CORRELATION OF SEVERITY OF ELECTROCARDIOGRAPHIC CHANGES AND TROPONIN LEVEL IN ACUTE CORONARY SYNDROME

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The level of troponins and change in electrocardiograms are two corner stones for the diagnosis of acute coronary syndrome (ACS).

The aim of the study was to investigate the correlations between electrocardiographic (ECG) changes and troponin status in ACS.

The examined population involved 333 patients admitted to the Coronary Care Unit with the admittance diagnosis of ACS. Of exceptional interest was the myocardial infarction without ST elevation (NSTEMI) which included 50% of patients.

The changes in electrocardiogram: existence and depth of ST-segment depression on admittance during the treatment and discharge; changes on T wave and forming of new Q wave. Advantage is early appearance of electrocardiographic changes before troponins elevation. Troponins (T and I) were examined for positive and negative results and top of concentration. This method's advantages are sensitivity and specificity.

Results: ST-segment depression of 1 and 2 mm was found in 21% of patients; 3-4 mm in 10% and \geq 5 mm in 2.63% of patients. Troponin was positive in 40% of patients. In 65 (34%) patients, there was no electrocardiographic change except for positive troponin.

Conclusion: High sensitivity and specificity of troponins were proved in ACS diagnosing and there was good correlation with depth of ST-segment depression. This is of special interest in making NSTEMI diagnosis and risk stratification. Troponin level in combination with depth of ST-segment depression identifies much more serious coronary arterial disease and much more effective early invasive strategy. *Acta Medica Medianae* 2007;46(2):9-15.

Key words: acute coronary syndrome, ECG changes, troponins (T and I), NSTEMI

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Introduction

Within acute coronary syndrome (ACS) there are patients with wide variation of clinical course and subsequent cardiac events risks. In order to select an appropriate therapeutic approach for each patient, it is necessary to ensure precise diagnostics and assessment of further cardiac events risks. The assessment should be made in very early stage, during the admission procedure, should be based on directly available clinical, electrocardiographic and easily available, reliable tests by the patients bed and on laboratory data, particularly on sensitive and specific biomarkers. Primary assessment must be repeatedly revised in the light of continuous symptoms, signs and additional information based on ECG and biochemical monitoring, as well as the assessment of the left heart chamber function (1).

Second diagnostic tool is 12-lead ECG, providing the earliest available objective information for risk stratification of the most of ACS patients;

while the ST depression segment qualitative importance on ACS patients basic ECG is recongnized clinically, the quantification of these phenomena is rarely used in clinical practice. In recent evaluation of patients from the PARAGON A study, the authors documeted prognostic significance of qantitative ST segment depression for one-year mortality among patients with non-ST segment elevation ACS. In patients with ST \downarrow \geq 2 mm in 2 or more adjacent leads, the probability of dying was 6 times higher within 1 year than it was the case with patients without ST depression (2).

Introduction of cardiac troponins measurements in the routine clinical practice was an important cornerstone for continuation of much more effective early risk stratification of ACS presented patients. Higher levels of cardiac troponins are related to worse outcome in ACS patients both with ST segment elevations MI and non-ST segment elevation, respectively (2). Because the cardiac troponin T requires some time to emerge, ECG changes are more directly available in the acute ischemic event, their potential complementary role in risk stratification of ACS presented patients is of interest (2,3).

More than one third of Mis were not diagnosed in Frammingham's study. Sheifer at al. reported that at least one fourth of all MIs have not been clinically recognized and that their lethality was the same as in those recognized Mis (1). In the presence of normal ECG appearance, ACS is not excluded. In patients with ischemiaconsistent symptoms and normal ECG, there may be approximately found 4% of those with APNS, and 1 - 6% will have the evidence of myocardial necrosis (i.e., NSTEMI).

Although the ST changes prognostic value on admission of patients with non ST - ACS elevation is known, the use of ECG on discharge is unknown. Therefore, by using PARAGON-B troponin substudy, the authors assessed ST depression prevalence both on admission and discharge, probability of new Q-wave development on discharge, and additionally, prognostic values of these changes. This study throws light on dynamic ECG changes, occuring between the admission and discharge in ACS patients without ST elevations, permits further risk stratification and determines the probability of 6-month dying and/or reMI. However, the incidence of new Qwave, its relation to ST segment status and prognostic implications of these findings are not clearly understood (3).

Aims

The aim of the paper was to investigate the value of cardiac markers in ACS diagnostics, especially within APNS/NSTEMI group, correlation between ECG markers and cardiac troponins levels, as well as their prognostic significance.

Material and methods

The studied population involved the patients from the Cardiology Clinic Coronary Unit in Nis, treated in the period of 2002, 2003 and 2004.

During the three-year time interval, there were 2775 patients admitted to the Coronary Unit, in all kinds of urgent cardiological conditions. Of that number, there were singled out 1568 patients or 56.50% with ACS working diagnosis on admission.

By applying the inclusion criteria, the population of 333 patients was selected. Many patients could not enter the studied population because of determination to deal with multimarker study, which resulted in rejection of all patients who did not have the criteria for multimarker examination (two markers and two determinations, at least).

It is obvious that the largest number of the patients examined belong to the NSTEMI group, virtually 50%, which is significant having in mind the examination subject. The increase of this ACS form was observed in big studies while simultaneously, a gradual decrease of STEMI was noted.

There were 251 male patients, or 2/3, while the number of female patients was 106 or 1/3. The mean age of male examinees was $61,86\pm 11,02$ years, and of female ones - $64,19\pm10,14$ years. Although females were older 2.33 years on average, the difference was not statistically significant (t=1,870; p>0,05).

There were 12.2% of the patients under the age of 49, 31.3% from 50-59, 33.9% from 60-69 and 22.6% more than 70 years old. Most of examinees belonged to the population aged 50 to 59 years as well as 60 to 69 years. The other two age subgroups were represented in somewhat lower percentage.

The total follow-up period lasted 3 months. The control check-ups were performed in the 1st and 3rd month from the discharge and included clinical examination, ECG, establishing of the course of disease in terms of recurrent angina, reinfarction, revascularization or percutaneous intervention, as well as the outcome.

ECG was recorded twice during the admission procedure: in the admission office and immediately after the patient's placement in the Coronary Unit (within 10-15 min. period). All patients were followed up on the monitor, 24 hours, at least. ECG analysis: ECG was recorded in 12-lead format, with paper speed of 25 mm/sec. with correct calibration of 1 mV. ST segment depression occurred when J point was in depression for 1 mm or more and it was followed by horizontal or low-running ST depression with the least duration of 0.08 sec. in two adjacent precordial leads or two extremities leads. Q wave or Q wave equivalent was being determined by the use of Selvester QRS screening criterium. The finding was designated as Q-wave if its duration was \geq 30 ms in aVF, \geq 40 ms in leads I and aVL, \geq 40 ms in more than two V4,V5 or V6 or any other Q wave in V2. Additionally, Q-wave equivalent is an acceptable finding as R-wave \geq 40 ms in V1, or R-wave ≤ 1 mm and ≤ 10 ms in V2. Myocardial infarction is defined either as a new Q wave (duration ≥0.04 sec., or at least one fourth of Rwave height in two or more adjacent leads) or increase of myocardial necrosis markers (troponin), new episodes of chest pain with combination of new troponin elevations. Laboratory testing is the target examination and it included heart necrosis biomarkers in the first place, troponin T and troponin I, myoglobin, then, classic enzyme markers of necrosis: CK-MB and CK-MB mass and finally, the kidney function indicator - creatinine.

Troponin examination had two phases. In the first phase, myoglobin and troponin T determination method was used by immunoessay application method performed before the patients in the Cardiology Clinic Coronary Unit. The apparatus used was ROCH Cardiac Reader. This method enabled examination of 210 patients at the beginning of this investigation. After that, there was introduced the technology of troponin I determining in the Central laboratory of Clinical Center Nis. By this method, 128 more patients were examined. The second examination phase consisted of determining troponin I by the method Abbott Laboratories Diagnostic Division AxSYM, Abbott Park, IL 60064 of USA, applied in the Central laboratory of Clinical Center Nis.

Myoglobin: Quantitative immunologic test for specific detection of myoglobin in blood, apparatus ROCH Cardiac Reader. The function of kidneys was examined via blood creatinine levels. There were accepted boundary values of the Central laboratory of the Clinical Center Nis (Creatinine 53-115 mmol/l).

Statistical analysis of data regarding the obtained results significance was obtained via: percentual relationship, t-test and χ^2 test, Odds ratio (OR), Fisher test, and Kappa accord measure.

Results

The differences in numerical and percentual ratios on admission and discharge were generated by transition of one number of patients from one to another category (unstable angina pectoris on admission, into stable on discharge, as well as NSTEMI into STEMI) (Table 1). Thus, in admission diagnoses, the most frequent were APNS 182 or 50.98%, followed by STEMI with 106 or 29.69% and the least NSTEMI 66 or 18.49%. In discharge diagnoses, NSTEMI number was significantly increased to 120, or 33.4%, while APNS number dropped to 109, or 30.4%. APS also increased from 2 on admission to 21 on discharge, which makes 5.8%, as the result of troponin application as a key diagnostic parameter.

Table 1: ACS forms structure on admision & discharge

Diagnosis	Initial dia	agnosis	Final diagnosis		
Diagnosis	Frequency	%	Frequency	%	
NSTEMI	66	18.49	120	33.4	
STEMI	106	29.69	105	29.2	
APNS	182	50.98	109	30.4	
APS	2	0.56	21	5.8	
Silent ischemia	1	0.28	2	0.8	
Total	357	100.00	357	100.0	

By distinguishing target NSTEMI population based on consensus document ESC/ACC, exceptional TnT and I sensitivity, high myoglobin sensitivity and standard diagnostic potentials of CK-MB were noted.



Graph 1. Positive markers frequency in NSTEMI patients

In statistically significant percentage, patients had positive findings to TnT in relation to myoglobin (94.4% to 83.3%; χ^2 =4.29; p=0.039<0.05) and in relation to CK-MB (94.4% to 62.2%; χ^2 =24.06;

p=0.000<0.001 OR=10.19; 3.27<OR<35.31). Myoglobin was, statistically significantly, more frequently positive than CK-MB (χ^2 =9.00; p=0.003<0.01 OR=3.04; 1.37<OR <6.88). Data indicated that troponin T was more sensitive marker of necrosis compared to CK-MB for 32.2%. Myoglobin has shown high sensitivity as an early marker with positive values in 83.3%, which proves its appropriateness for early diagnostics of myocardial necrosis.

In statistically significant higher percentage, patients had positive findings to TnI in relation to CKMB (93.2% to 62.2%; χ^2 =14.86; p=0.000<0.001 OR=8.31; 2.28<OR<35.8). There was no statistically significant difference between TnI and myoglobin in positive findings (χ^2 =2.31; p=0.129 n.s.). Data showed that TnI was more sensitive marker of myocard necrosis compared to CK-MB for 31% (Graph 1).

The study of the population and ST deperession severity showed that most of the patients had ST depression (1 mm and 2 mm, each by 21%), the subgroups with great deperession (3 and 4 mm about 10%), and the greatest - 5 mm in 2. 63% (Graph 2).



Graph 2. ECG analysis of ST segment depression level in group APNS/NSTEMI

It can be observed that 65 patients or 34.21% did not have ST depression on admission ECG, but among them, 36.4% had troponin test positive, which may impact the therapeutic decisions. There was a significant correlation between ST depression and positive TnT findings. In all ST depression patients subgroups, a statistically significantly high troponin level (χ 2=9.54, p=0.008<0.01) was recorded (Table 2).

Table 2. Group structure with ST↓ APNS/NSTEMI

ST ↓value	TnT –		Tn	Total	
(mm)	n	%	n	%	TULAI
Without (0)	13	24.1	24	36.4	37
1-3 mm	36	66.7	26	39.4	62
4+ mm	5	9.3	16	24.2	21
Total	54		66		120

TnI levels are much more elevated with ST depression depth increase.

Levels of Troponin I were more expressed with icreasing of ST depression (Table 3).

Table 3. ST↓ >APNS/NSTEMI group structure

ST↓ value	TnI –		Tn	Total	
(mm)	n	%	n	%	Total
Without (0)	13	56.5%	15	35.7%	28
1-3 mm	10	33.5%	23	54.7%	33
4+ mm			4	9.6%	4
Total	23		42		65

ST depression prognostic capacity shown in the Table 4 - Mortality rose with ST depression depth, being highest in the subgroup with depression exceeding 4 mm.

Table 4. Total lethality in patients NSTEMI with ST $\downarrow > 0.5$

ST (mm)	Died		Sur	Total	
51¥ (IIIII)	n	%	n	%	TOLAT
0.5< ST↓ ≤ 2			31	100.0	13
2< ST↓ ≤ 4	2	7.7	24	92.3	26
ST↓ > 4	1	33.3	2	66.7	3
Total	3	5.0	57	95.0	60

There were no T-wave changes in 45.1% and T-wave changes in terms of negative and two-phase T-waves in 54.9% of the patients. Criteria mentioned in the section Material and methods were observed. The changes in T wave showed a lower prognostic value; however, around 40% of the patients with T wave changes had TnT positive results, which may be significant in therapeutic decision making. In correlation of T wave ECG changes and the TnI level, that relationship was more expressed, reaching 50% of positive results (Table 5).

Table 5. T wave ECG changes and TnT level correlation in NSTEMI

	TnT-		TnT+	
T wave changes (±/-)	n	%	n	%
No changes	3	4.2	37	52.1
T wave change	1	1.4	30	42.3
Total	4	5.6	67	94.4

T wave changes related to increased TnI levels were found in 50.0% (Table 6).

Table 6. Relationship of T wave ECG changes and TnI level in NSTEMI

T wave changes (+/-)	Tr	ιI–	TnI+	
	n	%	n	%
No changes	2	4.5	19	43.2
T wave changes	1	2.3	22	50.0
Total	3	6.8	41	93.2

Development of pathological Q wave during hospitalization or on discharge had a big prognostic

significance. Formation of Q wave occurred with troponin level increase. Out of 220 patients with APNS/NSEMI, with no Q-wave on admission, 18, or 8.18% patients developed Q-wave during hospitalization (Table 7).

Table 7. Presentation of patients with admission DG APNS/NSTEMI who developed pathological Q wave

Parameter	Q-w disc	ave on charge	No Q-wave on discharge		
	n	%	n	%	
No Q-wave on admission	213	91.82	18	8.18	

In 10 patients, presented as NSTEMI on admission, a new Q-wave was developed, which makes 13.51% of TnI positive, while in the troponin negative group, Q wave was not developed, which was statistically significant. (Fisher p=0.011<0.05) (Table 8).

 Table 8. TnI level in patients who subsequently developed pathological Q wave

Darameter	TnI –		Tr	Total	
raiametei	n	%	n	%	
No Q-wave on discharge	27	36.49	37	50.00	64
Q-wave on discharge			10	13.51	10
Total	27	36.49	47	63.51	74

Discussion

Testing covered a very significant number of patients, practically all successive patients being admitted to the Cardiology Clinics of Nis Coronary Unit with ACS diagnosis on admission.

Gender and age analyses of studied population show that males were 2.5 times more prevalent than females, while females, in return, were 2.3 years older than males. Women were found to have less serious and extensive coronary disease. According to the experience of extensive studies, women lag behind men, in terms of morbidity and mortality, by 7 to 10 years. The number of diseased women aged 75 equals the number of diseased men aged 65. This is considered to be the result of female sex hormons protective effect. Having in mind that women live longer, the total number of the diseased is almost equal (4).

The analyses of patients' structure on admission and discharge reveal significant difference in ACS forms frequency, generated by the application of cardiac necrosis markers. Thus, on admission, the most frequent ACS form in our population was APNS, in 182 patients or 50.98%, while on discharge, it was NSTEMI in 120 patients or 33.4%. Also, the role of miocardial necrosis markers in negative selection after admission was reported, reflected in significant increase of the number of patients with the diagnosis of stable angina (APS number increased, from 2 to 21), which enabled patients' transfer to lower level of care or discharge from hospital. Patients with APS, as a rule, were not admitted to the Coronary Unit, except in case that APNS was suspected.

After the changes in the structure of admission diagnoses due to enzymic status, the ACS forms frequency in our patients was as follows: NSTEMI 49.25%, STEMI 31.34% and APNS 19.40%. ACS forms' distribution in a big GRACE study was somewhat different. Most of the patients were with APNS 40%, STEMI 32% and NSTEMI 20%.

Ilic at al., in their analysis of patients with ACS, treated in the Institute in Niska Banja Coronary Unit, found a similar frequency of patients, with and without ST segment elevation, higher frequency of male patients. There was no significant difference in the age structure (5).

The examination results also lead to the conclusion that troponin status was in excellent correlation with the severity of coronary disease and with long-term mortality of these patients. The results correlated well with ECG data and they were also superior in relation to CK-MB results.

In our study, 10 patients presented on admission as NSTEMI, developed a new Q wave, which makes 13.51% TnI positive, while in the troponin negative group there were no developments of Q wave, which is statistically significant.

In PARAGON-B TnT substudy, patients with new ST \downarrow on discharge had higher reMI and dying frequencies per each 6 months, when compared to those who have never had ST↓ (20.6% vs 7.4%) and (20.6 vs 8.3%). Patients with persistent $ST\downarrow$ on discharge had higher frequency of dying, (re)MI or dying composite and (re)MI in 6 months then those without $ST\downarrow$, either on admission or discharge (6 vs 0.9%) (16.3 vs 7.4%) (20 vs 8.3%) interdependently. A group with new ST \downarrow on discharge had higher (re)MI and dying frequencies per 6 months than the group without such changes. Survival of patients without $ST\downarrow$, either on admission or discharge significantly differ when compared to patients with persistent ST \downarrow and those who had their ST \downarrow normalized on discharge. Additional relative dying risk per 6 months among patients with persistent $ST\downarrow$ on discharge vs those without ST \downarrow , was 5.18%. Patients with persistent $ST\downarrow$ had significantly higher frequency of dying /(re)MI when compared to patients without $ST\downarrow$, both on admission and discharge ECGs and those with normalized ST \downarrow on discharge. Additional relative risk of duying /(re)MI per 6 months among patients with normalized ST \downarrow v.s. those without ST \downarrow , was 1.20 to 2.14, and among patients with persistent $ST\downarrow$ on discharge vs those without $ST\downarrow$, additional relative risk was 2.58. (2,3,10)

There was no statistically significant difference in prevalence of Q waves on admission and discharge ECGs within the unstable angina and NSTEMI. Among the patients without ST depression, in both admission and discharge ECGs, the patients with non-ST elevation MI had significantly higher

prevalence of Q waves on discharge than the patients with unstable angina.

Studies have shown that ST-segment depression on admission ECG is related to unfavourable short-term and long-term outcomes. As evident from admission characteristics of those with persistent ST depression on discharge, such patients were older, most probably diabetics, with higher frequency of previous miocardial infarction and heart failure: their Kilip class on admission and higher TnT elevation suggest higher risk from future events.

Schechtman at al. have shown that ST depression on discharge ECG in patient presented with NSTMI is independent significant predictor of bad prognosis. These findings, perhaps, may represent big residual areas of hypoperfused ischemic myocard of critically stenozed infarction responsible artery, hibernated myocard or continuous silent myocardial ischemia, and in that way predisposed for unfavourable events (6).

Kleiger at al. have shown that patients with non-ST MI may develop Q wave during hospitalization or on discharge. Most of those who subsequently developed Q wave (70%) do that within the first 3 days. This study provided new information regarding a prognostic value of Q waves on discharge ECG in patients with non-ST elevation of ACS. Even after exclusion of patients with hospital reMi, those with Q wave on a discharge ECG had significantly higher mortality each 6 months. This study confirms the prognostic value of ST segment depression ≥ 1 mm on admission ECG and also demonstrates that dynamic changes, incurring between admission and discharge ECGs in patients with non-ACS elevation, will permit further stratification of these patients. Moreover, this study provides new information related to Q waves prevalence on discharge ECG in patients with non-ST elevation of ACS and their relatedness to bad long-term outcome. Thus, additional changes on discharge ECG for ACS patients treatment will be useful in tailoring corresponding follow-ups and strategies of treatment (3).

The current study is the first one in identification that the continued multilead ST segment monitoring may be useful for prospective identification of patients to benefit from antithrombotic therapy. Furthermore, continuous multilead ST segment monitoring may be an additional means for targeted carrying out of antithrombotic therapy in heterogene population of patients with unstable coronary arterial disease (7).

In combination, marker appearance is to ensure integrated and improved demarcation of ACS risks spectrum: with the least frequency of unfavourable outcomes observed in cTnT negative patients without ST depression (8.4%) and with greatest frequency as observed in cTnT positive patients with ST depression $\ge 2 \text{mm} (26,8\%) (2)$.

Unstable coronary arterial disease increases the TnT level, and the appearance of ST segment depression correlates with worse prognosis. In FRICS II study it was evaluated if the TnT level alone or in combination with ST depression identify much more serious coronary arterial disease or much more efficient early invasive strategy. Invasive strategy reduces dying/MI to 12 months in a group with ST depression and TnT level \geq 0,03 µg/l from 22.1 to 13.2%.

Elevation of TnT level and ST depression in electrocardiographic results were, in essence, related to the increased risk of future events. In this study, the worst prognosis was seen in patients with a combination of TnT level \geq 0,03 µg/l and ST depression, with 22% dying frequency or MI and 5.9% mortality per each 12 months, both were twice higher compared to the other part of population study (8).

In unstable coronary aterial disease, the troponin level increase is related to worse prognosis. The elevated troponin level, as well, was found to identify responders for treatment with antithrombotic drugs. The patients with ST segment depression, as well, are at higher risk of future cardiac events. FRICS II study randomized patients with unstable coronary arterial disease to early invasive vs non-invasive strategy. Invasive strategy after 12 months brought about significant reduction of both dying and MI. In this substudy of FRISC II study, the authors investigated if the TnT level alone, or in combination with occurence of ST segment depression, may indicate angiographic severity of coronary arterial disease and identify groups of patients with different benefits from early invasive strategy (9).

Conclusion

Troponin high sensitivity and specificity were proved in diagnosing acute coronary syndrom, as well as their relatedness to ST deperession size, changes in T wave and appearance of a new Q wave. In our study, troponin values were particularly valuable in diagnosing NSTEMI and risk stratification.

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KORELACIJA TEŽINE ELEKTROKARDIOGRAFSKIH PROMENA I TROPONINSKOG STATUSA U AKUTNOM KORONARNOM SINDROMU

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Nivo troponina i promena elektrokardiograma su dva ugaona kamena za dijagnozu akutnog koronarnog sindroma (AKS).

Cilj rada bio je ispitivanje korelacije elektrokardiografskih (EKG) promena i troponinskog statusa u AKS. Ispitivanu populaciju je činilo 333 bolesnika koji su primljeni u Koronarnu jedinicu sa prijemnom dijagnozom AKS. Od posebnog interesa bio je miokardni infarkt bez ST- segment elevacije (NSTEMI) koja je obuhvatala 50% bolesnika.

Praćene su promene u elektrokardiogamu: postojanje i dubina ST-segment depersije na prijemu, tokom lečenja i otpustu, promene na T talasu i formiranje novog Q zubca. Prednost je rana pojava elektokardiogramskih promena pre javljanja troponina. Vršeno je ispitivanje troponina (T i I) u pogledu pozitivnih ili negativnih vrednosti kao i vrha koncentracije. Prednost ove metode je bila senzitivnost i specifičnot. ST-segment depresija 1 i 2 mm nađena je kod 21% bolesnika, 3-4 mm u 10% i \geq 5 mm u 2,63%. Troponin je bio pozitivan kod 40% bolesnika. Kod 65 bolesnika (34%) nije bilo elektrokardiogramskih promena ali su imali pozitivan troponin.

Dokazana je visoka senzitivnost i specifičnot troponina za dijagnozu AKS kao i dobra korelacija sa dubinom ST-segment depresije. Ovo je naročito važno pri postavljanju dijagnoze NSTEMI i stratifikaciji rizika. Nivo troponina u kombinaciji sa dubinom ST-segment depresije identifikuje mnogo ozbiljniju koronarnu bolest i mnogo efikasniju ranu invazivnu strategiju. Acta Medica Medianae 2007;46(2):9-15.

Klučne reči: akutni koronari sindrom, NSTEMI, troponin T, troponin I, EKG promene