Utility of the Serum Biochemical Markers CPK, CPK MB Mass, Myoglobin, and Cardiac Troponin T in a Chest Pain Unit. Which Marker Determinations Should Be Requested and When?

Javier Fernández Portales, José A. García Robles, Javier Jiménez Candil, Esther Pérez David, Juan R. Rey Blas, Leopoldo Pérez de Isla, Óscar Díaz Castro and Jesús Almendral.

Servicio de Cardiología. Hospital General Universitario Gregorio Marañón. Madrid. España.

Background. The prognostic value of biochemical markers in relation to time since onset of chest pain was evaluated in an emergency room with a chest pain unit.

Methods. In a single-center, prospective study we included 321 consecutive patients admitted to the emergency room with suspected unstable angina IIIB and an evolution of less than 12 hours. Blood samples were collected for CPK, CPK MB mass, myoglobin, and cardiac troponin T assays 6, 12, and 18 h after the onset of pain. ROC curve analysis was carried out to compare biochemical markers in terms of cutoff values and time since onset of pain. We determined the relation between prognosis and biochemical markers before and after adjustment for baseline characteristics.

Results. CPK mass and myoglobin showed the maximum sensitivity and specificity for new ischemic recurrences 6 hours after the onset of chest pain with laboratory cutoff values. We had to wait 12 h after the onset of pain for troponin T to be useful using the laboratory cutoff value (0.1 ng/ml). A single determination 6 hours after onset of chest pain of cardiac troponin T above 0.04 ng/ml was the most sensitive and specific marker for new ischemic recurrences.

Conclusions. A single blood determination of cardiac troponin T 6 hours after the onset of chest pain complete the prognostic stratification in combination with clinical and ECG variables. The best cutoff point of cardiac troponin T, based on univariate and multivariate analysis, was 0.04 ng/ml 6 h after the onset of chest pain.

Key words: *Unstable angina. Prognosis. Myoglobin.*

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Utilidad clínica de los distintos marcadores biológicos CPK, CPK MB masa, mioglobina y troponina T en una unidad de dolor torácico. ¿Cuándo, cuáles y cómo pedirlos?

Objetivos. Se pretende evaluar el rendimiento pronóstico de los marcadores bioquímicos en pacientes que consultan en un servicio de urgencias con una unidad de dolor torácico.

Métodos. Estudio monocéntrico y prospectivo de 321 pacientes consecutivos con sospecha de angina inestable IIIB y menos de 12 h de evolución. Se analizó CPK, CPK MB masa, mioglobina y troponina cardíaca T a las 6, 12 y 18 h del inicio del cuadro. Se comparó la utilidad pronóstica según el punto de corte y tiempo de evolución de los síntomas, analizando la concordancia entre las determinaciones y comprobando su valor independiente mediante análisis multivariado de regresión logística.

Resultados. La CPK masa y la mioglobina alcanzaron las máximas sensibilidad y especificidad para nuevos episodios isquémicos en los límites del laboratorio a las 6 h, no así en la troponina T, en la que hay que esperar a las 12 h con los límites prefijados por el laboratorio. Un punto de corte de troponina cardíaca T superior a 0,04 ng/ml a las 6 h del dolor torácico se convierte en la variable aislada con una mayor relación sensibilidad-especificidad para nuevos episodios isquémicos y aporta, además, una excelente concordancia con la determinacion a las 12 h.

Conclusiones. Una única determinación bioquímica de troponina T a las 6 h del inicio del dolor torácico parece suficiente para completar la estratificación pronóstica añadiéndola a variables clínicas y de electrocardiograma. El mejor punto de corte pronóstico de troponina T se sitúa en 0,04 ng/ml a las 6 h del inicio del dolor torácico.

Palabras clave: *Angina inestable. Pronóstico. Mioglobina.*

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Correspondence: Dr. Javier Fernández Portales.
Parras, 39, 3 E. 10004 Cáceres. España.
E-mail: portales70@hotmail.com

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ABBEVIATIONS

AMI: acute myocardial infarction.
CPK: creatinphosphokinase.
CPK-MBa: creatinphosphokinase cardiac activity.
CPK-MBm: creatinphosphokinase cardiac mass.
cTnT: cardiac troponin T.
ROC: receiving operator characteristic.
CI: confidence interval.
RR: relative risk.
ECG: electrocardiogram.

INTRODUCTION

The new biochemical markers that detect of lesser degrees of necrosis, and, therefore, are more sensitive indicators than the classic creatinphosphokinase (CPK), are a milestone in the evaluation of patients with acute coronary syndrome without ST segment increase.[1] This fact is reflected in the new guidelines for the definition of acute myocardial infarct (AMI) recently published by the European Society of Cardiology and the American College of Cardiology.[2]

At present we have a significant number of biochemical tests for the evaluation of the presence of a minimal myocardial lesion; nevertheless, the prognostic ramifications of these markers at the moment that chest pain begins has not been taken into consideration, but rather from the moment of admission in the emergency room, so that the relationship between the marker concentration and the time the pain has been present has necessarily been heterogeneous.

The magnitude of the problem is considerable, given that the number of patients who present in the emergency room with a clinical history compatible with myocardial ischemia is large. From 5% to 8% of the total number of patients admitted to the emergency room are seen for this reason.[3]

The aim of this study is to standardize the biological markers as a function of the time over which the symptoms develop, to extract the cut-off values for their diagnostic usefulness at various points in time, and to evaluate the prognostic value of taking 1 or 2 measurements.

METHODS

This is a prospective observational single-center study that included consecutive patients who went to the emergency room between March, 1998 and December, 1999 with a suspected diagnosis of prolonged unstable angina in the face of non-Q-wave AMI of less than 12 hours of evolution.

All patients were evaluated by the cardiologist or cardiology resident, who established the presumed diagnosis of acute coronary syndrome without persistent ST segment elevation.

We excluded from the study those patients with: *a)* persistent ST segment elevation, per fibrinolysis analysis; *b)* an electrocardiogram (ECG) that cound not be interpreted in the setting of a high suspicion of AMI due to segment contraction defects on echocardiogram, when the treating physician decided to perform emergency coronary angiography; *c)* secondary angina; *d)* documented AMI during the 2 previous weeks; *e)* concomitant disease with a poor short-term prognosis; *f)* a history of more than 12 hours of chest pain, or *g)* renal insufficiency (creatinine >2 mg/dL).

We extracted samples of the cardiac markers (CPK total activity, CPK-MBa, CPK-MBm, cardiac troponin T [cTnT], and myoglobin) at 6 hours and at 12 hours (for total CPK and CPK-MBa an additional sample was taken at 18 hours) after the beginning of the chest pain that was the motive for the admission. We decided not to collect a sample upon patient admission in order to standardize all measurements with the beginning of the chest pain. Similarly, an ECG was performed upon admission to the emergency room and at 6, 12, and 18 hours following admission.

The definition of an infarct was made in accordance with the criteria in force in 1998/1999. Therefore, 3 categories were considered with regard to the performance of the biological markers: *a)* no elevation of enzymes; *b)* elevation of the markers to less than the level required for the diagnosis of AMI (CPK>2 × the normal level), and *c)* non-Q-wave AMI with the absence of the development of pathological Q-wave and a total CPK elevation that was double maximum laboratory values (400 UI/L) with CPK-MBa greater than 10% of the total.

Upon admission the patients were classified according to the presence of chest pain and electrocardiogram changes, resulting in 3 categories: *a)* without chest pain on admission; *b)* with chest pain but without appreciable ST segment changes on ECG, and *c)* chest pain with reversible ST changes or permanent decline on ECG.

All the ECG studies were evaluated by at least 2 cardiologists, with those cases in doubt being decided with assistance of a third cardiologist, and noting a description of the ST segment evolution with the pain in the clinical history.

The maximum normal values of the different markers according to the central laboratory were: CPK<200 UI/L, CPK-MBm<5 ng/dL, myoglobin<60 ng/dL, and troponin T<0.1 ng/dL.

The measurement of CPK cardiac mass, myoglobin, and cardiac troponin T were made by immunoanalysis with an Elecys (CARDIAC T) analyzer (Roche®). All

samples were analyzed immediately by technicians who were unaware of the patients´ clinical data.

The results of the biochemical tests were known by the treating physicians and were interpreted according to their criteria, without performance protocols as a function of the results.

All patients´ pain was brought under control for at least the first 12 hours after admission and antiaggregate, anti-anginous, and anticoagulant treatment were administered at the discretion of the treating physician.

Episodes were considered new if they occurred after admission to the emergency room and until discharge or clinical evaluation 15 days later; the cases of failure and the cases of ischemic recurrence were defined by the occurrence of a new episode of angina that required emergency revascularization, a new AMI defined by an enzyme increase in CPK following admission, or according to ECG evidence. We also considered new ischemic episodes those where primary ventricular fibrillation was present and treated and the development of cardiac insufficiency that was not present at the time of admission and that required additional treatment, which was noted in the clinical history.

We performed a descriptive analysis of the variables obtained upon admission, expressed in percentages, means or averages, depending on the distribution of the values. To compare the continuous variables, we used the Student *t* test to obtain independent samples in case the Kolmogorov-Smirnov test results were not significant. When we were not able to assume the normal value of a variable, we used the non-parametric Mann Whitney U test.

We performed univariate analysis of the variables using the χ^2 test for qualitative variables and the Student *t* test for continuous variables.

We carried out ROC diagnostic curves for new episodes for each of the markers and at 6 hours and 12 hours from the initiation of chest pain. We considered the cut-off points where the sensitivity and specificity were at a maximum to be optimal cut-off values.

We compared the samples for each marker at different times, in order to objectify the positive concordance of the samples as a function of the time of evolucion from the beginning of the chest pain, using the cut-off values accepted by the laboratory and those at which the sensitivity-specificity ratio was highest. The concordance was evaluated by kappa analysis, also showing the confidence interval (CI) for the parameter.[4]

We performed a multivariate regression logistic analysis for new ischemic episodes via the forward stepwise technique, including the prognostic variables that the literature classically considers prognostic at the time of admission to the emergency unit (age,[5] sex,[5] cardiovascular risk factors,[6] pain and ECG changes, abnormal baseline ECG,[7] evolutionary T-wave changes,[7] previous ischemic heart disease or peripheral vascular disease, or both,[6] and the presence of prolonged chest pain during the previous 15 days[6,7]), finally adding the biological markers separately; that is to say, a measurement was entered for each model. We evaluated the relative risk for each measurement according to the laboratory cut-off value and the greatest prognostic value per univariate ROC curve. We selected for the final model the best adjusted variables with a lower confidence interval (CI) and we included those interactions that were significant.

RESULTS

We included in our study 321 consecutive patients who went to the emergency room between March, 1998 and December, 1999 with the suspected diagno-

TABLE 1. **Baseline patient characteristics**

	n=321 (%)
Sex	
Men	226 (70.4)
Dyslipemia	163 (50.8)
AHT	202 (62.9)
Previous ischemic heart disease	142 (42)
Previous AMI 78 (24)	
Previous angina 64 (19.9)	
Previous CAP 41 (12.8)	
Previous Qx 22 (6.9)	
Familial ischemic heart disease	31 (9.7)
Peripheral vascular disease	
Claudication	39 (12.1)
CVA 16 (5)	
Tobacco use	
Ex-smoker	87 (27.1)
Smoker	93 (29)
Diabetes	
Diet	18 (5.6)
Treatment	80 (24.9)
Pain and ST changes on admission	
Without pain	114 (35.5)
Pain without ST changes	91 (28.3)
Pain with ST changes (increase)	26 (8.1)
Pain with ST changes (decrease)	90 (28.8)
Baseline ECG	
Normal	144 (44.9)
Increased	ST 26 (8.1)
Decreased	ST 54 (16.8)
T-wave	70 (21.8)
Pacemaker	8 (19)
CRBB	19 (8)
Evolutionary ECG changes	
No	223 (69.5)
ST decrease	8 (2.5)
Negative T	89 (27.7)
Not available	1 (0.3)

AHT indicates arterial hypertension; AMI, acute myocardial infarct; CAP, coronary angioplasty; Qx, revascularization surgery; CAV, cerebrovascular accident; ECG, electrocardiogram; CRBB, complete right branch block.

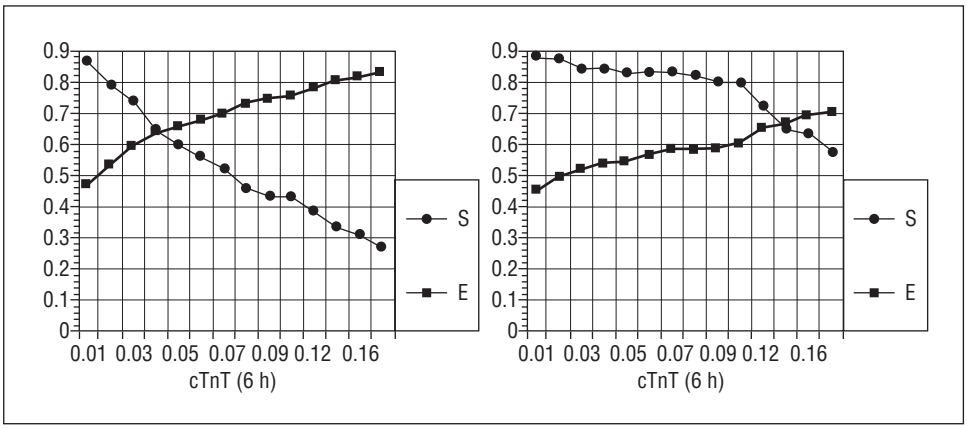

Fig. 1. Sensitivity and specificity for new episodes at various cTnT cut-off values. Measurements were made at 6 hours and 12 hours after the beginning of chest pain.

sis of prolonged unstable angina or non-Q-wave AMI. Six patients went to the emergency room more than 6 hours after the beginning of chest pain, and the first enzyme test could not be performed. The mean age of the patients was 67.5 years of age with an interquartile range of 13 years of age (Table 1).

Episode analysis

There was a 25% occurrence rate of new episodes, with a mortality rate of 1.9%. Nine percent of patients were discharged from the emergency room and the rest of the patients were admitted to the hospital.

Twenty-five percent of patients (n=81) developed complications during their hospital course, the most frequent of which (74%) was the return of chest pain despite medication, and the treating physician decided to perform emergency cardiac catheterization (n=60) as a consequence. Ninety percent of these patients were found to have serious heart disease of at least 1 vessel (n=52) and they underwent emergency revascularization in 88% of cases (n=47). In the 8 patients who did not have serious coronary lesions, coronary spasm was found in 3 patients, an intramyocardial bridge with intense lumen compromise was found in 2 patients, and idiopathic dilated myocardiopathy with complete block of the left branch was found in 3. The rest of the complications occurred much more rarely: congestive heart failure (n=12), AMI (n=3), and cardiorespiratory arrest (n=6).

It was not possible to confirm the initial diagnosis of acute coronary syndrome in 26% of patients, and no events were observed during follow-up. The final diagnosis of AMI was made in 26.1% of the patients who had 40% of the episodes, and 47% of patients were diagnosed with unstable angina with 30% of the episodes.

TABLE 2. **Univariate analysis of biological markers for episodes**

	Episodes (n)	Without episodes (n)	*P*
CPK 6 h (UI/L)	161.11 (79)	140.59 (236)	.0117
CPK 12 h (UI/L)	368.74 (81)	199.94 (240)	.0003
CPK 18 h (UI/L)	461.96 (81)	214.48 (240)	.0001
CPK-MBm 6 h (ng/mL)	16.87 (79)	12.65 (236)	.0001
CPK-MBm 12 h (ng/mL)	54.24 (81)	21.62 (240)	.0001
Myoglobin 6 h (ng/mL)	211.56 (79)	119.33 (236)	.0001
Myoglobin 12 h (ng/mL)	183.79 (81)	89.60 (240)	.0001
cTnT 6 h (ng/mL)	0.28 (79)	0.20 (236)	.0001
cTnT 12 h (ng/mL)	0.70 (81)	0.37 (240)	.0001

cTnT indicates cardiac troponin T.

Relationship of biological markers to episodes

The analysis of the biological markers at 6 hours and at 12 hours from the beginning of the chest pain correlated with the prognosis in a univariate manner with the limits established by the laboratory (Table 2).

Table 3 shows the different values of sensitivity, specificity, and the positive and negative predictive values for later episodes during the admission of patients in the sample group at 6 hours and 12 hours following the beginning of chest pain, using the established laboratory values. In the case of troponin T, we also indicated the optimum cut-off value at 6 hours as indicated by the ROC curve (cTnT, 0.4 ng/mL) (Figure 1).

ROC curves were created and the area below the curve was estimated for the different biochemical markers with regard to the presence of new episodes.

Optimum cut-off values of the biological markers for predicting episodes and concordance between measurements

Of note, the points of greatest sensitivity and specificity for the distinct cardiac troponin T and CPK-MBm values, with regard to prognosis, varied significantly according to the amount of time that had passed after the symptoms first occurred. The univariate ROC curve indicated that troponin T at 12 hours had a rela-

TABLE 3. **ROC curves and diagnostic performance for each pre-established cut-off value**

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC area (%)
Myoglobin (60 ng/mL) 6 h	71	52	33	81	63
Myoglobin (60 ng/mL) 12 h	60	58	33	81	61
CPK (200 UI/mL) 6 h	24	82	31	76	60
CPK (400 UI/mL) 6 h	4	95	21	75	
CPK (200 UI/mL)12h	51	74	39	82	63
CPK (400 UI/mL) 12 h	25	87	38	77	
cTnT (0.04 ng/mL) 6 h	64	63	37	83	67
cTnT (0.1 ng/mL) 6 h	43	75	37	80	
cTnT (0.1 ng/mL) 12 h	79	60	40	89	70
CPK-MBm (5 ng/mL) 6 h	78	54	36	88	66
CPK-MBm (5 ng/mL) 12 h	68	58	36	85	67

CTnT indicates cardiac troponin T; PPV, positive predictive value; NPV, negative predictive value.

tionship to sensitivity and sensitivity that was similar to that obtained at 6 hours (ROC area at 12 hours=0.70 vs ROC area at 6 hours=0.67), in such a way that by changing the cut-off point it was possible to obtain the same sensitivity and specificity at 6 hours as at 12 hours.

In the case of troponin T, values greater than 0.04 ng/mL at 6 hours had the highest sensitivity and specificity values; nevertheless, at 12 hours the most profitable values were around 0.1 ng/mL, coincident with those recommended by the laboratory (Figure 1). With CPK-MBm and myoglobin, the optimum cut-off values were the same as those already established by the laboratory at 6 hours.

Utilizing the limits established by the laboratory, we correlated the positive values of each of the markers at 6 hours from the beginning of chest pain with the positive values obtained at 12 hours from the beginning of chest pain. The concordance was good, and was maximal in the case of CPK-MBm with the limits pre-established by the laboratory (0.83; 95% CI, 0.78-0.88) and also very good for troponin T (0.81; 95% CI, 0.75-0.87) using the cut-off points that were optimum on the ROC curve for prognosis calculated at 6 hours and at 12 hours (cTnT>0.1 ng/mL at 12 hours and cTnT>0.04 ng/mL at 6 hours) (Table 4).

Concordance with the pre-established laboratory limits for troponin T (>0.1 ng/mL) was poor for the measurements made at 6 hours, as 59% of the measurements that were positive at 12 hours were not positive at 6 hours (Kappa=0.57).

TABLE 4. **Concordance of measurements at 6 hours and at 12 hours**

	% 6 h	% 12 h	Kappa	95% CI
cTnT>0.1 ng/mL	29.2	49	0.57	0.49-0.65
cTnT>0.04 ng/mL	48.3	56.1	0.79	0.73-0.85
cTnT>0.1 ng/mL (12 h)				
cTnT>0.04 ng/mL (6 h)	48.3	49	0.81	0.75-0.87
CPK-MBm>5 ng/mL	48.3	54	0.83	0.78-0.88
CPK>400 UI/mL	4.4	15.8	0.39	0.24-0.54
Myoglobin>60 ng/mL	54	46	0.70	0.62-0.78

CTnT indicates cardiac troponin T; CI, confidence interval.

TABLE 5. **Relative risk of new episodes for each of the biochemical markers included in the model**

	RR (95% CI)	*P*
Myoglobin (60 ng/mL) 6 h	20.3 (2.4-168.5)	.001
Myoglobin (60 ng/mL) 12 h	6.6 (1.6-27.1)	.03
CPK-MBm (5 ng/mL) 6 h	11.3 (2.2-57.6)	.001
CPK-MBm (5 ng/mL) 12 h	25.4 (3.0- 208.3)	.0001
cTnT (0.1 ng/mL) 6 h	1.4 (0.2-7.8)	.12
cTnT (0.1 ng/mL) 12 h	30.7 (3.7- 252.5)	.0001
cTnT (0.04 ng/ml) 6 h	24.1 (2.9-200.8)	.0001

RR indicates relative risk; cTnT, cardiac troponin T; CI, confidence interval. Each measurement is included separately in a prognostic model that included the following independent variables: age of more than 70 years, pain and ECG changes, previous ischemic heart disease, and previous prolonged chest pain.

Multivariate analysis of the different biological markers

Multivariate logistical regression analysis was performed to correlate the variables from the first 6 hours and 12 hours with the cardiac episodes that developed later. The independent variables identified were age of more than 70 years (RR=1.61; *P*=.08), the presence of previous ischemic heart disease (RR=2.21; *P*=.01), previous prolonged chest pain (RR=2.44; *P*=.03), and pain with ST changes (RR=7.86; *P*=.001). The various biological markers were incorporated into this model in order to evaluate in what measure they provided prognostic value for a model that only contained clinical variables and ECG results available at the time of admission (Table 5).

TABLE 6. **Concordance between CPK-MBm and cTnT at 12 hours**

			cTnT>0.1 ng/mL		Total
			No	Yes	No. (%)
CPK-MBm>5 ng/dL	No	n (%)	144 (44.9)	4 (1.2)	148 (46.1)
	Yes	n (%)	17 (5.3)	156 (48.6)	173 (53.9)
Total		n (%)	161 (50.2)	160 (49.8)	321 (100)

Kappa=0.87; 95% CI, 0.82-0.92.

The markers were analyzed separately at 6 hours and 12 hours from the initiation of symptoms. The RR values as well as their CI were found to be very similar for CPK-MBm and troponin T once they were introduced separately into the model, so that their diagnostic value was very similar. The majority of patients with elevated troponin also had elevated CPK-MBm. Only 1.2% of patients (4) had a cTnT level over the level established by the laboratory without elevation of the CPK-MBm; of these, 2 patients (50%) had cardiac episodes. On the other hand, 5.3% (15 patients) had elevated CPK-MBm values without elevated troponin values. Of the 15 patients with increased CPK-MBm but without increased cTnT at 12 hours, only 1 (6.3%) had a cardiac episode, with a much better prognosis than the patients with an elevated cTnT and CPK-MBm at 12 hours (39.7%) (Table 6).

Model adjustment was shown to be greater in the model that included the measurement of troponin T with a cut-off value of 0.04 ng/mL at 6 hours after the beginning of chest pain (RR=24; *P*=.001) (Table 5).

DISCUSSION

Relationship with previous studies

Previous prognostic studies concerning the use of biological markers have not taken into account the amount of time elapsed from the time the chest pain began.[8-10] They are usually correlated with the amount of time elapsed from the time of admission to the emergency room. This method, although simpler to employ, causes the loss of the necessary information that should accompany a variable that changes as a function of time, such as biological marker. In an initial study, Hamm[9] correlated the absence of increased total CPK measured by enzyme activity (CPK>200 UI/L) plus an elevation in troponin T (>0.2 ng/L) in any sample taken after 6 hours from admission with the patient´s prognosis. The percentage of patients with unstable angina who had elevated troponin T was 39% in the Hamm series, while in our series this value reached 49%, probably because the positive value limit was 0.2 ng/L. For this last value, our patients had an elevated cTnT in 35.8% of cases, very similar to the series described.

Relationship between CPK mass and cTnT

The use of CPK measured as a mass and not as an activity level overcomes many of the limitations of the latter, gaining in sensitivity and specificity.[11] In our series, the sensitivity and specificity for prediction of episodes was very similar at 12 hours after the beginning of the chest pain, whether using CPK-MBm values or cTnT values; nevertheless, up to 5.3% of patients had elevated CPK-MBm without elevated cTnT, with a better prognosis than those with elevated cTnT and CPK-MBm; we attributed this discordance to false positive CPK-MBm values.

The limits that were pre-established by the laboratory for different measurements were based on the kinetics of liberation in patients with AMI in whom an increase in ST segment was detected.[8] The kinetics of liberation did not necessarily correspond with patients with acute coronary syndromes without ST segment increases. These patients are different in a physiopathological sense, so that it is less probable that a completely obstructed pericardial artery would be encountered as a cause of the AMI, with liberation of markers for necrosis, more rapidly and for less time than in those patients with an increase in ST and obstructed epicardial artery. The Cardiac Markers Cooperative Group[12] attempted to resolve the enzyme kinetics of the various markers and compare their sensitivity and specificity with those that are standard for an infarct located in a CPK mass greater than 7 ng/mL in some samples obtained. In 14.8% of cases the patients had elevated troponin T without elevated CPK-MBm; the prognosis for these patients was not evaluated. This study shares with our study the extraction of a sample related to the amount of time the chest pain has been evolving; nevertheless, later episodes experienced by these patients were not studied, so the prognostic information regarding these markers was lost.

It appears to be a fact that there are patients with elevated cTnT who do not have elevated CPK-MBm. We have not been able to confirm this greater sensitivity, which has been attributed to the fact that we extracted both samples at the same time and at least 6 hours after the last episode of chest pain, the moment at which both markers might have been elevated by the chest pain that led to the emergency room admis-

sion. The series by Lindahl et al,[13] Zimmerman et al,[12] Hamm et al,[9] Polanczyk et al,[10] and Antman[14] confirmed the existence of this discordance between the 2 markers, but they did not clarify the moment at which the discordance occurred and what the tendency was for troponin elevation that did not accompany an elevation of CPK-MBm. This may be related to the permanence in the blood of detectable values of cTnT caused by a recent infarct.

In our study, we correlated the values of the markers at 6 hours and 12 hours with later cardiac episodes in both a univariate and multivariate manner. For univariate analysis we chose troponin T as an early marker (at 6 hours), and we analyzed this same marker at 12 hours. Nevertheless, the point of greatest diagnostic value was not the same at 6 hours as at 12 hours, as at 6 hours a cTnT value that was the same as or greater than 0.04 ng/mL would be preferable, and at 12 hours a cTnT value higher than 0.1 ng/mL would be preferable. This is a finding that has not been described previously, as in other studies cTnT enzyme liberation either has not been correlated with patient prognosis, or the studies were performed without taking into account how long the chest pain had been present. Lindahl et al,[13] in their series that was part of the FRISC study, observed that patients with troponin levels lower that the limit established by the laboratory already had a worse prognosis. There were 5 groups or quintiles in the series, the second of which (troponin level greater than 0.06 ng/mL and less than 0.018 ng/mL) showed a difference when compared with the first group (troponin value less than 0.06 ng/mL) with regard to death and infarct 30 days later of 10.5% vs 4.3%, respectively (*P*=.02), indicating that values lower than the cut-off values may provide prognostic information.

CPK-MBm has a prognostic value that is very similar to than of troponin T, with the advantage of possibly being an even earlier marker,[15] with a greater number of patients having positive values at 6 hours post initiation of chest pain, at the pre-established laboratory level (5 ng/mL), although with a higher percentage of false positives. In the study by DeFilippi et al[16] the cTnT values were compared with the CPK-MBm values in simultaneous samples without the latter causing a significant change in the model when the cTnT value had already been included. cTnT was chosen for the final model as it possesses a superior prognostic value to CPK-MBm. When both markers were introduced into the logistical regression models in previous studies (cTnT y CPK MBm)[10,13,17] the amount of information shared by the 2 variables was such that the second to be put into the model had no independent value at all. In our study, a similar situation occurred with the measurements made at 12 hours post initiation of chest pain; in the model that included CPK-MBm, a value higher than 5 ng/mL carried with it an RR of 25.4 (*P*=.001). On the other hand, the model that included cTnT greater than 0.1 ng/mL carried with it a greater risk than the CPK-MBm value (RR=30.7; *P*=.001). Nevertheless, when we attempted to include both markers in the same model, neither of them was independent of the other.

With regard to the necessity for seriation of markers as a function of time, this does not appear to be justified as the concordance of positive values between the measurements taken at 6 hours and 12 hours for both CPK-MBm and cTnT is quite good, and does not provide greater prognostic information.

Usefulness of myoglobin in the chest pain unit

A myoglobin value of more than 60 ng/mL at the measurement taken at 6 hours had an independent prognostic value; nevertheless, there was poor concordance between the measurements taken at 6 hours and 12 hours, and the value thus lost its prognostic power on both univariate and multivariate analysis as we drew further away from the start of the chest pain. This behavior of myoglobin coincides with its kinetics of liberation, with a rapid increase and a wash-out that is also early. The narrow window of detection is useful to evaluate phenomena such as re-infarct, where a new increase in myoglobin could have quickly washed out the myoglobin from the first infarct. In our series, 83% of patient with a myoglobin value greater than the laboratory limit at 6 hours after the beginning of chest pain presented with a lower myoglobin level at 12 hours, suggesting that a re-elevation of myoglobin suggests the presence of a re-infarct.

Our study was limited by being an observational study in which the treating physicians were aware of the biochemical data. Although there were no specific actuation protocols with regard to biological markers, it was not considered ethical to hide the results of the biochemical tests, so that a skew could exist with regard to the classification of episodes as a function of the biochemical tests. Although the novelty of this study is the use of standardized markers at the moment symptoms begin, defining the amount of time the pain had been evolving with precision was not easy, as the perception of this value is subjective and its character often fluctuates.

In summary, chest pain without an increase in ST segment requires specific biochemical tests, performed at the moment the chest pain starts and at the very least at 6 hours after the initiation of symptoms. A single measurement of cTnT higher than 0.04 ng/mL at 6 hours from the initiation of chest pain appears to be an adequate marker, in conjunction with the clinical data and ECG, for the prediction of a patient´s prognosis in the emergency room.

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