Cardiac Death and Stored Electrograms in Patients With Third-Generation Implantable Cardioverter-Defibrillators

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Objectives. We sought to utilize terminal stored intracardiac electrograms (EGMs) to study the electrophysiologic events that accompany mortality in patients with third-generation implantable cardioverter-defibrillators (ICDs).

Background. Despite their ability to effectively terminate ventricular tachyarrhythmias, cardiac mortality in patients with ICDs remains high. The mechanisms and modes of death in these patients are not well understood.

Methods. We retrospectively analyzed clinical data and stored EGMs from patients enrolled in the clinical trial of the Ventritex Cadence ICD. Of the 1,729 patients 119 died during 6 years of follow-up. The final recorded EGM was reviewed. Postimplant EGMs as well as 50 control EGMs were used to define normal EGM characteristics.

Results. There were 36 noncardiac deaths (30%) and 83 cardiac deaths (70%). Of the cardiac deaths, 55 (66%) were nonsudden and 28 (34%) were sudden. When cardiac deaths were analyzed, 46 (55%) had no stored EGMs within 1 h of death, implying that the deaths were not directly related to tachyarrhythmias. In 37 cardiac deaths (18 nonsudden, 19 sudden), stored EGMs were present within 1 h of death. In these 37 deaths, the final EGM recorded was wide (>158 ms) in 33 (89%). Wide EGMs were interpreted as ventricular tachycardia in 27 and ventricular fibrillation in 6. In 13 of the 33 patients (39%) with wide EGMs, therapy was not delivered by the ICD, as it incorrectly detected a spontaneous termination of the arrhythmia. EGMs were significantly wider if recorded within 1 h, as compared with those recorded from 1 to 48 h before death (261 ± 124 vs. 181 ± 93 ms, p = 0.04).

Conclusions. Only 37 patients (31%) who died after placement of an ICD had a stored EGM within 1 h of the time of death, suggesting that the majority of deaths (69%) were not the immediate result of a tachyarrhythmia. When EGMs were recorded, they were wide in 89% of patients. These wide EGMs most likely represent intracardiac recordings of electromechanical dissociation. Thus, of the 119 deaths, 112 (94%) were not the immediate result of a tachyarrhythmia.

(J Am Coll Cardiol 1998;32:1056–62)
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Sudden cardiac death (SCD) is responsible for ~300,000 deaths annually in the United States (1). The understanding of the causes of sudden death has evolved dramatically over the past 20 years. Mobile cardiac rhythm recordings have revealed a high incidence of ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients who have a sudden cardiac death (2–4). This leads to the concept that the prevention or rapid treatment of VT and VF could prevent SCD. In response to this concept, the implantable cardioverter-defibrillator (ICD) was developed. Currently available ICDs can efficiently recognize and terminate ventricular tachyarrhythmias in the vast majority of cases (5,6). These third-generation ICDs are also able to store intracardiac electrograms (EGMs) from tachyarrhythmic episodes. These EGMs can be retrospectively analyzed to aid in the diagnosis of arrhythmia (7). Several retrospective and prospective studies have suggested that the use of ICDs decreases the rate of SCD in high risk patients (8–12). Despite the ability of ICDs to detect and terminate ventricular tachyarrhythmias, overall mortality for patients with depressed ventricular function who have undergone placement of ICDs remains substantial (8,13).

Several investigators have investigated the clinical modes of death in patients with earlier generation ICDs. These studies were limited by the lack of EGM data from the ICD during the terminal events. This study was undertaken to analyze the stored EGMs from patients who had a third-generation ICD and subsequently died. These EGMs were compared with clinical data and previously stored EGMs in an attempt to identify the modes of death, as well as the EGM characteristics associated with these deaths.

Methods

Initial clinical trial. The Ventritex Cadence is a third-generation noncommitted ICD capable of storing EGMs surrounding both delivered and aborted antitachycardia therapy
A 33-s EGM is recorded by the device, sampled at 256 Hz, from an endocardial or epicardial sensing electrode (Fig. 1). The gain setting is automatically adjusted in response to amplitude changes in the sensed signals. In addition, the gain setting is automatically increased by one step (1.5 times the previous gain) after the delivery of a shock. If the ensuing signal saturates the device filter, the recording gain immediately returns to the preshock setting. If three subsequent sensed signals continue to saturate the filter, the recording gain decreases further. The stored EGMs can subsequently be retrieved from the ICD through a programmer, during routine interrogation, and printed at a paper speed of 25 mm/s (14). The ICD interpretation of the arrhythmia is provided during interrogation. In addition, the date and time of each event are recorded.

The clinical trial of this device enrolled patients from July 1989 until April 1993. Clinical follow-up was obtained until April 1995. Over the course of the trial, 1,729 patients had an ICD placed. The following clinical data were collected for each patient at the time of device implantation: the patient’s age, gender, ejection fraction (calculated by echocardiography, radionuclide scans or left ventriculography), weight, height, presence or absence of pacemaker, etiology of structural heart disease, documented arrhythmias (arrhythmia morphology and cycle length), antiarrhythmic medications at the time of implantation, antiarrhythmic medications that failed before device implantation and ICD lead configuration and placement (unpublished data, 1989). In addition, each patient underwent device testing during implantation. At the time of implantation, all patients underwent induction of VF, with rescue shocking by the ICD, to ensure proper ICD function. The stored EGMs from these postimplantation test episodes were used as paired controls, to define the normal EGM width after therapy delivery in each patient.

When a patient in the study died, the device was interrogated and all stored EGMs were retrieved. The EGMs were collected and returned to the study sponsor and the Food and Drug Administration for further review. After receiving written permission from the trial investigators, we reviewed the clinical data and stored EGMs for all patients who died before April 1995. The available clinical data, including physician notes at the time of death (available in 98% of cases), autopsy data (available in 15% of cases) and death certificates (available in 2% of cases) were reviewed in an attempt to determine the exact cause of death.

**Figure 1.** Stored EGM from the Cadence ICD in a control subject. The EGM is recorded at 256 Hz from a bipolar sensing lead in the right ventricle. The time, in seconds, is displayed at the bottom of the strip. The sharp signals, lasting ~100 ms, represent ventricular depolarization. This EGM initially depicts a rhythm, consistent with atrial fibrillation (A). The rhythm spontaneously converts into a more rapid rhythm (B), which meets detection criteria for VT, and antitachycardia pacing is delivered (C) in an attempt to terminate the rhythm. This intervention causes an acceleration of the arrhythmia (D), and a shock is delivered (E), with the resultant termination of the tachyarrhythmia (F) and resumption of a slower rhythm, consistent with sinus rhythm.
In addition, the clinical characteristics and stored EGMs from 50 study patients who were alive as of April 1995 were used as a control group. These EGMs were recorded during either postimplantation testing or spontaneous episodes of ventricular tachyarrhythmias. All EGMs were recorded after delivery of an appropriate shock by the ICD.

Classification of clinical cause of death. The cause and time of death were determined by reviewing the available clinical data, including physician notes at the time of death, death certificates and autopsy data. In cases where the precise time of death was not available, the death was assumed to have occurred >1 h from the final recorded EGM.

Deaths were classified using a modified Cardiac Arrhythmia Suppression Trial (CAST) approach, as described by Pratt et al. (15). Deaths were classified as sudden cardiac (SCD) if they were unexpected and occurred within 1 h of the onset of new symptoms or if the death was unwitnessed and unexpected, unless a specific noncardiac cause could be confirmed. Deaths were classified as nonsudden cardiac (NSCD) if they were of cardiac origin but did not meet the criteria for SCD. Deaths were classified as noncardiac if they occurred as a result of factors that were not primarily cardiac. Deaths that were due to noncardiac causes were also reviewed.

Analysis of terminal EGMs. Two EGMs were reviewed for each patient who had a cardiac death—the EGM obtained at postimplantation device testing and the final stored EGM before death. The date and time of each EGM were recorded. EGMs recorded within 1 h of the clinically derived time of death were considered relevant to the death. The stored EGMs were further reviewed to determine the type of arrhythmia detected, the accuracy of the device in diagnosing the arrhythmia, the therapy delivered by the device, the rhythm present after therapy delivery and the accuracy of the device in recognizing the final rhythm. In addition, the width of the EGM signal was measured manually by two independent observers. EGM signals >2 SD above the EGM signal width obtained at postimplantation testing were classified as wide. The width of the postshock EGM signal from the patients who survived the trial was also measured.

Statistical analysis. Statistical analysis was performed using StatSoft Statistica Software, Version 4.1. Continuous variables were expressed as the mean value ± SD. Continuous variables were compared using the Student t test and analysis of variance. For multiple comparisons, the Tukey Honest Significance Difference (HSD) for Unequal Sample Sizes–Spjotvoll & Stoline test were used in conjunction with analysis of variance. Dichotomous variables were compared using the chi-square test. p values <0.05 were considered significant.

Results

Baseline characteristics. The baseline characteristics of the study group and control group are shown in Table 1. The two groups were similar in terms of age, ejection fraction, etiology of cardiac disease and indications for device implantation. The majority of study patients (89%) had coronary artery disease, severely decreased left ventricular systolic function (mean left ventricular ejection fraction 28 ± 11%) and monomorphic VT as the indication for implantation of the device (85%) and died within a relatively short time after device implantation (11.5 ± 11.9 months). Fifty-nine percent of the patients were receiving antiarrhythmic medications at the time of device implantation. The sensing electrode was endocardial in 40 patients (33%) and epicardial in 79 (66%).

Clinical causes of death. The clinical causes of death in the study group are depicted in Figure 2. Eighty-three deaths were due to cardiac causes, 28 of which were sudden and 55 were nonsudden. There were 36 noncardiac deaths (Table 2). In three noncardiac deaths, the cause of death could not accurately be determined.

Time of death. The clinically derived time of death in the study group could be accurately identified in 70 (84%) of the 83 cardiac deaths. The precise time (within 1 h) of the remaining 13 deaths could not be accurately determined. These

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**Table 1.** Baseline Clinical Characteristics of Patients Who Died During the Initial Trial of Ventritex Cadence Implantable Cardioverter-Defibrillator and of Control Subjects Who Survived the Trial

<table>
<thead>
<tr>
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<th>Patients (n = 119)</th>
<th>Control Subjects (n = 50)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>67.1 ± 8.2</td>
<td>64.8 ± 9.7</td>
<td>0.11</td>
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<tr>
<td>Gender (%male)</td>
<td>90</td>
<td>82</td>
<td>0.71</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>28 ± 12</td>
<td>30 ± 12</td>
<td>0.52</td>
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<tr>
<td>Time to death (months)</td>
<td>11.5 ± 11.9</td>
<td>N/A</td>
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<tr>
<td>Underlying cardiac disease (%)</td>
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<tr>
<td>Coronary artery disease</td>
<td>89</td>
<td>76</td>
<td>NS</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>11</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Indication for implantation* (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVT</td>
<td>85</td>
<td>82</td>
<td>NS</td>
</tr>
<tr>
<td>PVT/VF</td>
<td>15</td>
<td>18</td>
<td>NS</td>
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*Fifteen percent of patients had multiple indications for device implantation. These patients were classified as having MVT as their indication for implantation. Data are presented as the mean value ± SD or percentage of patients. MVT = monomorphic ventricular tachycardia; PVT = polymorphic ventricular tachycardia; VF = ventricular fibrillation.
deaths were regarded as occurring >1 h from the time of the final EGM.

**EGMs and clinical cause of death.** *Cardiac mortality.* The final stored EGMs were reviewed for all patients who had a cardiac death. Of the 83 patients who had a cardiac death (28 sudden and 55 nonsudden), stored EGMs had been recorded within the final hour of life in 37 (19 sudden and 18 nonsudden), indicating that the device had sensed a heart rate that exceeded the tachycardia detection rate. Thus, there were no stored EGMs in the final hour of life in 46 of patients (55%), indicating that the device did not detect a heart rate exceeding the tachycardia detection rate. Given the proven ability of the device to accurately detect ventricular tachyarrhythmias (6), the remaining 46 deaths most likely occurred in the absence of a sustained ventricular tachyarrhythmia. These deaths were most likely associated with a bradyarrhythmia or electromechanical dissociation (EMD) that was not recorded.

In 18 (68%) of the 28 SCDs, stored EGMs were recorded within 1 h of the time of death, indicating that the heart rate had exceeded the tachycardia detection rate. The ICD detected the resumption of what it perceived as sinus rhythm at the conclusion of each of these episodes. In 12 of these deaths (22%), the stored EGM was recorded within 10 min of the time of death, suggesting that the device was successful in terminating the perceived arrhythmia, but was unable to terminate the condition resulting in the death of the patient. In the remaining 43 patients (78%), EGMs were not recorded in the final minutes before death.

In 19 (68%) of the 28 SCDs, EGMs were stored from within 1 h of the clinically determined time of death, indicating that the heart rate had exceeded the tachycardia detection rate. The ICD detected the resumption of what it perceived as sinus rhythm at the conclusion of each of these episodes. In 15 of these deaths (54%), the stored EGM was recorded within 10 min of the time of death, suggesting that the device was successful in terminating the perceived arrhythmia, but was unable to terminate the condition resulting in the death of the patient. In the remaining 13 patients (46%), EGMs were not recorded in the final minutes before death.

**Noncardiac mortality.** The final stored EGM was reviewed for all patients who had a noncardiac death. Of the 36 patients who had a noncardiac death, stored EGMs had been recorded within the final hour of life in one. This patient was admitted with intractable bleeding from a peptic ulcer. He had one stored EGM, which revealed a tachyarrhythmia. The arrhythmia was appropriately detected and treated by the device, with the resumption of a nontachyarrhythmic rhythm, consistent with sinus rhythm.

**Characteristics of terminal EGMs.** *EGM width.* The relation between EGM width and time to death for cardiac deaths with stored EGMs is presented in Figure 3. The mean EGM width in these patients at postimplantation device testing was 113 ± 19 ms. In the control group, the mean EGM width after delivery of therapy was 108 ± 20 ms. There was no significant difference in EGM width between the control group and the study group at postimplantation testing (p = 0.91). EGMs that preceded death by <1 h were significantly wider than those that preceded death by >1 h (261 ± 124 vs. 181 ± 93 ms, p = 0.01). The EGMs from those patients who died <1 h after the final stored event were significantly wider than those obtained during postimplantation testing (181 ± 93 vs. 113 ± 19 ms, p = 0.05).

The relation between EGM width and clinical cause of death was studied. Patients who had a SCD within 1 h of the final ICD-detected episode had an EGM width 295 ± 150 ms. The signal width of the final recorded signal in patients who had a NSCD within 1 h of the final EGM was 227 ± 69 ms (p = 0.08) (Fig. 4). Wide EGM signals were present in 17 (89%) of the 19 patients who had a SCD and 13 (72%) of the 18 patients who had a NSCD (p = NS).

**Wide EGMs.** There were 30 wide EGMs recorded in the final hour of life among the patients who had a cardiac death.
These EGMs were interpreted by the ICD as VT in 26 (86%) and VF in 6 (14%). The device delivered therapy in 18 (55%) of the 33 wide EGMs. In 13 patients (43%), the ICD ultimately delivered a shock to treat the rhythm. In 5 patients (17%), the ICD only delivered antitachycardia pacing. In 12 patients (40%), the ICD delivered no therapy because the ICD falsely detected spontaneous termination of the perceived arrhythmia. Examples of wide EGMs are presented in Figure 5.

The cycle length of the wide EGM recorded in the final hour of life was 848 ± 247 ms in patients who had a NSCD and 757 ± 251 in patients who had a SCD. There was no significant difference in cycle length between the two groups (p = 0.3) (Table 3).

**Discussion**

Current attempts to treat SCD are based on the premise that the vast majority of these episodes are due to ventricular tachyarrhythmias. However, recent evidence suggests that intractable bradyarrhythmias and EMD may cause some SCDs. We undertook this study to further define the arrhythmias that immediately precede cardiac death in patients with ICDs.

Given the proven ability of ICDs to detect tachyarrhythmias (10,11), as well as the low incidence of device failure, deaths that were not accompanied by ICD discharges (thus stored EGMs) within the final hour of life are unlikely to be related to tachyarrhythmias. There were no discharges in 55% of the cardiac deaths within 1 day of death, and among those with discharges in the final day of life, there were no discharges in the final 10 min of life in 37%, implying that a sizable number of patients with cardiac death did not die as the direct result of a tachyarrhythmia. If cardiac deaths are further examined, 67% of NSCDs and 32% of SCDs did not occur with an ICD discharge in the final day of life. Even among patients with an ICD discharge in the final day of life, few (21% of NSCDs and 33% of SCDs) had an ICD discharge within the final 10 min of life. This implies that the majority of patients in both groups did not die as the direct result of a tachyarrhythmia. These deaths were most likely the result of EMD and/or brady-arrhythmia, which were fatal despite the back-up pacing capabilities of the ICD. There is no evidence that these deaths were due to the inability of the device to effectively terminate tachyarrhythmias.

When cardiac death was accompanied by ICD discharge in the final hour of life, the EGM signals that accompanied the final episodes were usually wide and fractionated, which were misinterpreted by the device as representing ventricular tachyarrhythmias. In 39% of these cases, the device detected a spontaneous termination of the tachyarrhythmia, despite the fact that the signals were unchanged. The remainder of the patients with wide EGMs received therapy from the device, which was unsuccessful. The inability of the ICD to convert these wide signals to normal sinus rhythm, as well as the increased prevalence of wide EGMs as the clinically determined time of death approaches, suggests that these wide signals most likely represent EMD, which current ICD algorithms are unlikely to recognize or terminate. It is unlikely that these wide EGMs represent episodes of refractory VT or VF, as they occurred at rates below 100/min. It is also unlikely that these fractionated EGMs were due to the development of intraventricular conduction abnormalities that developed in the interval between device implantation and death. Although morphologic changes in EGM characteristics have been associated with the development of bundle branch block (16), no changes in EGM width have been reported. The possibility that these EGM signals represent potentials recorded within the zone of slow conduction of a reentrant arrhythmia is remote, as they had not been seen during earlier tachyarrhythmic events in the same patients or in the control group. The wide EGMs noted represent only a proportion of all episodes of EMD, as many episodes may have been associated with EGM signals that were not excessively wide or fractionated.

The majority of cardiac deaths in this study group appear to be due to EMD or intractable bradyarrhythmias, or both. This is consistent with the recognized efficacy of ICDs in terminating ventricular tachyarrhythmias. Our data agree with those of Luu et al. (17), who reported that bradyarrhythmias and EMD were responsible for a large fraction of sudden death in patients awaiting heart transplantation. Changes in the underlying cardiac substrate, such as progression of underlying disease caused by ischemia or electrolyte imbalances, may limit the ability of the ICD to prevent all episodes of SCD.

There are several limitations associated with our retrospective study. Attempts to precisely ascertain the cause of death were hampered by a relative lack of autopsy data. Previous reports have documented the importance of autopsy data to precisely determine the cause of death (16).

There are limitations in the digital recordings produced by this device. The quality of a digital signal is dependent on the sampling rate as well as the gain used for the recording. We were unable to ascertain the precise gain settings used during each event. However, it is unlikely that the wide EGMs we observed were the result of changes in the recording gain of the ICD. The protocol by which the Cadence automatically changes gain after the delivery of a shock could cause an initial
overgaining” of signals, but this would quickly be corrected. The wide EGM signals we report persisted without appreciable change for a substantial period. In addition, wide EGMs were observed exclusively in close proximity to the time of death. If these signals were the result of device malfunction, lead fracture or electromechanical interference, we would expect that they would not be present at or near the time of death.

We were unable to correlate the wide EGM signals with surface electrocardiographic tracings or other clinical variables, which could prove our hypothesis that these signals represent EMD. However, the clinical setting in which these

Figure 5. Examples of wide EGMs. Panel 1 depicts a wide rhythm, with EGM signals >158 ms (A). This is interpreted as VT by the device, and antitachycardia pacing is delivered (B), without an appreciable change in the arrhythmia. The wide EGM signals continue and become progressively more disorganized toward the end of the episode (C). The device detects a spontaneous termination of the tachyarrhythmia after delivery of antitachycardia pacing. Panel 2 depicts an extremely wide signal that is interpreted by the ICD as VF (A), and a shock is delivered (B). After the shock, the EGM signal remains extremely wide (C), although somewhat less fractionated. The postshock EGM is interpreted by the device as depicting successful termination of VF. Panel 3 depicts an extremely wide signal (A), as well as noncapturing pacing spikes from a permanent VVI pacemaker that had also been implanted (B). The wide EGM is sensed by the device as VF, and a shock is delivered (C), which terminates all spontaneous electrical activity. After the shock, ineffective bradycardic pacing continues (D).

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<th>Table 3. Characteristics of Wide Intracardiac Electrograms</th>
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<td>SC</td>
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<td>848 ± 247</td>
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<td>295 ± 150</td>
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Wide EGMs denotes the fraction of patients in each group with stored EGMs recorded within the final hour of life that depicted wide signals. Data are presented as the number of patients or the mean value ± SD. EGM = intracardiac electrogram; NSCD = nonsudden cardiac; SCD = sudden cardiac death.
signals occurred, as well as the highly unusual depolarization pattern they represent, is strongly suggestive of EMD.

Clinical implications. Despite their proven ability to effectively terminate tachyarrhythmias, some episodes of SCD will continue to occur in patients with ICDs. These deaths will most likely occur as a result of EMD or bradyarrhythmias, or both. Future attempts to utilize stored EGMs to document the timing and mechanisms responsible for sudden death will require the development of ICD systems that are able to record other physiologic variables, such as chest impedance, pH, instantaneous stroke volume, body temperature, intracardiac pressure and body motion. These factors, when combined with stored EGMs, may allow the ICD to provide valuable information on the pathophysiologic changes that occur at the time of death.

We acknowledge Ventritex and the Cadence investigators for allowing us access to the Cadence trial data base. We also thank William G. Stevenson, MD, for his review and helpful suggestions, and Mrs. Susan Henry for her secretarial assistance.

References