fizjoterapia polska
nr 3/2016 (16)

Wpływ kontrolowanego treningu fizycznego na poziom NT-pro BNP i frakcje wyrzutową lewej komory serca u chorych po ostrym incydencie wieńcowym

Impact of controlled physical exercise on NT-proBNP level and ejection fraction in patients with acute coronary disease – original paper

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Streszczenie

Wstęp.Cel. Ocena efektów kontrolowanego treningu fizycznego na poziom NT-proBNP i frakcję wyrzutową lewej komory serca w zależności od czasu i rodzaju treningu fizycznego.
Materiał i metody. Do badań włączono 83 chorych. Dwie grupy uczestniczyły w dwu- i czterotygodniowych treningach interwałowych na cykloergometrach rowerowych oraz w ćwiczeniach ogólnousprawniających. Grupa kontrolna poddana była jedynie treningowi ogólnousprawniającemu. We wszystkich grupach wykonano test immunoenzymatyczny celem oceny poziomu NT-proBNP oraz badanie echokardiograficzne celem oceny frakcji wyrzutowej.
Wyniki. Zaobserwowano zmiany poziomu NT-proBNP oraz parametrów echokardiograficznych. W grupie 1, po dwóch tygodniach treningu, wartości NT-proBNP zmniejszyły się o 13.2%. W tej samej grupie, wartość EF istotnie wzrosła z 51,23% do 51,95%. W grupie 2, po czterech tygodniach usprawniania, stwierdzono spadek poziomu NT-proBNP o 29%. Wartość EF istotnie wzrosła, z 50,62% do 51,69%. Końcowe wartości NT-proBNP w grupie kontrolnej w porównaniu z wartościami początkowymi zmniejszyły się o 3,9%. Zaobserwowano również nieistotny wzrost EF z 47,06% do 47,13%.
Wnioski. Wyniki badań wskazują, że kontrolowany trening fizyczny w ramach rehabilitacji kardiologicznej zmniejsza poziom NT-proBNP, a także poprawia frakcję wyrzutową lewej komory serca u chorych po ostrym incydencie wieńcowym.

Słowa kluczowe:

rehabilitacja kardiologiczna, peptydy natriuretyczne, frakcja wyrzutowa, ostre zespoły wieńcowe

Abstract

Purpose. Assess the effect of a controlled physical training on the level of NT-pro BNP and left ventricular ejection fraction depending on the time and type of physical exercise.
Methods. Eighty-three patients were included in the study. Two groups participated in interval training on a cycle ergometer and exercise improving general physical. Control Group participated in exercise improving general physical only. The immunoenzymatic test for qualitative determination of the NT – proBNP level and echocardiographic examination was performed in all groups.
Results. The authors observed changes in NT-proBNP level testing and echocardiographic examination. In the group I, after a 2-week training, the NT-proBNP value decreased by 13.2%. In the same group, mean EF values were significantly increased, from 51.23% to 51.95%. In the group II a 29% reduction of the NT-pro BNP level was observed. EF values were significantly increased, from 50.62% to 51.69%. As for final NT-proBNP values in the control group, a decrease of the peptide level by 3.9% was observed, compared to initial values. In the same group, a non-significant increase of the EF value was observed, from 47.06% to 47.13%
Conclusions. Findings of the studies confirm that cardiac rehabilitation decrease of the NT-proBNP level and improves LVEF in patients with acute coronary disease.

Key words:

cardiac rehabilitation, natriuretic peptide, ejection fraction, acute coronary disease

Abbreviations
ANP – atrial natriuretic peptyd BNP – B – type natriuretic peptide
CAD – coronary artery disease
EF – ejection fraction
HF – heart failure
LVEF - left ventricular ejection fraction
MET – metabolic equivalent
NT proBNP – N – terminal pro – brain natriuretic peptide

Introduction

The assessment of levels of natriuretic peptides and left ventricular function seems to be important in patients qualified for cardiology rehabilitation. That is associated with possible unfavourable reactions that may be caused by an improper physical exercise in that group of patients. Uncontrolled, intensive physical exercise increases pressure in cardiac cavities, which leads to stimulation of natriuretic peptides secretion, and may influence an improper reconstruction of the myocardium, including the left ventricle, and affecting its contractility. Moreover, it increases tension of the sympathetic nervous system, leading to increased plasma levels of peptides and noradrenalin [1, 2]. Coronary artery disease (CAD) causes injury to the myocardium and failure of its function as a pump, leading in consequence to development of heart failure (HF) symptoms. Various vasoconstrictive and diuretic substances are produced as a part of compensatory measures, in order to maintain a correct stroke volume and peripheral perfusion. The most potent ones are catecholamines, vasopressin, as well as renin, angiotensin and aldosterone. On the other hand, natriuretic peptides are synthesized and secreted by cardiomyocytes in response to pressure or volume overload of cardiac cavities [3, 4].

Natriuretic peptides are neurohormones belonging to the group of polypeptides. There are the following natriuretic peptides: atrial natriuretic peptyd – ANP, B – type natriuretic peptide – BNP, and N – terminal pro – brain natriuretic peptide – NT-proBNP. BNP and NT-proBNP are used for diagnostic purposes. Stability of BNP at room temperature is approx. 4 hours, compared to stability of NT-proBNP of 7 days. That long stability is one of the reasons for which the natriuretic peptide is routinely assayed [5]. Increased BNP/NT-proBNP is a predictor of unfavourable course of the disease, the need for hospitalisation and cardiac death [6, 7].

One of the most important, and yet unresolved questions is, if a regular physical exercise used as a part of cardiology rehabilitation, may by an effective mean of prevention or reversal of morphological and associated functional changes of the left ventricle. Whereas there is evidence that a proper training leads to improved tolerance of stress, quality of life, and favourable changes in neurohormonal profile and in skeletal muscles, its effect on the myocardium and central haemodynamic mechanisms has not been sufficiently clarified [8, 9, 10].

The purpose of the study was to assess the effect of a controlled physical training as a part of a complex cardiology rehabilitation, on the level of NT-proBNP and left ventricular ejection fraction (LVEF) in patients with a history of acute coronary event, depending on time and type of the training.

Material and Methods

Eighty-three patients, aged 48–79 (61±7.3) were included in the study. Of that number there were 51 men and 32 women who suffered from acute coronary disease. All the patients were referred to be cardiac rehabilitated in not later than one month following the occurrence of acute coronary disease.

The patients were qualified to the training program on the basis of results of exercise test performed on Cardiovit – CS 200 mobile treadmill, in the Bruce protocol. The reason for inclusion in the test was the achieved load ≥ 5 MET. Such a result allowing the patients to qualify at least for model B of the second stage of cardiac rehabilitation. The ground for exclusion from the test was the occurrence of at least one of the following factors for risk stratification of cardiac rehabilitation: ejection fraction (EF) <40%, horizontal depression of the ST segment on exertion, complex ventricular arrhythmia at rest and on exertion, physical efficiency <5 MET, pathological reaction to physical strain – decrease or no systolic arterial pressure or heart rate which should accompany greater workload. All the patients included in the study underwent pharmacological treatment in compliance with the guidelines of the Polish Cardiac Society. It remained the same within the last three weeks.

Training session

After initial examinations the patients were randomly divided into three study groups. Group I (n=27) participated in a two-week and Group II (n=27) in a four-week cardiac rehabilitation which consisted of sessions of controlled interval training on Ergoline cycle ergometers. The training sessions were held five times a week before noon. Each training session lasted 32 minutes and was conducted according to a formerly arranged schedule. It started with a warm-up with about a ten-Watt load. It was followed by 5 four-minute episodes during which the load was gradually increasing. The load in the particular intervals was growing as long as to the middle of the session. Next, it decreased to the initial level; there were two-minute periods of rest with a ten-Watt load. The peak load of initial training sessions and maximum heart rate on exertion was equal to 50% of the load obtained during the electrographic exercise test. During the exercise test the patients' blood pressure was monitored and they underwent electrocardiogram examination. Apart from interval exercises, the authors also introduced breathing exercise, resistance training exercise for small muscle groups of the upper and lower limbs and relaxation exercise. The exercise was initiated after the interval exercise and it lasted 20 minutes. During the exercise the exertion did not exceed category 11-13 on the 6-20 Borg scale. Before and after the exercise session the patients' heart rate and arterial blood pressure were monitored. Group III (n = 29) consisted of patients who were not admitted to the program, interval training, because of the presence of one of the characteristics of the risk stratification of patients undergoing cardiac rehabilitation. In the control group was performed breathing exercises, active exercises free individual peripheral joints and muscle groups, and relaxation exercises. Exercise time was 30 minutes and 9-10 points are not exceeded according to the Borg scale. The average stay in the group was 19 ± 32 days.

NT – pro BNP level testing

The immunoenzymatic test for qualitative determination of the NT-proBNP level was performed in study groups. The

equipment Cobas h 232, qualitative tests Cardiac NT-proBNP for determination of NT-proBNP in whole blood, pipettes and heparinized test tubes from Roche were used. For the determination, 150 µL of blood was collected from the basilic vein into a heparinized test tube. From the test tube blood was transferred to the test. After several minutes test results were read from the apparatus' display. Blood was collected from patients after 15 minutes of rest. The study in all group was performed twice: before and after completion of cardiology rehabilitation.

Echocardiographic examination

The investigation was performed using the transthoracic method. The investigation was performed by a single experienced specialist, using the Acuson CV 70 equipment and the electronic ultrasound processor with operating frequency of 3,5 MHz. Left ventricular systolic function was evaluated according to valid recommendations of the American Society of Echocardiography. The investigation was performed in parasternal and apical projections, 4- and 5-locular, with assessment of the ejection fraction using the Simpson method. The mean EF value of three subsequent cardiac cycles was recorded. The echocardiographic investigation was performed twice: before and after a cycle of trainings.

The statistical analysis

Data were analysed with the statistical suite PQStat ver. 1.4.2.324.

On the first stage of data processing, descriptive statistics, characterising study group of patients were developed. For interval variables, mean values were calculated with 25-75% confidence intervals and standard deviations, as well as medians and limits of upper and lower quartiles. Age results for study groups were compared using the Kruskal-Wallis test and the Dunn's post-hoc test. Results of analysed parameters in study groups were compared using the Wilcoxon test. Differences were declared statistically significant if the level of the test probability was lower than the accepted significance level of $p<0.05$. The test probability at the level of $p<0.01$ was accepted as highly significant.

The study was approved by the Ethical review Board of the Medical University of Lodz (No. RNN/226/11/KB)

Results

Baseline clinical data of the studied patients are presented in table 1. In addition to the age of patients, there was no statistically significant difference between the groups in terms of baseline clinical variables and treatment.

The analysis of assessed parameters in study groups

No statistical differences between study groups were found for initial and final NT-proBNP values ($p=0.5209$ vs $p=0.4407$), contrary to EF values that proved significant both before the rehabilitation ($p=0.023$) and after it ($p=0.0122$).

Mean NT-pro BNP values became reduced in all groups, compared to initial values. In the group I, after a 2-week training cycle, the NT-proBNP value decreased by 13.2%. In the same group, mean EF values were significantly increased, from 51.23% to 51.95%. (table 2).

Table 1. Baseline clinical data of the studied patients

	Baseline clinical data of the studied patients			
	Group I n=27	Group II n=27	Group III n=29	p
Sex male: female	18:9	20:7	20:9	
Age (years)	60.18±8.52	61.65±8.24	74.38±4.50	<0.0001
BMI (kg/m2)	25.75±5.42	27.62±4.22	27.62±4.22	NS
Duration of illness (years)	14.24±4.8	15.35±2.1	13.62±2.9	NS
Number of patients treated with CABG	18	20	19	NS
Number of patients treated with PCI	9	7	10	NS
Smoking duration (years)	31.34±6.4	32±4.2	31.24±6.1	NS
Number of smokers in the group	24	26	23	NS
Medications:				
Beta - blockers	27	27	29	NS
Statins	27	27	29	NS
ACE inhibitors	27	27	29	NS
Aspirin	27	27	29	NS

Values are expressed as mean ± SD

NS = non significant

Table 2. Results of NT-proBNP and EF before and after rehabilitation in group I

	Period	Descriptive statistics							Wilcoxon Test
		Mean	SD	Minimum	Lower quartile	Median	Upper quartile	Maximum	
NT-proBNP [pq/ml]	before	777.50	699.43	40.00	387.00	569.50	956.00	3000.0	0.0045
	after	674.64	648.43	40.00	250.00	556.50	880.00	2890.0	
EF [%]	before	51.23	7.54	27.00	47.00	53.50	55.00	60.00	0.0033
	after	51.95	7.05	30.00	47.00	55.00	56.00	60.00	

In the group II a 29% reduction of the NT-pro BNP level was observed after conclusion of the cardiology rehabilitation. EF values were significantly increased, from 50.62% to 51.69% (Table 3).

Table 3. Results of NT-proBNP and EF before and after rehabilitation in group II

	Period	Descriptive statistics							Wilcoxon Test
		Mean	SD	Minimum	Lower quartile	Median	Upper quartile	Maximum	
NT-proBNP [pq/ml]	before	613.08	617.40	21.00	165.00	451.50	730.00	2405.0	0.0015
	after	434.88	390.69	21.00	193.00	361.00	556.00	1793.0	
EF [%]	before	50.62	5.45	41.00	47.00	50.50	54.00	60.00	0.0006
	after	51.69	5.32	42.00	48.00	51.50	56.00	60.00	

As for final NT-proBNP values in the control group, a decrease of the peptide level by 3.9% was observed, compared to initial values. In the same group, a non-significant increase of the EF value was observed, from 47.06% to 47.13% after the rehabilitation (Table 4).

Table 4. Results of NT-proBNP and EF before and after rehabilitation in control group

	Period	Descriptive statistics							Wilcoxon Test
		Mean	SD	Minimum	Lower quartile	Median	Upper quartile	Maximum	
NT-proBNP [pq/ml]	before	1325.1	1792.6	42.00	56.00	333.50	1720.0	4762.0	0.0019
	after	1273.9	1784.7	20.00	56.00	247.00	1690.0	4652.0	
EF [%]	before	47.06	6.89	40.00	41.50	45.50	51.00	66.00	1.0000
	after	47.13	6.96	40.00	41.50	45.50	51.00	66.00	

Discussion

The effect of physical training on the NT-proBNP and EF level is not clearly defined. Natriuretic peptides are biochemical markers used in cardiologic diagnostics. They are a group of polypeptides exerting a diuretic, natriuretic and vasodilating effect. One of them is the N- terminal pro-brain natriuretic peptide (NT-proBNP). Its applicability in the diagnostics of heart failure, differentiation of cardiologic and other causes of acute angina, as well in prognosis of acute coronary syndromes is widely documented [11]. Determination of the marker is also increasingly often used in patient undergoing cardiology rehabilitation.

Numerous studies indicate a favourable effect of the controlled physical training on stabilisation of the plasma NT-proBNP level [12]. Giallauria et al. noted a significant decrease of NT-proBNP after conclusion of rehabilitation in 22 patients with recent history of myocardial infarction. The peptide level reduction from 1498±438 to 470±375 pg/ml ($p=0.0026$) was observed, after 3 months of training. In the control group with no physical exercise over the same period of time, no changes of study parameters were observed [13].

In our study, in three study groups, the initial NT-proBNP values were: 777.5 pg/ml in the Group I, 613.08 pg/ml in the Group II, and 1325.1 pg/ml in the Group III. Non-significant differences of results between study groups were found ($p=0.5209$). After conclusion of the rehabilitation cycle, a highly significant reduction of the NT-proBNP level was found in all groups. However, the greatest changes were observed in the Group II, with a 29% ($p=0.0015$) reduction of the peptide level after 4 weeks. A similar observations were reported by Berent et al. [14]. After a rehabilitation period lasting on average 25±4 days and involving interval training and walks, the authors observed a highly significant, 29% reduction of NT-proBNP level ($p=0.001$) in a group of 359 patients. Those results are also confirmed by Conraads et al., who observed a significant reduction of the NT-proBNP level, from 2124±397 pg/ml to 1635±304 pg/ml ($p=0.046$) in HF patients, compared to a non-training group, demonstrating no changes of the marker level [15]. The decrease of the concentration of NT-proBNP under the influence of a controlled physical exercise may be related to its effects on increase stroke volume and cardiac output as a result of improvement of left ventricular systolic function of the heart [16]. However, the effect of physical exercise on reduction of the NT-proBNP level is not that unequivocal. A different opinion is expressed by Nillson et al. who found no significant differences of results between two groups of patients (total number of patients - 78): a study group using interval trainings ($n=39$), and a control group ($n=39$), after 12 months of follow-up [17]. Also Arad et al. observed no significant changes in NT-proBNP values in 28 patients after 18 weeks of training [18]. On the other hand, Montiel-Trujillo et al. indicated an initial increase of the NT-proBNP level caused by physical training, and a final absence of reduction of the peptide level compared to initial values ($p=0.71$) [19]. However, some other studies, including our own, support the opinion that a controlled physical training realised as a part of a complex cardiology rehabilitation, has

a significant effect on reduction of the NT-proBNP level in patients [20].

The association between the left ventricular function and a physical training is a complex one. It depends on age, general fitness, comorbidities, and even a patient's mental condition [21].

In their study Erbs et al. demonstrated a significant ($p<0.001$) increase of EF, up to 33.5±5.7%, in patients with chronic heart failure and mean EF of 24.1±5.1% training for 12 weeks, compared to the control group [9]. A similar result was reported by Arad M et al. analysing 28 patients subject to a 18-week rehabilitation. Their EF increased significantly by 11% [18]. It is suggested that the mechanism of improvement is associated with stimulation of synthesis of vascular endothelial growth factor. The process leads to formation of new, thin vessels that undergo a partial organisation into bigger collaterals, and partially support the mycocardial microcirculation. Another mechanism may be associated with expression of the nitrogen oxide synthase gene, caused by a regular physical training [22]. However, there are reports of a neutral effect of physical training on the left ventricular function and morphology. Bacior et al. found no effect of a controlled training on LVEF, with a significant improvement of exercise capacity and parameters of the sinus rhythm [8]. Despite that fact that those observations are consistent with studies performed by other authors, they are important in the perspective that there had been opinions regarding a negative effect of a controlled physical exercise on injured LV expressed some time ago [11,23]. In our study, an improved LVEF was observed in the analysed groups. The highest increase, at the level of 2.1 %, was noted in the group II, and the increase observed in groups I and III was 1.4% and 1%, respectively. In groups I ($p=0.0033$) and II ($p=0.006$) the results were statistically significant. It should be noted that mean EF values in patients were 51.23% in the Group I, 50.62% in the Group II, and 47.06% in the Group III. Therefore, no signs of a clear left ventricular dysfunction were observed. Also Jiang et al. demonstrated improved left ventricular function, expressed as increased EF. In 35 with a recent history of myocardial infarction, with a mean EF of 55±8.6%, subject to a 3-month training, the EF value increased up to 60±8% ($p<0.05$). Results obtained for the control group ($n=29$) were not significant ($p>0.05$), and EF results differences between both groups proved significant ($p<0.05$) [24].

Conclusions

1. A significant increase of left ventricular ejection fraction was observed in groups of patients subject to 2- and 4-week cardiology rehabilitation.
2. A significant decrease of the NT-proBNP level was observed, irrespectively of time and type of a physical training in the study groups.
3. The results indicate that a training program based on intervals seems to have an important value in the complex cardiology rehabilitation, increasing its efficacy.

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