Cardiac Troponin T in Chest Pain Unit Patients Without Ischemic Electrocardiographic Changes: Angiographic Correlates and Long-Term Clinical Outcomes

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OBJECTIVES

We prospectively evaluated the relation between cardiac troponin T (cTnT) level, the presence and severity of coronary artery disease (CAD) and long-term prognosis in patients with chest pain but no ischemic electrocardiographic (ECG) changes who had short-term observation.

BACKGROUND

Cardiac TnT is a powerful predictor of future myocardial infarction (MI) and death in patients with ECG evidence of an acute coronary syndrome. However, for patients with chest pain with normal ECGs, it has not been determined whether cTnT elevation is predictive of CAD and a poor long-term prognosis.

METHODS

In 414 consecutive patients with no ischemic ECG changes who were triaged to a chest pain unit, cTnT and creatine kinase, MB fraction (CK-MB) were evaluated $10 \text{ h after symptom onset.}$ Patients with adverse cardiac events, including death, MI, unstable angina and heart failure were followed for as long as one year.

RESULTS

A positive (>0.1 ng/ml) cTnT test was detected in 37 patients (8.9%). Coronary artery disease was found in 90% of 30 cTnT-positive patients versus 23% of 144 cTnT-negative patients who underwent angiography ($p<0.001$), with multivessel disease in 63% versus 13% ($p<0.001$). The cTnT-positive patients had a significantly ($p<0.05$) higher percent diameter stenosis and a greater frequency of calcified, complex and occlusive lesions. Follow-up was available in 405 patients (98%). By one year, 59 patients (14.6%) had adverse cardiac events. The cumulative adverse event rate was 32.4% in cTnT-positive patients versus 12.8% in cTnT-negative patients ($p=0.001$). After adjustment for baseline clinical characteristics, positive cTnT was a stronger predictor of events (chi-square $=23.56$, $p=0.0003$) than positive CK-MB (>5 ng/ml) (chi-square $=21.08$, $p=0.0008$). In a model including both biochemical markers, CK-MB added no predictive information as compared with cTnT alone (chi-square $=23.57$, $p=0.0006$).

CONCLUSIONS

In a group of patients with chest pain anticipated to have a low prevalence of CAD and a good prognosis, cTnT identifies a subgroup with a high prevalence of extensive and complex CAD and increased risk for long-term adverse outcomes. (J Am Coll Cardiol 2000;35:1827–34) © 2000 by the American College of Cardiology

Previous studies have convincingly demonstrated that in patients with chest pain, ischemic electrocardiographic (ECG) changes and a high clinical suspicion of an acute coronary syndrome (ACS) (e.g., myocardial infarction [MI] or unstable angina [UA]), cardiac troponins T (cTnT) and I (cTnI) are powerful independent predictors of MI or death during follow-up (1–6). However, many of the five million people with chest pain who present each year to the emergency department (ED) in U.S. hospitals have normal or nondiagnostic ECGs (7–9). Indeed, the frequency of ECG changes indicative of ischemia or infarction in a large population with acute chest pain evaluated in the ED was reported to be only 26% (8). Therefore, the diagnosis of acute MI or ischemia based on presenting symptoms and the ECG is often challenging. Consequently, as many as two-thirds of patients with chest pain are admitted from the ED for “rule-out MI evaluation” or referred for short-term
observation in specialized chest pain units (CPUs) (10,11). Only a minority of these patients without ischemic ECG changes are ultimately diagnosed with ischemic heart disease (9,12–14), and, typically, <7% are diagnosed with MI on the basis of cardiac enzymes (15). These patients generally have excellent short- and long-term prognoses (14,16,17). However, those who have elevated creatine kinase (CK), and CK-MB fraction (CK-MB) levels are at increased risk for recurrent ischemia, MI and death (8,16,18).

Although cardiac troponin levels are often measured in this setting, to our knowledge there are no published studies addressing their long-term prognostic value in patients with chest pain but no ECG evidence of acute myocardial ischemia. In addition, no data are available on the relation between troponin levels and the prevalence and severity of coronary artery disease (CAD) in such a population.

This prospective study was undertaken in patients with chest pain but no ischemic ECG changes who were triaged to a CPU with the following aims: 1) to assess the incidence of cTnT elevation; 2) to describe coronary angiographic features in relation to cTnT levels; and 3) to evaluate the additional prognostic value yielded by cTnT over CK-MB and traditional clinical risk factors for predicting long-term adverse cardiac events.

**METHODS**

**Study patients.** The study group consisted of 414 consecutive patients referred to the CPU from January 1996 through February 1997 at the University of Texas Medical Branch at Galveston, a 938-bed, tertiary health care facility. For acceptance to the CPU, the patient was required to have <7% probability of an acute MI, as determined by the algorithm developed by Goldman et al. (15). This required the absence of new ST segment or T wave changes diagnostic or suggestive of myocardial injury or ischemia. Patients with ECG confounders (left bundle branch block or ventricular paced rhythm) were excluded because they had been shown to be at high risk for in-hospital ischemic complications (1,3). Additional exclusion criteria included systolic blood pressure >200 mm Hg or <90 mm Hg; three or more beats of ventricular tachycardia; evidence of heart failure; febrile illness; or any comorbid disorder that would prolong the patient’s hospital stay beyond a 23-h observation period. The study protocol was approved by the Institutional Review Board of the University of Texas Medical Branch at Galveston.

**Clinical and ECG data collection.** Data regarding the quality, duration and frequency of chest pain, as well as clinical risk factors, were collected in a prospective, standardized manner. On serial ECGs recorded before diagnostic biochemical testing, new ST segment elevation ≥0.2 mV in the precordial leads or ≥0.1 mV in the limb leads and ST segment depression ≥0.1 mV or T wave inversion were exclusion criteria. All ECGs were interpreted independently by two attending cardiologists who had no knowledge of the cardiac marker results. A discrepancy between readers resulted in exclusion of the patient from the study.

**Biochemical markers of myocardial injury.** All patients had a visually interpreted qualitative Cardiac T Rapid Assay (Roche Diagnostics, Indianapolis, Indiana), quantitative cTnT (ES-300 Instrument, Roche Diagnostics), total CK activity and CK-MB mass (Stratus II Instrument, Dade, Miami, Florida) drawn simultaneously at ≥10 h after the onset of chest pain or ≥10 h after presentation if the time of symptom onset was uncertain. The CK, CK-MB and cTnT rapid assay results were available for clinical decision-making. The qualitative cTnT rapid assay has a lower limit of detection (0.18 to 0.2 ng/ml), as described by the manufacturer and published elsewhere (19). The quantitative cTnT results were determined using the ES-300 instrument and Cardiac-T ELISA Troponin T reagents. Initially, when this study was conceived, an abnormal quantitative cTnT value was considered to be >0.2 ng/ml (6). On the basis of data published during the enrollment period (3), a quantitative cTnT value >0.1 ng/ml was considered positive in this study. The 200 patients studied after July 1996 also had cTnT values reported using the Enzymun-Test second-generation assay (Enzymun assay) run on the ES-300 instrument. There were no individual discrepancies between the two assays that crossed over the cutoff of 0.1 ng/ml. Because of the higher discriminator value of the qualitative cTnT rapid assay, all results reported in this study are based on quantitative cTnT ELISA assay results. A CK-MB mass >5 ng/ml was considered positive.

**Coronary angiography.** All patients with a positive cTnT rapid assay (n = 22) or CK-MB (n = 23) were referred for coronary angiography. In addition, a large cohort (n = 150) with a negative cTnT test underwent angiography for the following reasons: 1) randomization to immediate cardiac catheterization, as part of a long-term resource utilization protocol (n = 99) (14); and 2) clinical indications for angiography, including positive noninvasive stress test (n = 25), a known history of MI or CAD (n = 20) and physician’s discretion (n = 6).
Cine angiographic films were analyzed independently by two experienced operators who had no knowledge of the patients' clinical information, cTnT and CK-MB values. Differences were mediated by consensus. All diameter stenoses visually estimated as ≥50% underwent quantitative coronary analysis performed with a digital caliper by one observer (Mitutoyo Corp., Tokyo, Japan). The accuracy of this method has been validated previously and compares well with computerized methods (20). Based on 40 randomly selected coronary segments in eight patients, the intraobserver intraclass correlation coefficient was 0.98 (95% confidence interval [CI] 0.97 to 0.99) and the interobserver intraclass correlation coefficient was 0.99 (95% CI 0.99 to 1.0) for caliper measurements in our laboratory.

The lesions were assessed in two orthogonal views that had the least vessel overlap and foreshortening using end-diastolic frames, and the projection showing the smallest lumen diameter was selected for measurements. The mean of three measurements of minimal lumen diameter and angiographically normal reference diameters proximal and distal to the lesion were used to calculate the percent diameter stenosis. Significant CAD was defined as ≥70% lumen narrowing of a major epicardial artery or its branches. In classifying the number of diseased vessels, a left main stenosis ≥50% was regarded as equivalent to two-vessel disease. Stenosis location was evaluated by utilizing a simplified coronary tree scheme, as previously described (21). Lesion length was measured as the distance from the proximal to the distal lesion shoulder. Complex lesion morphology was defined as any significant stenosis with overhanging edges or irregular borders, including lesion ulceration or severe, diffuse irregularities. Intraluminal thrombus was defined as a filling defect, usually globular in shape, with surrounding homogeneous contrast opacification in three or more sides and identification in multiple views (22).

Follow-up and adverse cardiac events definition. Patients were followed up for a minimum of six months by telephone interviews. Adverse events were defined as follows: 1) death from any cause; 2) cardiac death, defined as sudden, unexplained death or death related to MI, heart failure or arrhythmia without a secondary cause; 3) nonfatal MI, defined as chest pain associated with a positive CK-MB test with return to a normal value; and 4) the need for hospital admission owing to UA (rest or accelerating chest pain associated with CAD determined by either angiography, a positive noninvasive stress test or new ST-T wave changes on the ECG) or heart failure (signs or symptoms of congestion believed to be secondary to cardiac dysfunction). The diagnosis and hospital periods were also evaluated by review of the hospital records, when available.

Statistical analysis. Continuous variables are expressed as the mean value ± SD. The Student t test and the chi-square test with Yates’ correction were used to compare differences between groups for continuous and categoric data, respectively. Survival and freedom from adverse events were estimated using life-table survival techniques and compared using the log-rank test.

Cox proportional hazard modeling was used to examine individual and joint relations between clinical and biochemical variables and the binary outcome (cumulative adverse cardiac events at one year). The proportional hazards assumption was verified by excluding a crossover between survival curves for each binary variable. Conformity to the assumption of a linear gradient for continuous or ranked variables was graphically examined by plotting the observed and predicted values for the outcome over the range of each predictor. We found no significant change in the odds ratios over time. Therefore, analyses include outcomes over the entire duration of follow-up. Given the limited number of events, only the significant univariate correlates were entered into the multivariate analyses to minimize the risk of model overfitting. The predictive ability of multivariate models was expressed through the likelihood ratio chi-square value. The incremental prognostic information yielded by cTnT and CK-MB over clinical variables was assessed by the change in the chi-square obtained by adding each biochemical variable to a clinical model. The stability of the risk estimates was internally verified through bootstrap procedures. For all tests, a two-sided p value < 0.05 was regarded as significant. Computations were performed using the Statistica, version 5.1 (StatSoft Inc.) software package.

RESULTS

Clinical characteristics. Of the 414 study patients, cTnT was positive in 37 (8.9%) (0.89 ± 0.99 ng/ml, median 0.48 ng/ml) and negative in 377 (91.1%). Their clinical characteristics are compared in Table 1. Patients with positive cTnT tests were significantly older and more frequently male, had a higher incidence of diabetes and more frequently presented with typical chest pain.

Coronary angiographic findings. Among the 37 cTnT-positive patients, 32 underwent coronary angiography. Of the five patients who did not, four had a negative cTnT rapid assay and CK-MB, and one patient refused. Two of 32 patients had previous coronary artery bypass graft surgery with native three-vessel disease and were excluded from the angiographic analysis. Of the remaining 30 patients, 27 (90%) had significant CAD, 19 of whom (63%) had multivessel disease. Only three patients did not show ≥70% coronary stenoses. Two of these patients had two-vessel stenoses of 40% to 60%, no regional wall motion abnormalities and a positive CK-MB test that subsequently returned to normal, suggesting myocardial injury. The other patient had no angiographic evidence of CAD and no regional wall motion abnormalities, but had end-stage renal disease and continued to have a persistently elevated CK-MB level.

Among the 377 cTnT-negative patients, 150 underwent coronary angiography. Of these, six had previous bypass surgery and were excluded from the angiographic analysis.
Of the remaining 144 patients, 33 (23%) had significant CAD, 19 of whom (13%) had multivessel disease.

Table 2 compares the angiographic findings of the 30 cTnT-positive patients with those of the overall group of 144 cTnT-negative patients and with a subgroup of 99 patients with negative cTnT test who were randomly assigned to angiography (as outlined in Methods). The prevalence and extent of CAD were significantly greater in patients with a positive cTnT test than in those with a negative cTnT test, either in the overall group or the subgroup randomized to coronary angiography.

As shown in Table 3, cTnT-positive patients had a significantly higher percent diameter stenosis and a greater frequency of calcified lesions, occlusive lesions and stenoses with a complex morphology. Intracoronary thrombus was not identified in any of our patients.

**Patient outcomes.** During the initial hospital period, there were no deaths; coronary revascularization was performed in 16 (43%) of 37 cTnT-positive patients versus 11 (3%) of 377 cTnT-negative patients (p < 0.001). Long-term follow-up (mean 11 ± 3.7 months) was obtained in 405 (98%) of 414 patients, including all cTnT-positive and 368 cTnT-negative patients. Overall, there were 59 (14.6%) adverse cardiac events, including 2 deaths (0.5%), 5 MIs (1.2%) and 52 hospital admissions for UA (n = 46, 11.3%) or heart failure (n = 6, 1.5%). One patient died of noncardiac causes (suicide).

Figure 1 illustrates the incidence and time distribution of adverse events in patients with a positive or negative cTnT test. The life-table survival plot shows separation of the curves after one month and a difference in events that modestly widened throughout the course of one year. Freedom from any adverse event at 12 months was 66% in cTnT-positive versus 87% in cTnT-negative patients (p = 0.0004). Freedom from cardiac death or MI was 95% in cTnT-positive versus 99% in cTnT-negative patients (p = 0.03).

Figure 2 illustrates the relations between cTnT and CK-MB results and the occurrence of long-term adverse events. For the 368 cTnT-negative patients, the concordance with negative simultaneous CK-MB was high (99%). However, only 54% of the patients with a positive cTnT test had a simultaneous positive CK-MB test. The cumulative adverse event rate in cTnT-positive patients was 32.4% (12 of 37 patients), significantly higher (p = 0.001) than that of 12.8% (47 of 368) in cTnT-negative patients. The 30% (7 of...
23 patients) event rate in CK-MB-positive patients was higher, with a trend toward statistical significance (p = 0.055), than that of 13.6% (52 of 382) in patients with a negative CK-MB test.

**Predictors of adverse events.** Univariate Cox regression models were estimated for each of the clinical variables listed in Table 1. Four had a significant correlation with the occurrence of adverse events within one year of initial presentation: age ≥65 years, hypertension, diabetes and a history of MI. These four variables, as predictors of adverse events, formed our clinical model.

The prognostic impact of biochemical markers was tested by estimating four multivariate Cox regression models that included our significant clinical variables. The four multivariate models are listed in Table 4. The first model, the clinical model, is a significant predictor of adverse events at one year (likelihood ratio chi-square = 18.49, p = 0.001). The addition of the CK-MB result (positive or negative) to the clinical model showed a statistically significant joint association with the five variables (p = 0.0008), but the increase in predictive ability in the clinical model was not significant (change in chi-square: 21.08 - 18.49 = 2.59, p = 0.11). When the cTnT result (positive or negative) was added to the clinical model, its contribution to risk stratification was statistically significant (change in chi-square = 5.07, p = 0.024). Furthermore, a positive cTnT test was a significant predictor of risk in this model (odds ratio [OR] 2.28, 95% CI 1.17 to 4.46; p = 0.02). Finally, when both...
biochemical markers were added to the clinical model, the chi-square increase from the model with cTnT alone was trivial (change in chi-square = 0.01, \( p = 0.92 \)), indicating that CK-MB provides no additional information. Figure 3 shows the individual ORs and 95% CIs from the multivariate model, including clinical predictors and cTnT results.

In a subgroup analysis of patients with a negative CK-MB test, the combination of clinical predictors and cTnT results maintained a significant explanatory power (chi-square = 18.09, \( p = 0.0029 \)). In this model, a positive cTnT test was the only significant predictor of adverse events (OR 2.53, 95% CI 1.04 to 6.16; \( p = 0.04 \)).

### DISCUSSION

To our knowledge, this study is the first to demonstrate that in patients with chest pain but no ischemic ECG changes, cTnT measurement provides better clinical and long-term prognostic information than traditional clinical and biochemical markers. First, in a group with an anticipated low prevalence of ischemic heart disease, cTnT elevation identifies a group with severe and diffuse CAD and angiographically complex coronary morphology. Second, although our results confirm that patients with chest pain but no ischemic ECG changes have a low risk of future MI or cardiac death (1,23,24), those with a positive cTnT test represent a subset at relatively high risk, who show a continued increase in the probability for cardiac events throughout one-year follow-up.

#### Cardiac TnT in low risk patients in the CPU

We carefully selected patients at low risk for MI using the previously validated Goldman algorithm (15). This is an important distinction from the incidence of cTnT elevation and its prognostic value in patients with ACS and ischemic ECG findings reported in previous, large troponin studies (2–6). Such patients have a prevalence of CAD >80% and a high risk for acute MI (25). Compared with these previous patients with ACS in whom the incidence of cTnT or cTnI elevation ranges from 24% to 48% (2–6), cTnT was only elevated in 8.9% of our patients, which is in keeping with the 10% positive cTnT rate reported by Hamm et al. (1) in a subgroup of patients with chest pain with normal ECGs evaluated in the ED. In addition, our patients’ characteristics also appear consistent with those of other patients in the CPU, including a high prevalence of risk factors for CAD (26).

#### Coronary angiographic findings

A unique aspect of our report is the inclusion of extensive angiographic data. Elevation of cTnT was correlated with angiographic evidence of significant CAD in 90% of our patients and intermediate CAD in an additional 6%. Furthermore, cTnT-positive patients had predominantly multivessel disease, greater coronary narrowing and frequently complex lesion morphology. These results are in keeping with data from patients with ACS and ischemic ECG changes, showing that positive cTnT results predict the presence of complex and severely obstructive plaques (27). The fact that angiographic features from our cTnT-positive patients are similar to those observed in the majority of patients with typical ACS presentations (22) suggests a common pathogenesis, which, as previously reported, relates to plaque disruption, with or without angiographically detectable thrombus (28). Therefore, cTnT elevation indicative of minor myocardial injury in patients with chest pain but no ischemic ECG changes may represent part of a continuous spectrum of ACS. We speculate that myocardial injury either took place days before presentation or was the result of microembolization, either of which might be missed by the ECG or CK-MB assay.

#### Long-term risk stratification

Our study is the first to address the long-term prognostic value of cTnT in low risk patients with chest pain. The available data on the use of cardiac troponins for short-term risk stratification in subsets of patients with chest pain but no ischemic ECG changes are controversial (1,29,30). Polanczyk et al. (29) reported...
that cTnI was not a significant predictor of in-hospital cardiac events. In contrast, Green et al. (30) found a positive cTnT test to be a significant predictor of cardiac events at 14 days, but it provided no additional prognostic information as compared with CK-MB. Although differences in the patient groups studied and the choice of end points preclude a direct comparison with the present study, our long-term follow-up data extend the previous observations, showing that the increased probability of adverse events in cTnT-positive patients becomes evident during the first month of follow-up and persists over one year. We found that after accounting for differences in clinical risk factors, a positive cTnT test conferred more than a twofold independent risk for long-term adverse outcomes. Our results also suggest that little information is to be gained by measuring CK-MB for long-term adverse outcomes. Our results also suggest that little information is to be gained by measuring CK-MB levels in addition to cTnT in these patients.

It is significant that a relevant proportion of the events (predominantly UA) occurred in patients who had both negative cTnT and CK-MB tests. This is consistent with the finding of Karlson et al. (17), who observed that >50% of patients seen in the ED with chest pain and ischemic heart disease, but not requiring admission, needed medical attention for chest pain during the next year. Although coronary angiographic features would probably have predicted the susceptibility to adverse events in these patients, the modest event rate (13%) associated with a negative cTnT test, along with a low incidence of CAD in this group, suggests that a strategy of routine coronary angiography is neither clinically justified nor cost-effective after a low risk presentation. As in patients with ACS with ischemic ECG changes, use of biochemical markers, such as C-reactive protein, or routine stress testing before CPU release may ultimately have a complementary role to cTnT for risk stratification (31,32).

Study limitations. Several limitations of the present study merit discussion. One is that a positive cTnT test was an indication for coronary angiography. However, the inclusion of nearly 100 cTnT-negative patients who were randomly assigned to angiography should correct, in part, for a “work-up” bias. This group can be expected to reflect the anticipated low prevalence of CAD in a low-risk population (9,12–14). The higher revascularization rate in cTnT-positive patients, potentially driven by performance of routine angiography per protocol, may have ultimately improved prognosis (33). Therefore, the ability of cTnT to predict events may have been underestimated.

Reliance on coronary angiography may underrepresent the frequency of intracoronary thrombus, as compared with angioscopy (34). However, we detected no thrombi, which may be related, in part, to our methods, including the selection of patients (none of whom exhibited ECG changes of ischemia) and the strict angiographic criteria for detecting thrombus (22). Of note, in patients with UA, the reported incidence of thrombus is highly variable, ranging from 1% to 52% (35).

Obtaining immediate quantitative cTnT results was not technically feasible at the time our study was performed; thus, only bedside cTnT results were available to the physician on duty. The unavailability of quantitative markers to clinicians is not without precedent. In previous large studies evaluating the prognostic usefulness of cardiac troponins in high-risk patients, clinicians did not have access to any troponin result and made decisions on the basis of CK-MB values only (2–6). In our study, reliance on only CK-MB mass would have resulted in many more cTnT-positive patients inadvertently being excluded from the angiographic protocol. However, because of the higher cut-off value of the rapid assay, our analysis was based on quantitative cTnT results, which today can be obtained easily and quickly.

This study used the first-generation ELISA assay for cTnT, which has been replaced by second- and third-generation assays. These have a greater specificity for the cTnT cardiac isoform (36). Approximately 50% of the patients enrolled in the present study had both first- and second-generation assays tested. There were no individual discrepancies between the two assays that crossed over the cut-off value of 0.1 ng/ml. Therefore, it is unlikely that the greater specificity of the later generation assays would have significantly impacted the results.

In the present study, clinical and ECG predictors are used for triage and management until biochemical markers are determined at 10 h after arrival or symptom onset. This sampling time was specifically chosen to maximize the sensitivity of both cTnT and CK-MB (37,38), which appears appropriate to allow detection of minimal cardiac marker rises such as those occurring in our low-risk group of patients. Inclusion of an additional cTnT value on presentation should not change the total number of patients with positive tests, and therefore is unlikely to have an impact on its prognostic value.

Lastly, as expected, the incidence of MI or cardiac death was low during follow-up in our group (1,23,24). On the basis of our event rates, a multivariate analysis of these end points alone would have required a study of ~8- to 10-fold magnitude (39), which is beyond the scope of a single-institution experience.

Conclusions. For patients who had short-term observation for chest pain in the absence of ischemic ECG changes, cTnT elevation had a strong association with the presence of severe and complex CAD. Prognostically, a positive cTnT test is an independent and powerful predictor of future adverse cardiac events. Therefore, cTnT measurement should be an integral part of diagnostic workup in these patients with chest pain, as it provides a simple method to identify those at risk of future ischemic complications that would not otherwise be differentiated by clinical history or CK-MB results. Further research will clarify whether patients in the CPU with positive cTnT results will
benefit from early and aggressive medical therapy, as is now being administered to patients with ischemic ECG changes.

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