 cm, respectively. None of these leads were steroid eluting.

Statistical Analysis

Quantitative data are expressed as mean±SD.
**Results**

**Study Patients**

The hearts from 8 patients were available for evaluation. Their demographic data are shown in Table 1. Five specimens were obtained at cardiac transplantation, and 3 were obtained after death. Of those who died, the first expired after a self-inflicted gunshot wound (patient 1) and has been reported previously. The other deaths occurred in patients awaiting cardiac transplantation, 1 of progressive heart failure and cardiogenic shock (patient 3), and 1 of cardiac arrest (patient 6).

**ICD Lead System Data**

Data regarding the ICD leads are presented in Table 2. Those manufactured by Cardiac Pacemakers, Inc had delivered monophasic shocks in 4 cases and biphasic shocks in 3 cases, by both external testing equipment and the implanted ICDs. The Ventritex lead had been used to deliver only biphasic shocks via an external testing device and a biphasic ICD.

**Gross Morphology**

The gross anatomical findings were consistent among all cases. Each lead had been implanted at the right ventricular apex and entwined in trabeculae (Figure 1). The tip of the lead was embedded in the right side of the interventricular septum in 5 cases but in the right ventricular free wall in 3 cases.

In all 7 cases of chronic lead implantation, there was an encircling band of fibroelastice tissue surrounding the lead (Figures 1 and 2). This band encased the lead up to the level of the tricuspid valve, and in 5 cases, it actually attached the lead to the valve itself (Figure 1). In 1 case, the lead had penetrated a valve leaflet (Figure 1B). The lead of patient 6 was implanted 8 days before death (Figure 1C and ID). It was easily extracted by the application of mild tension. In this case, there was no fibrous tissue encasing the lead. Instead, there was thrombotic material adherent to it and the immediately adjacent myocardium. Traction was applied to the lead of patient 3 to explant it at autopsy. Even though enough tension was applied to separate the wire coils of the lead, myocardium still remained attached (Figure 1F).

**Microscopic Changes**

After removal of the leads by traction and incision of the surrounding fibroelastic band, the interventricular septum was sectioned transversely, starting just below the lead and extending basally at 3- to 5-mm intervals (Figure 2). In all cases, there was a dense fibroelastic reaction at the electrode-myocardial interface. This reaction was most severe at the tip of the electrode and extended up the lead, producing a ring of fibroelastic tissue surrounding the lead and a fibrous scar in the adjacent myocardium (Figure 2) ranging from 250 to 1200 μm in thickness. The trichrome stain (Figure 2B and 2C) demonstrates that this fibroelastic tissue contains both fibrous connective tissue (green) and elastic tissue (purple).

The fibroelastic tissue scar associated with the leads was focal and well circumscribed. Adjacent to this confluent scar were variable degrees of interstitial fibrous connective tissue insinuated between the myocardial fibers of the interventricular septum. In many cases, there was an interesting radial pattern of interstitial fibrosis, almost suggesting lines of electrical injury from focal points on the ICD lead (Figure 2C).

In patient 2, who received shocks 7 days before death, and in patient 6, who had received shocks on the day of death, there was evidence of acute cell injury (Figure 3). In these patients, there were small areas of necrosis within the interventricular septum near the leads and no evidence of

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**TABLE 1. Demographics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (at Implant), y</th>
<th>Sex</th>
<th>LVEF</th>
<th>Substrate</th>
<th>Circumstance of Examination</th>
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<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>0.18</td>
<td>CAD</td>
<td>Death</td>
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<td>2</td>
<td>42</td>
<td>M</td>
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<td>CM</td>
<td>Transplantation</td>
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<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>0.18</td>
<td>CM</td>
<td>Transplantation</td>
</tr>
<tr>
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<td>39</td>
<td>M</td>
<td>0.10</td>
<td>CM</td>
<td>Transplantation</td>
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<tr>
<td>5</td>
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<td>F</td>
<td>0.29</td>
<td>CM</td>
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<tr>
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<td>51</td>
<td>M</td>
<td>0.17</td>
<td>CAD</td>
<td>Death</td>
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<td>38</td>
<td>M</td>
<td>0.42</td>
<td>CAD</td>
<td>Transplantation</td>
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<tr>
<td>8</td>
<td>60</td>
<td>M</td>
<td>0.20</td>
<td>CAD</td>
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<tr>
<td>Mean±SD</td>
<td>47±11</td>
<td></td>
<td>0.24±0.10</td>
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</table>

LVEF indicates left ventricular ejection fraction; CAD, coronary artery disease; and CM, cardiomyopathy.

**TABLE 2. Lead Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lead Model (Manufacturer)</th>
<th>ICD Model (Manufacturer)</th>
<th>Implant Duration, d</th>
<th>Total Shocks, n</th>
<th>Total Energy, J</th>
<th>Days Since Last Shock</th>
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<td>1550 (CPI)</td>
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<td>865</td>
<td>29</td>
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<td>1555 (CPI)</td>
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<td>81</td>
<td>2670</td>
<td>7</td>
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<td>215</td>
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<td>V112D (VTX)</td>
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<td>0</td>
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<tr>
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<td>V100 (VTX)</td>
<td>960</td>
<td>13</td>
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<td>924</td>
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<td>1720 (CPI)</td>
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<td>...</td>
<td>640±452</td>
<td>30±22</td>
<td>830±763</td>
<td>251±297</td>
</tr>
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</table>

CPI indicates Cardiac Pacemakers, Inc; VTX, Ventritex, Inc.
acute necrosis in any other areas of the heart. Patency of blood vessels in the areas of fibrosis suggests that the changes were not due to ischemia.

Finally, the microscopic findings observed in the hearts with chronically implanted ICD leads were apparently related to the leads themselves. Sarcoidosis was found unexpectedly in patient 4 at pathological examination. The fibrosis associated with the ICD lead was distinct from that associated with the sarcoid (Figure 4A and 4B). Patient 8 had both pacemaker and ICD leads (Figure 4C and 4D). Minimal fibrosis associated with the pacemaker lead contrasts with marked fibrosis associated with the ICD lead. Furthermore, in this and all other patients, the interstitial fibrosis was always in the septum along the current pathway of ICD shocks. In contrast, myocardium not in the current pathway, such as the free wall, was devoid of these changes (Figure 4D).

Discussion

The electrode-myocardial interfaces of the hearts examined in this study were characterized by intense endocardial fibrosis. Each lead was encased by a ring of fibroelastic tissue and associated with fibrosis of the interventricular septum and often the right ventricular free wall. Fibrosis involved the tricuspid valve in 5 patients, and the lead perforated the valve in 1 patient. Microscopically, interstitial fibrosis was adjacent to each lead, and acute cell injury was present only in patients who had recent shocks. The observed pathological changes may explain changes in pacing and defibrillation thresholds, defibrillation impedance, and sensing performance that have been reported. The fibrosis almost certainly explains the difficulty that can be encountered when transvenous ICD leads are explanted.

The inflammatory reaction incited by pacemaker leads has been well described. A well-orchestrated response to tissue injury begins with thrombus formation and activation of the complement and fibrinolytic systems. Fluid, protein, and blood cells enter tissue adjacent to the lead, producing an acute inflammatory reaction mediated by neutrophils, macrophages, foreign body giant cells, and fibroblasts. Granulation tissue forms that progresses to a fibrous connective tissue scar.

There is ample evidence that transthoracic, epicardial, and endocardial shocks can all cause myocardial damage. Dahl et al showed that transthoracic shocks caused myocardial necrosis in dogs and that shorter time intervals between discharges and small paddle sizes led to greater necrosis. Thus, repetitive shocks from small ICD endocardial leads might also cause myocardial injury. Furthermore, Babbs et al showed that the effective, damaging, and lethal electrical doses of transthoracic shocks led to injury and mortality in a dose-dependent manner. Van Vleet et al concluded that single transthoracic damped sinusoidal shocks were accompanied by a large margin of safety over the defibrillation threshold, with a 12-fold suprathreshold shock required to produce death, a 6-fold suprathreshold shock required to produce macroscopic damage, and a 3-fold suprathreshold shock necessary to induce microscopic damage. Because ICDs usually operate at much lower energies, the chance of tissue injury may be minimized. However, endocardial deliv-

e may be more hazardous. Doherty et al showed that the threshold for significant injury was \( \approx 30 \) J in dogs receiving countershocks applied directly to the heart.

The myocardial changes associated with endocardial defibrillator leads are probably attributable to both shocks themselves and a foreign body reaction. Van Vleet et al implanted leads in dogs to which no shocks were given. At necropsy, cardiovascular changes included formation of a fibrous sheath over the lead along its course in the veins, right atrium, and right ventricle; adhesion of the leads to adjacent venous and cardiac structures, including the tricuspid valve; endocardial fibrosis; and partial penetration of the myocardium at the apex of the right ventricle by the lead tips. Many of these changes were observed in our human counterparts.

Transvenous shocks in animals are associated with myocardial necrosis. Barker-Voelz et al showed that necrosis was concentrated at the distal electrode through which shocks were given. Because all animals were killed 48 hours after shock delivery, the development of fibrosis could not be assessed. However, Van Vleet et al assessed cardiac damage in dogs with chronically implanted defibrillation electrodes through which 4 episodes of multiple shocks were delivered. At 26 weeks, mechanical injury from the lead on the right side of the heart was manifest by endocardial fibrosis and fibrous sheath formation. Although the fibrosis was most marked at contact points adjacent to portions of the leads that were not adherent to the myocardium, flat areas of endocardial fibrosis were seen at the electrode-myocardial interface, and the leads were covered by an extensive fibrotic sheath as in our patients. Although microscopic evidence of necrosis was detected in 50% of the dogs, the severity was felt to be insignificant.

Because of the injury produced, high-energy shocks have been used to produce animal models of left ventricular failure. Nevertheless, energies used are much greater than those used clinically for defibrillation, virtually always >100 J. However, because the work discussed above demonstrates a dose-response relationship for myocardial injury, lower-energy shocks may have important effects that could be difficult to recognize clinically. For example, Perkins et al described changes in the hearts of 4 men who died as a result of myocardial infarction and were treated for recurrent cardiac arrest with 8 to 55 countershocks of 2.5 to 50 J delivered via a temporary catheter. Myocardial necrosis secondary to the catheter was present in 1 of the 4 hearts studied. Similarly, Avital et al reported the absence of detectable myocardial injury in patients receiving intraoperatively or spontaneous shocks after operation.

Both interstitial and confluent (replacement) fibroses were associated with ICD leads. Interstitial fibrosis itself is not unique to patients with cardiomyopathy. On the other hand, confluent fibrosis is less frequent in nonischemic cardiomyopathy but is the norm in patients with scars resulting from myocardial infarction. Although in both patients with coronary artery disease and dilated cardiomyopathy scar formation is more prominent on the left rather than the right side of the heart, our patients had extensive interstitial fibrosis on the right side of the heart adjacent to the lead,
suggesting a relationship between the presence of the lead and the scars themselves.

Clinical Implications
First, there is an increase in the defibrillation threshold that occurs with time in patients with nonthoracotomy ICD systems.23–26 One possible cause is myocardial fibrosis at the electrode-tissue interface. Because this threshold increase is more common for ICD systems that deliver monophasic than those that deliver biphasic shocks, it is possible that biphasic shocks not only defibrillate more effectively but also cause less cellular dysfunction than monophasic shocks. We saw no differences in the histology of patients with monophasic and biphasic ICDs. Furthermore, because ICD leads differ from standard bradycardia pacing leads (stiffer, larger, exposed coil), factors other than shocks may be important in the genesis of fibrosis.9 Because it is the coils and shocks delivered through them that seem to incite the fibrotic reaction, there is no reason to suspect that the reported changes are specific to any one manufacturer or material.

For non–steroid-eluting pacemaker leads, the pacing threshold increases in a time-dependent manner, usually...
within the first 2 months. In contrast, the pacing threshold for transvenous ICD leads increases over time without an early peak. This may be another consequence of fibrosis at the electrode-tissue interface. With the introduction of steroid-eluting transvenous ICD leads, fibrosis at the electrode-tissue interface and other alterations, such as increases in the defibrillation and pacing thresholds, may be attenuated. Serial pacing threshold data are not available for our patients because the first 4 had devices that did not have pacing capability; of the 4 others, 1 died 8 days after ICD implantation; and 2 followed elsewhere had no threshold data available.

Although “proarrhythmia” from ICDs is an infrequently reported event, arrhythmia exacerbation by ICDs does occur. This may be another consequence of fibrosis at the electrode-tissue interface. With the introduction of steroid-eluting transvenous ICD leads, fibrosis at the electrode-tissue interface and other alterations, such as increases in the defibrillation and pacing thresholds, may be attenuated. Serial pacing threshold data are not available for our patients because the first 4 had devices that did not have pacing capability; of the 4 others, 1 died 8 days after ICD implantation; and 2 followed elsewhere had no threshold data available.

Although “proarrhythmia” from ICDs is an infrequently reported event, arrhythmia exacerbation by ICDs does occur. When observed, it is usually a consequence of the delivery of therapy, arrhythmia acceleration, or new arrhythmias. On the other hand, the myocardial fibrosis that develops at the electrode-tissue interface may be responsible for new reentry circuits and possibly arrhythmogenesis.

As ICD leads age, lead failure will be recognized with greater frequency. The fibrous sheath that develops around pacemaker leads sometimes necessitates the use of dilating sheaths and forceful traction for extraction. Given the more intense inflammatory reaction and larger fibrous sheaths that encase ICD leads and attach to intracardiac structures, such as the tricuspid valve, more complicated extraction is to be expected. The contrasting degrees of fibrosis associated with the pacemaker and ICD leads in patient 8 provide support for this speculation (Figure 4).

**Study Limitations**

Our discussion of the clinical implications of the findings reported here is purely speculative. First, we do not have pacing or defibrillation threshold data for the patients studied to correlate the intensity of the fibrotic changes with alterations of these parameters. Second, although we suggest that the explantation of ICD leads is more difficult than of pacemaker leads, comparative data are not available. Finally, because our series was small and all patients either had died or had their hearts examined after cardiac transplantation, this series may not be representative of all patients with transvenous ICD leads. Nevertheless, the consistency of the findings suggests that these morphological changes may be common to all patients with these lead systems.

**Areas for Future Study**

With the advent of more efficacious waveforms and energy delivery systems, defibrillation may be accomplished with less energy that in turn could lead to less myocardial damage. Furthermore, steroid-eluting leads may cause less myocardial damage...
fibrosis. These events could make changes in the defibrillation and pacing thresholds less important clinically. Whether the pathological changes described here will also be of importance in atrial defibrillation is unknown. Further study is required.

References


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