Prognostic Value of Troponin T in Hospitalized Patients with Angina or Non-ST-Segment Elevation Myocardial Infarction

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Introduction and objectives. Cardiac troponins are highly specific and sensitive for detecting minimal myocardial damage. The aim of our study was to determine the prognostic value of troponinT levels in patients hospitalized for suspected angina or myocardial infarction without ST-segment elevation.

Patients and method. We recorded the frequency of death, acute myocardial infarction, heart failure, or need for coronary revascularization in the three months after the onset of symptoms in 346 consecutive patients admitted for suspected acute coronary syndrome, excluding those who developed myocardial infarction with persistent ST-segment elevation.

Results. Serum troponin T levels were ≥ 0.1 ng/ml in 133 patients (troponin T positive group) and lower in 213 patients (troponin T negative group). The relative risk (RR) and 95 percent confidence intervals (95% CI) of individual and grouped events for the troponin T positive group were 3.2 (95% CI, 1.4-7.3; p = 0.006) for death; 2.8 (95% CI, 1.43-5.51; p = 0.003) for death or myocardial infarction; and 2.8 (95% CI, 1.6-5.0; p < 0.001) for death, myocardial infarction or heart failure. Diabetes mellitus and troponin T levels ≥ 0.1 ng/ml had independent prognostic value after adjusting for age, sex, and electrocardiographic changes; with RR 2.5 (95% CI, 1.01-5.9) for death, myocardial infarction or heart failure.

Conclusions. The prognosis of patients hospitalized for chest pain who do not immediately develop transmural necrosis depends on serum troponin T levels at hospital admission. Troponin T levels ≥ 0.1 ng/ml almost triple the risk of major events in the three months after the acute episode. The prognostic value of troponin T is independent of age, sex, presence of diabetes mellitus, and electrocardiographic changes.

Key words: Unstable angina. Myocardial infarction. Prognosis. Proteins.
INTRODUCTION

The high number of patients who go to the emergency room because of chest pain requires the availability of certain specific complementary tests that can help identify those patients who require hospital admission and, at the same time, are useful for the later categorization of the level of risk for those patients who present with acute coronary syndrome (ACS). These applications are important in terms of clinical significance, and are also important from the point of view of economic considerations. For several decades the biochemical markers used to confirm myocardial damage have been creatinphosphokinase (CPK) and its MB fraction (CPK-MB) which, although useful, do not allow for adequately identifying patients with minimum myocardial necrosis; has low specificity in certain subgroups of patients (such as those with concomitant muscle damage, thyroid disease, or renal failure); and have limited prognostic ability.

The troponins are structural proteins that are important in actin-myosin binding that is produced during muscle contraction. There are 3 troponins: T (TnT), I (TnI), and C, which, by acting on the actin filaments, regulate the force and speed of muscular contractions. Since different genes codify the myocardial and skeletal variants of TnT and TnI, there are sequences of amino acids that bind to specific monoclonal antibodies that do not cross-react between the 2 variants.

Recently, these cardio specific contractile proteins have been shown to be good predictors of short-term and long-term adverse events in patients with ACS, and also show heightened sensitivity and specificity for the detection of myocardial damage. Considering the above factors, the aim of our study was to determine the prognostic value of elevated concentrations of TnT in patients with clinical chest pain admitted to the hospital for suspected acute ischemic cardiopathy and who, during their admission, did not develop a myocardial infarction with persistent ST segment elevation.

PATIENTS AND METHODS

Patients

We performed a retrospective cohort study of 346 patients (225 men and 121 women) with a mean age of 67.6 years (±11.3 years; range, 20 to 89 years), selected from among patients for suspected ACS who were admitted to the intensive care unit or the cardiology service (or both) of our hospital over a 20 month period. We excluded patients who, during hospital admission, developed an infarct with persistent ST segment elevation.

The inclusion criteria for the study were: a) patients admitted either to the intensive care unit or directly to the cardiology unit with clinically suspected acute ischemic cardiopathy. This group included patients with unstable angina (prolonged, at rest, mixed, of recent onset or onset of less than 48 hours); effort angina; potentially anginous chest pain or acute myocardial infarct (AMI) without ST segment elevation, or both; b) and patients who had at least one blood test to measure TnT values between 5 and 24 hours after the onset of the chest pain that motivated the visit to the emergency department.

We included patients with an ST segment elevation only when there was a previous record of such by ECG results which, when compared with the results of the tracing obtained on arrival at the hospital did not show significant changes, or when the elevation was transitory and resolved while the patient was in the emergency department and did not require fibrinolitic treatment.

We excluded patients who developed an infarct with persistent ST segment elevation that lasted for several hours over a 24 hour period, patients who had a documented AMI during the previous 30 days, and patients in whom a measurement TnT values was not performed or in whom the measurement was made at a time other than the previously described period.

Methods

We used TnT STAT Elecsys system to measure TnT values. This is an in vitro immunological test for the quantitative measurement of TnT in human plasma and serum. This electrochemiluminescence immunoanalysis was created for use in the Boehringer Mannheim Elecsys 1010 and 2010 automatic analyzers. A sandwich technique is used that lasts 9 minutes and consists of:

- An initial incubation of the sample: 15 µl with a specific biotinylated monoclonal antibody against TnT and a specific monoclonal antibody against TnT marked with ruthenium chelate, forming a sandwich complex.
A second incubation, with the incorporation of microparticulate covered with streptavidine; in which the complex form is fixed during the solid phase for interaction between biotin and streptavidine.

The reaction mix is transported to the reading cell where, using magnetism, the micro particles are temporally fixed to the surface of the electrode. The nonfixed substances are later eliminated with the ProCell reactive. Upon application of a defined electric current a chemoluminescent reaction is produced whose light emission is measured directly with a photomultiplier. The measurement intervals are between 0.010 ng/mL and 25.00 ng/mL.

For the monoclonal antibodies used, analytic specificity has shown the following crossed reaction: human TnT of the skeletal musculature, 0.001%; human cardiac TnI, 0.002%; human tropomyosin of the skeletal musculature, 0.001%; human cardiac tropomyosin, 0.1%, and human cardiac light chain myosin 1, 0.003%.

**Measurements and data analyzed**

We divided the selected patients into 2 groups; one with positive troponin T (+TnT), consisting of patients with TnT values of 0.1 ng/mL or higher, and 1 with negative TnT (-TnT), consisting of patients with TnT values of less than 0.1 ng/mL. In both groups we analyzed age, sex, cardiovascular risk factors (arterial hypertension [AHT], dyslipemia, smoking, diabetes mellitus, and obesity); history of ischemic heart disease; and initial electrocardiogram (ECG). Finally, we reviewed the presence of major cardiovascular events: death, nonfatal AMI, congestive heart failure (CHF), and the need for revascularization over 3 months after the date of hospital discharge (after the admission that resulted in the patient’s inclusion in the study). This information was obtained by reviewing the patient’s clinical history, by personal interview, and by telephone interview with the patients.

**Statistical analysis**

The data is expressed as mean values±standard deviation (X±SD). Statistical study of the 2 groups (positive TnT and negative TnT) was performed by Student t test for continuous variables and the χ² for discrete variables, defining the limit of significance as P<0.05. In order to calculate sample size, we assumed that 20% of the patients with positive TnT and 8% of the patients with negative TnT would present with death or nonfatal AMI during the follow-up period, in accordance with the data provided by Stanford University to the authors of the recent consensus guidelines of the American Heart Association (AHA) and the American College of Cardiology (ACC). In order to detect this 12% difference in events with a statistical power of 80% and an alpha error of 0.05, a sample size of at least 130 patients per group was required (a total of 260 patients). For prognostic evaluation of isolated or combination events, we calculated the relative risks with 95% confidence intervals (95% CI). To prove that the prognostic value of TnT plasma values was independent of other variables during the first 24 hours, we calculated the relative risk (RR) of presenting increased concentrations after adjustment for age, sex, diabetes mellitus (which occurred much more frequently in the positive TnT group), and a decline or elevation of the ST segment, and performed an unconditional multivariate logistic regression analysis. We considered TnT, ECG, age, and sex as predictive factors for combination events.

**RESULTS**

Of the 346 included in the study, 133 were in the positive TnT group and 213 were in the negative TnT group. The 2 groups were compared with respect to age (69.16 years±12.3 years positive group and 66.6 years±10.6 years negative group) and sex, with 38.3% of the positive TnT group and 32.9% of the negative TnT group consisting of women. We observed a significantly higher frequency of diabetes mellitus being treated orally or with insulin in the positive TnT group (36.8% vs 19.2% of the negative TnT group; P<0.001). Electrocardiographic changes upon admission occurred more frequently in the positive TnT group with regard to ST segment elevation (9.8% vs 2.3%; P<0.05) and for ST segment decline (25.5% vs 9.4%; P<0.001). The frequency of normal
electrocardiographic recordings was greater in the negative TnT group: 71.4% vs 36.1% (P<.001) (Table 1).

Although analysis of the major events that occurred during the 3 months after the date of discharge occurred more frequently in the group of patients with positive TnT (death, 12% vs 3.7%; CHF, 5.3% vs 1.9%; AMI, 3.8% vs 1.9%; need for revascularization, 7.5% vs 5.2%), the data showed statistical significance only with regard to the group of patients who died (P=.006). Nevertheless, we did obtain significant results when the events were considered in combination. Thus, the RR of presenting with events in the positive TnT groups was 2.80% for the death-AMI group (95% CI, 1.43%-5.51%; P=.003) and 2.80% for the death-AMICHF group (95% CI, 1.6%-5.0%; P<.001) (Table 2). When we eliminated from the whole group those patients who presented with elevated CPK-MB values, the RR that they would experience major isolated or combined events were similar or slightly higher (Table 3).

After adjustment for age, sex, diabetes mellitus with pharmacological treatment, and ventricular repolarization changes on ECG during the first 24 hours (taking into consideration both ST segment displacements=1 mm and T-wave variations), only diabetes mellitus and the presence of elevated TnT

<table>
<thead>
<tr>
<th>Course</th>
<th>No.</th>
<th>+TnT (%)</th>
<th>-TnT (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>24</td>
<td>12.0</td>
<td>3.7</td>
<td>3.2</td>
<td>1.4-7.3</td>
<td>.006</td>
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<tr>
<td>AMI</td>
<td>9</td>
<td>3.8</td>
<td>1.9</td>
<td>2.0</td>
<td>0.55-7.3</td>
<td>NS</td>
</tr>
<tr>
<td>CHF</td>
<td>11</td>
<td>5.3</td>
<td>1.9</td>
<td>2.8</td>
<td>0.84-9.39</td>
<td>NS</td>
</tr>
<tr>
<td>Revascularization</td>
<td>21</td>
<td>5.2</td>
<td>1.46</td>
<td>1.46</td>
<td>0.64-3.33</td>
<td>NS</td>
</tr>
<tr>
<td>Death/AMI</td>
<td>33</td>
<td>15.8</td>
<td>5.6</td>
<td>2.8</td>
<td>1.43-5.51</td>
<td>.003</td>
</tr>
<tr>
<td>Death/AMI/CHF</td>
<td>44</td>
<td>21.1</td>
<td>7.5</td>
<td>2.8</td>
<td>1.6-5.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarct; CHF, congestive heart failure; +TnT, positive troponin T; -TnT, negative troponin T; NS, non significative.

<table>
<thead>
<tr>
<th>Course</th>
<th>No.</th>
<th>+TnT (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>22</td>
<td>15.6</td>
<td>4.14</td>
<td>1.8-9.5</td>
<td>&lt;.001</td>
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<td>AMI</td>
<td>8</td>
<td>4.4</td>
<td>2.37</td>
<td>0.61-9.25</td>
<td>NS</td>
</tr>
<tr>
<td>CHF</td>
<td>9</td>
<td>5.6</td>
<td>2.96</td>
<td>0.81-10.76</td>
<td>NS</td>
</tr>
<tr>
<td>Revascularization</td>
<td>18</td>
<td>7.8</td>
<td>1.51</td>
<td>0.60-3.76</td>
<td>NS</td>
</tr>
<tr>
<td>Death/AMI</td>
<td>30</td>
<td>20.0</td>
<td>3.55</td>
<td>1.78-7.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death/AMI/CHF</td>
<td>39</td>
<td>25.6</td>
<td>3.40</td>
<td>1.89-6.13</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

+CPK-MB indicates CPK-MB elevation over the upper laboratory limit; AMI, acute myocardial infarct; CHF, congestive heart failure; +TnT, positive troponin T; NS, non significative.

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>3.0</td>
<td>1.2-7.3</td>
<td>.012</td>
<td>3.0</td>
<td>1.2-7.2</td>
<td>.012</td>
</tr>
<tr>
<td>+TnT</td>
<td>2.5</td>
<td>1.01-6.0</td>
<td>.037</td>
<td>2.5</td>
<td>1.01-5.9</td>
<td>.037</td>
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<td>ECG</td>
<td>1.1</td>
<td>0.8-1.7</td>
<td>.506</td>
<td>1.1</td>
<td>0.7-1.7</td>
<td>.506</td>
</tr>
<tr>
<td>Age</td>
<td>1.4</td>
<td>0.8-3.6</td>
<td>.467</td>
<td>1.4</td>
<td>0.6-3.5</td>
<td>.467</td>
</tr>
<tr>
<td>Sex, M</td>
<td>1.5</td>
<td>0.6-4.0</td>
<td>.332</td>
<td>1.5</td>
<td>0.6-4.0</td>
<td>.332</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; AMI, acute myocardial infarct; CHF, congestive heart failure; RR, relative risk of cardiac events after adjustment for the remaining variables.
values continued to have independent prognostic value. The RR and 95% CI were 2.5% (range, 1.01%-6.0%) for death or AMI) and 2.5% (range, 1.01%-5.9% for death, AMI, or CHF [Table 4]).

DISCUSSION

Evaluating patients with acute chest pain who present to the emergency department presents a challenge. ECG has low sensitivity and, in the case of unstable angina, ECG changes are, often, nonspecific. For several decades the biochemical markers used to confirm myocardial damage have been CPK and its MB fraction. Although useful, these are imperfect for establishing an early diagnosis that allows prompt identification of high-risk patients. On the other hand, in those patients who present with unstable angina or myocardial infarct without ST segment elevation, the smaller increases in the CPK-MB values have limited the prognostic value of identifying the subgroups of patients who will experience major cardiac events (death or nonfatal AMI). The association of 3 cardiac markers (myoglobin, CPK-MB, and troponin) seems to be more useful in the individual study of each of these in order to establish earlier and more efficient risk categorization.

Troponin cardiac isoforms are codified by genes that are distinct from those that come from skeletal muscle; therefore, an increase in their value is highly specific for myocardial involvement. Several studies of patients with ACS have shown that TnT and TnI are good predictors of short-term, and long-term adverse events and possess high sensitivity and specificity for the detection of myocardial damage. Their particular liberation is a useful tool for the evaluation of episodes that are suggestive of ischemic heart disease, whether acute or after several days have already passed since the onset of the episode. This is due to its double kinetic effect, with rapid liberation (3-4 hours) of TnT or TnI fraction dissolved in the cytoplasm of the cardiomyocytes and a more sustained liberation (elevated concentrations for up to 5 to 9 days, with a maximum of 14 days), of a majority fraction that corresponds to the troponin that is structurally bound to the tropomyosin complex. Therefore, a single assessment, if it is early on with respect to the onset of symptoms (in general, less than 4 hours), is inappropriate for determining risk. On this topic, a study that analyzed the usefulness of the troponins in categorizing chest pain in an emergency department proved that only 58% of patients who presented with at least a positive test had ischemic heart disease it when the first test was performed, making a new assessment advisable after 4 to 6 hours. In the TnT sub study of GUSTO IIA study, 68% of the 474 patients with a negative result at initial evaluation had a positive result later (at 8 hours). In our study, in order to avoid false negative results, 1 of the criteria was to have available at least 1 test result 5 hours after the onset of chest pain.

The principal conclusion that can be drawn from the results of various studies analyzing the value of troponin in patients with ACS is the short-term and long-term prognostic and therapeutic implications that troponin values possess. In the previously mentioned GUSTO IIA sub study, which included high-risk patients of all ages with ACS of up to 12 hours onset, the detection of concentrations of TnT higher than 0.1 ng/ml (36% of the total number of patients included) constituted an independent predictor of mortality within the following 30 days in all the electrocardiography subgroups. Among the patients in whom an AMI was excluded according to the classic criteria (in other words, with elevated CPK-MB concentrations), elevated TnT values identified a subgroup (25% of total patients) with minor myocardial damage, but in whom the occurrence of cardiac events during follow-up was the same as for those patients with a confirmed infarct. A TnT finding of less than 0.1 ng/mL 12 hours after the start of chest pain excluded the diagnosis of an AMI and facilitated the discharge of the patient from the coronary care unit, as well as involving a length of hospital stay. The predictive negative value obtained for TnT was calculated at 98.9%. It must be pointed out that TnT, the same as CPK-MB, revealed a predictive capability for mortality, but only TnT maintained its independent predictive value when a multivariate adjustment was made for different patient characteristics. Other studies with different follow-up periods have shown similar results.

The absolute TnT values have permitted classifying patients with unstable angina into low-risk, intermediate-risk, and high-risk groups, with the observation that the risk of death in the months after an acute episode is proportionate to the absolute troponin values.

The prognostic value of troponin elevation in ACS most likely has to do with its proven association with the presence of more complex coronary lesions and with a thrombotic component that is more evident in patients who present with chest pain and troponin elevation than in patients who present with chest pain without troponin elevation. In addition, the presence of elevated troponin in patients with chest pain coincides with a greater prevalence of changes in repolarization, 3-vessel disease, refractory angina, previous infarct, the need for percutaneous coronary or surgical intervention, and complications during percutaneous intervention. A meta-analysis of the studies published in English on the predictive value of abnormal troponin values in patients with ACS without ST segment elevation, which included 7 clinical trials and 19 cohort studies, and total
of 11,963 patients, showed that patients with elevated TnT or TnI tripled the mortality rate (odds ratio [OR], 3.1) as compared with those patients who presented with normal troponin levels, in a follow-up that ranged from 2 weeks to 1 year in duration.\textsuperscript{46}

The fact that there are negative results in determining troponin levels has been shown to be important with regard to prognosis.\textsuperscript{3,33,34,49} Therefore, in a study that evaluated the early and late risk for patients with ACS using TnT values, the short-term mortality was null and nonfatal events were scarce in the group with low TnT concentrations.\textsuperscript{1} In another study, an only a 1.1% incidence of events was found among patients with all negative TnT measurements.\textsuperscript{34} A substudy of the FRISC study analyzed TnT values during the first 24 hours following ACS in combination with the results of a stress test. During a 5-month follow-up period, death or AMI occurred in only 1% of cases in whom both tests were negative, and this percentage increased to 50% when both tests were abnormal. The TnT was found to be a predictor of cardiovascular risk that is better than CPK-MB.\textsuperscript{50}

Although the percentage of events is significantly less than that in patients with elevated troponin, its negativity should not be interpreted as indicating an absence of cardiovascular risk. In the series by Hamm et al.,\textsuperscript{34} 4 of the 20 patients who died and 3 of the 14 patients with AMI had low TnT values on all tests. Among our patients, 11.92% of the negative TnT group had major events in the following 3 months, with a mortality rate of 3.97% and an AMI rate of 1.99%.

On the other hand, it is likely that the cut-off point of 0.1 ng/mL was somewhat elevated for differentiating patients with significant myocardial damage from those without, as analysis of the placebo group in the GUSTO IV study showed that death or the presence of an infarct during the first 30 days after an ACS without an ST segment elevation was clearly increased in those patients with TnT numbers higher than 0.03 ng/mL.\textsuperscript{51}

The prognostic value of troponins in ACS without ST segment elevation appears to be greater than that provided by ST segment changes, with the particularity that the latter are observed in a much smaller percentage of patients and, therefore, its negative predictive value is more limited. Thus, in a study of 598 patients in which an exhaustive search for ST changes during the first 6 hours of an acute episode was made with 12-lead patient monitoring, repolarization changes could only be documented in 15% of patients, while the TnT was increased in 27% of patients.\textsuperscript{52} In our study, we were not able to corroborate the independent predictive capability of cardiovascular events with corresponding ECG changes. This was probably because the electrocardiographic tracing was not monitored during the first hours of admission, so that, apparently, transitory changes in repolarization could occur without being noticed. In a 30-day follow-up of patients with ACS, elevated troponins predicted a 20% risk of mortality or infarct, while the presence of an ST segment decline at the time of admission coincided with an 8% risk.\textsuperscript{53} When TnT is elevated in patients with ACS and ST segment changes during the initial hours, the prognostic value of both methods appears to be additive, so that death or the appearance of an AMI during the year following the acute picture can occur in up to 52% of patients.\textsuperscript{52}

The presence of diabetes mellitus and elevated TnT numbers were found to be the only prognostic predictors in our study (Table 4). The worse prognosis for unstable angina in diabetic patients has already been established,\textsuperscript{54} and could be related to a greater incidence of ulcerated coronary atherosclerotic plaques and intracoronary thrombi.\textsuperscript{55} Our results are in line with those referred to and suggest that the determination of elevated troponin numbers in patients with suspected ACS is accompanied by a worse prognosis, with an increased risk of major cardiac events in the short term. The presence of low TnT concentrations may help us to place patients in a low-risk group, but does not rule out the existence of ischemic cardiopathy.

**Limitations**

This is a retrospective study and, although the number of cases studied is sufficient for analyzing the association of death and AMI, its statistical power is more limited for isolated cardiac events. The decision as to whether or not admit a patients was made by the internists in the hospital emergency department, either on their own or, in some cases, as advised by a cardiologist or another emergency medicine specialist. The pertinence of requesting a measurement of plasma TnT values was guided by the clinical judgment of the above-mentioned internists and, both the request and the final decision regarding the hospitalization of the patient did not follow a predetermined protocol. Treatment for patients included in the study was not uniform, as the last patients seem who had positive TnT received treatment with low molecular weight heparin (LMWH) and the first patients to be admitted did not, which could somewhat influence the prognosis in favor of the those last treated. We only evaluated patient baseline ECGs in the emergency department, which at times did not coincide with the clinical manifestations present, which accounts for the fact that the electrocardiographic changes are frequently not available. Therefore, we considered conjointly any repolarization change (transitory ST segment elevation, ST segment decline, or T-wave inversion) in the multivariate analysis to calculate the independent prognostic value of TnT.
CONCLUSIONS

The results of our study allow us to conclude that the patients admitted for suspected ACC who do not immediately develop a transmural infarct have a prognosis that is different according to the TnT values at the time of admission; the prognosis is worse in the presence of elevated values. Therefore, numbers equal to or greater than 0.1 ng/ml nearly triples the risk of major cardiac events during the first 3 months after the acute anginous episode. The prognostic value of plasma TnT values is independent of age, sex, the presence of diabetes mellitus, and electrocardiography findings.

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