

TROPONINS, EXERCISE TESTS AND CORONAROGRAPHY ASSESSMENT OF THE SEVERITY IN ACUTE CORONARY SYNDROME

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Despite the advances in diagnostics and treatment in acute coronary syndrome (ACS), there is still a problem of undesirable events after ACS, which increases the chance of mortality by 10%. Verification of patient who may be candidates for these undesirable events is the basis for the prevention, treatment and decrease in mortality.

One of the strategies which gives good results is a combination of monitoring of troponin levels, symptom-limited exercise tests and coronarography.

The correlation of cardiac markers values in acute coronary syndrome and severity of coronary disease is estimated by exercise stress tests and coronarography, as well as by impact of the markers on therapy choice.

The study enrolled 450 patients. Laboratory analysis involved troponin T and I (TnT, TnI), myoglobin, CK-MB and CK-MB mass. Ergometric and invasive examinations were done at the end of hospitalisation.

There is a significant relation in positive exercise stress tests in troponin-positive patients, which is statistically significant. Analysis of exercise stress test showed statistically significant increase of positive findings in troponin-positive ones ($p < 0.05$). Out of 104 coronarographies in the group with two diseased coronary vessels, there were 46,4% of Tn-positive, compared to 29% of troponin-negative patients, which can also be seen in the group with ≥ 3 diseased coronary vessels (3,2 vs 14,8%). Out of 104 coronarographed patients, 29 (8,1%) underwent PTCA, and 25 (7%) ACBG. Statistically significance occurred in choosing patients for PTCA in comparison to Tn status ($p < 0.05$), which was not the case in the group selected for ACBG.

In our research, a good diagnostic and prognostic troponin value was established and confirmed by statistically significant correlation of troponin values and exercise stress tests findings on discharge. They were a reliable indicator of degree and severity of coronarographic finding, as well as a guideline in choosing invasive strategy treatment. *Acta Medica Medianae 2012;51(4):5-12.*

Key words: troponin, acute coronary syndrome, exercise stress test, coronary angiography

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Introduction

Fast plaque progression has been described as a major characteristics of unstable angina. Angiography provides only a single view of the disease which is dynamic. The sooner applied angiography during acute phase, the more serious lesions are found. Therefore, there is justification for a more aggressive approach and much better effect in early invasive treatment in these patients. When troponin levels are elevated, more thrombotic material is present in coronary lesions, thus explaining higher risk of new myocardial damage and better response to mechanical procedures, as well as to antithrom-

botic treatment. Also, the other risk indicators, such as age, diabetes, previous MI and previous angina are connected with much more serious CAD, and thus with greater benefits from early invasive treatment (1-3).

An urgent strategy in early risk stratification in patients with medicament-stabilised unstable angina is a combination of myocardial markers of necrosis and ECG indicators of residual myocardial ischemia. Another strategy is a combination of predictive characteristics of troponin in 24 hours since admission to hospital and predischARGE symptom limited test. These measurements showed that they are independent predictors of death or nonfatal MI in 5 months. Moreover, a combined approach allows better risk discrimination than single measurements (4).

ACC/AHA guidelines for treatment of unstable angina and NSTEMI recommended that low level exercise stress test can be done in low risk patients who were nonsymptomatic in 12 to 24 hours, while symptom-limited tests can be done in patients without ischemia in 7 to 10 days (5).

Elevated TnT levels in patients with unstable angina are predictors of adverse events. As there is no satisfactory therapeutic concept for such high risk patients, Heesch et al. (6) studied a cardiac risk before, during and after coronary revascularisation in patients with unstable angina, stratified according to TnT status. In troponin-positive patients, the clinical symptoms were much more refracted to medical treatment, coronarography was done much earlier, and they had a higher incidence of cardiac events before revascularisation. Angiogram for troponin-positive patients discovered a more serious coronary artery disease, which demanded revascularisation. After coronary interventions, there were more complications. Therefore, troponin testing is a reliable predictor in patients with unstable angina, and such a high frequency has been observed earlier, especially when joined with coronary interventions (6).

Material and methods

This study enrolled patients who were treated in the period 2002-2005 at the Coronary Unit of Cardiology Clinic in the Clinical Center Niš.

In the four-year period, 3.700 patients, all with cardiac urgent conditions were admitted into the Coronary Unit. Patients having the diagnosis of ACS on admission, the total of 2001 (54.08%), were excluded from that group.

The total follow-up period lasted three months. Health control check-ups were done in the first and third month after discharge from hospital, and they involved clinical examination, ECG, determination of the course of the disease concerning recurrent angina, reinfarction, revascularisation or percutaneous interventions, as well as the results.

Using inclusive criteria, the total of 450 patients were separated. Many patients could not join the examined group because this study is a multimarker one, so all the patients who did not have criteria for multimarker examination (at least two markers and at least two determinations) were excluded.

It was obvious that most of the examined patients belonged to the group NSTEMI, that is 49%, which is significant regarding the aim of the study. Increase of this type of ACS was noticed in large studies, while there is a gradual decrease in STEMI at the same time (Graph 2).

The total number of male patients was 297 or 2/3, female patients 153 or 1/3. Mean age in male patients was $62,46 \pm 10,8$ years and $64,8 \pm 10,5$ years in females. Although the females were older by about 2,4 years that difference was not statistically significant. There were 11,9% of patients under the age of 49, 30,2% of patients between 50-59 years of age, 35,1% of patients between the age of 60-69 and 22,8% patients over 70 years of age. The largest number of patients was between 50 and 59, then between 60 and 69, while the other two age

groups were present with a slightly lower percentage.

ECG was recorded during admission twice: in admission room and immediately after hospitalisation in Coronary Unit (within 10-15 minutes). All the patients were monitored for at least 24 hours. ECG analysis: ECG was recorded in a 12-lead form at a paper speed of 25mm/s with correct calibration of 1mV. ST segment depression appeared when J point was in depression by 1mm or more and was followed by horizontal or downsloping ST depression of at least 0.08 sec. in two adjacent precordial leads or two extremity leads. Q-wave or Q-wave equivalent was determined by Selvester QRS screening criterium. Finding was marked as Q-wave if it lasted ≥ 30 ms and aVF, ≥ 40 ms in leads I and aVL, ≥ 40 ms in more than two V4, V5 or V6 or any Q-wave in V2. Additionally, Q-wave equivalent is an accepted finding as R-wave ≥ 40 ms in V1, or R-wave ≤ 1 mm and ≤ 10 ms in V2.

Myocardial infarction is defined either as a new Q-wave (lasting ≥ 0.04 sec. or at least 1/4 of the R height in two or more adjacent leads) or as increase of markers of myocardial necrosis (troponin); a new episode of the chest pain with a combination of new troponin elevation are needed for making the diagnosis of myocardial infarction within seven initial days.

Laboratory analysis was an aimed one, including cardiac necrosis biomarkers, firstly troponin T and troponin I, myoglobin, then classic enzyme markers of necrosis: CK-MB and CK-MB mass, and finally indicator of renal function-creatinine.

Troponin evaluation had two phases. In the first phase we used an immunoassay method for determining myoglobin and troponin T – bedside assay in the Coronary Unit at the Cardiology Clinic. ROCH Cardiac Reader was used. By this method, 210 patients were examined in the beginning of the examination. After that, a new technology for determining troponin I was introduced in the central laboratory of the Clinical Center Niš. By this method, another 240 patients were examined. The second phase of examination was determining troponin I by method of Abbott Laboratories Diagnostic Division AxSYM, Abbott Park, IL 60064 from the USA, used in the Central laboratory of the Clinical Center Niš.

Quantitative immunological test for specific detection of myoglobin in blood was performed by the apparatus ROCH Cardiac Reader. Renal function was estimated by creatinine values in blood. Borderline values of Central laboratory of the Clinical Center were accepted (creatinine 53-115 mmol/l).

Early exercise stress tests was done at the end of hospitalisation in 284 patients, but not in 166 patients, or 36,8%. The primary aim of this test was to confirm the concord of troponin values results and positive exercise tests level.

Coronarography was done in 248 patients and was indicated in another 112 patients; it was

not performed in 90 patients. The largest number of coronarographies was done at the Department for Invasive Diagnostics at Cardiology Clinic, while smaller number of coronarographies was done in other centers. The key interest of coronarography study was to compare the coronarographic finding regarding the number of involved blood vessels and troponin status.

Statistic analysis of data significance was done by percentage relation, t-test and χ^2 test, Odds ratio (OR), Fisher test and Kappa measurement agreement.

Results

Applying inclusive criteria, 450 patients were included. Many patients could not be involved into examined group because the study was a multimarker one, so all the patients who did not meet criteria for multimarker examination (at least two markers and at least two determinations) were excluded.

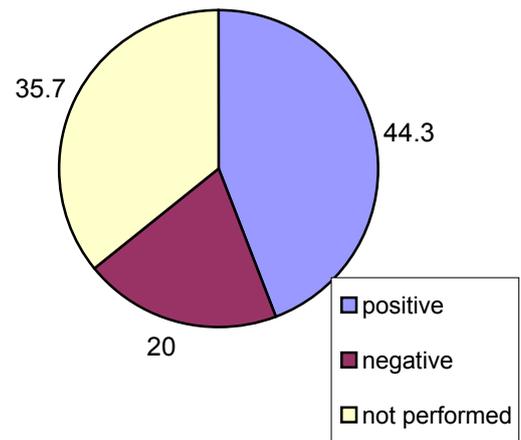
It was obvious that the most of the examined patients belong to NSTEMI group, about 49%, which is significant regarding the aim of the study. The presence of STEMI was diagnosed in 30% and UAP in 21%.

By including the aimed group NSTEMI on the basis of consensus document ESC/ACC, high TnT and TnI sensitivity was observed, as well as high myoglobin sensitivity and standard diagnostic possibilities CK-MB. The patients had, in statistically significant percentage, positive findings to TnT compared to myoglobin (93.6% to 82.8%; $\chi^2=5.12$; $p<0.05$) and compared to CK-MB (93,6% to 63,9%; $\chi^2=23.1$; $p<0.001$ OR=9.4; $3.25<OR<34.2$). Myoglobin was statistically significantly more often positive than CK-MB ($\chi^2=8.2$; $p<0.01$ OR=3.14; $1.32<OR<7.1$).

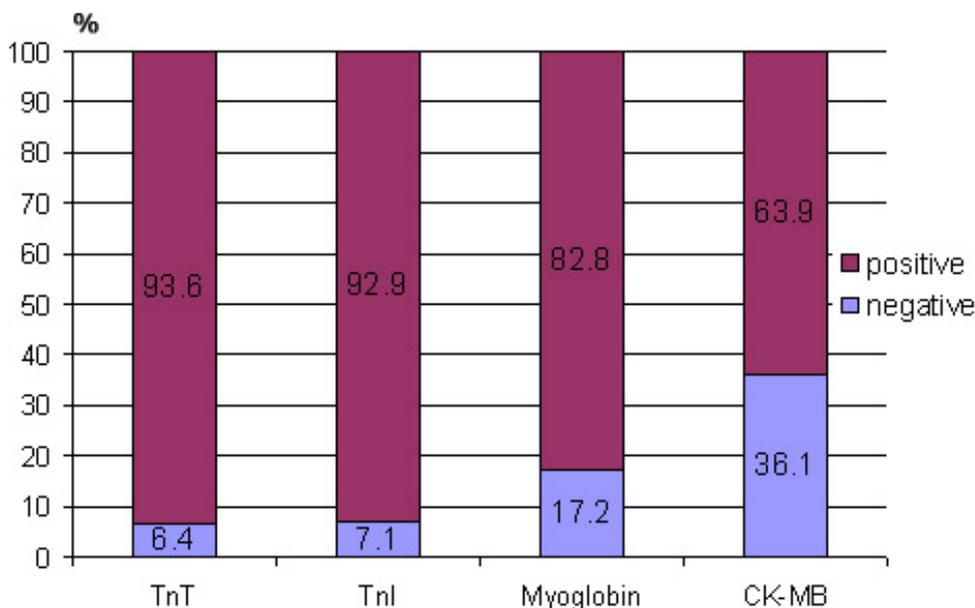
From the obtained data it is clear that troponin T was a more sensitive necrosis marker compared to CK-MB for 36,1%. Myoglobin showed high sensitivity as an early marker with positive values in 82.8%, proving to be a sensitive marker for early diagnostics of myocardial necrosis.

The patients had, in statistically significant higher percentage, positive findings to TnI compared to CKMB (92,9% to 63,9%; $\chi^2=12.4$; $p<0.001$ OR=7.5; $2.18<OR<32.5$). TnI and myoglobin were not statistically significantly different in positivity of the findings ($\chi^2=2.22$; $p=0.14$ n.s.). From the obtained data it can be seen that TnI was a more sensitive marker of myocardial necrosis compared to CK-MB for 32% (Graph 1).

Exercise stress testing was done in 284 patients with ACS, or 63,1%. There were 44,3% of positive tests, 20% of negative and not performed in 35.7% (Graph 2).



Graph 2. Tabular survey of performed exercise stress test



Graph 1. Positive markers frequency in patients with NSTEMI

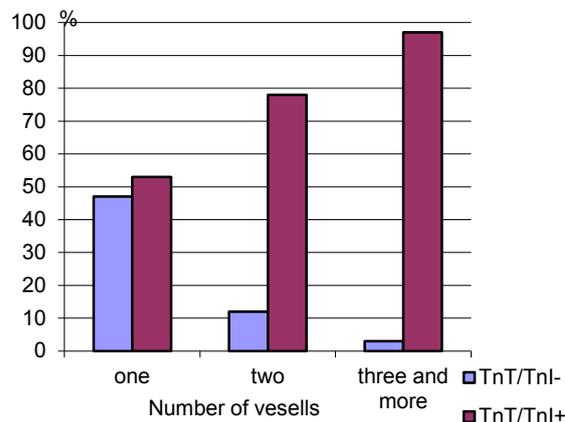
There is significant relation in positive exercise stress tests in patients who had positive TnT levels on admission. This difference is statistically significant ($\chi^2=5.6$; $p<0.05$) (Table 1).

By analysing the exercise stress tests results of TnT and TnI in united population, it can be seen that increase of positive tests is higher and statistically significant in the group with elevated troponin levels on admission ($\chi^2=5.2$; $p<0.05$ statistically significant) (Table 2).

A significant number of coronarographies was done ($n=248$), and in another 112 patients there were indications for coronarography because of recurrent angina or because of hemodynamic reasons. In the follow-up period of three months, they were on waiting list ($\chi^2=4.0$; $p>0.05$ n.s.).

In the group of patients with two diseased coronary vessels there were 78% troponin positive ones compared to 12% troponin negative patients. This increase can also be seen in the group with three or more diseased coronary vessels (3 vs. 97%), but this difference is not statistically significant (Graph 3)

Out of 248 patients who underwent coronarography, 79 (32%) underwent PTCA procedure and 32 (13%) bypass revascularisation. Statistic significance was present in choosing patients for PTCA procedure compared to troponin status (Fisher $p<0.05$) (Table 3).



Graph 3. Coronarography findings and troponin status relation

In patients selected for ACBG, troponin status was of no influence (Fisher $p=$ NS) (Table 4).

Discussion

This research is in fact an implementation of so far obtained knowledge about cardiac biomarkers, troponins, having an enormous contribution in fundamental knowledge of pathophysiological events in onset, duration and treatment of ACS. It is a about one of the key cardiological

Table 1. Exercise stress test and TnT status relation

Exercise Stress Test	TnT -		TnT +		Total
	n	%	n	%	
Negative	40	45.5	23	18.9	63
Positive	48	54.5	99	81.1*	147
Total	88	100.0	122	100.0	210

* $p<0.05$

Table 2. Exercise stress test and TnT/TnI status relation

Exercise Stress Test	Tn (T + I) -		Tn (T + I) +		Total
	n	%	n	%	
Negative	64	36.0	20	18.9	84
Positive	114	64.0	86	81.1*	200
Total	178	100.0	106	100.0	284

* $p<0.05$

Table 3. Ttroponin status and PTCA relation

PTCA	Tn (T + I) -		Tn (T + I) +		Total
	n	%	n	%	
PTCA -	72	96.0	97	56.1	169
PTCA +	3	4.0	76	43.9*	79
Total	75	100.0	173	100.0	248

* $p<0.05$

Table 4. Troponin status and ACBG relation

ACBG	(TnT +TnI)-		(TnT +TnI)+		Total
	n	%	n	%	
ACBG -	71	95.0	145	83.9	216
ACBG +	4	5.0	28	16.1	32
Total	75	100.0	173	100.0	248

NS

problems in diagnosing non-Q infarction compared to unstable angina, to diagnostics of small myocardial necrosis which bears a considerable risk (7).

By analyzing gender and age of our examined group, it can be seen that males were two and a half times more present than females, while females were 2,3 years older than males. Women had less serious and less extensive coronary disease. According to large studies experience, women are behind men in morbidity and mortality by 7 to 10 years. The number of sick women at the age of 75 is the same as the number of sick men at the age of 65. It is thought to be a consequence of protective role of women's sex hormones. Since women live longer, the total number of the sick is almost the same (6,7).

By analysing the structure of patients on admission and on discharge, a significant difference in frequency of ACS forms, made by implementation of cardiac necrosis markers, can be observed. Thus, on admission, the most frequent form of ACS in our population was UAP in 182 patients, or 50,98%, and on discharge NSTEMI in 120 patients, or 33,4% (7).

Ilić et al. in their analysis of patients with ACS treated at the Coronary Unit of the Institute in Niška Banja, found similar frequency in patients with or without ST segment elevation and more frequency in male patients. There was no significant difference considering the age (8).

Necrosis markers findings in the examined group of patients with NSTEMI are of significant interest. There is a high level of positive results in troponin analysis, TnT in 71 patients, or 94,4% and toponin TnI in 44 patients, or 93,2%. By correlation of troponin values, using, until recently valid, a golden rule for myocardial necrosis CK-MB (119 patients) or 62,2% positive, it can be seen that it was possible to verify more myocardial necrosis or infarctions by troponins, even for 32% for TnT and 31% for TnI. A finding of considerable number of positive results of myoglobin (66 patients or 83,3%) is worth of our attention, because it is the earliest marker of myocardial necrosis. Although myoglobin has been criticized for low specificity, high sensitivity is very useful for early selection of patients in the intensive care units. A high degree of correlation of TnT and TnI with CK-MB was found (7).

Exercise stress tests showed very good compatibility with positive troponin status, indicating that such patients should be send to invasive diagnostics.

Exercise stress testing has traditionally been used for detection of significant obstructive coronary diseases among patients with stabile form of chest pain, and as a stress test before coronary angiography. Among the patients with NSTEMI ACS, primary aims of exercise stress test were confirmation of the diagnosis of coronary disease and prognosis prediction. Exercise stress tests were predictive for future cardiac events in cases of stabile coronary disease in patients (4).

Biochemical markers for myocardial impairment detection play the key role for assessment and treatment of patients with ACS. When clinicians have to perform basic triage, treatment and monitoring on time-sensitive tests results, there are tests for fast and appropriate diagnostic option, complementary with central laboratory tests. This is particularly true when choice of effective therapy depends on cardiac biomarkers. Studies have demonstrated a connection between troponin results and effects of glycoprotein IIb/IIIa antagonist and LMWH, which was demonstrated. In this scenario, troponins are surrogate markers of active thrombotic process.

Biomarkers must not be taken as exclusive methods. Used along with information from history taking, physical examination and 12-lead electrocardiogram, cardiac markers help in establishing the diagnosis of myocardial infarction, risk assessment of subsequent clinical events and in planning further evaluation and treatment. Moreover, biomarkers have potential to ensure insight in specific pathophysiology of coronary ischemia for individual patients. Reaching each of these aims, cardiac troponins are highly specific and sensitive markers of myocardial impairment, functioning as a reliable way for defining prognosis and conducting therapy for patients with ACS.

According to findings of our examination, there is a very good correlation of troponin status and coronarographic finding, which can be seen from data that the highest troponin level and the most frequent occurrence of positive troponins are found in double or triple vessel disease, with characteristics of complex changes. A conclusion is that troponin status is a reliable predictor of severity of coronary disease and angiographic finding and a safe parameter in indicating urgent coronographies and interventional procedures.

Despite the risk in all the interventional procedures, FRISC II showed a persistent reduction in mortality in invasive group during the study period. So, in spite of high increase of early periprocedural myocardial infarction, there was no early mortality in the invasive group. The results of coronary artery bypass surgery in unstable CAD were the best when surgery was done after a few days of stabilisation on intensive antithrombotic and antiischemic therapy (9).

TnT elevation in patients with unstable angina is predictable for negative events. As there is no appropriate therapeutic concept for such high risk patients, Heeschen and Hamm (6) studied cardiac risk before, during and after coronary revascularisation in patients with unstable angina stratified according to TnT status.

According to these authors' findings, troponin-positive patients had much more serious coronary artery disease which demanded revascularisation (69% vs 59%). Also, after coronary intervention there were more complications (dying or MI 15,3% vs 4,8%). During 30 day follow-up, cardiac risk remained elevated in troponin-positive patients. So, TnT fast testing reliably

identifies high-risk patients with unstable angina. High frequency of the events was observed earlier, especially joined with coronary intervention. Early risk stratification plays a key role in selecting patients who will most benefit from the therapy. The above mentioned authors have studied coronary intervention results according to TnT status. Meanwhile, eight patients developed acute infarction before angiography. In 108 TnT-positive patients, the angiogram showed significant changes in at least one vessel. After considering all troponin positive patients, revascularisation was done by PTCA in 50% and ACBG in 11%. On the contrary, in troponin-negative patients there was much less significant stenosis, so 46% of patients underwent revascularisation. It is interesting that in troponin-positive patients after coronary intervention there were more recurrent cases of anginas pectoris, in relation 4,8% vs 2,2%. Contrary to other studies, in this one TnT status was taken for diagnostic and therapeutic decision making during hospitalization. Angiographic studies indicated that thrombus, in patients with unstable angina, is thrombocytes rich, in contrast to fibrin thrombus observed in patients suffering from AMI (5).

Ambroze et al. investigated the relation between troponin status and angiographic finding in patients with UA or NSTEMI. Complex lesions were found in 72% of troponin-positive patients and 41% in troponin-negative ones. Presented data from the study supported the hypothesis that troponin elevation was joined with the presence of complex lesions (plaque disruption and/or thrombosis). Supporting previous observations that microinfarction, possibly secondary, because of embolisation of distal vascular bed, is a pathophysiological mechanism for positive troponin in patients with unstable angina and NSTEMI. Another mechanism for troponin positivity with the presence of thromb involves temporary total occlusion, vasospasm or occlusion of small lateral branches at the lesion site. Sensitivity and specificity of elevated troponin for the presence of lesion complex was moderate with positive predictable values of 72%. Compared to angiography, angiography is relatively non-sensitive in discovering intracoronary thromb, although highly specific for their presence. It is probable that many troponin-positive patients have intracoronary thromb which can be detected angiographically. The authors also presented a claim that the presence of complex lesions was not always joined with troponin positivity (10)

Numerous clinical studies have shown that interventions, especially revascularisations, can be performed by following troponin values. In

that case, very low borderline values are used for cTnT 0,01 mg/l (9-12).

In our investigation, out of 104 patients who had coronarography performed, 29 patients (8,1%) underwent PTCA procedure, 25 patients (7%) underwent bypass revascularisation. Statistical significance was reported while choosing patients for PTCA procedure in relation to troponin status, while in patients selected for ACBG troponin status was of no influence (7).

Unstable coronary artery disease increases the TnT level and occurrence of ST segment depression in poor prognosis. In FRISC II study, it was evaluated if TnT level alone and combined with ST depression identified much more serious coronary artery disease or more efficient invasive strategy. Invasive strategy reduces death/MI to 12 months with both ST depression and TnT level $\geq 0,03$ mg/l from 22,1 to 13,2%. Patients with unstable coronary artery disease with a combination of TnT level $\geq 0,03$ mg/l and ST depression have poorer prognosis. In these patients, early invasive strategy will significantly decrease death/MI (9).

In unstable coronary artery disease, elevation of troponin level is associated with poorer prognosis. Also, the patients with ST segment depression have a greater risk of future cardiac events. FRISC II study randomized patients with unstable coronary artery disease to early invasive vs noninvasive strategy. Invasive strategy led to significant reduction of both death and MI. In this substudy of FRISC II study, authors investigated if TnT level alone, or in combination with occurrence of ST segment depression, can indicate angiographic severity of coronary artery disease and identify the group of patients with different benefits from early invasive strategy (9,15,16).

Coronary angiography remains an essential device in examination and risk stratification in patients with ACS. Serious coronary lesions are more frequent in patients with ischemic signs, that is, with segment depression or with troponin elevation (17).

Conclusion

In our investigation, both diagnostic and prognostic troponin values were established, confirmed by statistically significant correlation of troponin values and exercise stress tests findings on discharge.

Cardiac troponin levels in patients with acute coronary syndrome were reliable factors for the degree and severity of coronarographic finding, as well as a guideline in choosing invasive treatment strategy.

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TROPONINI, TEST FIZIČKIM OPTEREĆENJEM I KORONAROGRAFSKA PROCENA OZBILJNOSTI AKUTNOG KORONARNOG SINDROMA

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Uprkos napretku u dijagnostici i lečenju akutnog koronarnog sindroma (ACS), i dalje postoji problem neželjenih događaja nakon ACS, koji povećavaju šanse smrtnosti za 10%. Verifikacija pacijenata koji mogu biti kandidati za ove neželjene događaje je osnov za prevenciju, lečenje i smanjenje smrtnosti.

Jedna od strategija koja daje dobre rezultate je kombinacija praćenja nivoa troponina, testova fizičkim opterećenjem i koronarografije.

Korelacija vrednosti srčanih markera u akutnom koronarnom sindromu i ozbiljnosti koronarne bolesti procenjena testovima fizičkim opterećenjem i koronarografijom, kao i uticaja markera na terapiju izbora.

Studija je obuhvatila 450 pacijenata. Laboratorijske analize su uključile troponin T i I (TNT, TNI), mioglobin, CK-MB i CK-MB mass. Ergometrijska i invazivna ispitivanja su rađena na kraju hospitalizacije.

Postoji značajana povezanost u pozitivnim testovima fizičkim opterećenjem kod troponin pozitivnih pacijenata, što je statistički signifikantno. Analiza testova opterećenja pokazala je statistički značajan porast pozitivnih nalaza kod troponin pozitivnih ($p < 0,05$). Od 104 koronarografija u grupi sa dva obolela koronarna krvna suda bilo je 46,4% Tn pozitivnih, u poređenju sa 29% troponin negativnih pacijenata, što se takođe može videti u grupi sa ≥ 3 obolela koronarna krvna suda (3,2 vs 14,8%). Od 104 koronarografisanih pacijenata kod 29 (8,1%) je urađena PTCA i kod 25 (7%) ACBG. Statistički značajna razlika bila je kod pacijenata sa PTCA u odnosu na status Tn ($p < 0,05$), dok to nije slučaj u grupi sa ACBG.

U našem istraživanju dobra dijagnostička i prognostička vrednost troponina je zasnovana i potvrđena statistički značajnom korelacijom između vrednosti troponina i testova fizičkim opterećenjem na otpustu. Oni su bili pouzdani pokazatelj stepena i ozbiljnosti koronarografskih nalaza, kao i vodič u izboru invazivne strategije lečenja. *Acta Medica Medianae 2012;51(4):5-12.*

Ključne reči: troponin, akutni koronarni sindrom, test fizičkim opterećenjem, koronarna angiografija