



## Association between serum concentration of parathyroid hormone and left ventricle ejection fraction, and markers of heart failure and inflammation in ST elevation myocardial infarction patients treated with primary percutaneous coronary intervention

Udruženost serumske koncentracije paratireoidnog hormona i ejeckione frakcije leve komore, markera srčane insuficijencije i inflamacije u akutnom infarktu miokarda sa ST elevacijom lečenim primarnom perkutanom koronarnom intervencijom

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### Abstract

**Background/Aim.** Previous studies have shown increased serum concentration of parathyroid hormone (PTH) in acute myocardial infarction and heart failure. In this study we examined the relationships between parathyroid hormone status and biochemical markers of myocardial injury and heart failure, as well as electrocardiographic (ECG) and echocardiographic indicators of infarction size and heart failure. **Methods.** In 390 consecutive patients with ST segment elevation myocardial infarction (STEMI), average age  $62 \pm 12$  years, laboratory analysis of serum concentrations of creatine kinase MB isoenzyme (CK-MB), C-reactive protein (CRP) and intact PTH and plasma concentration of brain natriuretic peptide (BNP) were done during the first three days after admission. All patients were treated with primary percutaneous coronary intervention (PCI). Exclusion criterion was severe renal insufficiency (glomerular filtration rate  $\leq 30$  mL/min). Serum concentration of PTH was measured on the 1st, 2nd and, in some cases, on the 3rd morning after admission and maximum level of PTH was taken for analysis. Patient cohort was divided into four groups according

to quartiles of PTH maximum serum concentration (I  $\leq 4.4$  pmol/L; II  $> 4.4$  pmol/L and  $< 6.3$  pmol/L; III  $\geq 6.3$  pmol/L and  $< 9.2$  pmol/L; IV  $\geq 9.2$  pmol/L). Selvester's ECG score, left ventricle ejection fraction and wall motion index (WMSI) were determined at discharge between 5–14 days after admission. **Results.** We found that LVEF at discharge significantly decreased ( $p < 0.001$ ) and WMSI at discharge and ECG Selvester's score significantly increased across the quartiles of PTH max. level ( $p < 0.001$  for both parameters). BNP, CRP and CK-MB isoenzyme level significantly increased across the quartiles of PTH max. level ( $p < 0.001$ ;  $p < 0.001$  and  $p = 0.004$ , retrospectively). **Conclusion.** The patients in the 4th quartile of PTH had significantly lower LVEF and higher WMSI and Selvester's ECG score at discharge. This group of patients also had higher levels of BNP, CRP and CK-MB in blood in the early course of STEMI.

**Key words:**  
parathyroid hormone; st elevation myocardial infarction;  
heart failure; biomarkers.

### Apstrakt

**Uvod/Cilj.** U prethodnim studijama pokazano je povećanje serumske koncentracije paratireoidnog hormona (PTH) u akutnom infarktu miokarda i srčanoj insuficijenciji. U ovom istraživanju ispitali smo odnos između paratireoidnog statusa i biohemijskih, elektrokardiografskih i ehokardiografskih pokazatelja veličine infarkta i srčane insuficijencije. **Metode.** Kod 390 bolesnika sa akutnim infarktom miokarda sa elevacijom ST segmenta (STEMI), prosečne dobi  $62 \pm 12$  godine, učinjene

su laboratorijske analize serumske koncentracije kreatin kinaza MB frakcije (CK-MB), C-reaktivnog proteina (CRP) i intaktnog PTH i koncentracija u plazmi moždanog natriuretskog peptide (BNP) tokom prvih tri dana od prijema. Svi bolesnici su lečeni primarnom perkutanom koronarnom intervencijom (PKI). Bolesnici sa težom bubrežnom insuficijencijom isključeni su iz studije (klirens kreatinina  $\leq 30$  mL/min). Serumska koncentracija PTH određivana je prvog, drugog i, u nekim slučajevima, trećeg dana posle prijema i najveća dobijena koncentracija je uzeta za analizu.

Kohorta bolesnika je podeljena u četiri grupe na osnovu kvartila maksimalne izmerene serumske koncentracije PTH (I  $\leq$  4.4 pmol/L; II  $>$  4.4 pmol/L i  $<$  6.3 pmol/L; III  $\geq$  6.3 pmol/L i  $<$  9.2 pmol/L; IV  $\geq$  9.2 pmol/L). Selvesterov EKG skor, ejekciona frakcija leve komore (EFLK), i indeks pokretljivosti zidova leve komore (WMSI) su određivani na otpustu bolesnika, između 5–14 dana hospitalizacije. **Rezultati.** Ustanovljeno je da se na otpustu EFLK statistički značajno smanjuje ( $p < 0.001$ ), WMSI i EKG Selvesterov skor statistički značajno povećavaju sa većim kvartilima PTH max. koncentracije ( $p < 0.001$  za oba parametra). BNP, CRP i

CK-MB nivoi značajno se povećavaju sa većim kvartilima max. koncentracije PTH ( $p < 0.001$ ;  $p < 0.001$   $p = 0.004$ , retrospektivno). **Zaključak.** Bolesnici u četvrtom kvartilu PTH imaju manju EFLK i veći Selvesterov EKG skor i WMSI od ostalih bolesnika. Ovi bolesnici takođe imaju i značajno veću koncentraciju BNP, CRP i CK-MB u ranoj fazi akutnog infarkta miokarda sa ST elevacijom (STEMI).

#### Ključne reči:

**paratireoidni hormon; infarkt miokarda sa st elevacijom; srce, insuficijencija; biološki pokazatelji.**

## Introduction

Parathyroid hormone (PTH) has some cardiovascular effects which can be important for response to acute myocardial injury and acute heart failure<sup>1-4</sup>. Through the receptors on smooth muscle cells, PTH induces systemic arterial and coronary vasodilatation<sup>5-7</sup> and through the receptors on cardiomyocytes it produces chronotropic and inotropic effect on the heart<sup>5-7</sup>. It is one of the main messengers for the mobilization and homing of bone marrow derived stem cells which can partly regenerate the damaged myocardial muscle<sup>8-11</sup>.

The serum concentration of PTH increases in acute ST elevation myocardial infarction (STEMI)<sup>12, 13</sup> and can even predict mortality in critically ill patients<sup>14</sup>. Catecholamine stress and autonomic nervous system are probably the main inducers of the increased PTH release in circulation during acute myocardial infarction<sup>15-17</sup>. Large myocardial infarction causes haemodynamic compromise and huge reaction of supra-adrenal gland and sympathetic nervous system which activate several hormonal systems including PTH which play an important role in the struggle to maintain sufficient circulation and perfusion of the vital organs<sup>18</sup>.

We have previously shown that PTH can be a marker of acute heart failure in patients with STEMI treated with primary percutaneous coronary intervention (PCI). The aim of this study is to establish correlations between serum concentration of PTH and several parameters which are associated with the prognosis of STEMI patients such as Selvester's ECG score, left ventricular ejection fraction (LVEF), wall motion score index (WMSI), and conventional biomarkers of heart failure, brain natriuretic peptide (BNP), C-reactive protein (CRP) and creatine kinase MB isoenzyme (CK-MB).

## Methods

### *Study population and design*

In this study, we included 390 consecutive patients admitted to the Coronary Care Unit of the Military Medical Academy (MMA) in Belgrade between December 2008 and June 2015 because of the STEMI. The diagnosis of STEMI was established according to current guidelines of the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) (typical chest pain lasting  $>$  20 minutes, electrocardiographic (ECG)

changes consisting of ST-segment elevation in at least two contiguous precordial leads  $\geq$  2 mm in men over the age of 40 years,  $\geq$  2.5 mm in men below the age of 40 years,  $\geq$  1.5 mm in women in leads V2–V3 and/or  $\geq$  1.0 mm in other leads, or horizontal or descending ST depression  $\geq$  0.5 mm and/or T inversion  $\geq$  0.1 mV in V1–V3 precordial leads with prominent R wave or R/S ratio  $>$  1 with hypokinesia or akinesia of the posterior left ventricle wall at admission echocardiography examination, confirmed with plasma CK-MB or troponin serum concentration elevation. All patients were treated with primary PCI (less than 12 hours after beginning of the chest pain) with adjunctive drug therapy and according to the ESC and the ACC/AHA guidelines. There was no age limit for study enrollment.

At admission, detailed medical history was taken for all patients, especially with regard to risk factors for ischemic heart disease and a complete physical examination with 12-lead ECG. Urgent laboratory analysis were also done for all patients at admission, including troponins and CK-MB. CK-MB was taken every 6 hours during the first 24 hours and maximum concentration was taken for analysis. Blood samples for PTH, BNP, CRP were taken from an antecubital vein at 8 am, i.e. before a meal. PTH serum concentration was measured on the first and second morning after admission, if the second measurement was higher than the first one, the third measurement was done. The highest concentration was taken for analysis. CRP was taken on the first and second morning and highest concentration was taken for analysis. BNP was taken on the first morning after admission. Echocardiographic assessment was done before discharge for all patients, usually on the days 5 to 8 of hospitalization.

The main exclusion criterion was low creatinine clearance (less than 30 mL/min). Beside renal dysfunction, other exclusion criteria were the presence of known malignant, infectious or autoimmune disease and death during the first 24 hours of the first hospitalization day.

The study was conducted according to the Declaration of Helsinki and was approved by the MMA Ethical Committee. Written informed consent was obtained from all participating patients.

### *Clinical and echocardiographic assessment*

For all patients detailed history of risk factors for coronary artery disease was taken and complete physical examination at the admission to assess hemodynamic stability.

Selvester's ECG score was done as an ECG method for estimating myocardial infarction size. We used simplified score of 37 criteria, 29 point system for scoring ECG at discharge. All patients underwent a two-dimensional Doppler echocardiography examination at discharge (GE Vivid 7 and Philips iE 33) which was performed in the left lateral position. Left ventricle (LV) systolic function was assessed by ejection fraction and WMSI. Left ventricular ejection fraction was quantified by the Simpson method according to the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) guidelines. Wall motion score index was calculated according to 17-segments model (ASE and EAE guidelines).

#### *Coronary angiography*

All coronary angiograms were done in MMA. Angiographic thrombolysis in myocardial infarction (TIMI) flow grade of the infarction artery was estimated before and after completion of PCI according to four grades of flow according to standard TIMI criteria<sup>19</sup>. Multivessel disease was defined as 70% or greater stenoses in at least one major epicardial artery and 50% or greater stenoses in at least one other major coronary artery<sup>20</sup>. All angiograms were reviewed by two independent interventional cardiologists.

#### *Laboratory testing*

Creatine kinase MB was determined in the serum of patients by immunoinhibition method on the commercial Dimension Clinical Chemistry System (Siemens Healthcare Diagnostics), at admission and every 6 hours during the next 24 hours. C-reactive protein extended range was determined in the serum of patients with a particle enhanced turbidimetric immunoassay on commercial Dimension system on the first and second day in the morning before a meal. Brain natriuretic peptide was determined in plasma by chemiluminescence immunoassay (ADVIA Centaur XP analyzer; Siemens Medical Solutions, Fernwald, Germany) on the first day of hospitalization in the morning before a meal. Intact PTH serum levels was determined from the venous blood sample withdrawn on the first, second and third (if the patient had the second level of PTH lower than the first one and was clinically stable, we did not take the 3rd sample) morning after admission, before a meal (15±8 hours from the admission). Intact PTH was measured in fresh serum during 4 hours from sampling by a commercial two-site sandwich immunoassay using chemiluminometric detection technology. Intact PTH was measured on ADVIA Centaur analyzer (Siemens Medical Solutions, Fernwald, Germany). The reference range from the test is 1.60–7.00 pmol/L and intra-assay coefficient of variation is 2.7%.

#### *Statistical analysis*

In the study we used the methods of descriptive statistics: continuous variables are presented as a mean with standard deviation (SD), or as a median with interquartile ran-

ge (IQR) depending on the distribution of data. Categorical variables are reported as counts with percentages. According to the quartiles of maximum PTH serum concentration, the patients were split into 4 groups. Differences between the distribution of categorical variables among the 4 groups of patients were estimated by the  $\chi^2$  test. Differences in age, systolic blood pressure and heart rate were calculated with two-way ANOVA. The differences among the levels of LVEF, WMSI, plasma levels of BNP, serum levels of CK-MB and CRP and Selvester's score were compared across the quartiles of PTH maximum with Kruskal Wallis test. *P* value less than 0.05 was considered significant. The differences between quartile 1 and 2, quartile 2 and 3 and quartile 3 and 4 for all variables were tested by the Mann-Whitney test (*p* value less than 0.05 was also considered significant). All analyses were performed by using the SPSS version 21 (SPSS Inc, Chicago, IL, USA).

### **Results**

There were 390 patients included in the study, average age  $62 \pm 12$  (ranging from 32 to 87 years), where 108 (27.7%) were females and 282 (72.3%) were males.

We divided all patients in quartiles according to serum concentration of parathyroid hormone (I  $\leq 4.4$  pmol/L; II  $> 4.4$  pmol/L and  $< 6.3$  pmol/L; III  $\geq 6.3$  pmol/L and  $< 9.2$  pmol/L; IV  $\geq 9.2$  pmol/L). The demographic and clinical characteristics of the patient population are shown in Table 1.

#### *The demographic and clinical characteristics of the patients*

We studied 390 patients and three quarters of them were men ( $p = 0.050$ ). There was a statistically significant difference between quartiles of the patients by the age ( $58 \pm 11$  vs.  $60 \pm 12$  vs.  $63 \pm 12$  vs.  $67 \pm 12$ ) respectively  $p < 0.001$ . Also, there was a significant difference among quartiles of the patients in the data of arterial hypertension ( $p = 0.038$ ) and diabetes mellitus ( $p = 0.008$ ). With the higher PTH max. level, the incidence of hypertension was higher. However, information about diabetes was questionable because diabetes was less common in the 2nd quartile of PTH max. which is probably an incidental finding. We did not find a significant difference between quartiles of the patients in the data of active smoking ( $p = 0.166$ ) and hypercholesterolemia ( $p = 0.688$ ).

There were significantly larger number of patients with Killip class greater than I in the 4th quartile of PTH max. level than in the 1st (11.5% vs. 1.0%;  $p < 0.001$ ). In accordance with that data, we found that heart rate on the admission was significantly higher in the 4th quartile of PTH max. level than in the 1st quartile ( $84.9 \pm 24.7$  beats/min vs.  $74.2 \pm 18.8$  beats/min;  $p = 0.001$ ), but, on the contrary, systolic blood pressure on the admission showed no significant difference among quartiles of PTH max. level ( $132.2 \pm 23.3$  mmHg vs.  $132.6 \pm 25.3$  mmHg vs.  $137.0 \pm 29.8$  mmHg vs.  $126.2 \pm 35.3$  mmHg;  $p = 0.078$ ).

Table 1

The demographic, clinical and procedure related characteristics of the patients						
	All	Q1	Q2	Q3	Q4	<i>p</i>
Age (years), mean ± SD	61.57 ± 12.016	58.42 ± 10.915	59.98 ± 12.205	62.94 ± 11.667	66.63 ± 11.778	< 0.001
Female, n (%)	108 (72.3)	23 (5.8)	22 (5.6)	26 (6.7)	37 (9.57)	0.050
Risk factors, n (%)						
active smokers	197 (51.4)	55 (14.4)	53 (13.8)	50 (13.1)	39 (10.1)	0.166
arterial hypertension	282 (72.3)	63 (16.2)	66 (16.9)	75 (19.2)	78 (20.2)	0.038
diabetes mellitus	101 (26.0)	34 (8.7)	14 (3.8)	24 (6.2)	29 (7.5)	0.008
hypercholesterolemia	217 (56.4)	50 (13.0)	57 (14.8)	58 (15.1)	52 (13.5)	0.688
Infarction related artery territory, n (%)						0.739
LM	2 (0.5)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	
LAD	170 (43.6)	40 (10.3)	42 (10.8)	41 (10.5)	47 (12.1)	
RCx	61 (15.6)	12 (3.1)	15 (3.8)	17 (4.4)	17 (4.4)	
RCA	157 (40.3)	45 (11.5)	39 (10.8)	41 (10.5)	32 (8.2)	
Killip class > 1 at admission, n (%)	66 (16.9)	4 (1.0)	7 (1.8)	10 (2.6)	45 (11.5)	0.000
Previous infarction, n (%)	56 (14.4)	15 (3.8)	11 (2.8)	8 (2.1)	22 (5.6)	0.021
Multivesel disease, n (%)	256 (65.8)	52 (13.4)	65 (16.7)	72 (18.5)	67 (17.2)	0.017
Systolic arterial pressure at admission, mean ± SD	132.07 ± 28.961	132.24 ± 23.332	132.64 ± 25.371	137.00 ± 29.798	126.23 ± 35.327	0.078
Heart rate at admission, Mean ± SD	77.83 ± 20.938	74.23 ± 18.842	74.62 ± 18.842	74.65 ± 18.951	84.93 ± 24.710	0.001
Total ischemic time in hours – median (IQR)		3.00 (2.00-6.00)	4.00 (2.50-7.50)	3.00 (2.88-6.00)	5.00 (3.00-9.00)	0.002
TIMI flow before PCI, n (%)						
0/1	297 (76.2)	74 (19.0)	78 (20.0)	72 (18.5)	73 (18.5)	0.799
0/3	48 (12.3)	10 (2.6)	11 (2.8)	14 (3.6)	13 (3.3)	
TIMI flow after PCI, n (%)						0.001
0/1	14 (3.6)	2 (0.5)	1 (0.3)	3 (0.8)	8 (2.1)	
0/3	318 (81.5)	92 (23.6)	79 (20.3)	80 (20.5)	67 (17.2)	
Implantation of stents, n (%)	337 (86.4)	89 (22.8)	85 (21.8)	87 (22.3)	76 (19.5)	0.102
GP inhibitors, n (%)	97 (24.9)	25 (6.4)	23 (5.9)	27 (6.9)	22 (5.6)	0.898
Clopidogrel before PCI, n (%)	321 (82.3)	70 (17.9)	82 (21.0)	85 (21.8)	84 (21.5)	0.12
Ticagrelor before PCI, n (%)	69 (17.7)	28 (7.2)	15 (3.8)	14 (3.6)	12 (3.1)	

**LM – left main coronary artery; LAD – anterior descending artery; RCx – right circumflex artery; RCA – right coronary artery; IQR – interquartile range; TIMI – thrombolysis in myocardial infarction; PCI – primary percutaneous coronary intervention; SD – standard deviation; Q1 – first quartile; Q2 – second quartile; Q3 – third quartile; Q4 – fourth quartile.**

Every seventh patient had a previous myocardial infarction, i.e. 56 (14.4%) patients and we found that the number of patients with a previous myocardial infarction was significantly higher in the quartile 4 ( $p = 0.021$ ).

The time from symptom onset until reperfusion occurred was defined as total ischemic time (TIT). It was significantly different among quartiles of PTH max. level ( $p = 0.002$ ). In the 1st quartile of PTH max. TIT was 3.00 (IQR 2.00–6.00) hours and in the 4th quartile TIT was 5.00 (IQR 3.00–9.00) hours.

#### *Procedure related characteristics of the patients*

As described in the methodology of this study, all patients were treated with primary PCI. About two thirds of the patients had multivessel disease, i.e. 256 (65.8%) patients. There were statistically significant differences among quartiles of the patients according to the presence of multivessel disease (52, 13.4% vs. 65, 16.7% vs. 72, 18.5% vs. 67, 17.2%;  $p = 0.017$ ). Also, we analyzed which artery was most commonly infarction related artery (IRA). Infarct related artery in almost half of the cases was left anterior descending (LAD) artery, i.e. in 170 (43.6%) patients

LAD was IRA. Right coronary artery (RCA) was IRA in 157 (40.3%) patients, left circumflex artery (LCx) was IRA in 61 (15.6%) patients and left main (LM) coronary artery in 2 (0.5%) patients. Statistically significant differences among quartiles of the patients according to the IRA were not found ( $p = 0.739$ ).

TIMI flow grade of the infarction-related artery was assessed before and after PCI by two interventional cardiologist. Before PCI, majority of the patients (76.2%) had TIMI flow grade 0 or 1 and no statistically significant differences among quartiles of the patients were found ( $p = 0.799$ ). Majority of patients (81.5%) had TIMI flow grade 3 after PCI and no statistically significant differences among quartiles of the patients according to TIMI flow grade after PCI were found ( $p = 0.001$ ).

Majority of patients (86.4%) had stent implantation during PCI and there were no statistically significant differences among quartiles according to the stent implantation ( $p = 0.102$ ). One-quarter of the patients received glycoprotein (GP) inhibitors before PCI with no statistically significant differences among quartiles ( $p = 0.898$ ). All patients received oral antiplatelet therapy with aspirin and a P2Y<sub>12</sub> receptor blocker. Majority of the patients received clopidogrel (82.3%) and ticagrelor was

used in 17.7% of all patients. There were no statistically significant differences found among quartiles of the patients according to the oral antiplatelet therapy ( $p = 0,120$ ).

#### *Relation between Selvester's ECG score, LVEF and WMSI with quartiles of PTH*

Selvester's ECG score significantly increased in the 4th quartile of PTH level ( $p < 0.001$ ), as shown in Figure 1. As a continuous variable Selvester's ECG score is presented as the median with IQR. Quartile 1 had value 9.00 (IQR 4.50–18.00), quartile 2 had value 9.00 (IQR 3.00–15.00), quartile 3 had value 12.00 (IQR 6.00–21.00) and quartile 4 had value 15.00 (IQR 9.00–24.00). It could be concluded, that the 4th quartile of PTH max. level, i.e. PTH level above the reference limit, had the significantly higher Selvester's ECG score.

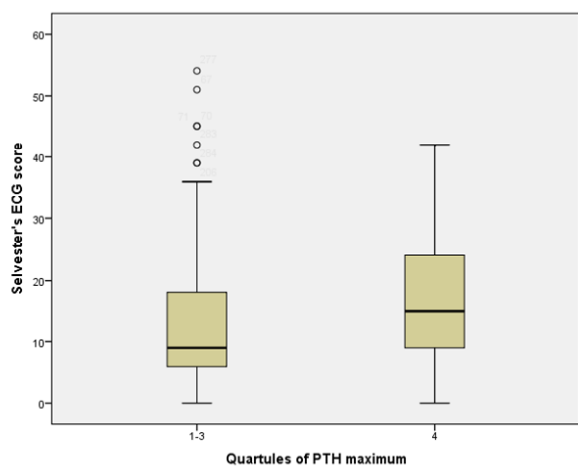
Ejection fraction significantly decreased in the fourth of PTH level ( $p < 0.001$ ) as shown in Figure 2. Medians with IQR for ejection fraction were: for the 1st quartile 50.00% (IQR 45.00–55.00%), for the 2nd quartile 50.00% (IQR 43.00–55.00%), for the 3rd quartile 48.00% (IQR 45.00–55.00%) and for the 4th quartile 40.00% (IQR 32.25–50.00%). The 4th

quartile of PTH max. (PTH serum concentration above reference range) had significantly lower ejection fraction.

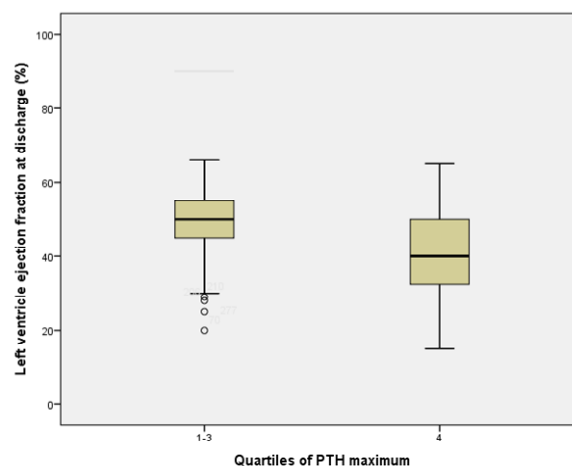
WMSI at discharge significantly increased in the 4th quartile of PTH level ( $p < 0.001$ ), Figure 3. Medians with IQR for WMSI were: for the 1st quartile 1.31 (1.19–1.50), for the 2nd quartile 1.37 (1.19–1.61), for the 3rd quartile 1.38 (1.25–1.56) and for the 4th quartile 1.6250 (1.3100–1.8100). The patients in higher PTH max. quartiles had more pronounced regional myocardial dysfunction.

#### *Relation between BNP, CRP and CK-MB with quartiles of PTH*

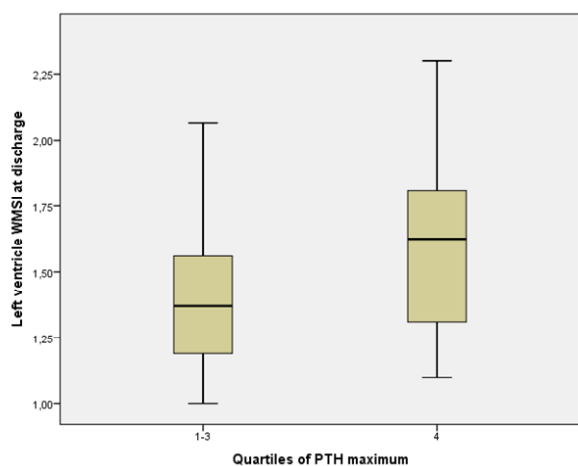
Brain natriuretic peptide level significantly increased in the 4th quartile of PTH level ( $p < 0.001$ ; Figure 4). Medians with IQR for BNP are: for the 1st quartile 199.49 pg/mL (87.43–296.55 pg/mL), for the 2nd quartile 163.90 pg/mL (80.20–320.00 pg/mL), for the 3rd quartile 251.50 pg/mL (111.30–449.10 pg/mL) and for the 4th quartile 580.63 pg/mL (232.33–1007.90 pg/mL). Thus, the patients in all 4 quartiles had median BNP level higher than a cut-off point recommended by the ESC guidelines for acute heart failure.



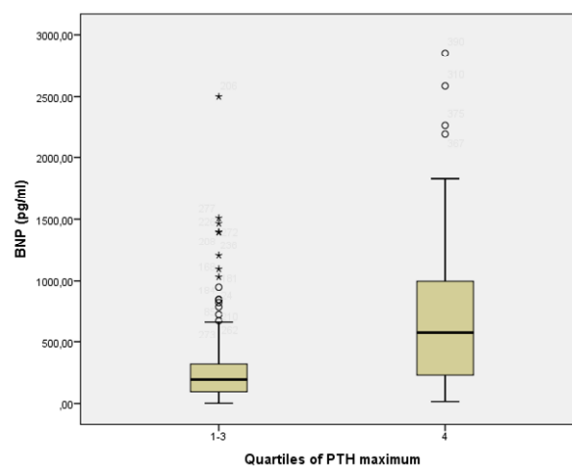
**Fig. 1 – Value of Selvester's electrocardiography (ECG) score, the 4th versus other three quartiles of parathyroid hormone (PTH) maximum concentration,  $p < 0.001$ .**



**Fig. 2 – Left ventricle ejection fraction (LVEF), the 4th versus other three quartiles of parathyroid hormone (PTH) maximum concentration,  $p < 0.001$ .**



**Fig. 3 – Value of wall motion score index (WMSI), the 4th versus other three quartiles of parathyroid hormone (PTH) maximum concentration,  $p < 0.001$ .**

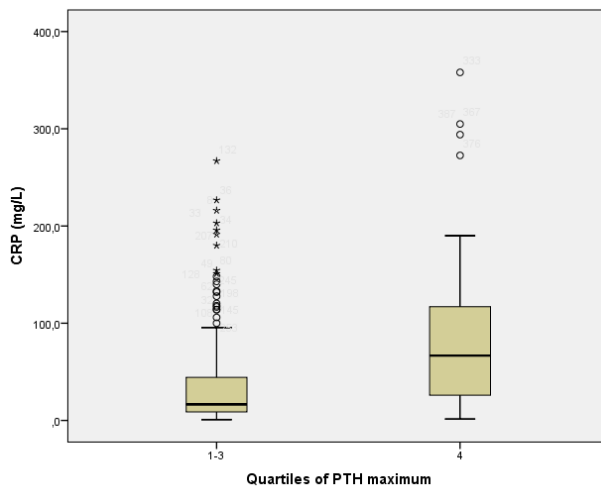


**Fig. 4 – Brain natriuretic peptide (BNP) concentration, the 4th versus other three quartiles of parathyroid hormone (PTH) maximum concentration,  $p < 0.001$ .**

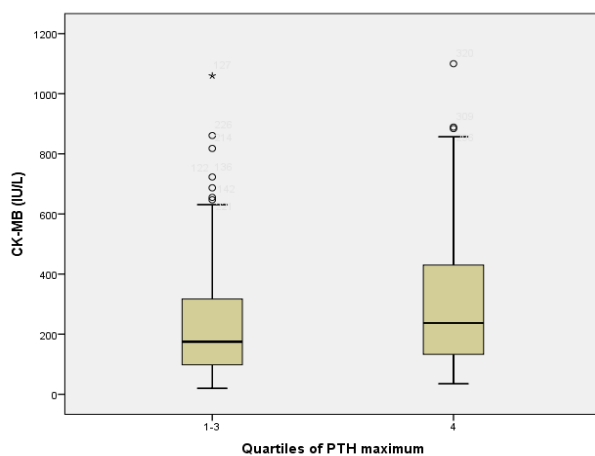
C-reactive protein also significantly increased in the 4th quartile of PTH level ( $p < 0.001$ , Figure 5.) CRP serum level had median value with IQR for the 1st quartile 14,000 mg/L (8.200–26.250 pg/mL), for the 2nd quartile 16.000 mg/L (8.780–43.000), for the 3rd quartile 24.330 mg/L (9.938–49.725 pg/mL) and for the 4th quartile of PTH max. level value of 66.750 mg/L (25.000–120.500 pg/mL). The 4th quartile of PTH max. (PTH serum concentration above reference range) had a very high median CRP level of 66.750 mg/L.

Finally, CK-MB level significantly increased in the 4th quartile of PTH level ( $p = 0.004$ , Figure 6). Medians with IQR for CK-MB were: for the 1st quartile 160.50 IU/L (85.75–269.75 IU/L), for the 2nd quartile 192.00 IU/L (97.50–355.50 IU/L), for the 3rd quartile 209.50 IU/L (112.75–341.50 IU/L) and for the 4th quartile 237.00 IU/L (132.50–437.00).

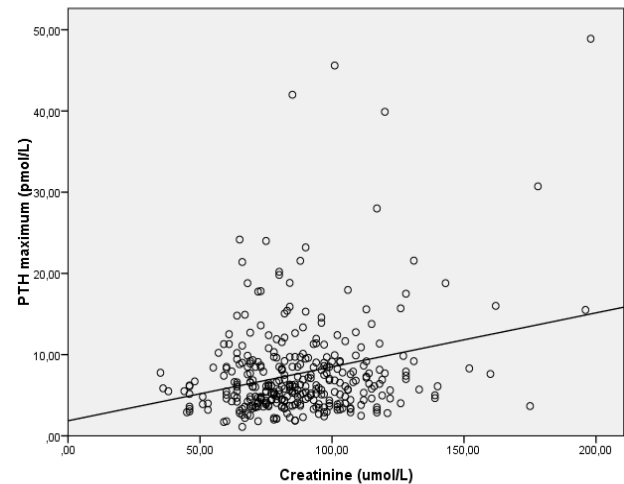
There was also significant correlation between serum PTH maximum levels and serum creatinine concentrations at admission (Figure 7). However, there were no significant differences among the values of LVEF, WMSI, Selvester's score and CK-MB across the quartiles of creatinine (data not shown). This means that PTH has independent from creatinine level, an association with mentioned parameters.



**Fig. 5 – C-reactive protein (CRP) concentration, the 4th versus other three quartiles of parathyroid hormone (PTH) maximum concentration,  $p < 0.001$ .**



**Fig. 6 – Creatine kinase-MB isoenzyme (CK-MB) concentration, the 4th versus other three quartiles of parathyroid hormone (PTH) maximum concentration,  $p < 0.001$ .**



**Fig. 7 – Relationship between the maximum serum concentration of parathyroid hormone (PTH) and serum creatinine at admission in ST elevation myocardial infarction (STEMI) patients.**

*Analysis of the statistical significance of differences among the individual quartiles for the ECG, echocardiography and biochemical markers of prognosis of acute myocardial infarction*

When we analyzed whether there was a statistically significant difference (Mann-Whitney test) between the individual quartiles of the above listed markers of prognosis in acute myocardial infarction, we noticed that there was no statistically significant difference between quartiles 1 and 2, nor 2 and 3, but only between quartiles 3 and 4 of PTH max. levels for all of these markers except for CK-MB max. concentration (Table 2). The 4th quartile of PTH max. serum concentration, therefore, had significantly higher levels of all markers of poor prognosis in acute myocardial infarction (Figures 1–6). For CK-MB max. concentration, we did not find a statistically significant difference between the 1st and 2nd or between the 2nd and 3rd or between the 3rd and 4th quartile, but this does not mean that there was no difference between the 4th and the 1st quartile or the 3rd and the 1st quartile, and therefore, as stated above, there was a statistically significant increase in CK-MB max. concentration with higher quartiles of PTH max.

## Discussion

In our patients with STEMI, who were treated with primary PCI, PTH maximum levels, which were on the upper limit of reference range and above this limit, were significantly associated with markers of larger infarct size and heart failure. Half of the study patients were in the 3rd and 4th quartile of PTH levels (the upper limit of reference range and above this limit) and all of them had the clinical, ECG, echocardiographic and biochemical markers of larger myocardial infarction size and heart failure.

Clinically, patients in the 3rd and 4th quartile of PTH max. had higher Killip class at admission. They also had a

**Table 2**  
**The statistical significance of differences between quartiles of parathyroid hormone (PTH) maximum levels for analyzed electrocardiographic (ECG), echocardiographic and biochemical markers of prognosis of acute myocardial infarction**

Parameter	I vs. II quartile	II vs. III quartile	III vs. IV quartile
	<i>p</i>	<i>p</i>	<i>p</i>
Selvester's QRS score	0.391	0.094	0.008
LVEF	0.694	0.273	0.001
WMSI	0.517	0.422	0.001
BNP	0.968	0.105	0.001
CRP maximum	0.438	0.193	0.001
CK-MB maximum	0.099	0.676	0.100

**LVEF – left ventricle ejection fraction; WMSI – wall motion score index; BNP – brain natriuretic peptide; CRP-C-reactive protein; CK-MB – creatine kinase-MB isoenzyme; *p* – probability.**

history of previous myocardial infarction and a longer total ischemic time. On coronary angiography, patients in the 3rd and 4th quartile of PTH max. level had significantly higher incidence of multivessel disease and TIMI flow after PCI in these patients was significantly less frequently grade 3. Accordingly, echocardiographic prognostic factors in myocardial infarction correlated with the PTH serum level, ejection fraction significantly decreased and WMSI significantly increased across the quartiles of PTH max. level. Selvester's ECG score was shown to correlate with infarction size. In our study Selvester's ECG score was significantly higher in higher PTH max. quartiles. The most widely used biochemical prognostic markers in acute myocardial infarction are CKMB, CRP and BNP. All these three markers in our study correlated with the PTH level and increased across the quartiles of PTH max. level.

#### *Possible pathogenesis of PTH level increase in acute myocardial infarction (AMI)*

Several studies have shown that there is an increase in PTH serum level in acute myocardial infarction. In study of Joborn et al.<sup>13</sup> serum concentration of PTH was increased in early course of acute myocardial infarction (AMI) as compared to the reference day number 7. In the same period, mean values of total and ionized calcium did not change significantly, but PTH correlated negatively with serum calcium. Conversely, PTH correlated positively with plasma and platelets epinephrine. That is one possible explanation for significant elevation of PTH in large AMI. It is well known that AMI increases sympathoadrenal activity<sup>15</sup>. *In vivo* and *in vitro* studies have shown that epinephrine can directly stimulate secretion of PTH and indirectly by lowering plasma total and ionized calcium<sup>16, 17</sup>. Carlstedt et. al.<sup>14</sup> reported that PTH was stronger predictor of mortality than APACHE II score in patients in emergency department. The highest PTH levels were observed in patients with myocardial infarction and congestive heart failure. The reason for this observation remained unclear. Hypocalcaemia was not found in these patients and there was no clear association with proinflammatory cytokines. They also assumed that catecholamines could be responsible for elevation of PTH.

To the best of our knowledge, there is only one study of PTH secretion in acute heart failure. Sugimoto et al.<sup>20</sup> inclu-

ded in a study 266 patients admitted for acute decompensated heart failure (HF) without acute coronary syndrome. The authors in this study, contrary to the findings in chronic heart failure, found that the low-normal levels of PTH were associated with higher 1-year all-cause mortality. They concluded that the PTH was somehow necessary in the acute heart failure. In experimental studies it was demonstrated that PTH exerted vasodilating effect on blood vessels and positive chronotropic and inotropic effect on the heart<sup>7</sup>. There is evidence that this might be beneficial in heart failure even when PTH level increase is small and close to the upper limit of the normal range<sup>21</sup>. Also, since the authors of this study excluded from the trial the patients with acute coronary syndrome, where it was observed in the earlier, as well as in our study that PTH serum concentration was elevated, it could be concluded that ischemic myocardium in some way contributes to the increased secretion of PTH. In experimental studies of the application of PTH in myocardial infarction, PTH contributes to mobilization and homing of stem cells from bone marrow in ischaemic myocardium and has a regenerative role<sup>8-11</sup>. There is a need to investigate whether PTH serum concentrations in myocardial infarction is sufficient for this effect.

Selvester's ECG score is an ECG method for estimating myocardial infarction size and thus provides prognostic information after myocardial infarction<sup>22</sup>. We used simplified Selvester's score of 37 criteria, 29 point system<sup>23</sup>. Selvester's score kept the same predictive value in the era of PCI as it used to in the era of thrombolytic therapy. Roubin et al.<sup>23</sup> showed that QRS score correlated well with survival rate, ejection fraction and Killip class. As the score increased, survival rates and ejection fraction decreased. In a study of Tjandrawidjaja et al.<sup>24</sup> with STEMI patients treated with primary PCI, higher QRS scores were associated with male gender, higher heart rate, worse Killip class, noninferior infarction location, greater ST-segment deviation, and longer times to reperfusion and also with impaired culprit artery flow before and after PCI and more frequent multivessel disease. These findings are consistent with our findings; Selvester QRS score was higher with higher serum PTH concentration and that group of patients had higher Killip class, longer ischemic time, faster heart rate on admission and also poorer TIMI flow after PCI and more often multivessel disease.

After AMI, LVEF is of a prognostic significance. It has been shown in numerous studies that ejection fraction below

30–40% is strong predictor of all-cause cardiovascular mortality and sudden cardiac death (SCD)<sup>25–27</sup>. Also, there is a good correlation between LVEF and infarction size<sup>28, 29</sup>. Pride et al.<sup>28</sup> showed that there was a linear relation between infarction size and LVEF only for moderate to large infarcts, but not for small infarcts. In our study, patients in the 4th quartile of PTH max. level had median LVEF 40%, therefore patients with PTH serum level above the upper limit of the normal range had the EF that indicated worse prognosis and larger infarction size.

LVEF is a marker of global LV systolic function, whereas WMSI allows regional wall motion analysis, i.e. evaluation of LV regional dysfunction. Similar to the LVEF, WMSI is a strong predictor of all-cause mortality after AMI<sup>27</sup>. Mortality increases exponentially with decreasing LVEF, whereas it increases linearly with increasing WMSI<sup>27</sup>. In the study of Eek et al.<sup>29</sup> a good correlation was found between infarction size and WMSI and global longitudinal strain. They found that wall motion score index > 1.30 accurately identified patients with substantial infarction (≥ 12% of myocardium). In our study, 4th quartile of PTH max. level had median WMSI 1.68, indicating in that way a larger infarction size and worse prognosis.

In acute STEMI, different biomarkers are used in short term and long term disease prognosis<sup>30</sup>. We investigated association of PTH with three most commonly used biomarkers: CK-MB which indicates myocardial necrosis, CRP which is a marker of inflammation and BNP which is elevated mainly in response to left ventricular overload, but also in conditions of myocardial ischemia.

It was shown that BNP had predictive value for adverse events in STEMI infarction as well as in non-STEMI and unstable angina pectoris. Similarly, both of these markers are used in different studies of its prognostic value in acute coronary syndrome. Richards et al.<sup>31</sup> examined the predictive value of BNP, NT-proBNP and radionuclide LVEF for adverse events (death, heart failure and new myocardial infarction) in AMI. LVEF and the B-type natriuretic peptides were proved to be powerful independent predictors for adverse outcomes and the combination of NT-proBNP (or BNP) with LVEF (< 40%) substantially improved risk stratification. Besides, investigators concluded that both B-type peptides had similar utility as prognostic markers when measured early in the course of a broad spectrum of acute coronary syndromes. Velders et al.<sup>32</sup> evaluated the prognostic value of high-sensitivity cardiac troponin T, NT-proBNP and growth differentiation factor-15 (GDF-15) in STEMI treated with primary PCI. They concluded that biomarkers provided additional prognostic value for CVD beyond clinical risk factors and extent of coronary artery disease with NT-proBNP and GDF-15 being most valuable. In these studies, BNP/NT-pro BNP were measured at admission or in the first 24 hours up to 96 hours after the onset of symptoms depending on the type of acute coronary syndrome. We measured BNP value in 24 hours from the onset of symptoms. We found that the BNP plasma concentration significantly increased with higher quartiles of PTH max. level. Interestingly, median value of BNP in the 1st quartile was

199.49 pg/mL (IQR 87.43–296.55 pg/mL) which is a high level, i.e. 100 pg/mL is recommended cut-off value for acute onset of heart failure. The 1st quartile, however, involves a stable patients with smaller infarction size. This could be explained by the role of ischemia on BNP release from ventricular myocardium<sup>33,34</sup>.

CRP is well established risk factor in the pathogenesis of atherosclerosis. The role of CRP in acute myocardial infarction was investigated in several studies. Sano et al.<sup>35</sup> showed that elevated CRP serum concentration within 6 hours after the onset of symptoms of AMI might reflect the inflammatory activity of a ruptured plaque. Later in the course of AMI, elevated serum CRP levels may be caused by a inflammatory response to myocardial necrosis. Lagrand et al.<sup>36</sup> have concluded in experimental study that CRP localizes in infarcted, necrotic tissue and promotes local complement activation and subsequently tissue damage. Nikfardjam et al.<sup>37</sup> found that elevated CRP level on admission in patients with AMI predicted short term and long term mortality. Ohlmann et al.<sup>38</sup> in their study of patients with STEMI treated with primary PCI found that plasma concentrations of CRP measured 48 hours and 72 hours after PCI correlated with infarction size. Admission CRP level as well as level at 48 hours after PCI predicted 6-month mortality. They found that CRP level in this patients reached a peak value after a median interval of 49 hours after the admission. Sanchis et al.<sup>39</sup> have also found that CRP level increased after admission and reached its peak after 48 hours. It could be concluded, that CRP level in AMI depends on time from the pain onset until admission<sup>40</sup> and reperfusion therapy. We measured CRP on the first and second day after admission and a peak CRP serum value was reached around 48 hours after admission, what is in concordance with previous studies. We found that CRP level was significantly higher with higher PTH max. quartiles.

There is a number of studies which confirmed correlation between serum levels of CK-MB and infarction size and prognosis after AMI. Most of these studies are from the time before the thrombolytic therapy or from the thrombolytic therapy era<sup>41, 42</sup>. Only Nienhuis et al.<sup>43</sup> showed that peak CK-MB was independent predictor of LVEF and 1-year mortality in patients after primary PCI for STEMI. In current guidelines, troponin is the preferred biomarker to use in patients with acute coronary syndrome (ACS), but CK-MB is considered as the best alternative when troponin assay is not available. We used CK-BM because of better availability of this assay in our hospital. In our study the 4th quartile of PHT max. level had significantly higher CK-MB level (median value 237.00 IU/L, interquartile range 132.50–437.00 IU/L). This finding is very similar to finding of Nienhuis et al.<sup>43</sup> where CK value in the 3rd quartile was > 281 IU/L.

#### *Study limitation*

The present study is part of our larger study of PTH concentration and kinetics in STEMI. The relationship of PTH and other factors of mineral metabolism was described in our previous paper. In this paper we wanted to point out association of PTH and clinical, echocardiographic and biochemical markers of infarction size and heart failure. We



didn't take biochemical markers on admission, although in some studies this was done. This was not always possible to make and, beside that, total ischemic time was significantly different among quartiles of patients and since biochemical markers are dependent on this time, we decided to take samples for biochemical markers on the 1st, 2nd and 3rd day after the admission and to take maximum level for analysis as it was done in some other studies.

## Conclusion

Patients with STEMI and elevated concentration of PTH (the lower cut-off for the 4th quartile of PTH was 9.2 pmol/L) in the early phase of disease had several markers of worse prognosis, high Selvester's ECG score, low LVEF, increased WMSI, and higher blood concentrations of BNP, CRP and CK-MB.

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