Elevated Troponin I Levels in Patients With Acute Coronary Syndrome Without ST Elevation Are Associated With Increased Complexity of the Culprit Lesion

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Introduction. The prognosis in patients with acute coronary syndrome without persistent ST segment elevation (NSTEACS) differs depending on cardiac troponin levels. Clinical practice guidelines published by the Spanish Society of Cardiology and the ACC/AHA consider patients with NSTEACS and markedly elevated troponin levels as high risk patients. The aim of this study was to identify factors related to markedly elevated troponin I levels in NSTEACS.

Patients and Method. We measured troponin I levels in 219 consecutive patients with NSTEACS and normal CK-MB values, and identified 2 groups: patients with markedly elevated troponin levels (more than 10-fold the normal upper limit), and patients with normal or slightly elevated troponin levels (less than a 10-fold increase above the normal limit). We also analyzed clinical and angiographic variables. Logistic regression was used to calculate age- and sex-adjusted associations for the main variables.

Results. Forty-one patients (19%) had markedly elevated troponin levels, and 178 (81%) showed normal or slightly elevated troponin I levels. Patients with markedly elevated levels had more frequently prolonged angina, class IIb angina, more severe ECG changes, a higher number of diseased vessels on coronary angiography, and greater severity of the culprit lesion. The culprit stenosis in these patients was more often ulcerated, showing visible thrombus, and eccentric, bifurcated and irregular. Class IIIb angina characterized as ulcerated, showing visible thrombus, and patients with NSTEACS are associated with a more severe clinical presentation and increased complexity of the culprit lesion on coronary angiography.

Key words: Acute coronary syndrome. Troponin. Coronary angiography. Ulceration. Thrombus.

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Introduction. Los pacientes con síndrome coronario agudo sin elevación del segmento ST se asocian a estenosis coronarias más complejas

Introducción. Los pacientes con síndrome coronario agudo sin elevación persistente del segmento ST (SCASEST) presentan un pronóstico distinto según los valores de troponina. Las Guías de Práctica Clínica (SEC y ACC/AHA) estratifican a los pacientes con SCASEST y marcada elevación de troponinas como pacientes de alto riesgo. El objetivo del estudio ha sido identificar los factores asociados a las elevaciones importantes de los valores de troponina en estos pacientes.

Pacientes y método. Se ha analizado a 219 pacientes con SCASEST y valores de la isoenzima MB de la creatincinasa normales en que se determinó los valores de troponina I. Según estos valores, se diferenciaron en pacientes con troponina marcadamente elevada (≥ 10 veces el límite superior de la normalidad) y pacientes con troponina normal o ligeramente elevada (< 10 veces el límite normal). Se analizó una serie de variables clínicas y angiográficas. Los análisis principales se realizaron mediante regresión logística ajustando por sexo y edad.
INTRODUCCIÓN

Imunoassay techniques developed in recent years allow measurement of blood levels of troponin I and troponin T,1-3 markers of myocardial injury that have proved to be more sensitive and specific than those formerly used for this purpose.4-6 Elevations of these new markers correlate with a higher number of ischemic events during follow-up.6,7 and they have facilitated diagnosis and prognosis in patients with non-ST segment elevation acute coronary syndrome (NSTEACS). Recently, updates of the Clinical Practice Guidelines of the Sociedad Española de Cardiología [Spanish Society of Cardiology (SEC)]6 and the American College of Cardiology/American Heart Association (ACC/AHA)7 for the management of patients with NSTEACS were published. Both publications have established that the magnitude of troponin elevation is a determining factor in prognosis, such that patients with markedly elevated troponin levels (≥10 times the upper normal limit) should be stratified initially as high-risk patients.6,7 Several studies have identified the factors associated with elevated troponins in NSTEACS patients,8-10 although it is still uncertain which factors are related to substantial increases in these markers and what potential triggering mechanisms are involved. The aim of this study was to identify the clinical and angiographic factors associated with markedly elevated troponin I levels in patients with NSTEACS.

PATIENTS AND METHODS

Inclusion Criteria

Consecutive patients admitted to our center with a diagnosis of NSTEACS were assessed. Determination of troponin I, creatine kinase MB fraction (CK-MB) and total creatine kinase (CK) was performed at 6-hour intervals starting from the final pain symptom leading to hospitalization up to the first 24 hours. Patients also had to have undergone coronary angiography during hospitalization to be enrolled in the study.

Exclusion Criteria

Patients with NSTEACS were excluded if they showed CK-MB elevations greater than or equal to twice the normal limit (CK-MB ≥0.42 µKtal/L). We also excluded patients with moderate to severe kidney failure (creatinine ≥130 mmol/L) and those with post-infarction angina, since they might have troponin elevations unrelated to their present ischemic event.

Samples for plasma troponin I measurement were processed and analyzed with immunoassay techniques (Dimension® Dade Behring; reference RF421C) by stat laboratory personnel who were blinded to the patients’ symptoms. Patients were divided into 2 groups according to their troponin I level: patients with markedly elevated plasma troponin I (≥10 times the upper normal limit) and patients with negative or slightly elevated troponin levels (<10 times the upper normal limit). Troponin I was considered positive when the value exceeded the detection limit of the method (0.20 ng/L).
Variables Analyzed

Clinical demographic variables, cardiovascular risk factors, and coronary disease history were analyzed in all patients. With regard to the ischemic episode leading to hospitalization, we recorded the type of angina according to the Braunwald classification, the presence of prolonged angina (duration ≥20 min), the existence and severity of electrocardiographic (ECG) changes with the pain (no ECG changes, T-wave alterations, ST segment depression ≤1 mm, ST segment depression >1 mm, or transient ST segment elevation and/or transient bundle branch block), territory affected by ischemia, medical treatment administered, time between hospital admission, and catheterization, ischemic events during hospitalization (recurrent angina, acute myocardial infarction [AMI], or death), and need for revascularization during hospitalization.

When clinically indicated, cardiac catheterization (coronary angiography and ventriculography) was performed by the attending cardiologist using standard percutaneous techniques. Coronary angiography studies were analyzed specifically for this investigation by an experienced independent observer who was blinded to the patients’ clinical and analytical data and only knew which artery may have been related to the ischemic episode causing the symptoms. The following angiographic variables were recorded: a) number of vessels with significant lesions; b) artery and lesion causing the ischemia; c) percentage of stenosis in the culprit artery; d) TIMI flow grade of the culprit artery; e) location, morphological characteristics and complexity (ACC/AHA classification) of the culprit lesion, and f) presence of ulcer or thrombus, or dissection of the lesion. A lesion was defined as significant when flow-limiting stenosis was greater than 50% of the vessel diameter. The severity of stenosis was assessed by a quantitative coronary analysis system (CAAS-II, Cardiovascular Angiography Analysis System mark II). Thrombus was considered to be present when an intraluminal contrast defect was visible in at least 2 orthogonal projections. Left ventricle ejection fraction was calculated by contrast ventriculography (Dodge method) or echocardiography (Simpson method, 4 chambers).

Statistical Analysis

All data were analyzed by SPSS for Windows, version 9.0. A comparative analysis was done between the 2 groups established: patients with markedly elevated troponin levels versus patients with negative or slightly elevated troponin levels. Quantitative values were compared with Student’s t test and expressed as mean ± standard deviation (SD). The non-parametric Mann-Whitney U test was used when the sample did not follow a normal distribution. Qualitative variables were analyzed with the chi-square test or Fisher’s exact test, where appropriate, and results were expressed as absolute value and percentage. Identification of independent factors associated with marked troponin elevation was done with multivariate logistic regression analysis, adjusted for age and sex. Statistical significance was set at a P-value of <.05.

RESULTS

Among a total of 345 patients admitted to our hospital for NSTEACS during the enrollment period (July 2000 to December 2001), 219 patients (64%) were included in the study. The reasons for exclusion were the following: concomitant CK-MB elevation (60 patients), coronary angiography not performed (42 patients), kidney failure (12 patients), post-infarction angina (6 patients), and analytic determinations lacking (6 patients). Among the 219 patients included, 41 patients (19%) presented markedly elevated troponin I levels (≥10 times the normal value) with a mean value of 4.69 ng/L and 178 patients (81%) had negative levels or slightly to moderately elevated levels (<10 times the normal value), with a mean of 0.45 ng/L. Among this second group, 138 patients (78%) showed negative troponin levels and 40 patients (22%) showed slightly to moderately elevated levels.

Table 1 shows the analysis of baseline clinical variables in patients with markedly elevated troponin I levels as compared to the remaining patients. There were no differences between the two groups in baseline demographic characteristics, coronary risk factors or history of coronary disease. However, the angina episode leading to hospitalization in patients with highly increased troponin I was prolonged, occurred at rest, or was classified as Braunwald IIIb more frequently. Moreover, these patients had presented the most severe initial electrocardiographic changes. With regard to initial treatment, the group with high troponin I levels had been treated more often with unfractionated or low-molecular-weight heparin, beta-blockers, or IIb/IIIa receptor inhibitors. Concerning the angiographic variables (Table 2), more vessels had significant lesions in the patients with markedly elevated troponin I than in those with negative or low troponin elevation, and the culprit lesion causing the symptoms had much more complex characteristics, including a higher incidence of thrombus, eccentricity, ulcer or dissection, location in a vessel bifurcation, and classification as ACC/AHA Lesion Class B2 or C.

The following clinical and angiographic variables were included in the multivariate analysis: prolonged...
angina, Braunwald class IIIb angina, severe ECG changes, number of vessels with significant lesions, stenosis caused by the culprit lesion, and morphologic characteristics of the lesion. Among these factors, one clinical variable, Braunwald class IIIb angina (OR=3.12; 95% CI, 1.1-8.6; \( P = .029 \)) and 3 angiographic variables, location of the culprit lesion in a bifurcation (OR=6.04; 95% CI 2.5-14.3; \( P = .003 \)), presence of ulcer (OR=3.2; 95% CI,1.07-9.7; \( P =0.036 \)), and presence of thrombus (OR=2.7; 95% CI, 1.15-6.3; \( P =.021 \)) in the lesion, were identified as factors independently associated with markedly elevated troponin I levels (Table 3 and Figure). The subgroup of patients with slightly to moderately elevated troponin levels was analyzed separately. Although some variables showed trends to a higher frequency than that seen in patients with normal troponin levels, the differences were not statistically significant.

Regarding the course of the condition during hospitalization (Table 4), patients with markedly increased troponin I showed a higher incidence of ischemic events during hospitalization and a higher incidence of revascularization procedures.

**DISCUSSION**

In a series of 219 patients with NSTEMI and normal CK-MB levels, marked troponin I elevation (≥10 times the upper normal limit), was observed more
frequently in patients with more severe angina, more
pronounced electrocardiographic changes, and coronary
angiography findings of more extensive coronary
disease, in which the culprit lesions showed complex,
morphologically complicated characteristics.
Multivariate analysis identified Braunwald class IIIb
angina and three angiographic characteristics (location
of the culprit lesion in a bifurcation, presence of ulcer
and presence of thrombus in the lesion) as variables
related with marked troponin I elevations, regardless of
age or sex.

Various studies in patients with NSTEACS have
shown that elevated troponin levels correlate with a
higher number of ischemic events during follow-
up\textsuperscript{7,13,15} and have predictive value with respect to
cardiac death.\textsuperscript{10} Antman et al\textsuperscript{11} observed that troponin

| TABLE 2. Angiographic Variables for Patients With Markedly Elevated Troponins Versus Remaining Patients* |
|----------------------------------------------|----------|----------|
| Days hospitalized/catheterization           | 5±4      | 6±3      | .247     |
| No. vessels with significant lesions        | 1.95±1   | 1.56±1   | .038     |
| Three-vessel disease                        | 16 (39%) | 46 (26%) | .001     |
| Left main coronary artery disease           | 3 (7%)   | 7 (4%)   | .430     |
| AD culprit artery                           | 19 (46%) | 70 (39%) | .697     |
| RCA culprit artery                          | 10 (24%) | 38 (21%) | .772     |
| Stenosis culprit lesion, %                  | 80±9     | 70±24    | .001     |
| TIMI flow <3 in culprit vessel              | 8 (20%)  | 32 (18%) | .819     |
| Characteristics culprit lesion              |          |          |          |
| Thrombus                                    | 19 (46%) | 33 (18%) | .001     |
| Eccentric                                   | 34 (83%) | 105 (59%)| .015     |
| Ulcer                                       | 10 (24%) | 10 (6%)  | .001     |
| Dissection                                   | 8 (19%)  | 7 (4%)   | .001     |
| In bifurcation                               | 18 (44%) | 17 (9%)  | .0001    |
| ACC/AHA B2/C                                 | 25 (62%) | 70 (39%) | .016     |
| LV ejection fraction, %                     | 62±11    | 62±12    | .991     |

*ACC/AHA indicates American College of Cardiology/American Heart Association; RCA, right coronary artery; A, anterior descending artery; unl, upper normal limit; NS, non-significant; TIMI, thrombolysis in myocardial infarction; LV, left ventricle.

| TABLE 3. Odds Ratio and 95% Confidence Intervals of the Variables Included in the Multivariate Analysis to Determine Factors Associated With Markedly Elevated Troponin |
|---------------------------------|--------|----------|--------|
| Variables                       | OR     | 95% CI   | P      |
| Braunwald IIIb angina           | 3.124  | 1.125-8.678 | .029  |
| Severe ECG changes              | 1.456  | 0.326-8.946 | .952  |
| Beta-blocker treatment          | 1.933  | 0.511-7.314 | .332  |
| LMWH treatment                  | 0.628  | 0.214-1.841 | .397  |
| Number of vessels               | 0.879  | 0.496-1.557 | .658  |
| Percentage stenosis             | 1.020  | 0.968-1.075 | .463  |
| Eccentric lesion                | 0.432  | 0.103-1.803 | .249  |
| Presence thrombus               | 2.713  | 1.106-6.342 | .020  |
| Presence ulcer                  | 3.201  | 1.071-9.712 | .030  |
| Lesion in bifurcation           | 6.040  | 2.557-14.32 | .003  |
| Presence dissection             | 1.803  | 0.465-7.846 | .940  |

*ECG indicates electrocardiogram; LMWH, low-molecular-weight heparin; OR, odds ratio; CI, confidence interval.

Fig. 1. Location and characteristics of the culprit lesion in patients with NSTEACS and markedly elevated troponin I levels (≥10×unl) as compared to patients with normal or slightly to moderately elevated troponin. Incidence of thrombus, ulceration and location in a bifurcation is much more frequent in patients with highly increased troponin I levels.

NSTEACS indicates non-ST segment elevation acute coronary syndrome; unl, upper normal limit.
level correlated with the prognosis, independently of the angiographic findings. In addition, the update of the Clinical Practice Guidelines for the management of patients with NSTEACS recently published by the SEC \textsuperscript{16} and by the ACC/AHA \textsuperscript{17} have established that the magnitude of troponin elevation has a determinant prognostic implication, such that patients with markedly elevated troponin levels (>10 times the upper normal limit) should be initially stratified as high-risk. The in-hospital course seen in our patients upholds this recommendation.

Several studies have identified a series of factors associated with elevated troponins in patients with NSTEACS.\textsuperscript{18-25} As compared to patients with normal troponin values, patients testing troponin-positive have more extensive coronary disease,\textsuperscript{23} as well as more severe\textsuperscript{23} and more complex\textsuperscript{21,22,25} culprit lesions with a higher incidence of thrombus.\textsuperscript{21-25} In addition, patients with positive markers show more compromised flow (TIMI 0-1) in the artery causing the symptoms.\textsuperscript{21,22} Only 1 study has analyzed the factors associated with different levels of troponin elevation in patients with NSTEACS.\textsuperscript{26} In a substudy of the FRISC II investigation assessing the potential mechanism for the prognostic capability of troponin, Lindaht et al\textsuperscript{26} found that patients with markedly elevated troponin had presented more severe initial electrocardiographic alterations and showed a higher incidence of visible thrombus and complete occlusion of the circumflex artery on coronary angiography. It is important to stress that, within the inclusion criteria for the FRISC II study, patients could present troponin elevations and also CK-MB elevations.\textsuperscript{27}

The patients included in the present study had elevated troponin I, but CK-MB values were normal. The exclusion of patients with elevated CK-MB makes our sample more homogeneous, responds more precisely to the aim of the study, and avoids the participation of patients with potentially different pathophysiological mechanisms.

In the univariate analysis, a series of clinical variables (prolonged angina, more severe presentation, pronounced electrocardiographic changes) were documented more often in the patients with highly increased troponin levels. Among these factors, the only clinical variable in the multivariate analysis independently associated with patients having markedly elevated troponin levels was Braunwald angina class IIIb. Nevertheless, the notable initial manifestations in patients with highly elevated troponin might indicate the severity of the myocardial injury produced and be a clinical result of the underlying pathophysiological mechanism, without contributing to the etiology.

The data from this study suggest that the phenomenon of microembolization could be one of the main mechanisms causing markedly elevated troponin levels in patients with NSTEACS. Three angiographic variables were independently associated with high troponin increases. Lesions with ulceration or thrombus have been classically considered to have a greater potential for distal embolization, and the location of lesions in a vessel bifurcation means that they are subjected to an acceleration of flow (Venturi effect)\textsuperscript{28} which, upon impact with a fragile plaque, could produce greater microembolization.

Ejection fraction values in our patients were similar regardless of their initial troponin I levels. It is possible that the predictive value of elevated troponin I in NSTEACS patients is not completely explained by its influence on the state of ventricular function. It has been suggested that increased troponin levels may be a marker of the degree of extension of the coronary disease.\textsuperscript{29} Patients with highly increased troponins in our series showed much more extensive disease on angiography.

**Limitations**

The hypothesis that more prolonged transient occlusions with sustained ischemia in the culprit stenoses are the main mechanism for the highest troponin elevations cannot be ruled out in the present study. However, TIMI flow in the culprit artery was

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**TABLE 4. Ischemic Events During Hospitalization in Patients With Markedly Elevated Troponin Versus Remaining Patients**

<table>
<thead>
<tr>
<th>Event</th>
<th>Troponin I=10×unl n=41</th>
<th>Troponin I&gt;10×unl n=178</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, AMI or recurrent angina</td>
<td>20 (49%)</td>
<td>58 (32%)</td>
<td>.04</td>
</tr>
<tr>
<td>Death</td>
<td>2 (5%)</td>
<td>2 (1%)</td>
<td>.16</td>
</tr>
<tr>
<td>AMI</td>
<td>2 (5%)</td>
<td>5 (3%)</td>
<td>.389</td>
</tr>
<tr>
<td>Recurrent angina</td>
<td>19 (46%)</td>
<td>58 (32%)</td>
<td>.071</td>
</tr>
<tr>
<td>Revascularization</td>
<td>28 (71%)</td>
<td>93 (52%)</td>
<td>.031</td>
</tr>
<tr>
<td>PCI</td>
<td>24 (58%)</td>
<td>75 (42%)</td>
<td>.054</td>
</tr>
<tr>
<td>Coronary surgery</td>
<td>5 (12%)</td>
<td>10 (10%)</td>
<td>.757</td>
</tr>
</tbody>
</table>

*AMI indicates acute myocardial infarction; PCI, percutaneous coronary intervention; unl, upper normal limit.*
similar in both groups of patients, and percentage of stenosis was not identified as an independent variable in the multivariate analysis, although coronary angiography was performed five to six days after the clinical episode. Patients with markedly elevated troponin were more often given heparin or IIb/IIIa receptor inhibitors as initial treatment. The mean time between the onset of symptoms and the coronary angiography study in this group was 5 to 6 days. These factors might have played a part in underestimating the angiographic incidence of thrombus in the culprit lesion. The observed reduction in the incidence of visible thrombus with the use of IIb/IIIa receptor inhibitors has been found to be very modest, however. Moreover, the time elapsed before coronary angiography was similar between the patients with and those without elevated troponins. Both aspects could have contributed to underestimation of the incidence of thrombus in patients with markedly elevated troponin levels; however, they do not modify the main conclusions of our study.

CONCLUSIONS

Marked elevations of troponin I in patients with NSTEACS were associated with more severe clinical presentations and culprit stenosing lesions with more complex morphologic characteristics on coronary angiography.

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