Serum levels of NT- pro ANP, BNP, NT-pro BNP and function of the left atrium in patients with heart failure and preserved ejection fraction after myocardial infarction

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Serum Levels of NT- pro ANP, BNP, NT-pro BNP and Function of the Left Atrium in Patients with Heart Failure and Preserved Ejection Fraction after Myocardial Infarction

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Abstract. The objective of our study was to evaluate the levels of natriuretic peptides in patients (pts) with heart failure with preserved ejection fraction (HFpEF) in 12 month after ST elevation myocardial infarction (STEMI) with a focus on the function of left atrium (LA) and left ventricular (LV) filling pressure. 55 pts were included in the study. 6-minute walk test was performed. Echo exam was performed by the diagnostic system VIVID 7. BNP in whole blood was determined using the Triage ® Meter BNP test. The serum levels of NT-pro BNP, NT-pro ANP («Biomedica», Austria) were determined in blood samples by enzyme-linked immune-sorbent assay (ELISA). LA volume index were differences (16.03±3.39 ml/m2; 25.36±8.26 ml/m2; 29.41±9.46 ml/m2 accordingly I, II, III class) depending on severity of HF. Well as E/E' ratio were differences (7.5±1.4; 9.8±5.1; 13.5±7.6 accordingly I, II, III class) depending on severity of HF. The LA volume index correlated with levels of NT-pro ANP (R=0.29; p=0.04), levels of NT-pro BNP (R=0.37; p=0.01), levels of BNP (R=0.51; p=0.0001). The LV filling pressure correlated with levels of NT-pro ANP (R=0.45; p=0.002), levels of NT-pro BNP (R=0.49; p=0.001), levels of BNP (R=0.37; p=0.01).

INTRODUCTION

Increased left atrium (LA) volume is a strong predictor of mortality after ST segment elevation myocardial infarction (STEMI) and provides superior prognostic information compared with conventional left ventricular (LV) systolic and diastolic function measurements and clinical data [1]. However, the optimal treatment for STEMI allows to prevent the adverse postinfarction remodeling and to preserve LV ejection fraction (EF) [2-5]. Overall, the evolution of cardiovascular mortality appears extremely encouraging, showing that, in many European countries, coronary artery disease (CAD) mortality had been decreased by >50% in just three decades [6]. Wherein, the number of patients (pts) with chronic heart failure (CHF) is increasing. It is important that the preserved LV EF in pts with HF (HFpEF) is not associated with favorable prognosis [7-9]. In this HFpEF is a multifactorial disease, the pathophysiology which is not fully studied. Similarly there is no effective treatment, which would reduce mortality from this disease.

Plasma levels N-terminal pro-atrial natriuretic peptide (NT-pro ANP) levels are also elevated in CHF and after acute MI [9-12]. Besides this NT-pro ANP is a strong predictor of mortality in pts with unstable CAD independent of level troponin T and other risk factors of CAD [13]. ANP and brain natriuretic peptide (BNP) exhibit similar hormonal effects and the secretion of both peptides are stimulated by myocardial ischemia and pressure overload [14–16]. However the level of gene expression, ANP and BNP are regulated differentially [14]. Accordingly, elevations of NT-pro ANP and NT-pro BNP in pts with HFpEF might reflect distinct pathological processes in accordance with myocardial ischemia. Therefore, simultaneous determination of these peptides might improve the

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risk assessment of patients with HFpEF. The aim of our research - to determine the levels of NT- pro ANP, BNP, NT-pro-BNP in pts with HFpEF in 12 months after STEMI and relationship between the serum levels of natriuretic peptides, the index-volume of the LA and LV filling pressure.

MATERIALS AND METHODS

The cross-sectional study included 55 patients with symptoms and signs of HFpEF 12 months after STEMI. The exclusion criteria were severe systemic illness, significant chronic pulmonary disease, infiltrative or hypertrophic cardiomyopathy, constrictive pericarditis, known chronic hepatic disease, severe chronic kidney disease, and atrial fibrillation. The average age of patients was 66±9 years. Detailed physical examination, ECG, and echocardiography were performed. Exercise tolerance was assessed by a 6-minute walking distance test. Two-dimensional echocardiography was performed using ultrasonic system (GE Vivid 7; GE Corporation, USA). All measurements were obtained as per the criteria recommended by the American Echocardiography Society [17]. The detailed protocol and results we described earlier [18]. BNP in whole blood was determined using the Triage ® Meter BNP test. The serum levels of NT-pro BNP, NT-pro ANP («Biomedica», Austria) were determined in blood samples by enzyme-linked immune-sorbent assay (ELISA).

Analysis of clinical and instrumental data was done according to the New York Heart Association (NYHA) functional HF classification system: NYHA class I (Group 1), NYHA class II (Group 2), and NYHA class III (Group 3). Control group consisted of 14 healthy volunteers, who had no signs of HF, matched by sex and age with the patients of the study group (Tab. 3).

Statistical analysis was performed using the software package «Statistica 6.0» and SPSS 17.0. The unpaired Student's t-test was used to determine the statistical significance of continuous variables for intergroup comparison; the module ANOVA/MANOVA was used for multiple (more than two) comparisons. Non-random associations between the categorical variables were determined using the Fisher's exact test or $\chi 2$; the Kruskal-Wallis ANOVA test was used for multiple comparisons in some cases. Relationships between the pairs of quantitative indicators were estimated using Pearson's linear correlation coefficient (r) or rank correlation Spearman's coefficient in the analysis of ordinal and quantitative traits (R). A P value of <0.05 was considered significant.

RESULTS

Among the enrolled patients, 29 (53%) were men; 30 (55%) patients had anterior myocardial infarction 12 months before the study; 44 (70%) patients underwent angiography due to STEMI 12 months before the study. 27 (61%) pts had multivessel CAD; complete revascularization by the percutaneous coronary intervention (PCI) was achieved in 19 (44%) of them [18].

There was no exacerbation of CAD in patients for 12 months following STEMI. Most patients had NYHA class II (49%). Class II of angina was found in the majority of patients (53%). In addition, we found that the HF severity depended on the patient’s age. The main symptom of HF was dyspnea; the chest X-ray showed signs of cardiomegaly. A third of pts had edema; one fifth of the pts had paroxysmal nocturnal dyspnea. The symptoms and signs of fluid retention were more prominent in pts with the NYHA class III, these pts had higher incidence of arrhythmias. All the pts, involved in the study, received recommended treatment after STEMI including aspirin (54 patients, 98%), clopidogrel (6 patients, 11%), β-blockers (45 patients, 82%), ACE inhibitors (46 patients, 84%), calcium channel blockers (12 patients, 22%), diuretics (18 patients, 33%), and statins (31 patients, 56%).

The average levels of NT-pro ANP, NT-pro BNP and BNP were increased to 8.82 ± 4.45 nmol/l, 293.04 ± 289.66 pg/ml and 172.7±198.3 pg/ml, respectively. The increased levels of BNP (>100 pg/ml) were found in 27 (50%) patients; the minimum BNP value was 5.0 pg/ml while the maximum BNP level was 1.050 pg/ml. The levels of NT-pro ANP, NT-pro BNP and BNP were significantly higher in patients with the NYHA class III. Increase in NT-pro ANP, NT-pro BNP and BNP values depended on the functional classes of HF: NT-pro ANP in pts with I class was 3.34 (2.88-4.81) nmol/l, II class was 8.56 (4.38-10.40) nmol/l, III class was 10.95 (7.90-13.78) nmol/l ($p <0.05$). The levels of NT-pro BNP in pts I class match 46.36 (22.46-56.10) pg/ml, II class 122.35 (42.79-185.90) pg/ml, III class 410.65 (258.70-781.20) pg/ml ($p <0, 05$). BNP values were equal 9.35 (7.60-11.0) pg/ml in I class; 82.45 (32.90-121.0) pg/ml in II class, 202.50(147.0-431.0) pg/ml in class III ($p<0.05$) (Tab. 1). Echocardiographic measurements are shown in Tab. 2.

TABLE 1. Serum levels of BNP, NT-pro BNP, NT-pro ANP (Me (Q25-Q75))

Parameters	NYHA class			Control
	Group 1 (n=6)	Group 2 (n=27)	Group 3 (n=22)	group (n=14)
BNP, pg/ml	9.35 (7.60 -11.0) *	82.45 (32.90-121.0) *	202.50 (147.0-431.0) *	8.70 (3.0-14.60)
NT-pro BNP, pg/ml	46.36 (22.46-56.10)*	122.35 (42.79-185.90)*	410.65 (259.70-781.20)*	2.71 (0-6.72)
NT-pro ANP, nmol/l	3.34 (2.88 – 4.81) *	8.56 (4.38 – 10.40)	10.95 (7.90 – 13.78) *	2.48 (1.16 – 3.16)

* - the differences between groups.

TABLE 2. Echocardiographic parameters of the patients

Parameters	All (n=55)	Group 1 (n=6)	Group 2 (n=27)	Group 3 (n=22)	p
LA (mm)	38.06±4.33	34.33±4,03	37.57±3.85	39.82±4.30*	0.02
LA volume index / BSA (ml/m^2)	25.84±9.18	16.03±3.39	25.36±8.26	29.41±9.46*	0.005
Lateral Sm, ms	7.16±1.69	7.33±1.21	7.66±1.71	6.44±1.61**	0.06
A velocity, cm/sec	0.84±0.22	0.67±0.12	0.84±0.21	0.88±0.24*	0.05
Sep E/E`	13.85±4.89	11.8±3.79	12.95±4.80	15.84±4.91	0.09
Lat E/E`	10.9±6.17	7.5±1.4	9.8±5.1	13.5±7.6	0.001
Average E/E`/	11.9±3.8	9.1±1.9	11.0±4.6**	14.1±5.9*	0.05

* the differences between the NYHA classes I and III, ** the differences between NYHA classes II and III. HR – heart rate; LA – left atrial; RV – right ventricular; LV – left ventricular; EDD – end-diastolic diameter; SWT – septal wall thickness; PWT – posterior wall thickness; MM – mass myocardial; MI – mass index; EDV - end-diastolic volume; ESV – end-systolic volume; EF – ejection fraction; MVBF – minute volume of blood flow; Sm – myocardial systolic peak velocity; E – myocardial early-diastolic wave; A - myocardial atrial diastolic wave; IVRT – isovolumic relaxation time; E` - myocardial early-diastolic wave mitral annulus.

The pts were divided into two additional groups. The first group represented pts with normal LV filling pressure, and a second group with high LV filling pressure. After analyzing the levels of markers NT-pro ANP, NT-pro BNP, BNP depending on the LV filling pressure, received significant differences between the groups (Tab. 3). In the first group the average levels of NT-pro ANP, NT-pro BNP and BNP were lower 6.8 ± 3.4 nmol/l, 185.68 ± 245.98 pg/ml and 99.94 ± 119.71 pg/ml, while the second group were higher to 12.07 ± 4.8 nmol/l, 472.80 ± 303.65 pg/ml and 275.18 ± 195.70 pg/ml, respectively.

TABLE 3. Levels of BNP, NT-pro BNP, NT-pro ANP depending on the filling pressure of the left ventricle (Me (Q25-Q75))

Biomarker	Pts with HFpEF (All) n=46	Control group n=14	Pts with normal LV filling pressure (group 1) n=15	Pts with high left LV pressure (group 2) n=31
BNP pg/ml	172,78 ± 198,29	8,48 ± 7,62	99,94 ± 119,71 *	275,18 ± 195,70 *
NT-pro BNP pg/ml	293,04 ± 289,66	2,33 ± 5,03	185,68 ± 245,98 *	472,80 ±303,65 *
NT-pro ANP nmol/l	8,82 ± 4,45	2,48 ± 1,61	6,8 ± 3,4 *	12,07 ± 4,8 *

* - *the differences between groups*

In order to determine of echocardiographic signs in the studied pts, depending on the level of NT-pro ANP, we divided all pts into quartiles. NT-pro ANP levels in the first quartile ranged from 2.3 - 4.6 nmol/l, in the second quartile from 5.23 - 9.85 nmol/l, in the third quartile from 10.1 - 13.78 nmol/l and in the fourth quartile from 15.27 - 20.27 nmol/l. Parameters of cardiac assessment according to NT-pro ANP levels are presented in Tab. 4.

It turned out that among the pts included in the 4th quartile, more frequently found anterior MI complicated with HF NYHA class III with echocardiographic signs of increased LV filling pressure. This was confirmed by the higher levels of BNP, NT-pro BNP in these pts. However, a significant difference in the volume index of the left atrium was not.

TABLE 4. Parameters of cardiac assessment according to NT-pro ANP levels

Parameters	1rd quartile NT-pro ANP n=12	2rd quartile NT-pro ANP n=19	3rd quartile NT-pro ANP n=14	4rd quartile NT-pro ANP n=6	p-value
Ejection fraction (%)	55 (46-67)	52 (45-63)	53 (45-64)	51 (46-56)	ns
LVEDD (mm)	50 (41-65)	48 (32-61)	51 (41-61)	46 (37-53)	ns
LV MM index [g/m^2]	129.2 (67.6-254.1)	114.9 (37.5-220.9)	142.6 (96.3-195.5)	141.7 (87.6-205.5)	ns
LA- Index (ml/m²)	23.3 (12-40.1)	25.7 (11-42.6)	25.7 (13-42.3)	31.3 (17.1-45.2)	ns
E (cm/s)	63 (24-102)	64.3 (39-113)	77.3 (37-135)	59 (36-80)	ns
A (cm/s)	82.3 (46-130)	85 (55-113)	91.4 (49-139)*	65.6 (44-94)*	0.06
E/A ratio	0.8 (0.4-1.26)	0.8 (0.5-1.19)	0.9 (0.5-1.66)	1.0 (0.6-1.82)	ns
E' septal (cm/s)	5.5 (4.0-7.0)*	5.13 (3.0-9.0)	4.9 (3.0-9.0)	4.0 (3.0-6.0)*	0.03
E' lateral (cm/s)	7.6 (3.0-11.0)	7.6 (5.0-12.0)*	7.92 (3.0-12.0)	3.8 (2.0-7.0)*	0.002
E/E' septal ratio	11.9 (4.8-20.4) *	12.8 (8.3-22.6)	16.24 (7.4-25.0)*	15.38 (8.3-20.0)	0.05
E/E' lateral ratio	9.7 (3.0-25.6) *	8.5 (5.0-14.1)	11.8 (3.7-27.0)*	18.34 (7.14-28.0)	0.05
BNP (pg/ml)	69.6 (5.0-316.0)*	127.6 (11.0-537.0)	266.8 (52.3-1050.0)	340.3(89.2-751.0)*	0.003
NT-pro BNP(fmol/ml)	140.5 (11.13-571.3)*	248.6 (15.4-1061.0)	378.7(21.2-905.0)	506.1(110.2-872.2)*	0.006
NYHA III (%)	1(8%)	8 (42%)	8 (57%)	5 (83%)	0.02
Increased LV filling pressure (%)	2 (16%)	3 (20%)	6 (50%)	4 (80%)	0.02
Anterior myocardial infarction (%)	4 (33%)	8 (42%)	10 (71%)	6 (100%)	0.01

NT-pro ANP levels in the first quartile ranged from 2.3 - 4.6 nmol/l, in the second quartile from 5.23 - 9.85 nmol/l, in the third quartile from 10.1 - 13.78 nmol/l and in the fourth quartile from 15.27 - 20.27 nmol/l.

At the same time revealed a positive correlation between the volume - index of the LA and NT-pro ANP, NT-pro BNP, BNP. The LA volume index correlated with levels of NT-pro ANP (R=0.29; p=0.04), levels of NT-pro BNP (R=0.37; p=0.01), levels of BNP (R=0.51; p=0.0001). Importantly, the levels of NT-pro BNP and NT-pro ANP were not as high as it is typical for patients with HF and systolic dysfunction.

In order to assess the levels of natriuretic peptides according to the ventricular filling pressure, and all pts were further divided into 3 groups. E/E` average < 8 (Group 1), E/E` average 8-13 (Group 2), E/E` average>13 (Group 3). Was revealed a positive correlation between the levels of natriuretic peptides and LV filling pressure. The LV filling pressure correlated with levels of NT-pro ANP (R=0.45; p=0.002), levels of NT-pro BNP (R=0.49; p=0.001), levels of BNP (R=0.37; p=0.01).

DISCUSSION

According to the new strategy [19] in the diagnosis and treatment of HF with normal LVEF, there is a need for better phenotyping of pts with symptoms and signs of HF with preserved LVEF. Taking into the account the fact that HF with normal LVEF is a heterogeneous disease which includes not only cardiac abnormalities such as left ventricular diastolic dysfunction, moderate decrease in left ventricular systolic function, impaired atrial function, but also extracardiac abnormalities and comorbidities, i.e. hypertension, atrial fibrillation, diabetes, renal or pulmonary disease, anaemia, obesity, and deconditioning, and this may contribute to the HFpEF syndrome.

The objective of our study was to evaluate the levels of natriuretic peptides in patients with HFpEF LV after MI with a focus on the function of LA and LV filling pressure. Previous studies reported that LA volume helps to identify HFpEF [20] with sensitivity and specificity (close to 80%) similar to our results.

The LA acts as an effective volume sensor producing the natriuretic peptide and other neurohormones as a result of increased stress on the walls of the atrium, and emptying rate depends on the compliance of the LV [21]. Therefore, when LA does not deal with ventricular filling due to passive and active normal blood flow, there is a compensatory increase in pressure LA. In turn, the thin wall LA cannot restrain increased pressure protractedly, and this causes dilation of its cavity [22].

Chronic high blood pressure overload LA contributes to disorder of energy myocardial metabolism, damage of contractile proteins and atrophy of muscle cells that eventually leads to fibrosis of LA's walls. Accordingly, the fail of compensation with the development of clinically significant signs of HFpEF is probable at this stage. Thus, if direct or indirect signs of increased pressures of LV filling with elevated levels of NT-pro ANP, NT-pro BNP or BNP identified, it is reasonable to suggest the presence of HFpEF with high probability regardless of assessment method [22]. As a rule these pts are characterized by older age, a long history of hypertension and diabetes, and more severe coronary disease [23].We received positive correlation between the index - volume of the LA and the levels of NT-pro ANP, NT-pro BNP and BNP which is consistent with other studies [9-13].

The main unresolved question is how to treat optimally pts with a pathological LV filling, especially if LV EF is normal or only moderately reduced. There is no intervention studies conducted with hard endpoints in which sampling of pts was based on the violation of LV filling to date. However, the assessment of flow and the ratio E/E` can provide important information about the status of hemodynamics and a guide to the use of vasodilators and diuretics.

We have established that the LA volume - index of pts with NYHA II and III was higher which indirectly indicates that the atrial "pumping" partly engaged in the filling of the LV at rest while diastolic reserve reduced. Since much of blood in slow relaxation enters LV during atrial systole, atrial "pumping" is already partly activated in the filling of the LV at rest, and as a result diastolic reserve reduces during physical exertion. Therefore, proper filling of the LV during physical activity occurs at the expense of the increasing pressure in the LA, which leads to the rapid emergence of dyspnea. Increased pressure in the LA eventually leads to dilatation, and it is eventually reflected in the increase of NT-pro ANP P, NT-pro BNP and BNP.

CONCLUSION

We found that levels of NT-pro ANP, NT-pro BNP and BNP in pts with preserved LVEF in 1 year after STEMI increased accordingly to functional classes of HF. Well as showed a positive correlation between the levels of NT-pro ANP, NT-pro BNP, BNP and index-volume of the LA. High pressure of filling of the LV was associated with increasing in NT-pro ANP, NT-pro BNP and BNP. Definition of the level of NT-pro ANP does not represent an additional diagnostic significance in cases with such pts in comparison with the BNP and NT-pro BNP.

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