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TROPONIN T IN UNSTABLE ANGINA PECTORIS

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Summary. *Unstable angina pectoris is nowadays defined as an acute coronary syndrome commonly marked by a non-specific electrocardiogram changes. For this reason, unstable angina is associated with problems in its differentiation and diagnosis. Due to the development of biochemical methods, it has become possible to determine the levels of highly specific cardiac troponin T (TnT) in a short period of time and thereby to take the right direction in approaching the patient with acute coronary syndrome (ACS) and short-term prognosis.*

The aim of the study was to determine TnT values in patients on admission to Coronary Unit of the Clinic for Cardiovascular Diseases of the Clinical Center-Niš, to identify new events during the follow-up, and to assess the possibilities of this marker application in short-term prognosis.

A total of 30 patients were treated, with an average age of 61±10.85 years, of whome 18 were males and 12 females. Anamnestic data were taken that relate to pain and risk factors, and a detailed laboratoty analysis was done that also included determination of values of cardiac specific enzymes. Troponin T was determined quantitatively on the Cardiac Reader analyzer on the site of blood sample, in the Coronary Unit. All treated patients were monitored during their hospitalization and all through control examination after six week's time for possible new events.

Troponin T was detected in 12 (40%) patients with unstable pectoral angina at 0.18+0.07 ng/ml value. Of these patients, six developed a new event during the follow-up for acute myocardial infarction (AMI). Exitus was not registered. On control examination, seven patient were identified to have undergone coronarograpgy and to have TnT value of 0.17+0.05 ng/ml. In four patients, no change on electrocardiogram was observed.

The study allowed for distinguishing the group termed as troponin T positive angina. These patients have not only a worse prognosis but are also in need of cardiosurgical intervention suggestive of their coronography finding.

Key words: *Unstable angina pectoris, troponin T, coronography, minor myocardial damage*

Introduction

Acute coronary syndrome (ACS) occurs in a wide range of patients with the "chest pain" symptom or other symptoms triggered by cardiac ischemia. These symptoms are frequently indistinguishable from one another for they include all ischemia episodes that are manifest as (1, 2):

- Unstable angina pectoris
- Non-Q wave myocardial infarction
- Q wave myocardial infarction

The unification of these manifestations under a single term is based on the understanding that all three are triggered by the same pathophysiological mechanisms. Namely, the underlying pathological substrate is a vulnerable atherosclerosis plaque that is subject to fissure, erosion or rupture, leading to intravascular thrombosis, vasoconstriction and micro-embolism, and preventing oxygen supply to the heart (3, 4). Depending on ischemia duration, degree of occlusion, development of collateral circulation, and spontaneous thrombus regression, ACS is present with diverse clinical presentations (5). Unstable angina pectoris is commonly associated with an intraluminar thrombus (20-50% of all cases). The studies based on angioscopy and angiography have shown that in a majority of cases these mural thrombi do not occlude but only cause restriction in blood supply through a given artery. This may lead to short, usually 10-20 minutes in duration, transient episodes of thrombus occlusion by a labile thrombus. A mass of aggregated thrombocytes, generated by separation of a thrombus localized in the epicardial coronary artery, may be blocked in distal microcirculation. This leads to microvascular damage and reduced blood supply, on one side, and to the microscopic foci of myocardial necrosis, on the other. Thrombocytic aggregates abundantly express receptors of glycoprotein IIb-IIIa, proceed through myocardial capillary circulation and reenter the system circulation facilitating the thrombus response to the rupture of atherosclerosis plaque.

The diagnostic value of biochemical markers is the target of extensive scientific research, the aim of which is identification of high-risk patients with typical or atypical clinical symptoms and/or non-diagnostic ECG findings.

Myocardial necrosis may be recognized by occurrence of various proteins released in the bloodstream

from damaged myocytes such as myoglobin, cardiac troponin T and I, and many others. Detection of these markers allows for establishing diagnosis for myocardial necrosis and for assessment of the integrity of necrotic myocytic membrane, which makes it possible for intracellular macromolecules to diffuse into the intestinal tract and further into the lymph and cardiac microcirculation. These markers are specific for myocardial tissue, while absent from other muscles and organs. The speed of their release after ischemia or necrosis and their persistence in the blood are sufficient for establishing diagnosis and assessment of damage itself.

Troponin T, a widely described marker, exerts nearly 100% specificity for the myocardial tissue and a high sensitivity by even being released from microscopic zones of myocardial necrosis (6, 7, 8). One of the three proteins that make the troponin complex is located on thin filaments of the contractile muscle apparatus. It participates in the regulation of striated muscles contraction. Three different molecules of troponin have to date been identified in man: troponin T, troponin I (present by various isoforms in the skeletal and heart muscle), and troponin C.

Troponin T is not detectible in the blood of healthy subjects, but appears 2-8 hours after onset of myocardial tissue ischemia. About 6% of troponin T (TnT) is decomposed to cytosol, which may be responsible for the initial increase in the blood as soon as the cells become permeable. The remaining 94% is structurally connected and continually released by proteolytic degradation. In AMI, the values remain elevated for two weeks (9, 10). A broad diagnostic time period of cTnT allows for diagnosis of subacute myocardial infarction at a later stage after CK MB restores to normal values.

APNS contains an independent prognostic marker, the predictor of mortality. There is a positive correlation between the levels of cTnT (>0.1 ng/ml).

Patients and Methods

The aim of the study was to determine the values of troponin T in patients with unstable angina pectoris on admission to Coronary Unit of the Clinic for Cardiovascular Diseases of the Clinical Center-Niš, and to evaluate the use of this marker in short-term prognosis within six weeks' period of follow-up.

The study involved 30 hospitalized patients with APNS diagnosis, established in accordance with the WHO criteria:

- Angina pain of less than 30 minutes duration
- Changes on electrocardiogram (ECG)
- Absence of the increase in cardiac specific enzymes

On examination, the patients were taken data about chest pain including localization, duration, character, pain spread, time of onset, and triggering factors. A specific attention was paid to risk factors for coronary heart disease.

The manifestations of residual ischemia were monitored through the occurrence of:

- Recurrent angina
  (spontaneous angina pains registered as ECG changes)
- Infarction after APNS
- Exitus letalis

A complete laboratory analysis was done and the values of cardiac specific enzymes CK and their isoform CK MB were determined.

The values of troponin T were determined on the Cardiac Reader analyzer, on the site of blood sample, in the Coronary Unit of the Clinic for Cardiovascular Diseases of the Clinical Center-Niš. This new instrument for quantitative determination of immunoassays is of considerable assistance in diagnostic classification of acute coronary syndromes, together with timely examination and therapeutic approach immediate to hospitalization, at the moment when ECG does not show specific dynamics. Speed and simplicity of the operation are based on the insertion of a paper roll into appropriate slot in the analyzer and on the application of 150mg of a fresh blood sample with addition of heparin with no prior freezing.

The test paper roll for cTnT contains two monoclonal antibodies specific for this troponin complex that makes a "sandwich" with TnT in the blood sample. Erythrocytes are removed from the sample, plasma proceeds through the detection zone where "sandwiches" compile (TnT complexes) along the line of streptavidin turning red (signalling line). The released golden antibodies accumulate along the control line, visually signalling that the test is valid. The test line (signalling) increases proportionate to the quantity of troponin in the blood. The optical system of the Cardiac Reader recognizes two lines and registers the intensity of the signalling line. The software converts the intensity of the reading into a quantitative result displayed on the monitor. The range of measure is between 0.1ng/ml and 2.0 ng/ml; the values outside this range appear as Low/High (Table 1). The response period after the result begins to display is 12 minutes, and it takes two minutes to recognize the sample.

Table 1. Baseline characteristic of study population

Baseline characteristics	Patients 30 (100%)
Male n (%)	18 (60)
Age (median, SD)	61.7 $\pm$ 9.54
Risk factors n (%)	
Smokers	18 (60)
Hypertension	18 (60)
Diabetes mellitus	7 (23)
High HDL	15 (50)
Family history of MI	24 (80)*
Body mass index n (%)	
18.5-24.9 kg/m^2	7 (23)
$\geq$ 25 kg/m^2	16 (54)
$\geq$ 30 kg/m^2	7 (23)
Previous UA n (%)	16 (60)
Previous AMI n (%)	12 (40)
New event n (%)	6 (20)

The patients were followed-up for new events and possible lethal outcome over the entire period of hospitalization

Control Examination: The patients were admitted for control examination six weeks later. The examination included:

- clinical examination and interview with the patient
- electrocardiogram examination
- general laboratory analysis
- data obtained after coronography or surgical intervention (single or double by-pass)

Results

Risk factors were noted for cardiac ischemia that are commonly defined as harmful factors of inner and outer environment and that individually or in association participate in this disease occurrence. It was necessary to determine the intensity of the "overall exercise" due to lifestyle, biochemical and physiological (variable) as well as personal (invariable) characteristics (Table 1).

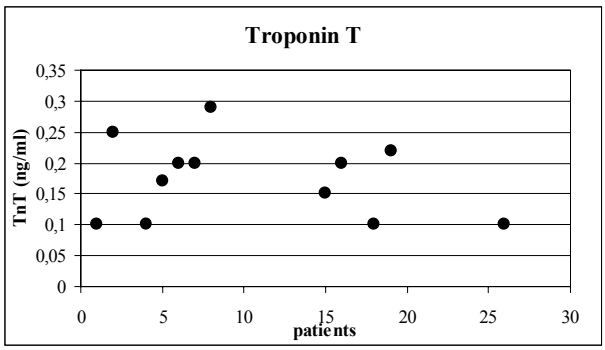

Fig. 1. Troponin T in the treated group

In the treated group, the average patient age was 61±10.85 years. There were 18 (60%) males and 12 (40%) females.

ECG Changes

The contemporary trend in monitoring the ECG changes allows for distinguishing patients with acute coronary syndrome (those with unstable angina and those with Q wave infarction) on the basis of ST segment depression or elevation, both, or T wave inversion. A specific problem arises in patients with cardiac pain who on admission to the Clinic do not show changes on ECG. The treated patients exert changes given in Table 2.

The most frequent finding was ST depression, registered in 37% patients with APNS, followed by ST segment elevation in 20%, both ST depression and elevation in 13% cases, and only 10% cases with changes that affected T wave. No changes were registered in 10% patients.

Table 2. ECG in unstable angina pectoris

ECG	APNS
ST elevation + depression	4
ST elevation	6
ST depresssion	11
T wave changes	3
Without changes	6

Markers of necrosis in unstable angina pectoris

In the group with APNS, 12 patients (40%) had elevated values of troponin T (Figure 1) with a mean value of 0.18±0.07ng/ml, whilst in 18 patients (60%) the values of this marker were not detected. The values of CK and CKMB were within the referential range.

In the same group, a total of six patients experienced a new coronary event. All were registered with increased troponin T values at the time of hospitalization (0.16±0.05 ng/ml). ECG showed ST depression and elevation in two cases, depression in one case, T wave affected by change in two patients, and no change in one patient. The values of creatine kinase and its isoform were within the referential range and did not suggest micro-necrosis.

On control examination, seven patients were determined to have undergone invasive diagnosis. Coronography suggested the need for single or double by-pass. At the moment of hospitalization, these patients also showed elevated values of troponin T (0.17 ± 0.05 ng/ml), whilst standard cardio-specific enzymes were within the normal range. ECG generally showed insufficiently specific changes (no elevation of ST segment). The values of troponin T did not reveal a statistically significant difference between those under coronography and those with developed myocardial infarction in the course of follow-up (Table 3).

Table 3. Markers of necrosis in APNS in relation to new event

APNS	New event	Coronography
ECG ST depression	1	3
ST depression+elevation	2	1
T wave abnormalities	2	1
Without changes	1	2
Troponin T ng/ml	0.16 ± 0.05	0.17 ± 0.05
Myoglobin ng/ml	45.5 ±21.9	44 ±16.35
CK (IU/L) (x±SD)	83.37 ±37.7	83.42 ±30.93
CK MB (IU/L) (x±SD)	19.46 ± 5.28	19.82 ± 7.77

Discussion

Cardiac troponins are used as highly sensitive and specific markers for detection of myocardial damage. Particularly useful is troponin T, which, as a protein of the contractile apparatus, is unique to the primary structure of cardiac muscle. At our Clinic, it is possible to determine the levels of troponin T, whilst detection of troponin I still remains impossible. Due to the development of ELISA immunoassay, a possible increase in the

level can be determined in two minutes, and a quantitative result is obtained in nine minutes.

This marker has a broad time period, for the increase in the values occurs as early as one hour after onset of the symptom, reaching sensitivity level of 50% within three to four hours, and maintaining the elevated values during the next 14 days for troponin T, that is, 10 days for troponin I. It is also possible to detect myocardial damage in approximately 30% patients classified under unstable angina on the basis of anamnesis, ECG, myoglobin, and CK MB.

A heterogeneous group of patients with unstable angina pectoris is defined as a clinical syndrome located between angina pectoris and myocardial infarction in a wide range of patients with coronary disease. Therefore, it involves various clinical presentations of transient episodes of myocardial ischemia. Upon ECG finding, the diagnosis is established on the basis of the absence of increase in standard cardiac specific enzymes. However, the values of troponin T may be increased even though CK MB fails to increase. According to several studies in the field, such patients have a 5-10% higher incidence of a new cardiac event (NSS or AMI). Patients with increased cTnT level are most likely to maintain a six-month risk that is the same as in patients with definite myocardial infarction. Improvement of sensitivity of laboratory methods results in introduction of a new diagnostic class termed Minor Myocardial Damage (MMI) or troponin T unstable angina. It should be noted that:

- Early detection of abnormalities have a higher predictive value than late measurements
- Presence of troponin correlates with the existing destruction of coronary plaque
- High level of troponin is predictive of future coronary events

A positive troponin T finding (>0.1ng/ml) was registered in 40% patients diagnosed with unstable angina pectoris. Of them, 6 (50% relative to those with elevated values, and 20% relative to all patients in this group) developed myocardial infarction during the follow-up. At the moment of hospitalization, ECG did not reveal the signs of ST segment elevation, and none of the patients showed ECG changes. The values of standard enzymes were within the normal range and did not show any myocytic damage. Such results are supportive of MMD occurrence and indicative of the necessity for early detection of cardiac troponin T in patients with acute coronary events, for they provide prognostic data for short-term prognosis. As there were no patients with lethal outcome, it was impossible to determine the TnT values in a possible progression of the coronary event. Alan Wu et al. (11) from the Faculty of Medicine of Harford University in Connecticut followed 486 patients of whom 30% developed myocardial infarction, and one fifth underwent coronary revascularization. The values of cTnT ranged between 0.1-0.2 ng/ml. Similar results were reported by Hamm et al. (12), whose study reveal that 33 out of 109 patients from four European centers had TnT values within the aforementioned range, and about 30% developed AMI. In support of the previous reports, Luscher et al. (13), in the TRIM study (Thrombin Inhibition in Myocardial Ischemia) and on the basis of cTnT values, distinguish the group of unstable angina pectoris with the elevated TnT level, emphasizing that it has a worse prognosis compared to the group with no elevation. About 11.8% patients develop a new event, which is a slightly decreased number compared to other studies. The value that is used for stratification of the risk is >0.1ng/ml, in contrast to the previously reported value of 0.2. The authors used the values obtained within the first six hours after coronary event.

The control examination provided the data about the outcome of coronography within the group. This diagnostic procedure was performed in a total of 23% patients, whilst all patients underwent cardiosurgical intervention for single or double by-pass. These patients, at the moment of hospitalization, also showed the presence of troponin T. Of them, two did not have any changes on ECG, and none had elevated values of CK and CK MB. The results also suggest the sensitivity and specificity of the markers in APNS.

Lindahl et al. (14), after treating 974 patients, conclude that the increased TnT value of up to 0.06 ng/ml imparts minor myocardial infarction (MMD) within the first six months after the event, and that according to that level patients diagnosed with unstable angina pectoris or non-Q Wave myocardial infarction should be the ones with the value of about 0.6, whilst any elevation above 0.6 classifies patients into the group with massive myocardial infarction. The treated patients were thus divided into those at low, medium, and high risk (<0.6, 0.6-1.8, and >1.8 ng/ml, respectively).

Limitations of the study: For financial reasons, it was impossible to monitor the increase in TnT level within hospitalization period and all through the moment it ceases to be detectable in the blood.

Combined application of myoglobin, as the most sensitive cardiac marker, and troponin T, as the most specific one, represents an effective means for diagnosis of patients with chest pain and suspected of having myocardial damage, as well as for prognosis of new events. All this has been confirmed by this study.

Conclusion

Troponin T in patients with APNS showed a high specificity. It helped to distinguish a group of patients at high risk in the follow-up period of six weeks. This group can be labeled as Troponin T-positive angina and is marked by an elevated level of damage requiring coronography and adequate cardiosurgical intervention.

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TROPONIN T U NESTABILNOJ ANGINI PEKTORIS

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Kratak sadržaj. *Nestabilna angina pektoris u današnje vreme se definiše kao akutni koronarni sindrom često praćen ne karakterističnim elektrokardiogramskim promenama zbog čega predstavlja diferencijalno - dijagnostički problem. Zahvaljujući razvoju biohemijskih metoda danas je u kratkom vremenskom intervalu moguće odrediti nivoe visoko specifičnog kardio troponina T i time se brzo orijentisati u prilazu pacijentu sa akutnim koronarnim sindromom (AKS) i kratkoročnoj prognozi.*

Cilj studije bio je odrediti vrednosti troponina T (Tn T) u trenutku prijema u Koronarnu jedinicu Klinike za kardiologiju u Nišu, nove događaje u periodu praćenja kao i mogućnost primene ovog markera u kratkoročnoj prognozi.

Ispitano je 30 bolesnika prosečne starosti 61 $\pm$ 10.85 godina i to 18 muškaraca i 12 žena. Notirani su anamnestički podaci o bolu i faktorima rizika, detaljno urađen laboratorijski pregled koji je obuhvatio i proveru vrednosti kardiospecifičnih enzima. Troponin T određivan je kvantitativno na aparatu Cardiac Reader na mestu uzimanja krvi, u Koronarnoj jedinici. Ispitanici su praćeni kako tokom hospitalizacije tako i do kontrolnog pregleda urađenog nakon 6 nedelja u smislu pojave novog događaja.

Troponin T bio je detektibilan u 12 (40%) bolesnika sa nestabilnom anginom pektoris i to u vrednostima od 0.18 + 0.07 ng/ml. Od njih 6 je razvilo novi događaj u periodu praćenja u smislu infarkta miokarda (AMI), nije bilo egzitusa. Na kontrolnom pregledu utvrđeno je da je 7 bolesnika bilo podvrgnuto koronarografiji i da su oni imali vrednosti Tn T 0.17 + 0.05 ng/ml dok elektrokardiogram nije pokazivao karakteristične promene u 4 bolesnika.

Sprovedeno ispitivanje izdvaja grupu označenu kao Troponin T pozitivna angina. Ovi bolesnici imaju ne samo lošiju prognozu nego i potrebu za kardiohirurškom intervencijom shodno koronarografskom nalazu.

Ključne reči: *Troponin T, nestabilna angina pektoris, koronarografija, minorno oštećenje miokarda*