Cardiac Troponin I in Perioperative Myocardial Infarction after Coronary Artery ByPass Surgery

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INTRODUCTION

Perioperative myocardial infarction (PMI) after coronary artery bypass graft surgery (CABG) is a serious complication and one of the most frequent causes of morbidity and mortality in these patients.1 The true incidence is unknown,2,3 although bibliographic references have cited figures of about

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Background and aims. Myocardial infarction after coronary artery bypass grafting is a serious complication and one of the most common causes of perioperative morbidity and mortality. The present study was designed to determine the relevance of serum cardiac troponin I as a specific diagnostic marker for perioperative myocardial infarction.

Methods. A cohort of 64 patients undergoing coronary artery bypass grafting was enrolled for prospective study. Postoperative blood samples were extracted and analyzed for total creatine kinase (CK), CKMB and cardiac troponin I activity. Perioperative infarction was defined as the development of new Q waves in the postoperative electrocardiogram together with congruent regional wall motion abnormalities in the echocardiogram and CK values greater than 400 IUL with MB fraction greater than 40 IUL.

Results. Perioperative infarction occurred in 12 patients. Higher cardiac troponin I values were observed in patients experiencing perioperative myocardial infarction than in those without infarction (P<.001). Cardiac troponin I values higher than 12 ng/ml 10 h after release of the aortic clamp best detected the presence of perioperative myocardial infarction, with an area under the characteristic receiver operating curve of 0.91 (95% CI, 0.82-0.97), a sensitivity of 90.9%, and a specificity of 88.5%.

The mean stay in the intensive care unit was significantly longer for patients who suffered perioperative myocardial infarction (6.5±8.6 days) than for patients without perioperative infarction (4.7±7.5 days) (P<.005).

Conclusions. Cardiac troponin I elevation appears to be an early, specific marker for the diagnosis of perioperative myocardial infarction after coronary artery bypass grafting.

Key words: Myocardial infarction. Cardiovascular diseases. Revascularization. Coronary artery bypass. Creatine kinase.

Troponina I cardiaca en el infarto de miocardio perioperatorio tras cirugía de revascularización coronaria

INTRODUCCIÓN

El infarto de miocardio perioperatorio tras cirugía de revascularización coronaria constituye una complicación grave y una de las causas más frecuentes de morbimortalidad. El objetivo de este estudio es determinar el poder de la troponina I cardiaca como marcador específico para su diagnóstico.

Métodos. En un estudio de cohortes prospectivo se incluyeron a 64 pacientes sometidos a revascularización coronaria. Se obtuvieron analíticas postoperatorias para determinar la actividad de la creatincinasa, su isoenzima MB y troponina I cardiaca. Se realizaron electrocardiogramas y ecocardiogramas, que se compararon con los preoperatorios.

Se definió al infarto perioperatorio como el desarrollo de nuevas ondas Q en el electrocardiograma con anomalidad de la motilidad segmentaria congruente en el ecocardiograma y elevación de la creatincinasa por encima de 400 UI/l con MB por encima de 40 UI/l.

Resultados. Doce pacientes sufrieron infarto perioperatorio. En todos ellos los valores de troponina I cardiaca resultaron superiores a los de los pacientes sin infarto (P<.001). En los pacientes con infarto perioperatorio los valores de troponina I cardiaca por encima de 12 ng/ml a las 10 h tras desclamping aórtico resultaron los más eficientes para su diagnóstico, con un área bajo la curva de 0,91 (intervalo de confianza [IC] del 95%, 0,82-0,97), sensibilidad del 90.9% y especificidad del 88.5%.

La estancia media en UCI fue significativamente más larga para los pacientes con infarto (6,5 ± 8,6 días) (p < 0,005).

Conclusions. La elevación de la troponina I cardiaca en el postoperatorio inmediato tras cirugía de revascularización coronaria constituye un marcador temprano y específico para el diagnóstico de infarto de miocardio perioperatorio.

10%-15%, with a percentage of false positives of 4%-8%. In a recent multicenter study, a large variation in the incidence of PMI has been found between different participating centers, with an approximate mean incidence of 19%.6

The main reason for these discrepancies is we do not have an easily applicable diagnostic gold standard for PMI at the bedside, unlike non-surgical acute myocardial infarction.7-10

Elevation of creatine kinase (CK) and its myocardial isoenzyme (CK-MB), as well as electrocardiographic disturbances, are frequent findings in the postoperative period of coronary artery bypass graft (CABG) surgery in the absence of myocardial damage.11 This confusion makes the diagnosis of this pathology difficult and has lead to the coining of terms like «possible» or «probable PMI» to classify patients with post-CABG infarction.12

Troponin I is one of the subunits of the tropomyosin complex. It has two isoforms in skeletal muscle and an isoform in heart, each one coded by a different gene and with structural differences detectable by immunoassay. Cardiac troponin I (cTnI) is highly specific of myocardial lesions, is detected quickly, and remains elevated for 7-10 days.13,14

Some studies report the usefulness of troponin I and T in the diagnosis of PMI as more specific serological markers15-23 with respect to classic markers, although experience is limited and large series are lacking.

The objective of this study is to evaluate the potential of cTnI in the diagnosis of PMI in patients who undergo CABG, as well as to determine the optimal extraction time and the cutoff values with the best performance.

METHODS

A study of prospective cohorts of patients undergoing scheduled CABG was designed, excluding emergency procedures and patients undergoing associated cardiac valve replacement or aneurysmectomy.

Sixty-four patients were recruited for inclusion in the study.

The following variables obtained in the preoperative period were analyzed: age and sex, cardiovascular risk factors (diabetes mellitus, arterial hypertension), previous heart surgery, presence of heart failure assessed according to the New York Heart Association (NYHA), acute myocardial infarction in the previous 3 months, as well as the hemodynamic and angiographic findings obtained in the preoperative echocardiogram and cardiac catheterization. Two classic indices of preoperative risk were also calculated24,25 (Table 1).

The surgical and anesthesia data are collected and analyzed in Table 2.

During the postoperative period, blood samples were obtained for the determination of myocardial enzymes (CK, CK-MB, and cTnI) 2 h, 6 h, 10 h, 14 h, 20 h, 26 h, 32 h, 38 h, 44 h, 50 h, and 56 h after aortic unclamping. Systematically, an electrocardiogram (ECG) was made at admission, 12 h, and 24 h of the stay in the intensive care unit (ICU), and whenever the clinical situation of the patient required it. All the ECGs were analyzed by the same observer (an experienced specialist in cardiological intensive care) and compared with the preoperative recording.

A transthoracic echocardiogram was made before discharge from the ICU according to the recommendations of the American Society of Echocardiography.26 In patients with a poor acoustic window, transesophageal echocardiography was
performed. All the studies were analyzed by a cardiology specialist who was an expert in echocardiography and they were compared with the preoperative echocardiogram.

The diagnosis of PMI was defined as a peak CK>400 IU/L with CK-MB>40 IU/L, together with the appearance in the ECG of a significant new Q wave according to the Minnesota criteria (≥30 ms and ≥0.1 mV in two or more contiguous leads). 27 and an echocardiographic image of disturbances in the segmental contractility in an area consistent with the ECG disturbances.

The intrahospital mortality was recorded.

**Laboratory analysis**

The total CK concentration was measured at 37°C using the Oliver method with N-acetylcysteine reactivation. CK-MB activity was determined by means of immunoassay using the Würzburg method. The enzymatic values considered normal with these methods are CK<180 IU/L and CK-MB<24 IU/L.

Cardiac TnI was determined by immunoassay with particles of chromium dioxide covered with monoclonal antibodies that recognize TnI molecules. The minimum detectable concentration of TnI using this method is <0.45 ng/mL. 28

**Anesthesia and surgical technique**

All patients were premedicated 1 h before surgery with morphine (0.1 mg/kg), scopolamine (0.2-0.4 mg/kg), and diazepam (0.1 mg/kg). Anesthesia was induced with fentanyl (10-25 µg/kg), diazepam (0.1-0.2 mg/kg) and pancuronium bromide (0.1 mg/kg). Anesthesia was maintained with supplements of the same drugs and low-dose isofluorane (0.6-1%). In all cases the ECG, invasive blood pressure (radial artery), central venous pressure, nasopharyngeal temperature, and diuresis were monitored continuously.

A bolus of sodium heparin (3-5 mg/kg) was administered before beginning extracorporeal circulation.

The surgical intervention was carried out by medial sternotomy with aortic and right atrial cannulation. Extracorporeal circulation was carried out by non-pulsatile flow (2.4±0.2 L/min/m²) and moderate systemic hypothermia (29°C). Cardiac arrest was induced by the infusion of cold cardioplegia solution, initially anterogradely and then every 30 min retrogradely.

**Statistical analysis**

The qualitative variables are presented with the distribution of frequencies and compared by means of the Chi-square or Fischer exact test. Quantitative variables were expressed as the mean and standard deviation and analyzed by the Student t test if they satisfied normality criteria for the variable in two categories. If not, the Mann-Whitney non-parametric test was used.

To study the evolution in time of the different TnI determinations, analysis of the variance of repeated measures was made (Manova).

ROC curves were prepared to determine the most sensitive and specific discriminatory point for the variables studied (CK, CK-MB, and cTnI), and compared by non-parametric tests. In every comparison of hypotheses, the null hypothesis with a type I or α error of 0.05 was rejected. The sensitivity, specificity, and likelihood ratios were calculated for a 95% confidence interval (CI).

Statistical analyses were made with the SPSS v.9.0 computer application.

**RESULTS**

**Demographic and clinical characteristics**

The study sample was constituted by 64 patients who underwent scheduled CABG. PMI was diagnosed in 12 patients (18.7%). The data collected in the preoperative period and during surgery are summarized in Tables 1 and 2.

The mean stay in the ICU was significantly longer for patients with PMI (6.5±8.6 days) than for patients without PMI (4.7±7.5 days) (P<.005). The overall mortality was 4.6%, or 3 patients, 2 of which pertained belonged to the group of patients with PMI, resulting in a mortality rate for this group of 16.6%. In both patients, the clinical cause of death was directly attributable to PMI.

**Biochemical results (Table 3)**

There were statistically significant differences (P<.001) between the TnI values in patients with and without PMI at any determination point (Figure 1).

The most efficient CK-MB values also appeared 10 h after aortic unclamping. At this point (10 h), cTnI>12 ng/mL resulted in a sensitivity of 90.9% (95% CI, 57.1-99.5) and a specificity of 88.5% (95% CI, 75.9-95.2), with a positive likelihood ratio of 7.88 (95% CI, 3.73-17.11), negative likelihood ratio of 0.10 (95% CI, 0.02-0.43), and an area under the curve of 0.91 (95% CI, 0.82-0.97) (Figure 2).

The most efficient CK-MB values also appeared 10 h after aortic unclamping, with a sensitivity of 72.2% (95% CI, 39.3-92.7), specificity of 90.4% (95% CI, 88.4-99.9), positive likelihood ratio of 37.81 (95% CI, 4.25-272.40), negative likelihood ratio of 0.27 (95% CI, 0.10-0.73), and area under the curve of 0.91 (95% CI, 0.81-0.97).
DISCUSSION

In an uncomplicated postoperative period after heart surgery, there are frequent nonspecific electrocardiographic disturbances with elevation of CK values and, occasionally, CK-MB, as a result of the surgical technique itself (cannulation of the right atrium, cardioplegia, prolonged surgery, etc). 29-31 This has made it difficult to apply the classic diagnostic criteria of acute myocardial infarction,32 so terms like probable or possible PMI have been coined. 12 In the case of limited PMI without newly acquired Q waves, the difficulty is greater and myocardial necrosis may be overlooked or overdiagnosed.

Similarly, the echocardiogram has demonstrated low specificity in this context, because of its scant ability to discriminate between zones of true necrosis and «stunned myocardium.»11 The performance of other, more complex, complementary tests could decrease the number of false positives, but they would complicate the bedside evaluation of the patient.33

Cardiac TnI is a highly specific marker of myocardial lesion, with the same or better sensitivity as CK-MB. Studies have already assigned a diagnostic value to it in this context. Several publications suggest that cTnI is more specific in the detection of PMI with respect to other more «classic» biochemical parameters, which would reduce false positives. The limits for the values and chronological sample extraction times for which the technique has the maximum diagnostic yield have not yet been well

TABLE 3. Sensitivity and specificity of different serological cutoff points

<table>
<thead>
<tr>
<th>Time from aortic unclamping</th>
<th>2 h</th>
<th>6 h</th>
<th>10 h</th>
<th>26 h</th>
<th>38 h</th>
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<tr>
<td>Cardiac troponin I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PMI (ng/mL)</td>
<td>&gt;6</td>
<td>&gt;11.6</td>
<td>&gt;12</td>
<td>&gt;17</td>
<td>&gt;11</td>
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<tr>
<td>Sensitivity (%)</td>
<td>75</td>
<td>90.9</td>
<td>90.9</td>
<td>72.7</td>
<td>81.8</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>80.8</td>
<td>88.5</td>
<td>88.5</td>
<td>94.2</td>
<td>90.4</td>
</tr>
<tr>
<td>Total CK</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMI (IU/L)</td>
<td>&gt;419</td>
<td>&gt;484</td>
<td>&gt;761</td>
<td>&gt;1100</td>
<td>&gt;1243</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>66.7</td>
<td>72.7</td>
<td>81.8</td>
<td>81.8</td>
<td>54.5</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>78.8</td>
<td>71.2</td>
<td>82.7</td>
<td>90.4</td>
<td>92.3</td>
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<td>CK-MB</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PMI (IU/L)</td>
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<td>&gt;50</td>
<td>&gt;103</td>
<td>&gt;70</td>
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<td>72.7</td>
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</tr>
<tr>
<td>Specificity (%)</td>
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<td>80.8</td>
<td>98.1</td>
<td>88.5</td>
<td>80.8</td>
</tr>
</tbody>
</table>

No. of patients=64. PMI indicates perioperative myocardial infarction; CK, creatine kinase; CK-MB, myocardial isoenzyme of creatine kinase.

Fig. 1. Variation in time of troponin I values after surgery in patients with and without perioperative myocardial infarction (PMI). CI indicates confidence interval.

Fig. 2. Comparative analysis of creatine kinase (CK) ROC curves, myocardial isoenzyme of CK (MB-CK) and cardiac troponin I (cTnI) in patients with perioperative myocardial infarction (PMI). A indicates area under the curve; CI: confidence interval.
In the study presented, cTnI was evaluated in the postoperative period of heart surgery by serial determinations. In the first 26 h after surgery, the cTnI values reached significantly greater postoperative levels at any determination point in the patients who were later diagnosed as perioperative myocardial infarction. Previous studies that have correlated peak cTnI levels with cardiac events have obtained findings similar to ours. 34

By analyzing the ROC curves, we obtained the determination point that was most efficient for the diagnosis of PMI, which appear in our series 10 h after aortic unclamping. Similar studies have assigned a diagnostic role to cTnI in PMI. In the studies in which cTnI was measured with the same immunoassay method, Bonnefoy et al 19 found a diagnostic cutoff point at cTnI $>$ 10 ng/mL 10 h after aortic unclamping, and Alyanakian et al 20 found a cutoff point $>$ 15 ng/mL. Gensini et al 21 cite cTnI $>$ 9.2 ng/mL at 12 h, and Sadony et al 22 propose cTnI $>$ 11.6 ng/mL at 24 h of aortic unclamping. Nevertheless, we cannot overlook that fact that different methods for measuring cTnI could result in lower diagnostic values, as in the case of the study by Mair et al, 16 or the study recently published by Carrier et al. 35 We should not forget the fact that the number of patients in our study was so small makes it likely that the cutoff points for cTnI will change in larger series.

CONCLUSION

To summarize, cTnI is a marker at least as early and as specific as CK-MB in the diagnosis of PMI during the postoperative period of heart surgery. The finding of cTnI $>$ 12 ng/mL 10 h after aortic unclamping in our study appeared to be the most efficient for the diagnosis of this pathology. Nevertheless, larger series to confirm or validate the cutoff points for this clinical applicability are necessary.

REFERENCES

23. Gensini GF, Fusi C, Conti AA. Cardiac troponin I and Q-wave