Sudden Death in Patients With Implantable Cardioverter Defibrillators

The Importance of Post-Shock Electromechanical Dissociation

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OBJECTIVES
The purpose of this study was to determine the mechanisms of sudden death (SD) in patients with ventricular tachyarrhythmias (ventricular tachycardia/ventricular fibrillation [VT/VF]) treated with an implantable cardioverter defibrillator (ICD).

BACKGROUND
Despite ICD therapy, some patients with VT/VF still die suddenly. Optimal ICD use requires determination of the mechanisms of these residual SDs.

METHODS
We reviewed 320 patient deaths during trials of Medtronic transvenous ICD systems (Medtronic Inc., Minneapolis, Minnesota). Sudden deaths were further categorized according to mechanism. Post-shock electromechanical dissociation (EMD) describes a scenario where VT/VF was appropriately detected and treated by an ICD shock that restored a physiologic rhythm, but death still occurred immediately by EMD.

RESULTS
A mode of death could be ascribed for 317 patients—90 (28%) were sudden, 156 (49%) were nonsudden cardiac, and 71 (22%) were noncardiac. A mechanism of SD was proposed for 68 patients—20 (29%) had post-shock EMD, 17 (25%) had VT/VF uncorrected by shocks, 11 (16%) had primary electromechanical dissociation, 9 (13%) had incessant VT/VF, 5 (7%) had VT/VF after their ICD was deactivated or removed, and 6 (9%) had single instances of various other terminal events. Only New York Heart Association functional class independently predicted SD by post-shock EMD.

CONCLUSIONS
The most common mechanism of SD in patients with an ICD is VT/VF treated with an appropriate shock followed by EMD. As this mechanism accounted for 29% of the SDs to which a cause could be ascribed, this mechanism of SD warrants further investigation. (J Am Coll Cardiol 2002;39:1323–8) © 2002 by the American College of Cardiology Foundation

Patients who have had sustained ventricular tachycardia/ventricular fibrillation (VT/VF) without a transient or reversible cause are at high risk of VT/VF recurrence and sudden death (SD) (1–3). Of the therapeutics proposed for these patients, the implantable cardioverter defibrillator (ICD) best prevents follow-up mortality (4–6). Nevertheless, SDs still occur in patients with an ICD (7–39). Accordingly, optimal use of ICD therapy requires determination of the mechanisms of these residual SDs.

The goal of this study was to determine the mechanisms of death of patients with a non-thoracotomy ICD, with emphasis on the mechanisms of SD (40).

METHODS
Data were obtained from the events committee review of ICD patient deaths during pre-clinical studies of Medtronic non-thoracotomy ICDs (Medtronic Inc., Minneapolis, Minnesota) from 1994 to 1999. Each patient provided consent for this review. The events committee accessed, whenever possible, descriptions of the terminal event by the patient’s family, paramedic and emergency room reports, clinical summaries by attending physicians, physician/nursing progress notes, death certificates and post-mortem interrogation of the ICD memory logs. Deaths were first classified as sudden or nonsudden using definitions summarized below. Nonsudden deaths were further classified as cardiac or noncardiac. Finally, a specific cause was ascribed.

Definitions. Definitions proposed by the North American Society of Pacing and Electrophysiology policy conference (40) on standardized reporting of ICD patient outcomes were used. Sudden death was defined as that occurring within 1 h of onset of symptoms or unexpected and unwitnessed death during sleep. Nonsudden cardiac deaths were those with a central cardiac cause that were not sudden. Other deaths were noncardiac deaths.

Sudden deaths that began with VT/VF were further subgrouped. A detection failure death was that secondary to VT/VF with rates within the detection zones of the ICD that did not evoke an ICD response. A shock failure death was that due to VT/VF appropriately treated by the ICD with its full complement of shocks (four to six depending on
the ICD model) without terminating VT/VF. A redetection failure death was that due to VT/VF appropriately treated by the ICD with less than its full complement of therapies with persistence of VT/VF that was not recognized by the device. Incessant VT/VF was that appropriately detected and effectively treated by the ICD but which immediately recurred over and over to death. Post-shock electromechanical dissociation (EMD) describes a scenario where VT/VF was appropriately detected and effectively treated by four or less ICD shocks that restored a cardiac rhythm with the physiologic rate (40 to 150 beats/min) but that was then immediately followed by EMD and death.

**Statistical analysis.** Continuous data are presented as mean ± 1 SD and were compared using Student t test. Categorical data are presented as ratios (%) and were compared using the chi-square statistic. Independent predictors of post-shock EMD were sought using logistic regression analysis. A two-tailed p value of <0.05 was used to exclude the null hypothesis.

**RESULTS**

**Study population.** From 1994 to 1999, 4,889 patients participated in pre-clinical trials of Medtronic nonthoracotomy ICDs (models 7219, 7220, 7221, 7223, 7250 and 7273) in Canada and the U.S. and were followed for a total of 2,971 patient-years. During that time, 320 deaths occurred in 257 men and 63 women of mean age 68 ± 11 years with a mean New York Heart Association (NYHA) class of 2.4 ± 0.8 and a mean left ventricular ejection fraction (LVEF) of 0.27 ± 0.13. Their structural heart disease was coronary artery disease in 274 (86%), congestive cardiomyopathy in 26 (8%), hypertrophic cardiomyopathy in 7 (2%), valvular heart disease in 7 (2%), congenital long-QT interval syndrome in 2 (0.6%) and amyloid heart disease in 1 (0.3%). Three (1%) patients had no structural heart disease.

**Modes of death.** Three (1%) deaths could not be classified, because no other information was available. Of the remaining 317 deaths, 90 (28%) were sudden, 156 (49%) were nonsudden cardiac, and 71 (22%) were noncardiac. Compared with patients with nonsudden cardiac or noncardiac deaths, patients with SD were younger and tended to have more coronary artery disease and less nonischemic congestive cardiomyopathy (Table 1). Patients with nonsudden cardiac death were more likely to be in NYHA class III/IV and to have a low LVEF than patients with SD who, in turn, were more likely to be in NYHA III/IV and to have a low LVEF than patients with nonsudden cardiac death. Patients with SD were more likely to die in a hospital or a hospice than were patients with nonsudden cardiac or noncardiac death (Table 2). Patients with nonsudden cardiac death were more likely and patients with nonsudden cardiac death were least likely to have an appropriate ICD therapy during follow-up. Patients with SD were more likely to have died with an active ICD and to have that ICD interrogated after death. Finally, patients with nonsudden cardiac death were more likely to be receiving an antiarrhythmic drug at the time of death. There were no significant differences in the prevalence of beta-adrenergic blocking agent drug use.

**Mechanisms of death.** Of the 71 patients with noncardiac death, the cause was respiratory in 20 (28%), sepsis in 16 (22%), gastrointestinal in 10 (14%), carcinoma in 9 (13%), cerebrovascular in 7 (10%), renal in 5 (7%), other vascular (two dissecting abdominal aortic aneurysms and one pulmonary embolus) in 3 (4%) and trauma in 1 (1%) patient.

The most common cause of nonsudden cardiac death was progressive heart failure—129 (83%) of 156 patients. An additional 17 (11%) died of nonsudden consequences of VT/VF, 3 (2%) died of the nonsudden consequences of EMD, 3 (2%) died as a consequence of cardiac transplantation, 2 (2%) died of infective endocarditis, 1 (1%) died of cardiac tamponade, and 1 (1%) died as a consequence of coronary artery bypass grafting.

Of the 90 SDs, the probable mechanism of death could

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**Table 1. Patient Characteristics (Before ICD Implantation) by Mode of Death**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>n</th>
<th>All Deaths</th>
<th>Sudden Deaths</th>
<th>Nonsudden Cardiac</th>
<th>Noncardiac Deaths</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>317</td>
<td>67.8 ± 11.0</td>
<td>64.8 ± 11.0</td>
<td>69.2 ± 10.3</td>
<td>68.8 ± 12.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Men</td>
<td>317</td>
<td>80%</td>
<td>83%</td>
<td>78%</td>
<td>82%</td>
<td>NS</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>317</td>
<td>85%</td>
<td>92%</td>
<td>83%</td>
<td>83%</td>
<td>0.098</td>
</tr>
<tr>
<td>CCM (%)</td>
<td>317</td>
<td>8%</td>
<td>3%</td>
<td>12%</td>
<td>7%</td>
<td>0.07</td>
</tr>
<tr>
<td>Class III/IV (%)</td>
<td>303</td>
<td>43%</td>
<td>39%</td>
<td>53%</td>
<td>24%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>281</td>
<td>0.27 ± 0.13</td>
<td>0.27 ± 0.15</td>
<td>0.24 ± 0.10</td>
<td>0.33 ± 0.15</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**CAD** = coronary artery disease with or without prior myocardial infarction; **CCM** = nonischemic cardiomyopathy; **Class III/IV** = New York Heart Association heart failure function class III or IV; **ICD** = implantable cardioverter defibrillator; **LVEF** = left ventricular ejection fraction; n = number of patients with complete data; p value = statistical significance level by either analysis of variance or contingency table chi-square analysis, as appropriate.
be determined in 68 (76%) (Fig. 1). Only 13 (19%) of the 68 adjudicated SDs did not involve VT/VF—11 from primary EMD, 1 from a primary bradyarrhythmia and 1 from status asthmaticus. The other 55 (81%) of the 68 adjudicated SDs involved VT/VF. In five (9%) of these 55 patients, the ICD had been deactivated or removed. Otherwise, no instances of ICD failure to initially detect VT/VF were recognized. However, one patient experienced redetection failure. Failure to terminate VT/VF with all ICD therapies occurred in 17 cases (34% of SDs due to VT/VF in patients with a functioning ICD). Incessantly recurrent VT/VF occurred in nine cases (18% of SDs due to VT/VF in patients with a functioning ICD). One patient died of untreated VT with a rate below the programmed ICD detection zone, one died after conversion of supraventricular tachycardia to VT/VF by the ICD, and one died due to a motor vehicle accident precipitated by successfully treated VT/VF. Nevertheless, most SDs due to VT/VF in patients with a functioning ICD were due to post-shock EMD—20 cases (29% of the 68 SDs to which a mechanism was ascribed, 36% of the 55 SDs due to VT/VF, and 40% of the 50 SDs due to VT/VF in patients with a functioning ICD).

### Table 2. Patient Characteristics (After ICD Implantation) by Mode of Death

<table>
<thead>
<tr>
<th>Attribute</th>
<th>n</th>
<th>All Deaths</th>
<th>Sudden Deaths</th>
<th>Nonsudden Cardiac</th>
<th>Noncardiac Deaths</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LED (Js)</td>
<td>306</td>
<td>14.6 ± 16.8</td>
<td>15.1 ± 6.8</td>
<td>14.8 ± 6.9</td>
<td>13.4 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>317</td>
<td>143 ± 133</td>
<td>135 ± 128</td>
<td>152 ± 134</td>
<td>137 ± 124</td>
<td>NS</td>
</tr>
<tr>
<td>OP-MORT (%)</td>
<td>317</td>
<td>17%</td>
<td>18%</td>
<td>16%</td>
<td>17%</td>
<td>NS</td>
</tr>
<tr>
<td>In-hosp (%)</td>
<td>317</td>
<td>70%</td>
<td>29%</td>
<td>88%</td>
<td>80%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICD Rx (%)</td>
<td>317</td>
<td>55%</td>
<td>54%</td>
<td>63%</td>
<td>39%</td>
<td>0.005</td>
</tr>
<tr>
<td>ICD ON (%)</td>
<td>317</td>
<td>75%</td>
<td>94%</td>
<td>68%</td>
<td>66%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICD INTERRO (%)</td>
<td>238</td>
<td>44%</td>
<td>54%</td>
<td>42%</td>
<td>32%</td>
<td>0.036</td>
</tr>
<tr>
<td>AA (%)</td>
<td>312</td>
<td>51%</td>
<td>41%</td>
<td>60%</td>
<td>41%</td>
<td>0.005</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>317</td>
<td>16%</td>
<td>20%</td>
<td>13%</td>
<td>17%</td>
<td>NS</td>
</tr>
</tbody>
</table>

AA = antiarrhythmic drug therapy at time of death; Beta-blocker = beta-blocker drug therapy at time of death; ICD = implantable cardioverter defibrillator; ICD ON = ICD active at time of death; ICD Rx = appropriate ICD therapy supplied before terminal event; ICD INTERRO = post-mortem ICD interrogation performed (of those ICDs that were active at time of death); In-hosp = after admission to a hospital or hospice; LED = lowest intra-operative energy of successful defibrillation; n = number of patients with complete data; OP-MORT = percentage of deaths that were in the operative period; p value = statistical significance level by either analysis of variance or contingency table chi-square analysis, as appropriate.

**Figure 1.** Frequency distribution pie chart for adjudicated mechanisms of SD of 68 consecutive patients with a non-thoracotomy implantable cardioverter defibrillator (ICD) during pre-clinical device evaluation. The portion labeled VT/VF-OTHER includes one each of conversion of supraventricular tachyarrrhythmia to ventricular fibrillation (VF), untreated ventricular tachycardia (VT) (as programmed), failure to redetect VT/VF after a shock therapy and trauma from a motor vehicle accident secondary to treated VT/VF. EMD = electromechanical dissociation.
Post-shock EMD. Post-shock EMD followed one shock in eight patients, two shocks in five patients, three shocks in four patients and four shocks in three patients. The mean magnitude of the final shock was 31.0 ± 7.8 J and was the maximum output of the ICD in 17 patients. The post-shock cardiac rhythm was documented in 15 patients, being idioventricular in seven, ventricular paced in four and sinus rhythm in four patients.

Two clinical factors were associated with post-shock EMD—a lower LVEF and NYHA class of III/IV (Tables 3 and 4). Only the latter was an independent predictor of post-shock EMD by logistic regression. The hazard ratio for patients with NYHA class III/IV to experience SD by post-shock EMD rather than by another mechanism was 2.3 (95% confidence interval: 1.15 to 4.61).

DISCUSSION

The important observations of this study are that SD is still a common mode of death in VT/VF patients treated with an ICD and that post-shock EMD is the most common mechanism of SD in these patients. Finally, post-shock EMD is associated with high-energy shocks in patients with advanced congestive heart failure.

Previous studies—modes of deaths in ICD patients. The distribution of modes of death reported in the present study are in general agreement with those previously reported (6–39). These reference studies reported the modes of death of 1,576 VT/VF patients treated with an ICD—23% of the deaths were sudden, 48% were nonsudden cardiac, and 27% were noncardiac. In the present study, 28% of deaths were sudden, 49% were nonsudden cardiac, and 22% were noncardiac.

Nineteen reference studies (6–8,10–12,16–18,21,25,26,30, 36,38,39,41–43) reported mechanisms of 71 SDs in VT/VF patients with a functioning ICD. Thirty-three (46%) of these SDs did not involve VT/VF—13 (18%) resulted from a primary bradyarrhythmia, 11 (15%) resulted from primary EMD, and 9 (13%) were due to anatomic catastrophes. The present study noted fewer SDs due to bradyarrhythmias, likely as a consequence of the pacing capabilities of newer ICDs. The reference studies suggest that incessant VT/VF (26%) and shock failure (18%) are frequent mechanisms of SD in patients with a functioning ICD whose death involved VT/VF. The present study supports these suggestions, albeit with reversed frequency. As in the present study, combined experience of the reference studies indicate that other mechanisms of SD in this setting are rare, with the exception of post-shock EMD. Although the reference studies have not recognized the unique nature of post-shock EMD as a mechanism of SD, they describe events similar to post-shock EMD in 18 (25%) of their 71 adjudicated mechanisms of SD. The higher frequency of post-shock EMD in the present study is likely due to its prospective inclusion as a category of SD.

Potential mechanisms of post-shock EMD. It is possible that post-shock EMD is an epiphenomenon arising from some other fatal event, such as global myocardial ischemia, that produces collateral VT/VF. Correction of this collateral VT/VF would not prevent death. Alternatively, the VT/VF may be the primary event. Appropriate ICD function then replaces VT/VF with shock-induced EMD. Which of these circumstances is operative cannot be determined from the data of this study. Nevertheless, clinical experience, biologically-plausible associations and previous descriptions support the probability that many of these deaths result from ICD shocks that are either too frequent, too closely spaced or too large in magnitude.

<p>| Table 3. Patient Characteristics (Before ICD Implantation) by Mechanism of Death |</p>
<table>
<thead>
<tr>
<th>Attribute</th>
<th>n</th>
<th>All Sudden Deaths</th>
<th>Post-Shock EMD</th>
<th>Not Post-Shock EMD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>68</td>
<td>63.7 ± 10.8</td>
<td>64.4 ± 10.3</td>
<td>63.4 ± 11.0</td>
<td>NS</td>
</tr>
<tr>
<td>Men (%)</td>
<td>68</td>
<td>82%</td>
<td>85%</td>
<td>81%</td>
<td>NS</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>68</td>
<td>91%</td>
<td>90%</td>
<td>92%</td>
<td>NS</td>
</tr>
<tr>
<td>CCM (%)</td>
<td>68</td>
<td>3%</td>
<td>5%</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>Class III/IV (%)</td>
<td>66</td>
<td>36%</td>
<td>60%</td>
<td>26%</td>
<td>0.008</td>
</tr>
<tr>
<td>LVEF</td>
<td>63</td>
<td>28.4 ± 15.7</td>
<td>22.5 ± 9.7</td>
<td>30.9 ± 17.2</td>
<td>0.049</td>
</tr>
</tbody>
</table>

p value = statistical significance level by either Student t test or chi-square analysis, as appropriate. Abbreviations as in Table 1.

<p>| Table 4. Patient Characteristics (After ICD Implantation) by Mechanism of Death |</p>
<table>
<thead>
<tr>
<th>Attribute</th>
<th>n</th>
<th>All Sudden Deaths</th>
<th>Post-Shock EMD</th>
<th>Not Post-Shock EMD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LED (Js)</td>
<td>65</td>
<td>15.5 ± 7.0</td>
<td>17.9 ± 7.1</td>
<td>14.5 ± 6.9</td>
<td>0.077</td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>68</td>
<td>126 ± 126</td>
<td>163 ± 154</td>
<td>110 ± 111</td>
<td>0.117</td>
</tr>
<tr>
<td>OP-MORT (%)</td>
<td>68</td>
<td>22%</td>
<td>30%</td>
<td>23%</td>
<td>NS</td>
</tr>
<tr>
<td>In-hosp (%)</td>
<td>68</td>
<td>37%</td>
<td>60%</td>
<td>46%</td>
<td>NS</td>
</tr>
<tr>
<td>ICD Rx (%)</td>
<td>68</td>
<td>50%</td>
<td>100%</td>
<td>90%</td>
<td>0.129</td>
</tr>
<tr>
<td>ICD INTERRO (%)</td>
<td>63</td>
<td>73%</td>
<td>53%</td>
<td>66%</td>
<td>0.140</td>
</tr>
<tr>
<td>AA (%)</td>
<td>66</td>
<td>62%</td>
<td>74%</td>
<td>81%</td>
<td>NS</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>66</td>
<td>79%</td>
<td>74%</td>
<td>81%</td>
<td>NS</td>
</tr>
</tbody>
</table>

EMD = electromechanical dissociation; p value = statistical significance level by either Student t test or chi-square analysis, as appropriate; other abbreviations as in Table 2.
Shock induced myocardial dysfunction. Animal models have demonstrated a vast array of potentially deleterious consequences of DC shocks including changes in cellular morphology (44–48), biochemical function (49), electrophysiologic function (45,47–49) and hemodynamic function (49). Of importance, many of these functional changes have been demonstrated to last for minutes to hours as opposed to seconds (47–49). Furthermore, DC shocks of high field-strengths have been shown to cause death in dogs secondary to EMD (45,48).

These animal studies (44–49) demonstrated that dysfunction, damage and death require shock magnitudes considerably in excess of that used clinically. Using the pharmacologic dose-response curve approach, Babbs et al. (46) determined the median effective shock dose (correction of VF) (ED50), the median toxic shock dose (myocyte necrosis) (TD50) and the medial lethal shock dose (death) (LD50) of overdamped sine wave DC shocks in dogs. Expressed as total energy, the ED50, TD50 and LD50 were 1.5 J/kg, 30 J/kg and 470 J/kg, respectively. The dose response curves for defibrillation efficacy and for death did not overlap. However, the positions of these dose response curves in humans with heart disease may be different than those of dogs with normal hearts.

Many of the morphologic (50), biochemical (51), electrophysiologic (51) and hemodynamic (52) adverse effects of high-intensity DC shocks reported in animals models have also been noted, albeit with lower frequency, in patients who have received DC shocks of clinically relevant intensities. As in animal models, many of these functional changes have been demonstrated to last for minutes to hours as opposed to seconds (52).

The immediacy of post-shock EMD suggests that necrosis is not required for the phenomenon. Instead, it is likely that an immediate functional abnormality is responsible. This probability is supported by reports of severe hemodynamic deterioration after internal DC shocks during ICD implantation procedures (42,52). Furthermore, these instances of hemodynamic deterioration were predicted by poor left ventricular function. A severe manifestation of this phenomenon could be expressed as SD due to EMD.

Clinical significance. The frequency of post-shock EMD as a mechanism of SD in patients with an ICD recommends development of preventative measures. Such measures might include better patient selection (42,53), use of the minimum shock strength compatible with effective defibrillation (54), lead systems that avoid focal myocardial concentration of the potential gradients of the DC shock (55), shock waveforms that reduce the probability of myocyte dysfunction (56), pharmacologic therapies that reduce the occurrence of the phenomenon (57) and ICD therapies that treat the EMD should it occur (58).

Conclusions. Review of the causes of 320 deaths in VT/VF patients treated with an ICD revealed that 28% of these deaths are still sudden. The most common mechanisms of these SDs was VT/VF treated with an appropriate DC shock resulting in EMD and death. Post-shock EMD, which we have also termed cardiac annihilation (59), accounted for 29% of the 68 SDs to which a mechanism was ascribed, for 36% of the 55 SDs due to VT/VF and for 40% of the 50 SDs due to VT/VF in patients with a functioning ICD in place. Recognition of this phenomenon will prompt further investigations into its mechanism(s). Prevention of the phenomenon should lead to an improvement in the efficacy of ICD therapy.

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