ISCHEMIC HEART DISEASE

Is troponin I useful for predicting in-hospital risk for unstable angina patients in a community hospital? Results of a prospective study

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Introduction and objectives. Before including troponin I detection in the daily practice of our hospital we performed a prospective study to determine its real usefulness and to establish the best cut-off point.

Methods. We studied 82 consecutive patients admitted with unstable angina to a community hospital. Troponin I was determined (>10 h after chest pain). Patients were referred to a tertiary hospital for catheterization/revascularization if clinical events developed.

Results. Twenty-five patients (31%) suffered events during admission: recurrent angina in 23 cases (28%); heart failure in 5 (6%); exitus in 3 (4%); myocardial infarction in 1 (1%). The cut-off point for troponin I that best predicted events was 0.1 ng/ml. Patients with troponin I >0.1 (34 patients, 42%) experienced more events [47 vs. 19%; OR = 3.8 (1.4-10.4); P=.01] and had higher rates of recurrent angina (42 vs. 19%), heart failure (12 vs. 2%) and exitus (9 vs 0%). Patients with ECG changes and troponin I > .1 showed a significantly higher percentage of events (63%) than those with ECG changes alone (23%) or troponin I > .1 alone (15%) or those without ECG changes and troponin I < 0.1 (17%) (P< .0001).

Conclusions. Troponin I elevation is useful for predicting in-hospital risk for unstable angina patients admitted to a community hospital. A low cut-off value (0.1 ng/ml) predicts events. The association of ECG changes and high troponin I identifies a population at very high risk; however, the absence of both variables in patients with a diagnosis of unstable angina does not preclude the development of events.

Key words: *Unstable angina. Prognosis. Enzymes. Electrocardiography.*

¿Es la troponina I útil para predecir el riesgo

hospitalario en pacientes con angina inestable ingresados en un hospital comarcal? Resultados de un estudio prospectivo

Introducción y objetivos. Antes de incluir la troponina I en la práctica diaria de nuestro hospital, realizamos un estudio prospectivo para determinar su utilidad real y el mejor punto de corte.

Métodos. Estudiamos a 82 pacientes consecutivos ingresados por angina inestable en un hospital comarcal. Se determinó la troponina I (> 10 h del episodio de dolor torácico). Los pacientes fueron remitidos a un hospital terciario para cateterismo/revascularización en caso de algún acontecimiento clínico.

Resultados. Durante el ingreso se detectaron acontecimientos en 25 casos (31%): angina recurrente en 23 (28%), insuficiencia cardíaca en 5 (6%), infarto en 1 (1%) y muerte en 3 (4%). El mejor punto de corte de la troponina I para predecir acontecimientos fue 0,1 ng/ml. Los 34 pacientes (42%) con troponina I > 0,1 presentaron más acontecimientos (47 frente a 19%; OR = 3,8 [1,4-10,4]; p = 0,01), angina recurrente (42 frente a 19%), insuficiencia cardíaca (12 frente a 2%) y fallecimiento (9 frente a 0%). Los pacientes con cambios ECG y troponina I > 0,1 sufrieron más acontecimientos (63%; p < 0,0001) que aquellos con sólo cambios ECG (23%) o troponina I > 0,1 (15%), o aquellos sin cambios ECG y troponina I < 0,1 (17%).

Conclusiones. La troponina I es de utilidad para predecir el riesgo hospitalario en pacientes con angina inestable en un hospital comarcal. Un punto de corte bajo (0,1 ng/ml) predice la aparición de acontecimientos. La asociación de cambios ECG y troponina I positiva identifica a un grupo de alto riesgo; sin embargo, la ausencia de ambas variables en pacientes con un diagnóstico de angina inestable no asegura una buena evolución.

Palabras clave: *Angina inestable. Pronóstico. Enzimas. Electrocardiografía.*

INTRODUCTION

Unstable angina is the main reason for admission to the cardiology unit of community hospitals. Effective and reliable stratification of risk as promptly as possible in these patients is one of the most frequent tasks of the clinical cardiologist.[1,2]

The detection of troponin elevation in patients with unstable angina (indicative of minimal myocardial damage not detectable by the classic enzyme markers) has constituted in recent years a first-rank risk marker in these patients. Nevertheless, some questions must be considered before applying published results to the daily practice of a community hospital: Most of these papers correspond to studies made in tertiary hospitals (where invasive treatments are easily available) and many of them are multicenter studies that have not been specifically designed to determine the usefulness of troponin *per se*, but the effectiveness of different treatments. The cut-off point for predicting events varies widely. Finally, there is little published data from Spanish hospitals and even less from community hospitals.

For these reasons, before introducing troponin I into daily practice for the stratification of risk in patients with unstable angina, we decided to make a prospective study to assess the true usefulness of this parameter and its relation with classic predictors, and to ascertain the best cut-off point for our center.

METHODS

Study group

The study group was constituted by 82 consecutive patients admitted to our hospital from January to August 2000 with a final diagnosis of unstable angina (confirmed by the responsible cardiologist after examining the clinical evolution and results of all complementary studies, in addition to troponin I). Fifty-seven patients (70%) were men, mean age was 67±10 years; 51 patients (62%) had angina at rest and 31 (38%) had effort angina. Postinfarction angina was excluded to eliminate any possible distortion of results with respect to troponin. The characteristics of the study group are summarized in Table 1.

In accordance with the usual protocol, all patients were treated with acetylsalicylic acid, low-molecular-

TABLE 1. Characteristics of the study group

Antecedents of infarction	25/81 (31%)
Antecedents of angina	37/81 (46%)
Antecedents of ischemic heart disease	46/81 (57%)
Antecedents of diabetes	19/80 (24%)
Antecedents of dyslipidemia	33/81 (41%)
Age >70 years	38/82 (47%)
Smoker	34/76 (45%)
Male sex	57/82 (70%)
Arterial hypertension	47/81 (58%)
Ejection fraction <50%	17/54 (32%)
ECG changes with pain	32/80 (40%)
Troponin >0.1 ng/ml	34/82 (42%)
Troponin (median, 25-75 percentiles)	0.05 (0.02-0.39) ng/ml
Angina at rest	51/82 (62%)
Previous antianginal treatment	31/82 (38%)
Braunwald class 3b	42/82 (51%)

The percentage of patients with each variable is indicated (with respect to the total number of cases in which the variable was reliably recorded).

weight heparin at an anticoagulant dose, nitrates, and beta-blockers (unless contraindicated). Cardiac catheterization was requested from the referral tertiary hospital (for revascularization in the case of favorable coronary anatomy) in patients with infarction, heart failure, or recurrent angina. If the clinical evolution was favorable, stress testing or dobutamine-echocardiography was performed before release. If the result was negative or low risk for ischemia, the patient was discharged, but if it was positive (with medical treatment), catheterization was requested.

Considering the reality of community hospitals, significant events during hospital admission were defined as the presence of infarction, heart failure, recurrent angina (reappearance of angina in the cardiology ward, confirmed by the responsible cardiologist, after administration of antiplatelet, antithrombotic, and antianginal treatment), or cardiac death. These are the events that a clinical cardiologist in a community hospital must anticipate as soon as possible so as to indicate more aggressive treatment; in the present study the usefulness of troponin in obtaining an early prediction of these events was assessed. Data were collected prospectively during the hospital stay.

Complementary tests

An electrocardiogram was made (ECG) at the time of admission to the emergency service, admission to the ward, 24 h after admission, at discharge, and whenever the patient complained of chest pain. In 32 cases (40%), dynamic changes with pain were detected (ST segment depression of 1 mm or more in any lead except Vr, which normalized when pain disappeared in 30 cases; reversible ST segment

elevation in 2 cases).

Creatine phosphokinase (CPK and subunit MB) controls were made at arrival to the emergency service, at 6 h and after admission to the ward; if any CPK determination was more than two times the reference value, the patient was diagnosed as infarction and excluded from the study group. Later determinations were made in relation to the clinical evolution. Enzyme elevation (after three normal analyses) was considered an event (infarction) in a patient initially hospitalized for unstable angina.

Troponin I was determined in the ordinary laboratory tests routinely made in patients on the first morning of admission. In every case, the determination was made 10 to 24 h after the episode of chest pain that motivated admission. The cardiologists responsible for patients did not have access to the result of the troponin study and the laboratory personnel were unaware of the patient's clinical evolution. The intention was to assess the true power of this marker in predicting hospital events without adapting clinical management to the result of this determination.

Troponin I was determined in a Stratus-CS analyzer, by solid-phase radial partition immunoanalysis. The product resulting from enzyme reaction with 4-methylumberilphoshate was measured by fluorometry, and was directly proportional to the concentration of troponin I in the sample.

Statistical analysis

Parametric variables were expressed as mean±standard deviation and non-parametric variables as medians (25th percentile-75th percentile). Qualitative variables were expressed as percentages and compared using the chi-square test. The odds ratio (OR) and 95% confidence interval (CI) were determined.

Univariate analyses of survival were made using Kaplan-Meier curves (logarithmic ranges) and multivariate analyses by Cox multiple regression (including variables that presented $P<.1$ in univariate analysis). The ORs of the variables shown to be independent predictors were calculated.

The cut-off point of troponin I (0.1 ng/ml) was obtained by ROC curves (the point closest to the upper left angle for the prediction of clinical episodes).

In all cases, $P<.05$ was considered significant. The statistical analysis was made with the SPSS 9.0 statistical package (Chicago, Illinois, U.S.A.).

RESULTS

Clinical evolution

In the analysis of the 82 patients in the study group during hospital admission, recurrent angina was detected in 28%, heart failure in 6%, infarction in 1%, and cardiac death in 4%; altogether, 31% of the patients had one or more of these events. A pre-discharge stress test was performed in 54% of cases, coronary catheterization in 33%, and revascularization in 18%.

Troponin I. Univariate analysis

In 42% of the cases (34 patients), troponin I>0.1 ng/ml. No differences were found in the medical history of these patients compared with those who had troponin I<0.1 ng/ml (48 patients, 58%) (Table 2).

Patients with troponin I elevation had more episodes (47% versus 19%; OR=3.8 [1.4-10.4]; $P=.01$), more recurrent angina (42% versus 19%; OR = 3.2 [1.2-8.7]; $P=.04$), a greater frequency of electrocardiographic changes (59% versus 27%; OR=3.9 [1.5-10.2]; $P=.008$), and more need for cardiac catheterization (53% versus 25%; OR=3.4 [1.3-9.2]; $P=.02$) and revascularization (37% versus 11%; OR=4.6 [1.4-15.5]; $P=.02$) than patients with negative troponin (Table 2). A non-significant tendency was observed for patients with troponin I elevation to have a higher incidence of heart failure (12% versus 2%), cardiac death (9% versus 0%), and positive stress test (44% versus 18%) (Table 2).

Prediction of events. Univariate and multivariate analysis

The patients with events (recurrent angina/heart failure/infarction/death) had a more frequent history of angina (40% versus 20%; $P=.08$), ischemic heart disease (75% versus 49%; $P=.06$), dyslipidemia (58% versus 33%; $P=.06$), ejection fraction <50% (45% versus 22%; $P=.1$), dynamic electrocardiographic changes with pain (65% versus 30%; $P=.008$), troponin I >0.1 ng/ml (64% versus 32%; $P=.01$), and Braunwald angina type 3b (at rest and without triggers) (64% versus 42%; $P=.1$). In Table 3 are shown the OR of these variables for predicting episodes.

As observed, troponin I and ECG changes were the variables most consistently related with the occurrence of events. When both variables were associated, there was a large difference in the incidence of episodes in patients with positive troponin I and ECG (12/19; 63%). In contrast, the incidence of episodes was very similar in patients with positive troponin I and negative ECG (2/13; 15%), positive ECG and negative troponin I (3/13; 23%), and negative ECG and negative troponin (6/35; 17%) (Figure 1).

It seems that the variable positive troponin and ECG (as opposed to a single positive variable or both negative) was associated much more often with the

TABLE 2. **Differences in antecedents and clinical evolution of patients with troponin I >0.1 ng/ml (n=34) and troponin I<0.1 ng/ml (n=48)**
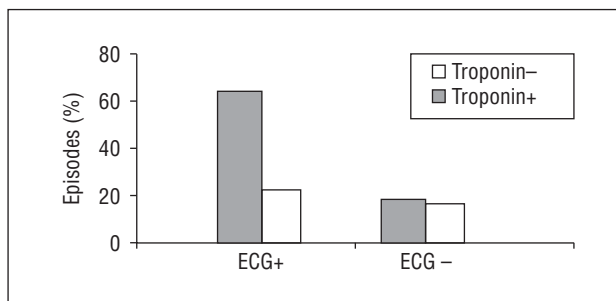
	Troponin I >0.1 ng/ml	Troponin I <0.1 ng/ml	P	OR (95% CI)
Antecedents of infarction	38%	25%	.2	1.8 (0.7-4.7)
Antecedents of angina	38%	51%	.3	0.6 (0.2-1.5)
Antecedents of ischemic heart disease	53%	60%	.6	0.7 (0.3-1.9)
Antecedents of diabetes	29%	20%	.4	1.7 (0.6-4.8)
Antecedents of dyslipidemia	44%	38%	.6	1.3 (0.5-3.1)
Age >70 years	47%	47%	.9	1.0 (0.4-2.4)
Smoker	53%	39%	.2	1.8 (0.7-4.5)
Male sex	76%	65%	.3	1.8 (0.7-4.8)
Arterial hypertension	68%	51%	.2	2.0 (0.8-5.0)
Ejection fraction <50%	35%	29%	.8	1.3 (0.4-4.1)
ECG changes with pain	59%	27%	.008	3.9 (1.5-10.2)
Braunwald class 3b	56%	44%	.4	1.6 (0.7-3.9)
Recurrent angina	42%	19%	.04	3.2 (1.2-8.7)
Heart failure	12%	2%	.2	6.1 (0.6-57.6)
Death	9%	0%	.1	2.5 (0.9-3.5)
Myocardial infarction	1%	0%	.2	2.5 (0.9-3.3)
Episodes	47%	19%	.01	3.8 (1.4-10.4)
Positive stress test	44%	18%	.1	3.6 (0.9-14.2)
Catheterization	53%	25%	.02	3.4 (1.3-9.2)
Bypass procedures	37%	11%	.02	4.6 (1.4-15.5)

The odds ratio (OR) and 95% confidence intervals (CI) of presenting a variable in relation to troponin I>0.1 ng/ml are shown.

TABLE 3. **Variables related with the presence of episodes. Univariate and multivariate analysis**

	Univariate		Multivariate	
	P	OR	p	OR
Antecedents of angina	.08	2.6 (0.9-7)	NS	
Antecedents of ischemic heart disease	.06	3.1 (1-8.9)	.007	4.6 (1.5-13.8)
Dyslipidemia	.06	2.8 (1-7.5)	NS	
Ejection fraction <50%	.1	2.9 (0.9-9.7)	NS	
ECG changes with pain	.008	4.4 (1.6-12.3)	NS	
Troponin I>0.1 ng/ml	.01	3.8 (1.4-10.4)	NS	
Braunwald class 3b	.1	2.4 (0.9-6.5)	NS	
Troponin I > 0.1 ng/ml and ECG changes with pain	.0001	7.8 (2.5-24.3)	.0001	7.2 (2.8-18.3)
Age	.6	1.2 (0.4-3.3)	NS	
Diabetes	.5	1.1 (0.4-3.3)	NS	

The odds ratio (OR) of variables related to the presence of intrahospital events (P<.1) in univariate analysis is shown. Multivariate analysis including all these variables, age, and the presence or absence of diabetes was made. Antecedents of ischemic heart disease and the combined variable troponin >0.1 ng/ml–ECG changes with pain were found to be independent.

Fig. 1. The percentage of intrahospital clinical episodes (death/infarction/hear failure/recurrent angina) based on the electrocardiogram (ECG) and troponin I. Patients with electrocardiographic changes (ECG+) and troponin I>0.1 ng/ml (troponin+) had significantly (P<.0001) more episodes (63%) than patients with ECG+ and negative troponin (23%), ECG– and positive

occurrence of events (63% versus 18%; OR=7.8 [2.5-24.3]; *P*<.0001). In fact, when this variable was included in multivariate study of all the variables that obtained *P*<.1 in univariate analysis (indicated at the beginning of this chapter), together with the variables age and diabetes (which were not significantly related with the prediction of episodes in univariate analysis but did constitute a confusion factor), we found that the only variables independently related with the occurrence of events were a history of ischemic heart disease (OR=4.6 [1.5-13.8]; *P*=.007) and the association of positive troponin-ECG (OR=7.2 [2.8-18.3]; *P*<.0001) (Table 3).

DISCUSSION

In the present study we found that troponin I was a useful marker for early stratification of the risk of suffering episodes in patients hospitalized for unstable angina in a community hospital. A low cut-off point (0.1 ng/ml) is good predictor of events (in accordance with the reagent used and study endpoints). A subgroup at greater risk could be easily and objectively identified in the first hours of admission: patients with elevation of troponin and dynamic electrocardiographic changes with pain. The absence of troponin I elevation in patients with a diagnosis of unstable angina reduced, but did not eliminate, the risk of episodes.

Troponin and risk stratification in unstable angina

The risk stratification of patients admitted for unstable angina is undoubtedly one of the most frequent activities of cardiologists in daily practice. Factors like the pressure on hospital services and early therapeutic decisions (invasive or conservative treatment), and the demand of patients and their families for prognostic information, mean that the cardiologist requires objective and reliable information that can be obtained quickly and easily. This information should help to differentiate from the very first moment between cases in which initial medical treatment is probably suitable and risk assessment can be limited to pre-discharge stress tests, and patients with a high-risk profile who require more aggressive treatment. It is easily comprehensible that the circumstances of community hospitals (patients must be transferred to other hospitals for coronariography and revascularization) make this information particularly important.

In recent years, studies have been developed and published in which the variables identified are related with the probability of suffering events. Troponin elevation without elevation of the classic markers of infarction in patients with angina has been presented as a sign of minimal myocardial damage (undetectable by means of elevation of the classic enzymes) that is associated with a less favorable prognosis. Its usefulness in the selection of patients with chest pain in emergency services and its reliability in the diagnosis of infarction have been demonstrated, although it does not provide an earlier diagnosis than the classic enzyme markers or myoglobin.

Nevertheless, there are some questions to consider before actually applying this parameter to daily practice for risk stratification in a community hospital. The available studies are almost all multicenter studies made in hospitals where invasive treatments are easily available. They have usually been designed to identify patients who can benefit from one drug or procedure or another, as opposed to evaluating the real risk of patients, sometimes with contradictory results. On the other hand, the variability of the cut-off points is important for defining a threshold without previous experience. Finally, the information available in Spain and applicable to the reality of practice in community hospitals is scant.

For these reasons, before including troponin I as a risk marker in patients hospitalized for unstable angina (with all its implications), we decided to undertake this prospective study to analyze its value objectively. Unlike other studies, the cardiologist and laboratory personnel did not have information about their respective findings, in order to avoid influencing case management. To facilitate the work of the clinician and laboratory, and given the goal of analyzing the prognosis of all patients admitted, a single sample obtained was for ordinary laboratory tests in every case, 10 h or more after admission for chest pain (when troponin has reached its plateau).[15]

Troponin I elevation was related with a higher incidence of all episodes (death, recurrent angina, heart failure, need for catheterization, revascularization, or positive pre-discharge stress test) that a cardiologist practicing in a community hospital would be interested in predicting from outset. Our results confirm those of most previous studies regarding the performance of this marker in predicting risk. We confirmed this in the setting of a community hospital without repeated analyses (by simply including this analytical parameter in the routine laboratory tests performed on the first morning of admission).

Another point that we considered was the variability of cut-off points. Since the references cited report very different cut-off points according to the center, reagent, or variables defined as events, we defined the cut-off point (0.1 ng/ml) using a ROC curve of troponin I values with respect to the episodes that we consider significant in daily practice.

Troponin I and electrocardiographic changes

In spite of the availability of new biochemical markers of risk, the ECG is still an objective and very useful tool for identifying patients hospitalized for unstable angina who have a less favorable prognosis. Fundamentally the detection of ST segment depression with the ischemic episode is associated with a high risk in these patients.[5,8,17,18]

The detection of dynamic electrocardiographic changes with pain was, together with troponin I elevation, the principal predictor of events in patients hospitalized for unstable angina in our community hospital. The objective nature of both variables (elevation or not of enzymes, and presence or absence

of electrocardiographic changes), their easy availability and precocity (reliable data are available for risk stratification in the first hours of admission of the patient) make both of them helpful tools for the clinical cardiologist in the community hospital setting, where rapid prognostic and therapeutic conclusions are essential.

In addition, the nature of these two variables (electrocardiographic changes and troponin I elevation) seems synergic. Thus, in the study group (consecutive patients hospitalized with a diagnosis of unstable angina), the clearly high-risk subgroup (63%) was the subgroup that had troponin elevation and electrocardiographic changes. The rest of the subgroups (which had a single or none of these variables present) had a similar risk (around 20%). A minimal troponin elevation (without concomitant electrocardiographic changes) probably involves a low risk.

It is also noteworthy that patients with negative troponin I had a similar risk, whether or not they had electrocardiographic changes. However, the size of the study group does not allow a more exhaustive analysis to be made. It is likely that this subgroup contains patients with an inconclusive ECG without enzyme elevation, which may involve situations in which the diagnosis and prognosis are doubtful. Nevertheless, the association of both parameters (minimal myocardial damage detected by troponin and severe ischemia detected by electrocardiogram) provides more assurance and consistently identifies a subgroup with a high risk.[5,8]

It was not the aim of this study to assess the best management strategy but to determine the value of troponin I determination in a community hospital. However, it seems logical that patients admitted for unstable angina who show electrocardiographic changes and troponin elevation are at high risk (63%) and constitute a manageable percentage of the total (19/82; 23%), so from the beginning they should receive maximum treatment, special monitoring, and prompt referral (without further stratification) to the reference hospital for coronariography and possible revascularization.

Although the elevation of troponin I (without electrocardiographic changes or elevation of other enzymes) also indicates a greater risk and various studies suggest that such patients should be aggressively managed, such a strategy, while probably practicable in tertiary hospitals, present important logistic problems in community hospitals. In our group of consecutive patients, almost half of them had troponin I elevation; but it seems impractical to refer half of the unstable angina patients in the area directly to the reference hospital for invasive management.

In addition, the risk of patients with a single positive variable was similar to that of patients with no positive variable (around 20%). These findings suggest that patients without positivity of both variables should be stabilized by medical treatment and their risk should be stratified by a pre-discharge stress test. Such patients should be referred for invasive treatment only if the clinical evolution or results of the pre-discharge stress test justify it.

Finally, another interesting finding was the positive evolution of patients with unstable angina in the absence of either electrocardiographic changes or troponin elevation. As in other studies, we found that these patients had a smaller risk of suffering events, but were by no means free of risk. In fact, the incidence of episodes was very similar (around 20%) to that of patients who had one positive marker (troponin or ECG). Therefore, it again seems that complementary tests are clearly helpful in defining the risk profile, but clinical assessment is fundamental. Patients with a diagnosis of unstable angina (by interview) must be hospitalized (or sent to a chest pain unit) even if troponin or the ECG is negative. An early stress test would probably help to further stratify these patients.[12-16,20]

In addition to the ECG and troponin, the other variable that had independent valor in predicting episodes was the presence of previous ischemic heart disease. Such patients probably have more advanced coronary artery disease and are more vulnerable to episodes (particularly repeated angina in the first days of admission).

Limitations

In accordance with newly published guidelines, some patients in the group (those who had troponin I elevation) would have been diagnosed as acute myocardial infarction. In any case, we felt that it would be useful to make a prospective study before applying the results of these parameters to daily practice, given the important implications that this measure has.

CONCLUSIONS

Troponin I is a helpful tool for risk stratification in patients admitted to a community hospital for unstable angina.

A low cut-off point (0.1 ng/ml) is the most reliable (considering the reagent used and objectives defined) for predicting the occurrence of events.

The predictive power of troponin I seems to be synergic with that of the ECG. The subgroup of patients with abnormalities in both variables has the highest probability of episodes and probably will benefit from a more aggressive treatment.

The absence of troponin elevation reduces the risk but does not eliminate it. Therefore, these patients

require further stratification before discharge.

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