

ARTICLE

Effect of Exercise-Based Cardiac Rehabilitation on Cardiorespiratory Fitness in Adults with Congenital Heart Disease

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ABSTRACT

Background: The purpose of this study was to investigate whether patients with adult congenital heart disease (ACHD) benefit from exercise-based cardiac rehabilitation (CR) short- and long-term with regard to improvement of cardiorespiratory fitness. **Methods:** Cardiopulmonary exercise tests (CPET) completed by ACHD patients between January 2000 and October 2019 were analysed retrospectively. Linear mixed models were performed for peak oxygen consumption (VO_2) with patients as random effect and age, sex, disease classification, preceding surgery (≤ 3 months) and preceding CR (≤ 4 weeks for short term and >4 weeks for long term) as fixed effects. **Results:** 1056 CPETs of 311 ACHD patients with simple (7), moderate (188) or great (116) complexity heart defects were analysed. The 59 patients who completed a CR (median age 27 yrs, 38% females) increased peak VO_2 from before to after CR by a median of 2.7 (IQR -0.6 to 5.5) ml/kg/min. However, in the multivariate mixed model, peak VO_2 was non-significantly increased short-term after CR (β 0.8, 95%CI -0.7 to 2.4), not maintained long-term after CR (β 0.0, 95%CI -1.7 to 1.6) but significantly reduced after surgery (β -5.1, 95%CI -7.1 to -3.1). The 20 CR patients after surgery increased their peak VO_2 by 6.2 (IQR 3.6-9.5) ml/kg/min, while the 39 CR patients without preceding surgery increased it by 0.9 (IQR -1.5 to 3.1) ml/kg/min. **Conclusions:** The increase in peak VO_2 with CR was mainly due to recovery from surgical intervention. The small independent benefit from CR was not maintained long-term, highlighting the potential to improve current CR concepts in ACHD populations.

KEYWORDS

Grown-ups with congenital heart disease; exercise training; cardiac rehabilitation; surgical intervention; peak oxygen consumption; cardiorespiratory fitness



1 Introduction

Almost one percent of all newborns are born with a congenital heart disease (CHD) [1]. Diagnoses vary from simple over moderate to great complexity. Due to the improved medical care, life expectancy in these patients has grown over the last decades, which has led to a growing population of adults with CHD (ACHD) patients [2,3].

Most patients with CHD are relatively sedentary [4]. Exercise intolerance is a major problem for ACHD patients, significantly restricting their quality of life [5,6], and increasing their risk for severe cardiac complications including arrhythmia and heart failure [7]. Furthermore, it may increase their risk for late complications such as heart failure and sudden cardiac death [8–10]. Consequently, incorporation of physical exercise into the daily routine is also recommended for ACHD patients [11].

Exercise capacity varies significantly across the spectrum of ACHD patients [7]. The lowest oxygen consumption (peak VO_2) as measure of cardiorespiratory fitness was found in patients with complex heart disease (e.g., univentricular circulation, Eisenmenger syndrome). At the other end of the spectrum, patients with simple heart defects were found to have the highest peak VO_2 . However, cardiorespiratory fitness was still significantly reduced when compared with normal healthy people [12].

A number of studies have assessed the effect of exercise training interventions [13–17] or cardiac rehabilitation (CR) [18–22] on exercise capacity in ACHD patients. Most of these studies have shown favourable short-term effects. However, only one study has addressed long-term (3 years) maintenance of this benefit and has found that the short-term (10 weeks) beneficial effects of CR in patients with a systemic right ventricle did not persist over a three-year follow-up period [23]. Given this lack of evidence with regard to long-term benefits of exercise-based CR on exercise capacity in ACHD patients, we retrospectively examined data of our out-patient ACHD clinic. ACHD patients at our clinic perform cardiopulmonary exercise tests at regular 2–3 yearly intervals. Some of them have completed CR at some stage either because of physical deconditioning or after open chest surgery. The aim of this study was to assess if cardiorespiratory fitness improved short and long-term after CR and whether this effect was independent of the recovery process from preceding surgical intervention.

2 Methods

2.1 Trial Design

This study was a retrospective, single-centre study performed at a large tertiary referral centre. The study complied with the Declaration of Helsinki and the local Ethics Committee approved the research protocol. All patients provided informed consent either for the SACHER registry [24] or for the Insel hospital general informed consent.

2.2 Study Population

Patients who were clinically followed-up at the Center for Congenital Heart Disease of the University Hospital Bern and performed cardiopulmonary exercise tests (CPET) at the Centre for Preventive Cardiology and Sports Medicine of the University Hospital of Bern between beginning of January 2000 and end of October 2019 were assessed for inclusion. Inclusion criteria were adults with congenital heart disease (minimal age 18 years) and completion of at least two CPETs within the inclusion period. Severity of CHD was rated according to ACHD AP classification guidelines [25] into mild, moderate and severe.

2.3 Outcome and Assessments

Cardiopulmonary exercise testing (CPET) was performed in ACHD patients as routine clinical work-up at usually 2- or 3-year intervals. During instable medical periods, CPET exams were performed more frequently. CPETs were always performed before enrolment in CR as well as after completion of CR.

CPETs were performed on a cycle ergometer and gas exchange was measured using a spirometry system (Jaeger Oxycon Pro, ViaSys Healthcare GmbH). Ramp protocols were selected for every patient individually in order to achieve voluntary exhaustion within 8–12 min. Patients were encouraged to maintain revolutions per minute (rpm) constant at between 60 and 70 rpm. The ramp test was terminated when the patient reached exhaustion and stopped cycling (or could not maintain 60 rpm) despite verbal encouragement to continue. Peak VO_2 was defined as the highest VO_2 averaged over 8 breathing cycles.

Primary outcome was peak VO_2 relative to body weight. In addition, the predicted peak VO_2 was calculated according to Wasserman [26].

2.4 Cardiac Rehabilitation

Exercise-based CR consisted usually of 36 90-min training sessions, 2–3 times per week, lasting for 12–18 weeks. Patients trained on a cycling ergometer for 38 min during each session after which they performed resistance, agility, balance, stretching or relaxation training. Cycling training was mostly performed as continuous moderate intensity training, some fitter patients also performed some sessions as high-intensity interval training (HIIT) after an initial phase of continuous training. Workload at the beginning of CR was set at 50–60% of peak Watt reached at the CPET before the start of CR. After the first training session, training intensity was adjusted by Borg scale (targeting 13 to 14). HIIT training protocol started with 10 min warm-up at the intensity of 25% peak Watt. The main HIIT phase consisted of 4×4 cycles, each consisting of 4 min at a load of 80% peak Watt and 3 min at 25% of peak Watt. Perceived exertion was aimed at 15 to 16 on the Borg scale.

2.5 Data Handling and Statistical Analysis

All data were analysed with R (Version 3.6.1, 2019). Clinical data and CPET data were merged from patients with available consent and subsequently encoded. We further reduced the data set to patients who had data from at least 2 CPETs during the period of January 2000 and October 2019. For patients who completed a CR in this time period, data from CR were also retrieved. If patients completed more than one CR in the observation period, only data from the first CR were used. In this case, only CPETs before the first CR including data from follow-up CPETs before initiation of second CR were used. Baseline data are described as frequencies or means with standard deviations (or medians with interquartile ranges) as appropriate. A categorical variable to indicate whether the CPET was performed after a CR was defined and coded as follow: 0, no CR prior to CPET; 1, CPET 0–4 weeks after completion of CR; 2, CPETs performed >4 weeks following completion of CR.

To account for the confounding variable of preceding surgical intervention, we defined a binary categorical variable. If patients underwent an open chest surgery within 3 months prior to the CPET or a minimally invasive (catheter-based) intervention within 1 month prior to CPET, the surgery variable was coded as 1, otherwise as 0.

Linear mixed models were performed for the primary outcome peak VO_2 , with patients included as random effect. The following factors were included as fixed effects: Age, sex, disease classification, preceding surgery (categorical variable) and preceding CR (categorical variable).

3 Results

3.1 Patients Characteristics

A total of 696 patients were assessed for eligibility. Reasons for excluding 385 patients are listed in (Fig. 1). 1052 CPETs of 311 ACHD patients (38% female) including 59 patients with CR and 252 without CR were included in the analyses (Fig. 1). Patient characteristics are summarized in (Tab. 1). Median peak VO_2 of the whole population was 25.6 ml/kg/min (IQR 20.2–32.5 ml/kg/min). A frequency

plot of peak VO_2 relative to body weight as well as of predicted separately for the 196 patients with mild or moderate defects and 116 with complex CHD is shown in the appendix (Appendix A, [Supplement Fig. 1](#)).

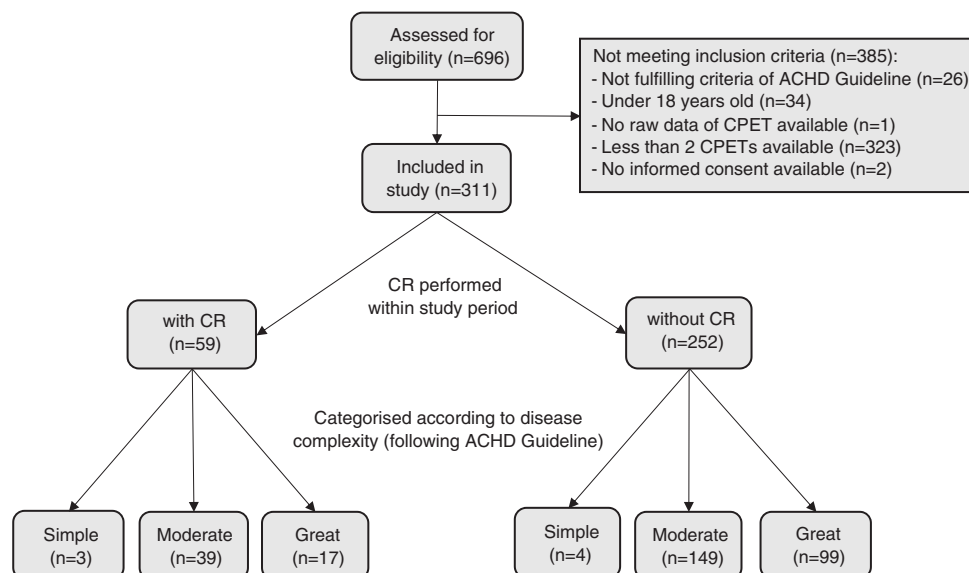


Figure 1: Patient flow. ACHD, Adults with congenital heart disease; CPET, cardiopulmonary exercise test; CR, cardiac rehabilitation

Table 1: Patient characteristics indicated as median (interquartile range) or number of patients (%)

Characteristics	All (n = 311)	With CR (n = 59)	Without CR (n = 252)
Age [years]	27 (20, 40)	29 (20, 42)	27 (20, 38)
Age group			
18–30 years	181 (58.2%)	32 (54.2%)	149 (59.1%)
30–50 years	100 (32.2%)	21 (35.6%)	79 (31.4%)
50–65 years	27 (8.6%)	5 (8.5%)	22 (8.7%)
65–79 years	3 (1.0%)	1 (1.7%)	2 (0.8%)
Female Sex	119 (38.0%)	21 (36.0%)	98 (39.0%)
CHD complexity			
Great	116 (37.3%)	17 (28.8%)	99 (39.3%)
Moderate	188 (60.5%)	39 (66.1%)	149 (59.1%)
Simple	7 (2.2%)	3 (5.1%)	4 (1.6%)
CHD diagnosis			
Aortopathy	3 (1.0%)	1 (1.7%)	2 (0.8%)
Bicuspid aortic valve	46 (14.8%)	13 (22.0%)	33 (13.1%)
Double outlet right ventricle	18 (5.8%)	1 (1.7%)	17 (6.7%)
Ebstein anomaly	18 (5.8%)	2 (3.4%)	16 (6.4%)
Tetralogy of Fallot	71 (22.8%)	15 (25.4%)	56 (22.2%)

Table 1 (continued).

Characteristics	All (n = 311)	With CR (n = 59)	Without CR (n = 252)
Fontan circulation	18 (5.8%)	2 (3.4%)	16 (6.4%)
Non-compaction	3 (1.0%)	2 (3.4%)	1 (0.4%)
Pulmonary stenosis	19 (6.1%)	2 (3.4%)	17 (6.7%)
Shunt	28 (9.0%)	7 (11.9%)	21 (8.3%)
TGA with arterial switch or Rastelli operation	17 (5.5%)	3 (5.1%)	14 (5.6%)
Systemic right ventricle	60 (20.0%)	8 (13.5%)	52 (20.6%)
Cyanosis	5 (1.6%)	3 (5.1%)	2 (0.8%)
Other defects	5 (1.6%)	0 (0%)	5 (2.0%)
Number of available CPETs			
2	126 (40.5%)	11 (18.6%)	115 (45.6%)
3	73 (23.5%)	15 (25.4%)	58 (23%)
4	55 (17.7%)	8 (13.6%)	47 (18.7%)
5	20 (6.4%)	3 (5.1%)	17 (6.7%)
6	20 (6.4%)	8 (13.5%)	12 (4.8%)
7	7 (2.4%)	5 (8.5%)	2 (0.8%)
8	3 (0.9%)	2 (3.4%)	1 (0.4%)
9	3 (0.9%)	3 (5.1%)	0 (0%)
10	3 (0.9%)	3 (5.1%)	0 (0%)
11	1 (0.3%)	1 (1.7%)	0 (0%)
Follow-up time [yrs]			
with 2 CPETs	2.99 (1.84, 4.44)	0.61 (0.36, 0.72)	3.07 (2.04, 4.62)
with more than 2 CPETs	7.5 (5.0, 10.6)	6.3 (2.4, 10.6)	7.7 (5.4, 10.6)

CHD, congenital heart disease; TGA, transposition of the great arteries; CPET, cardiopulmonary exercise testing.

Fig. 2 shows the output of the linear mixed model. Peak VO_2 [ml/kg/min] was non-significantly increased short term after CR (β 0.8, 95% Confidence Interval (CI) -0.7 ; 2.4) and not increased long term after CR (β 0.0, 95%CI -1.7 ; 1.6). Peak VO_2 was significantly reduced by age, female sex, complex CHD and preceding surgery.

The 59 patients who completed CR attended a median of 24 (IQR 18–29) training sessions at a median work load of 47 (39, 50) Watts over a duration of 15 (12, 19) weeks (CR data was not available in eight of the CR patients). In the CR patients, peak VO_2 increased from before to after CR by a median of 2.7 (IQR -0.6 to 5.5) ml/kg/min (Fig. 2). However, this increase was strongly mediated by preceding cardiac surgery, with 20 patients after cardiac surgical intervention showing a median increase of 6.2 (IQR 3.6–9.5) ml/kg/min, while 39 patients without surgical intervention had a median increase of 0.9 (IQR -1.5 to 3.1) ml/kg/min (Fig. 3). In an additional linear model for change in peak VO_2 [ml/kg/min] for the 59 CR patients (adjusted for age, sex, disease complexity, preceding surgery, rehabilitation duration and baseline peak VO_2), preceding cardiac surgery was the strongest independent predictor for improvements in peak VO_2 (β 5.29, 95%CI 2.75–7.82, Tab. 2).

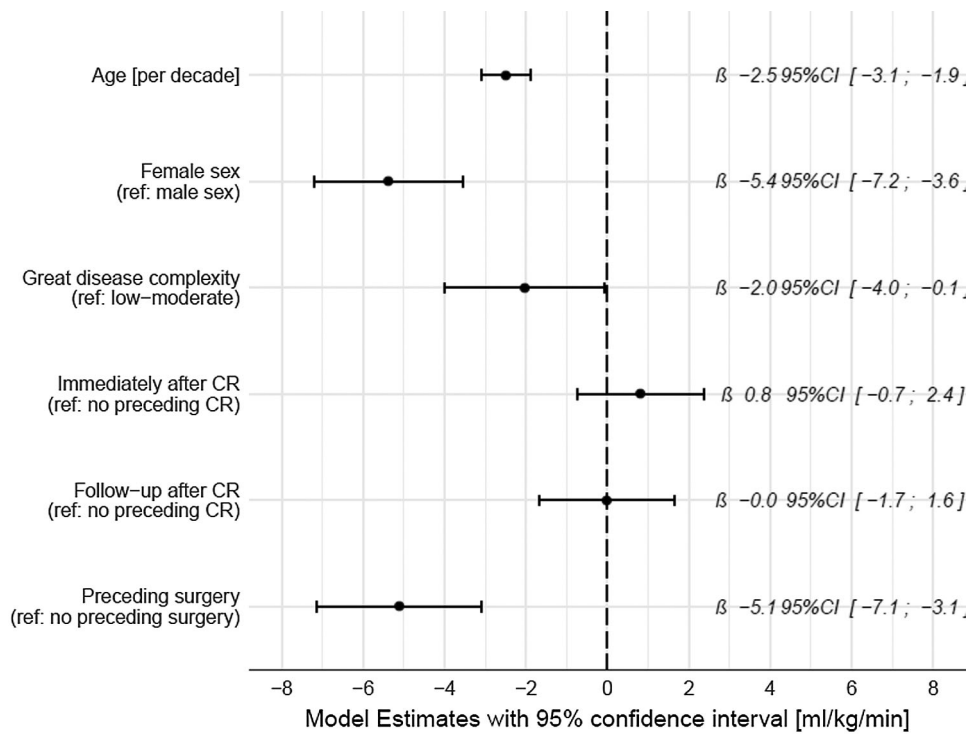


Figure 2: Coefficient plot of the linear mixed model for peak VO_2 [ml/kg/min]. Patients were entered into the models as random effects. CR, cardiac rehabilitation

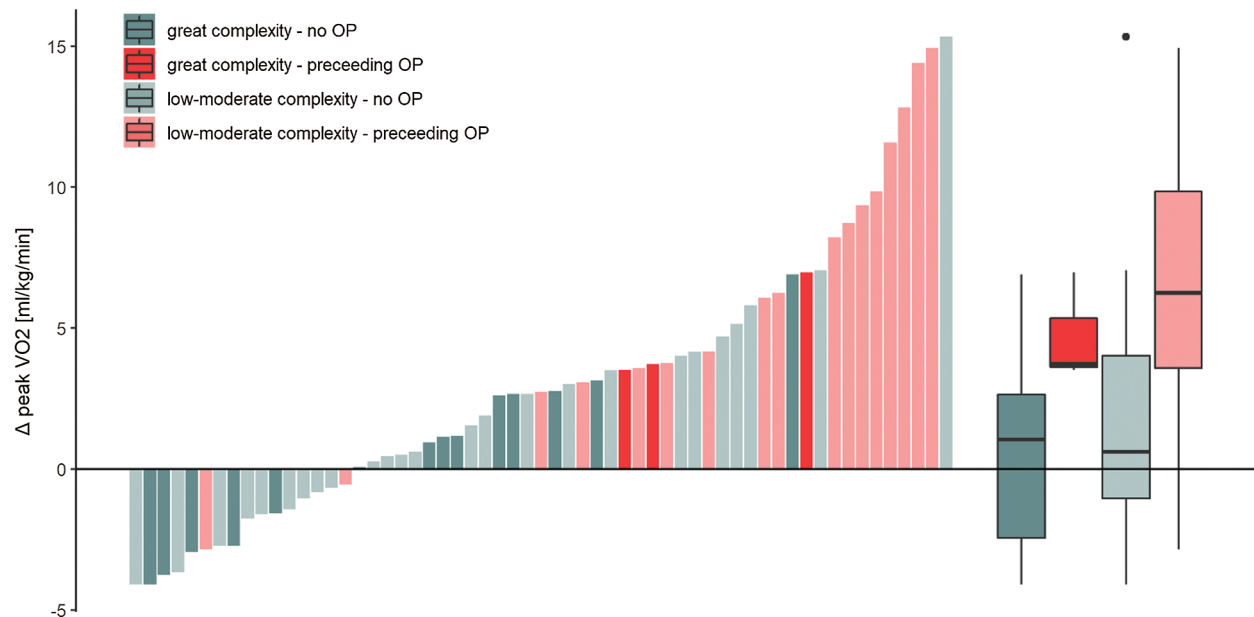


Figure 3: Individual changes (bars) from before to after CR in peak VO_2 [ml/kg/min] of patient who completed CR. Patients who underwent an intervention prior to cardiac rehabilitation are depicted in red, while those who did not have surgical intervention within 6 months prior to CR are shown in green. OP, surgical procedure

Table 2: Linear model for change in peak VO₂ in a subset of patients undergoing cardiac rehabilitation

<i>Predictors</i>	Change in peak VO ₂ [ml/kg/min]		
	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Intercept	4.61	−0.46 to 9.69	0.074
Age [years]	−0.11	−0.20 to −0.01	0.024
Female sex (ref: male sex)	−1.14	−3.60 to 1.33	0.360
Great disease complexity (ref: low-moderate)	−2.24	−4.86 to 0.38	0.093
Preceding surgery (ref: no preceding surgery)	5.29	2.75 to 7.82	<0.001
CR duration [days]	0.00	−0.01 to 0.01	0.924
Peak VO ₂ at start of CR [ml/kg/min]	−0.11	−0.27 to 0.06	0.194
Number of observations	59		
R ² /R ² adjusted	0.359/0.285		

CR, cardiac rehabilitation.

Cardiorespiratory fitness in patients who did not complete CR after cardiac surgery (n = 7) also increased by a median of 5.8 (IQR 4.7–7.8) ml/kg/min at the next follow-up CPET.

4 Discussion

In this retrospective study cardiorespiratory fitness was assessed in ACHD patients at several time points over a median of 3 years in patients with two and median of 7.5 years in patients with more than two CPETs. We found that cardiac surgical interventions had a large effect on peak VO₂ (−5.1 ml/kg/min) but CR only had a non-significant and minor independent effect short-term (0.8 ml/kg/min), which was lost long-term. CR was often performed following surgical interventions, however, the recovery in peak VO₂ which was measured after completion of CR was also found in patients not performing CR.

Our results confirm the findings of van der Bom et al. [23] who followed up patients enrolled in a randomized controlled exercise intervention study by Winter et al. [16]. This study included 28 patients with a systemic right ventricle into a 10-week exercise intervention with thrice-weekly 42-min interval training sessions. Patients of the exercise group improved their peak VO₂ 3.4 (95% CI 0.2–6.7) ml/kg/min more than the control group not enrolled into an exercise program [16]. Three years later, 22 patients of the exercise group and 18 patients of the control group were assessed again, at which time there was no difference between the groups anymore [23].

To our knowledge, this is the first study who assessed the independent effects of both, CR and surgical interventions in a clinical cohort of ACHD patients. Surgical or minimally invasive interventions are often the trigger for cardiologists to recommend an ambulatory CR and the motivation for patients to regain their physical fitness. Our study results imply that most of the 5.1 ml/kg/min recovery in peak VO₂ after surgical interventions also occurred in patients not completing CR and that there was only a small independent gain due to CR. Previous studies have consistently found improvement of exercise capacity with exercise training interventions, mostly in the form of exercise-based CR. While some studies were designed as longitudinal studies without a control group [20,27], other studies compared patients completing CR to those who chose not to attend CR [18]. A few randomized controlled trials have also been performed [15–17,22], however, some of these randomized trials included fewer than 10 patients per group [14,28].

Most exercise intervention studies explicitly excluded patients with preceding surgical interventions. Compared to the median improvement in peak VO₂ of 0.8 ml/kg/min in our patients without preceding surgical interventions, these studies found larger benefits with improvements of 1.6–1.8 ml/kg/min

[13,14,17], or even 2.2–4.0 ml/kg/min [16,18,28]. The study performed by Winter et al. [16] achieved a mean improvement of 2.2 ml/kg/min by a 10-week programme of high-intensity exercise training thrice weekly. However, it was not clearly stated whether patients with preceding surgery were excluded. A comparable improvement of 2.2 ml/kg/min was found in a pilot study on nine patients randomized to exercise-based 12-week CR [28]. The third study reaching markedly higher improvements in cardiorespiratory fitness (4.0 ml/kg/min) compared to our study was a study on 31 patients who chose to complete a 4-week exercise-based CR with daily exercise sessions [18]. Importantly, the increase of a mean respiratory exchange ratio (RER) of 0.94 at baseline to 1.3 after CR indicates that part of the 4 ml/kg/min improvement was due to a higher exertion level at the follow-up testing. In our 39 patients who completed CR without preceding cardiac surgery, median RER was 1.15 both before and after CR.

The only study who found a comparable improvement to our study (1 ml/kg/min) was a study with congenital heart disease-associated pulmonary arterial hypertension patients performing a 3-week exercise-based CR with 90 min of exercise 7 days/week [20]. However, their patients had a mean peak VO_2 at CR start of 11.4 ml/kg/min, which was much lower than the median exercise capacity of 25.6 ml/kg/min in our patients.

Many studies found significantly improved exercise capacity in the exercise group, but not the control group, however, these studies did not test whether the improvements in the exercise group were significantly greater than those in the control group [14,15,17,19,27,28]. Namely, in all of these studies cardiorespiratory fitness also increased by trend in the control group, often by about half the increase of the control group. The smaller (non-significant) increase found in the control group gives an indication on the size of familiarization effect with the testing procedure. Non-significant improvements found in the control group were between 0.3–0.9 ml/kg/min in some studies [14,15,17,28], but were zero [18] or even negative (–0.5 and –1.9 ml/kg/min) in other studies [16,22]. We found only one previous study that took non-CR related changes in exercise capacity into account and found a significant difference between the changes in cardiorespiratory fitness between the exercise and control group [22]. Their increase in peak VO_2 after a 12-week home training was 1.8 ml/kg/min, which was about double the increase found in our study, however, it was not explicitly stated that they excluded patients with preceding cardiac surgery.

Our results on long-term changes in peak VO_2 are in agreement with the only previous study in ACHD patients who assessed long-term effects of CR on peak VO_2 and who found no persistent effect at three years follow-up [23]. Sustenance of gains in peak VO_2 and long-term adherence to increased levels of physical activity have been found to be a challenge also in various other cardiac populations after cardiac rehabilitation [29,30].

The main limitation of this study is its retrospective design. Data was gathered over a duration of almost twenty years, therefore, changes in equipment and software took place during this time. However, this is unlikely to have introduced a systematic error, as CRs and surgical interventions were distributed over the whole time period. Further, this study focussed on the improvement of cardiorespiratory fitness, which is only one of several outcomes that may be improved by CR. Patient reported outcomes, such as quality of life also reflect physical function and may be more clinically relevant [5].

The main strength of this study was the longitudinal design in a clinical setting with standardized CPET with comparable levels of exertion, where patients had multiple assessments before and after CR but also after surgical interventions. This allowed a valid comparison of the independent effects of CR and surgical interventions, as CR is indicated and often performed after a surgical intervention to regain fitness and physical function. In our clinical setting, CR was feasible and safe, there were no major complication during training session with only occasional minor complications, such as dizziness and/or nausea, upon which the training session was interrupted or terminated.

5 Conclusions

Our study on retrospective data from a clinical setting showed that there was a small and insignificant increase in exercise capacity from CR when adjusted for preceding surgery, age and sex. Preceding surgery greatly reduced exercise capacity and mediated improvements in patients undergoing CR. Subsequent recovery was also seen in patients after cardiac surgery not completing CR. We found no long-term effect of CR on exercise capacity, highlighting the potential to improve current concepts of CR in the ACHD population. We recommend a personalised approach that offers comprehensive and individually tailored CR programmes [31] who identify facilitators and barriers to physical exercise and take these into account when formulating long-term physical activity goals to improve long-term adherence.

Author Contributions: PE, TG, TM, KW, CD, MS, MG, DT and MW contributed to the conception or design of the work. TG and CB contributed to the acquisition of the data. PE, TM, TG and CB performed the analyses. PE drafted the manuscript. All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Data Sharing: Data sharing of anonymized data may be possible upon request to the corresponding author.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

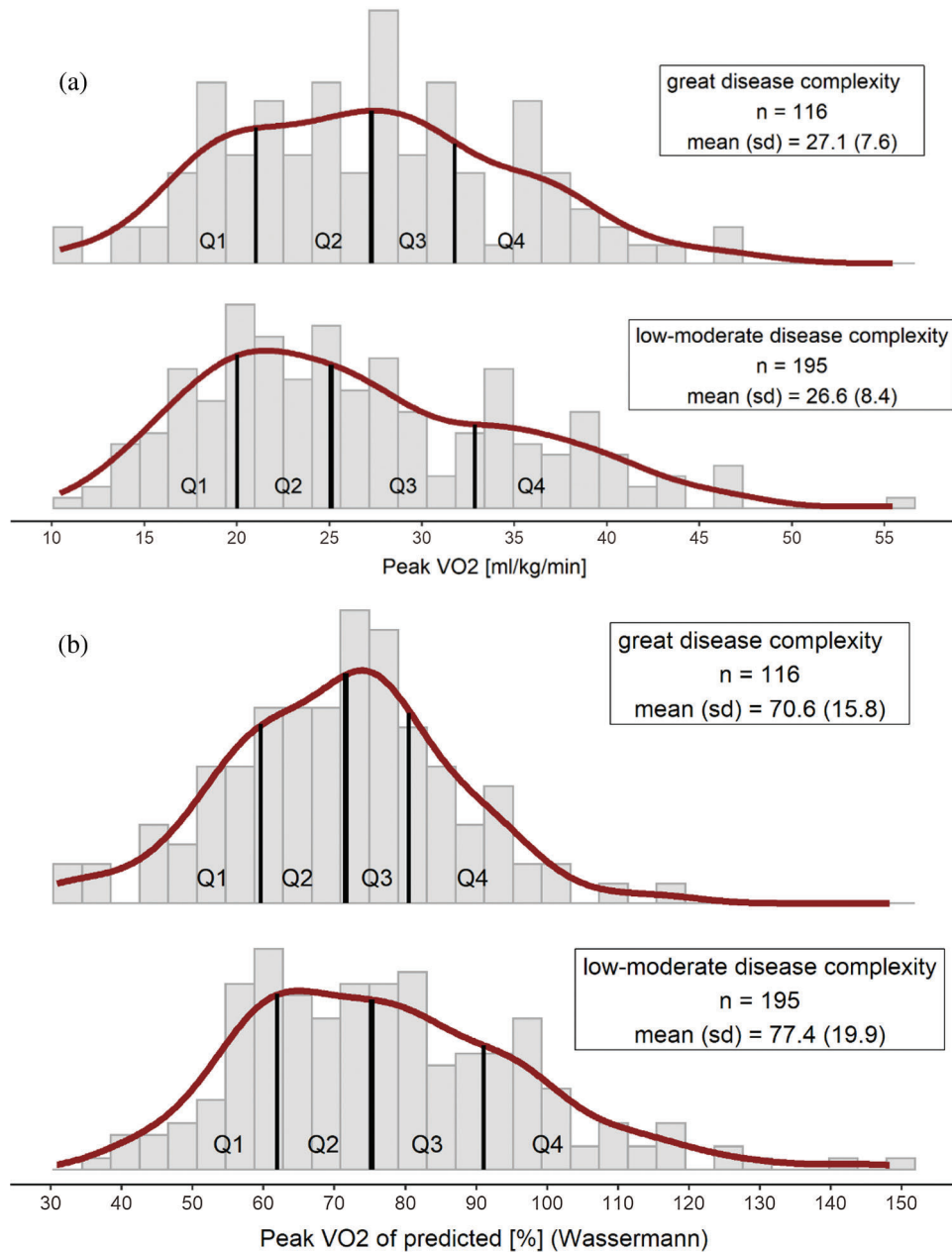
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Appendix A



Supplement Figure 1: Histogram of peak VO₂ in units relative to body weight (a) and of predicted values according to Wasserman [26] (b) for patients with great (top panels) versus mild and moderate (bottom panels) disease complexity