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Impact of aerobic interval training and continuous training on left ventricular geometry and function: a SAINTEX-CAD substudy

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ABSTRACT

Background: Increase of exercise capacity (peak VO_2) after cardiac rehabilitation improves outcome in patients with coronary artery disease (CAD). Systolic and diastolic function have been associated with peak VO_2, but their role towards improvement of exercise capacity remains unclear. It is unknown which exercise intensity has the most beneficial impact on left ventricular (LV) geometry and function in CAD patients without heart failure.
Methods: 200 stable CAD patients without heart failure were randomized to 3 months of aerobic interval training (AIT) or aerobic continuous training (ACT). Cardiopulmonary exercise test and transthoracic echocardiography were scheduled before and after 3 months of training.
Results: At baseline, a higher peak VO_2 correlated with lower LV posterior wall thickness ($p = 0.002$), higher LV ejection fraction ($p = 0.008$), better LV global longitudinal strain ($p = 0.043$) and lower E/e′ ($0 = 0.001$). After multivariate stepwise regression analysis only E/é remained an independent predictor of peak VO_2 ($p = 0.042$). Improvement of peak VO_2 after 3 months of training correlated with reverse remodeling of the interventricular septum ($p = 0.005$), enlargement of LV diastolic volume ($p = 0.007$) and increase of LV stroke volume ($p = 0.018$) but not with other indices of systolic or diastolic function. Significant reduction of the interventricular septum thickness after cardiac rehabilitation was observed ($p = 0.012$), with a trend towards more reverse remodeling after ACT compared to AIT ($p = 0.054$). In contrast, there were no changes in other parameters of LV geometry, diastolic or systolic function.
Conclusion: Systolic and diastolic function are determinants of baseline exercise capacity in CAD patients without heart failure, but do not seem to mediate improvement of peak VO_2 after either AIT or ACT.

1. Introduction

It is widely recognized that exercise-based cardiac rehabilitation in patients with coronary artery disease (CAD) improves cardiovascular mortality, morbidity and health-related quality of life [1]. Improved exercise capacity after cardiac rehabilitation, as assessed by peak oxygen uptake (VO_2), has been shown to be an independent predictor of cardiovascular mortality after acute myocardial infarction (AMI) and coronary artery bypass grafting (CABG) [2].

Exercise capacity is confounded by many factors, including age, female sex, body mass index and comorbidities [3]. Assessing the potential influence of left ventricular geometry and function is therefore complex. Although the role of systolic function remains unclear, parameters of diastolic function have consistently been related with exercise capacity in large series of patients with and without CAD [4,3].

In most rehabilitation centers, CAD patients are prescribed aerobic continuous training (ACT) at a moderate exercise intensity of 60 tot 80% of peak VO_2 [5], whereas a recent meta-analysis in patients with CAD [6] suggests that aerobic interval training (AIT) at a higher training intensity yields more improvement in exercise capacity. Besides a larger increase of peak VO_2, Wisløff et al. [7] found improvement of systolic function and more reverse left ventricular remodeling after AIT compared to ACT in CAD patients with reduced left ventricular ejection

Abbreviations: CAD, coronary artery disease; VO_2, oxygen uptake; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; ACT, aerobic continuous training; AIT, aerobic interval training; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; HR, heart rate; GLS, global longitudinal strain; LVOT VTI, velocity-time integral of the forward stroke volume; SPAP, systolic pulmonary artery pressure.

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fraction (LVEF). However, at present there is no convincing evidence of beneficial impact of cardiac rehabilitation on left ventricular systolic function in CAD patients without impaired left ventricular function with conflicting data on improvement of diastolic function [8,9,10,11].

The SAINTEX-CAD study is a randomized multi-center trial that was designed to test the hypothesis that AIT results in a larger increase of peak VO_2 than ACT in 200 stable CAD patients without heart failure [12]. The hypothesis of this substudy is that AIT results in more beneficial left ventricular remodeling and in more improvement of left ventricular function than ACT. Furthermore, we hypothesized that these beneficial alterations would be associated with improvement of peak VO2 after training. Therefore, the purpose of this substudy is to investigate whether:

1) AIT and ACT differ regarding their impact on left ventricular geometry and parameters of systolic and diastolic function.
2) These parameters are determinants of baseline exercise capacity in CAD patients without heart failure.
3) Changes of exercise capacity might result from beneficial influence on these parameters.

2. Material and methods

The rationale and detailed study design of the SAINTEX-CAD study has been published previously [12].

2.1. Study design

200 CAD patients referred for cardiac rehabilitation were enrolled at two Belgian centers (University Hospital of Antwerp, $n = 100$; and University Hospital of Leuven, n = 100) between November 2010 and March 2013. Inclusion criteria were [12]: 1) angiographically documented CAD or previous AMI, 2) a LVEF >40%, 3) on optimal medical treatment, 4) stable with regard to symptoms and medication, and no evidence of residual ischemia for at least 4 weeks, and 5) included between 4 and 12 weeks following AMI, percutaneous coronary intervention (PCI) or CABG. After obtaining written informed consent, patients were randomized to a supervised training program for three months of AIT or ACT on a 1:1 basis using an online randomization protocol. Patients were scheduled for a cardiopulmonary exercise test and a comprehensive transthoracic echocardiography before and after three months of training.

The study complied with the Declaration of Helsinki [13] and was approved by the Ethics Committee of both centers.

2.2. Exercise training

All patients were scheduled for a supervised three-weekly training session on a bicycle during three months. The AIT group cycled 38 min, starting with a 10-minute warm-up at 60–70% of peak heart rate (HR), followed by 4 × 4-minute intervals at 85–95% of peak HR and 4 × 3-minute active pauses at 50–70% of peak HR. The ACT group cycled 47 min, starting with a 5-minute warm-up at 60–70% of peak HR, followed by 37 min continuous cycling at minimum 70–75% of peak HR, and ending with a 5-minute cool-down at 60–70% of peak HR.

2.3. Cardiopulmonary exercise test

A cardiopulmonary exercise test was performed on a bicycle ergometer using an individualized ramp protocol (10 W + 10 W/min or 20 W + 20 W/min) with continuous registration of electrocardiography and gas exchange values. Peak VO_2 was determined as the mean value of three measures of VO_2 during the final 30 s of exercise. Current medication was not interrupted before the cardiopulmonary exercise test.

2.4. Echocardiography

A comprehensive two-dimensional transthoracic echocardiography was performed at rest in the left lateral supine position using a Vivid 7 or Vivid 9 cardiovascular ultrasound system equipped with a M5S transducer (GE Healthcare, Little Chalfont, UK). All data obtained by echocardiography were analyzed off-line with an EchoPAC workstation (GE Medical Systems, Horten, Norway). Conventional B-mode, color Doppler, pulsed and continuous wave Doppler images were acquired in still or cine-format using ECG-gating. All measurements were averaged over three cardiac cycles for patients in sinus rhythm and 5 cycles for patients with atrial fibrillation. End-systolic and end-diastolic left ventricular diameters were measured with M-mode in the parasternal long-axis view according to current recommendations [14]. Left ventricular volumes and LVEF were quantified by the modified Simpson's method in the apical 4- and 2-chamber view. Global longitudinal strain (GLS) was obtained by averaging speckle tracking-derived longitudinal strain values from the 4-, 2- and 3-chamber apical views in a 16 segment model [15]. The velocity-time integral of the forward stroke volume (LVOT VTI) was measured by pulsed wave Doppler at the left ventricular outflow tract in the apical 5-chamber view. Parameters of diastolic function were assessed as recommended [16]: mitral *E*- and A-wave velocities and the deceleration time were measured with pulsed wave Doppler at the tips of the mitral leaflets in the apical 4-chamber view; the e′ velocity was obtained by tissue Doppler imaging in the septal position of the mitral annulus and the isovolumetric relaxation time was measured by continuous wave Doppler between the left ventricular outflow tract and the mitral leaflet tips in the apical 5-chamber view. The transtricuspid pressure gradient was measured by continuous wave Doppler of the regurgitant tricuspid jet in the apical 4-chamber view. The systolic pulmonary artery pressure (SPAP) was calculated as the sum of the maximal transtricuspid pressure gradient and an estimate of the right atrial pressure based on inferior caval vein dimension and collapsibility [17].

2.5. Statistical analysis

Results are expressed as mean ± standard deviation or percentage unless otherwise specified. All statistical analyses were performed using SAS (SAS® 9.3, Sas Institute, Inc., Cary, NC, USA). Data were tested for normality using the Shapiro-Wilk test. Baseline comparisons were performed using independent sample *t*-test or Chi-square test where appropriate. The AMI group comprised all patients who had AMI or AMI + PCI. Patients who had CABG, whether or not in combination with AMI or PCI, were categorized in the CABG group. The PCI group consisted of patients following PCI without prior AMI or CABG. As there were baseline group differences for age and pathology, differences over time between groups (= interaction) were analyzed by univariable two-way repeated measures analysis of covariance (ANCOVA) with age and pathology as covariates. Bivariate Pearson correlation analysis followed by multivariate stepwise regression analysis (with adjustment for age, gender and body mass index) was performed to identify determinants of exercise capacity at baseline. Pearson correlation analysis was also performed to detect possible correlations between % changes of VO_2 and parameters of systolic and diastolic function. Statistical significance was set at a two-tailed probability of $p < 0.05$.

3. 3. Results.

3.1. Study population

Baseline demographic and clinical characteristics of the study population are summarized in Table 1. There were no significant differences between groups, except for age and pathology. Patients randomized to AIT were younger and had more AMI and less PCI compared to the ACT group. At baseline 194 echocardiographic exams were available