NT-proBNP in patients after acute coronary syndrome with ST segment elevation subjected to early posthospitalization cardiologic rehabilitation

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Abstract

Introduction: In the group of patients with acute coronary syndromes, both BNP (brain natriuretic peptide) and NT-proBNP provide independent and additional diagnostic information and have high predictive value. The aim of the study was to estimate NT-proBNP concentrations under the effect of exercise training in patients following myocardial infarction with ST segment elevation, treated with primary PTCA and intracoronary stent placement.
Material and methods: The examinations were performed in two groups matched as regards age, gender, infarction location, risk factors and troponin level. Group I included 17 men, who within the last 2-3 weeks had acute coronary syndrome with ST segment elevation and were treated with primary angioplasty and intracoronary stent placement. These patients were qualified for 12-day exercise training. Group II comprised 14 men, who for the same reasons were treated with primary angioplasty but according to the risk stratification criteria for patients qualified for rehabilitation were not subjected to rehabilitation exercises on a cycloergometer.
Results: In group I, after exercise cycle completion a statistically significant decrease in NT-proBNP concentration was observed. In group II, no statistically significant change in NT-proBNP concentration was noted. In group I, a statistically significant increase in EF was detected and in group II, EF did not improve significantly after the period of observation. Both in group I and II a significant negative correlation was observed between NT-proBNP concentration and EF.
Conclusions: Taking into account that NT-proBNP is a sensitive and specific marker of left ventricular function, the results of our studies confirm the value of cardiologic rehabilitation as a useful therapeutic method in patients after myocardial infarction, making easier the restoration of normal left ventricular function.

Key words: NT-proBNP, acute coronary syndrome, cardiologic rehabilitation.

Introduction

Brain natriuretic peptide (BNP) represents a family of natriuretic peptides which also includes: atrial natriuretic peptide (ANP), secreted in the atria; C-type natriuretic peptide (CNP), secreted at the level of the vascular epithelium; and dendroapsis natriuretic peptide (DNP), discovered not long ago in viper venom [1].

Biological activity of natriuretic peptides is realized through a system of peripheral receptors (type A, B and C) localized in various tissues, among others in epithelial cells and renal tubules [2]. Natriuretic peptides neutralize the effects of excessive activation of the renin--angiotensin-aldosterone system (RAA). BNP acting natriuretically, similarly as ANP, takes part in the body's water balance. Its diuretic activity reduces the volume of the vascular bed and is an important element of the mechanism of arterial pressure endogenic regulation [3]. BNP is released from ventricular myocardium cadriomyocytes in response to increasing pressure or volume overload. Elevated BNP concentration was observed in circulatory system diseases with increased ventricular overload, e.g. in heart failure being the consequence of right and left ventricular dysfunction resulting from acute coronary syndromes (with and without ST segment elevation) [4].

Elevation of plasma BNP concentration is a recognized index of the degree of left ventricular dysfunction and has proved to be of high prognostic value, enabling the prediction of death due to heart failure or acute coronary syndrome not resulting in death [5, 6].

Every rehabilitation procedure aims to restore optimal fitness or at least develop the body's compensatory functions. This principle also concerns the cardiovascular system. Exercise training through periodic increase of heart rate is a factor intensifying angiogenesis, which results in exercise-induced increase of the left ventricular ejection fraction (EF) and in the improvement of global myocardial contractility [7]. Furthermore, exercise restores endothelial balance: there is an increase in endothelium-derived relaxing factor (EDRF) and endothelium-derived hyperpolarizing factor (EDHF) synthesis and endothelin-1 (ET-1) release inhibition [8]. Fundamental studies of Sullivan from Duke University, in patients with heart failure, determined the effect of controlled exercise training on the increase of pulmonary ventilation capacity and the increase of blood flow in extremities [9]. The beneficial effect of physical training – increased cardiac output or oxygen consumption by myocardium – has also been confirmed by other authors [10]. Numerous researchers have observed the beneficial effect of cardiologic rehabilitation in reducing left ventricular systolic dysfunction expressed by ejection fraction improvement and decreased plasma NT-proBNP concentration.

The aim of the study was to estimate NT-proBNP concentration under the effect of exercise training in patients after myocardial infarction with ST segment elevation, treated with primary PTCA with a stent.

Material and methods

Two groups of subjects were studied. Group I included 17 men, mean age 53.6 years, who within the last 2-3 weeks had acute coronary syndrome with ST segment elevation and were treated with primary angioplasty and intracoronary stent placement. These patients were qualified for 12-day exercise training.

Group II comprised 14 men, mean age 64.3, who for the same reasons were treated with primary angioplasty but according to the risk stratification criteria for patients qualified for rehabilitation were not included into the training group. The following qualification criteria were considered: EF <40%, the occurrence of complex ventricular arrhythmia at rest and on exertion, horizontal depression of ST segment on exertion, physical efficiency <5 MET, pathological reaction to exercise, that is lack of increase or decrease of systolic arterial pressure or heart rate proportionally to the increase of load, and finally clinical data – ischaemia after revascularization or heart failure. A rule was accepted that when one of the above was observed, the patient was qualified to group II. A set of exercises such as breathing, isometric, of small muscular groups, and relaxation considered to be safe while undertaking rehabilitation treatment in the group of high risk patients, was suggested to all group II patients.

Patients in both groups were subjected to simultaneous pharmacological therapy according to currently in force standards of the Polish Cardiac Society.

Patients from both groups were subjected to exercise test on a moving track to estimate the level of tolerated exercise. A modified Bruce's protocol was applied in group II. In this group in four cases the patients were not qualified on the basis of exercise test owing to weak tolerance of exercise.

In both groups echocardiography was performed twice with a 3.5 MHz transducer: before and on completion of the training cycle. In each case the same person performed the examination. Ejection fraction (EF) was investigated with Simpson's method. Means from the measurements in three cardiac cycles were accepted for estimation according to the recommendations of the American Society of Echocardiography. Group I patients were subjected to rehabilitation in 12-day exercise training. Interval training was applied on a cycloergometer with increasing load from 25 to 40 watts.

The level of NT-proBNP was tested twice in all patients with ready immunoenzymatic kits by ELISA method (Biomedica). In group I blood was collected from the basilic vein at rest, before and after the training cycle, while in group II before and after a comparable period of observation (12 days).

The investigated groups were compared taking into account parameters which could affect the level of NT-proBNP secretion. The following parameters were compared: myocardial infarction location, risk factors and also the level of troponin release.

Statistical analysis was performed with STATISTICA PL. 5.1 on the basis of the determination

Table I. NT-proBNP concentration in studied groups (A – before, B – after rehabilitation)

Group		Min	Max	Me	Mean	SD	Significant differences before – after
Group I	A	67.3	461.5	160.7	**192.09**	±110.18	**p<0.05**
	B	41.4	226.6	85.8	**99.91**	±45.82	
Group II	A	186.7	460.7	199.0	**267.58**	±112.22	p>0.05
	B	143.9	412	190.7	**243.80**	±107.33	

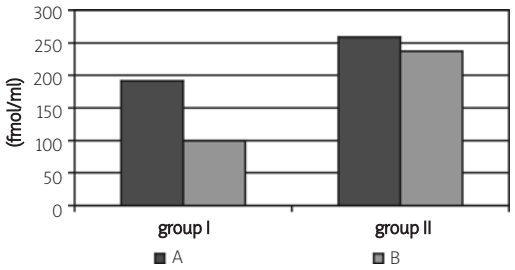

Figure 1. Comparison of NT-proBNP concentrations in studied groups (A – before, B – after rehabilitation)

of means of the variables and their standard deviations. Differences between the investigated groups were estimated with chi-square test. To find the normal distribution, variation of the distribution of the investigated variables was checked with W. Shapiro-Wilk test, and variances homogeneity with F test. Further analysis was performed with Student's t-test for unmatched pairs. Correlation between the tested parameters was analysed by calculating Pearson's correlation coefficient (r). The results are considered statistically significant at the level of significance <0.05 (p<0.05).

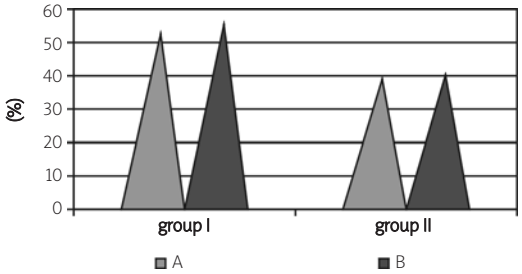

Figure 2. Comparison of EF in studied groups (A – before, B – after rehabilitation)

Results

The studied groups were comparable as regards infarction location (p=0.998), risk factors (p=0.774) and troponin release (p<0.684).

In group I the determined NT-proBNP concentration was 192.09 fmol/ml before rehabilitation. After completion of the training cycle a statistically significant decrease in NT-proBNP concentration was observed to the value 99.91 fmol/ml. In group I initial NT-proBNP concentration was 267.58 fmol/ml. After completion of the period of observation a statistically insignificant decrease in NT-proBNP was noted to the value 243.80 fmol/ml (Table I, Figure 1).

After completion of the training cycle a significant improvement in physical fitness was observed. Mean efficiency in group I before rehabilitation was 6 MET, while on completion it was 9 MET. In group II no significant improvement was observed in the range of physical efficiency after the period of observation. Mean efficiency in this group was 3 MET and after the observation period 4 MET.

In group I, EF calculated before the training cycle was 53.65%, while after rehabilitation the value of EF increased statistically significantly to 56.65%. In group II, at the beginning of observation EF was 38.40% and after completion no significant improvement of EF was noted (Table II, Figure 2).

Both in group I and II a significant negative correlation was observed between NT-proBNP concentration and EF: respectively in group I: r=0.872 (Figure 3) and in group II r=0.755 (Figure 4), p<0.05.

Discussion

The principle goal in rehabilitation of patients after myocardial infarctions is to restore the organ's optimal efficiency, in this case of heart lesioned by acute

Table II. Ejection fraction (EF) in studied groups (A – before, B – after rehabilitation)

Group		Min	Max	Me	Mean	SD	Significant differences before – after
Group I	A	42	63	54	**53.65**	±5.30	**p<0.05**
	B	45	65	57	**56.65**	±5.56	
Group II	A	30	47	40	**38.40**	±12.35	p>0.05
	B	30	50	42	**39.85**	±12.20	

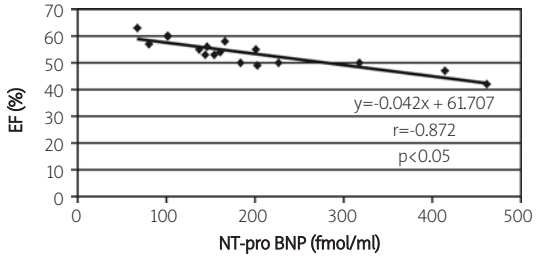

Figure 3. Correlation between NT-proBNP concentration and EF in group I after rehabilitation

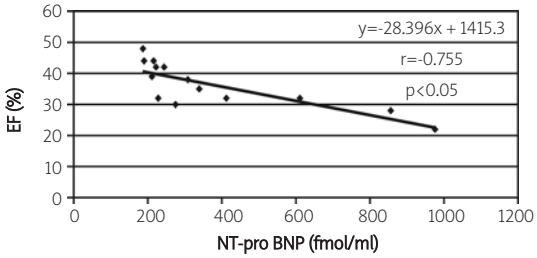

Figure 4. Correlation between NT-proBNP concentration and EF in group II after observation period (without rehabilitation)

ischaemia, or to develop its compensatory function. This aim can be achieved by selecting exercises and load adequate for the age and the organism efficiency, indispensable for activation of the organ to restore its primary efficiency [12]. Systolic dysfunction is a clinical equivalent of myocardial ischaemia because to maintain normal contractility the heart must continuously restore energetic reserves. Prolonged ischaemia causes gradual endogenic glycogen utilization [13]. Excessive supply of free fatty acids (FFA) and mininal oxygen metabolism cause increased oxidation of fatty acids [14]. In ischaemic myocardium, energetically little effective and consuming about 10% of oxygen, the process of FFA oxidation remains the main source of energy. Reversal of energetic substrates metabolism for the benefit of FFA results in quicker exhaustion of already poor oxygen reserves and rapid decrease of ATP production which is not sufficient for preservation of normal function of cardiomyocyte [15]. In clinical practice metabolic disorders lead to left ventricular systolic dysfunction with hypokinesis or akinesis of ischaemic segments [16]. Lack of radical improvement in oxygen supply to the myocardium leads to its irreversible damage. On the other hand, restoration of coronary perfusion is not equivalent to the normalization of metabolism. Increased oxygen availability activates an enzymatic complex related to carnitine responsible for FFA transport to mitochondria and thus limiting the rate of glucose oxidation [17]. The role of oxygen free radicals should not be neglected either. They are produced excessively in the period of reperfusion. Free radicals effectively change the properties of the sarcolemma by lipid peroxidation in the cell membrane, making it more permeable to calcium ions [18]. Excess of ionized calcium activates proteolytic enzymes responsible for the formation of microlesions in the area of contractile elements. They are reversible, although their restitution is slow. Paradoxically, after coronary flow restoration the normal function of previously ischaemic left ventricular segments is not necessarily restored because altered contractility is associated with transient myofilament dysfunction [19].

The aim of angioplasty is to recanalize an oblitarated coronary artery responsible for myocardial infarction. The blood flow is radically restored in the main coronary vessels, but usually with perfusion disturbances in small coronary arteries [20]. In the ischaemic heart, a poorly developed system of arterial anastomoses is also observed, particularly in subjects with a short history of the disease. Together with persisting impairment of metabolism in the area of myocardial infarction, the described factors to a great extent are responsible for left ventricular systolic dysfunction after infarction. BNP is a biochemical marker of systolic dysfunction. In the group of patients with acute coronary syndromes both BNP and NT-proBNP submit independent and additional diagnostic information and have high predictive value in this group of patients [21]. The authors of the Val-Heft trial recommend the use of both neurohormonal markers in clinical practice for monitoring the effectiveness of the treatment and mortality prognostication in the group of patients with heart failure [22]. In our own studies a significant decrease in NT-proBNP concentration was observed after rehabilitation in patients treated with PTCA. In the control group, the patients were not subjected to rehabilitation and a significant decrease in plasma NT-proBNP concentration was not observed. Also in the group of patients subjected to rehabilitation a significant increase in EF was observed, while in the control group after the period of observation EF practically did not change.

Ginuzzi et al. investigated changes of NT-proBNP concentration in the group of patients after transmural myocardial infarction, who were included in the training programme. The interests of the authors focused on the effect of physical training on left ventricle dimension and its systolic function – postinfarction contractility disorders. Significant increase in end-diastolic volume and EF was observed as compared to the control group [23]. Condraads et al. observed a significant decrease in plasma NT-proBNP concentration in patients with postinfarction heart failure after rehabilitation with increasing training load at the end of the programme. A significant decrease in left ventricular end-systolic dimension was also observed [24]. The results of other studies also confirm beneficial effect of exercise training in patients after

myocardial infarction. Numerous authors indicate that programmed physical exercise in this group of patients markedly increases left ventricular function after infarction, which is reflected by proportional increase in EF [25]. Improvement of myocardial contractility results from better metabolism of cardiomyocytes through restoration of balance in the range of FFA oxidation and simultaneous increase in the share of oxygen metabolism in ATP synthesis. Normal phosphorylation of high-energy residues increases energy reserves indispensable for activation of repair processes in damaged myofilaments and thus contributes to quicker restoration of normal systolic function of the damaged segment of the left ventricle. Opening of the artery responsible for myocardial infarction in the course of PTCA significantly improves perfusion of the ischaemic area. However, medium and small coronary vessels should be mentioned. They are responsible for blood supply to distant segments of the myocardium. The role of collaterals in the heart is emphasized particularly in relation to hypertrophic myocardium [26]. Furthermore, their importance also in non-hypertrophic myocardium exposed to extreme ischaemia during infarction before restoration of artery patency should not be underestimated. Physical exercise and regular controlled acceleration of heart rate in the course of rehabilitation of patients increases the secretion of vascular growth factors, intensifying at the same time angiogenesis. This process distributed in time contributes additionally to heart perfusion improvement after myocardial infarction [27].

The increase in EF in correlation with the decrease in NT-proBNP concentration observed in our study seems to confirm the regression of myocardial degeneration after infarction. The significant increase in exercise efficiency in group I after rehabilitation is clinical evidence of the improvement of left ventricular systolic function associated with rehabilitation. Such a dependency was not observed in group II.

Conclusions

The results of the study allow us to state that exercise training applied in patients after myocardial infarction within the range of cardiologic rehabilitation contributes to the improvement of left ventricular systolic function, which is reflected by increased EF with accompanying decrease in plasma NT-proBNP concentration.

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