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Troponin T in the evaluation of prognosis in patients with unstable angina

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Abstract: Cardiac troponin T (TnT) is a regulatory contractile protein not normally found in blood. Minor elevations of TnT in patients with unstable angina have been associated with an increased risk of subsequent death or Acute Myocardial Infarction (AMI). We used a neewly developed enzyme immunoassay for TnT to determine whether its presence in the serum of patients with unstable angina was a prognostic indicator. We screened 105 hatients with unstable angina (23 with accelerated or subacute angina and, 82 with acute angina at rest) for TnT every eight hours for two days after admission to the hospital. The outcomes of interest during the hospitalization were death and myocardial infarction. Troponin T was detected (range 0.20 to 3.64 μg per liter; mean 0.78; median, 0.50) in the serum of 32 of the 82 patients. (39 percent) with acute angina at rest. of the 33 patients who were positive for TnT, 10 (30 percent) had myocardial infarction (3 after coronary artery bypass surgery), and 5 of these died during hospitalization. In contrast only 1 of the 50 patients with angina at rest who were negative for troponin T had an acute myocardial infarction ($p<0.001$), and this patient died ($p=0.03$). Thus, 10 of the 11 patients with myocardial infarctions had detectable levels of TnT; troponin T was not detected in any of the 23 paitents with accelerated or subacute angina and none of these patients died. Conclusion: Cardiac troponin T is a cheap, simple and prognostically very useful indicator in patients with unstable angina.

Key Words: *Troponin T, Unstable angina*

Introduction

Unstable angina is important cilinically because of its frightening and disabling nature and the distinct possibility that it heralds acute myocardial infarction (1) Postmortem studies reveal that fatal events are frequently preceded by the result of the fissuring of atheromatous plaques with subsequent activation of platelets, thrombus formation and episodic embolization (1, 2).

Troponin T is a structurally bound protein found in striated muscle cells. Cardiac troponin T can be differentiated from its isoforms in skeletal muscle by immunologic techniqus, and it is not detectable in the serum of healthy people. Circulating troponin T is therefore a highly sensitive and specific marker of myocardial-cell injury (2-5).

Minor elevations of TnT in patients with unstable angina have been associated with an increased risk of subsequent death or acute myocardial infarction (4-6).

Methods

Patients: The study population consisted of 105 consecutive patients (27 women and 78 men; mean age (+SD), 61-10 years) who were admitted because of chest pain during the last 72 h. and ST depr. or T-inv. in ECG were included. All patients were followed for 6 months. Patients with myocardial infarction documented within the previous two weeks who had valvular heart diseease or cardiomyopathy were excluded. Reviewers unaware of the patients'troponin T values categorized them as follows, using Braunwald's classification of unstable angina; (10 patients were assigued to class 1 (severe or accelerated angina of new onset), 13 patients to class 2 (subacute angina at rest -i.e., not active within the previous 48 hours) and 82 patients to calss 3 (angina at rest during, the previous 48 hours).

All the patients were given bed rest and an intensive medical regimen that included nitrates (given orally in 81 paitents and intravenously in 55) beta blockers (61 patiens), and calcium-channel blockers (75 patients), All

the patiens received aspirin or heparin according to local practice.

Standard 12-lead electrocardiography was performed routinely at the time of admission and during episodes of chest pain. The electrocardiograms were evalutade blindly for evidence of reversible byocardial ischemia, defined as transient ST elevation ST depression and T-wave inversion.

Study Protocol

The study protocol was approved by the ethics committee at the University of Erciyes After informed con sent was obtained from esch patient, 10 ml of blood was collected within six hours of admission to the hospital and every eight hours there after for two days. The samples were kept at room temperature for 20 minutes to allow clotting, were centrifuged, and were then stored at -200°C. The values listed for troponin T represent the peak concentrations during each collection period.

Analytic techniques

The biochemical analysis was performed by technicians unaware of the patients histories for the quantitative determination, of serum troponin T an enzyme immunologic assay (Boehringer, Germany) was used. Based on a technique using streptavidin, this single-step sandwich assay allows serial determination of blood samples to be made within two hours, The test is carried out in microprocessor-controlled photometers (E>22, Boehringer and requires streptavidin-coated tubes as the solid phase and two monoclonal antihuman cardiac troponin T antibodies. During a 60-minute incubation period, the antigen is bound by one biotinylated and one peroxidase labeled antibody.

This complex adheres to the test-tube wall because of the high-affinity streptavidin-biotin interaction. After two washing steps, the substrate chromogen solution (ABTS, Boehringer) is added. Substrate conversion im quantified by the occurenece of a change in color at 405 mm, which directly correlate with the concentration of troponin T in the blood sample. The level of sensitivity of this test is 0.20 μg per liter. Values > 0.20 μg per liter were considered positive for troponin T in this study.

Statistical Analysis

All the results are expressed as means+SD except as stated otherwise, An exploratory analysis of data was performed with the Freeman-Halton test (two tailed) in the groups with and detectable levels of troponin T. Continuous variables were analyzed with unpaired t-tests. P values <0.05. were considered to indicate statistical significance.

Positive predicitive value was calculated as the number of true positive test results, among all positive test results observed, and negative predicitive value as the number of true negative test resutls among all negative test results observed.

Results

The 23 patients was with class 1 or 2 unstable angina. In none of the 138 blood samples from these patients was troponin T measurable, and these patients had no cardiac events during hospitalization.

In contrast 32 (39 percent) of the 82 patients with acute angina at rest (class 3) had measurable levels of troponin T was measurable (at levels>0.20 μg per liter) in the first or second sample obtained after admission. In the remaining five patients, the first serum sample with detectable level of troponin T was obtained 16 to 24 hours after admission and was associated with recurrent episodes of angina at rest. two representative patterns of troponin T release are shown in figure 1. In 50 of the 82 patients with angina at rest (61 percent) no troponin T could be measured.

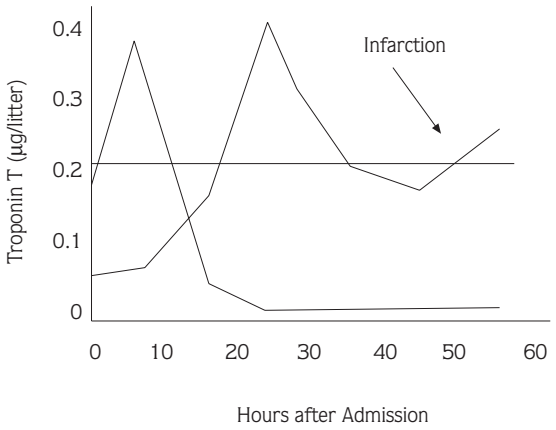

Figure 1. Representative patterns of Release of Troponin T in Patients with Unstable Angina

The patients with and those without measurable levles of troponin T did not differ with respect to baseline clinical characteristics and treatment (table 1). Coronary angiography in 62 patients with calss 3 angina revealed comparable degrees of coronary disease in the groups positive and negative for troponin T (table 1) The six patients with normal coronary arteries had no measurable troponin T in serum.

Table 1. Clinical Data on 82 patients with Angina at Rest (Braunwald Class 3) According to Whether They Were Negative or Positive for Troponin T.

Variable	Negative (n=50	Positive (n=32)
Age (yr)		
Mean	60±10	64±11
Range	30-81	42-81
Sex (M) F	34/16	26/6
Medication used		
Oral nitrates	36	24
Intravenous nitrates	30	22
Beta-blockers	24	16
Calcium-channel blockers	36	21
Heparin alone	2	2
Aspirin alone	17	9
Aspirin and Heparin	29	21
Angiographic Findings		
No of vessels with stenosis ≥70%		
0	5	0
1	6	5
2	12	11
3	12	7
Lenf main coronary artery		
disease stenosis >50%	1	2
Angiography not performed		
Electrocardiographic changen	14	7

Table 2. Interventions and Cardiac Events during Hospitalization in Patients with angina at rest according to Whether. They Were Negative or Positive for Troponin T

Variable	Negative (n=50)	Positive (n=32)	p Value*
Intervention			
Angioplaty	14	15	NS
Bypass grafting	8	7	NS
Cardiac events			
Acute infarction	1	10	<0.001
Perioperative	0	3	
Deaths	1	5	0.03
After infarction	1	2	
After bypass graftingn	0	3	

* NS denotes not significant

Table 3. Major Cardiac Events during Hospitalization and Date of Occurrence*

Patient No	Age/Sex	Troponin T µg/liter	Cardiac events	Day, after admission
1	48/M	0.37	Infarction	3
2**	57/M	0.20	Death after infarction	7
3	79/F	0.22	Death after infarction	5
4	72/M	1.09	Death after infarction	7
5	58/F	0.48	Death after bypass surgey and infarction	10
6	74/M	0.53	Death after bypass surgey and infarction	8
7	78/M	0.29	Death after bypass surgey and infarction	3
8	71/M	0.80	Death after bypass surgey and infarction	5
9	67/M	1.05	Infarction	6
10	76/M	0.89	Infarction	2
11	65/M	0.32	Infarction	4

* Values of <0.20 mg perliter for troponin T were considered normal. Infaction denetes acute myocardial infarction, and bypass surgery coronary artery bypass surgery

** This patient wes claccified as negative for troponin T

During hospitalization, coronary angioplasty was necessary in 30 patients (14 negative and 15 positive for troponin T) and bypass surgery was performed in 16 patients (8 negative and 7 positive). The differences between the groups were not statistically significant (Table 2).

Clinical outcomes during hospitalization (duration, 21+7 days) were related to the presence of detectable levels of serum troponin T, of the 33 patients who were positive for troponin T 10 (30 percent) had acute myocardial infarction within 2 to 10 days after hospitalization that were associated with new ST elevations (table 3). All patients with infarction were treated with aspirin. In two patients (patients 10 and 11, table 3) the vessel with an infarct could be opened by coronary angioplasty within two hours after the onset of symptoms. Three infarcts occured after coronary by pass surgery and resulted in death. Five of the 33 patients who were positive for troponin (15 percent) died during hospitalization. In contrast, only 1 of the 50 patients who were negative for troponin T (2 percent) had an acute myocardial infaction; 17 occured seven days. After admission, and the patient died. The incidence of myocardial infarction ($p<0.001$) and death ($p=0.03$) was significantly different between the groups positive and negative for troponin T (table 2).

Ten of the 11 acute myocardial infarction were preceded by the detection of measurable levels of serum troponin T. The positive predictive value of a detectable level of troponin T for acute myocardial infarction in this population of patients was 30 percent, and the negative predictive value was 98 percent. Of the 11 patients with myocardial infarction, 8 had neasurable levels of troponin T in the serum sample obtained within six hours of admission. In two other patients (patients 1 and 7) troponin T was first detected in the four th sample (on day 2) after recurrent episodes of angina at rest (Table 3) of the 62 serum samples obtained from these 11 patients, 51 had measurable levels of troponin T.

Discussion

Unstable angina is a critical phase of ischemic heart disease, but there are no reliable, noninvasive methods of assigning patients to different prognostic categories. An unfavorable outcome has been linked with the occurence of frequent episodes of symptomatic or silent myocardial ischemia during 48 hours of intensive medicla therapy (7, 8). A subgroup of high-risk patients can be identified by the detection of transient shifts of the ST-T segment on serial electrocardiograms (9).

Previous studies in patients have shown that higher sensitivity and specificity for the detection of mycardial-cell injury are provided by measurements of circulating levels of cardial muscle, multiple isoforms of the contractile proteins myosin and actin and the regulatory proteins troponyosin and the troponin compyex have been found (10). Among these proteins, troponin T and troponin I appear to be unique cardiac antigens (10, 11, 12) Recently specific monoclonal antibodies have been developed against cardiac troponin T that have essentially no cross-reactivity with their isoforms in skeletal muscle (12). The assay for troponin T used in this study allows measurements in serum samples to be made within two hours, and it therefore appears suitable for routine use (12).

Troponin T was not elevated in serum samples from patients with subcute or accelerated angina (classes 1 and 2 of braun wald (13). However troponin T was found in 39 percent of patients with persistent angina at rest when blood samples were obtainde at eight-hour intervals for two days after admission to the hospital. (Ten of 11) in- hospital mycardial infarctions occurred in patients whose serum was positive for troponin T.

Besides the unfavorable outcomes in patients with measurable levels of troponin T who were treated medically, our patients appeared to be at higher risk during coronary-artery bypass surgery. Surgery in patients with angina at rest that is refratory to medikal treatemnt is known to be associated with higher complication rates (14, 15). All three fatal perioperative myocardial infarctions in out series occurred in petinets with measurable levels of troponin T in the serum.

In unstable angina, reversible as well as irreversible cell injury may occur. Troponin T is found in myocytes in both a small free cytosolic pool and a langer structurally bound fraction (16, 17). A loss of cell-membrane integrity during severe ischemia results in only transient leakage from the cytosolic pool, irreversible cell damage with degradation of myofilaments, however is followed by a delayed but continuous liberation of the bound troponin T farction. Accordingly in acute mycardial infacrtion, a biphasic pattedrn of release with peaks at 14, hours and three to five days has been demonstrated (3, 17, 18). The presence of circulating cardiac proteins in patients with unstable angina may be explained by the intermittent critical reduction of flow as a result of intracoronary thrombus formation, resulting in reversible damage to the cell membrane, and also by minor local cell necrosis due to thrombotic microembolization (5, 18).

The present results suggest that measurement of troponin T in serum allows a useful prediction of risk in patients with unstable angina (19, 20) Cardiac risk during hospitalization may be estimated by measurement of troponin T soon after admission to the hospital, and such measurement may help to guide decisions about management.

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