The effect of regular physical activity on the left ventricle systolic function in patients with chronic coronary artery disease

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Short title: The effect of physical activity on the left ventricle systolic function

Summary:

Objective: The purpose of this study was to assess the influence of aerobic training on the left ventricular (LV) systolic function.

Methods: Thirty patients with stable coronary artery disease, who had participated in the conducted 3-month physical training, were retrospectively divided into 2 cohorts. While patients in the cohort I (n=14) had continued training individually for 12 months, patients in the cohort II (n=16) had stopped training after finishing the conducted program.

Rest and stress dobutamine/atropine echocardiography was performed in all patients before the training program and 1 year later. The peak systolic velocities of mitral annulus (Sa) were assessed by tissue Doppler imaging for individual LV walls. In addition, to determine global LV systolic longitudinal function, the four-site mean systolic velocity was calculated (Sa glob).

According to the blood supply, left ventricular walls were divided into 5 groups: A- walls supplied by nonstenotic artery; B- walls supplied by coronary artery with stenosis ≤ 50%; C- walls supplied by coronary artery with stenosis 51-70%; D- walls with stenosis of supplying artery 71-99%; and E- walls with totally occluded supplying artery.

Results: In global systolic function, the follow-up values of Sa glob in cohort I were improved by 0.23±0.36 as compared with baseline values at rest, and by 1.26±0.65 cm/s at the maximal load, while the values of Sa glob in cohort II were diminished by 0.53±0.22 (p=NS), and by 1.25±0.45 cm/s (p<0.05), respectively.

Concerning the resting regional function, the only significant difference between cohorts in follow-up changes was found in walls E: 0.37±0.60 versus -1.76±0.40 cm/s

(p<0.05). At the maximal load, the significant difference was found only in walls A
(0.16±0.84 versus -2.67±0.87 cm/s; p <0.05).

Conclusion: Patients with regular 12-month physical activity improved their global left
ventricle systolic function mainly due to improvement of contractility in walls supplied
by a totally occluded coronary artery.

Key words: coronary artery disease – aerobic training - left ventricle systolic function

Introduction

Beneficial effects of cardiac rehabilitation (CR) on secondary prevention of patients with coronary artery disease are now well-established. The major objective benefits are an increased exercise capacity (Hambrecht et al. 2000) and reduced rates of cardiac events and mortality (Oldridge et al.1988, Hadkell et al.1994). In addition, beneficial effects on coronary risk factors – blood pressure, lipid levels, glucose metabolism, body weight, as well as on the endothelial function and psychological well-being were proved (Shephard and Balady 1999).

On the other hand, only limited data exists concerning the effect of CR on left ventricular (LV) function. Some authors suggest improvements in cardiac function (Klecha et al. 2007, Hambrecht et al. 2000, Belardinelli et al.1996, Giannuzzi et al.1997), whereas others have not found any significant differences between exercise training groups and controls (Dubach et al.1997, Giannuzzi et al.2003). The different results may be due to differences in intensity and duration of training, measurement techniques or patient populations. However, in majority of the studies, LV function has been evaluated by LV ejection fraction (EF) measurements. It is well known that LVEF quantification using standard two-dimensional (2D) echocardiography is strongly dependent on image quality and endocardial border delineation.

Tissue Doppler imaging (TDI) is an echocardiographic technique employing the Doppler principle to measure the velocity of myocardium. Pulsed-TDI permits quantification of regional longitudinal myocardial velocities with high temporal resolution and is feasible even in poor acoustic windows. Hence, TDI offered a potentially more accurate quantitative assessment of both regional and global LV

function including even more minor changes in systolic LV function that are not detectable during 2D echocardiographic evaluation of LVEF.

The purpose of this study was to assess the influence of aerobic training on the LV systolic function using TDI measurements.

Patients and methods

Patient population and study protocol

The study comprised 30 patients with stable coronary artery disease (proved by the coronary angiography performed before the study). All of them had participated in the conducted 3-month physical CR training. The continuation of physical training was recommended to all patients. After 1 year period, these patients were retrospectively divided into 2 cohorts. While patients in the cohort I (n=14) had continued training individually for 12 months, patients in the cohort II (n=16) had stopped training after finishing the conducted CR program.

Rest and stress dobutamine/atropine echocardiography was performed in all patients before the training program and 1 year later. For the evaluation of regional systolic LV function, the pulsed TDI was used.

According to the blood supply, LV walls were divided into 5 groups: A- walls supplied by nonstenotic artery; B- walls supplied by coronary artery with stenosis $\leq$ 50%; C- walls supplied by artery with stenosis 51-70%; D- walls with stenosis of supplying coronary artery 71-99%; and E- walls with totally occluded supplying artery.

The study was in accordance with the Declaration of Helsinki (2000) of the World Medical Association, was approved by the institutional ethics committee and written consent was obtained from each patient.

Physical training

All patients had participated in the conducted outpatient CR. The program offered 3 months of 3 times per week sessions. Each session lasted for 60 minutes and consisted of 3 different phases: 10 minutes warm-up, period of aerobic exercise on bicycle ergometer with load intensity at the level of anaerobic threshold (20 minutes), period of resistance training performed on combined training machine (20 min), and relaxation period (10 min). Aerobic exercise intensity was individually prescribed according to symptom-limited spiroergometry (Blood Gas Analyser, MedGraphics, USA) that was provided before training period for the evaluation of anaerobic threshold.

The 9-months individual training of cohort I consisted of regular physical activity performed for a minimum of one hour at least three times a week. As a regular physical activity the patients have been asked to choose either cycling, riding a velo-ergometer or swimming.

Echocardiography

Using commercially available equipment Philips Sonos 5500 (Andover, USA) with a 2.5MHz transducer, echocardiographic examinations were performed in one centre by one experienced echocardiographer. 2D images of standard views and pulsed TDI of apical 4- and 2-chamber views were acquired and recorded on videotape for off-line analyses. The peak systolic velocities of myocardium adjacent to the mitral annulus (Sa) were assessed by TDI for individual LV walls: septum, lateral, anterior, and inferior walls. In addition, to determine global LV systolic longitudinal function, the four-site mean systolic velocity was calculated (Sa glob). Velocities were evaluated at rest and at the maximal load.

Dobutamine echocardiography was performed in all patients. Dobutamine was infused with mechanical pump, starting at a dose of 5 µg/kg/min. At 3-minute intervals, the dose was increased incrementally to 10, 20, 30, 40 µg/kg/min until a maximal dose was reached or target heart rate was attained. Intravenous atropine was given in one bolus dose of 0.5mg if the target heart rate was not reached. After the test has been terminated, patients were monitored until baseline condition returned.

Statistical analysis

The changes of global and regional systolic function of individual LV wall groups were compared between cohorts at rest and at the maximal load. To assess normal distribution of variables, the Kolmogorov-Smirnov test was used. An unpaired t-test and Mann-Whitney U test were applied to compare the values of parameters between cohorts; $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics and coronary angiography findings of patients are shown at Table 1 and 2. The majority of parameters have been similar in the two groups – just differences between the number of men and women and the difference between patients age in both cohorts have been found. No serious adverse events were found in either group during the follow-up.

The changes of Sa value after follow-up in different groups of LV walls are shown in Table 3. In global systolic function, the values of Sa glob in cohort I were improved by 0.23 ± 0.36 as compared with baseline values at rest, and by 1.26 ± 0.65 cm/s at the maximal load, while the values of Sa glob in cohort II were diminished by 0.53 ± 0.22 (p=NS), and by 1.25 ± 0.45 cm/s (p<0.05), respectively.

Concerning the resting regional function, the only significant difference between cohorts in follow-up changes was found in walls E: 0.37 ± 0.60 versus -1.76 ± 0.40 cm/s (p<0.05). At the maximal load, the significant difference was found only in walls A (0.16 ± 0.84 versus -2.67 ± 0.87 cm/s; p <0.05). Sa changes in other walls was not significant.

Discussion

Effect of CR on global LV systolic function

The present investigation suggests that long-term exercise training can improve LV systolic function in patients with coronary artery disease. Previous works have shown variable results in relation to influence of CR on the LV function (Klecha et al.2007, Hambrecht et al.2000, Belardinelli et al.1996, Giannuzzi et al.2003). The failure to assess changes in LVEF in some studies may have several reasons. It may be the result of different study populations, kind and intensity of the training programs or the measurement techniques (Webb-Peploe et al.2000). Only patients with chronic heart failure or after myocardial infarction with moderate-to-severe LV dysfunction were included in the majority of studies assessing the influence of CR on LV function. In comparison with them, our patients had only slight depression of LVEF and not all of them underwent clinical myocardial infarction.

The intensity and duration of CR necessary for LV function improvement have not yet been sufficiently evaluated. In the analysis in the work of Piepoli (Piepoli 2004) the data suggested that only long-term duration over 28 weeks of CR may be required to reach benefits in mortality and adverse events rates. The antiremodelling effect of training with a trend towards improvement of LV functional parameters was found after 6-month training in the work of Klecha et al (Klecha et al.2007). On the other hand, the work of Hambrecht (Hambrecht 2000) demonstrated that an intense CR program can improve resting LVEF in 2 weeks. In our work, just 1-year CR improved LV systolic function, while the 3-month training did not provide the sustained long-term functional improvement.

The utilization of LVEF, as an evaluated parameter of LV function, could be one of the main factor contributing to the failure of some previous studies to shown the

effect of CR. LVEF is a load-dependent parameter and is very rough to assess expected slight changes of LV function. EF evaluated by 2D echocardiography is strongly dependent on image quality and endocardial border delineation. In contrast, TDI is robust, reproducible and may be more sensitive marker of LV longitudinal systolic function and it is feasible even in poor echocardiographic windows. Hence, TDI allows evaluation of even minor changes in LV function that are not detectable by 2D assessment. In several published data, TDI has been applied to stress echocardiography in order to overcome the limitation of only visual analysis (Cain et al.2001, Fathi et al.2001, Bougault et al.2008, Duzenli et al.2008, Garcia et al.2006).

Effect of CR on regional LV systolic function

This present study is the first trial to evaluate the effect of CR on regional LV systolic function in relation to blood supply of individual LV walls. TDI was chosen for this purpose, because it permits quantification of regional longitudinal myocardial systolic velocities with a high temporal resolution and can overcome the limitation in the subjective echocardiographic evaluation of regional ventricular function (Reuss et al.2005).Our data showed that the effect of CR on LV systolic function is caused mainly through the improvement of contractility in walls supplied by a totally occluded coronary artery. The effect of physical training and LV global and regional function was assessed by TDI also in the study of Deljanin-Ilic and al (Deljanin-Ilic et al.2007). After 6 months, LV EF increased significantly as well as the regional systolic myocardial function at the previously infarcted wall only in the training group.

Mechanisms of this training effect have not yet been established. The most likely explanation is the combination of beneficial changes in ventricular wall tension and favorable adaptation in the coronary circulation. The physical training may have beneficial effect on changes in autonomic balance toward a vagal predominance, which could limit the deleterious effects of sympathetic hyperactivity on the LV remodeling and function, analogously to treatment with beta blockers.

In patients with stable coronary artery disease, augmented delivery of blood to ischemic myocardium has been shown to take place in response to physical training (Hambrecht 2004). The beneficial effect of CR on morbidity and mortality has been attributed to the growth of collateral vessels between healthy and under-perfused myocardial regions (Shephard and Balady 1999). This theory was documented for example by work of Zbinden et al where beneficial dose-response effect of 3-month endurance exercise training on collaterals has been found (Zbinden et al.2007). However, other human studies have failed to document consistently the formation of collaterals. The main reason for different results may have been the lack of sensitivity of angiography to detect small coronary collaterals. The collateral growth and other coronary vascular changes may improve function of chronically hypoperfused myocardium.

Furthermore, CR has been shown to favourably affect blood flow rheology, thereby possible improving of myocardial perfusion. The improvement in myocardial blood flow to the infarcted area may lead to recovery of both global and regional LV function (Schuler et al.1992). Although our study cannot elucidate the possible mechanism of regional functional improvement, we speculate, that combination of autonomic system changes and especially the development of collaterals may have

facilitated partial functional recovery of dysfunctional but viable myocardial regions supplied by a totally occluded coronary artery.

Study limitations

Our study had several limitations. The study was retrospective, not randomized. The interpretations of results could be limited by a relatively small sample size in both cohorts. Also our study can be influenced by the difference between the number of men and women and the difference between patients age in both cohorts, because age and gender are determining factors for training effects - smaller improvements of women as well as a negative relation between age and improvement in exercise performance is known (Vanhees et al.2004).

Another limitation is the fact, that the 9-months training of cohort II have been performed as an outpatient individual training without any supervision. The information about frequency and intensity has been obtained only from patient's anamnesis during their regular visits in outpatient department. However, very different types of training programmes are described in literature and in some studies, a home-based CR had no significant differences in the main outcomes compared with the centre-based programme (Jolly et al.2009) or an outpatient CR led to further improvement of followed parameters in comparison to supervised CR in a hospital (Benzer et al.2007).

Certainly, further research is required, especially in order to optimize the effectiveness of CR programs and to better understand the mechanisms responsible for the improvements related to CR training.

Conclusion

In our study, patients with regular 12-month physical activity improved their global left ventricle systolic function mainly due to improvement of contractility in walls supplied by a totally occluded coronary artery.

Acknowledgments

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Table 1. Characteristics of the study population

Parameter	Cohort I (n = 14)		Cohort II (n = 16)	
Age (years)	60	(10)	69*	(8)
Men	13	(93 %)	8*	(50 %)
Diabetes mellitus	4	(29 %)	5	(31 %)
Hypertension	14	(100 %)	16	(100 %)
Hyperlipidemia	14	(100 %)	15	(94 %)
Previous myocardial infarction	10	(71%)	9	(57%)
LV EF (%)	50.4	(2.9)	47.9	(2.7)
No of stenotic arteries (≥70%)	2.1	(0.2)	1.6	(0.2)
Medication				
Aspirin	14	(100 %)	15	(94 %)
Beta blocker	14	(100 %)	16	(100 %)
ACE inhibitor	10	(71 %)	11	(70 %)
Statin	13	(93 %)	16	(100 %)
Diuretics	4	(29 %)	5	(31 %)
Nitrates	8	(57 %)	11	(69%)

The values are expressed as the mean supplied by standard error (in parentheses) or

number (%) of subjects.

LV = left ventricle; EF = ejection fraction; No = number; ACE = angiotensin-

converting enzyme; * $p < 0.05$ between cohorts

Table 2. Coronary angiography finding in cohorts

Cohort	I (n = 14)			II (n= 16)		
	LAD	LCX	RCA	LAD	LCX	RCA
no stenosis	3 (21%)	2 (14%)	3 (21%)	3 (19%)	6 (38%)	5 (31%)
stenosis ≤ 50	4 (29%)	7 (50%)	0 (0%)	2 (13%)	4 (25%)	4 (25%)
stenosis 51-70%	2 (14%)	2 (14%)	3 (21%)	1 (6%)	1 (6%)	2 (13%)
stenosis 71-99%	3 (21%)	1 (7%)	3 (21%)	4 (25%)	3 (19%)	2 (13%)
totally occluded	2 (14%)	2 (14%)	5 (36%)	6 (38%)	2 (13%)	3 (19%)

The values are expressed as number of arteries (%)

LAD = left anterior descending artery; LCX = left circumflex; RCA = right coronary artery

Table 3. Changes of Sa value after follow-up in different groups of LV walls at rest and at the maximal load

Cohort	At rest		At the maximal load	
	I (n = 14)	II (n = 16)	I (n = 14)	II (n = 16)
Wall group				
A	-1.56±0.93	-0.86±0.38	0.16±0.84	-2.67±0.87*
B	1.29±0.63	0.62±0.58	3.83±1.13	0.56±1.05
C	-0.64±0.69	0.14±0.88	-0.42±1.02	-0.58+1.92
D	-0.09±0.86	-0.10±0.30	-2.82±1.19	-2.29±0.86
E	0.37±0.60	-1.76±0.40*	1.70±1.43	0.02±0.78
All (global function)	0.23±0.36	-0.53±0.22	1.26±0.65	-1.25±0.45*

The values are expressed as the mean supplied by standard error (in parentheses)

Sa = peak systolic velocity of mitral annulus; LV = left ventricle;

Wall groups : A- walls supplied by nonstenotic artery; B- walls supplied by artery with coronary stenosis ≤ 50%; C- walls supplied by artery with stenosis 51-70%; D- walls with stenosis of supplying artery 71-99%; and E- walls with totally occluded supplying artery.

 * p< 0.05 between cohorts