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Prognostic value of serum parathyroid hormone in ST-elevation myocardial infarction patients

Prognostička vrednost paratireoidnog hormona u serumu kod bolesnika sa infarktom miokarda sa elevacijom ST segmenta

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Abstract

Background/Aim. Parathyroid hormone (PTH) is an important messenger in the regeneration process which might influence the outcome of patients with ST-segment elevation myocardial infarction (STEMI). The aim of this study was to investigate the role of PTH in comparison to other traditionally used markers for the prediction of heart failure in STEMI patients. **Methods.** In 165 consecutive patients with STEMI treated with primary percutaneous coronary intervention (PCI), blood concentrations of PTH, C-reactive protein (CRP), B-type natriuretic peptide (BNP), creatine kinase MB (CK-MB) and admission glycaemia (AG) were measured during the first three days after admission and correlated to the primary outcome – episodes of acute heart failure in the period of six months. **Results.** The area under the ROC curve of the maximal serum concentration of PTH was the largest among the measured biomarkers (0.867 *vs* 0.835 *vs* 0.832 *vs* 0.627 *vs* 0.619, for PTH, CRP, BNP, CK-MB and AG, respectively) for the prediction of primary outcome. The maximal PTH level adjusted to several risk factors had an independent prediction value for primary outcome ($p < 0.001$). In addition, PTH improved the prediction of primary outcome when added to the other markers in the model [c-statistic with BNP, CRP, CK-MB and AG was 0.908 (95% CI 0.849–0.967)], and when PTH was added, it was 0.931 (0.883–0.980), with $p < 0.001$ for the discrimination. **Conclusion.** Serum concentration of PTH early in the course of STEMI can predict acute heart failure episodes in the first six months in patients treated with primary PCI.

Key words:
myocardial infarction; heart failure; biological markers; parathyroid hormone; natriuretic peptides; creatine kinase; c-reactive protein; blood glucose; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Paratireoidni hormon (PTH) značajan je glasnik u regeneracionim procesima i može uticati na ishod kod bolesnika sa infarktom miokarda sa ST elevacijom (STEMI). Cilj ovog rada bio je da se ispita uloga PTH u poređenju sa drugim uobičajenim markerima za predviđanje srčane slabosti kod bolesnika sa STEMI. **Metode.** Kod 165 bolesnika sa STEMI, lečenih primarnom perkutanom koronarnom intervencijom, prva tri dana hospitalizacije merene su vrednosti u serumu: PTH, B-tipa natriuretskog peptida (BNP), kreatin-kinaze miokarda (CK-MB), C-reaktivnog proteina (CRP) i glikemije na prijemu, te je ispitivan uticaj na primarni ishod – epizode akutne srčane slabosti u periodu od šest meseci. **Rezultati.** Površina ispod ROC krive bila je najveća u poređenju sa ostalim markerima (0,867 *vs* 0,835 *vs* 0,832 *vs* 0,627 *vs* 0,619), za PTH, CRP, BNP, CK-MB i glikemiju na prijemu za predviđanje primarnog ishoda. Maksimalna vrednost PTH imala je nezavisnu vrednost predviđanja za primarni ishod ($p < 0,001$). **Zaključak.** Serumske koncentracije PTH u ranoj fazi STEMI mogu predvideti epizode akutne srčane slabosti u prvih šest meseci kod bolesnika lečenih primarnom perkutanom koronarnom intervencijom.

Ključne reči:
infarkt miokarda; srce, insuficijencija; biološki pokazatelji; paratireoidni hormoni; natriuretski peptidi; kreatin kinaza; c-reaktivni protein; glikemija; osetljivost i specifičnost.

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Introduction

The most important role of parathyroid hormone (PTH) is to maintain of calcium homeostasis. However, PTH has several important cardiovascular effects which may be relevant for some pathophysiological states, such as myocardial infarction or acute heart failure [1]. In experimental studies, PTH showed positive inotropic and chronotropic action on myocardium, as well as vasodilatatory effect on arteries [2]. Parathyroid hormone in myocardial infarction may be important messenger in the regenerative process because it takes important role in the mobilization and homing of stem cells [3–5].

On the other hand, chronically higher levels of PTH are associated with arterial hypertension and increased mortality in patients with chronic renal failure, stable coronary disease, chronic heart failure and even healthy elderly men [6–8].

However, not much is known regarding PTH blood concentrations, dynamics and prognostic value in acute myocardial infarction (AMI). More than 20 years ago Ljunghall et al. [9] found elevated levels of PTH in patients with AMI. However, the role and potential prognostic significance for PTH in AMI patients are unknown. Several studies have shown a significant derangement in Ca-VitD-PTH axis in severely ill patients in correlation with higher mortality rate [10, 11].

Therefore, the aim of our study was to determine the serum concentration of PTH in patients with ST elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) during the first three days of hospitalization and to investigate the association between serum PTH level and episodes of the acute heart failure in a six-month period of time after STEMI.

Methods

The study included 165 consecutive patients with the first STEMI, admitted to the Coronary Care Unit of the Military Medical Academy in Belgrade, between March 2010 and November, 2012. The diagnosis of STEMI was established if a patient had typical chest pain lasting > 20 minutes less than 12 hours before admission, and typical electrocardiographic changes with increase of serum creatine kinase-MB (CK-MB) or troponin concentration elevation above 99% of the reference value. All the patients were treated with the reperfusion therapy, primary percutaneous coronary intervention (pPCI) or thrombolysis with adjunctive urgent PCI according to the guidelines [12, 13]. There was no age limit for study enrollment. The main exclusion criterion was elevated admission serum creatinine level above 115 μmol/L. The other exclusion criteria were the presence of known malignant, infectious or autoimmune disease and death inside the first 24 hours from the symptom onset. All the patients have had scheduled follow-up in the first six months.

The control group presented as the cohort of patients who did not develop acute heart failure symptoms through the 6-months follow-up period.

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

Outcomes

The primary outcome was the presence of signs and symptoms of acute heart failure during the 180 days of follow-up after STEMI. The primary outcome was diagnosed during initial hospitalization and through the scheduled visits at 30 and 180 days from the day of admission by the physicians who do not participate directly in the study. Acute heart failure was defined as the presence of typical symptoms and signs required intravenous application of diuretics, re-hospitalization or the need for the increased dosage of oral diuretic therapy.

Laboratory testing

Glycaemia was measured at admission by using commercial Dimension® Clinical Chemistry System. C-reactive protein (CRP) extended range was determined in the serum of patients with turbidimetric immunoassay on commercial Dimension system at the first, second and third day in the morning before meal. Creatine kinase-MB was determined in the serum of patients by the immunoinhibition method on the commercial Dimension® Clinical Chemistry System, at admission and every 6 hours during the next 24 hours, and every 8 hours during the next 48 hours. B-type natriuretic peptide was determined in plasma samples on the commercial ADVIA Centaur analyzer (Siemens Medical Solutions, Fernwald, Germany) using direct chemiluminescence immunoassay.

Parathyroid hormone and total calcium serum concentrations

Intact parathyroid hormon and total calcium serum levels were determined from the venous blood sample withdrawn at the first, second and third morning after admission before meal. Intact PTH was measured in fresh serum inside the 4 hours from the sampling by a commercial two-site sandwich immunoassay using chemiluminometric detection technology. Intact PTH is measured on the ADVIA Centaur analyzer (Siemens Medical Solutions, Fernwald, Germany). The reference range from the test was 1.60–7.00 pmol/L and intra-assay coefficient of variation was 2.7%.

Total serum calcium levels were measured using the calcium o-cresolphtalein method adapted to commercial colorimetric assay on the Siemens Dimension® Clinical Chemistry System with the intra-assay coefficient of variation of 1.9% .

Statistics

Following the test of statistical normality (Kolmogorov-Smirnov test), continuous variables were presented as mean ± standard deviation (SD), or with a skewed distribution as median [interquartile range (IQR)] and quartiles. Biomarker levels were analyzed as continuous variables and as categori-

cal values – quartiles of values for all patients in the study. Categorical variables were reported as counts with percentages. Differences in categorical variables were tested by χ^2 test and between continuous ones with Student's *t*-test or Fisher's oneway ANOVA with Boferroni adjustment. Oneway ANOVA with repeated measurements was applied when the values of PHT and total calcium in three time points were analyzed.

To assess the diagnostic value of each marker, nonparametric receiver operating characteristic (ROC) curves were generated by plotting the sensitivity *vs* 1-specificity. For each marker the optimal cut-off point, sensitivity and specificity were obtained. The areas under the curves (AUC), 95% confidence interval (CI), significance of discriminative power of the marker according to Hanley and McNeil test, and the differences between ROC curves according to de-Long test were calculated.

Unadjusted and adjusted (for all variables which can influence the hazard rate) Cox proportional hazard regression models were used to show the hazard rate for the positive outcome with comparison of the IV quartile of each marker with the other three quartiles.

The Kaplan–Meier method with Log rank test was used to describe and analyze significant differences between survival curves based on quartiles of PTH values.

All analyses were performed using SPSS version 21 (SPSS Inc, Chicago, IL, USA), Stata Version 10.1 (Stata-Corp, College Station, TX), or R-statistical software.

Results

The characteristics of the patients are shown in Table 1. During a 180-day follow-up, 36 (21.8%) of the patients had at least one episode of acute heart failure. The patients with acute heart failure episodes were older, had higher thrombolysis in myocardial infarction (TIMI) risk score at admission and more frequently TIMI2 flow through the infarction related coronary artery after PCI comparing to the control group.

Table 1

Basic demographic and procedural characteristics in patients with and without congestive heart failure symptoms

Patients characteristics	Congestive heart failure symptoms		*p*
	Yes (n = 36)	No (n = 129)	
Age (years), mean ± SD	71 ± 11	60 ± 11	< 0.001
Female, n (%)	12 (33.3)	33 (25.6)	0.399
Risk factors, n (%)			
history of hypertension	31 (86.1)	92 (71.3)	0.085
active smoking	13 (36.1)	73 (56.6)	0.038
diabetes	11 (30.6)	34 (26.4)	0.673
hypercholesterolemia	17 (47.2)	77 (59.7)	0.189
Time from pain onset to reperfusion (hours)			
median	4.0	4.0	0.447
interquartile range	3.0–7.7	2.5–9.0	
TIMI score			
median	7.0	3.0	< 0.001
interquartile range	5.2–9.5	2.5–9.0	
Reperfusion therapy, n (%)			
primary PCI	33 (91.7)	118 (91.5)	1.000
urgent PCI after thrombolysis	3 (8.3)	11 (8.5)	
Multivessel disease, n (%)	28 (77.8)	82 (63.6)	0.161
Infarct related artery, n (%)			
left anterior descending	19 (52.8)	62 (48.1)	0.707
ramus cirkumflexus	6 (16.7)	20 (15.5)	0.592
right coronary artery	11 (30.6)	47 (36.4)	0.559
TIMI flow before PCI, n (%)			
TIMI 0/1	25 (69.4)	99 (76.7)	0.388
TIMI 2	8 (22.2)	12 (9.3)	0.046
TIMI 3	3 (8.3)	18 (14.0)	0.572
TIMI flow after PCI, n (%)			
TIMI 0/1	1 (2.8)	1 (0.8)	0.390
TIMI 2	12 (33.3)	13 (10.1)	0.001
TIMI 3	23 (63.9)	115 (89.1)	0.001
Stent implantation, n (%)	30 (88.9)	117 (90.7)	0.753
Negative ST segment resolution after reperfusion, n (%); (157 patients)	17 (50.0)	40 (32.3)	0.070

TIMI score – thrombolysis in myocardial infarction; PCI – percutaneous coronary intervention.

Parathyroid hormone and total calcium levels in the patients with acute myocardial infarction

Serum concentrations of PTH decreased significantly over three days in the control group, but the decrease did not rich significance in the group of patients who already had symptoms of heart failure, or who had episodes of acute heart failure during the next 6 months (Figure 1a). Among the patients with primary outcome, 31 (86.1%) of them had PTH concentration at the first day above the upper limit of the normal range for the assay (1.6–7.0 pmol/L). However, in the control group 35 (27.1%) of the patients had PTH serum concentration higher than the upper limit of the normal value. Concentrations of serum PTH were significantly higher for all three measurements between the patients with positive primary end-point and the control group [10.84 (7.62–15.65) *vs* 5.31 (3.90–7.50) pmol/L, $p < 0.001$; 9.20 (6.90-13.59) *vs* 4.42 (3.52–5.42) pmol/L, $p < 0.001$; 7.31 (6.03–9.64) vs. 3.95 (3.15–5.51) pmol/L, $p = 0.001$ for measurement at 24, 48 and 72 hours after admission, respectively].

Total serum Ca^{2+} did not significantly change during the first three days after admission in both groups (Figure 1b). There was no significant difference in total serum Ca^{2+} levels during the first three days between the patients with acute heart failure and controls.

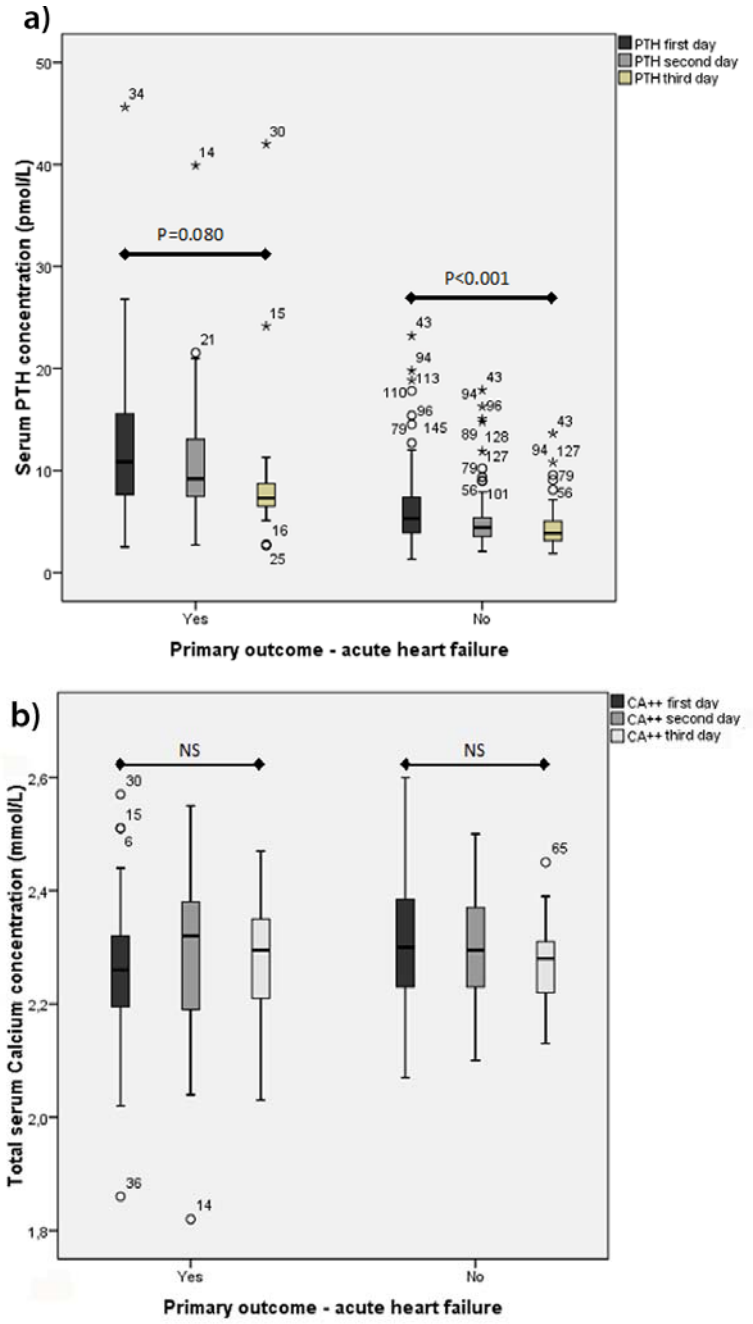

Fig. 1 – a) Serum values of parathyroid hormone (PTH), and b) total serum Ca^{2+} concentration according to the presence of primary outcome – acute heart failure at six months. Boxes in dark gray – the first day, light gray – the second day, and white – the third day from admission.

Biomarkers and clinical outcome

During 180 days follow-up 36 (21.8%) of the patients had at least one episode of non-fatal heart failure. Cox proportional hazards models were created using quartiles of all five biomarkers separately in the univariate and multivariate analysis where important variables (age, gender, the presence of diabetes, hypercholesterolemia, hypertension, TIMI risk score for STEMI, total ischemic time, and TIMI-flow before and after PCI) were included into the model for the adjustment of hazard ratios (Table 2). In the unadjusted models values in the upper quartile compared to other three quartiles of admission glycaemia (HR 1.73; 95% CI 0.87–3.42; $p = 0.113$), maximum CK-MB (HR 1.55; 95% CI 0.77–3.10; $p = 0.215$), maximum C-reactive protein (CRP) (HR 4.23; 95% CI 2.18–8.18; $p < 0.001$), maximum BNP (HR 7.14; 95% CI 3.55–14.35; $p < 0.001$) and maximum PTH (HR 9.78; 95% CI 4.68–20.42; $p < 0.001$) were associated with the occurrence of acute heart failure during the six months follow-up. In multivariable analysis adjusted hazard ratios on age, gender, smoking, the presence of diabetes, hypertension and hypercholesterolemia, time from the pain onset to reperfusion, TIMI risk score and the TIMI flow before and after PCI, were similar for admission glycaemia and CK-MB, slightly attenuated for CRP and BNP and unchanged for PTH: HR 1.51, 95% CI 0.60–3.78, $p = 0.373$ for admission glycaemia; HR 1.42, 95% CI 0.68–2.99, $p = 0.344$ for maximum CK-MB; HR 2.62, 95% CI 1.24–5.54, $p = 0.011$ for maximum CRP; HR 4.19, 95% CI 1.84–9.49, $p = 0.001$ for maximum BNP and HR 8.98, 95% CI 3.58–22.52, $p < 0.001$ for maximum PTH, respectively.

The areas under the ROC curves (Table 3 and Figure 2) for the primary outcome were the greatest for maximum PTH comparing to other four markers. Pairwise comparison

Table 2

Comparison of the levels of biomarkers in the patients with and without congestive heart failure symptoms with Cox proportional hazard regression models

Biomarkers*	Congestive heart failure symptoms		Unadjusted Hazard rate, (95% CI); *p*	Adjusted †Hazard rate, (95% CI); *p*
	with (n = 36)	without (n = 129)		
Admission glycaemia (mmol/L),				
mean ± SD	10.70 ± 5.65	8.83 ± 3.76	1.34 (1.04–1.72); 0.025§	1.68 (1.10–2.55);0.014§
median (IQR)	8.40 (7.55–11.32)	7.70 (6.55–9.45)	1.62 (0.82–3.16); 0.160	1.31 (0.57–2.99); 0.522
Q1 – n, %‡	4, 11.1	36, 27.9	R	R
Q2 – n, %‡	10, 27.8	32, 24.8	e	e
Q3 – n, %‡	9, 25.0	32, 24.8	f.	f.
Q4 – n, %‡	13, 36.1	29, 22.5	1.73 (0.87–3.42); 0.113	1.51 (0.60–3.78); 0.373
Maximum CK-MB (IU/L),				
mean ± SD	248.86 ± 130.70	202.74 ± 151.13	1.25 (0.94–1.66); 0.122§	1.22 (0.89–1.67);0.215§
median (IQR)	237.0 (145.25–334.75)	159 (89.50–278.00)	2.35 (1.16-4.79); 0.018	2.01 (0.93-4.36); 0.076
Q1 – n, %‡	4, 11.1	37, 28.7	R	R
Q2 – n, %‡	7, 19.4	34, 26.4	e	e
Q3 – n, %‡	13, 36.1	29, 22.5	f.	f.
Q4 – n, %‡	12, 33.4	29, 22.5	1.55 (0.77–3.10); 0.215	1.42 (0.68–2.99); 0.344
Maximum CK-MB (IU/L),				
mean ± SD	101.02 ± 80.48	35.25 ± 41.10	1.64 (1.37-1.96); < 0.001§	1.42 (1.10–1.83);0.007§
median (IQR)	79.55 (43.05–133.93)	17.36 (9.25-48.05)	12.32 (3.77–40.23); < 0.001	7.62 (2.23-26.70); 0.001
Q1 – n, %‡	-	41, 31.8	R	R
Q2 – n, %‡	3, 8.3	38, 29.5	e	e
Q3 – n, %‡	13, 36.1	29, 22.5	f.	f.
Q4 – n, %‡	20, 55.6	21, 16.3	4.23 (2.18-8.18); < 0.001	2.62 (1.24–5.54); 0.011
BNP (pg/mL),				
mean ± SD	831.71 ± 582.50	246.23 ± 246.03	1.88 (1.56–2.28); < 0.001§	1.76 (1.33-2.32); < 0.001§
median (IQR)	768.20 (348.14-1225.00)	182.16 (93.71–304.05)	8.86 (3.13–25.09); < 0.001	4.57 (1.46-14.34); 0.009
Q1 – n, %‡	3, 8.3	38, 29.5	R	R
Q2 – n, %‡	1, 2.8	40, 31.0	e	e
Q3 – n, %‡	8, 22.2	34, 26.4	f.	f.
Q4 – n, %‡	24, 66.7	17, 13.2	7.14 (3.55-14.35); < 0.001	4.19 (1.84-9.49); 0.001
Maximum PTH (pmol/L),				
mean ± SD	15.33 ± 9.97	6.38 ± 3.65	1.65 (1.41–1.94); < 0.001§	1.54 (1.20–1.96); < 0.001§
median (IQR)	12.57 (8.88–18.59)	5.40 (4.00–7.73)	12.38 (3.79–40.42); < 0.001	8.15 (2.39–27.79); < 0.001
Q1 – n, %‡	1, 2.8	40, 31.0	R	R
Q2 – n, %‡	2, 5.6	39, 30.2	e	e
Q3 – n, %‡	7, 19.4	35, 27.1	f.	f.
Q4 – n, %‡	26, 72.2	15, 11.6	9.78 (4.68–20.42); < 0.001	8.98 (3.58–22.52); < 0.001

*** Not normally distributed according to Kolmogorov-Smirnov test (Ln transformation was applied and all calculations were done with transformed values).**

† Hazard rates adjusted by age, gender, smoking, the presence of diabetes, hiperholesteronemia and hypertension, time from the pain onset to reperfusion, TIMI score, and the TIMI flow before and after PCI.

‡ Quartiles generated according to distribution of percentiles for all the patients

§ Hazard rates and confidence intervals are expressed *per* standard deviation increase.

Ref – reference value.

CK-MB – creatine kinase-myocardial band; CRP – C-reactive protein; BNP – B-type natriuretic peptide; PTH – parathyroid hormone; TIMI – thrombolysis in myocardial infarction; PCI – percutaneous coronary intervention.

Table 3

Areas under the curves (AUC) of biomarkers for the prediction of congestive heart failure symptoms

Biomarkers	Congestive heart failure symptoms at 180 days *					
	AUC	95% CI	*p*	Cut-off	Sensitivity	Specificity
Admission glycaemia (mmol/L)	0.619	0.518–0.720	0.029	7.1	83.3	39.5
Maximum CK-MB (ng/mL)	0.627	0.532–0.722	0.020	160	75.0	52.7
Maximum CRP (mg/mL)	0.835	0.773–0.898	< 0.001	22.8	100.0	58.1
BNP (pg/mL)	0.832	0.741–0.923	< 0.001	320	80.5	78.1
Maximum PTH (pmol/L)	0.867	0.799–0.936	< 0.001	8.8	77.8	83.7

***Significance levels of pairwise comparison (deLong et al. [14]) of ROC curves: Admission glycaemia *vs* Maximum CK-MB, Maximum CRP, BNP, Maximum PTH (0.941, 0.0002, 0.0006, 0.0001, respectively); Maximum CK-MB *vs* Maximum CRP, BNP, Maximum PTH (0.0001, 0.0008, 0.0001, respectively); Maximum CRP *vs* BNP, Maximum PTH (0.9554, 0.4719, respectively); BNP *vs* Maximum PTH (0.5199). CK-MB – creatine kinase-myocardial band; CRP – C-reactive protein; B-type natriuretic peptide; PTH – parathyroid hormone.**

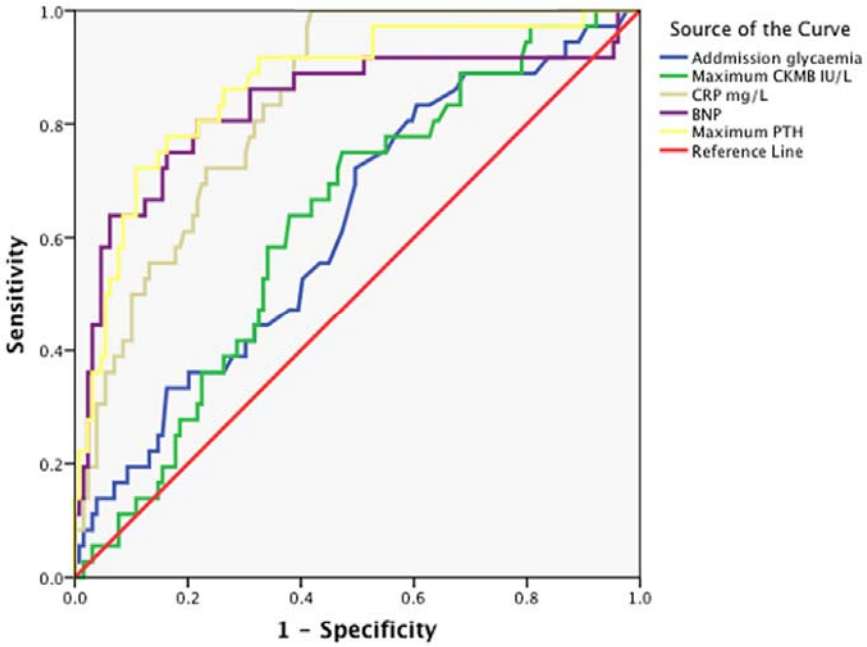

Fig. 2 – Receiver operating characteristic (ROC) curves of biomarkers for primary outcome. CK-MB – creatine kinase-myocardial band; CRP – C-reactive protein; BNP – B-type natriuretic peptide; PTH – parathyroid hormone.

of ROC curves showed that the ROC curve of maximum PTH was better predictor of a six-month primary outcome than admission glycaemia and maximum CK-MB ($p < 0.001$ and $p < 0.001$, respectively). However, there was no significant difference between ROC curves of maximum CRP and PTH as well as BNP and PTH ($p = 0.472$ and $p = 0.520$, respectively) for the prediction of primary outcome. ROC curve analysis was used to establish the best cut-off values of biomarkers for the prediction of primary outcome. For the prediction of primary outcome, maximum PTH > 8.8 pmol/L had sensitivity 77.8 and specificity 83.7, and BNP, for the value greater than 320 pg/mL, similarly had sensitivity 80.5 and specificity 78.1.

Kaplan-Meier plots discovered a higher risk of the six-month primary outcome in the fourth and third quartile of maximum PTH ($p < 0.001$, Breslow test, Figure 3).

Discussion

Our study demonstrates that an increased serum level of PTH is associated with episodes of acute heart failure in the first six months after STEMI, in patients treated with contemporary reperfusion therapy. When we analyzed models of predictive value of PTH for this primary outcome with other four well established biomarkers: admission glycaemia, maximum CK-MB, maximum CRP and BNP, measured during the first three days of infarction, PTH significantly improved predictive value with all individually, but BNP. PTH was not inferior as a predictor of primary outcome compared to conventionally used BNP.

Different biomarkers are used for the prognosis in patients with myocardial infarction [15–21]. We used the most widely and routinely applied biomarkers for the comparison

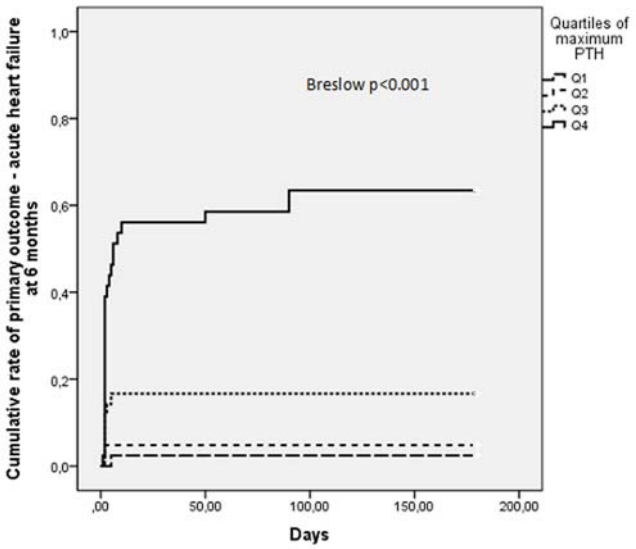

Fig. 3 – Kaplan-Meyer curve for parathyroid hormone (PTH) maximum. Time to acute heart failure symptoms at 180 days according to the quartiles of maximum levels of serum PTH.

with PTH to investigate the predictive models for one of the most important consequences of myocardial infarction and that is the episode of acute heart failure in the first six months after admission. Admission glycaemia in STEMI patients is the consequence of excessive secretion of several hormones and catecholamines into blood and it is associated with heart failure and death irrespective of their diabetic status [15, 16]. Several studies proved the predictive value of serum CRP levels for the outcome in STEMI patients treated with primary PCI [17–19]. BNP is a good prognostic determinant for left ventricular remodeling as well as for other primary outcomes like all-cause mortality in STEMI patients [20, 21]. Creatine kinase and its' isoenzyme creatine kinase-MB was also a good marker of infarction size and can be useful for the prognosis of STEMI [22, 23]. In the large cohort of STEMI patients, Nienhuis et al. [22] have shown that peak CK-MB values were an independent predictor of left ventricle ejection fraction and one-year mortality in STEMI patients treated with primary angioplasty.

Several biochemical markers involved in calcium homeostasis are investigated as prognostic factors in acute coronary syndrome. A low serum calcium concentration at admission in the large cohort of Chinese STEMI patients was an independent predictor of in-hospital mortality [24]. Similarly, low serum levels of 25(OH)D vitamin levels in STEMI predicted well in-hospital and one-year mortality in patients with acute coronary syndrome [25]. In our study, all four traditionally used markers had good predictive value for the primary outcome. Analysis of ROC curves illustrated that maximum PTH level has had the largest area under the curve among all markers, but that the difference between PTH and BNP was not significant and the specificity and sensitivity for their cut-off values, as predictors for primary outcome, were similar.

The increase of serum PTH in STEMI patients are probably due to increased neurohumoral activation with high blood levels of catecholamines and sympathetic activity [26–28]. A significant linear correlation between plasma and platelet epinephrine concentrations and plasma PTH blood levels was found in patients with AMI [29].

What would be potential explanation for the role of PTH in patients with AMI? Direct cardiovascular effects of PTH and its involvement in the regeneration process might be the explanation. Adult cardiomyocytes have PTH-1 receptor which is up-regulated in the state of ischemia [30]. PTH causes influx of Ca^{2+} into cardiomyocytes with positive inotrope and chronotrope action which may represent a compensatory process in patients with myocardial infarction and acute heart failure [1]. On the other hand, PTH effects L-type Ca channels on smooth muscle cells and causes arterial vasodilatation which contribute to the decreased afterload and better myocardium perfusion in the state of acute heart failure [31]. In the mice model of myocardial infarction, PTH reduced the infarction size by the inhibitory effect on apoptosis which is important mechanism of cell death in ischemic myocardium [32].

The role of PTH as important messenger in the regeneration process after myocardial infarction is very intriguing. Through the receptors on osteoblasts, PTH induced secretion of several cytokines, including interleukin (IL)-6, IL-11, vascular endothelial growth factor (VEGF), chemokine stromal cell-derived factor 1 (SDF)-1 and granulocyte colony-stimulating factor (G-CSF) and regulated the stem cell niches environment in the bone marrow and proliferation and mobilization of stem cells [33]. PTH has the pivotal role in mobilization and homing of bone-marrow-derived stem cells into the ischemic myocardium and can provoke neovascularization, decrease the infarction size and improve survival of animals with myocardial infarction [3–5].

Mechanisms which influence the increment of PTH in myocardial infarction depend on the infarction size and the hemodynamic disturbance. Elevated blood levels of catecholamines, increased sympathetic activity, hypocalcemia and hyperphosphatemia, are all associated with severe, large myocardial infarction and signs of acute heart failure and can inc-

rease blood levels of PTH [24–27]. Therefore, cardiovascular and regenerative action of PTH is proportional to the extent of the myocardial damage and that is possible reason for the good predictive value of serum PTH level early in the course of infarction.

Limitation of the study

There are several limitations of this study. Admission PTH level was not obtained. A relatively small number of patients precludes the statistically powered separate analysis for death outcome. Some newer biomarkers which are more expensive and not widely available [34] were not used in this trial.

Conclusion

We concluded that data from our trial show for the first time that one hormone – PTH has a good predictive value for the six-month outcome in STEMI patients, at least as good as traditionally used markers such as admission glycaemia, CRP, CK-MB and BNP. This finding implies the possible important role of PTH in STEMI and further investigation is needed.

Declaration of interests

The authors have no conflict of interest to declare.

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