



Safety and effectiveness of home-based, self-selected exercise training in symptomatic adults with congenital heart disease: A prospective, randomised, controlled trial

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ABSTRACT

Background: The purpose of this prospective randomised controlled trial was to assess whether home-based, self-selected exercise training is safe, results in high compliance and improves exercise capacity in symptomatic adults with congenital heart disease (CHD).

Methods: Forty adults with moderate or severe CHD (40 ± 12 years, 56% male, New York Heart Association [NYHA] II/III 37/3) were randomly assigned, stratified by CHD complexity, either to home-based exercise training or usual care. The exercise training protocol consisted of three exercise sessions per week for six consecutive months. Patients were free to choose any sports of their preference.

Results: Thirty-four patients (each randomisation group $n = 17$) completed the protocol and were analysed. The majority was involved in high-dynamic sports (76%); none had to discontinue the training programme due to exercise-related adverse events. More than 70% adhered to the exercise programme at or above the target training level. Peak VO_2 increased significantly in the exercise group by $+1.7 \pm 2.7 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$ ($p = 0.025$), whereas it remained unchanged in the control group by $+0.8 \pm 2.2 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$ ($p = 0.184$). No significant changes were found in serum N-Terminal pro-brain natriuretic peptide levels or quality of life in either randomisation group or between groups.

Conclusions: In symptomatic adults with moderate or severe CHD, home-based exercise training of their preference appeared safe, with good compliance and favourable effects on exercise capacity. Our results demonstrate that it is appropriate to stimulate our patients to regularly perform moderate to vigorous physical activities, in absence of medical restrictions.

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1. Introduction

Previous studies in adults with congenital heart disease (CHD) have shown favourable effects in the majority of patients participating in exercise training programmes—increasing exercise capacity and quality of life [1–3]. Nevertheless, many patients with CHD are physically inactive [4]. This may be due to low confidence [5], as many perceive their symptoms and fear of health issues as the major limitation that prevents them from exercising [6]. On the other hand, patients were previously often encouraged towards a more sedentary lifestyle as a result of environmental overprotection and uncertainty of practitioners regarding the potential harmful effects of exercise [7]. Previous studies on exercise

training generally included merely asymptomatic patients with CHD [3,8]. Consequently, the effects—*beneficial* or *harmful*—of exercise training in symptomatic CHD patients remain largely unknown.

In acquired heart failure, numerous studies have established unequivocally that regular exercise is related to better long-term prognosis and reduced risk of cardiovascular death [9]. Recently, home-based exercise training programmes have been introduced to increase access and reach a broader range of patients. It is anticipated that home-based exercise programmes enhance patients' self-efficacy and facilitate a lifelong implementation of regular physical activity, with increased adherence, since it takes into consideration the preference of the individual patient. Indeed, Swan et al. showed that home-based exercise programmes could be similarly effective in improving clinical and health-related quality of life compared to supervised rehabilitation programmes, with evidence of marginally higher levels of programme completion and adherence up to one year [10].

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The major challenge for the *symptomatic* adult CHD population remains to ensure safe participation in regular physical activity in order to avoid the detrimental effects associated with sedentary lifestyle [11]. Currently, limited data are available on exercise prescription in regards to safety, feasibility, and efficacy. Therefore, the aim of the Exercise Training in Grown-Ups with Congenital Heart Disease (EXTRA-GUCH) trial was to evaluate the safety and effectiveness of home-based, unsupervised, self-selected, long-term exercise training in symptomatic adults with moderate to severe CHD.

2. Methods

2.1. Trial design

This study was a prospective, single-centre, parallel group, randomised controlled trial performed in a tertiary care hospital in The Netherlands. The study complies with the Declaration of Helsinki and the research protocol was approved by the local Ethics Committee. All patients provided written informed consent prior to randomisation. The trial was registered at clinicaltrials.gov (NCT02825472).

2.2. Study population

Eligible patients were adults with CHD and New York Heart Association (NYHA) class II or III symptoms, included in the CONgenital CORvitia database, the Dutch nationwide registry and DNA-bank for adults with CHD. Medical records were reviewed to determine NYHA class, and in case of uncertainty, patients were contacted personally. Exclusion criteria were NYHA class I or IV, presence of exercise-induced arrhythmia, major comorbidities or limitations that could interfere with exercise training, recent (≤ 6 months) major cardiovascular events or procedures, cyanosis at rest, a resting blood pressure >200 mm Hg and/or diastolic blood pressure >110 mm Hg, pregnancy (wish) or mental or physical incapability to participate in a home-based exercise training programme.

2.3. Outcome and assessments

All patients received the same number of examinations at baseline and 6 months after randomisation. Examinations included medical history, current medication use, physical examination, 12-lead electrocardiography, cardiopulmonary exercise testing (CPET), biochemical analysis and quality of life questionnaires.

CPETs were performed according to the guidelines of the American Thoracic Society [12], using a cycle ergometer (Corival CPET, Lode BV, The Netherlands). Sample line and turbine were changed prior to each test to prevent clogging by humidity and maintain hygiene, followed by flow and gas calibration according to the manufacturer's specifications. After 3 min of rest, unloaded pedalling for 3 min was performed followed by a linear increase in workload, which was estimated based on the w/kg method as described by Nowacki [13]. All patients were exercised until exhaustion, followed by active recovery for 5 min. Maximal exercise capacity was determined via a breath-by-breath gas analysis system (Cosmed Quark PFT, Rome, Italy) using a bidirectional 28 mm digital turbine. Continuous measurements of minute ventilation, oxygen consumption, carbon dioxide production, 12-lead electrocardiography and blood pressure and blood oxygenation were performed during the test. Omnia 1.4. software (COSMED Srl, Italy) was used for raw breath-by-breath data collection, processing and analysis. The same experienced team performed all examinations and measurements. Test results at baseline were reviewed by investigators to identify significant arrhythmias or ischemia that would prevent safe exercise training, and determine appropriate heart rate ranges for exercise training.

Blood samples for N-terminal probrain natriuretic peptide (NT-proBNP) were collected 30 min before CPET.

Quality of life was assessed in both groups by the Medical Outcomes Study Short Form 36 item (SF-36) health survey [14] and CHD-TNO/AZL Adult Quality of Life (CHD-TAAQOL) questionnaire [15].

The primary safety outcome was a composite of all-cause mortality or all-cause hospitalization during or within 3 h after exercise. The secondary safety outcome was a composite of all exercise related injuries for which medical consultation was necessary. Primary efficacy endpoint was the change in peak VO_2 from baseline to 6 months between patients from the randomisation groups. Secondary endpoints were the changes in serum NT-proBNP levels and health-related quality of life.

2.4. Randomisation and intervention

After informed consent, patients were randomly assigned to either an exercise group or control group using a block randomisation scheme, stratified by CHD severity (simple/moderate vs. severe complexity [16]).

Patients randomised to the exercise group were assigned to a home-based exercise training programme, with a target training regimen of minimum 3 sessions of 45 min per week for the duration of six consecutive months. In order to individualize training intensity, the maximal 80% of heart rate reserve was determined during the baseline CPET. Patients in the exercise group were provided heart rate monitors (Beurer GmbH, Ulm, Germany) to verify that their training programme was within the predetermined submaximal heart rate range. Training sessions and compliance was monitored and documented

using patient diaries and email follow-up at 3 months, respectively. To further enhance patients' compliance and facilitate implementation of regular physical activity into their daily lives, patients were encouraged to choose (a variety of) sports of their preference.

Patients randomised to the control group did not receive any formal advice on exercise training, and were neither encouraged, nor discouraged to participate in sports. All patients were asked to continue habitual daily activities, even if these included regular physical exercise.

2.5. Statistical analysis

Sample size calculation was based on the primary endpoint of change in peak VO_2 . Assuming a standard deviation of $3.3 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$, 20 patients per group were required to detect a difference of $3 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$ between the two randomisation groups after six months (2-sided α of 0.05, 80% power).

Descriptive data were summarized as number with percentage, mean \pm standard deviation, or median with interquartile range (IQR), as appropriate. Baseline differences between the treatment groups were tested with the independent student *t*-test or Chi-square test. The primary analysis included all patients who completed the 6 months follow-up. Within subject comparisons were performed by paired Student *t*-tests or Wilcoxon signed-rank tests, as appropriate. Differences in the main efficacy outcomes measures were performed by regression analysis including baseline values and CHD severity and the interaction terms with treatment allocation as independent variables in order to obtain the correct standard error. Statistical analyses were performed using SPSS 24.0 (SPSS, Inc., Chicago, IL, USA) and Rstudio (R Project for Statistical Computing, Vienna, Austria). A two-tailed *p*-value of 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Forty adults with CHD and NYHA II/III were enrolled and randomly assigned (Fig. 1). The patient characteristics are summarized in Table 1. The exercise and control groups had similar baseline characteristics including age, CHD severity, NYHA classification, or medication. In addition, there were no significant differences in any of the outcome variables between the randomisation groups at baseline (e.g., non-significant difference in peak VO_2 , $p = 0.212$, and NT-proBNP levels, $p = 0.260$). In total, 34 patients completed the follow-up ($n = 17$ in each randomisation group). The primary reasons for withdrawal were related to the time consuming nature of the training programme ($n = 3$) or personal/health reasons (not cardiovascular related) ($n = 2$).

3.2. Compliance to exercise programme

Patients in the exercise training group reportedly exercised for a median of 2.5 h per week. Thirteen of the 17 patients in the exercise training group exercised at or above the target training level of $2 \frac{1}{4}$ h per week. The remaining four patients exercised at least 1 h per week. The main reason patients could not fully adhere to the training regimen was lack of time related to work or family commitments.

3.3. Characteristics of sports preference

The types of sports performed by patients in the exercise group are displayed in Fig. 2. The majority of patients engaged in high-dynamic sports (76%) and a small subset of those patients (23%) practiced sports both at the highest static and dynamic level, such as rowing, cycling and ice-skating.

3.4. Safety

Performance of exercise training was well tolerated. No patient experienced a cardiovascular event that occurred during or within 3 h after training. Three patients experienced minor exercise related injuries for which medical consultation was necessary, such as knee sprain, mild palpitations (no arrhythmia was objectified) or minor head injury. At follow-up CPET, one patient from the exercise group experienced a self-limiting supraventricular arrhythmia (<1.5 min) during the recovery phase and low-dose β -blocker was initiated,

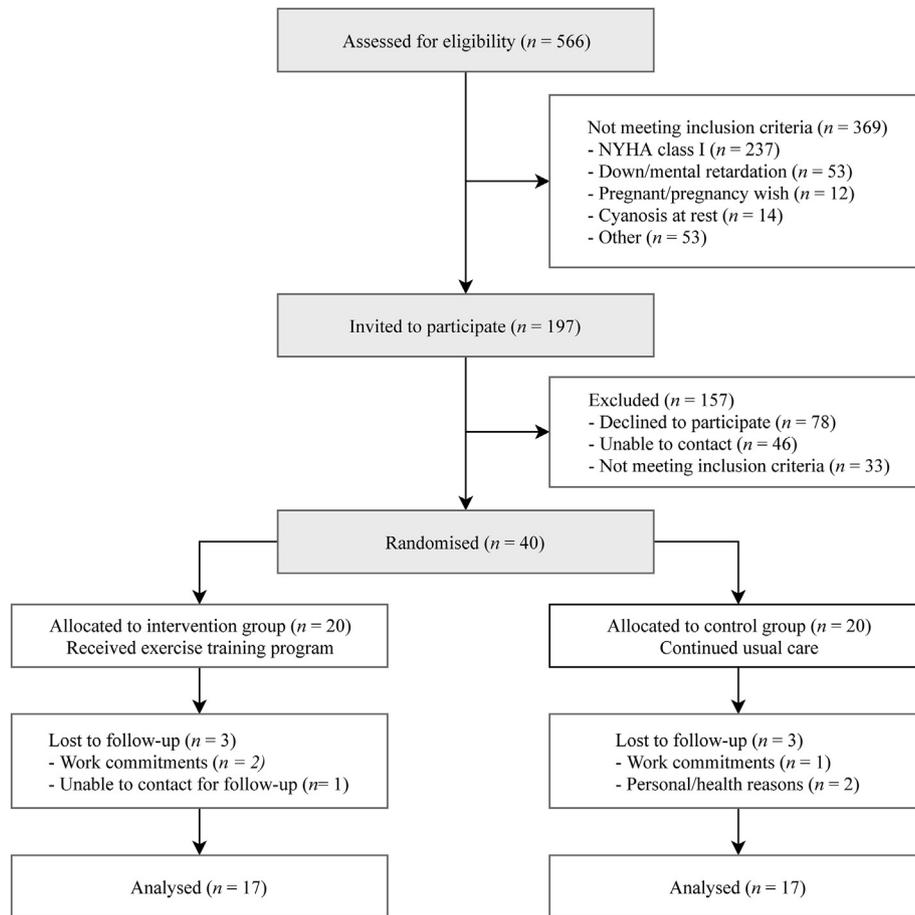


Fig. 1. Flowchart of included patients.

another patient from the exercise group had sporadic multiform ventricular premature complexes during exercise and recovery, which were treated conservatively. NYHA class in one patient from the

control group deteriorated from II to III, whereas one patient from the exercise group improved from II–III to II.

Table 1
Baseline characteristics.

Characteristics	Exercise group (n = 20)	Control group (n = 20)
Age (years)	39.9 ± 8.6	40.0 ± 15.4
Sex, male	9 (45%)	13 (65%)
Body surface area (m ²)	3.78 ± 0.89	3.48 ± 0.79
NYHA class II/III	19/1	18/2
Pacemaker in situ	3 (15%)	3 (15%)
ICD in situ	4 (20%)	1 (5%)
CHD complexity ^a		
Moderate	9	6
Severe	11	14
CHD diagnosis		
Tetralogy of Fallot	7	5
Transposition of the great arteries	8	5
Fontan circulation	2	7
Pulmonary atresia	1	2
Other	2	1
Previous surgical intervention	20 (100%)	17 (85%)
Medication		
β-blocker	8 (40%)	8 (40%)
ACE-i/ATII	6 (30%)	4 (20%)
Diuretics	2 (10%)	3 (15%)
Anti-arrhythmic drugs	1 (5%)	5 (25%)
No medication	6 (30%)	6 (30%)

Data are mean ± standard deviation, n (%) or n/n.

ACE-i = angiotensin converting enzyme inhibitor; ATII = angiotensin II receptor antagonist; CHD = congenital heart disease; ICD = implantable cardiac defibrillator; NYHA = New York Heart Association.

^a Classification according to Warnes et al. [16].

3.5. Cardiopulmonary exercise tests

Peak VO_2 significantly improved in the training group by $+1.6 \pm 2.7 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$ (equals increase relative to baseline +7%, $p = 0.025$), whereas the peak VO_2 remained unchanged in the control group $+0.8 \pm 2.2 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$ (equals increase relative to baseline +3%, $p = 0.184$, Fig. 3 and Supplementary Table 1). However, there was no significant difference in increase of peak VO_2 between the randomisation groups ($p = 0.056$). Predicted percentage of peak VO_2 and test duration also significantly increased with training (mean change $5 \pm 9\%$ predicted peak VO_2 , $p = 0.037$, and $00:33 \pm 0:34 \text{ min}$, $p = 0.001$). There was also a trend towards higher peak blood pressure and oxygen pulse after training (Supplementary Table 1). In subgroup analyses, trained patients with severe CHD complexity ($n = 9$) significantly improved their peak VO_2 whereas trained patients with moderate CHD complexity ($n = 8$) showed no improvement (mean change $3.0 \pm 1.9 \text{ vs. } -0.04 \pm 2.5 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$, $p = 0.012$). Also, patients who exercised at or above the target training level ($n = 13$) showed a larger increase in peak VO_2 compared to those who exercised less ($n = 4$) (mean change $+2.2 \pm 2.7 \text{ vs. } -0.2 \pm 1.5 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$, $p = 0.121$).

3.6. Laboratory tests

No significant changes in serum NT-proBNP levels during follow-up in the exercise or control group were observed, nor between the randomisation groups (change 0 (IQR -106 - 26) vs. 3 (IQR - 37 - 47) ng/L respectively, $p = 0.168$ between groups).

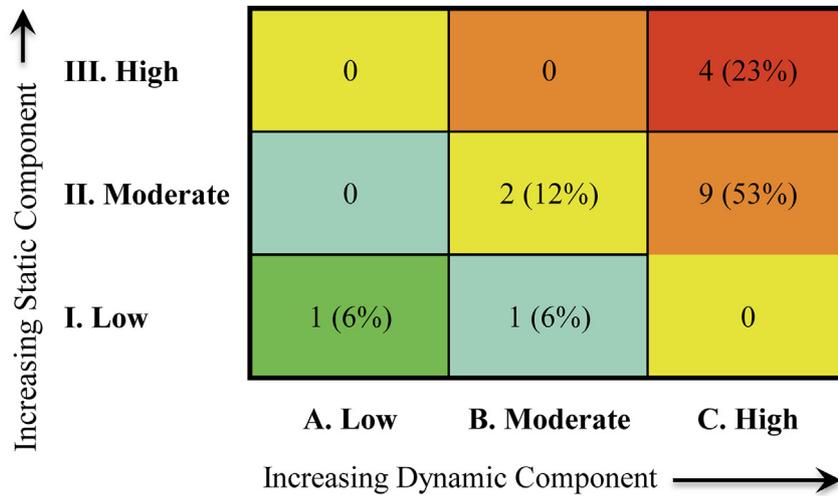


Fig. 2. Classification of sports participations. The figure is adapted from the study of Mitchell et al. [29].

3.7. Quality of life

Quality of life assessed by the SF-36 and CHD-TAAQOL questionnaires remained unchanged during follow-up and was similar in the exercise and control group (Supplementary Figs. 1 and 2).

4. Discussion

This study is the first randomised controlled trial of exercise training performed solely in symptomatic (NYHA II and III) adults with CHD and the first to investigate a home-based, self-selected exercise programme in this population. The key finding is that many different types of (strenuous) exercise can be performed safely at home without medical

supervision. Our data reinforce that most sports are safe and beneficial even in symptomatic patients with complex CHD.

4.1. Exercise training in heart failure

Exercise training is a well-established adjunct therapy in acquired heart failure. Substantial evidence shows that exercise markedly affects the prognosis, reducing mortality and hospitalizations, but also improving functional capacity, exercise duration, and health-related quality of life [9,17]. Accordingly, the American and European heart failure guidelines have recognized exercise training or regular physical activity at a class I level A [18,19]. Although the rationale behind the benefits of physical exercise seems equally applicable to the CHD population with heart failure, the body of evidence in this patient population is far less

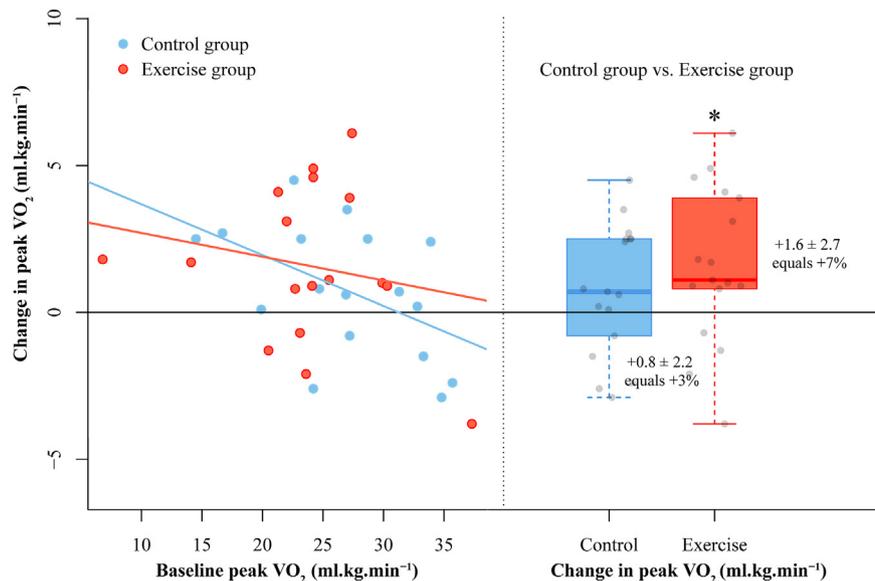


Fig. 3. Change in peak VO_2 . Left graph shows peak VO_2/kg at baseline (x-axis), and change of peak VO_2/kg from baseline after 6 months (y-axis). The blue circles represent patients of the control group, and the red circles represent patients of the exercise group. The solid lines display the regression lines for each group respectively. Change in peak VO_2/kg correlated with baseline peak VO_2/kg in the control group ($r = 0.489$, $p = 0.046$), but not in the exercise group ($r = 0.201$, $p = 0.440$). Right graph shows the change of peak VO_2/kg in the control vs. exercise group after 6 months. A significant increase in peak VO_2 is demonstrated in the exercise group ($p = 0.025$), whereas the control group shows a small improvement ($p = 0.184$). *Difference between the randomisation groups was not significant ($p = 0.056$).

considerable and practitioners have been reluctant to encourage patient with CHD to participate in exercise training. In a recent review of exercise training in symptomatic CHD patients [3], only 3 studies were reported to include symptomatic patients (a total of 57 individuals, age range 18–63 years); another six studies included both asymptomatic and symptomatic patients. All studies described positive effects in exercise capacity and quality of life, but only evaluated traditional supervised rehabilitation or walking programmes with a short duration (10–15 weeks). Studies with longer-term, non-supervised, high intensity training programmes and/or self-selected sports participation had not yet been performed.

4.2. Safety concerns

Ideally, regular physical exercise in adults with CHD should be performed in the home setting, without medical supervision, as an integrated part of daily life. The uncertainty and safety concerns regarding the risk of sudden cardiac death has led to exercise restrictions in patients with CHD, despite none of the previous trials in CHD reporting serious adverse events related to exercise training [3,4,20]. Similarly, we observed no major cardiovascular events in symptomatic and complex CHD patients, in spite of the unsupervised programme and 76% of patients engaging in high-dynamic sports and a small proportion (23%) practicing both high-dynamic and -static sports. Based on a large multinational registry, including 25,790 adults with CHD, Koyak et al. [21] reported that only 17 of the identified 171 sudden cardiac deaths (10%) occurred during exercise (~1.5% of overall proportion of 1189 deaths). Reassuringly, these relatively low rates of exercise-related mortality in adults with CHD are further supported by a Dutch nationwide study, reporting that sudden cardiovascular death occurred during exercise in 8% of the 70 cases among 8000 adults with CHD [22]. In comparison, in the general population the overall burden of sports-related sudden death is 4.6 cases per million per year, with an overwhelming majority occurring among those older than 35 years [23]. Taking together the available evidence, it should be noted that the individual risk of sudden cardiac death during exercise training appears to be relatively low in adults with CHD. Moreover, a growing number of CHD patients nowadays reach older age and will consequently succumb to acquired cardiovascular disease. Therefore, the cardioprotective effects of physical activity are becoming increasingly important and should be weighed against the potential risks [24].

4.3. Exercise effects

Our results show beneficial effects on exercise capacity in patients stimulated to regularly engage in home-based exercise. However, we observed individual variability in the ultimate responses, with four non-responders among those with an insufficient training stimulus. This may explain the overall relative low gain in peak VO_2 in the exercise group (1.6 vs. average 2.6 $\text{ml}\cdot\text{kg}\cdot\text{min}^{-1}$ in previously reported studies [20]). In addition, we observed a small improvement in peak VO_2 in the control group potentially due to either increased exercise training by these patients, who were reminded of the importance of exercise training when invited to participate. Notwithstanding the observed moderate improvements of exercise capacity, we believe our data support the findings from other studies that, given an adequate training stimulus, the vast majority of individuals will show a clear physiological response to exercise training. Interestingly, we observed a greater improvement in exercise capacity within patients with severe CHD compared to those with moderate CHD, even though most characteristics were comparable between the two groups (Supplementary Table 2). This may be explained by the age-associated difference in response to exercise training, as patients with severe CHD were almost 15 years younger. Previously Woo et al. [25] described that elderly healthy persons were not able to increase their peak VO_2 by training to the same

degree as their younger counterparts, probably due to limitations in maximal heart rate and diastolic filling rates.

4.4. Individualized exercise prescription

Long-term uptake of and adherence to physically active lifestyle remains challenging [26]. We hypothesized that when choosing one's own sports programme, this would improve patients' adherence and facilitate easier implementation of regular physical activity into their daily lives. Although our results support encouragement of patients to practice different kinds of sports and enjoy a physically active lifestyle, exercise prescription may not always be as straightforward, and both individual risk factors and the nature and intensity of the intended sport should be weighed when advising patients. In this regard, we would like to stress the importance of individual sports consultation. The Working Group on Grown-up Congenital Heart Disease of the European Society of Cardiology has recently published concise and practical recommendations regarding this subject [11]. Budts et al. [11] herein present a step-wise structured approach to establish an individualized exercise prescription based on clinical experience and exclusion of high risk features for arrhythmias, complications, and death. This systematic approach should not only further reduce the risk of events, but also help overcome the uncertainties of physicians, patients and their families, and instructors supervising their sporting activities.

4.5. Limitations

Our study has several limitations. The study was conducted at a single-centre hospital and the sample size was small, although reasonable compared with prior studies. As such, our study had limited power and the results on safety should be interpreted with caution. Although we aimed to include equal numbers of NYHA II and III patients, most patients were only mildly symptomatic which may limit the generalizability of our results to symptomatic patients. It is noteworthy that one-third of our cohort had higher peak VO_2 values than expected based on their NYHA class, limiting the possibility to significantly improve their exercise capacity. While this may appear surprising, we acknowledge that NYHA classification relies heavily on subjective perception of symptoms, and, thus, may lead to both underestimation as well as overestimation of the severity of physical limitation. Indeed, Lim et al. [27] reported in a systemic review, involving 2645 patients, that despite a general inverse correlation between NYHA class and peak VO_2 , large heterogeneity in peak VO_2 existed within each NYHA class. Moreover, Diller et al. [28] observed a widespread distribution in peak VO_2 , ranging from <10 to >50 $\text{ml}\cdot\text{kg}\cdot\text{min}^{-1}$, in allegedly asymptomatic adult CHD patients. The exercise training protocol was home-based, which makes verification of compliance difficult. However, previous studies have established that home-based exercise can be as effective as supervised, centre-based exercise programmes, with high compliance [10]. Because of the nature of the intervention, an important limitation of all studies on exercise training is that it is not possible to blind patients to treatment assignment. The motivation of the patients randomised to the exercise group could influence the final performance of the exercise test, and the self-reported outcomes and patients' lifestyle. On the other hand, this unavoidable bias could be considered paradoxically as one of the favourable components of the training programme. Lastly, we did not investigate the effect of strength training or high-intensity training as separate entities, as patient numbers did not allow for such subgroup analyses. Future clinical trials will need to further address the different components of training programmes, including this distinction between types of training, and the intensity and duration, but also need to consider the generalisability of trial populations (spectrum of CHD; more severe heart failure symptoms) and interventions to enhance the longer-term maintenance of exercise training.

5. Conclusions

In symptomatic adults with CHD, home-based, self-selected exercise training was safe and associated with good compliance and beneficial effects on exercise capacity. Our results demonstrate that it is appropriate to stimulate our patients to regularly perform moderate to vigorous physical activities, in absence of medical restrictions. Although our study raises no major safety concerns, recommendations for practicing sports should always take the unique medical history of the patient into consideration.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.12.042>.

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