Cardiac Troponin-I Elevations After Thoracic Surgery. Incidence and Correlations With Baseline Clinical Characteristics, C-Reactive Protein, and Perioperative Parameters

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Introduction and objectives. The exact incidence of cardiac troponin-I elevation after thoracic surgery and its correlation with other clinical parameters has not been fully described. The aims of this study were to determine the frequency of postoperative cardiac troponin-I elevation following lung or pleural surgery for suspected cancer, and to investigate correlations with baseline clinical characteristics, the C-reactive protein level, and perioperative parameters.

Methods. Fifty consecutive patients were enrolled in the study. In each patient, the following parameters were measured: clinical characteristics and C-reactive protein level at baseline, cardiac troponin-I level on postoperative days 1, 3 and 5, and blood pressure, heart rate and ECG parameters every day from the day of the operation until postoperative day 5.

Results. The cardiac troponin-I level was elevated postoperatively in 20% of patients. There were significant associations with either a history of coronary artery disease or the presence of more than two coronary risk factors (80% vs. 32.5%; P=.011), a history of chronic antiplatelet therapy (50% vs. 17.5%; P=.046), pneumonectomy compared with less invasive procedures (40% vs. 10%; P=.041), pericardiectomy (30% vs. 2.5%; P=.022), and transient ST-segment alterations on perioperative ECGs (60% vs. 20%; P=.02). No significant correlation was found between cardiac troponin-I elevation and the baseline C-reactive protein level.

Conclusions. Cardiac troponin-I elevation occurs frequently after thoracic surgery and it is associated with clinical markers of coronary artery disease, extensive surgical procedures, and ischemic changes observed on perioperative ECGs.

Key words: Surgery. Troponin. C-reactive protein. Myocardial injury.

Elevaciones de la troponina I cardíaca tras la cirugía torácica. Incidencia y correlaciones con las características clínicas basales, la proteína C reactiva y los parámetros perioperatorios

Introducción y objetivos. La incidencia real de las elevaciones de la troponina I cardíaca tras la cirugía torácica y su correlación con otros parámetros clínicos no está plenamente definida. El objetivo de este estudio fue evaluar la frecuencia de las elevaciones postoperatorias de la troponina I cardíaca después de cirugía pulmonar o pleural por sospecha de cáncer e investigar las correlaciones con los perfiles clínicos basales, con la proteína C reactiva y los parámetros perioperatorios.

Métodos. Se registró a 50 pacientes consecutivos y se midieron los siguientes parámetros en cada paciente: variables clínicas basales y concentración de la proteína C reactiva, concentración de troponina I cardíaca en los días 1, 3 y 5 del postoperatorio, electrocardiograma, presión arterial, y frecuencia cardíaca diarias desde el día de la operación hasta el día 5 del postope- ratorio.

Resultados. Se produjeron elevaciones postoperatorias de la troponina I cardíaca en el 20% de los pacientes y éstas estaban significativamente asociadas con los antecedentes de coronariopatía o más de 2 factores de riesgo coronario (el 80 frente al 32.5%; p = 0,011), los antecedentes de tratamiento antiagregante plaquetario crónico (el 50 frente al 17.5%; p = 0,046), la neumonectomía comparada con los procedimientos menos invasivos (el 40 frente al 10%; p = 0,041), la pericardiectomía (el 30 frente al 2.5%; p = 0,022) y las modificaciones transitorias del segmento ST en el electrocardiograma perioperatorio (el 60 frente al 20%; p = 0,02). No se observó correlación significativa entre las elevaciones de la troponina I cardíaca y la proteína C reactiva basal.

Conclusiones. Las elevaciones de la troponina I cardíaca después de la cirugía torácica son frecuentes y están asociadas con marcadores clínicos de coronariopatía.
La cirugía quirúrgica extensa y cambios isquémicos en el electrocardiograma perioperatorio.


INTRODUCTION

Despite recent advances in risk stratification and prophylaxis, cardiac complications continue to develop after a significant number of noncardiac surgical procedures.1,2 In particular, the incidence of myocardial infarction during or after noncardiac surgery has a marked clinical impact and is predictive of a short-term and a long-term adverse prognosis.3,5

Most of the data on perioperative cardiac complications correspond to series of patients subjected to vascular surgery, a circumstance that may introduce a bias when these data are extrapolated to other surgical settings. Thoracic surgery has been found to be associated with a relatively low incidence of postoperative myocardial infarction.6,8 However, this type of infarction is difficult to detect, mainly due to the low prevalence of accompanying angina and the low sensitivity and specificity of the conventional diagnostic tools, such as electrocardiogram (ECG), and creatine kinase MB levels.2,9,10

There are no prospective studies that specifically measure cardiac troponin (cTn) I or T, which are recommended biochemical markers of myocardial lesions,11 during the period following thoracic surgery.

Strategies based on clinical algorithms and indices have been proposed in order to standardize the evaluation of preoperative risks and reduce the cardiac morbidity and mortality associated with noncardiac surgery.10 However, their efficacy for predicting the incidence of myocardial lesions following thoracic surgery has never been evaluated.

The pathophysiology of postoperative myocardial infarction differs somewhat from that of infarctions that occur outside the surgical setting since there are specific factors (cytokine release, sympathetic activation, hypercoagulability, or hemodynamic fluctuations) secondary to the surgery and to the reversal of the anesthesia, or related to the underlying disease, that can trigger the ischemic cascade.10

Inflammation plays an important role in the pathogenesis of atherosclerosis and thrombosis of the plaque.12 The C-reactive protein (CRP) concentrations independently predict the incidence of cardiovascular complications in a wide range of subjects, including those who are apparently healthy, patients with known atherosclerotic disease, candidates for surgical or percutaneous coronary revascularization, and renal transplant recipients.13-16 It could be postulated that preoperative activation of systemic inflammation, secondary to diseases related to the surgery or to a manifest or occult atherosclerosis, favors the incidence of episodes of postoperative myocardial damage. To the best of our knowledge, the relationship between the baseline CRP and postoperative myocardial damage, expressed as postoperative cTnI elevation (PCTIE), has never been evaluated in noncardiac surgery. Other perioperative variables that might correlate with PCTIE are: changes in the ECG and ischemic symptoms, duration and extension of the surgical procedure, and hemodynamic instability.

The objective of this study was, therefore, to evaluate the incidence of PCTIE in patients subjected to thoracic surgery and investigate whether PCTIE correlate with the baseline clinical features, the predictors of perioperative cardiac risk, CRP and the perioperative parameters.

METHODS

Patients

From May to December 2004, we recruited 50 consecutive patients who were scheduled to undergo major lung or pleural surgery (a foreseeable postoperative hospital stay of 5 or more days) at Hospital Universitario de S. Paolo in Milan, Italy. The protocol was approved by the hospital ethics committee, and written informed consent was obtained from all the patients.

The exclusion criteria were: age less than 18 years, decompensated heart failure and recent acute coronary syndrome (less than 30 days earlier).

Data Collection

A detailed clinical history was recorded for each patient. The risk factors included age (over 65 years), diabetes (insulin-dependent or non-insulin-dependent), hypertension (with drug therapy), hypercholesterolemia (treated with drugs or defined by a total cholesterol level over 200 mg/dL), renal failure (serum creatinine over 177 µmol/L), and coronary artery disease, which was defined as a history of myocardial infarction or...
angina, or angiographic evidence of significant coronary stenoses.

Preoperative cardiac medication was maintained until the morning of the surgery, and was resumed as soon as possible after the operation. Antiplatelet medication was discontinued 1 week before surgery. Adjuvant perioperative treatment with beta-blockers was administered according to the criteria of the anesthetist. If the hemoglobin fell below 8 g/dL, blood transfusions were administered during the postoperative period. All the patients underwent general anesthesia.

We recorded the surgical technique, the duration of the operation, any prolonged period (over 10 minutes) of perioperative hemodynamic instability (a variation of at least 30% from the baseline systolic pressure or 30% per minute from the baseline heart rate). Twelve-lead ECG was performed and the arterial blood pressure and heart rate were measured daily, prior to and after surgery (from the first to the fifth postoperative day, between 7 and 9 in the morning). The changes in ECG that were taken into account were: new-onset ST segment depression of 1 or more, new-onset ST segment elevation of 1 mV or more, changes in the T wave with respect to the baseline ECG, and abnormal Q-wave of new onset.

Blood samples for the measurement of CRP were collected at the time of hospital admission. Venous blood samples for cTnI measurements were obtained on postoperative days 1, 3, and 5, between 7 and 9 in the morning, on the assumption that each determination would permit the detection of any myocardial lesion that had developed over the preceding 48 hours. Given the clinical stability of the participating population, it was assumed that the baseline cTnI concentrations were not elevated. The serum samples for the measurements of CRP and cTnI were immediately centrifuged at 2000 g for 15 minutes and stored at –80°C until the end of the study, at which time they were all analyzed.

The CRP was determined by means of nephelometry using a highly sensitive commercially available assessment system (Cardiophase® hsCRP, Dade Behring Marburg GmbH, Marburg, Germany). The upper limit for a normal CRP level recommended by the manufacturer was 3 mg/L, with a coefficient of variation of less than 10%.

To measure cTnI, we used Access AccuTnI (Beckman Coulter, Inc, Fullerton, California, United States), a commercially available, second generation method. The cTnI concentration was considered to be elevated when it surpassed the predefined cut-off point of 0.06 µg/L. This is the upper reference limit for the 99th percentile in a reference population, with a coefficient of variation of less than 10%.

The medical team in charge of the perioperative management was not informed of the determinations of the study nor the results, and was free to request supplementary preoperative diagnostic tests and/or coronary revascularization, as well as additional evaluation of the clinical status, ECG or cardiac-specific markers if symptoms of acute coronary syndrome, heart failure, or arrhythmias developed. Clinical myocardial infarction was diagnosed by the same medical team, independently of the present study, in agreement with the current guidelines of the joint European Society of Cardiology and the American College of Cardiology (ACC) committee for the redefinition of myocardial infarction.11

As has been pointed out above, our study did not involve continuous electrocardiographic monitoring throughout the entire perioperative period. Thus, it could be that certain asymptomatic changes in the ECG might have gone undetected.

Due to this limitation and to the low sensitivity and specificity of the perioperative electrocardiographic changes, isolated ischemic changes in the ECG were not considered to be complications in the statistical analysis.

The baseline cardiac risk profiles of the patients were also stratified according to the guidelines of the ACC/American Heart Association (AHA) for preoperative cardiovascular evaluation and the revised cardiac risk index by Lee et al.1,2,17

We also evaluated the hypothesis that an easily obtained clinical marker of coronary atherosclerotic disease, whether documented or probable (history of coronary artery disease or more than 2 coronary risk factors) could correlate with PCTIE.

Most of the clinical parameters employed in our analysis were taken from the thrombolysis in myocardial infarction (TIMI) risk score for unstable angina or non-ST elevation myocardial infarction.18

Statistical Analysis

The continuous variables were expressed as the mean and standard deviation (SD) when they presented a normal distribution and as the median and range when the distribution was not normal. The Kolmogorov-Smirnov test was utilized to evaluate the normal distribution.

The categorical data were expressed as percentages.

The major analysis in this study was a dichotomous comparison of patients with or without PCTIE. The continuous variables were compared using Student’s t test or the Mann-Whitney U test, when appropriate, and the categorical variables were compared with χ² or Fisher’s exact test. All the tests were 2-sided and a P value equal to .05 was considered to indicate statistical significance.

RESULTS

Ten (20%) of the participating patients presented PCTIE (range, 0.07-0.53 µg/L), detected on the first postoperative
day in 6 (60%), on day 3 in 3 (30%), and on day 5 in 1 (10%). There were no deaths, nor did the medical team diagnose any cases of myocardial infarction during the period of observation or the hospital stay.

Table 1 shows the demographic and clinical data classified according to the presence or absence of PCTIE. The prevalence of patients with stable coronary artery disease or with multiple coronary risk factors was considerable, but no patient had a history of heart failure or severe valve disease.

Of the preoperative variables studied, only a history of coronary artery disease or more than 2 coronary risk factors and chronic antiplatelet therapy were found to have a significant correlation with the presence of PCTIE ($P=.01$ and $P=.046$, respectively).

No significant correlation was observed between PCTIE and baseline CRP.

None of the patients underwent left or right posterolateral thoracotomy. The details of the operations appear in Table 2. None of the patients received beta-blockers during or immediately after surgery. Two patients had to be reintubated and admitted to the postoperative intensive care unit due to respiratory insufficiency. Twenty percent of the patients required blood transfusions during the postoperative period.

None of the patients with PCTIE complained of angina pectoris, nor were significant differences observed between those who presented PCTIE and those who did not in terms of the incidence of prolonged hemodynamic instability during the perioperative period (Table 3).

A more invasive surgical approach was significantly associated with PCTIE (pneumonectomy vs less extensive procedures, $P=.041$; pericardiotomy vs the absence of pericardiotomy, $P=.02$). A significant relationship was observed between transient ST-segment changes and PCTIE ($P=.02$), but none of the patients developed Q waves or any other permanent ECG changes.
The major finding of this study was the notable incidence (20%) of myocardial damage during the perioperative period, evaluated on the basis of PCTIE, in patients undergoing elective lung or pleural surgery. This rate is higher than that found in other series involving thoracic surgery (less than 5%) or that reported in the current ACC/AHA guidelines, and is equivalent to the incidence normally attributed to vascular surgery.\textsuperscript{1-4,6-8}

The differences in the incidence of myocardial lesions observed from one surgical series to another could be the result of methodological differences, such as the heterogeneity in the diagnostic criteria utilized and the limited accuracy of the tools usually employed to define perioperative myocardial infarction in the pre-troponin era. The relatively high incidence of PCTIE in our study may be secondary to the low cTnI threshold value utilized, the cut-off point of which is lower than that usually employed for myocardial infarction. However, even minor PCTIE reflect myocardial damage, and it has been shown that they predict a poorer postoperative outcome.\textsuperscript{3-5}

Moreover, previous studies have not systematically assessed either the cTnI or the cTnT status during the entire critical period following thoracic surgery; thus, some asymptomatic episodes of myocardial lesions have probably gone undetected.\textsuperscript{6-8}

Most of the PCTIE in our study occurred on the first postoperative day, but the period of vulnerability was longer, a circumstance that lends support to the indications on the part of the ACC/AHA that those patients at risk for perioperative myocardial infarction be supervised for more than 48 hours after surgery.\textsuperscript{1,2}

A number of studies\textsuperscript{1,2,9,10} have pointed out the subtle nature of the perioperative myocardial lesion, and our series has confirmed it: in fact, the attending physicians, who were not informed of the results of our study, did not diagnose a single case of myocardial infarction.

Given the absence of angina and of persistent electrocardiographic changes, the transient changes observed by the medical team in the routine and supplementary ECG were not considered to be of ischemic nature or to require additional studies, such as cTnI determinations or echocardiogram.

It is a well known fact that beta-blockers, which prevent cardiac morbidity during the perioperative period in high-risk surgical patients, are underutilized at the present time,\textsuperscript{19,20} probably because of the fear of the specific collateral effects of these drugs. The lack of beta-blockers during the perioperative period could have had an unfavorable effect on the frequency of PCTIE in our series.

The results of the present study indicate that a simple strategy, based on a detailed clinical history, physical examination, and interpretation of the ECG, can help to predict the risk of postoperative myocardial damage in patients who are to undergo thoracic surgery.

In fact, an index that is easy to calculate (a history of coronary artery disease or more than 2 coronary risk factors) and a history of chronic antiplatelet therapy,
which is usually administered to vascular patients, helped to identify those subjects with a higher probability of developing PCTIE. The antiplatelet therapy was discontinued prior to surgery due to the risk of the hemorrhages associated with it and to the lack of data that support its use to reduce perioperative cardiovascular complications.21

It has been pointed out that the sudden withdrawal of aspirin prior to surgical procedures may increase cardiovascular morbidity and mortality.22 Thus, the association between the antiplatelet therapy and the PCTIE observed in our study may be explained in part by the discontinuation of the treatment itself. PCTIE have also been shown to correlate with deviations of the ST segment in the perioperative ECG.

It should be taken into account that all these variables (coronary artery disease, more than 2 coronary risk factors, previous antiplatelet therapy, ST segment deviation) are independent and well-validated predictors of a poorer clinical outcome in patients admitted due to acute coronary syndrome.18

In contrast, the clinical variables predictive of risk according to the ACC/AHA and the Lee cardiac risk index did not correlate significantly with the PCTIE. These findings do not coincide with the results of previous works that demonstrated the efficacy of these indices for the prediction of cardiovascular complications in patients undergoing noncardiac surgery.23,24 This discrepancy could depend on the different types of surgery (thoracic versus vascular surgery in most of the previous studies) and on the clinical outcomes considered (asymptomatic PCTIE vs clinically manifest events).

The present study reveals no significant correlation between the PCTIE and hemodynamic instability during the perioperative period, a circumstance that can change the balance between the needs and the delivery of myocardial oxygen. McFalls et al25 demonstrated that preventive coronary revascularization prior to major elective vascular surgery in clinically stable patients has no positive influence on the incidence of postoperative myocardial infarctions, defined by increases in cTnI. Together, these data support the hypothesis that mechanisms other than epicardial stenosis that limit the flow (for example, epicardial artery spasm, microvascular obstruction, thrombosis of vulnerable coronary plaques) could participate in the pathogenesis of perioperative myocardial damage.

Inflammation plays a central role in coronary artery disease, and increases in CRP predict coronary events in apparently healthy individuals.12,13 Systemic inflammatory activation originates in the atherosclerotic vessels,26 but there are data that indicate that, in addition to being a marker of atherosclerosis, systemic inflammation might itself promote it.12,13 Treatment with statins reduces perioperative cardiac complications in patients who undergo vascular surgery.27 In addition to reducing the serum cholesterol concentration, the antiinflammatory effect of statins may stabilize the atherosclerotic plaques.

These indirect tests further support the role of inflammation in the pathogenesis of postoperative myocardial lesions. Data from recent studies indicate that the preoperative serum CRP concentrations can predict the prognosis in patients undergoing cancer surgery,28,29 but the correlation between the baseline CRP and PCTIE in thoracic surgery had never been studied. Assuming that a proinflammatory state can produce PCTIE in a critical and stressful situation like the perioperative period, we evaluated the correlation between the baseline CRP and PCTIE in patients with possible extravascular inflammatory foci and a high prevalence of coronary artery disease or coronary risk factors.

The lack of statistically significant correlation between CRP and PCTIE could be due to the small sample size and to the wide dispersion of the CRP concentrations, which may have masked its predictive power.

Despite the low degree of surgical stress expected because of the short mean duration of the operations performed in the present study, PCTIE correlated significantly with more invasive surgical techniques, such as pneumonectomy or associated pericardiectomy, in comparison with less extensive surgical approaches. This finding indicates that local trauma and the metabolic pathways activated by the operation may play a role in the incidence of myocardial damage following thoracic surgery.

Limitations

The findings of this study do not provide a temporal relationship between PCTIE and the surgical intervention, and the statistically significant correlations can not establish a causal relationship.

The small sample size limits the power of this study and impedes the formulation of generalizations based on the clinical findings. However, the study design itself, which involved the detection of several parameters and the plasma cTnI concentration over a relatively long period, made it difficult to recruit a larger series of patients.

In some cases, the PCTIE may have reflected the preoperative cTnI concentrations, rather than be the result of the procedure. Unfortunately, as the baseline cTnI was not determined, this possibility cannot be completely ruled out.

On the other hand, it should be pointed out that all the patients presented stable cardiac function prior to surgery. This fact, together with the relatively low prevalence (22%) of diabetes (which can be associated with clinically silent coronary events), makes the presence of undetected preoperative elevations in cTnI improbable.

In this study, we have considered cTnI elevations to be secondary to ischemic injury. However, the release of
cTnI observed in patients undergoing pneumonectomy or pericardiectomy could be regulated by mechanisms other than myocardial ischemia: the extension of the inflammatory process to the surface layers of the myocardium, caused by pericardial manipulation, and an increase in right ventricular afterload, which can complicate pneumonectomy. Moreover, given the low sensitivity and specificity of ECG and the infrequency of ischemia-related symptoms in the perioperative setting,1,2,9 the current criteria for the diagnosis of myocardial infarction11 are rarely applicable in surgical patients.

Our findings, however, coincide with the study of Landesberg et al involving a series of patients undergoing vascular surgery31 that showed a significant correlation between ST segment depression in continuous electrocardiographic monitoring during the postoperative period and the PCTIE. This suggest that the perioperative myocardial lesion is secondary to prolonged episodes of myocardial ischemia.

Despite the accuracy of data collection over a relatively long postoperative period, hemodynamic and electrocardiographic monitoring were not continuous. As a result, transient asymptomatic hemodynamic fluctuations or electrocardiographic changes of the same nature can not be ruled out. Given the frequency of blood sampling to determine cTnI concentrations, it was not possible to evaluate the significance of the myocardial damage on the basis of the changes in the slope of the cardiac biomarker curve. The estimation of a gradient of risk based on the magnitude of the PCTIE, however, was not among the evaluation criteria employed in the present study, and the frequency of the postoperative cTnI measurements was greater than that proposed in the current AHA/ACC guidelines.1,2 Perioperative elevations of cTnI have been shown to predict short-term and long-term clinical events.3,5 Our study is clearly not designed to evaluate this point; to begin with, it does not include clinical follow-up. Thus, we consider it necessary to assess the prognostic power of cTnI elevations following thoracic surgery.

In this report, there could be a number of confounding factors that would interfere with the predictive power of PCTIE, such as the uncertain etiology of the myocardial damage and the presence of other prognostic determinants, mainly related to cancer, which can obscure the role of the variables predictive of cardiovascular risk.

**CONCLUSIONS**

Although the results of the present study are not conclusive, they show that thoracic surgery is associated with a significant incidence of PCTIE, and that these elevations are associated with clinical markers of coronary artery disease, extensive surgical procedures and ischemic changes in the perioperative ECG, but not with baseline CRP concentrations or prolonged hemodynamic fluctuations.

Prospective studies on a wider scale will be required to confirm our results and evaluate specifically the predictive power of elevations of cTn following thoracic surgery.

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