Effects of Implantable Cardioverter Defibrillator Implantation and Shock Application on Biochemical Markers of Myocardial Damage

Thomas Schlüter, Hannsjörg Baum, Andreas Plewan, and Dieter Neumeier

Background: Implantable cardioverter defibrillator (ICD) implantation is a common approach in patients at high risk of sudden cardiac death. To check for normal function, it is necessary to test the ICD. For this purpose, repetitive induction and termination of ventricular fibrillation by direct current shocks is required. This may lead to minor myocardial damage. Cardiac troponin T (cTnT) and I (cTnI) are specific markers for the detection of myocardial injury. Because these proteins usually are undetectable in healthy individuals, they are excellent markers for detecting minimal myocardial damage. The objective of this study was to evaluate the effect of defibrillation of induced ventricular fibrillation on markers of myocardial damage.

Methods: This study included 14 patients who underwent ICD implantation and intraoperative testing. We measured cTnT, cTnI, creatine kinase MB (CK-MB) mass, CK activity, and myoglobin before and at definite times after intraoperative shock application.

Results: Depending on the effectiveness of shocks and the energy applied, the cardiac-specific markers cTnT and cTnI, as well as CK-MB mass, showed a significant increase compared with the baseline value before testing and peaked for the most part 4 h after shock application. In contrast, the increases in CK activity and myoglobin were predominantly detectable in patients who received additional external shocks.

Conclusions: ICD implantation and testing leads to a short release of cardiac markers into the circulation. This release seems to be of cytoplasmic origin and depends on the number and effectiveness of the shocks applied.

The Implantation of an implantable cardioverter defibrillator (ICD) is a common approach in patients with ventricular tachycardia or who have survived cryptogenic sudden cardiac death (1). To check for normal ICD function, it is necessary to test the system and to determine the defibrillation threshold. The defibrillation threshold is defined as the lowest energy, in joules (J), for defibrillation of induced ventricular fibrillation (VF). However, repeated episodes of electrical therapy can have disadvantageous effects on myocardial performance (2, 3).

The cardiac isoforms of troponin T (cTnT) and troponin I (cTnI) are highly specific markers for the detection of myocardial damage. After myocardial ischemia but also as a result of other myocardial stress, such as myocarditis, cTnI and cTnT are released into the circulation (4, 5) where they can be detected with sensitive immunoassays (6, 7).

This study assesses the extent of myocardial injury after ICD implantation and testing by the release of the cardiospecific markers cTnT and cTnI in relation to other, not fully cardiospecific, markers of cardiac ischemia: creatine kinase (CK), CK-MB mass concentration, and myoglobin.

Materials and Methods

Patients and Samples
Between February and November 1998, 14 patients (12 men, 2 women; median age, 63.5 years; range, 44–78
years) with high risk of ventricular tachyarrhythmia and scheduled for implantation of an ICD were included in this study (Table 1). Revascularization steps (angioplasty and stenting, or bypass grafting) had been completed in all patients suffering from coronary artery disease (CAD) before starting the implantation procedure. One patient was rejected because of signs of myocardial ischemia. None of the other 13 patients had stable or unstable angina. Eight patients suffered from CAD, two from cardiomyopathy (CMP), and two from valvular heart disease (VHD). One patient had both CAD and CMP, and another had CMP and VHD. All patients gave their informed consent to participate in this study. Blood samples were collected at four time points: before and 1, 4, and 24 h after intraoperative shock application. The samples before and 1 h after testing were drawn from a radialis catheter (for invasive blood pressure measurements); the samples 4 and 24 h after testing were drawn from peripheral veins.

After clotting and centrifugation, the serum samples were stored at −70 °C until analysis.

METHODS

Implantation and ICD used. ICD systems from Guidant Corporation, Cardiac Pacemakers (Models 1749, 1782, 1783, and 1849) and from Medtronic, Inc. (Models 7250 and 7227) were used. Tined, steroid-eluting electrodes were used in 10 patients (Medtronic “Sprint” 6942/6932 and Cardiac Pacemakers Endotak Endurance: 145), and tined, non-steroid-eluting electrodes were used in 4 patients (Cardiac Pacemakers Endotak Endurance: 135). In five patients, additional steroid-eluting “screw-in” leads (Medtronic 6940) for atrial sensing were implanted.

Each patient received a 1-J test shock before every testing episode. VF was induced with a shock-on-T induction with 1.2 J. For determining the defibrillation threshold, the verification technique was used. Intermediate energies that successfully defibrillate the patient and provide an adequate energy margin are determined in the verification procedure. This technique is widely accepted because it does not require the subject to be tested with energies that do not defibrillate as the threshold method does (8). If the first shock was effective, the physician could repeat the testing with the same energy or stop further testing. In case of failure, the system automatically applied a second shock with maximum energy. Implantation criteria were met if induced VF could be terminated one time with a shock of ~10–15 J to maximum output or if two subsequently induced VF episodes could be defibrillated successfully with 10–15 J to maximum output.

In case of missing implantation criteria, repositioning of the ventricular lead was performed before retesting. In one patient (patient 5), the physician decided not to reposition the electrode although the second shock after the first repositioning (shock 4) was ineffective and VF had to be terminated with an effective 31-J shock. Instead of repositioning, the physician tested again and defibrillated successfully with 23 J. In another patient (patient 18), the electrode had to be repositioned twice, and the patient received two external 360-J shocks. Three patients received atrial shocks through a additional lead for terminating atrial fibrillation.

To guarantee myocardium recovery between the ischemic episodes produced by VF, care was taken not to induce VF within 5 min after the previous testing episode.

Analytical procedures. cTnT and CK-MB were measured with an electrochemiluminescence immunoassay on an Elecsys® 2010 analyzer (Roche Diagnostics). The cTnT assay uses two monoclonal antibodies specific for the cardiac isoform of TnT and has <0.01% cross-reactivity with skeletal muscle troponin T. The CV is 5.1% at the cutoff of 0.1 μg/L for cTnT, and for CK-MB, the CV is 3.9% at 5.98 μg/L; the cutoff is 5 μg/L (9). cTnI was measured on a Dimension® RxL analyzer (Dade Behring) using the TROP Flex™ reagent cassette. This assay uses two monoclonal antibodies specific for two different epitopes on the cTnI molecule. The cross-reactivity with skeletal troponin I is <0.1%. The CV is 9.4% at 0.5 μg/L, and the cutoff is 0.4 μg/L. Myoglobin was measured on a BN 2 analyzer (Dade Behring) using an immunonephelometric assay (N-Latex Myoglobin). The CV is 4.8% at 85 μg/L, and the cutoff is 70 μg/L. Total CK activity was measured on a Vitros® 950 IRC (Ortho Clinical Diagnostics) at 25 °C. The CV is 3% at 70 U/L, and the cutoff is 80 U/L for men and 70 U/L for women. All assays were

### Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Cardiovascular disease</th>
<th>All patientsa (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.5 (44−78)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>12/2</td>
</tr>
<tr>
<td>LV-EF,a %</td>
<td>45 (18−70)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>9</td>
</tr>
<tr>
<td>Dilated CMP</td>
<td>4</td>
</tr>
<tr>
<td>VHD</td>
<td>3</td>
</tr>
<tr>
<td>Cumulative energy, J</td>
<td>38 (17−194)</td>
</tr>
<tr>
<td>Number of shocks</td>
<td>2 (1−10)</td>
</tr>
<tr>
<td>Additional leads</td>
<td>5</td>
</tr>
</tbody>
</table>

a Data are presented as median and range.
b LV-EF, left ventricular ejection fraction.

### Table 2. Comparison of significance of deviations.

<table>
<thead>
<tr>
<th></th>
<th>After 1 h vs before</th>
<th>After 4 h vs before</th>
<th>After 24 h vs before</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnT</td>
<td>0.0093</td>
<td>0.0077</td>
<td>0.0094</td>
</tr>
<tr>
<td>cTnl</td>
<td>NS</td>
<td>0.0186</td>
<td>NS</td>
</tr>
<tr>
<td>CK-MB</td>
<td>0.006</td>
<td>0.0043</td>
<td>NS</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>0.0029</td>
<td>0.001</td>
<td>0.0012</td>
</tr>
<tr>
<td>CK</td>
<td>NS</td>
<td>0.02</td>
<td>0.0076</td>
</tr>
</tbody>
</table>

* NS, not significant.
performed according the recommendations of the manufacturers.

Statistics. Analyses were performed using a commercially distributed software package (Astute, Statistics Add-in for Microsoft Excel; DDU Software). To test for the differences in serum markers at baseline and after ICD implantation, the Wilcoxon matched-pairs signed-ranks test was used. Significance was estimated as $P < 0.05$.

Results
The $P$ values for all markers and all patients are shown in Table 2, which compares the serum samples drawn at 1, 4, and 24 h with the serum samples drawn before implantation and testing. Four hours after ICD implantation and testing, all markers showed significant increases compared with the baseline values before testing. In contrast, for cTnT and myoglobin, this was at all three time points after ICD testing.

The individual markers and the biochemical findings of all patients are shown in Table 3. In nine patients, cTnT was detectable. cTnI was detectable in eight patients, all of whom also had detectable cTnT values. cTnI peak concentrations above the cutoff were seen in three patients, two of whom also exceeded the cTnT cutoff. In both patients, we also found CK-MB mass increases over the cutoff. All of the patients with cTnT/cTnI peak concentration above the cutoff received two ventricular shocks; two patients had additional atrial screw-in electrodes, and one of them received three additional atrial shocks with lower energy. No repositioning had to be performed in all of these patients. There was a weak correlation between troponin increase and cumulative energy in all of the patients who received two effective ventricular shocks ($r = 0.647$ for cTnI and $r = 0.636$ for cTnT).

CK-MB mass concentrations above the cutoff were seen in four patients. One of these patients received three atrial and seven ventricular shocks (cumulative energy, 194 J). Additionally, the physician applied two external 360-J shocks, and the electrode had to be repositioned twice.

The CK activity increased to $>80$ U/L in five patients. Patient 18 showed the largest increase (164 U/L); this patient received the largest cumulative energy (194 J) and two external 360-J shocks. In two of the five patients showing CK activity $>80$ U/L, additional atrial leads were implanted (patients 7 and 18). In all of these five patients, CK showed no peak within 24 h.

Myoglobin concentrations peaked at $>70$ µg/L in nine patients. In three patients, additional atrial leads were implanted. The very high myoglobin peak concentration for patient 18 (291 µg/L) correlated with the high CK in this patient.

No patient who received only one shock showed detectable cTnT or cTnI values. When we compared the number of shocks and the increases in cTnT and cTnI, only patients receiving two effective shocks showed con-
energy direct current shocks produce myocardial damage. Animal experiments have suggested that repeated high-
ergically were 0.08 μg/L (range, 0–2.16 μg/L) for cTnI, 0.023 μg/L (range, 0–0.26 μg/L) for cTnT, and 2.5 μg/L (range, 0–14.93 μg/L) for CK-MB.

### Discussion

Animal experiments have suggested that repeated high-energy direct current shocks produce myocardial damage. The way the energy is delivered to the heart is an important factor that influences the release of cardiac markers into circulation. Intracardial applied shocks with rather low energy are probably more damaging than transhoracic shocks with high energy. Increasing CK and CK-MB concentrations after transhoracic shocks have been described, but it has been found that most of the CK released after transhoracic cardioversion derives from chest wall skeletal muscles, because cardiосpecific markers such as cTnT and cTnI show no or minimal increases after transhoracic shock.

We found increased serum concentrations of all markers, cTnT, cTnI, CK-MB, CK, and myoglobin, after ICD implantation. Patients who received only one shock showed no increases in cTnT, cTnI, and CK-MB mass above the cutoff values. All patients with cTnT and cTnI peak concentrations above the cutoff had received two ventricular shocks.

It is remarkable that patients who received more than two shocks, very high cumulative energy, and repositioning of the electrode (patients 5 and 18) had no (patient 5) or only marginal (patient 18) increases in cTnT and cTnI. Wrong positioning of the electrode leads to a higher number of ineffective shocks; these ineffective shocks therefore do not lead to a release of cTnT and cTnI from the myocardium. One patient received two additional external 360-J shocks. This patient showed only marginal increases in the specific markers cTnT, cTnI, and CK-MB mass, and large increases in the nonspecific markers CK and myoglobin. External shocks may lead only to a release from the thoracic skeletal muscles, which explains the large increases in CK activity and myoglobin in this patient.

Our results correlate well with those of Hurst et al. (15) and Runsiö et al. (10), who also found increased serum concentrations of cTnT and cTnI or cTnT and CK-MB after ICD implantation (Table 4). In contrast to these studies, we found a clearly visible lower postoperative peak value for cTnT, but also lower peak values for cTnI and CK-MB. This discrepancy is attributable to the lower cumulative energy used in our patients, but the assays used for determining the cardiac-specific markers, especially for cTnT, are also important influencing factors. For measuring cTnT, we used a highly specific second-generation assay with negligible cross-reactivity with skeletal muscle troponin T. The cTnT assay used by Hurst et al. (15) and Runsiö et al. (10) shows 2% cross-reactivity with skeletal muscle troponin T, leading to possible false-positive results.

Troponins T and I are structurally bound regulator proteins of the contractile apparatus of the skeletal muscle and myocardium. Only a small portion of both can be found as a soluble portion in the cytoplasm. For cTnT, this is ~6–8%; for cTnI, it is 2.5% (17). The release into the circulation is therefore characterized by two steps. In the first step, the cytoplasmic pool is released simultaneously with other cytoplasmic proteins, such as CK, CK-MB, and myoglobin. After loss of integrity of the contractile apparatus, cTnT and cTnI are released continuously until the infarcted area is healed. The first release can be measured in the blood ~4 h after damage, whereas the second release will occur into the serum after 24 h (18). Additionally, the half-time of both cTnT and cTnI is ~2 h (10). As shown in the Results, cTnT, cTnI, and CK-MB show a peak value after 4 h. Therefore, we suggest that the release of cTnT and cTnI is only from the small amount located in the cytoplasm. Cell necrosis would cause a second, additional release of disintegrated structurally bound proteins into circulation, which did not occur in our patients. CK showed additional increases even after 24 h. Each testing episode caused a short skeletal muscle spasm that could explain the further increase of CK after 24 h.

In conclusion, ICD implantation and testing often leads to a short release of cardiac markers into the circulation. The effectiveness of the individual shock, depending on the positioning of the electrode and the position of the heart in the electrical field, seems to influence the release of the cardiac-specific markers. Because the cardiac-specific markers cTnT and cTnI peak after 4 h, theoretically no cell necrosis can occur. It seems to be rather from cytoplasmic

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**Table 4. Comparison of our results with the studies of Hurst et al. (15) and Runsiö et al. (10).**

<table>
<thead>
<tr>
<th></th>
<th>This study</th>
<th>Hurst et al.</th>
<th>Runsiö et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak cTnT, μg/L</td>
<td>0.023 (0–0.26)</td>
<td>0.26 (0.02–6.46)</td>
<td>0.16 (0.008–0.350)</td>
</tr>
<tr>
<td>Peak cTnI, μg/L</td>
<td>0.08 (0–2.16)</td>
<td>0.8 (0.3–5.5)</td>
<td>Not done</td>
</tr>
<tr>
<td>Peak CK-MB, μg/L</td>
<td>2.5 (0.73–14.93)</td>
<td>Not done</td>
<td>5.8 (1.0–11.7)</td>
</tr>
<tr>
<td>Number of shocks</td>
<td>2 (1–10)</td>
<td>7.0 ± 2.5</td>
<td>5 (4–8)</td>
</tr>
<tr>
<td>Mean cumulative energy, J</td>
<td>38 (17–194)</td>
<td>111.2 ± 62.7</td>
<td>114 (94–174)</td>
</tr>
</tbody>
</table>

*a Data are presented as median and range except where otherwise indicated.
*Mean.
* SD.
origin as a result of a reversible change of permeability of the cellular membrane.

References