

Troponin-Positive, CK-MB-Negative Acute Myocardial Infarction: Clinical, Electrocardiographic and Angiographic Characteristics

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ABSTRACT: Objectives: We assessed the clinical, electrocardiographic (ECG) and angiographic characteristics of patients with acute coronary syndrome, increased troponin I (cTn-I) levels and normal creatine kinase levels. **Background.** Cardiac troponins are part of the new definition of acute myocardial infarction by the European Society of Cardiology and the American College of Cardiology. However, there are limited data regarding the angiographic characteristics of these patients. **Methods.** Between 1/2002 and 7/2004, a total of 50 consecutive cTn-I-positive, creatine kinase-negative patients were admitted to the intensive coronary care unit of our institution and underwent coronary angiography. **Results.** The mean cTn-I level was 10.7 ± 13.5 $\mu\text{g/L}$ and the mean creatine kinase was 106 ± 40 U/L (normal < 180 U/L). Admission ECG showed inverted T-waves in 42% of patients, ST-segment elevation in 36%, ST-segment depression in 20% and a normal ECG in 20%. A total of 168 lesions were analyzed, and 47 (28%) of these were considered to be nonsignificant lesions (< 50% diameter stenosis). Seven patients had normal or nonsignificant coronary artery disease (CAD) and the remainder had at least single-vessel disease. There were 12 patients with stenosis in the left main coronary artery, 6 patients had a visible clot in the artery, 5 of them located in the right coronary artery and 1 in the left circumflex. A total of 37 patients underwent coronary revascularization, the majority (62%) percutaneously, the rest were treated conservatively. **Conclusions.** Increased cTn-I levels in the presence of rest pain and normal creatine kinase is not a spurious finding, but may actually be a marker of advanced CAD. However, some of these patients may also have nonsignificant CAD.

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The recent introduction of cardiac troponin I (cTn-I) into daily routine practice allows for highly accurate, sensitive and specific determination of myocardial injury in patients with chest pain. Any increase in these markers implies myocardial necrosis and an impaired outcome for these patients, with increased risk of death.^{1,2} According to the Joint European Society of Cardiology/American College of Cardiology Committee, the presence of rest chest pain associated with elevated blood levels of cTn-I have become the cornerstone for the new definition of acute myocardial infarction (AMI).³ Since the

introduction of these changes in the definition of AMI, a new entity has been created regarding patients with increased troponin levels, but with normal creatine-kinase values. Although previous studies have determined the clinical characteristics and prognostic implication of cTn-I, coronary angiography has not been systematically performed in these patients and the angiographic characteristics have not been well determined⁴⁻⁶ The aim of the present study was to assess the clinical, electrocardiographic (ECG) and angiographic characteristics of AMI patients with elevated cTn-I and normal creatine-kinase levels.

Materials and Methods

Patient population. The patient cohort comprised 50 consecutive patients admitted to the intensive coronary care unit of our institution with chest pain at rest within the previous 48 hours. Patients with persistent ST-segment elevation in any of the ECGs or any increase in serum creatine-kinase above normal values during hospitalization were excluded from the study. All patients had normal renal function and underwent coronary angiography during hospitalization.

Methods. Serum samples for cTn-I and creatine-kinase are routinely obtained at our institution on admission and at 8-hour intervals during the first 24 hours. All analysis of the samples was performed at our center; cTn-I was assayed by an enzyme immunoassay, with normal values < 0.2 $\mu\text{g/L}$ (*Troponin ADV, AxSYM*[®], Abbott Laboratories, Redwood City, California). Creatine-kinase was assayed with an enzymatic assay, and normal values at our laboratory ranged between 30 IU/L and 180 IU/L. Routine standard 12-lead ECGs were performed on arrival to the emergency room and again at arrival to the intensive coronary care unit (CCU), then daily thereafter. ECG changes were assessed and analyzed by an independent reviewer (DS) who was blind to the laboratory results and to the angiographic analysis. ECGs were analyzed for the presence of Q-waves, ST-segment elevation, depression, inverted T-waves and bundle-branch block.

Coronary angiogram. Coronary angiography and angioplasty were performed in a routine fashion according to current guidelines with conventional catheter-based systems by the femoral approach using the Seldinger technique. Quantitative coronary angiographic analysis was performed by a dedicated technician, blinded to the clinical data and the purpose of this study using validated software (*CASS II, Pie Medical, The Netherlands*). The analysis of all lesions was performed in a single view, which minimized vessel overlap and foreshortening and maximized the

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Table 1. Baseline clinical characteristics.

	n = 50
Age (years)	60.8 ± 11.1
Female (%)	10 (20%)
Diabetes (%)	20 (40%)
Hypertension (%)	30 (60%)
Hyperlipidemia (%)	25 (50%)
Family history (%)	13 (26%)
Current smoker (%)	17 (34%)
Past smoker (%)	12 (24%)
Serum creatine (mg/dL)	0.87 ± 0.22
S/P myocardial infarction (%)	6 (12%)
S/P coronary artery bypass (%)	2 (4%)
S/P percutaneous coronary intervention (%)	9 (18%)
Normal left ventricular function (%)	38 (76%)
Ejection fraction (%)	56.3 ± 14.1
Peak troponin I (µg/L)	10.67 ± 13.5
Base creatine-kinase (U/L)	92.5 ± 39.1
Peak creatine-kinase (U/L)	105.7 ± 40.3

apparent severity of the narrowing. Percent stenosis was calculated from the minimal lumen diameter and a normal vessel reference value obtained as an extrapolation of the proximal and distal segments surrounding the stenosis. Lesion complexity was classified into Types A, B1, B2 and C according to the American Heart Association/American College of Cardiology grading system.⁷ Nonsignificant coronary artery disease (CAD) was defined as any narrowing < 50% in any vessel, and normal coronary arteries was diagnosed in patients with no stenosis ≥ 20%. The grade of atherosclerotic CAD (1-, 2- or 3-vessel disease) was also evaluated, and patients with a > 50% stenosis in the left main coronary artery were defined as having 2-vessel disease. Left ventricular function (LVEF) was calculated at the time of the coronary angiography using the area-length method.

Statistical analysis. Continuous variables are expressed as mean ± 1 standard deviation and categorical variables as percentages. For continuous variables, comparisons between the two groups for categorical values by the χ^2 or Fisher's exact test. Statistical analysis was performed using SAS software, (SAS Institute, Cary, North Carolina). A *p*-value < 0.05 was considered significant.

Results

Clinical and electrocardiographic characteristics. Between January 2002 and July 2004, a total of 50 consecutive patients with chest pain at rest, cTn-I above normal values and normal creatine-kinase laboratory values were admitted to the intensive CCU at our institution. The baseline clinical characteristics of these patients are shown in Table 1. The peak cTn-I level for the entire cohort was 10.7 ± 13.5 µg/L, whereas the mean cTn-I level for patients with normal coronary arteries was 18.1 ± 16.2 µg/L (range 4.6–50 µg/L). The baseline creatine-kinase was 92.5 ± 40.3 U/L, and the peak level was 106 ± 40 IU/L. ECG characteristics of all patients are shown in Table 2. A total of 16 patients (36%) had transient elevation of the ST-segment on their admission ECG, which returned to normal baseline

Table 2. Electrocardiographic characteristics.

	n = 50
T-wave inversion (%)	25 (50%)
ST-segment elevation (%)	16 (32%)
Inferior (%)	8 (50%)
Anterior (%)	6 (38%)
Lateral (%)	2 (12%)
ST-segment depression (%)	6 (12%)
Normal electrocardiogram (%)	11 (22%)
Right bundle-branch block (%)	8 (16%)
Left bundle-branch block (%)	2 (4%)
Left anterior hemiblock (%)	2 (4%)

Table 3. Angiographic characteristics (patient-based).

	n = 50
Normal coronaries (%)	4 (8%)
Nonsignificant coronary artery disease (%)	3 (6%)
One-vessel disease (%)	19 (38%)
Two-vessel disease (%)	12 (24%)
Three-vessel disease (%)	12 (24%)
Lesion Characteristics (lesion-based) (n = 168)	
AHA/ACC Class A	20 (12%)
AHA/ACC Class B1	47 (29%)
AHA/ACC Class B2	38 (23%)
AHA/ACC Class C	19 (12%)
Stenosis ≥ 50%	121 (72%)
Stenosis ≥ 70%	67 (40%)
In-stent restenosis (%)	2 (1.3%)
Thrombus (%)	7 (4.6%)
Total occlusion (%)	12 (7%)

Table 4. Quantitative coronary angiography analysis (lesion-based).

	n = 168
Minimal lumen diameter (mm)	0.94 ± 0.72
Percent diameter stenosis (%)	63.5 ± 12.0
Reference diameter (mm)	2.49 ± 0.83
Lesion length (mm)	8.2 ± 4.6
Plaque area (mm ²)	6.89 ± 7.0
Plaque volume (mm ³)	18.8 ± 27.8

upon admission to the intensive CCU (aborted myocardial infarction) and 11 patients (22%) had a normal ECG. The majority of patients with transient ST-segment elevation had these changes in the inferior leads. In the 34 patients without ST-segment elevation, 11 had the ST-depression localized in the anterior chest leads, and 5 of them in the inferior leads. Less than half of all patients (40%) were on aspirin treatment before admission, only 34% were on beta-blockers and < 30% were on statins or calcium channel-blockers.

Angiographic characteristics. Angiographic characteristics and the American Heart Association/American College of Cardiology classification according to lesion type are shown in Table 3. The quantitative coronary analysis is shown in Table 4 and the extent of CAD in Figure 1. A total of 168 lesions were analyzed, and 47 (28%) of these were considered to be nonsignificant lesions (< 50% diameter stenosis) and there

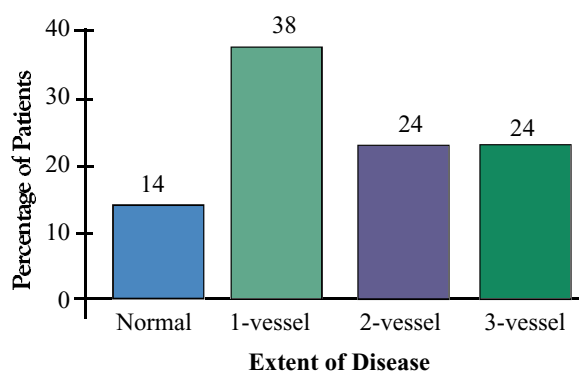


Figure 1. Angiographic characteristics of all patients.

were only 12 vessels (7%) that were totally occluded. A total of 121 lesions had flow-limiting arterial stenosis $\geq 50\%$ and 67 lesions (40%) were $\geq 70\%$. Seven patients had normal or non-significant coronary artery disease and the remainder had at least one-vessel disease, 35% of them were considered to be high risk lesions, classified as B2 or C. Of the 7 patients with normal or non-significant coronary artery disease, only 1 patient had transient ST-segment elevation, 6 patients developed T-wave inversion and none of them developed Q-waves. There were 12 patients with stenosis in the left main coronary artery, but only 1 of them was considered to be significant by quantitative coronary analysis. Six patients had a visible clot in the artery, five of them located in the right coronary artery and one in the left circumflex. In three patients it caused complete occlusion of the vessel. Four of these patients had transient ST-segment elevation and none of them had ST-segment depression or developed Q-waves. The overall left ventricular ejection fraction, as assessed by left ventriculogram at the time of angiography was normal ($56 \pm 14\%$) and only 4 patients had a left ventricular ejection fraction $< 35\%$ (1 with normal coronary arteries).

Short-term outcomes. Percutaneous coronary intervention was performed in 31 patients (62%) and 6 (12%) were referred to coronary artery bypass surgery. A conservative approach was used in 13 patients, which included patients without flow-limiting stenosis or lesions in small vessels not amenable to revascularization. There were no complications and all patients were discharged home.

Discussion

Our study shows that a majority of patients with elevated cTn-I in the presence of normal creatine kinase levels have significant coronary artery disease. This shows that increased troponin levels is not a spurious finding, but may actually be a marker of advanced coronary artery disease. The severity of coronary artery disease has shown in previous studies to correlate with prognosis of patients and until now our knowledge of the quantitative coronary angiographic characteristics of patients with increased cTn-I but normal creatine kinase levels has been limited. Almost half of these patients had significant CAD of at least 2 vessels and 18% had 3-vessel disease. There

were 12 totally occluded vessels and 1 patient had significant narrowing of the left main coronary artery. Interestingly, 14% of these patients were admitted to the intensive CCU and had no significant CAD, despite elevated cTn-I levels and ECG changes. These results correlate with data obtained from patients enrolled in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) Quality Improvement Initiative (CRUSADE) and the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (Eptifibatid) Therapy (PURSUIT) trial.^{6,8} In the CRUSADE Initiative, 18% of the patient population had increased troponin with normal creatine-kinase levels. However, only 33% of them underwent coronary intervention. In patients who were enrolled in the PURSUIT trial and who underwent in-hospital angiography, 88% had significant CAD (any stenosis $> 50\%$), 6% had mild CAD (any stenosis $\leq 50\%$), and 6% had no stenosis identified, which correlates with our data.⁸ Although the overall prevalence of false-positive serum cTn-I in the general population is low, it may be increased in patients with conditions other than acute coronary syndromes, such as sepsis, septic shock, myocarditis, heart failure, cardiac arrhythmias, renal failure, pulmonary embolism and cerebrovascular accidents,⁹ none of which was present in these patients.

Cardiac-specific troponins are gaining acceptance as the primary biochemical cardiac marker in patients with acute coronary syndromes. They have greater diagnostic sensitivity due to their ability to identify patients with lesser amounts of myocardial damage. Elevated levels of cTn-I convey prognostic information beyond that supplied by the clinical characteristics of the patient or the ECG at presentation. Furthermore, among patients without ST-segment elevation and normal CK-MB levels, elevated cTn-I or troponin T concentrations identify those at an increased risk of death and are thought to represent microinfarctions that result from microemboli from an unstable plaque.^{1,10}

Previous studies. These results are consistent with previous reports showing that patients with elevated troponin levels and normal creatine-kinase had a prevalence of angiographically significant coronary artery stenosis that closely correlated with patients who had an elevation of both markers.⁵ A previous study by Almeda et al⁵ showed that patients with increased levels of cTn-I and normal creatine-kinase levels had a higher prevalence of coronary artery stenosis $> 50\%$ compared to patients who had normal values of both markers (80% vs. 27%; $p = 0.001$), but similar to patients who had an elevation of both markers (87% vs. 80%; $p = \text{NS}$). Although patients with increased cTn-I levels and normal creatine-kinase had a higher prevalence of $> 70\%$ stenosis compared to patients with normal values of both markers (56% vs. 27%; $p = 0.03$), it was lower when compared to patients with increased levels of both markers (56% vs. 84%; $p = 0.02$). Our study goes one step further and makes a detailed angiographic analysis of the coronary artery anatomy in these patients. Furthermore, these studies have shown that despite a low-level elevation of cTn-I, these patients

are at an increased risk of future cardiac events, including death and myocardial infarction.^{1,11-13} In conclusion, patients with elevated cTn-I and normal creatine-kinase levels have significant CAD. Therefore, in patients with chest pain at rest, an increased troponin level in the presence of normal creatine-kinase is not a spurious finding, but may actually be a marker of advanced CAD. However, some of these patients may also have nonsignificant CAD.

Study limitations. This is a retrospective analysis of a consecutive series of patients. Only data on patients admitted to the intensive CCU were analyzed and only patients who underwent angiography were evaluated, thus a selection bias relating to the decision to perform angiography may have influenced the results. We did not assess the impact of in-hospital treatment regarding outcomes, although we believe it is beyond the scope of this manuscript.

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