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

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

Caroline M. Van De Heyning[a], Catherine De Maeyer[a], Nele Pattyn[b], Paul J. Beckers[a], Véronique A. Cornelissen[b], Kaatje Goetschalckx[c], Nadine Possemiers[a], Emeline M. Van Craenenbroeck[a], Jens-Uwe Voigt[c], Luc Vanhees[b], Bharati Shivalkar[a].

[a] Department of Cardiology, Antwerp University Hospital, Edegem, Belgium
[b] Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium
[c] Department of Cardiovascular Diseases, University Hospital of Leuven, Leuven, Belgium

Corresponding author

Caroline Van De Heyning
University Hospital of Antwerp
Wilrijkstraat 10
B-2650 Edegem
Belgium
Email: caroline.vandeheyning@uza.be
Tel: +3238213538
Fax: +3238302305

Funding

This work was supported by the Agency of Innovation by Science and Technology (IWT-project number 090870). VAC is supported by the Research Foundation Flanders as a Postdoctoral Fellow. EMVC is supported by the Research Foundation Flanders as a senior clinical investigator.

Wordcount: 2846

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.

Keywords: cardiac rehabilitation, coronary artery disease, systolic function, diastolic function, remodeling, echocardiography

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

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 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]. <u>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.</u>

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 minutes, starting with a 10-minute warm-up at 60-70% of peak heart rate (HR), followed by 4 x 4-minute intervals at 85-95% of peak HR and 4 x 3-minute active pauses at 50-70% of peak HR. The ACT group cycled 47 minutes, starting with a 5-minute warm-up at 60-70% of peak HR, followed by 37 minutes 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 Watt + 10 Watt/minute or 20 Watt + 20 Watt/minute) 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 seconds 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 iso-volumetric 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. 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 for analysis (AIT: n = 97 ; AMT: n = 97). As previously reported by Conraads *et al* [18], 26 patients failed to complete the three-month training program and were excluded from further analysis. A total of 164 patients had baseline and three month follow up echocardiographic exams (AIT: n = 81 ; ACT: n = 83).

Determinants of exercise capacity

Correlations between baseline clinical or echocardiographic parameters and peak VO_2 are depicted in Table 2 (left column). A higher peak VO_2 at baseline was significantly correlated with lower left ventricular wall thickness, more favorable indices of left ventricular systolic (LVEF and GLS) and diastolic function (E/e') and lower SPAP. No correlation was observed between exercise capacity and left ventricular cavity dimensions.

After multivariate stepwise regression analysis adjusted for age, gender and body mass index, only E/é remained an independent predictor of peak VO_2 (p=0.042) in contrast to left ventricular posterior wall thickness, LVEF and SPAP.

3.2 Changes in exercise capacity

As previously reported by Conraads *et al* [18], peak VO_2 equally improved in both groups after three months of exercise training (AIT: +22.7±17.6% vs. ACT: +20.3±15.3%; p-time 0.001, p-interaction 0.87). Correlations between % changes in peak VO_2 after training intervention and % changes of parameters regarding left ventricular geometry, systolic and diastolic function are shown in table 2 (right column). Improvement of peak VO_2 was correlated with reverse

remodeling of the interventricular septum, enlargement of diastolic volume and increase of stroke volume. In contrast, Pearson correlation analysis did not reveal correlations between changes in peak VO_2 and changes in other indices of systolic function nor parameters of diastolic function.

3.3 Changes in left ventricular geometry, systolic and diastolic function

Parameters of left ventricular geometry, systolic and diastolic function at baseline and after three months of training intervention are summarized in table 3. A significant reduction of interventricular septum thickness was observed (p-time = 0.012), with a trend towards more reverse remodeling in the ACT group compared to the AIT group (p-interaction = 0.054). However, there were no significant changes in posterior wall thickness or left ventricular cavity dimensions following AIT or ACT.

As previously shown by *Conraads et al* [18], training intervention resulted in lower resting heart rate and blood pressure. This decrease in heart rate coincided with a significant increase in LVOT VTI (p-time = 0.047), which implies an increase in forward stroke volume and maintenance of cardiac output, without differences between groups. In contrast, we did not observe improvement of LVEF or GLS, nor any of the indices of diastolic function.

<u>In 32 patients the beta-blocker dose was adjusted during follow-up. Exclusion of these patients did not influence the findings significantly, as shown in Table 4.</u>

4. Discussion

The present study shows no difference between AIT or ACT in CAD patients without heart failure regarding its impact on left ventricular geometry, diastolic and systolic function, except for a trend towards more reverse remodeling of the interventricular septum after ACT.

4.1 Impact of AIT and ACT on left ventricular geometry and exercise capacity

It has been demonstrated that cardiac rehabilitation results in reverse remodeling of LV dimensions in clinically stable patients post AMI with impaired LVEF [19]. Evidence suggests that more left ventricular remodeling might be achieved by AIT than by ACT in these patients [7]. In contrast, data regarding reverse remodeling after cardiac rehabilitation in CAD patients without heart failure are scarce. One recent non-randomized study in patients post AMI with a LVEF >45% found left ventricular reverse remodeling after ACT, but not in the control group [20]. In contrast, no beneficial effect on left ventricular geometry was observed after ACT in a cohort of patients post PCI [21]. Our study, comprising a larger study cohort than these previous studies, did not find reverse remodeling of left ventricular dimensions after either AIT or ACT regardless of the underlying pathology. Intriguingly, improvement of exercise capacity was rather associated with enlargement of end-diastolic dimensions leading to increased LVOT VTI; possibly this enlargement represents an adaptive mechanism to increase stroke volume in response to exercise training as is seen in athletes. In contrast to a small exercise study in healthy volunteers [22], we did not observe greater increase of LVOT VTI in the AIT group than in the ACT group.

Furthermore, we found a trend towards more reverse remodeling of the interventricular septum after ACT compared to AIT. Given the large sample size of our study cohort increasing the power for significance, this finding is probably not of clinical relevance. Interestingly, our data showed an association between improvement in exercise capacity and reverse

remodeling of the interventricular septum. Moreover, the left ventricular wall thickness was correlated with peak VO_2 at baseline. From a physiological point of view, a causal relationship between these two parameters seems illogical. *Mooren et al* [23] showed that microRNA 133a, which is altered by physical exercise and is expressed in skeletal muscle and heart cells, was moderately correlated with both peak VO_2 and interventricular septum thickness. In this respect, we hypothesize that similar underlying mechanisms that mediate intracellular processes, may play a role in the observed association between exercise capacity and left ventricular wall thickness. Reduction of diastolic blood pressure, as was observed in the SAINTEX-CAD study [18] after exercise training, might be an additional factor.

In the current study, a 3-month exercise training program was followed. However, training duration, volume and intensity could impact the exercise induced-effects on LV structure and function. In patients with ischemic cardiomyopathy, it has been shown that the anti - remodeling effects of exercise training are more prominent when training duration exceeded 6 months and training was initiated early after the initial event [19]. Whether this also holds true for CAD patients with preserved ejection fraction and normal LV volumes, should be studied in future trials.

4.2 Impact of AIT and ACT on left ventricular function and exercise capacity

It has been shown that AIT improves systolic and diastolic function in patients post AMI with heart failure [7]. In contrast, our study in CAD patients without heart failure found no improvement of these parameters after either AIT or ACT. These data are in line with the study of *Moholdt et al* [11] that randomized 38 patients post CABG between AIT and ACT; no difference in systolic longitudinal strain or E/e' was seen between both training groups after 4 weeks of training intervention. Another study of the same institute in stable CAD patients (n=17) [10] found a significant better mean left ventricular early diastolic strain rate after AIT,

but not in ACT; the conclusions from this study may be somewhat premature considering the very small sample size and the lack of improvement of more conventional indices of diastolic function. Previous larger studies that compared conventional medical treatment with ACT after AMI or PCI did neither show a clear benefit after training regarding systolic or diastolic function [8][9].

Our data confirm the findings of previous studies which showed that baseline indices of diastolic function (E/é) and systolic function (LVEF, left ventricular longitudinal systolic strain) are determinants of exercise capacity in CAD patients [4][24]. Several other studies did not observe these associations [25][26], but might have been limited by a small sample size. However, increase in peak VO_2 after training intervention in the present study did not correlate with changes of systolic or diastolic function. Consequently, increased exercise capacity after aerobic training does not seem to be mediated by eventual improvement of systolic or diastolic function in CAD patients without overt heart failure. *Conraads et al* [18] previously found a significant correlation between changes of peak VO_2 and changes of brachial artery flow-mediated dilation in our cohort of the SAINTEX-CAD study. Additionally, a higher amount of markers of worse endothelial health (endothelial microparticles) at baseline related inversely to changes in exercise capacity and flow-mediated dilation [27]. It seems therefore plausible that the main determinants of increased exercise capacity after cardiac rehabilitation in CAD patients without heart failure include endothelial factors, besides improved oxidative mechanisms in the skeletal muscle [23] and arterial compliance [28].

4.3 Limitations

First, systolic and diastolic function were assessed at rest. Left ventricular contractile reserve is a determinant of exercise capacity in CAD patients [26] and might play a role in improvement of exercise capacity after training intervention. Further studies with exercise

echocardiography are needed to elucidate the possible impact of exercise-based cardiac rehabilitation on left ventricular contractile reserve and its relationship with exercise capacity in CAD patients.

Second, LV dimensions and LVEF were measured by two-dimensional echocardiography in overweight patients (BMI 28 – 29) without the use of ultrasound contrast agents to improve endocardial border delineation.

Third limitation is underrepresentation of women in this cohort who tend to have different LV geometry to men, and so extrapolation of these findings to women may be problematic.

5. Conclusions

Our data did not reveal significant differences between AIT and ACT regarding their impact on left ventricular geometry, systolic or diastolic function. Improvement of exercise capacity after three months of training intervention in stable CAD patients was not related to alterations of conventional indices of systolic or diastolic function, although these parameters were correlated with peak VO_2 at baseline. We found a trend towards more reverse remodeling of the interventricular septum after ACT, and this remodeling was associated with increased peak VO_2 after three months of training.

Table 1. Demographic and clinical data study cohort at baseline.

	AIT (n=100)	ACT (n=100)	p-value
Demographic data			
Gender (M/F)	91/9	89/11	NS
Age (years)	57±9	60±9	p=0.023
Height (cm)	174±8	173±8	NS
Weight (kg)	85±14	85±14	NS
BMI (kg/m^2)	28.0±4.4	29±4	NS
Hypertension	58	46	NS
Diabetes	20	18	NS
Smoking (current/ex)	14/59	11/63	NS
LVEF (%)	57±9	57±8	NS
Reason for referral			
AMI	67	48	p=0.007
PCI	7	18	p=0.019
CABG	26	34	NS
Medication			
Aspirin	93	95	NS
Beta-blocker	84	83	NS
ACE inhibitor/ARB	77	72	NS
Diuretics	10	15	NS
Statin	97	99	NS
Digitalis	1	1	NS

Data are expressed as means ± standard deviation (SD) for continuous variables or as percentages for dichotomous variables. AIT, aerobic interval training ; ACT, aerobic continuous training ; n, number of patients ; M, male ; F, female ; NS, not significant ; BMI, body mass index ; LVEF, left ventricular ejection fraction ; AMI, acute myocardial infarction ; PCI, percutaneous coronary intervention ; CABG, coronary artery bypass grafting

Table 2. Correlations between peak VO_2 and parameters of left ventricular geometry, systolic function and diastolic function at baseline (n=194, left column) and between %changes in peak VO_2 and these parameters after three months of supervised exercise training (n=164, right column)

	Peak VO2, mL/kg/min			%Δ Peak VO2, mL/kg/min	
	r	p-value		r	p-value
LV geometry			*LV geometry*		
IVS (mm)	-0.126	0.084	%Δ IVS (mm)	-0.220	0.005
PW (mm)	-0.220	0.002	%Δ PW (mm)	-0.084	NS
LVEDD (mm)	0.029	NS	%Δ LVEDD (mm)	0.129	0.107
LVESD (mm)	-0.079	NS	%Δ LVESD (mm)	-0.007	NS
LVEDV (ml)	-0.041	NS	%Δ LVEDV (ml)	0.240	0.007
LVESV (ml)	0.085	NS	%Δ LVESV (ml)	0.176	0.050
Systolic function			*Systolic function*		
LVEF (%)	0.207	0.008	%Δ LVEF (%)	-0.014	NS
GLS (%)	-0.167	0.043	%Δ GLS (%)	0.113	NS
VTI LVOT (cm)	0.102	0.169	%Δ VTI LVOT (cm)	0.192	0.018
Diastolic function			*Diastolic function*		
E (cm/s)	-0.257	<0.001	%Δ E (cm/s)	-0.042	NS
A (cm/s)	-0.194	0.008	%Δ A (cm/s)	0.005	NS
E/A	-0.026	NS	%Δ E/A	-0.061	NS
e' (cm/s)	0.079	NS	%Δ e' (cm/s)	-0.018	NS
E/e'	-0.240	0.001	%Δ E/e'	0.010	NS
DT (ms)	-0.053	NS	%Δ DT (ms)	0.069	NS
IVRT (ms)	0.187	0.010	%Δ IVRT (ms)	0.038	NS
SPAP (mmHg)	-0.287	0.002	%Δ SPAP (mmHg)	0.078	NS

LV, left ventricular ; IVS, interventricular septum thickness ; PW, posterior wall thickness ; EDD, end-diastolic dimension ; ESV, end-systolic dimension ; EDV, end-diastolic volume ; ESV, end-systolic volume ; EF, ejection fraction ; GLS, global longitudinal strain ; VTI LVOT, velocity-time integral left ventricular outflow tract ; DT, deceleration time ; IVRT, iso-volumetric relaxation time ; SPAP, systolic pulmonary artery pressure ; Δ, difference between parameter at baseline and

after three months of supervised exercise training

	AIT (n=81)		ACT (n=83)		F-value		
	0 weeks	3 months	0 weeks	3 months	Time	Group	Interaction
LV geometry							
IVS (mm)	10.2±2.0	10.1±2.0	10.4±1.9	9.5±1.3	6.41 *	1.57 NS	3.74 **
PW (mm)	9.4±1.9	9.5±1.5	9.5±1.5	9.1±1.4	0.92 NS	2.22 NS	1.68 NS
LVEDD (mm)	49.3±5.6	49.3±5.7	49.0±5.2	49.3±5.4	0.07 NS	0.70 NS	0.04 NS
LVESD (mm)	31.5±5.5	30.9±6.0	31.3±6.5	31.5±5.9	0.09 NS	1.16 NS	0.36 NS
LVEDV (ml)	103±28	100±27	96±26	97±23	0.11 NS	0.59 NS	0.47 NS
LVESV (ml)	46±16	43±15	41±13	41±13	0.54 NS	0.54 NS	0.55 NS
Systolic function							
LVEF (%)	56.7±8.7	57.5±8.0	57.0±6.9	57.7±6.4	0.68 NS	0.05 NS	0.00 NS
GLS (%)	-16.5±3.2	-17.3±3.3	-18.1±2.8	-18.2±2.6	1.05 NS	4.90 *	0.75 NS
VTI LVOT (cm)	21.6±3.3	22.2±3.6	21.7±4.5	22.7±4.1	4.00 *	0.25 NS	0.39 NS
Diastolic function							
E (cm/s)	71.3±19.6	70.2±19.4	69.8±17.8	69.5±21.0	0.10 NS	0.78 NS	0.03 NS
A (cm/s)	64.3±18.0	64.2±19.6	66.6±18.4	67.4±17.3	0.03 NS	0.95 NS	0.05 NS
E/A	1.19±0.52	1.18±0.56	1.11±0.42	1.07±0.35	0.18 NS	3.31 NS	0.05 NS
e' (cm/s)	7.31±2.33	7.36±2.25	7.50±2.55	8.07±2.81	1.30 NS	2.13 NS	0.93 NS
E/e'	10.6±4.8	10.7±5.7	10.0±3.4	9.6±3.9	0.10 NS	2.71 NS	0.23 NS
DT (ms)	173±49	188±57	195±57	194±58	1.42 NS	6.03 *	1.52 NS
IVRT (ms)	95.4±22.6	95.9±17.7	97.3±17.9	92.7±17.1	0.97 NS	0.03 NS	1.43 NS
SPAP (mmHg)	22.3±8.3	22.9±7.8	22.4±5.8	22.8±6.7	0.17 NS	0.24 NS	0.01 NS

Table 3. Parameters of left ventricular geometry, systolic function and diastolic function at baseline and after three months of AIT or ACT.

Data are expressed as means ± standard deviation (SD). All data are corrected for age and pathology. AIT, aerobic interval training ; ACT, aerobic continuous training ; n, number of patients ; NS, not significant ; HR, heart rate ; SBP, systolic blood pressure ; DBP, diastolic blood pressure ; LV, left ventricular ; IVS, interventricular septum thickness ; PW, posterior wall thickness ; EDD, end-diastolic dimension ; ESV, end-systolic dimension ; EDV, end-diastolic

volume ; ESV, end-systolic volume ; EF, ejection fraction ; GLS, global longitudinal strain ; VTI LVOT, velocity-time integral left ventricular outflow tract ; DT, deceleration time ; IVRT, iso-

	AIT (n=67)		ACT (n=65)		F-value		
	0 weeks	3 months	0 weeks	3 months	Time	Group	Interaction
LV geometry							
IVS (mm)	10.5±2.0	10.4±2.0	10.3±1.6	9.5±1.3	3.94 *	6.78 *	2.35 NS
PW (mm)	9.5±1.9	9.6±1.5	9.4±1.5	9.0±1.4	0.24 NS	4.79 *	1.47 NS
LVEDD (mm)	48.9±5.7	48.8±5.7	49.0±5.3	49.2±5.8	0.00 NS	1.69 NS	0.04 NS
LVESD (mm)	31.4±5.6	30.6±6.1	31.1±7.0	31.6±6.4	0.05 NS	1.50 NS	0.79 NS
LVEDV (ml)	104±29	99±27	96±26	97±23	0.21 NS	0.27 NS	0.76 NS
LVESV (ml)	45±16	42±15	41±13	42±13	0.27 NS	0.03 NS	0.84 NS
Systolic function							
LVEF (%)	56.9±8.5	57.8±7.8	57.4±6.9	57.3±6.6	0.12 NS	0.41 NS	0.24 NS
GLS (%)	-16.3±3.2	-17.2±3.4	-18.1±2.9	-18.1±2.8	0.96 NS	3.30 **	0.82 NS
VTI LVOT (cm)	21.9±4.6	23.0±4.1	21.9±4.6	23.0±4.1	2.04 NS	0.71 NS	0.60 NS
Diastolic function							
E (cm/s)	71.1±18.7	69.3±17.1	67.6±16.1	67.7±16.3	0.16 NS	1.77 NS	0.22 NS
A (cm/s)	64.8±17.6	65.1±19.5	65.4±16.9	67.4±17.6	0.26 NS	0.04 NS	0.15 NS
E/A	1.19±0.56	1.17±0.60	1.11±0.44	1.08±0.38	0.17 NS	1.46 NS	0.01 NS
e' (cm/s)	7.11±2.27	7.13±1.90	7.46±2.66	8.01±2.88	0.98 NS	4.04 *	0.83 NS
E/e'	10.8±4.3	10.3±3.6	10.0±3.4	9.7±4.2	0.53 NS	1.77 NS	0.06 NS
DT (ms)	177±49	190±54	196±62	197±62	0.92 NS	3.54 **	0.87 NS
IVRT (ms)	96.6±22.9	97.5±18.3	98.1±17.7	92.4±17.8	1.04 NS	0.08 NS	1.91 NS
SPAP (mmHg)	22.4±8.9	23.4±8.1	22.4±5.8	22.6±7.3	0.21 NS	0.41 NS	0.08 NS

volumetric relaxation time ; SPAP, systolic pulmonary artery pressure. * $p<0.05$; ** $p=0.05$.

Table 4. Parameters of left ventricular geometry, systolic function and diastolic function at baseline and after three months of AIT or ACT in patients without change of beta-blocker dose.

Data are expressed as means ± standard deviation (SD). All data are corrected for age and pathology. AIT, aerobic interval training ; ACT, aerobic continuous training ; n, number of patients ; NS, not significant ; HR, heart rate ; SBP, systolic blood pressure ; DBP, diastolic blood pressure ; LV, left ventricular ; IVS, interventricular septum thickness ; PW, posterior wall

thickness ; EDD, end-diastolic dimension ; ESV, end-systolic dimension ; EDV, end-diastolic volume ; ESV, end-systolic volume ; EF, ejection fraction ; GLS, global longitudinal strain ; VTI LVOT, velocity-time integral left ventricular outflow tract ; DT, deceleration time ; IVRT, iso-volumetric relaxation time ; SPAP, systolic pulmonary artery pressure. * p<0.5 ; ** p<0.1.

Declaration of Conflicting Interests

All authors declare that there is no conflict of interest

Author Contributions

CMVDH, NPattyn, EMVC and BS drafted the manuscript. CDM, NPattyn, PB, VAC, EMVC, JUV, LV and BS conception and design of research; CDM, NPattyn, KG and NPossemiers acquired and collected data; CMVDH, CDM, NPattyn, EMVC and BS analyzed and interpreted data; CDM, PB, VAC, KG, NPossemiers, JUV and LV edited and revised the manuscript; all authors approved final version of manuscript.

References

[1] L. Anderson, N. Oldridge, D.R. Thompson, A.-D. Zwisler, K. Rees, N. Martin, R.S. Taylor, Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis, J Am Coll Cardiol. 67 (2016) 1–12.

[2] L. Vanhees, R. Fagard, L. Thijs, A. Amery, Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery, Am J Cardiol. 76 (1995) 1014–1019.

[3] J. Grewal, R.B. McCully, G.C. Kane, C. Lam, P.A. Pellikka, Left ventricular function and exercise capacity, JAMA. 301 (2009) 286–294.

[4] R. Fontes-Carvalho, F. Sampaio, M. Teixeira, F. Rocha-Gonçalves, V. Gama, A. Azevedo,

A. Leite-Moreira, Left ventricular diastolic dysfunction and E/E ratio as the strongest echocardiographic predictors of reduced exercise capacity after acute myocardial infarction, Clin Cardiol. 38 (2015) 222–229.

[5] U. Corrà, M.F. Piepoli, F. Carré, P. Heuschmann, U. Hoffmann, M. Verschuren, J. Halcox, Secondary prevention through cardiac rehabilitation: Physical activity counselling and exercise training, Eur Heart J. 31 (2010) 1967–1974.

[6] A.D. Elliott, K. Rajopadhyaya, D.J. Bentley, J.F. Beltrame, E.C. Aromataris, Interval training versus continuous exercise in patients with coronary artery disease: a meta-analysis, Heart Lung Circ. 24 (2015) 149–157.

[7] U. Wisløff, A. Støylen, J.P. Loennechen, M. Bruvold, Ø. Rognmo, P.M. Haram, A.E. Tjønna, J. Helgerud, S.A. Slørdahl, S.J. Lee, V. Videm, A. Bye, G.L. Smith, S.M. Najjar, Ø. Ellingsen, T. Skjærpe, Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study, Circulation. 115 (2007) 3086–3094.

[8] C.-M. Yu, L.S.-W. Li, M.-F. Lam, D.C.-W. Siu, R.K.-M. Miu, C.-P. Lau, Effect of a cardiac rehabilitation program on left ventricular diastolic function and its relationship to exercise capacity in patients with coronary heart disease: Experience from a randomized, controlled study, Am Heart J. 147 (2004) e24.

[9] R. Fontes-carvalho, A.I. Azevedo, F. Sampaio, M. Teixeira, N. Bettencourt, L. Campos, F.R. Gonçalves, V.G. Ribeiro, A. Azevedo, A. Leite-moreira, The effect of exercise training on diastolic and systolic function after acute myocardial infarction: a randomized study, Medicine. 94 (2015) e1450.

[10] B.H. Amundsen, Ø. Rognmo, G. Hatlen-Rebhan, S.A. Slørdahl, High-intensity aerobic exercise improves diastolic function in coronary artery disease, Scand Cardiovasc J. 42 (2008) 110–117.

[11] T.T. Moholdt, B.H. Amundsen, L.A. Rustad, A. Wahba, K.T. Løvø, L.R. Gullikstad, A. Bye, E. Skogvoll, U. Wisløff, S.A. Slørdahl, Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: A randomized study of cardiovascular effects and quality of life, Am Heart J. 158 (2009) 1031–1037.

[12] V.M. Conraads, E.M. Van Craenenbroeck, N. Pattyn, V.A. Cornelissen, P.J. Beckers, E. Coeckelberghs, C. De Maeyer, J. Denollet, G. Frederix, K. Goetschalckx, V.Y. Hoymans, N. Possemiers, D. Schepers, B. Shivalkar, L. Vanhees, Rationale and design of a randomized trial on the effectiveness of aerobic interval training in patients with coronary artery disease: The SAINTEX-CAD study, Int J Cardiol. 168 (2013) 3532–3536.

[13] W.M.A.G. Assembly, World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects, J Int Bioethique. 15 (2004) 124–129.

[14] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F.A. Flachskampf, E. Foster, S.A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M.H. Picard, E.R. Rietzschel, L. Rudski, K.T. Spencer, W. Tsang, J.U. Voigt, Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J Am Soc Echocardiogr. 28 (2015) 1–39.

[15] J.U. Voigt, G. Pedrizzetti, P. Lysyansky, T.H. Marwick, H. Houle, R. Baumann, S. Pedri, Y.

Ito, Y. Abe, S. Metz, J.H. yun Song, J. Hamilton, P.P. Sengupta, T.J. Kolias, J. D'Hooge, G.P. Aurigemma, J.D. Thomas, L.P. aolo Badano, Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging, Eur Heart J Cardiovasc Imaging. 16 (2015) 1–11.

[16] S.F. Nagueh, C.P. Appleton, T.C. Gillebert, P.N. Marino, J.K. Oh, O.A. Smiseth, A.D. Waggoner, F.A. Flachskampf, P.A. Pellikka, A. Evangelisa, Recommendations for the evaluation of left ventricular diastolic function by echocardiography, Eur J Echocardiogr. 10 (2009) 165–193.

[17] L.G. Rudski, W.W. Lai, J. Afilalo, L. Hua, M.D. Handschumacher, K. Chandrasekaran, S.D. Solomon, E.K. Louie, N.B. Schiller, Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography, J Am Soc Echocardiogr. 23 (2010) 685–713.

[18] V.M. Conraads, N. Pattyn, C. De Maeyer, P.J. Beckers, E. Coeckelberghs, V.A. Cornelissen, J. Denollet, G. Frederix, K. Goetschalckx, V.Y. Hoymans, N. Possemiers, D. Schepers, B. Shivalkar, J.U. Voigt, E.M. Van Craenenbroeck, L. Vanhees, Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: The SAINTEX-CAD study, Int J Cardiol. 179 (2015) 203–210.

[19] M. Haykowsky, J. Scott, B. Esch, D. Schopflocher, J. Myers, I. Paterson, D. Warburton, L. Jones, A.M. Clark, A meta-analysis of the effects of exercise training on left ventricular remodeling following myocardial infarction: start early and go longer for greatest

exercise benefits on remodeling, Trials. 12 (2011) 92.

[20] G. McGregor, D. Gaze, D. Oxborough, J. O'Driscoll, R. Shave, Reverse left ventricular remodelling – effect of cardiac rehabilitation exercise training in myocardial infarction patients with preserved ejection fraction, Eur J Phys Rehabil Med. 52 (2016) 370–378.

[21] K. Soleimannejad, Y. Nouzari, A. Ahsani, M. Nejatian, K. Sayehmiri, Evaluation of the effect of cardiac rehabilitation on left ventricular diastolic and systolic function and cardiac chamber size in patients undergoing percutaneous coronary intervention, J Tehran Heart Cent. 9 (2014) 54–58.

[22] J. Helgerud, K. Høydal, E. Wang, T. Karlsen, P. Berg, M. Bjerkaas, T. Simonsen, C. Helgesen, N. Hjorth, R. Bach, J. Hoff, Aerobic high-intensity intervals improve VO2max more than moderate training, Med Sci Sports Exerc. 39 (2007) 665–671.

[23] F.C. Mooren, J. Viereck, K. Kruger, T. Thum, Circulating microRNAs as potential biomarkers of aerobic exercise capacity, Am J Physiol Heart Circ Physiol. 306 (2014) H557-63.

[24] N.R. Van de Veire, O. De Winter, J. Philippé, M. De Buyzere, D. Bernard, M. Langlois, T.C. Gillebert, J. De Sutter, Maximum oxygen uptake at peak exercise in elderly patients with coronary artery disease and preserved left ventricular function. The role of inflammation on top of tissue Doppler-derived systolic and diastolic function, Am Heart J. 152 (2006) 297.e1-7.

[25] E. Aslanger, B. Assous, N. Bihry, F. Beauvais, D. Logeart, A. Cohen-Solal, Association between baseline cardiovascular mechanics and exercise capacity in patients with

coronary artery disease, Anatol J Cardiol. 16 (2016) 608–613.

[26] D.A. Morrison, J.R. Stovall, C. Barbiere, Left and right ventricular systolic function and exercise capacity with coronary artery disease, Am J Cardiol. 67 (1991) 1079–1083.

[27] E.M. Van Craenenbroeck, G. Frederix, N. Pattyn, P. Beckers, A.H. Van Craenenbroeck, A. Gevaert, N. Possemiers, V. Cornelissen, K. Goetschalckx, C.J. Vrints, L. Vanhees, V.Y. Hoymans, Effects of aerobic interval training and continuous training on cellular markers of endothelial integrity in coronary artery disease: A SAINTEX-CAD substudy, Am J Physiol Heart Circ Physiol. 309 (2015) H1876–H1882.

[28] E. Aslanger, B. Assous, N. Bihry, F. Beauvais, D. Logeart, A. Cohen-Solal, Value of baseline cardiovascular mechanics in predicting exercise training success, J Cardiopulm Rehabil Prev. 36 (2016) 240–249.