Evaluation of Myocardial Injury Following Repeated Internal Atrial Shocks by Monitoring Serum Cardiac Troponin I Levels*  

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**Introduction:** Electrical shocks delivered for atrial cardioversion (CV) may cause myocardial damage. The aim of this study was to assess the extent of myocardial injury caused by repeated intracardiac shocks delivered for low-energy internal atrial CV.

**Methods and results:** Thirty-five patients with chronic persistent atrial fibrillation (AF) of different etiologies underwent CV with delivery of synchronized biphasic shocks (3.0/3.0 ms) between two catheters positioned in the right atrium and the coronary sinus. Shocks were delivered according to a step-up protocol (50 V, 180 V, then steps of 40 to 56 V up to 500 V, if necessary). In 23 patients, AF was reinduced after baseline CV, and CV was repeated. Myocardial injury was monitored by measuring cardiac troponin I (cTnI) serum concentrations in blood samples taken at baseline and at 2, 4, 8, 12, and 24 h after the procedure, by means of an immunoenzymologic assay (normal values, < 0.6 ng/mL). A mean (± SD) of 6.9 ± 3.4 shocks per patient were delivered (range, 2 to 17). Shocks delivered in each patient had a maximal energy of 7.3 ± 4.0 J (range, 1.7 to 15.7). In 20 patients (57%), no evidence of myocardial injury (cTnI level, < 0.6 ng/mL) was found. In 13 patients (37%), mildly elevated cTnI levels (range, 0.7 to 1.4 ng/mL) in samples taken 4 to 12 h after CV suggested minor myocardial injury. In two patients (6%), higher cTnI levels were found in samples taken 4 to 8 h after CV (peak, 1.7 and 2.4 ng/mL), indicating a necrotic damage. Patients with no cTnI elevation, with mild cTnI elevation, or with cTnI levels > 1.5 ng/mL did not differ significantly with respect to the total number of shocks delivered, the mean amount of energy delivered, and the cumulative amount of energy delivered. No clinical complications were observed.

**Conclusions:** Following internal CV with the delivery of repeated shocks, minor elevations of cTnI serum levels could be detected in a significant proportion of patients, and this suggests subtle asymptomatic minor myocardial injury. The elevations of cTnI levels do not appear to be related to the number of shocks or to the amount of energy delivered.

(CHEST 2000; 118:342–347)

**Key words:** atrial fibrillation; cardioversion; myocardial injury; troponin

**Abbreviations:** AF = atrial fibrillation; CK = creatine kinase; CK-MB = cardiospecific isoenzyme MB of creatine kinase; cTnI = cardiac troponin I; CV = cardioversion; DC = direct current; NYHA = New York Heart Association

Transvenous internal cardioversion (CV) is a relatively new technique, and several studies both in the experimental and clinical setting have evaluated its efficacy, safety, and tolerability.1–7 The delivery of biphasic shocks at relatively low energies (< 6 to 10 J) between catheters placed in the right atrium and coronary sinus or in the left pulmonary artery resulted in the restoration of sinus rhythm, even in patients with long-standing chronic atrial fibrillation (AF) and despite previous ineffective transthoracic shocks.3–7 Moreover, an implantable device capable of delivering synchronized shocks (≤ 6 J) through intracardiac defibrillation leads has been evaluated in patients with recurrent paroxysmal AF that was refractory to medical treatment.8

Although high-energy, direct-current (DC), transthoracic countershock is a routine practice, it is still matter of controversy whether it can cause myocardial...
damage. In transthoracic CV, the detection of myocardial damage by measuring levels of serum creatine kinase (CK), its cardiacspecific isoenzyme MB (CK-MB), or myoglobin was difficult because of concomitant skeletal muscle injury. More recently, cardiac troponin I (cTnI), a cardiac regulatory protein found only in cardiac muscle, has been found to be a sensitive and specific marker of myocardial injury. Three studies evaluated plasma levels of cTnI following conventional transthoracic CV, but no study considered the extent of myocardial damage detectable after the delivery of intracardiac shocks.

The aim of this study was to assess the extent of myocardial injury detectable after repeated intracardiac shocks delivered for low-energy internal atrial CV.

**Materials and Methods**

**Patients**

Patients with a history of chronic AF in the persistent form, in whom the arrhythmia persisted for at least 1 month, were considered for enrollment into the study. Patients were excluded for the following criteria: age > 80 years; New York Heart Association (NYHA) class IV heart failure; myocardial infarction, unstable angina, or coronary interventional procedures within the preceding 30 days; clinical evidence of muscular disease; recent infections or recent trauma; a mean ventricular rate during AF of < 45 beats/min; ECG evidence of atrioventricular block; sick sinus syndrome; hypokalemia (potassium level, < 3.5 mmol/L); and severe renal or hepatic failure and severe hypoxia (PO2 level, < 55 mm Hg). All the patients gave written informed consent.

The anticoagulation guidelines of the American College of Chest Physicians were followed, therefore, patients were enrolled into the study only if they received oral warfarin treatment for at least 3 to 4 weeks with an international normalized ratio in the therapeutic range (2.0 to 3.5). In case a patient had an international normalized ratio of > 3.5, the procedure was deferred in order to avoid bleeding complications. The procedure was performed after a washout period for antiarrhythmic drugs (including digoxin) of at least five half-lives (6 months for amiodarone).

**Electrophysiologic Study and Atrial CV**

In the electrophysiology laboratory, catheters were positioned using fluoroscopy. For CV, two identical 6F catheters (Bihor 6000, Rhythm Technologies Inc; Jacksonville, FL) were employed that had two distal pacing/recording electrode rings and a 40-volt titanium defibrillating electrode that was 5.5 cm long and was placed proximal to the rings. The catheters were positioned in the right atrium by a femoral approach, with the tip in the right atrial appendage, and the coil was placed along the right atrial wall and in the coronary sinus through a puncture in the left subclavian vein, respectively. Additionally, a 6F bipolar or quadrupolar catheter was advanced from a femoral vein and was positioned in the right ventricular apex in order to provide accurate R-wave synchronization and backup ventricular pacing, if required. The coil catheters were connected to an external programmable cardioverter-defibrillator (right atrium negative, left atrium positive). A device (model HVS-02, Ventritex Inc; Sunnyvale, CA) was employed (device capacitance, 150 μF) for delivering biphasic symmetric (3.0/3.0-ms phase duration) shocks synchronized on the R wave. Biphasic shocks were delivered with the amplitude of phase 2 leading-edge voltage equal to phase 1 leading-edge voltage but with opposite polarity. Leading-edge voltages were programmed between 50 and 500 V according to a step-up protocol. For safety reasons, shocks were delivered only after R-R intervals between 500 and 1,000 ms. After the delivery of a test shock of 50 V to verify the proper R-wave synchronization, shocks were delivered in the following sequence, with a 2-min interval between shocks: 150, 240, 300, 360, 400, 450, and 500 V. After successful CV of baseline AF, AF was reinduced by atrial pacing in the high right atrium (extra stimuli or high-frequency bursts) in 23 patients, and a new series of shocks was delivered to restore sinus rhythm, beginning with a leading-edge voltage that was 80 V less than the previous effective shock voltage.

A shock was considered to be successful if a stable sinus rhythm was restored within 3 s of a shock. In this case, the sequence of shocks was terminated. Cardiac rhythm was continuously monitored during the procedure, and surface ECG was recorded on paper during the shock delivery. Premedication or sedation was not routinely administered before or during the procedure, according to a previously described protocol. Rather, shock-induced discomfort was monitored after each shock, and sedation, or general anesthesia, was administered at the patient’s request.

After the procedure, patients were monitored by telemetry for 48 h, and serial ECGs were performed.

**Laboratory Evaluations**

Blood samples were taken serially at baseline (8 AM), and then at 2, 4, 8, 12, and 24 h after the completion of the procedure. Venous blood was collected in gel-containing tubes for CK and CK-MB activity measurement and in ethylenediaminetetraacetic acid-coated tubes for cTnI and myoglobin measurements. Samples were centrifuged (2,000 g for 25 min), and CK and CK-MB activities were measured without delay by an enzymatic method (Dade Behring; Newark, DE). Values > 195 U/L and > 10 U/L, respectively, were assumed to be above the normal range. Plasma for measurement of the other variables was frozen and was stored at −20°C until analysis (performed within 4 weeks after collection). For measurement of cTnI and myoglobin a fluorometric enzyme immunoassay (Stratus II; Dade International; Miami, FL) was employed. The assessment of cTnI values in serum samples obtained from a population of 156 healthy subjects showed that the 97.5 percentile of distribution was below the minimal detectable cTnI concentration (< 0.35 ng/mL). A value of 0.6 ng/mL was assumed as the upper limit of normal values for cTnI. A value of cTnI ≥ 1.5 ng/mL (ie, ≥ 2.5 times the upper limit of the normal range) was assumed as a marker of overt necrotic damage. Mildly elevated cTnI levels (range, 0.7 to 1.4 ng/mL) were considered as markers of minor myocardial injury. Myoglobin, a value > 110 ng/mL was assumed above the upper limit of the normal range.

**Statistical Analysis**

Continuous variables were compared within the same patients using the Student’s t test for paired data. Data are reported as mean ± SD. Analysis of variance tests, and Bonferroni adjustment were used for comparisons between different patients; p values < 0.05 were considered to be significant. Linear correlations were analyzed by the Pearson product moment correlation test.
Results

Patients

Thirty-five patients (22 men, 13 women) with chronic persistent AF (mean duration, \( \pm 17 \pm 19 \) months; range, 1 to 61 months; median, 10 months) were enrolled in the study. The age of patients was 60 \( \pm 10 \) years (range, 36 to 74 years; median, 62 years). The underlying etiologies were the following: no structural heart disease (4 patients); hypertensive heart disease (11 patients); dilated cardiomyopathy (8 patients); hypertrophic cardiomyopathy (1 patient); restrictive cardiomyopathy (1 patient); mitral valve disease (6 patients); and coronary artery disease (4 patients). Eighteen patients were NYHA functional class I, and 17 patients were NYHA functional class II.

Internal Atrial CV

The procedure proved to be effective, with the restoration of a stable sinus rhythm in all the patients. The number of shocks delivered per patients was \( 6.9 \pm 3.4 \) (range, 2 to 17 shocks), including baseline CV and a second CV following AF reinduction (23 patients). In the latter group of patients, AF was reinduced as a consequence of a stimulation protocol that is in use at our institution for evaluating atrial vulnerability immediately after internal atrial CV. The maximal amount of energy delivered in a single patient was \( 7.3 \pm 4.0 \) J (range, 1.7 to 15.7 J), and the cumulative amount of energy delivered was \( 28.1 \pm 26.9 \) J (range, 1.9 to 113.1 J).

Laboratory Measurements for cTnI

According to measured peak cTnI levels, 20 patients (57%) had cTnI levels within the normal range (\( \leq 0.6 \) ng/mL), while 15 patients (43%) had peak cTnI levels that were above the upper limit of the normal range. The peak of abnormal cTnI values was detected in samples taken 4 to 12 h following CV. In detail, 13 patients (37%) had mildly elevated cTnI levels (range, 0.7 to 1.4 ng/mL), and 2 patients (6%) had elevated cTnI levels (\( \geq 1.5 \) ng/mL; i.e., \( \geq 2.5 \) times the upper limit of the normal range), which is suggestive of necrotic damage. In the whole population of 35 patients, basal cTnI values were \( 0.09 \pm 0.14 \) ng/mL (range, 0.0 to 0.5 ng/mL; median, 0.0 ng/mL).

In the 13 patients with mildly elevated cTnI levels (peak level between 0.7 and 1.4 ng/mL) following CV, the following types of underlying heart disease were found: no structural heart disease (2 patients); hypertensive heart disease (2 patients); dilated cardiomyopathy (4 patients); mitral valve disease (4 patients); and coronary artery disease (1 patient). In the two patients with elevated cTnI levels, the peak levels were 1.7 and 2.4 ng/mL, and the underlying types of heart disease were hypertensive heart disease and hypertrophic cardiomyopathy.

cTnI Levels and CV Parameters

The three groups of patients, stratified according to peak cTnI levels (within normal range, mildly elevated, or elevated), were compared, and no significant differences were found by analysis of variance with regard to the number of shocks delivered, the maximal amount of energy delivered, and the total amount of energy delivered (Table 1). Moreover, no significant correlations were found by Pearson test between peak cTnI levels and the number of shocks (r = 0.12; p = 0.46), the maximal amount of energy delivered (r = 0.11; p = 0.50), or the total amount of energy delivered (r = 0.07; p = 0.69).

CK and Myoglobin Changes

Comparing the group of 20 patients who had normal cTnI levels after CV (\( \leq 0.6 \) ng/mL) with the group of 15 patients who had abnormal cTnI levels after CV, no significant differences were found in basal CK levels (p = 0.18), basal myoglobin levels (p = 0.61), and basal cTnI levels (p = 0.67) (Table 2).

A trend toward higher peak CK levels in patients with abnormal cTnI levels was found, although the difference was without statistical significance.

Table 1—Comparison Between the Three Groups of Patients Stratified According to Peak cTnI Levels*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal (n = 20)</th>
<th>Mild Elevation (n = 13)</th>
<th>Elevation (n = 2)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shocks, No.</td>
<td>6.3 ± 3.5</td>
<td>8.1 ± 3.3</td>
<td>6.0 ± 1.4</td>
<td>0.31</td>
</tr>
<tr>
<td>Maximal energy delivered, J</td>
<td>6.7 ± 3.7</td>
<td>7.7 ± 4.5</td>
<td>10.3 ± 2.5</td>
<td>0.43</td>
</tr>
<tr>
<td>Total energy delivered, J</td>
<td>23.4 ± 23.6</td>
<td>35.3 ± 32.6</td>
<td>28.7 ± 10.4</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, unless otherwise indicated. cTnI levels are defined as follows: normal, \( \leq 0.6 \) ng/mL; mild elevation, 0.7 to 1.4 ng/mL; and elevation, \( \geq 1.5 \) ng/mL.
†Analysis of variance used. Differences were not significant.
Moreover, a within-group comparison of baseline values of cTnI, CK, and myoglobin, which was made at the highest value found after CV, showed that following CV a significant increase is detectable not only for cTnI, but also for myoglobin (Fig 1). This elevation occurred in the groups of patients who did and did not have abnormal cTnI levels. In patients with abnormal elevations of cTnI levels, CK also showed a significant increase (Fig 1).

**Complications**

No clinical complications occurred, and no ECG changes suggestive of transient myocardial ischemia and/or necrosis were observed in the days following internal CV.

Table 2—Comparison Between the Group of Patients With Normal and Abnormal cTnI Levels Following CVa

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal cTnI After CV (n = 20)</th>
<th>Abnormal cTnI After CV (n = 15)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnI, ng/mL</td>
<td>Basal 0.08 ± 0.12</td>
<td>0.10 ± 0.16</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>Peak 0.31 ± 0.20</td>
<td>1.03 ± 0.45</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CK, U/L</td>
<td>Basal 70 ± 28</td>
<td>85 ± 33</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Peak 83 ± 39</td>
<td>110 ± 42</td>
<td>0.063</td>
</tr>
<tr>
<td>Myoglobin, ng/mL</td>
<td>Basal 50 ± 22</td>
<td>47 ± 15</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>Peak 76 ± 36</td>
<td>76 ± 35</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*aValues given as mean ± SD.

Figure 1. Comparison of baseline values of cTnI, CK, and myoglobin to the highest value found in the hours following CV in patients without abnormal cTnI levels (top) or with abnormal cTnI levels (bottom).

**Discussion**

This is the first study in literature employing cTnI levels for monitoring myocardial damage following repeated intracardiac shocks delivered for atrial CV.

The study shows that elevations of cTnI levels above the normal range are detectable in a significant proportion of patients (43% of our population), although cTnI reached the values considered to be diagnostic for myocardial necrosis in only a few of them (6%). This finding suggests that some forms of minor myocardial injury occur following this procedure. This minor myocardial injury is easily detectable by measuring cTnI levels, but not by conventional cardiac markers. Indeed, cTnI has been demonstrated to be a marker with high specificity for cardiac injury.

The absence of the elevation of CK and myoglobin above the conventional upper normal ranges despite minor myocardial damage is not surprising considering previous similar findings in animal models of induced ischemia, from clinical observations of patients with acute coronary syndromes, and in patients submitted to radiofrequency catheter ablation.

CV of AF by DC shocks traditionally has been performed by the transthoracic technique, and controversial data have been reported on possible myocardial damage related to the procedure. Increased amounts of CK-MB activity and CK-MB mass were found after transthoracic CV in 9.3 to 50% of patients and were related to muscu-
lar lesions induced by DC shock. The negativity of cTnI in patients with elevations of CK-MB supported this interpretation.\(^{17}\) Nevertheless, Allan et al\(^{15}\) and Bonnefoy et al\(^{14}\) found elevations of cTnI following external CV in 8% and 11% of tested patients, respectively (not always associated with CK-MB elevation).

The use of low-energy internal atrial CV implies the following important differences with regard to the transthoracic technique: shocks are delivered by catheters that are in contact with the atrial walls and the coronary sinus; the effective level of energy used is 2 to 8% of the energy that is effective in conventional transthoracic CV, and biphasic shocks are delivered according to a step-up protocol.\(^{3-7}\)

The consistent creation of lesions in skeletal muscles is much less likely with internal CV, and the lack of myoglobin and CK elevations suggests this assumption. The results of the present study indicate that subtle, occult, and asymptomatic myocardial injury can be detected by cTnI levels in a significant proportion of patients (43%), without a direct correlation with the number of shocks delivered or with the amount of energy delivered.

Madrid et al\(^ {35}\) evaluated the myocardial damage induced by radiofrequency catheter ablation by troponin I and other markers. Peak cTnI levels were usually significantly higher than in the present study (4 ± 3.5 ng/mL) and were dependent on the type of ablation, the number of pulses delivered, and the need for electrical external CV. Although there are major obvious differences between radiofrequency ablation and internal CV, some findings are in accordance with our results. cTnI levels may increase above normal limits without significant increases in total CK activity.

The elevations of cTnI levels after internal CV are mild and transient (they occur within 4 to 12 h, with normal values returning at 24 h in all the cases) and are associated with significant elevations of CK and myoglobin, although within the so-called normal range. According to Allan et al,\(^ {15}\) minor degrees of myocardial injury, devoid of clinical significance, are not surprising following the delivery of DC shocks. In experimental studies,\(^ {9,10,36,37}\) myocardial injury induced by DC was confirmed both histologically and by enzyme analysis. Heat-induced necrosis,\(^ {11}\) electroperoration,\(^ {38}\) mitochondrial dysfunction, and free radical generation\(^ {39,40}\) could be the mechanisms involved. Moreover, the delivery of shocks by endocardial catheters implies that peak voltages are applied at electrodes placed in proximity to the atrial or coronary sinus wall where it is more probable that the above-mentioned effects could occur.

The effects of catheter shocks on atrial tissue have been studied in animals, where tissue abnormalities visible at microscopic examination have been reported.\(^ {41,42}\) Dunbar et al\(^ {43}\) found small foci of subendocardial necrosis adjacent to shock electrodes in two of three dogs that received 0.5-J shocks; moreover, two of the three dogs treated with 5-J shocks developed subendocardial necrosis. Kalman et al\(^ {42}\) found areas of hemorrhage and necrosis in the atrial wall and atrial appendage, which were more frequent when small surface area electrodes were employed.

In our view, the results of the present study do not imply a substantial change in the protocols for internal atrial CV, because the elevation of cTnI was not related to the number of shocks delivered or to the amount of energy delivered. Also, in the study reported by Allan et al\(^ {15}\) that deals with conventional transthoracic CV, no relationship was found between the number of shocks, the cumulative or peak amounts of shock energy, and the rise in cTnI levels.\(^ {15}\) Future studies of transvenous internal atrial CV could evaluate whether a single shock procedure, compared to a procedure employing a step-up protocol, would be able to limit troponin release. Moreover, attempts to reduce the energy requirements for internal CV by optimizing the shock delivery and the lead technology\(^ {42-44}\) or by pharmacologic interventions\(^ {45,46}\) are mandatory.

A direct prospective comparison, evaluating myocardial damage induced by internal atrial CV compared to external transthoracic CV would seem to be necessary to improve our knowledge in this field.

**Conclusion**

After internal CV, with the delivery of repeated shocks, minor elevations of cTnI levels are detectable in a significant proportion of patients, thus suggesting occult, asymptomatic myocardial injury. The elevations of cTnI do not seem to be related to the number of shock delivered or to the amount of energy delivered.

**Acknowledgment:** The authors thank Gabriella Mezzena, MD (Laboratory of Ospedale S. Bortolo, Vicenza, Italy), for technical assistance in the laboratory evaluations.

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