Long-term effects of physical training on cardiopulmonary exercise parameters in young patients with congenital heart diseases

Paolo Ferrero[1,2] , Isabelle Piazza[3], Giacomo Poggioli[4], Massimo Chessa[1,5] and Fabio Lorenzelli[4]

[1]ACHD Unit, Pediatric and Adult Congenital Heart Centre, IRCCS-Policlinico San Donato, San Donato Milanese, Italy; [2]University of Milano-Bicocca, Milano, Italy; [3]Emergency Medicine Department, ASST Papa Giovanni XXIII, Bergamo, Italy; [4]Sport Medicine, ASST Papa Giovanni XXIII, Bergamo, Italy and [5]Vita-Salute San Raffaele University, Milano, Italy

Abstract

Introduction: Physical activity is recognised as an important intervention in patients with CHD. However, more data on the actual magnitude of physical training impact on functional capacity in this group of patients are still warranted. We aim to assess effort tolerance in a contemporary cohort of patients with congenital heart disease, regularly following a training programme, in comparison with a matched control group. *Methods:* Patients with CHD followed at the sports medicine department, who had undergone cardiopulmonary exercise test between 2011 and 2019, were included. Variables recorded were maximum workload, absolute and indexed maximum oxygen consumption, maximum heart rate, absolute and indexed maximum O2 pulse, ventilatory equivalent of CO_2 and oxygen consumption/Work. Trend of cardiopulmonary parameters was analysed over time. Maximal workload, maximum oxygen consumption and ventilatory equivalent of CO_2 were compared with a control group of patients with a more sedentary lifestyle, matched for diagnosis, gender, age, and body mass index. *Results:* Among one hundred and eleven patients, 73 males (66%) were analysed. Median age was 14 (12–17) years. Twenty-nine patients (27%) were practising sports at competitive level. Maximum oxygen consumption and oxygen consumption % of maximum predicted were not significantly different at follow-up as compared with baseline. Follow-up of maximum oxygen consumption was 38.2 ± 9 ml/kg/min versus 38.6 ± 9.2 ml/kg/min (p = NS) and follow-up of %oxygen consumption was 88 ± 20 versus 87 ± 15 (p = NS). Ventilatory equivalent of CO_2 significantly improved in the last test as compared with the baseline: 30 ± 4 versus 33 ± 5 (p = 0.002). As compared with the control group, trained patients displayed a significantly higher maximum workload and oxygen consumption, while ventilatory equivalent of CO_2 was not significantly different. *Conclusions:* In our cohort, patients following a regular training programme displayed a significantly higher functional capacity as compared with not trained control group, irrespective of NYHA class. Objective functional capacity was stable over a median follow-up of 3 years.

CAMBRIDGE UNIVERSITY PRESS

Maximum oxygen consumption displays a wide variability in adult patients with CHD and is an independent prognostic factor. The single most important determinant of maximum oxygen consumption is the type of anatomy.[1] The expected trend of functional capacity in patients with CHD is to decline over time leading to significantly reduced maximum oxygen consumption as compared with the age-matched general population, irrespective of NYHA class. Such decline may have several causes, namely chronotropic incompetence, absence of subpulmonary ventricle, muscular deconditioning, balance between systemic, and pulmonary resistances, depending on anatomy.

Exercise training, by improving muscular metabolism, optimising body mass index, and promoting systemic and pulmonary vasodilatation, is an attractive therapeutical intervention in patient with CHD.[2] Nevertheless, evidence from the literature is still inconclusive showing improvement of functional capacity limited to only specific anatomies.[3]

Furthermore, different from adult CHD, reference value of maximum oxygen consumption based on large datasets has not been established so far in adolescent and young adults.[4–6]

This study aims to investigate cardiopulmonary exercise parameters in a cohort of young adult with CHD involved in physical training programme and to describe their long-term trend. The second objective of the study is to compare exercise metabolic parameters of individuals with CHD undergoing a regular physical training programme with a matched control group.

Methods

Patients with CHD and involved in sports activities either at recreational or competitive level were evaluated at the sports medicine department between 2011 and 2019. Competitive and recreational (or not competitive) levels were defined according to the criteria established by the Italian law. Patients belonging to a specific federation and undergoing training sessions and competitions on a defined schedule were considered as "competitive" while those performing physical activities on regular basis (at least twice a week) but not participating in formal events were labelled as "recreational." They all underwent serial cardiopulmonary exercise tests.

Ergometric tests were performed on a cycloergometer. Exercise protocol was tailored on the age and patient's weight. Patients exercised following a ramp protocol, with the workload selected according to the maximum theory.

Continuous 12 leads ECG and transcutaneous saturation were monitored during exercise while blood pressure was recorded every 2 minutes.

Ventilatory parameters were measured by a turbine coupled with a digital trasducer. Expired gas analysis was performed with a Vyntus CPX metabograph CareFusion™ using Rudolph masks adjusted to the face size.

All ventilation and metabolic parameters were recorded beat by beat and analysed averaging ten seconds.

The last cardiopulmonary exercise test was compared with the oldest one, conducted with the same protocol, whenever available, in order to assess exercise capacity trend. The following parameters were included: functional capacity expressed as maximum workload in Watts, maximum heart rate; maximum oxygen consumption (max VO2 ml/kg/min); oxygen pulse (VO2/HR), CO2 ventilatory equivalent (VE/VCO2) and VO2/Work slope. Ventilatory equivalent of CO2 slope was calculated between the 20 % and 80% of the entire exercise in order to exclude possible spurious estimations due to hyperventilation at the beginning of the exercise. All tests were conducted aiming at a respiratory exchange ratio higher than 1.1, that was assumed as index of adequate metabolic stress. Individuals practising sports were matched 1:1 for anatomical diagnosis, age (±2 years) and body mass index (±2) with a control cohort. Patients with haemodynamically significant residual defects, cardiovascular symptoms at rest, NYHA class > 2 were excluded in order to avoid confounders.

This study was approved by institutional review board (24/INT/2023).

Statistical analysis

Quantitative variables are expressed as mean ± SD or median (interquartile range) and compared with Student's t-test or Wilcoxon rank sum test. Comparison of quantitative observations at two different timeframes was performed by Student's t-test or Wilcoxon test for paired data. Normality of variables was assessed by visually inspecting the distribution histograms.

Categorical variables are expressed as counts or percentage and compared by chi-square or Fisher's exact test as appropriate. A p value < 0.005 was assumed as cut-off for statistical significance.

Statistical analysis was performed by STATA software.

Results

Among one hundred and eleven patients, 73 males (66%) were included in the analysis. Median age at last cardiopulmonary

exercise test was 14 (12–17) years. Median body mass index of the whole cohort was 19.7 (17–21). Twenty-nine patients (27%) have been practising sports at competitive level for a median time of 4 (2–7) years; for two patients, the information about the level of training involvement was not available. In the whole population, individuals performing sports at competitive level had a similar age and body mass index which displayed a lower prevalence of great complexity defects as compared to the "recreational training" group (Table2 suppl). Underlying anatomic diagnosis were transposition great arteries post-arterial switch operation (21 patients, 19%); tetralogy of Fallot (15 patients, 13%); aortic coarctation/ left heart obstructions (31 patients, 28%); atrio-ventricular septal defect (7 patients, 6%); Fontan (5 patients, 4%); pulmonary stenosis (9 patients, 8%); other diagnosis (18 patients, 16%). Thirteen patients (13%) were untreated while 31 patients (32%) had residual defects. (Table 1).

Table 2 summarises demographic and cardiopulmonary performance parameters according to the different anatomic categories. Maximum oxygen consumption and % predicted oxygen consumption displayed a significant variability among different underlying anatomies. (Fig. 1).

In fifty patients, more than one cardiopulmonary exercise test was available. In this subgroup, the last test was compared with the oldest one. Median time elapsed between the two tests was 1007 (663–1471) days.

Absolute value of maximum oxygen consumption and its predicted percentage at last test were not significantly different from the antecedent one: maximum oxygen consumption 38.2 ± 9 versus 38.6 ± 9.2 ml/Kg/min (p = 0.7); last % oxygen consumption 88 ± 20 versus 87 ± 15 (p = 0,8), oxygen consumption/Work 10 ± 2.4 versus 10 ± 1.6 (p = 0.9).

On the other hand, ventilatory equivalent of CO2 significantly decreases in the last test as compared with the baseline: 30 ± 4 versus 33 ± 5 (p = 0.002). (Table 3) (Fig. 2).

After matching, 46 couples sports practising/non-sports practising were analysed. As a result of the matching, age and body mass index were not significantly different between the two groups. Patients practising sports achieved a higher degree of metabolic stress as showed by a significantly higher median maximum respiratory exchange ratio: 1.17 (1.07–1.22) versus 1.10 (1.05–1.14), p = 0.04. Maximal workload, oxygen consumption and percentage of predicted maximum oxygen consumption were significantly higher in patient involved in sports activities: 141 (120–160) versus 110 (90–130) W, 36.75 (30.2–42.1) versus 28.7 (24–34.7) ml/Kg/min p < 0.001 and 84.5 (75–97) versus 61.5 (52–72)%, respectively. All p < 0.001.

On the other hand ventilatory equivalent of CO2 was not significantly different 29.2 (26.6–32) versus 27.7 (25–32.9) p = 0.4 (Table 4).

No complication related to the test occurred.

Discussion

Assessment of functional capacity has a well-consolidated role in the prognostic stratification of CHD patients. In our cohort of trained patients with CHD, maximum oxygen consumption was well preserved across all categories of anatomies, ranging from 39 (36–44) to 28 (23–32) ml/Kg/min. In a previous large dataset of adult patients with CHD, maximum oxygen consumption ranged from 28.7 ± 10.4 to 11.5 ± 3.6 ml/Kg/min.[1] This significant difference may be explained by a higher level of training, a lower age of our population, and the exclusion of patients with

Table 1. Demographic data. IQR: interquartile range, BMI: body mass index, TGA-ASO: transposition great arteries-arterial switch operation, TOF: tetralogy of Fallot, CoA: aortic coarctation, AVSD: atrioventricular septal defect.

	Last cardiopulmonary exercise test	Baseline cardiopulmonary exercise test
Number	111	50
Age, median (IQR)	14 (12–17)	12 (10–13)
BMI, median (IQR)	19.7 (17–21)	18 (16–21)
Male, n (%)	73 (66)	35 (70)
Competitive, n (%)	29 (27)	22 (44)
Anatomic diagnosis		
TGA-ASO, n (%)	21 (19)	9 (18)
TOF, n (%)	15 (13)	5 (10)
CoA-Left heart obstruction, n (%)	31 (28)	17 (34)
Ebstein, n (%)	5 (4)	3 (6)
AVSD, n (%)	7 (6)	5 (10)
Fontan, n (%)	5 (4)	1 (2)
Pulmonary stenosis, n (%)	9 (8)	3 (6)
Others, n (%)	18 (16)	7 (14)
Natural history, n (%)	13 (13)	8 (16)
Residual defects, n (%)	31 (31)	13 (30)

Eisenmenger physiology. However, previous study on a group of children and adolescent with CHD also reported a maximum workload significantly lower than our cohort.[5]

A main finding of this paper is that patient practising sport, despite a similar reported NYHA class, displayed a significantly higher objective functional capacity as compared with their counterpart with the same age, anatomy, and body mass index. Interestingly, ventilatory equivalent of CO_2 was not significantly different in subjects practising sport. This finding can be the result of the specific characteristics of our cohort which included young patients without pulmonary vascular disease.

Literature data on the effect of exercise training on cardiopulmonary fitness are still conflictual.

It has to be underlined that most of the studies assessing the impact of physical training on functional capacity of patients with CHD are based on heterogenous protocol of limited duration.[3,7–12]

Different from previous studies, we included patients that were involved in sports activities as part of their routine lifestyle. We can hypothesise that a training protocol of limited duration might not reproduce the effect of routine training on effort tolerance at long-term follow-up. We observed that functional capacity in terms of maximum oxygen consumption and % predicted maximum oxygen consumption remained stable over the follow-up period while ventilatory equivalent of CO_2 slope decreased. It has been demonstrated that a lower level of ventilatory equivalent of CO_2 is independently associated with a better prognosis in patients with CHD.[13] Efficiency of ventilation-perfusion coupling is a major component of ventilatory equivalent of CO_2 slope. In patients with CHD, pulmonary vascular function may be impaired because of global segmental pulmonary hypertension, pulmonary artery branch stenosis, lack of flow pulsatility, contributing to regional ventilation mismatch, and, therefore, impairing ventilation

efficiency. This is particularly relevant for specific categories of patients, such as Fontan, that have a passive not pulsatile pulmonary flow.[14] Routine physical training might counteract these pathophysiological mechanisms by optimising NO-mediated pulmonary vascular recruitment.[15]

Finally, involvement in regular training and surveillance of objective effort tolerance by cardiopulmonary exercise test may increase the detection rate of subclinical but potentially harmful residual defects. (supplementary material).

Larger numbers are needed in order to confirm these trends of exercise parameters in sportive patients with CHD in order to be able to perform sub-analysis in different anatomic categories.

Conclusions

In summary, these data indicate that cardiopulmonary exercise test is an useful and safe tool to monitor patients regularly involved in physical training. This group displayed a better-preserved effort tolerance as compared with age- and anatomy-matched controls. Furthermore, physical exercise in patients with CHD may contribute to the preservation of functional capacity over the years. Positive effect of exercise on pulmonary circulation, peripheral oxygen extraction, and weight control can explain this finding.

Limitations

This is an observational retrospective study. Although we introduced a matched control group, our population is very heterogeneous in terms of underlying anatomic diagnosis; hence, the results might be biased by not considering confounders. Moreover, the sample size is too small and likely underpowered to clearly exclude any significant variation in metabolic parameters by a robust repeated measures variance analysis.

Table 2. Demographic, metabolic, and respiratory parameters according to categories of diagnosis. W: IQR: interquartile range, workload, VO2: oxygen consumption, VE/VCO2: ventilatory equivalent of CO2.

	TGA post-ASO	TOF	CoA-Left heart obstruction	Ebstein	AVSD	Fontan	Pulmonary stenosis	Others
Demographic data								
n (%)	21 (19)	15 (13)	31 (28)	5 (4)	7 (6)	5 (4)	9 (8)	18 (16)
Age, median (IQR)	14 (12–16)	12 (10–16)	14 (12–17)	14 (13–16)	17 (13–19)	15 (14–26)	14 (12–20)	13 (10–17)
BMI, median (IQR)	19 (16–22)	18 (17–21)	20 (17–22)	18 (17–21)	21 (16–24)	21 (20–21)	21 (19–21)	19 (17–21)
Male, n (%)	14 (66)	11 (73)	22 (71)	3 (60)	4 (57)	2 (40)	6 (67)	11 (61)
Competitive, n (%)	5 (25)	2 (13)	12 (39)	1 (20)	2 (29)	0	3 (37)	4 (22)
Cardiopulmonary parameters								
Workload max (Watt), median (IQR)	140 (100–200)	140 (106–160)	140 (120–180)	143 (133–147)	120 (70–160)	120 (91–142)	150 (105–210)	105 (90–140)
Workload max pred (%), median (IQR)	90 (68–98)	82 (65–100)	93 (72–108)	95 (93–99)	81 (57–91)	68 (64–71)	95 (74–103)	86 (66–97)
VO2 peak (ml/Kg/min), median (IQR)	39 (36–44)	38 (30–44)	38 (35–45)	39 (25–41)	34 (27–41)	28 (23–32)	37 (32–43)	35 (29–42)
VO2 peak pred (%), median (IQR)	90 (80–102)	87 (80–97)	95 (80–103)	92 (73–103)	81 (68–94)	70 (68–71)	95 (81–98)	86 (75–95)
O2 pulse (ml/min/bpm), median (IQR)	9.5 (8.3–14.8)	9.4 (7.8–14.2)	11.3 (9.1–15)	8.3 (7.9–11.4)	9.4 (8.2–10.3)	7.6 (7.3–12.4)	9.6 (9.3–12.8)	8.5 (7.8–11.6)
O2 pulse pred (%), median (IQR)	95 (85–100)	87 (78–105)	99 (83–106)	80 (68–99)	87 (76–103)	80 (72–89)	90 (87–95)	90 (78–98)
VO2/Work (ml/min/W), median (IQR)	10.8 (10–12.3)	9.8 (9.3–10.6)	10 (9.3–11.9)	8.7 (7.8–11.8)	10.3 (9–11.3)	9 (9–9.5)	9.6 (9.4–11.8)	11 (8.8–11.5)
VE/VCO, median (IQR)	31 (28–33)	30 (28–34)	28 (26–30)	31 (30–33)	27 (25–32)	35 (34–36)	30 (28–32)	31 (28–34)

Table 3. VO2: oxygen consumption, VE/VCO2: ventilatory equivalent of CO2, AT: anaerobic threshold, HR: heart rate, FEV1: first-second forced expiratory volume.

	Baseline cardiopulmonary exercise test (n = 50)	Last cardiopulmonary exercise test (n = 50)	P value
VO2 max (ml/Kg/min), mean (±SD)	38.2 ± 9	38.6 ± 9.2	0.7
VO2 max pred (%), mean (±SD)	88 ± 20	87 ± 15	0.8
VE/VCO, mean (±SD)	33 ± 5	30 ± 4	**2**
Work Load max (Watt), mean (±SD)	119 ± 46	153 ± 56	**0.0001**
Work Load max (%), mean (±SD)	86 ± 21	90 ± 20	0.1
Work Load at AT (%), mean (±SD)	65 ± 9	64 ± 9	0.5
VO2/Work (ml/min/W), mean (±SD)	10 ± 2.4	10 ± 1.6	0.9
O2 pulse (ml/min/bpm), mean (±SD)	10.4 ± 4.8	11.6 ± 3.7	0.2
O2 pulse pred (%), mean (±SD)	94 ± 21	96 ± 17	0.6
HR max pred (%), mean (±SD)	84 ± 11	87 ± 9	**0.02**
FEV1 (%), mean (±SD)	98.3 ± 14	95.2 ± 14	0.1
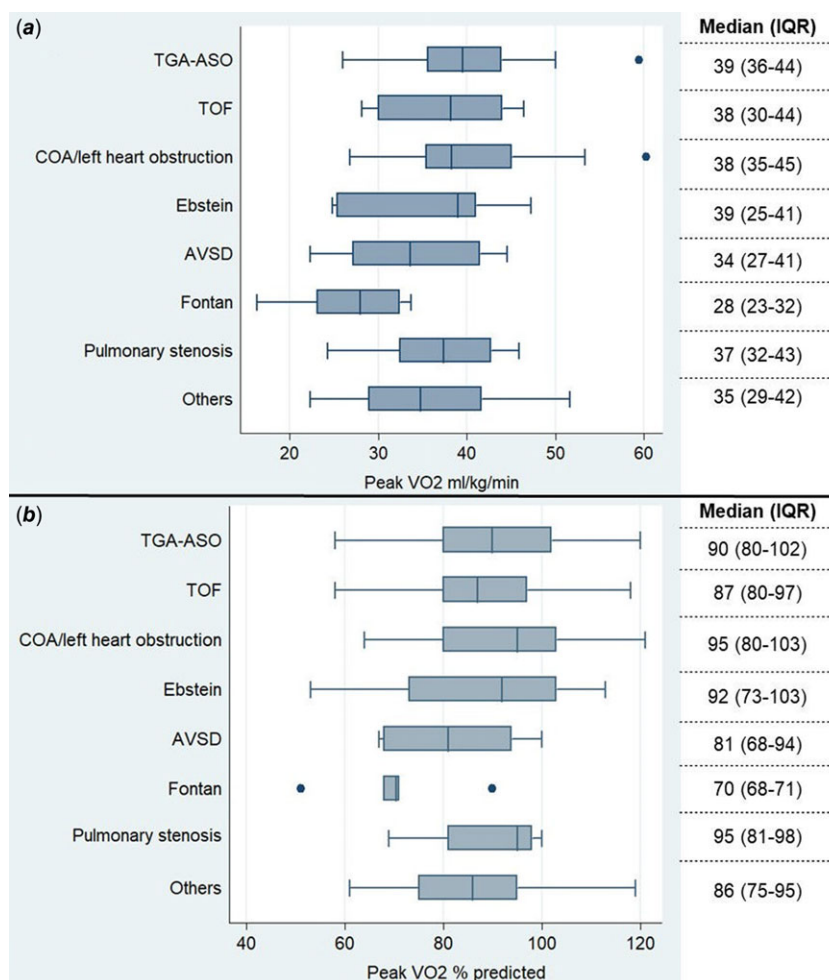
Figure 1. Maximum oxygen consumption (panel A) and percentage of maximum predicted oxygen consumption (panel B) according to anatomic diagnosis. TGA-ASO: transposition great arteries-arterial switch operation, AVSD = atrioventricular septal defect; CoA = aortic coarctation; TOF = tetralogy of Fallot.

Table 4. Comparison between patients with CHD undergoing physical training and control group.

	Trained group	Control group	p value
N	46	46	
Age, median(IQR)	15 (13–17)	15 (13–18)	0,8
BMI, median (IQR)	20.4 (18.6–21.3)	20 (18.7–23.3)	0,2
NYHA II, n (%)	11 (30)	13 (28)	0,6
Max RER, Median (IQR)	1.17 (1.07–1.22)	1.10 (1.05–1.14)	0,04
Max workload(W), median (IQR)	141 (120–160)	110 (90–130)	<0.0001
Peak VO2 (ml/Kg/min), median(IQR)	36.7 (30.2–42.1)	28 (25–34.7)	<0.0001
Peak VO2 predicted (%), median(IQR)	84 (75–97)	61 (52–72)	<0.0001
VE/VCO2 slope, median(IQR)	29 (26–32)	27.7 (25–32.9)	0,4
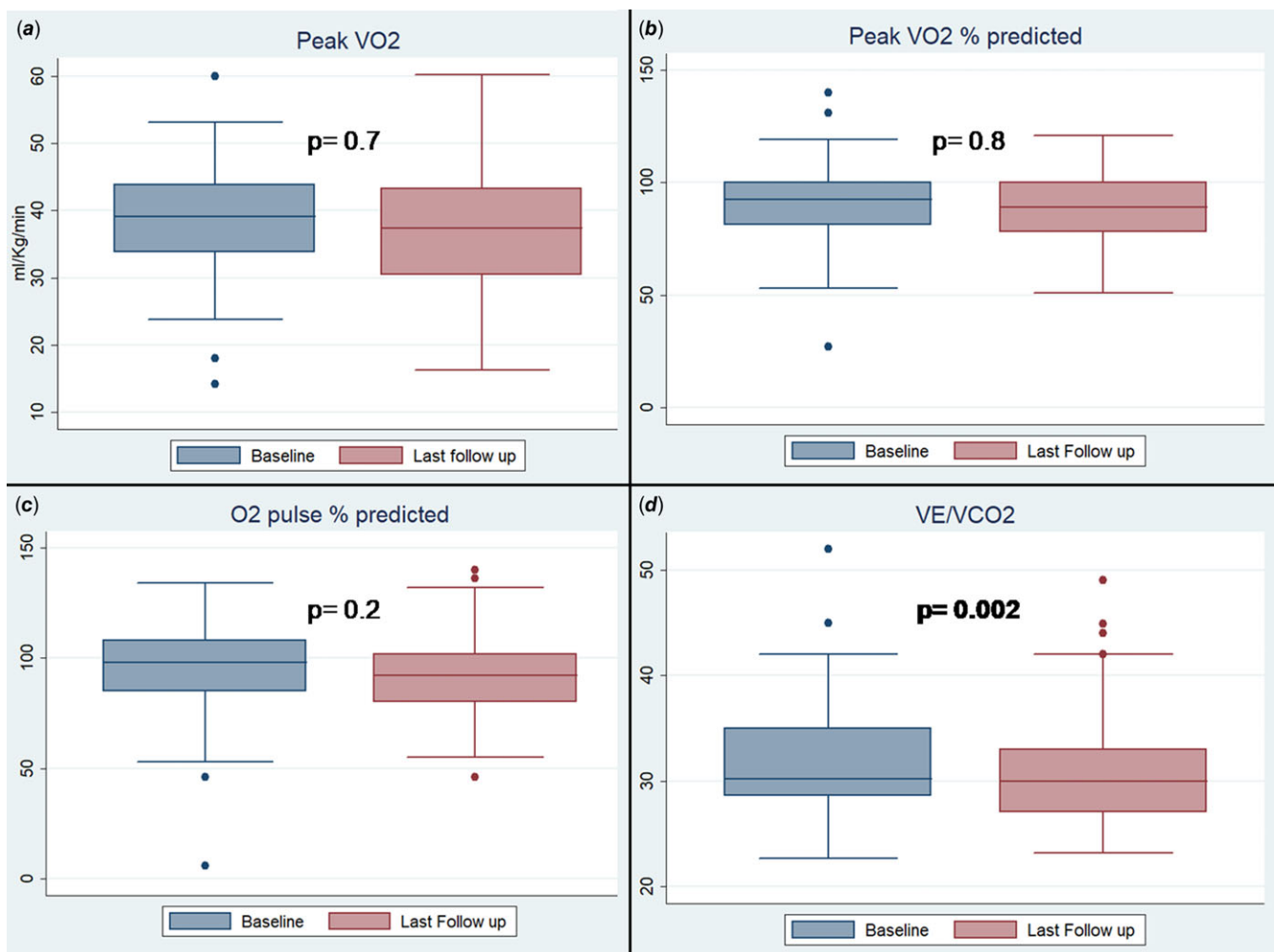
Figure 2. Pairwise comparison of maximum oxygen consumption (panel A) and percentage of maximum predicted oxygen consumption (panel B), percentage of maximum predicted O2 pulse (panel C) and ventilatory equivalent of CO2 (panel D).

References

1. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 2005; 112: 828–835.
2. Rhodes J, Ubeda Tikkanen A, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation 2010; 122: 1957–1967.
3. Duppen N, Takken T, Hopman MT, et al. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. Int J Cardiol 2013; 168: 1779–1787.
4. Paridon SM, Mitchell PD, Colan SD, et al. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. J Am Coll Cardiol 2008; 52: 99–107.
5. Norozi K, Gravenhorst V, Hobbiebrunken E, Wessel A. Normality of cardiopulmonary capacity in children operated on to correct congenital heart defects. Arch Pediatr Adolesc Med 2005; 159: 1063–1068.
6. Engelfriet P, Boersma E, Oechslin E, et al. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. Eur Heart J 2005; 21: 2325–2333.
7. Amiard V, Jullien H, Nassif D, Bach V, Maingourd Y, Ahmaidi S. Effects of home-based training at Dyspnea Threshold in children surgically repaired for congenital heart disease. Congenit Heart Dis 2008; 3: 191–199.
8. Fredriksen PM, Kahrs N, Blaasvaer S, et al. Effect of physical training in children and adolescents with congenital heart disease. Cardiol Young 2000; 10: 107–114.
9. Peja M, Boros A, Tóth A. Effect of physical training on children after reconstructive heart surgery. Orv Hetil 1990; 131: 2085–2086.
10. Klausen SH, Andersen LL, Søndergaard L, et al. Effects of eHealth physical activity encouragement in adolescents with complex congenital heart disease: the PReVaiL randomized clinical trial. Int J Cardiol 2016; 221: 1100–1106.
11. Duppen N, Etnel JR, Spaans L, et al. Does exercise training improve cardiopulmonary fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan circulation? A randomized controlled trial. Am Heart J 2015; 170: 606–614.
12. Dirks S, Kramer P, Schleiger A, et al. Home-based long-term physical endurance and inspiratory muscle training for children and adults with Fontan circulation-initial results from a prospective study. Front Cardiovasc Med 2022; 8: 784648.
13. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation 2012; 125: 250–259.
14. Banks L, McCrindle BW, Russell JL, Longmuir PE. Enhanced physiology for submaximal exercise in children after the Fontan procedure. Med Sci Sports Exerc 2013; 45: 615–621.
15. Taylor BJ, Coffman KE, Summerfield DT, Issa AN, Kasak AJ, Johnson BD. Pulmonary capillary reserve and exercise capacity at high altitude in healthy humans. Eur J Appl Physiol 2016; 116: 427–437.