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THE INFLUENCE OF METOPROLOL ON EXERCISE TRAINING EFFECTS IN PATIENTS WITH ISCHEMIC LEFT VENTRICULAR DYSFUNCTION

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Summary. *The aim of this study was to estimate the influence of chronic metoprolol treatment, which has been added to conventional heart failure, in patients with post infarction left ventricular dysfunction, on the effects of a one year physical training. Eighty-nine patients, who recently suffered myocardial infarction and also had left ventricular dysfunction with ejection fraction of 40% or less, were examined.The first part of the physical training program was carried out as residential rehabilitation in the course of three weeks. At the end of the residential phase of rehabilitation the functional capacity was increased in metoprolol group from 4.9±1.6 METs to 5.8±1.9 METs ($p<0.025$), and in the non beta blocker group from 4.8±1.8 METs to 5.4±1.8 METs (NS). After residential rehabilitation patients continued with unsupervised physical activity for a one year period. At the end of the one year physical training program the functional capacity increased in metoprolol group from 4.9±1.6 to 6.3±1.7 METs ($p<0.001$), and in the non beta blocker group from 4.8±1.8 to 5.7±1.9 METs ($p<0.01$). Both groups of patients have improved functional capacity due to physical training. Patients with metoprolol have shown greater functional capacity improvement (28.7%) than patients without the beta blocker (18.8 %, $p<0.05$), with statistical significance which appeared from the third month, and remained until the end of the one year training period. There were no complications during the training and no evidence of heart failure deterioration. Incidence of the nonfatal myocardial infarction was lower in metoprolol group, but without statistical significance (6.3% vs10.6 %). Also, annual mortality was lower in metoprolol group, 4.3% vs 7.1%, but again without statistical significance.*

Key words: *Heart failure, beta adrenergic blocker, physical training*

Introduction

In patients with heart failure neurohumoral activation is excessive and above compensatory need, and it has deleterious chronic effects on myocardial function, exercise tolerance, symptomatic status, morbidity and mortality. Medicaments that antagonize neurohumoral hyperactivity like ACE inhibitors and blockers of the beta adrenergic receptors have showed beneficial effects on morbidity and mortality. In patients with coronary artery disease beta blockers have a widespread clinical usage. Physical training is another procedure that suppresses sympathetic hyperactivity and is also commonly prescribed in patients with ischemic heart disease. There are questions about possibility to achieve training effect in patients who are treated with beta blockers, because sympathetic stimulation with adequate cardiovascular response is necessary for the exercise tolerance and attainment of the training effect.

The aim of this study was to estimate the influence of chronic metoprolol treatment, which has been added to conventional heart failure, in patients with post infarction left ventricular dysfunction, on the effects of a one year physical training on exercise capacity, left ventricular size and function, symptomatic status, morbidity and mortality

Subjects

Eighty-nine patients, who had recently suufered myocardial infarction (8 weeks to 5 months before) and also had left ventricular dysfunction with ejection fraction of 40% or less, were examined. Patients were divided in two groups (Table 1), in metoprolol group, patients were receiving selective beta blocker metoprolol for more than two weeks before entrying the study, and in non beta blocker group patients were not receiving beta blocker treatment. There were 38 males and 9 females (mean age 54.3±8.7 years) in metoprolol

group and 34 males and 8 females (mean age 55.2±8.1 years) in non beta blocker group. The study was non-randomized and patients had received beta blocker at the physician's discretion. Metoprolol was added to conventional treatment for heart failure and dose was not predetermined as a target dose, but was titrated on the basis of heart rate and blood pressure (average daily dose 50.3±28.2 mg), and was divided in two daily doses. Patients with manifested cardiac decompensation were excluded form the examination. Also, patients suffering from angina pectoris, non controlled arterial hypertension, and uncontrolable cardiac rhythm disorders were excluded from the study.

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Table 1. Patients baseline data, before physical training

	Metoprolol	Non beta blocker
Number of patients	47	42
Age years	54.3±8.7	55.2±8.1
Sex males	38 (81%)	34 (82%)
M.I. anterior	29 (62%)	25 (59%)
M.I. inferopost.	18 (38%)	17 (41%)
Time from acute M.I. month	3.5±1.4	3.4±1.6
Previous M.I.	13 (28%)	10 (24%)
AC bypass	11 (23%)	10 (24%)
NYHA II	34	29
NYHA III	13	13
LVEDd (mm)	59.5± 4.5	59.1±5.1
LVESd (mm)	37.4±3.8	38.2±3.9
EF (%)	32.4±3.4	31.7±4.0
ACE inhibitors	37 (78%)	35 (83%)
Diuretic	21 (45%)	20 (48%)
Digoxin	11 (23%)	10 (24%)
Long acting nitrate	31 (66%)	28 (67 %)

MI Myocardial infarction, LVEDd–Left ventricle end diastolic diameter, LVESd–left ventricle end systolic diameter, EF–ejection fraction

Methods

The left ventricular ejection fraction was measured by two-dimensional echocardiography using area length method. Patients were classified in NYHA classes according to symptomatic status and they had a moderate heart failure and NYHA II and III values. Exercise tests were symptom limited and were carried out on treadmill. Exercise test for functional capacity measurement has been performed in metoprolol group two days after stopping the beta blocker treatment. Body oxygen consumption was calculated in accordance to exercise tolerance on treadmill. Three days before exercise test for functional capacity measurement, patients had performed exercise test while had receiving complete medication, and in metoprolol group patients had carried out this test under the influence of the beta blocker. Results of this exercise test were used for physical training proscription.

The first part of the physical training program was carried out at the Institute for Prevention, Treatment and Rehabilitation of Rheumatic and Cardiovascular Diseases Niska Banja, as residential rehabilitation, and lasted three weeks, with six exercise sessions per week and duration of one our per session. Physical training consisted of calisthenics, cycling and outdoors walking. Walking paths were stratified in four levels according to the exercise intensity. Patients performed moderate degree of physical effort during exercise training up to 50% of the maximal effort level tolerated at initial exercise test. In this phase of exercise training, all physical activities were supervised. After residential rehabilitation patients continued with unsupervised physical activity for one year period. Physical training consisted of walking, 45 minutes three times a week. Exercise intensity during training was assessed by heart rate monitoring and effort level during training was up to 50% of the exercise intensity, tolerated during exercise test at the end of residential rehabilitation.

Results

The study groups did not differ in respect to patients' age, sexes, infarction localization, previous myocardial infarction and myocardial revascularisation (Table 1). There was no difference between groups with reference to the time elapsed from the acute phase of the myocardial infarction to the beginning of the study. There wasn't any difference between groups in symptomatic status, represented by NYHA category value. There wasn't any difference in echocardiographic parameters of the left ventricular size: diameters and volumes in diastole and systole, between groups on initial examination, before starting the exercise training (Table 1). No difference was found of the left ventricular ejection fraction between groups on initial examination: 32.4±3.4 % in metoprolol group and 31.7±4.0 % in non beta blocker group. Metoprolol was added to conventional heart failure treatment and there was no difference between groups in taking of usual heart failure and antianginal medicaments.

At the initial exercise stress testing, before physical training, there wasn't any significant difference between groups in exercise time and workload (Table 2). Functional capacity was 4.9±1.6 METs in metoprolol group and without significant difference from functional capacity in non beta blocker group 4.8±1.8 METs. Physical training was prescribed on the basis of initial exercise tolerance, and first part of rehabilitation was performed as a residential rehabilitation. There was no difference in exercise intensity during residential training program, duration of training and exercise session numbers and in exercise time-intensity index between groups. At the end of the residential phase of the rehabilitation the functional capacity was assessed again by exercise stress testing, with the same test protocol as initial exercise examination.

Patients in both groups have shown statistically significant improvement in functional capacity (Table

3). Exercise time in test was increased in metoprolol group from 6.96±1.92 min to 8.24±2.02 min ($p<0.01$) and was also increased in non beta blocker group from 6.84±1.88 min to 7.70±1.93 min ($p<0.05$). At the end of the residential phase of the rehabilitation, functional capacity was increased in metoprolol group from 4.9±1.6 METs to 5.8±1.9 METs ($p<0.025$) and was also increased in non beta blocker group, but non significantly from 4.8±1.8 METs to 5.4±1.8 METs (NS). In patients symptomatic status was improved: in metoprolol group from NYHA 2.27±0.51 to 2.01±0.59 ($p<0.05$) and in the non beta blocker group from NYHA 2.31±0.47 to 2.10±0.52 (NS).

Table 2. Initial exercise test

	Metoprolol (two days after stopping beta blocker)	Non beta blocker
Exercise time (min)	6.96±2.11	6.84±2.02
Treadmill work METs	4.9±1.6	4.8±1.8
Estimated VO2max (ml/kg/min)	17.2±5.6	16.8.8±6.3
Residential phase physical training data		
Training duration (wk)	3.1±0.8	3.0±0.8
Number of sessions	18.0±2.5	18.2±2.7
Exercise time – intensity index (min * %)	270±32	273±36
1 year training period		
Training duration (month)	11.0±2.9	11.3±2.4
Compliance (%)	74±11	72±13

Functional capacity was measured in metoprolol group two days after cutting off beta blocker treatment. Resting heart rate and systolic blood pressure were reduced in both groups at the end of residential training program (Table 4), but without statistical significance. Maximal exercise test values of the heart rate and systolic blood pressure were increased at the end of the program, but also without statistical significance. At the end of the residential phase of rehabilitation at the same sub maximal exercise level, the heart rate and systolic blood pressure were statistically significantly reduced in both groups, when compared with pre training values (Table 4). Patients performed the same effort level with lower values of myocardial oxygen consumption determinants at the end of the training program.

Three days before the exercise test for functional capacity measurement, patients performed an exercise test while receiving complete medication, and in metoprolol group patients had carried out this test under the influence of the beta blocker. Training effect, with lower sub maximal values of the heart rate and systolic blood pressure, at the end of the physical training program, was also demonstrated in exercise test with metoprolol, but on the lower levels of heart rate and blood pressure values, than in test two days after stopping beta blocker. (Table 4).

The second, unsupervised, home-based phase of rehabilitation lasted for one year period, and has consisted of outdoors walking 45 minutes per session, three times per week. Exercise intensity during training was assessed by heart rate monitoring and exercise intensity was up to 50 % of the maximal effort level tolerated in test. There was no difference in physical training duration 11.0±2.9 vs 11.3±2.4 months and in compliance with exercise sessions 74±11 % vs 72±13 % between groups.

Table 3. Residential phase physical training effects

	Metoprolol (two days after stopping beta blocker)		Non beta blocker	
Exercise capacity	Before	After	Before	After
Exercise time (min)	6.92±1.92	8.24±2.02 *	6.84±1.88	7.70±1.93 ❖
Treadmill work METs	4.9±1.6	5.8±1.9 ⋆	4.8±1.8	5.4± 1.8
Estimated VO_2max (ml/kg/min)	17.2±5.6	20.3±5.9 *	16.8±6.3	18.0±6.0 ❖
NYHA	2.27±0.51	2.01±0.59 ❖	2.31±0.47	2.10±0.52

❖ $p<0.05$, ⋆ $p<0.025$, * $p<0.01$

Table 4. Residential phase physical training effects

	Metoprolol (two days after stopping beta blocker)		Non beta blocker		Metoprolol with beta blocker	
Exercise capacity	Before	After	Before	After	Before	After
HR rest	84±11	82±13	86±12	83±14	71±12	70±13
SBP rest (mmHg)	128±18	125±17	129±20	127±18	129±20	123±17
HR submax	136±19	128±18 ❖	139±22	130±21 ❖	121±20	112±20 ❖
SBP submax (mmHg)	158±25	147±26 ❖	160±24	151±23 ❖	154±21	145±21❖
DPR submax	21.5±3.9	18.8±4.1 *	22.2±4.1	21.1±4.7 *	18.6±3.7	15.4±4.7 *
HR max	144±21	146±23	146±23	149±26	140±22	140±26
SBP max (mmHg)	167±27	169±30	169±27	171±25	162±27	165±25
DPRmax	24.1±4.6	24.7±5.2	24.7±5.2	25.5±5.4	22.7±5.2	23.1±5.4
Perceived exertion Borg scale	19.1±0.4	19.0±0.3	19.0±0.4	19.1±0.3	19.3±0.4	19.3±0.3

HR_{REST} -heart rate at rest, SBP_{REST} -systolic blood pressure at rest, HR_{SUBMAX} -heart rate at submaximal exercise, SBP_{SUBMAX} -systolic blood pressure at submaximal exercise, DPR_{SUBMAX} -double product of the heart rate and systolic pressure at submaximal exercise, HR_{MAX} -heart rate at maximal exercise, SBP_{MAX} -systolic blood pressure at maximal exercise level, DPR_{MAX} -double product of the heart rate and systolic blood pressure at maximal exercise, ❖ $p<0.05$, ⋆ $p<0.025$, * $p<0.01$,

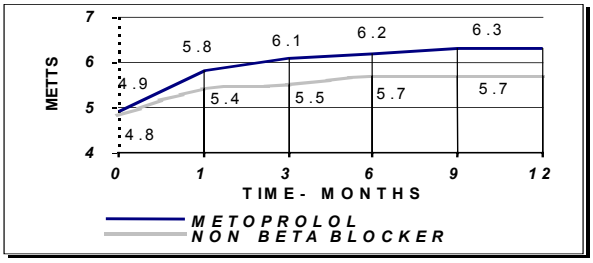

Fig. 1. Functional capacity in metoprolol group and non beta blocker group during one year physical training period.

At three months interval and at the end of one year physical training program patients have performed exercise tests, with the same exercise protocol as initial test. Patients in both groups have shown farther improvement in functional capacity (Fig. 1). At the end of the one year training period in metoprolol group exercise time during test has increased from 6.96±1.92 min to 8.95±2.12 min ($p<0.001$) (Table 5) and the functional capacity increased from 4.9±1.6 to 6.3±1.7 METs ($p<0.001$), and in non beta blocker group exercise time increased from 6.84±1.88 min to 8.11±1.87 min ($p<0.005$) and functional capacity increased from 4.8±1.8 to 5.7± 1.9 METs ($p<0.01$).

Both groups of patients with left ventricular dysfunction after myocardial infarction have improved functional capacity due to physical training. Patients with metoprolol have shown greater functional capacity improvement (28.7%) than patients without beta blocker (18.8 % $p<0.05$), when compared to the initial functional capacity before physical training, with statistical significance which appeared from the third months, and remained until the end of the one year training period. There were no complications during the training and no evidence of heart failure deterioration.

Both groups have also significantly improved symptomatic status at the end of the one year training period (Table 5). In metoprolol group symptomatic status has improved from NYHA 2.27±0.54 to 1.87± 0.52 ($p<0.001$) and in non beta blocker group has increased from NYHA 2.31±0.53 to 1.90±0.51 ($p<0.01$).

At the end of the one year training period echocardiographic examination in metoprolol group didn't show a significant decrease of the diameters of left ventricle in diastole and systole (Table 5). The ejection fraction increased statistically significantly from 32.4±3.4 to 34.6±5.4 % ($p<0.025$) in relation to initial echocardiographic examination, before starting the physical training program. In non beta blocker group diameters in diastole and systole have shown insignificant increase and the ejection fraction showed insignificant increase from 31.7±4.0 to 32.3±4.3 NS.

Incidence of the nonfatal myocardial infarction was lower in metoprolol group, but without statistical significance (6.3% vs 10.6%) (Table 6). Also, annual mortality was lower in metoprolol group, 4.3% vs 7.1%, but again without statistical significance.

Table 6. Effect of 1 year physical training

	Metoprolol	Non beta blocker
Reinfarction non fatal	3 (6.3%)	5 (10.6%)
Mortality 1 year	2 (4.3%)	3 (7.1%)
Sudden cardiac death	2 (4.3%)	3 (7.1%)

Discussion

In heart failure there is a neurohumoral activation which supports circulation. Sympathetic activation induces heart rate increases and arterial and venous vasoconstriction. Heart rate increment compensates reduced stroke volume, while venous constriction increases preload and improves ventricular contraction, and arterial vasoconstriction increases afterload and maintains the blood pressure. Activation of another compensatory component renin angiotensin aldosteron system also increases preload, and afterload..

Activation of sympathetic system and RAAS is unbalanced, excessive, above compensatory needs, and has deleterious chronic effects (1, 2, 3). Negative effects of the sympathetic excessive activation are influenced by α_1 and β_1 stimulation. Force of the myocardial contraction decreases with chronic heart rate increment (tachycardia cardiomyopathy). Calcium ion overload induces myocardial necrosis. Sympathetic system hyperactivity may stimulate abnormal cell growth with myocardial and vascular hypertrophy and remodeling,

Table 5. Effects of 1 year physical training

	Metoprolol (two days after stopping beta blocker)		Non beta blocker	
	Before	After	Before	After
Exercise time (min)	6.96±1.92	8.95±2.12 **	6.84±1.88	8.11±1.87 ❖❖
Treadmill work (METs)	4.9±1.6	6.3±1.7 **	4.8±1.8	5.7±1.9 *
Estimated VO_2 max (ml/kg/min)	17.2±5.6	22.1±5.7 **	16.8±6.3	19.9±6.4 ❖❖
NYHA	2.27±0.54	1.87±0.52 **	2.31±0.53	1.90±0.51 *
LVEDd (mm)	59.5±4.5	58.7±4.8	59.1±5.1	59.4±5.5
LVESd (mm)	37.4±3.8	36.5±3.9	38.2±3.9	38.8±4.1
EF (%)	32.4±3.4	34.6±5.4 ⋆	31.7±4.0	32..3±4.3

LVEDd Left ventricle end diastolic diameter, LVESd left ventricle end systolic diameter, EF ejection fraction,
⋆ $p<0.025$, * $p<0.01$, ❖❖$p<0.005$, **$p<0.001$

and may induce complex cell changes which lead to programmed cell death. Chronic afterload increment has negative effects on left ventricle function. Tachycardia, hypertrophy and exaggerated afterload level increase myocardial oxygen requirements and may induce myocardial ischemia. High sympathetic level provokes cardiac arrhythmias.

Deleterious effects of excessive chronic sympathetic activation in heart failure patients were manifested on myocardial structure, myocardial function, exercise tolerance, symptomatic status, morbidity and mortality. Procedures that suppress neurohumoral hyperactivity have showed beneficial effects. Suppression of the RAAS activation in heart failure by ACE inhibitors has shown improvement of myocardial function and reduction of morbidity and mortality. Although promising results of beta blocker trials in heart failure had appeared in early seventies, impressive results of ACE inhibitors in heart failure patients, have stimulated a great number of trials of the suppression of sympathetic component of the neurohumoral hyperactivity, in heart failure, with beta blockers. A great number of studies of beta blockers, especially with new beta antagonists in heart failure patients, have showed beneficial effects on myocardial function, symptomatic status, quality of life, morbidity and mortality (4, 5, 6, 7, 8, 9, 10, 11, 12). Sympathetic agonists and beta receptors stimulation in heart failure have showed good results only in short term use, and deleterious effects in long term treatment.

It is possible to suppress the excessive sympathetic activation on two levels: on central level and on peripheral, receptors level. Physical training is the procedure that suppresses central component, and beta blockers antagonize sympathetic activity on peripheral, receptors level. More complete sympathetic antagonism includes suppression on both central and peripheral level.

Physical training induces neurohumoral adaptation and decrement of the sympathetic activity level (13,14,15). Heart rate is reduced at rest. Maximal heart rate during exercise is increased and chronotropic reserve and functional capacity are augmented under the influence of physical training. Neurohumoral adaptation induced by physical training and reduced vasoconstrictive stimulus during exercise, increase the blood flow in the active muscles (14). Improvement of endothelial function in trained muscles and increase in capillary density also contribute to increase the blood flow in skeletal muscles during exercise, and functional capacity improvement.

Trained skeletal muscles structural and metabolic adaptation (16, 17) and stabilization of the neurohumoral system represent peripheral adaptive changes that enable improvement of the physical working capacity of heart failure patients for about 20% (2 ml/kg min oxygen consumption) (18, 19, 20). This degree of functional capacity improvement enables ordinary daily activities and independent life even in patients with severe heart failure and markedly reduced functional capacity. Central adaptations with structural and functional changes of the heart as left ventricular dilatation, hypertrophy, ejection fraction and coronary blood flow increment are induced by physical training of high exercise intensity and frequency and long training duration. Central adaptations are necessary for achievement of high level sports results, but are undesirable in cardiac patients, especially in patients with ischemic cardiomyopathy.

Patients with heart failure can improve functional capacity and symptomatic status under the influence of physical training, without deleterious effects on the left ventricular structure and function (21, 22, 23). Physical training in patients with left ventricular dysfunction and ejection fraction of 40% or less, after anterior myocardial infarction, has induced improvement in physical working capacity without negative effects on left ventricle size and volume, without decline of the ejection fraction (21). Physical training in patients with heart failure has increased physical working capacity without negative effects on left ventricular function and without increase of the pulmonary wedge pressure (21). High intensity physical training, two months after acute myocardial infarction in patients with ischemic cardiomyopathy has not shown deleterious effects on left ventricle volumes, ejection fraction and enddiastolic pressure, estimated by nuclear magnetic resonance (21). This examination has also not demonstrated expansive changes on the infracted segment of left ventricle. There are evidences of positive influence of the physical training in patients with heart failure, on the left ventricular diastolic function estimated by Doppler echocardiography and improvement of the left ventricle diastolic filling pattern.

In our study both groups of patients with left ventricular dysfunction after myocardial infarction have improved functional capacity under influence of physical training. Patients with metoprolol have shown a greater degree of functional capacity improvement than patients without beta blocker, in relation to the initial functional capacity, before physical training, with statistical significance which appeared from third month, and remain until the end of the one year training period. Our patients in both groups have significantly improved symptomatic status at the end of the residential phase of rehabilitation with further improvement of symptoms until the end of the one year training period.

Our patients who had received metoprolol have shown, at the end of the one year training period, non significant decrease of the diameters of left ventricle in diastole and systole but significant increase in the ejection fraction in relation to initial echocardiographic examination. Patients without beta blocker have not demonstrated these structural and functional favorable effects but have shown non significant increase in left ventricular diameters and also non significant increase of the ejection fraction.

Deleterious effects of physical training in patients with left ventricular dysfunction, early after myocardial infarction have been manifested on left ventricular structure and function with expansion of the infracted segment (24). Early after extensive myocardial infarction ventricular remodeling process may occurs spontaneously, with progressive deterioration of the left ventricular function (25). It is possible to achieve physical training effects with mild to moderate intensity of exercise (26). Lower exercise intensities, during physical training, that induced mild increase in ventricular wall stress has not been associated with ventricular remodeling (26).

Physical training of the patients with left ventricular dysfunction in our study started three months after myocardial infarction. We have performed moderate degree of physical effort during exercise training up to 50% of the maximal effort level tolerated at initial exercise test, before rehabilitation. We have examined patients in three months intervals during training period by echocardiography and have not found signs of left ventricular function deterioration. There were no complications during training in our examination.

Positive physical training effects in patients with beta blockers treatment with improvement of the exercise tolerance, has been demonstrated at sub maximal exercise levels during exercise stress testing (27, 28, 29, 30). After physical training program was completed, patients have performed the same sub maximal workload during exercise stress test with lower value of the heart rate and systolic blood pressure. Patients who received blockers have also consistently shown increment of maximal tolerated exercise level after rehabilitation.

There are disagreements between studies concerning the effects of physical training on maximal body oxygen consumption in patients with beta blockers, and some studies have not demonstrated increase in maximal body oxygen consumption after physical training program was completed (31). Maximal oxygen consumption during exercise depends on oxygen extraction capability from blood flow in active skeletal muscles and on maximal cardiac output. In patients who receive beta blocker cardiac output during maximal exercise is limited by restricted increment of heart rate and therefore maximal body oxygen consumption during cardio-pulmonary exercise test is not an optimal measure for evaluating the training effects (31, 32, 33). Few days after the termination of beta blocker treatment patients can demonstrate unlimited increase in heart rate during exercise stress testing and the physical training effects on the maximal body oxygen consumption increment can be evident

Coronary patients who received beta blockers have demonstrated better training results with a greater functional capacity improvement after physical training than patients without beta blocker (27, 28, 30, 32). Even more, patients with greater doses of beta blocker have shown better training effects with greater increment of the physical working capacity. In patients with stabile angina pectoris, beta blocker increases effort level when myocardial ischemia appears and by increasing ischemia threshold beta blocker enables greater exercise intensity during training with better training effects. In patients with heart failure and neurohumoral excessive activation there is a rapid and inordinate, non compensatory, increase in heart rate during mild exercise accompanied with breathless and chest discomfort due to excessive tachycardia and palpitation. Dyspnea during mild exercise can be a consequence of inordinate rapid heart rate and can represent palpitation equivalent in absence of significant pulmonary venous hypertension and congestion. Beta blockers restrain excessive heart rate increase during exercise, decrease sense of palpitation, and improve exercise tolerance and can enable greater effort intensity during training.

Metabolic effects of beta blockers in active skeletal muscles were observed as a decrease in ree fatty metabolism during exercise and shifting metabolic pathway toward glucose metabolism. By favoring glucose metabolism pathway which is energetically more efficient, beta blockers decrease oxygen consumption and in this manner may simulate functional capacity impairment. For that reason maximal oxygen consumption during exercise stress test may not be an optimal measure of physical training effects in patients who receive beta blocker (31, 32).

In patients with heart failure and chronic neurohumoral activation which induces down regulation of the β_1 receptors, there is an increase in the relative number of the β_2 receptors. More complete beta receptors blockade with non selective agents which antagonizes both β_1 and β_2 receptors has shown more apparent restricting effects on heart rate during exercise stress test, and more limiting effect on maximal oxygen consumption (10, 12). Incomplete beta receptor blockade, especially blockade using agents which enable up regulation of beta receptors during chronic treatment, has shown less pronounced restricting effects on heart rate and maximal oxygen consumption during exercise (4, 9). Improvement in functional capacity with increase in maximal oxygen consumption has been demonstrated in heart failure patients using metoprolol, selective beta blocker with property of up regulation of the beta receptors during chronic treatment. We have demonstrated physical training effect with increase in functional capacity in patients after myocardial infarction who received metoprolol.

Conclusion

In our study patients with metoprolol have shown greater degree of the functional capacity improvement than patients without the beta blocker, under the influence of physical training. Patients who received metoprolol have shown, at the end of the one year training period, significant increase in the ejection

fraction in relation to initial echocardiographic examination, while patients without the beta blocker have not demonstrated this favorable effect. Patients in both groups have significantly improved symptomatic status under the influence of the physical training.

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UTICAJ METOPROLOLA NA EFEKTE FIZIČKOG TRENINGA BOLESNIKA SA ISHEMIJSKOM DISFUNKCIJOM LEVE KOMORE

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Kratak sadržaj: *Cilj ispitivanja je bio da se proceni uticaj hronične terapije metoprololom, koji je bio dodat konvencionalnoj terapiji srčane insuficijencije bolesnika sa post infarktnom disfunkcijom leve komore, na efekte jednogodišnjeg fizičkog treninga. Ispitano je 89 bolesnika koji su nedavno preležali infarkt miokarda i imali disfunkciju leve komore sa ejekcionom frakcijom 40% ili manjom. Prvi deo fizičkog treninga je sproveden u Institutu Niška Banja u trajanju od tri nedelje. Na završetku ove faze rehabilitacije je funkcionalni kapacitet povećan kod bolesnika sa metoprololom sa 4.9±1.6 METa na 5.8±1.9 METa ($p<0.025$), a kod bolesnika koji nisu uzimali beta blokator je povećan sa 4.8±1.8 METa na 5.4±1.8 METa (NS). Posle završetka institucionalizovane rehabilitacije bolesnici su nastavili sa fizičkom aktivnošću u trajanju od godinu dana. Na kraju jednogodišnjeg programa fizi~čog treninga je funkcionalni kapacitet povećan u grupi bolesnika sa metoprololom sa 4.9±1.6 na 6.3±1.7 METa ($p<0.001$), a kod bolesnika bez beta blokatora sa 4.8±1.8 na 5.7 ± 1.9 METa ($p<0.01$). Obe grupe bolesnika su popravile funkcionalni kapacitet pod uticajem fizičkog treninga. Bolesnici sa metoprololom su pokazali veće poboljšanje funkcionalnog kapaciteta (28.7%) u odnosu na bolesnike bez beta blokatora (18.8 % $p<0.05$), sa statističkom značajnošću koja se pojavila od trećeg meseca studije i zadržala do kraja praćenog perioda. Nije bilo komplikacija u sklopu fizičkog treninga i nije bilo pogoršanja srčane insuficijencije. Učestalost nefatalnog infarkta miokarda bila je manja u grupi bolesnika sa metoprololom, ali bez statističke značajnosti (6.3% prema 10.6%). Godišnji mortalitet je takođe bio niži u grupi bolesnika sa metoprololom, bez značajnosti razlike.*

Ključne reči: Srčana insuficijencija, beta blokatori, fizički trenining

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