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EFFECTS OF EXERCISE TRAINING ON THE DOUBLE PRODUCT AND QT DISPERSION IN PATIENTS AFTER MYOCARDIAL INFARCTION: WHETHER THE LEFT VENTRICULAR EJECTION FRACTION HAS AN EFFECT ON THE BENEFIT

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The aim of this study was to examine the effect of exercise training on the double product (DP) and QT dispersion in patients after myocardial infarction and to determine whether the left ventricular ejection fraction (LVEF) had an effect on the benefit.

A total of 375 patients with previous MI were included in the study. Patients were randomly divided into a group that was included in the exercise training program (TG: 329 patients) and a group that did not train (NTG: 46 patients). All patients underwent an echocardiographic examination, standard ECG, corrected QT dispersion (QTdc) and exercise test, after which the training group was included in the exercise training program lasting 21 days.

Reduced left ventricular ejection fraction (RLVEF), less than 40%, was registered in 104 (31.6%) patients in TG, while in NTG it was registered in 16 (34.8%). At the beginning of the follow-up period, in TG, there was no significant difference in DP values, between patients with and without RLVEF (p-NS), while QTdc values were significantly higher in those with RLVEF ($p < 0.001$). After 21 days in TG, a significant decrease in DP (12.3 ± 1.8 vs. 11.7 ± 1.3 beat/min x mm Hg $x10^3$; $p < 0.01$) and QTdc (103.6 ± 28.3 vs. 96.1 ± 25.8 ms; $p < 0.05$) was registered in patients with RLVEF and a significant decrease in DP (11.9 ± 2.2 vs. 10.8 ± 1.6 beat/min x mmHg $x10^3$; $p < 0.001$) and QTdc (65.7 ± 25.4 vs. 58.6 ± 22.8 ms; $p < 0.005$) in those without RLVEF. In NTG patients, after a follow-up period of 21 days, no significant changes in DP and QTdc parameters were registered.

The results show that exercise training has a beneficial effect on DP and QT dispersion in patients with previous MI. LVEF has a significant influence on the benefit of exercise training, patients without RLVEF have a better benefit.

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Key words: *exercise, double product, coronary disease, QT dispersion, left ventricular ejection fraction*

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Introduction

Patients with previous myocardial infarction (MI) are at high risk for new adverse cardiovascular events, including cardiac death (1). After a myocardial infarction, patients have a significant reduction in physical exercise capacity, which is caused by damage to the myocardium and prolonged bed rest. Long-term physical inactivity leads to the weakness of skeletal muscles, damage to peripheral circulation and dysfunction of the autonomic nervous system. A decrease in physical exercise capacity leads to an increase in heart rate at rest and various forms of psychological disturbances. The significance of the reduction in physical exercise capacity mostly depends on the length of rest and the degree of the left ventricle dysfunction. The reduction of exercise tolerance is a consequence of reduced left ventricular function and skeletal muscle weakness, which is caused by reduced skeletal muscle perfusion and a significant increase in peripheral resistance. Increased heart rate at rest and inadequate increase in heart rate during exertion is the result of autonomic nervous system dysfunction. Mental problems in the form of depression and anxiety are a significant risk factor in patients with previous MI (2).

Exercise training in patients with previous MI improves physical exercise capacity, left ventricular function, has a positive effect on the patient's psychological status, reduces total mortality by 20%, cardiac mortality by 26% and reinfarction by 20% (3).

There are many causes for left ventricular dysfunction, but the most common reason is coronary disease. In patients with MI, abnormal movements of the left ventricular wall occur in the form of hypokinesia, akinesia, and dyskinesia due to the disturbance of the contractile function of the infarct zone. In patients with MI, the degree of reduction in left ventricular function depends on the size of the infarct zone. A reduction in diastolic compliance occurs if the infarction has affected eight percent of the left ventricular mass. When the contraction abnormality exceeds 15% of the left ventricular mass, there is a decrease in left ventricular ejection fraction (LVEF) and an increase in end-diastolic and end-systolic volume. Clinical signs of left ventricular dysfunction occur when the contraction abnormality exceeds 25%, and cardiogenic shock occurs when the infarction affects more than 40% of the left ventricular mass (4, 5).

Controlled exercise training has beneficial effects in patients with NIHA class I–III. An aerobic, dynamic type of exercise is recommended, such as riding a stationary or regular bicycle and walking. Aerobic training should be performed for 30–60 minutes, preferably 3–5 times during the week, and interval training is preferred. Patients in whom physical training does not improve physical capacity have a poor prognosis (6–8).

After an MI, a significant percentage of patients die of sudden cardiac death. In the Framingham study during a follow-up period of 30 years, sudden cardiac death was 6.7 times more common in coronary patients compared to other people (9).

QT dispersion (QTd) reflects heterogeneity in the repolarization of the myocardium and is a marker of myocardial ischemia and electrical instability, reflecting increased susceptibility to ventricular arrhythmias. According to numerous studies, QTd is an independent prognostic marker for arrhythmic events, cardiac mortality and sudden cardiac death, especially in coronary patients (10–12).

Given that QTd is an important prognostic marker in coronary patients and that patients after myocardial infarction are at high risk of new adverse cardiovascular events, the aim of this study is to examine the effect of exercise training on the double product (DP) and QT dispersion in patients after myocardial infarction and to determine whether the left ventricular ejection fraction has an effect on the benefit.

Material and methods

The research occurred at the Institute for Treatment and Rehabilitation Niška Banja, Niš, Serbia.

A total of 375 patients (96 females and 279 males), mean age 56.5 years, with previous MI, were included in the study, within 3 months after MI. Inclusion criteria were that patients were in sinus rhythm and free of atrioventricular blocks also no bundle branch blocks. Patients were randomly divided into a group that was included in the exercise training program (TG: 329 patients) and a group that did not train (NTG: 46 patients). Patients were of similar site of infarction and also had similar duration of baseline exercise test.

All patients underwent laboratory analyses, echocardiographic examination, standard ECG, corrected QT dispersion (QTdc) and an exercise test, after which the training group was included in an exercise program lasting 21 days.

Based on the results of the exercise test, the patients of TG received instructions for the degree of exercise activity. Patients were instructed to perform gymnastic exercises, use a bicycle ergometer and walk. Patients were also instructed not to change drug therapy during the 21-day follow-up period, after which laboratory tests, ECG, and exercise tests were performed again.

The QT interval was measured from a standard ECG, from the beginning of the QRS complex to the end of the T wave, where it joined the isoelectric line. The QT interval was measured in all ECG leads, and it was necessary to be able to measure a minimum of 8 leads for the patient to be included in the study. Bazett's formula was used to correct the QT interval according to heart rate (13). QTd was calculated as the difference between the maximum and minimum values of the QT interval found in any of the 12 ECG leads. The difference between the maximum and minimum corrected values of the QT interval, found in any of the ECG leads, is obtained from corrected QTd (QTdc).

Exercise tests were performed on all patients on a treadmill according to the Bruce protocol (14). The load tests were limited by submaximal heart rate (85% of the maximum heart rate), as well as the appearance of symptoms, complex heart rhythm disorders, and also the appearance of electropathological changes on the ECG. The following ECG criteria were used for a positive exercise test: the presence of horizontal or down-sloping ST segment depression ≥ 1mm; ST segment elevations ≥ 1 mm in leads without Q waves.

Echocardiographic examinations were performed in all patients while they were lying in the left lateral decubitus position. The M-mode technique, two-dimensional echocardiography and Doppler echocardiography, with the use of color Doppler, were used. A Siemens Acuson SC 2000 was used for echocardiographic examination. Measurement of the dimension of the left ventricle, and left ventricular wall thickness was performed using the M-mode technique with verification using a two-dimensional method, according to the criteria of the Penn Convention (15). LVEF was determined using two-dimensional echocardiography using the Simpson method (16).

Statistical Analyses

The values of the monitored parameters of the study groups are expressed as mean value ± SD. We compared clinical and biochemical data using the Student's t-test (expressed as mean value ± SD). Complete analyses were performed using software - SPSS v25 (SPSS, Chicago, IL, United States) with a statistical significance level set at $p \leq 0.05$.

Results

Reduced left ventricular ejection fraction (RLVEF), less than 40%, was registered in 104 (31.6%) patients in TG, while in NTG it was registered in 16 patients (34.8%).

At the beginning of the follow-up period, in TG, there was no significant difference in DP values, between patients with and without RLVEF, while QTdc values were significantly higher in those with RLVEF, Table 1.

After 21 days in TG, a significant decrease in DP, QTdc, total cholesterol, as well as LDL cholesterol was registered in patients with RLVEF, Table 2. TG with RLVEF achieved a significantly longer time in the second exercise test, Table 2.

After a 21-day follow-up period, in TG, a significant decrease in DP, QTdc, total cholesterol, as well as LDL cholesterol was registered in patients without RLVEF, Table 3. TG without RLVEF achieved a significantly longer time in the second exercise test, Table 3.

In NTG patients, after a follow-up period of 21 days, no significant changes in DP and QTdc parameters were registered, Table 4.

Table 1. Comparison of QTdc and double product in training group patients after myocardial infarction with and without reduced left ventricular ejection fraction, before starting with the program of physical training

Parameters	Patients after MI with RLVEF	Patients after MI without RLVEF	P
N	104	225	
Age (years)	57.3 ± 10.3	55.9 ± 9.5	NS
QTdc (ms)	103.6 ± 28.3	65.7 ± 25.4	0.001
DP (beat/min x mm Hg x10^3)	12.3 ± 1.8	11.9 ± 2.2	NS

QTdc- corrected QT dispersion; DP- double product; MI- myocardial infarction, RLVEF- reduced left ventricular ejection fraction

Table 2. Comparison of monitored parameters in the training group patients after myocardial infarction with reduced left ventricular ejection fraction before and after short-term exercise training

Parameters	Before short-term exercise training	After short-term exercise training	P
N	104	104	
QTdc (ms)	103.6 ± 28.3	96.1 ± 25.8	0.05
DP (beat/min x mmHg x10^3)	12.3 ± 1.8	11.7 ± 1.3	0.01
Total cholesterol (mmol/L)	5.2 ± 1.0	4.9 ± 1.2	0.05
LDL cholesterol (mmol/L)	2.9 ± 0.4	2.8 ± 0.3	0.05
Glycemia (mmol/L)	5.1 ± 1.1	4.8 ± 0.8	0.02
Time achieved on the exercise test (min)	4.9 ± 2.2	5.7 ± 1.9	0.005

QTdc- corrected QT dispersion; DP- double product

Table 3. Comparison of monitored parameters in the training group patients after myocardial infarction without reduced left ventricular ejection fraction before and after short-term exercise training

Parameters	Before short-term exercise training	After short-term exercise training	P
N	225	225	
QTdc (ms)	65.7 ± 25.4	58.6 ± 22.8	0.005
DP (beat/min x mmHg x10^3)	11.9 ± 2.2	10.8 ± 1.6	0.001
Total cholesterol (mmol/L)	5.0 ± 1.6	4.7 ± 1.3	0.025
LDL cholesterol (mmol/L)	2.8 ± 1.0	2.6 ± 0.8	0.02
Glycemia (mmol/L)	5.1 ± 1.8	4.7 ± 1.1	0.005
Time achieved on the exercise test (min)	5.3 ± 1.6	8.1 ± 1.8	0.001

QTdc- corrected QT dispersion; DP- double product

Table 4. Comparison of monitored parameters in the non-training group patients after myocardial infarction before and after a follow-up period of 21 days

Parameters	Before the follow-up period of 21 days	After the follow-up period of 21 days	P
N	46	46	
QTdc (ms)	76.9 ± 23.5	74.8 ± 25.6	NS
DP (beat/min x mm Hg x10^3)	12.1 ± 1.9	11.9 ± 1.7	NS
Total cholesterol (mmol/L)	5.1 ± 1.4	5.0 ± 1.7	NS
LDL cholesterol (mmol/L)	2.8 ± 0.8	2.8 ± 0.9	NS
Glycemia (mmol/L)	5.0 ± 1.9	4.9 ± 1.8	NS
Time achieved on the exercise test (min)	5.2 ± 2.4	5.8 ± 2.7	NS

QTdc- corrected QT dispersion; DP- double product

Discussion

An increased QTd reflects the regional difference in myocardial repolarization, and is also a prognostic marker for cardiac death in coronary patients (17–19). Our study showed that, before the start of exercise training treatment, patients after MI and RLVEF had significantly higher QTdc values compared to those without RLVEF. The left ventricle systolic function has a significant influence on the values of the QT dispersion parameters. A significant correlation between QTdc and LVEF in coronary patients has been shown (20). In coronary patients, fibrotic changes and myocardial ischemia reduce left ventricular function, increase sympathetic activity, directly through myocardial ischemia and reflexively through pressoreceptors, and reduce vagus activity and thus increase the dispersion of repolarization. It has been proven that the administration of noradrenaline significantly increases the values of QTd. In patients with heart failure, increased QTd values can identify those at high risk of cardiac death (21–23).

The results of our study indicate that after exercise training treatment in patients after MI, there is a significant reduction in QTdc values in both patients with RLVEF and those without RLVEF. A more significant decrease in QTdc was found in patients after MI without RLVEF. The greatest impact on the reduction of QTd is the improvement of the function of the autonomic nervous system since it has been shown that physical training significantly increases vagus tone and decreases sympathetic tone (24, 25). It is likely that the improvement in collateral blood flow in the myocardium contributed to the decrease in QTd parameters since ischemia has been proven to increase QTd. After successful reperfusion, in patients with acute MI, as well as in those with chronic myocardial ischemia, there is a significant decrease in QTd (26–29).

DP is an indirect indicator of myocardial oxygen consumption (30). The results of our study indicate that in post-MI patients, after exercise training treatment, a significant reduction in double product at rest was noted. The decrease in DP was more pronounced in those without RLVEF. This reduction of the double product reduces the demand of the myocardium for oxygen, as a result of which the time until the onset of angina pain in coronary patients is prolonged, and it is also a significant prognostic indicator in patients after MI (31).

After the exercise training program, a significant decrease in total cholesterol, as well as LDL cholesterol was registered in our patients after MI. In post-MI patients, lipid lowering due to statin therapy significantly increases survival and reduces cardiac mortality (2). The reduction of total cholesterol as well as LDL cholesterol in our patients after MI indicates the great importance of exercise training. Risk factors for cardiovascular diseases affect the speed of development of atherosclerosis. It is of great importance whether one or more risk factors are present, as well as their duration. Statins are first-line drugs for lowering LDL cholesterol, which should be included immediately (2, 32). Statin therapy reduces the level of LDL cholesterol and circulating highly sensitive CRP, improves endothelial function, reduces thrombogenesis and inflammatory components of arterial atheroma, and stabilizes atheromatous plaques (32).

A significant increase in exercise capacity was observed in our post-MI TG patients after exercise treatment. These patients achieved a significantly longer time and a higher level of load in the second exercise test.

Conclusion

The results show that exercise training has a beneficial effect on DP and QT dispersion in patients with previous MI. The left ventricular ejection fraction has a significant influence on the benefit of exercise training, patients without RLVEF have a better benefit. In patients after MI, exercise training significantly reduces myocardial oxygen consumption at rest and probably reduces the possibility of arrhythmias, more so in those without RLVEF.

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EFEKTI FIZIČKOG TRENINGA NA DVOJNI PROIZVOD I QT DISPERZIJU KOD BOLESNIKA SA PREŽIVELIM INFARKTOM MIOKARDA – DA LI EJEKCIONA FRAKCIJA LEVE KOMORE IMA UTICAJA NA BENEFIT

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Cilj ovog rada bio je da se utvrdi efekat fizičkog treninga na dvojni proizvod (eng. *double product* – DP) i QT disperziju kod bolesnika sa preživelim infarktom miokarda (eng. *myocardial infarction* – MI) i da se ispita da li ejekciona frakcija leve komore (eng. *left ventricular ejection fraction* – LVEF) ima uticaja na benefit od fizičkog treninga.

U studiju je bilo uključeno 375 bolesnika sa preživelim MI. Bolesnici su potom podeljeni u dve grupe – u jednoj grupi bili su bolesnici uključeni u program fizičkog treninga (TG: 329 bolesnika), dok su drugu grupu činili bolesnici koji nisu trenirali (NTG: 46 bolesnika). Svim ispitanicima urađeni su ehokardiografski pregled, dvanaestokanalni EKG, korigovana QT disperzija (QTdc) i test opterećenja. Nakon toga, ispitanici iz TG uključeni su u program fizičkog treninga u trajanju od tri nedelje.

Redukovana ejekciona frakcija leve komore (eng. *reduced left ventricular ejection fraction* – RLVEF), manja od 40%, bila je prisutna kod 104 (31,6%) bolesnika u TG i kod 16 bolesnika (34,8%) u NTG. Na početku perioda praćenja, u TG nije bilo značajne razlike u vrednostima DP-a između bolesnika sa RLVEF-om i onih bez RLVEF-a (p-NS), dok su QTdc vrednosti bile značajno veće kod bolesnika sa RLVEF-om ($p < 0,001$). Posle tri nedelje, u TG uočena je značajna redukcija QTdc (103,6 ± 28,3 prema 96,1 ± 25,8 ms; $p < 0,05$) i DP-a (12,3 ± 1,8 prema 11,7 ± 1,3 otkucaja/min x mmHg x10^3; $p < 0,01$) kod bolesnika sa RLVEF-om. Značajna redukcija QTdc (65,7 ± 25,4 prema 58,6 ± 22,8 ms; $p < 0,005$) i DP-a (11,9 ± 2,2 prema 10,8 ± 1,6 otkucaja/min x mmHg x10^3; $p < 0,001$) zapažena je i kod bolesnika bez RLVEF-a. Nasuprot tome, u NTG nije bilo bitnijih promena.

Rezultati su pokazali da fizički trening ima povoljan uticaj na DP i QTdc kod bolesnika sa preležanim MI. LVEF-a ima značajan uticaj na benefit od fizičkog treninga, s tim što je benefit veći kod bolesnika bez RLVEF-a.

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Ključne reči: *fizički trening, dvostruki proizvod, koronarna bolest, QT disperzija, ejekciona frakcija leve komore*