Cardiac troponin I and minor cardiac damage: biochemical markers in a clinical model of myocardial lesions

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Radiofrequency (RF) catheter ablation is the curative treatment of choice for many cardiac arrhythmias. After RF ablation there is always a small localized endomyocardial necrosis, necessary to abolish the arrhythmia. We designed this study to determine the serum concentrations of several cardiac markers in patients who underwent RF catheter ablation. The study shows a higher frequency of increase of serum cardiac troponin I (cTnI) than of creatine kinase (CK), the CK MB isoenzyme (CK-MB), or myoglobin. A pathological value of cTnI was found in 47 of 51 patients (92%) in the ablation group. The area under the ROC curve for cTnI was 0.9375, significantly higher than for the other biochemical markers (0.86, 0.76, and 0.75 for CK-MB, myoglobin, and CK, respectively), with $P < 0.05$. We conclude that the serum concentration of cTnI is the best biochemical marker for detecting the minor myocardial damage produced by RF ablation.

Radiofrequency (RF) catheter ablation has been shown to be a highly effective treatment for many cardiac arrhythmias. After RF ablation there may be a minimal increase in creatine kinase (CK), generally mild, which depends on the number of ablation pulses and the substrate of catheter ablation (1). Measurements of CK activity and of its MB isoenzyme (CK-MB) have been used routinely for detecting myocardial damage, usually in acute ischemic syndrome (2, 3). However, the sensitivity and specificity of these biochemical markers are far from 100%. Thus, more precise tests are needed, and new immunoassays to measure proteins of the heart are currently being investigated (4–6).

Cardiac troponin I (cTnI) is a newly available biochemical marker of myocardial lesions (7). The troponins, present as a group of three subunits in the troponin complex on the thin filament of muscle myofibrils, are involved in the regulation of muscle contraction. Troponin T is the tropomyosin-binding subunit, troponin I is the actomyosin ATPase-inhibiting subunit, and troponin C is the calcium-binding subunit (8–12). Only troponins T and I have cardio-specific isoforms. Troponin T was introduced first; however, most studies indicate that cTnI is as specific as or more cardio-specific than troponin T (13, 14) and that it is not detectable in sera of healthy volunteers. Therefore, its appearance in blood would be a clear signal of cardiac myocyte damage.

We designed this study to determine the frequency of increased serum concentrations of several cardiac biochemical markers in patients that underwent RF catheter ablation and to establish the sensitivity and specificity of cTnI for quantifying the presence of minor cardiac damage after ablation.

Materials and Methods

Patients and Methods

We included in this prospective study patients referred to the Arrhythmia Unit of our Hospital for electrophysiological study and/or RF catheter ablation. We excluded patients with recent ischemic events (<1 month) or those who recently required electrical cardioversion. An informed consent was obtained from all patients, in accordance with the ethics standards of our hospital and the Helsinki Declaration of 1975.

We analyzed the data of 51 consecutive patients who underwent catheter ablation. A control group of 16 patients, who underwent electrophysiological study without ablation, was also included and analyzed consecutively.
and prospectively. This control group was introduced to prove that the increases of serum cTnI and other biochemical markers were attributable either to the RF application or to the positioning of the intracardiac catheters, through mechanical lesions of the myocardium. We tried to isolate the effect of the RF lesion from the mechanical effect of the manipulating catheter.

The electrophysiological study was performed with the patient in a nonsedated and fasting state, with conventional techniques of intracardiac recording and pacing. Depending on the substrate for ablation, we introduced percutaneously two to four multipolar electrode catheters from the femoral artery or vein and, sometimes, from the internal jugular vein. The catheters were positioned in the high right atrium, the His bundle, the right ventricular apex, or left ventricle. Positioning of the diagnostic catheters was performed under biplane fluoroscopy, using standard projections.

Left accessory pathways were approached using the retrograde aortic technique, except in two patients, using a transseptal technique. Mapping and ablation were performed with a 7 Fr deflectable catheter with a 4-mm tip electrode (Ablat or Marin, Medtronic). The RF source was the Atakr from Medtronic, under temperature monitoring. We analyzed the following data in every ablation procedure: target, atrium or ventricle aspect, number of RF applications, total time of RF application, and mean temperature achieved. We included all the RF pulses used, both successful and failed or prematurely interrupted.

There were 23 female and 28 male patients in the ablation group, with a mean age of 42 ± 19 years. The control group was composed of 16 patients, 4 female and 12 male, with a mean age higher than that of the ablation group, 55 ± 20 years. The ablation group included 14 with left accessory pathways, 7 with right accessory pathways, 12 with atrio-ventricular nodal reentry tachycardia, 13 with atrial flutter or fibrillation, and 5 with ventricular tachycardia. In the patients of the control group, the electrophysiological study was indicated to study the AV node and sinus function in 2 patients, atrial flutter in 3 patients, and programmed electrical stimulation in 11 patients. The selection of patients to be included in the control or ablation group could not be randomized (although it was consecutive and prospective). Because of the different indications for these techniques, the control group has a slightly higher mean age and a different cardiac pathology. However, this should not influence the results of the study.

We determined and contrasted the serum concentrations of CK-MB mass, cTnI, myoglobin, and CK activity. We also registered any change in clinical status, modifications of the ST segment, and new arrhythmias after the procedure.

We collected peripheral blood samples for serum analysis (5 or 10 mL of blood, collected in dry vessels), according to a fixed schedule. The first sample (10 mL) was taken just after peripheral vein access (“initial” sample). The second blood sample of 5 mL (“basal”) was obtained after the catheters were positioned in the heart. The other blood samples (5 mL) were taken as follows: 20 min after the last RF application or after the procedure was completed, and at 2, 4, 8, 24, and 48 h afterwards. The samples were centrifuged just after collection, aliquoted, and frozen to −20 °C until processing. The mean time before processing was 25 ± 5 days.

We used 5 mL from the initial sample of blood to perform a routine biochemical study including: glucose, creatinine, urea, sodium, potassium, and calcium concentrations, and aspartate aminotransferase and lactate dehydrogenase activity, using standard techniques, with an analyzer Hitachi 747 (Boehringer Mannheim). The cardiac markers cTnI, myoglobin, and CK-MB mass were determined using the “sandwich” technique, with double monoclonal antibodies, by an automatic enzymofluorimunnoassay (radial bipartition) Stratus II (Baxter Dade). The CK activity was determined using an analyzer Integra (Roche). The reference ranges at our laboratory for the cardiac markers were as follows: CK, 35–200 U/L; CK-MB mass, 0.5–5 μg/L; myoglobin, 20–80 μg/L; and cTnI, 0.0–0.8 μg/L.

For obvious reasons, in our study there was no anatomic demonstration of injury to the myocardium in addition to the biochemical markers. Thus, a “gold standard” for the definition of sensitivity and diagnostic accuracy for each marker was difficult to find. However, we know that when we ablate an arrhythmogenic focus in the human myocardium, we see the direct electrophysiological effect of this lesion (i.e., the disappearance of an arrhythmia or a delta wave in a Wolff-Parkinson-White syndrome), which implies that a small tissue lesion has occurred. Moreover, when we applied a radio frequency in close contact to the myocardium to produce necrosis, we observed a rise of the temperature (monitored by a thermistor in the tip of the catheter). In all patients in the ablation group, we saw these electrophysiological effects of the lesion produced by the radio frequency, thus confirming the injury to the myocardium.

After the ablation or the electrophysiological study, the patients were evaluated twice each day. A physical examination was routinely performed once each day, as well as a 12-lead electrocardiogram, to observe modifications of the repolarization.

STATISTICS
Continuous variables were expressed as means and SDs when the distributions were documented to be gaussian after analyzing the frequency distributions by the Kolmogorov–Smirnov statistical test. The nonparametric Wilcoxon test was used when the variables lacked a gaussian distribution, and the data were expressed as median and interquartile range. To determine statistical differences between continuous variables, we used the Student t-test and ANOVA. To compare discrete variables, we used the...
\( \chi^2 \) test. A \( P \) value <0.05 was considered significant. The correlations between variables were assessed by linear regression (Pearson). To compare the performance of the biochemical markers, the ROC curves were estimated and the areas under these curves were calculated for every biochemical marker. The Z statistic, corrected with the method introduced by Hanley and McNeil (15), was used for comparison of the ROC curves. A Z value >1.86 was considered significant.

**Results**

The routine biochemical study for the different biochemical markers evaluated was within the health-related reference limits in 64 patients. Creatinine was increased in three patients (because of chronic renal failure). These three patients also had high values for myoglobin but values within the reference limits for CK activity, CK-MB mass, and cTnI.

We performed a study of sensitivity and specificity (in the control and ablation groups) to evaluate what would be the optimal cutoff concentration for cTnI. We selected four cutoff values (0.7, 0.8, 0.9, and 1.0 \( \mu \)g/L) with good values for sensitivity (93%, 93%, 87%, and 86%, respectively) and specificity (75%, 75%, 81%, and 88%, respectively). The mean of the baseline values of the 67 patients included in this study plus 2 SD, was 0.78 \( \mu \)g/L. Consequently, we decided to use the cutoff of 0.8 \( \mu \)g/L to discriminate between patients with or without cardiac damage.

**CONTROL GROUP**

Serum cTnI was increased in four patients (mean concentration of 1.22 ± 0.4 \( \mu \)g/L). Three of these patients presented peak values between 0.9 and 1.1 \( \mu \)g/L, lower than those found in patients after RF ablation. In the other patient, the highest release of cTnI was 1.9 \( \mu \)g/L (perhaps attributable to a difficult positioning of the catheters into the heart). In the same patient, CK activity (258 U/L) and CK-MB mass (6.4 \( \mu \)g/L) were increased. Three patients presented a mild increase of myoglobin (84, 91, and 103 \( \mu \)g/L).

The mean duration of the procedure was 93 ± 30 min, and the mean number of catheters used was 2.3 ± 1.0. In these four patients, we performed the electrophysiological study to induce ventricular tachycardia, which was finally induced in three of them. Eleven patients were studied for ventricular tachycardia, three were studied for atrial flutter, and two were studied for conduction and sinus node function study. We cannot conclude if the differences between these groups were significant. The number of catheters used did not differ because we routinely used two catheters for these studies.

**ABLATION GROUP**

No patient presented modifications of the ST segment after RF ablation, excluding those after Wolff-Parkinson-White syndrome ablation who presented the “electrical memory” (seven patients). No patient presented chest pain or symptoms suggestive of ischemic heart disease.

The concentrations of CK-MB mass, myoglobin, and cTnI were significantly higher in the ablation group than in the control group \((P <0.01)\). cTnI was the biochemical marker that showed abnormal values in 47 out of 51 (92%) patients who underwent RF ablation. In the other 4 patients, we observed small increases of cTnI, which did not achieve the cutoff concentration. CK-MB mass was increased in 63% of patients, almost two-thirds of cTnI. The CK activity increased to pathological values in 30% of the patients, and the myoglobin reached abnormal concentrations in 67%. In studies such as the present one, where the concentrations in samples collected serially are evaluated, it is also appropriate to know the peak value of every biochemical marker in the ablation group; therefore, we saw that CK activity and myoglobin would reach values triple their initial values after ablation in some patients. However, both cTnI and CK-MB mass have values even 30-fold higher than those of the initial samples (Table 1).

For the estimation of the diagnostic accuracy of cTnI and the other biochemical markers of myocardial lesions, we used the analysis of the ROC curves. The area under the ROC curve for cTnI was 0.9375 (SE, 0.0319). The area was 0.86 (0.0486) for CK-MB, 0.76 (0.0689) for myoglobin, and 0.75 (0.0745) for CK. Moreover, when the areas were compared using the Z statistic, cTnI was the only marker that presented statistically significant differences compared with the other markers \((P <0.05)\). CK-MB mass, CK activity, and myoglobin did not have statistically significant differences among them (Fig. 1).

After demonstrating the superior diagnostic accuracy of cTnI in comparison with the other biochemical markers, we analyzed the correlation between the peak cTnI and the following data obtained from the RF generator: number of applications, mean temperature, and total time of application. The best linear correlation was found between the peak concentration of cTnI and the number of RF applications, with a linear correlation coefficient of 0.688 \((P <0.0001)\). We also found good correlation between the peak concentration of cTnI and the total RF application time \((r = 0.672, P <0.0001)\). However, there apparently is no correlation between the peak concentration of cTnI and the mean temperature achieved \((r = 0.083; Table 2)\). We did the same analysis for the

<table>
<thead>
<tr>
<th>Table 1. Biochemical markers after RF ablation.*</th>
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<tr>
<td><strong>Control group</strong></td>
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<tr>
<td>CK, U/L</td>
</tr>
<tr>
<td>CK-MB mass, ( \mu )g/L</td>
</tr>
<tr>
<td>Myoglobin, ( \mu )g/L</td>
</tr>
<tr>
<td>cTnI, ( \mu )g/L</td>
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* Global results.
* Data are presented as median (interquartile range).
CK-MB mass. In spite of the good correlation between the peak concentrations of CK-MB mass and cTnI ($r = 0.741$, $P < 0.0001$) in the ablation group, the correlations between CK-MB and the mean temperature, number of applications, and total time were clearly lower to those found for cTnI (Table 2).

To determine if the release of cTnI, and thus the size of the myocardial lesion, was different for each arrhythmia targeted, we separated different groups. The mean peak cTnI released varied between the lowest for AV nodal reentry (1.5 ± 0.8 μg/L) and the highest for patients with atrial flutter (6.0 ± 5.7 μg/L; Table 3). It is important to observe that the correlation was different for every substrate targeted, being the worst for the AV node reentry tachycardia ($r = 0.25$, $P = 0.43$) and the best for the ablation of ventricular tachycardia ($r = 0.99$, $P < 0.0001$; Table 3). With ANOVA among these groups, a significant difference ($P = 0.11$) was not found. We found significant differences only between the groups of AV node reentry and atrial flutter/fibrillation ($P = 0.039$).

To determine if there were differences in the release of cTnI according to age and gender, we used ANOVA; we did not find statistically significant differences, with $P = 0.57$ and 0.7 for age and gender, respectively.

**KINETICS**

In the ablation group, the peak mean value of cTnI occurred 8 h after ablation. However, in some patients, we

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**Table 2. Correlation between the number of RF pulses, temperature, and total time of RF application, and CK-MB and cTnI.**

<table>
<thead>
<tr>
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<th>Number of RF applications</th>
<th>Temperature, °C</th>
<th>Total time of RF applications, min</th>
</tr>
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<tbody>
<tr>
<td>Mean ± SD</td>
<td>9.78 ± 11.55</td>
<td>57 ± 4.57</td>
<td>7.6 ± 10.9</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>1–52</td>
<td>49.5–70.3</td>
<td>0.23–53</td>
</tr>
<tr>
<td>$r$ value for CK-MB max, $^a$ ($P$)</td>
<td>0.234 (0.9)</td>
<td>0.086 (0.95)</td>
<td>0.177 (0.21)</td>
</tr>
<tr>
<td>$r$ value for cTnI max, $^a$ ($P$)</td>
<td>0.688 (&lt;0.0001)</td>
<td>0.083 (0.56)</td>
<td>0.672 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

$^a$n=51 patients.

$^b$max, peak concentration of the marker.
detected abnormal values as early as 20 min after RF ablation. At 48 h after ablation, only cTnI was markedly increased, whereas the other biochemical markers remained within health-related reference limits, except for a mild increase of the concentrations of CK. Similarly, the peak cTnI and the peaks values for myoglobin, CK, and CK-MB were always found before the expected time, in comparison with ischemic cardiac disease. Out of 51 patients, only 2 presented a double pattern of release of cTnI; both patients did not achieve abnormal concentrations for cTnI (both \( <0.8 \mu g/L \)). In the control group, we found normal release kinetics, without achieving abnormal concentrations. Although a doubling appeared (below the cutoff concentration), for the CK-MB and cTnI curves, it was because of the release of cardiac markers found in only some patients of the control group. Fig. 2 shows the mean kinetics for all the biochemical markers for both the control and the ablation group.

**Table 3. Peak release of cTnI for each arrhythmia.**

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>cTnI,(^a) ( \mu g/L )</th>
<th>Number of RF pulses(^a)</th>
<th>( r (P) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVNRT(^b)</td>
<td>1.5 ± 0.83</td>
<td>3 ± 2</td>
<td>0.25 (0.43)</td>
</tr>
<tr>
<td>Right AP</td>
<td>3.7 ± 2.86</td>
<td>11 ± 11</td>
<td>0.877 (0.0096)</td>
</tr>
<tr>
<td>Left AP</td>
<td>4.0 ± 3.31</td>
<td>5 ± 4</td>
<td>0.582 (0.029)</td>
</tr>
<tr>
<td>AFl/AF</td>
<td>6.0 ± 5.72</td>
<td>19 ± 16</td>
<td>0.574 (0.0403)</td>
</tr>
<tr>
<td>VT</td>
<td>4.6 ± 5.96</td>
<td>8 ± 12</td>
<td>0.998 (0.0001)</td>
</tr>
</tbody>
</table>

\(^a\) Data are presented as median ± SD.

\(^b\) AVNRT, AV nodal reentry tachycardia; AP, accessory pathway; AFl, atrial flutter; AF, atrial fibrillation; VT, ventricular tachycardia.

**Discussion**

This study demonstrates that RF catheter ablation creates a small lesion with low release of several biochemical markers. Notably, cTnI was increased in almost all of the patients, whereas the other biochemical markers remained within health-related reference limits or increased only slightly. The sensitivity cTnI for detection of ablation lesions was 92% vs 63% for CK-MB mass. Although the values of CK activity have been widely used in the past to monitor myocardial lesions after ablation (16), it was an inadequate marker in our study, with a sensitivity of only 30%. Of the 16 control patients, cTnI reached pathological values in 4 patients and CK-MB mass in 1. These increases could be caused by the mechanical lesion produced by the positioning of the catheters in the heart.

cTnI is thus the best marker to detect minor cardiac damage in both control and ablation groups. With the analysis of diagnostic accuracy performed using the ROC curves, the superiority of cTnI in comparison with the other biochemical markers clearly appears.

We also found in our study a moderate linear correlation, statistically significant, between the peak concentration of cTnI and the number of RF ablation applications (\( r = 0.688 \)) and the total time of RF application (\( r = 0.671 \)). However, it seems that no correlation exists between the
release of cTnI and the mean temperature achieved during the ablation (r = 0.083). This could be attributable to the temperatures used during this procedure, which usually are similar or have slight differences (in our study, the mean was 57 ± 5 °C); however, the number of applications (9.8 ± 11.6 applications) and the total time (7.6 ± 10.9 min) varied considerably among the patients. Thus, in view of the above data, because the temperature is a constant (we always performed the ablation under temperature monitoring), it seems clear that the myocardial lesions produced by the radio frequency are larger and release more cTnI with a higher number of applications and a longer total time of application.

The correlation was different for every arrhythmia targeted. This could be attributable to both the different technique used for every arrhythmia and the aspect of the endocardium treated (atrial or ventricular). The contact and pressure of the catheter on the endocardium could be different for every case (17, 18). The lowest release of cTnI was found in the AV node reentrant tachycardia, and the highest in the atrial flutter/fibrillation. These arrhythmias also required the lowest and the highest number of RF applications. In spite of the fact that, in our study, the group of patients treated for atrial arrhythmias released the highest amount of cTnI, when the release/number of applications ratio was evaluated, the highest relationship was obtained with the ventricular tachycardia ablation (with a lower number of applications, the patients had a considerable release of cTnI). The peak concentration of cTnI was higher for the left accessory pathway ablation than for the right accessory pathway ablation. The ablation of the left accessory pathways required fewer RF pulses than the right pathways. The ablation site for the right accessory pathways was usually found in the atrial endocardium (just above the tricuspid annulus), and there was probably lower pressure from the catheter.

In the ablation group, the biochemical markers reached peak values earlier than those usually found in the setting of ischemic heart disease (19). However, these values cannot be directly compared with the results of this study because different assays, standardized differently, were used. The ablation creates an immediate myocardial necrosis (which is usually slower, even for hours, in ischemic events). The release begins earlier, after the alterations of the cell membrane. The myoglobin peak, the earlier marker of myocardial infarction (2-3 h), was also found earlier in our study (20 min after ablation). The peak CK-MB and CK were also observed at 4 and 8 h after the procedure, respectively. However, after a myocardial infarction, they are usually seen at 12 and 24 h, respectively. cTnI reaches peak concentration after a myocardial infarction at 12–16 h (7, 19–21); in our study it reached the peak concentration at 8 h. However, the possibility that the peak was actually reached between 8 and 24 h exists, because we have no samples between these hours.

There are no published data about the release and kinetics of cTnI after RF catheter ablation; therefore, we cannot establish any comparison. We do have the data of the release of several cardiac biochemical markers, including cTnI, after a myocardial infarction. In one of these studies, in patients with myocardial infarction, the peak concentrations of cTnI ranged between 18.5 and 477 μg/L (19).

In our study, the cTnI peak was between 0.4 and 21.4 μg/L, with a mean of 3.9 μg/L. The typical peak value found in our study was, in most of the patients, low (ranging between 3 and 4 μg/L), well below of those found in the literature for myocardial infarction (19). No patient experienced perioperative myocardial infarction, according to the standard criteria for the diagnosis. This could be useful information to know in patients who might have the potential for other ischemic events or who may have clinical presentations that suggest this possibility. Although we demonstrate a relationship between peak values of cTnI and the size of the myocardial lesions, we need to be careful because the relationship of cTnI and its kinetics to the size of myocardial lesions is not well established. Further studies are needed to better evaluate this point.

References
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