Long-Term Prognostic Value of Troponin I in Patients Admitted to a Coronary Unit for Unstable Angina

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Introduction and objectives. Troponin I (TnI) is a useful marker of myocardial damage for the diagnosis and prognosis of acute coronary syndrome. The purpose of this study was to analyze the long-term prognostic value of the peak TnI concentration obtained within 48 h of admission to the coronary unit for unstable angina.

Methods. The study included 149 consecutive patients. Serial determinations were made of the MB fraction of creatine kinase (CK-MB) and TnI. Patients without CK-MB elevation were classified into two groups depending on the presence of high (n = 58) or normal (n = 91) troponin I values. We prospectively analyzed the clinical and evolutive factors related to the probability of death, new acute coronary event, or coronary revascularization at one-year of follow-up.

Results. There were no differences in the clinical characteristics between groups, except that patients in the group with high TnI values were older (69 vs. 64 years, p = 0.01). At one year of follow-up there were no differences in the incidence of new acute coronary events or coronary revascularization procedures; however there was a higher mortality in the group with high TnI (13 vs. 4%; p = 0.01). The independent predictors of mortality were prior myocardial infarction (RR = 3), elevated troponin I (RR = 3.2), left ventricular ejection fraction < 35% (RR = 10), and age > 70 years (RR = 15).

Conclusions. In patients with unstable angina a high troponin I value in the first 48 h of admission was associated with a higher mortality rate at one-year of follow-up.

Key words: *Troponin. Unstable angina. Infarction. Prognosis.*

Valor pronóstico tardío de la troponina I en los pacientes ingresados en una unidad coronaria por angina inestable

Introducción y objetivos. La troponina I (TnI) es un marcador de daño miocárdico utilizado en la estratificación pronóstica del síndrome coronario agudo. El objetivo del estudio fue analizar el valor pronóstico tardío del nivel máximo de TnI obtenido en las 48 h tras el ingreso en una unidad coronaria por angina inestable.

Métodos. Se incluyó a 149 pacientes consecutivos. Se realizaron determinaciones seriadas de la fracción MB de la creatincinasa (CK-MB) y TnI. Los pacientes sin elevación de la CK-MB fueron clasificados en dos grupos, en función de la presencia de TnI elevada (n = 58) o normal (n = 91). Se analizaron prospectivamente los factores clínicos y evolutivos relacionados con la probabilidad de muerte, nuevo episodio agudo coronario o revascularización coronaria tras un año de seguimiento.

Resultados. No se observaron diferencias entre los dos grupos en relación con las características clínicas, salvo la edad, que fue mayor en el grupo con TnI elevada (69 frente a 64 años; p = 0,01). Tras un año de seguimiento no se apreciaron diferencias en la incidencia de nuevos acontecimientos coronarios agudos ni en la revascularización; sin embargo, la mortalidad fue mayor en el grupo con TnI elevada (el 13 frente al 4%; p = 0,01). Los predictores independientes de mortalidad fueron el infarto previo (riesgo relativo [RR] = 3), TnI elevada (RR = 3,2), fracción de eyección < 35% (RR = 10) y edad > 70 años (RR = 15).

Conclusiones. En la angina inestable, un valor elevado de TnI dentro de las primeras 48 h del ingreso se asocia con un aumento de la mortalidad al año de seguimiento.

Palabras clave: *Troponina. Angina inestable. Infarto de miocardio. Pronóstico.*

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INTRODUCTION

The pathogenic mechanism most frequently associated with acute coronary syndromes (ACS) is thrombotic coronary occlusion, which in the majority of cases results from the rupture of atherosclerotic plaque.[1,2] Patients with ACS without ST segment

ABBREVIATIONS

CK: creatinkinase.
CK-MB: creatinkinase MB fraction.
ACS: acute coronary syndrome.
TnI: troponin I.
eTnI: elevated troponin.
nTnI: normal troponin I.

elevation are a heterogeneous population with regard to prognosis, and therefore determining the risk of future cardiac events in this group is important for making clinical decisions such as the choice of the most adequate treatment for each patient.[3]

Among the markers for myocardial damage, studying cardiac troponins is at present the target of clinical investigation in patients with ACS.[4,5] Cardiac troponin is a complex of 3 molecules, consisting of troponin T (TnT), troponin I (TnI), and troponin C. Of these, troponin T and I have been the objects of study due to their greater specificity for cardiac muscle. Cardiac troponins have a fraction dissolved in the cytoplasm of myocytes, which renders them specifically useful for detecting reversible (ischemic) or irreversible (necrotic) cellular lesions; they are also useful for later diagnosis, as serum concentrations remain elevated for at least a week after the onset of symptoms.[6]

The prognostic value of TnI in the short-term development of acute coronary syndromes has been shown in several clinical studies.[7,8] Nevertheless, there are no studies that have evaluated the long-term prognostic significance of this marker in patients with unstable angina who are admitted to a coronary care unit. The goal of this study is to verify whether differences exist in the long-term prognosis (12 months) among patients with angina who present with elevated TnI levels within 48 hours after admission and patients who present with normal TnI values.

PATIENTS AND METHODS

Patients

We included all patients admitted to the coronary care unit consecutively over a period of 8 months with a diagnosis of suspected unstable angina, as defined by the Braunwald classification[9] and with a course of less than 24 hours from the onset of symptoms. Exclusion criteria for the study were: renal insufficiency (defined by a creatinine value of more than 2), ST segment elevation on echocardiogram (ECG), a troponin testing higher than 3, elevation of cardiac enzyme values (creatinkinase [CK] and creatinkinase MB fraction [CK-MB]), and patients in whom acute ischemia was not confirmed because they did not meet the following criteria: changes in ST-T segment; elevated serum values in 2 or more samples of TnI; a positive result on submaximal ergometry; the presence of local areas of hypokinesia on echocardiography; or the presence of a significant lesion on coronary angiography. A total of 149 patients were included in the final study population.

Methods

This was a prospective study. Blood was drawn from all patients admitted to the coronary care unit from the moment of admission to the emergency department and every 6 hours thereafter for TnI, CK, and CK-MB for the next 48 hours. Measurement of TnI was performed with Beckman Access® immunoenzyme assay, and measurement of CK and CK-MB was performed by the Beckman Synchron cx® kinetic enzyme method.

We considered normal those values established as normal by the biochemistry laboratory (CK<200 U/L; CKMB<10 U/L; TnI<0.150 ng/mL). An acute myocardial infarct was considered to be present when the CK and CK-MB levels were more than 2 times the laboratory reference value. All patients were treated with intravenous heparin or low molecular weight heparin, beta blockers, intravenous nitroglycerine, and acetylsalicylic acid, except when contraindicated, independent of the TnI values (at the time of initiating the study, glycoprotein IIb-IIIa inhibitors were not used).

In all patients ventricular function was evaluated with echocardiography, isotopic ventriculography with Technetium 99, or contrast ventriculography during cardiac catheterization. In addition, at the time of hospital discharge a symptom-limited stress test was performed, according to the Bruce protocol, on all patients in whom the test was not contraindicated or who did not have limitations that prevented physical exertion.

Patient follow-up was performed retrospectively during the 12 months after discharge in an outpatient setting, with review at 1 month, 6 months, and at 1 year. The final study outcomes were death, readmission due to ischemic complications (infarct or unstable angina), and the need for revascularization (coronary angioplasty or surgery).

Statistical analysis

The patients were divided into 2 groups according to whether the maximum serum concentration of TnI in the 48 hours after admission was elevated or normal. For the nonadjusted analysis of the differences bet-

ween the 2 groups, we used χ^2 test for qualitative variables in χ^2 tables and the Student t test of independent samples for the quantitative variables. Analysis of survival rates and complication rates was performed with Kaplan-Meyer curves, using the logarithmic range test. Finaly, we applied a Cox multivariate model of proportional risks to identify the independent predictors of prognosis during the follow-up period.

RESULTS

Of the patients, 149 completed the study, with a mean age of 66 years±12 years (range 34 to 91 years); 115 men (77%) and 34 women (23%).

In accordance with the Braunwald classification,[9] the angina was of class IIIB type in 90% of patients; class IB type in 4% of patients; class IIA 0.7% of patients; class IIB in 2% of patients; class IIIA in 1.3% of patients, and class IIIC in 2% of patients. Of all the patients studied, 91 (61%) had normal TnI (nTnI) values and 58 patients (39%) had elevated TnI values (eTnI). The TnI concentrations at the time of admission were 0.030 ng/ml±0.060 ng/mL for the nTnI group and 0.300 ng/ml±0.400 ng/mL in the eTnI group, while the maximum values obtained in the serial blood draw curves were 0.050 ng/ml±0.100 ng/mL for the nTnI group and 0.700 ng/ml±0.700 ng/mL for the eTnI group.

Clinical variables were not significantly different between the 2 groups with regard to sex; risk factors (high cholesterol, arterial hypertension, diabetes mellitus, smoking); and treatment with beta-blockers and aspirin, and the mean age was significantly higher in the patients with eTnI compared with those with nTnI (69 years±12 years vs 64 years±12 years; *P*=.01) (Table 1).

We found differences, although not significant, between the 2 groups when we analyzed history of previous atherosclerotic disease. The patients in the nTnI group more frequently had a previous myocardial infarct (>1 month), peripheral ischemia, coronary angioplasty, previous cerebrovascular accident, and surgical coronary revascularization, and the eTnI group more frequently had a history of angina (Table 2).

We analyzed various prognostic factors to determine if differences existed between the groups with normal TnI and elevated TnI, the number of ergometry tests that could not be performed in each group, the percentage of electrically positive ergometry tests (defined by ST segment decline >1 mm at 80 ms of the J point), functional capacity (in metabolic equivalents of oxygen consumption [MET]), the ejection fraction, and the number of vessels with significant lesions on coronary angiography. We performed ergometry on 82 patients (55%), echocardiography on 147 patients (98.6%), and coronary angiography on 75 patients (50%). The patients who did not undergo ergometry were those who were unable to walk, who were scheduled for catheterization, or who had died. We only observed significant differences between the 2 groups in the presence of ST-T segment changes, which occurred more frequently in the group with eTnI (68% vs 46%; *P*=.007) (Table 3).

At 1-year follow-up, we compared the complications present in the 2 groups. Patients admitted for ischemic

TABLE 1. **Clinical patient characteristics for both groups**

	Normal TnI (n=91)	Elevated TnI (n=58)	Statistical significance *(P)*
Man/woman	72 (62%)/19 (55%)	43 (37%)/15 (45%)	NS
Age	64±12	69±12	.01
Hypercholesterolemia	65 (71%)	39 (67%)	NS
Diabetes	17 (18%)	9 (15%)	NS
Smoking	55 (60%)	30 (51%)	NS
AHT	43 (47%)	34 (58%)	NS
Beta blockers	29 (31%)	16 (27%)	NS
Aspirin	47 (51%)	23 (39%)	NS

TnI indicates troponin I; AHT, arterial hypertension; NS: not significant.

TABLE 2. **Previous atherosclerotic disease**

	Normal TnI (n=91)	Elevated TnI (n=58)	Statistical significance *(P)*
Cerebrovascular accident	5 (5.4%)	2 (3.4%)	NS
Myocardial infarct	33 (36%)	20 (24%)	NS
Peripheral ischemia	11 (12%)	4 (7%)	NS
Coronary angioplasty	8 (8.7%)	3 (5%)	NS
Surgical coronary revascularization	9 (9.8%)	2 (3.4%)	NS
Angina	42 (46%)	29 (50%)	NS

TnI indicates troponin I; NS, not significant

TABLE 3. **Prognostic factors**

	TnI normal (n=91)	TnI elevada (n=58)	Significación estadística *(P)*
ST-T changes on ECG	42 (46%)	40 (68%)	.007
Without ergometry	36 (39%)	31 (53%)	NS
Positive ergometry	28 (50%)	11 (40%)	NS
MET	4.9±4	3.5±4	NS
FE	56±13	57±16	NS
Number of vessels	2±0.8	2.2±0.8	NS

TnI indicates troponin I; ECG, electrocardiogram; EF, ejection fraction; MET, metabolic equivalents of oxygen consumption; NS, not significant.

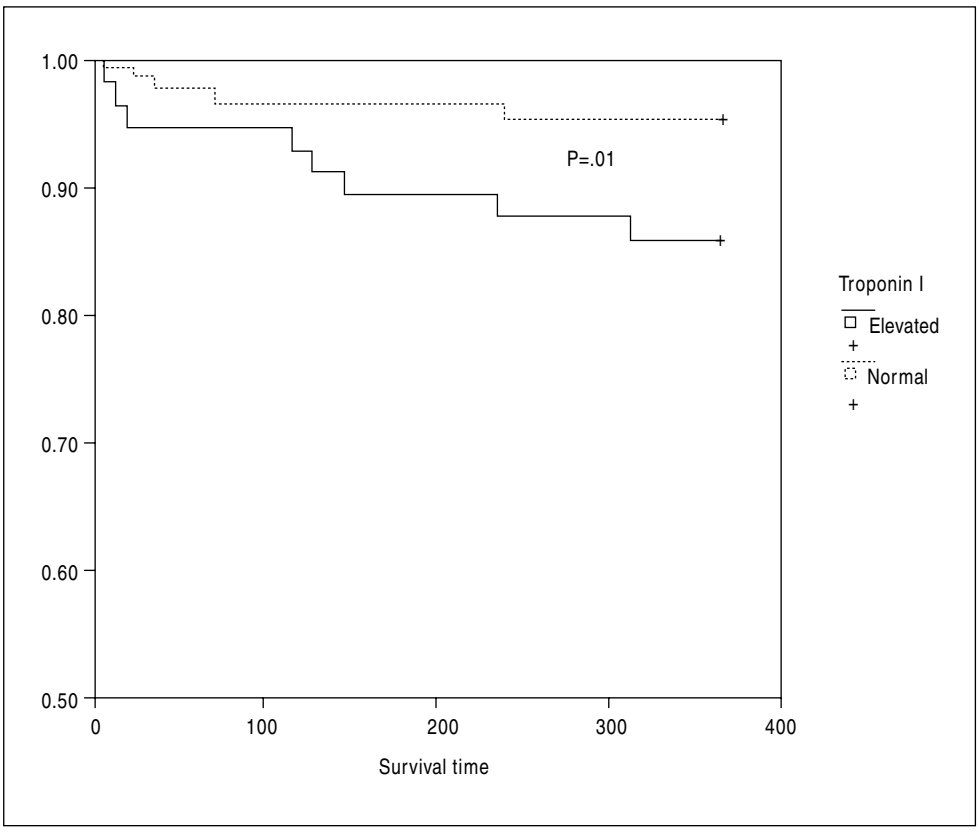

Fig. 1. Kaplan-Meyer survival curves in the group of patients with elevated troponin I and the group with normal troponin I at 1-year follow-up. A significantly higher mortality rate (*P*=.01) can be observed in the group with elevated troponin I.

complications (acute myocardial infarct, unstable angina with admission) were similar in both groups, and the need for revascularization by means of ACTP or surgery (due to severe ischemia, grave deterioration of ventricular function, or unstable angina refractory to medical treatment) was less in the group with elevated TnI values (nTnI, 32% of patients vs eTnI 27% of patients), although there were no statistically significant differences. With regard to mortality, the rate was significantly higher (*P*=.01) in the eTnI group (13% of patients) vs the nTnI group (4.3% of patients) (Figure 1).

Upon performance of a multivariate analysis we found the following to be independent predictors of mortality: previous infarct (RR, 3; 95% confidence interval [CI], 1-12; *P*=.05), elevated TnI concentration (RR, 3.2; 95% CI, 1-13; *P*=.05), an ejection fraction of less than 35% (RR, 10; 95% CI, 3-33; *P*=.001), and age greater than 70 years (RR, 15; 95% CI, 2-120; *P*=.01) (Table 4).

TABLE 4. **Independent predictors of mortality on multivariate analysis**

	RR	95% CI	*P*
ST-T changes on ECG	3	0.5-5	.6
Previous infarct	3	1-12	.02
Elevated TnI	3.2	1-13	.04
EF<35%	10	3-33	.001
Age>70 years	15	2-20	.001

RR indicates relative risk; CI, confidence interval; TnI, troponin I; EF, ejection fraction; ECG, electrocardiogram.

DISCUSSION

The first TnI sample taken in the emergency department seems to be a value with clear prognostic value,[4,5] although it may be negative due to the fact that the amount of time that elapses from the onset of pain may be small, so that is seems more logical to use the maximum value obtained during the first 24 to 48 hours from a series of samples. When this value is high, it has a high predictive value for adverse cardiac events;[7,8] it has been used to establish specific therapeutic interventions.[10] Our study is interesting because of its long-term analysis, since published studies using the first TnI sample value have analyzed adverse cardiac events in the short-term and medium term.[4,5,7,8,10-14]

In our sample, the patients with a maximum TnI value within the normal range have a tendency to a history of atherosclerotic disease that is higher than those patients with eTnI, which may be explained by the increase in collateral circulation in patients with atherosclerotic

disease, causing an acute coronary syndrome with a lower probability of myocardial damage, although this data has not been documented in any previous study.

The clinical characteristics and cardiovascular risk factors were similar in both groups, with only more advanced age in patients with eTnI being notable, although the mean age in both groups is similar to that described in previous studies.[14]

Upon analyzing cardiovascular complications at long-term followup, the patients with eTnI had similar ischemic complications (infarct or unstable angina requiring admission) and a higher, statistically significant, incidence of death. Although there was no significant difference between the percentage of patients revascularized during the course of the study, there was a tendency for an absence of coronary revascularization in the group of patients with eTnI, which may have influenced the long-term mortality rate in this group. Comparatively, the mortality rate in the group of patients with eTnI was higher than the combined studies (prospective and retrospective) analyzed in a recent meta-analysis.[14] The patients included in our sample are a high-risk group (90% had Braunwald class IIIB and were considered candidates for readmission to a coronary care unit) and had longer followup (increasing the probability of developing cardiac events), which would explain the greater rate of mortality in our series.

Upon analysis of other classic prognostic factors, a parallel is evident between the 2 groups (there were no significant differences in ejection fractions, ergometry positivity, the Duke ergometry index, and the number of vessels with significant lesions on coronary angiography), with the only exception being the presence of ST segment changes more commonly in the group with eTnI, although on multivariate analysis it was not shown that the changes on ECG were independent predictors of mortality.

Finally, multivariate analysis showed that only age of more than 70 years or greatly decreased ventricular function had a greater predictive power than an ETnI; this predictive value was even superior to other classic factors such as electrocardiographic changes or a history of myocardial infarct. Therefore, these characteristics in addition to TnI values are useful for deciding upon a more aggressive approach for the treatment of patients with signs of a poor prognosis, which is similar to other studies that used various factors in addition to TnI to determine prognosis and the course of treatment to follow.[12,13]

In conclusion, in our study we found an RR, 3.2 (range 1-13; *P*=.04) of mortality at 1 year, which is similar to that found on a meta-analysis of studies with TnT (12 studies) and TnI (9 studies) that found an RR, 4.2 for TnI and 2.7 for TnT of the occurrence of combined cardiac episodes (death and infarct).[14]

Study limitations

When our study was initiated, a consensus had not yet been reached by the European Society of Cardiology and the American College of Cardiology as to whether an elevation in troponins is indicative of myocardial infarct;[15] therefore, in our study design we considered that patients with eTnI values and normal CK-MB presented with unstable angina; today the design would possibly be changed, but we believe that, independent of the current classification, our study objectives continue to be valid, as ours was a prospective study of the prognostic evaluation of 2 groups of patients according to their troponin values, using treatment interventions that did not take into account the TnI value and could not have influenced the diagnosis. In spite of being a prospective study with a large number of patients, some factors that limit the study value must be taken into account, such as the fact that we did not know the value of troponin in patients who died before we could perform a series of extractions of TnI, as they were excluded from the study, as well as the fact that the patients studied were only those who were admitted to the coronary care unit, so that some high-risk patients with angina who were admitted to the hospital were not included in this study. On the other hand, we included a small percentage of patents with unstable angina that was not of the Braunwald IIIB type, whose prognosis was clear and in whom TnI values had less influence; nevertheless, these patients were not excluded as a selection skew was assumed, given that the objective of our study was to analyze the prognosis of all patients admitted to the coronary unit with unstable angina (those that the cardiologist on call had clinically determined to have a worse prognosis in spite of not being included in the IIIB group).

CONCLUSIONS

TnI is an independent predictor of long-term mortality in patients admitted to a coronary care unit who were diagnosed with unstable angina that is only surpassed by other known factors that have a strong influence prognosis such as a grave deterioration in ventricular function and age of more than 70 years. Nevertheless, the presence of elevated TnI values does not engender a greater probability of revascularization or ischemic complications.

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