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Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data

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Aims We aimed to investigate the distribution of exercise capacity across the spectrum of adult congenital heart disease (ACHD) using own data and the published experience and to provide diagnosis, gender-, and age- specific reference values.

Methods and results Publications describing exercise capacity in ACHD patients using cardiopulmonary exercise testing (CPET) were identified ($n = 2286$ patients in 23 papers). In addition, we included 2129 patients who underwent CPET at our own institution. The majority of patients (80%) had reduced peak oxygen uptake (peak VO_2) compared with normal values (defined as $<90\%$ of predicted peak VO_2). There were significant differences in peak VO_2 between subgroups of patients, with the lowest values seen in patients with Eisenmenger syndrome and complex heart disease. However, even in patients with simple lesions, peak VO_2 was on average significantly reduced compared with normal values. Based on a large number of observations we herewith provide gender- and age-specific peak VO_2 centile plots for the most common lesions (Tetralogy of Fallot, systemic right ventricle, Ebstein anomaly and Fontan–palliation) and relate disease-specific exercise capacity to that required for specific activities of daily life, sports, and occupations.

Conclusion We provide age-, gender-, and diagnosis-specific data on peak VO_2 levels across the spectrum of ACHD allowing to compare the exercise capacity of individual patients with that of their peer patients. These data should be helpful in interpreting CPET results, guiding therapy, and advising patients on activities of daily life, sports participation, and choice of occupation.

Keywords Adult congenital heart disease • Tetralogy of fallot • Transposition of the great arteries • Fontan procedure • Eisenmenger syndrome • Exercise test

Introduction

Most patients born with congenital heart disease are expected to reach adulthood in the current era.[1] Owing to the frequent late complications, however, many of them require and will benefit from life-long cardiac follow-up.[2,3] Among the different screening tools employed during such periodic follow-up, cardiopulmonary exercise testing (CPET) has emerged as one of the most valuable. It is non-invasive, enables risk stratification with regard to morbidity and mortality, and helps deciding on the need and timing of therapeutic interventions. The interpretation of CPET results in patients with adult congenital heart disease (ACHD) remains

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challenging, however. It is well known that exercise capacity is reduced in these patients. Relating exercise capacity to normal values obtained in healthy volunteers may, however, not tell the whole story in ACHD patients. It is obvious that one cannot expect an Eisenmenger patient to achieve a similar peak oxygen uptake (peak VO_2) as a patient with a simple cardiac lesion. As some (variable) level of impairment in peak VO_2 is to be expected it may be more helpful to interpret the achieved level of exercise capacity in comparison with what would be usual/expected given the patient's age, gender, and underlying diagnosis. Comparing an individual patient to his/her peer patients may inform clinicians if this represents a 'good' or 'bad' exercise capacity for a given patient group.

Exercise capacity has been assessed in many studies both in adult and paediatric patients with congenital heart disease. Protocols differ between centres and, thus, the results cannot be generalized to all patients with this disease. Ideally, every centre should develop its own database and reference values. Given the wide anatomic spectrum of ACHD patients and the variable patient volume attached to different centres, this may not be practicable for most centres. In the absence of such centre specific data, combining the available evidence may provide best estimates of expected exercise capacity. In addition to averaging out outliers by combining data, increasing patient numbers reduces stochastic uncertainty and should decrease variability of the data.

Our aim in this study was to[1] compare a large ACHD-CPET data set from our institution with CPET data reported in the literature;[2] to combine available data to investigate the expected peak VO_2 in relation to patient gender and age in the most prevalent ACHD diagnostic groups and, thus provide disease specific reference values and[3] to examine the potential relation between disease specific exercise limitation and activities of daily life/certain occupations, thus assisting clinicians in advising patients.

Methods

Patients

We retrospectively reviewed all cardiopulmonary exercise tests performed in ACHD patients between March 1999 and February 2011 at the Royal Brompton Hospital, London. Exercise tests had been performed as part of their routine clinical assessment.

We also searched PubMed for publications investigating cardiopulmonary exercise capacity in ACHD patients published between 01/01/1985 and 01/06/2011. The search was performed separately for every diagnosis listed in the *Table 1* using the MESH phrase 'exercise test' and the MESH phrase describing the disease.

Measurements

Details of the cardiopulmonary testing at the Royal Brompton Hospital have been published previously.[4] Briefly, CPET was performed in patients from our institution on a treadmill according to a modified Bruce protocol with an additional first stage at which the patient walks at a velocity of 1 mile/h and a gradient of 5% for 3 min. Oxygen uptake, carbon dioxide production, and ventilation were measured continuously using a computerized breath-by-breath analyser. The VE/VCO_2 slope was calculated by linear regression analysis of all data acquired during the exercise period.

Activities of life data

The minimal peak VO_2 required to perform daily life activities, sports, and selected occupations was calculated based on the 'Compendium of Physical Activities' maintained by the Arizona State University.[5] The Compendium provides energy costs for several hundred activities with metabolic equivalents values (MET) based on the published literature. The oxygen uptake (VO_2) for each activity was calculated by multiplying the MET value by $3.5\ mL \cdot kg^{-1} \cdot min^{-1}$. The values obtained represent average (peak) oxygen uptake. As subjects should be able to perform most of the listed activities continuously, without resorting to anaerobic metabolism, patients should remain below their anaerobic threshold (AT). Based on the mean relation of

Table 1 Cardiopulmonary exercise data published in the literature

Diagnosis	Patients with reported pVO_2				Patients with reported VE/VCO_2				
	n	Age	pVO_2	Male (%)	*n*	Age	VE/VCO_2	Male (%)	References
ASD	222	42.4	21.9 ± 7.9	47.7	78	45.0	32.3 ± 3.4	61.3	23,24,28,45
ccTGA	61	31.6	20.9 ± 7.4	55.7	21	30.0	37.2 ± 4.3	61.3	23,35,45
CoA	100	31.0	27.5 ± 7.0	61.2	28	27.0	30.1 ± 2.3	61.3	35,45
Complex	20	33.6	15.9 ± 3.4	50.0	—	—	—	—	35
Ebstein	230	22.9	21.1 ± 6.7	51.5	28	31	37.4 ± 2.6	61.3	19,23,30,35,45
Eisenmenger	43	41.8	13.0 ± 4.1	38.7	19	39.0	63.4 ± 5.8	61.3	35,45
Fontan	590	19.4	22.7 ± 5.8	57.6	65	23.0	40.2 ± 3.5	61.3	18,20,23,27,29,31,33,35–37,45
TGA-arterial switch	104	12.4	38.9 ± 9.1	63.5	60	13.3	30.7 ± 4.4	73.3	21,26
TGA-atrial switch	391	25.3	24.3 ± 7.5	64.5	274	26.3	33.4 ± 7.8	64.6	16,23,25,35
ToF	487	29.6	24.2 ± 6.8	55.3	124	26.0	31.1 ± 4.6	61.3	23,32,34,35,45
Valvular	38	32.0	26.6 ± 9.1	61.3	38	32.0	32.2 ± 2.9	61.3	45

Age is expressed in years, peak VO_2 (pVO_2) in mL/kg/min. VE/VCO_2 stands for VE/VCO_2 slope. ASD, atrial septal defect; TGA, transposition of the great arteries; ccTGA, congenitally corrected TGA; CoA, coarctation of the aorta; Complex, complex lesions including patients with cyanosis; ToF, tetralogy of Fallot; Valvular, collective of patients with various valvular lesions.

(VO_2 at AT)/peak VO_2 in our cohort (=0.70 ± 0.13) the VO_2 result was divided by 0.7 (peak VO_2 = MET · 3.5 mL · kg^{-1} · min^{-1} · 0.7^{-1}) to estimate the VO_2 at or below AT and therefore required to sustain activity levels for extended periods of time.

Statistical analysis

The distribution of data was assessed for normality using the D'Agostino–Pearson test and data were log-transformed if there was significant evidence for departure from normality. In case of normal distribution, the comparison between two groups was performed using unpaired *t*-test and Welch test in case of unequal variances. For data violating, a normal distribution Mann–Whitney *U* tests were used. Based on data reported in the literature, we have calculated a weighted mean and a pooled standard deviation for every subgroup as described previously.[6] Categorical variables were compared using χ^2 test. When more than two data sets were compared one-way ANOVA was used. All tests were performed two-sided.

The predicted peak VO_2 (i.e. reference value for healthy individuals) for men and women was calculated using the formula published by Wassermann taking the mean age in every subgroup as well as reported average weight and height.[7,8] In groups consisting of men and women, a weighted mean peak VO_2 was calculated. Centile curves for describing the relationship between peak VO_2, age and gender were generated using a combined method based on the Cole and Green as well as Rigby and Stasinopoulos algorithm using the GAMLSS package for *R*.[9–12] For all analyses, a *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using MedCalc for Windows, version 11.6.1.0 (MedCalc Software, Mariakerke, Belgium) and R-package version 2.13.0.

Results

Data of 4415 patients were analysed. This included 2129 patients from our own institution. *Table 2* provides information on underlying demographics, diagnosis, and distribution of peak VO_2 and VE/VCO_2 slope. The literature search revealed 23 papers reporting peak VO_2 data in 2286 and VE/VCO_2 data in 735 patients (*Table 1*).

The average of peak VO_2 and VE/VCO_2 slope was comparable between the own data and data reported in the literature for most diagnostic subgroups (*Table 2*, *Figure 1*). This is illustrated by the good visual agreement between histograms (representing the own data) and the density distribution lines (showing the distribution of the entire cohort). Only in patients with transposition of the great arteries (TGA) after arterial switch operation, peak VO_2 reported in the literature was significantly higher than that observed in our cohort (38.9 ± 9.1 vs. 31.9 ± 9.2 mL · kg^{-1} · min^{-1}, $P < 0.0001$). Our patients, however, were significantly older (21.6 ± 4.1 vs. 12.4 ± 3.2 years, $P < 0.0001$) compared with the published cohort. In addition, peak VO_2 values for patients with tetralogy of Fallot (ToF) from our institution and those reported in the literature were statistically significantly different (25.2 ± 8.5 vs. 24.2 ± 6.8 mL · kg^{-1} · min^{-1}, $P = 0.04$). The absolute difference in mean peak VO_2, however, was small (1.0 mL · kg^{-1} · min^{-1} being corresponding to ~4% of mean) and the high number of patients in this subgroup ($n = 1055$) probably accounts for the significance level.

Distribution of peak VO_2 and VE/VCO_2 slope in various subgroups

Owing to the differences in age, we compared peak VO_2 in every diagnostic subgroup with the predicted peak VO_2 for sedentary individuals of the same age and gender distribution (*Figure 1*) using reference values published by Wasserman *et al.*[7] There were significant differences in peak VO_2 between subgroups of patients ($P < 0.001$ on one-way ANOVA based on the own data). Peak VO_2 was found to be lowest in patients with Eisenmenger syndrome and complex heart disease (mean ± SD: 43 ± 13 and 46 ± 16% of predicted peak VO_2, respectively) and was highest in patients with TGA after arterial switch operation, in the cohort of patients with various forms of valvular heart disease and in patients with repaired aortic coarctation (89 ± 22,

Table 2 Cardiopulmonary exercise data from our own institution

Diagnosis	*n*	Age	pVO_2	VE/VCO_2	Male (%)	*P*-value, pVO_2	*P*-value, VE/VCO_2
ASD	128	44.8	22.4 ± 8.4	33.7 ± 10.8	37.5	0.58	0.27
ccTGA	68	36.0	21.1 ± 7.9	35.3 ± 13.8	52.9	0.88	0.54
CoA	119	30.3	27.8 ± 9.9	30.2 ± 8.2	63.0	0.80	0.95
Complex	85	31.7	15.7 ± 5.9	52.0 ± 19.5	52.9	0.88	—
Ebstein	102	38.2	21.7 ± 7.9	34.9 ± 10.1	52.0	0.48	0.2
Eisenmenger	76	39.4	12.2 ± 3.8	71.8 ± 55.0	28.9	0.29	0.51
Fontan	321	21.0	22.8 ± 7.4	34.4 ± 10.1	56.6	0.82	<0.0001*
TGA-arterial switch	46	21.6	31.9 ± 9.2	29.8 ± 4.7	78.3	<0.0001*	0.31
TGA-atrial switch	98	31.3	24.9 ± 7.5	33.5 ± 10.6	55.1	0.48	0.92
ToF	568	32.3	25.2 ± 8.5	31.7 ± 8.9	55.7	0.04*	0.47
Valvular	401	35.9	26.3 ± 9.9	32.6 ± 10.9	54.4	0.86	0.82
VSD	117	37.6	23.5 ± 9.3	34.1 ± 11.1	53.8	—	—

P-values compare corresponding sets of data (pVO_2 and VE/VCO_2) between *Tables 1* and *2*. Age is expressed in years, peak VO_2 in mL/kg/min. VE/VCO_2 stands for VE/VCO_2 slope. ASD, atrial septal defect; TGA, transposition of the great arteries; ccTGA, congenitally corrected TGA; CoA, coarctation of the aorta; Complex, complex lesions including patients with cyanosis; ToF, tetralogy of Fallot; Valvular, collective of patients with various valvular lesions; VSD, ventricular septal defect. *$P < 0.05$.

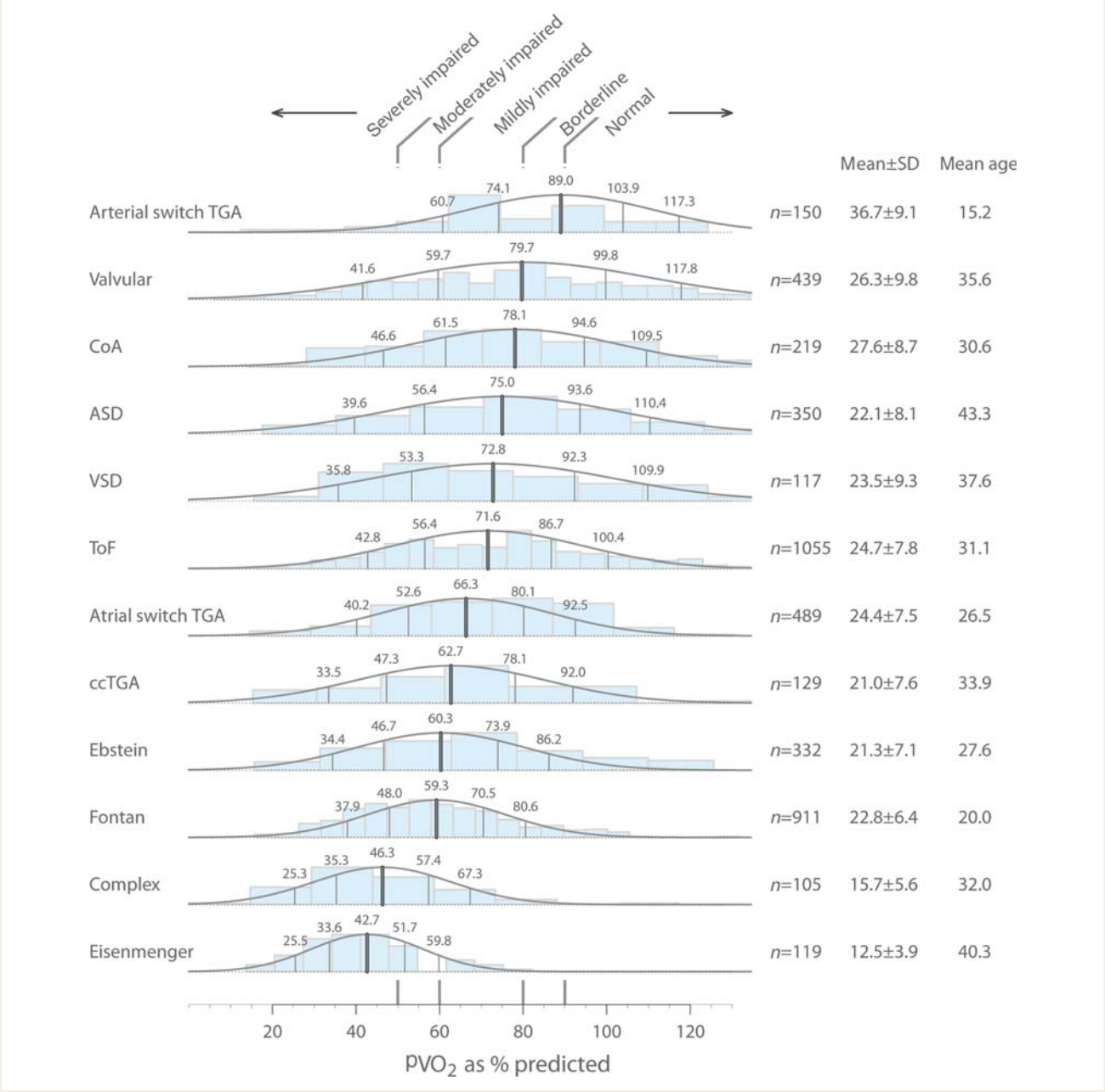

Figure 1 Peak oxygen uptake (peak VO_2) data expressed as % of predicted value. Histograms represent data from our own institution. The density lines above histograms and the numbers to the right of the graph relate to all patients with a given diagnosis. The numbers above the density lines indicate %peak VO_2 values for the 10, 25, 50, 75 and 90th centile. ASD, atrial septal defect; ccTGA, congenitally corrected TGA; CoA, coarctation of aorta; Complex, complex congenital heart disease (including univentricular hearts); Ebstein, Ebstein anomaly; Eisenmenger, Eisenmenger syndrome; Fontan, patients after Fontan palliation; TGA, transposition of the great arterial; ToF, tetralogy of Fallot; Valvular, mixed collective of patients with congenital valvular heart disease; VSD, ventricular septal defect.

80 ± 30, and 78 ± 25% of predicted peakVO_2, respectively). There were also significant differences in VE/VCO_2 slope ($P < 0.001$, on one-way ANOVA) with the highest values found in patients with Eisenmenger syndrome and complex heart disease (72 ± 55 and 52 ± 19, respectively) and the lowest values in patients with TGA after arterial switch and corrected aortic coarctation (30 ± 5 and 30 ± 8, respectively) (*Table 2*). *Table 1* informs about the distribution of peak VO_2 and VE/VCO_2 slope (mean and standard deviation) in published studies.

In most diagnostic subgroups men achieved significantly higher peak VO_2-values than women (*Table 3*). Therefore, when looking at the peak VO_2 levels required to perform various activities (such as movement, sporting activities, occupation, or home activities), more women than men were found to have an exercise

Table 3 Comparison between age, peak oxygen uptake (peak VO_2) and exercise time between men and women in the own population

	Age			pVO_2			Exercise time		
	Male	Female	*P*-value	Male	Female	*P*-value	Male	Female	*P*-value
ASD	50.1 ± 17.2	41.6 ± 17.4	0.01*	24 ± 10.3	21.4 ± 7.0	0.14	592 ± 255	576 ± 208	0.72
ccTGA	35.5 ± 13.7	36.5 ± 16.0	0.78	22.3 ± 8.5	19.7 ± 6.9	0.17	629 ± 190	506 ± 181	0.01*
CoA	29.3 ± 11.4	32.2 ± 10.8	0.18	30.9 ± 9.8	22.3 ± 7.2	<0.0001*	731 ± 243	624 ± 208	0.02*
Complex	32.6 ± 14.1	30.7 ± 10.9	0.49	16.6 ± 6.6	14.6 ± 4.9	0.10	448 ± 176	366 ± 162	0.03*
Ebstein	39.3 ± 15.1	36.0 ± 15.5	0.29	24.1 ± 8.3	19.1 ± 6.7	0.001*	619 ± 242	552 ± 185	0.13
Eisenmenger	37.4 ± 15.9	40.2 ± 12.7	0.46	11.9 ± 4.1	12.4 ± 3.7	0.62	325 ± 177	334 ± 158	0.83
Fontan	21.8 ± 8.6	23.5 ± 9.4	0.054	24.3 ± 8.5	20.1 ± 5.6	<0.0001*	654 ± 208	555 ± 147	0.0002*
Art. switch TGA	21.6 ± 4.1	20.9 ± 3.8	0.62	33.8 ± 9.0	25.2 ± 6.6	0.003*	820 ± 195	636 ± 135	0.004*
Atr. switch TGA	31.4 ± 10.2	31.2 ± 7.2	0.91	27.4 ± 7.3	21.8 ± 6.5	0.0001*	714 ± 211	555 ± 171	<0.0001*
ToF	33.1 ± 13.5	31.4 ± 12.3	0.13	27.2 ± 9.0	22.5 ± 6.8	<0.0001*	715 ± 217	609 ± 194	<0.0001*
Valvular	35.6 ± 15.4	36.1 ± 15.9	0.73	29.2 ± 10.5	22.7 ± 7.7	<0.0001*	697 ± 242	571 ± 226	<0.0001*
VSD	37.5 ± 16.5	37.9 ± 12.3	0.9	26.6 ± 10.0	19.9 ± 7.1	<0.0001*	663 ± 219	571 ± 197	0.03*

Age is expressed in years, peak VO_2 (pVO_2) in mL/kg/min, exercise time in seconds. ASD, atrial septal defect; TGA, transposition of the great arteries; ccTGA, congenitally corrected TGA; CoA, coarctation of the aorta; Complex, complex lesions including patients with cyanosis; ToF, tetralogy of Fallot; Valvular, collective of patients with various valvular lesions; VSD, ventricular septal defect. *$P < 0.05$.

capacity below the required threshold in each subgroup (*Figure 2*). Interestingly, at the lower end of the spectrum of exercise capacity, notably in Eisenmenger patients, no significant difference between men and women existed and, if anything, women had slightly higher peak VO_2 values.

Overall, there was a moderate correlation between peak VO_2 and age in our patients ($r = -0.35$, $P < 0.0001$). For the subgroups of patients with sufficient number of observations, centile curves relating peak VO_2 distribution to age and stratified by gender were generated to illustrate the average peak VO_2 and to show 10, 25, 75, and 90th percentiles (*Figure 3*).

In addition, *Figure 4* shows centile curves for percentage of predicted peak VO_2 in selected diagnoses, while *Figure 5* gives an overview over peak VO_2 in different diagnostic groups, splitting patients in three age groups.

Discussion

Peak VO_2 and VE/VCO_2 slope are well-established measures of exercise tolerance. They have been shown to correlate with New York Heart Association (NYHA) functional class, quality of life and to be strong independent predictors of morbidity and mortality, both, in the setting of heart failure and congenital heart disease.[13–15]

The distribution of exercise capacity across the spectrum of ACHD has been investigated by numerous studies.[16–37] Most of the studies performed so far however were small, single centre, based or focused on a limited number of diagnoses and, therefore, have provided only a limited overview of the distribution of exercise capacity in this growing patient population. Moreover, in most of these studies, values for exercise parameters were reported without taking into account patient age or gender. Since significant differences in exercise capacity between males and females exist, this latter aspect is, nevertheless, relevant. In this study, we aggregated the available data on exercise capacity in ACHD. Comparing CPET results in ACHD patients from our institution with the data published by other centres, we found that by and large no relevant difference in peak VO_2 and VE/CO_2 slope exists. To our best knowledge, this is the first study to indicate that exercise capacity data in ACHD patients can be generalized and results are not centre specific.

Exercise capacity distribution across the spectrum of ACHD patients

Our study confirms that exercise capacity differs significantly across the spectrum of ACHD. In accordance with previous studies, patients with Eisenmenger syndrome and complex congenital heart disease (including patients with univentricular circulation) were found to have the lowest peak VO_2 values and highest VE/VCO_2 slope values.[17,23] At the other end of the spectrum, patients with aortic coarctation and patients with TGA after arterial switch operation were found to have the highest peak VO_2 values and lowest VE/VCO_2 slope values. However, even in these latter groups, peak VO_2 values were on average significantly reduced when compared with normal values ($P < 0.0001$ for both). The observation that TGA patients after arterial switch operation had the highest peak VO_2 values among ACHD patients, may in part relate to the younger age of this patient group, but, it also suggests that despite being born with a lesion of high complexity (TGA) restoring normal anatomy and physiology early in life may result in almost normal exercise capacity later on in adolescent and adult. Comparing exercise capacity of TGA patients in the published literature with a mean age of ~12 years with our own cohort of patients (mean age ~22 years) revealed a reduced percentage predicted peak VO_2 in the latter. One could speculate that this reflects on-going morbidity and the onset of

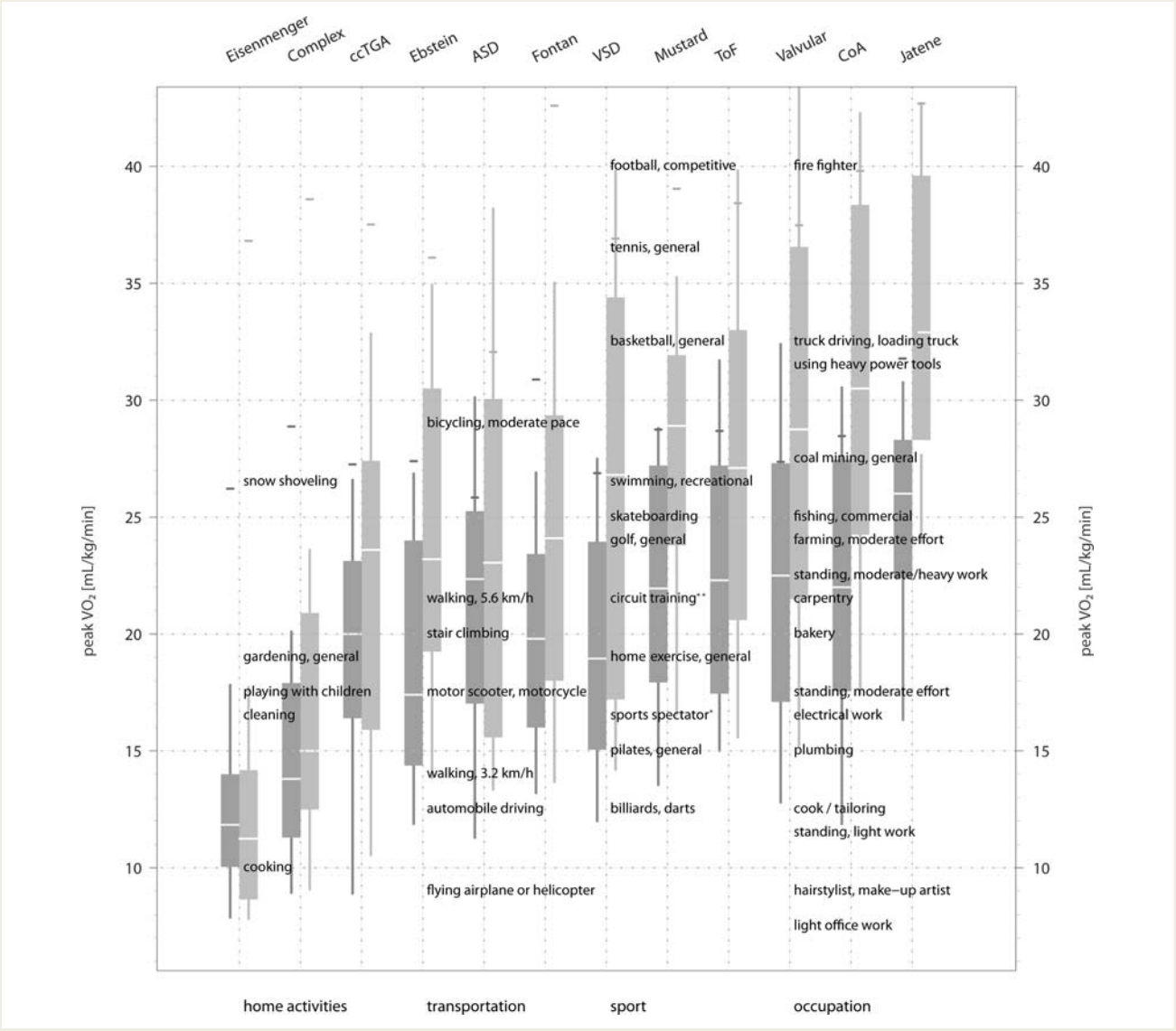

Figure 2 Peak oxygen consumption (peak VO_2) for various diagnostic groups stratified by gender and compared with oxygen consumption derived from estimated average energy expenditure for different types of activities based on values provided in the literature.[5] It should be noted that these are point estimates and differences depending on gender and anthropometric measures as well as dexterity or mechanical efficiency in performing an activity are likely to exist. For details see text. Each box and whiskers graph represents (from bottom to top) the 10, 25, 50, 75, and 90th quantile. Dark grey—female, light grey—male. The short horizontal lines plotted outside the boxes indicate 100% of the predicted peak VO_2 value. (*), sports spectator, very excited, emotional; (**), moderate effort.

late complications such as right ventricular outflow tract (RVOT) obstruction. In fact, Giardini *et al.* have recently reported that patients with RVOT obstruction have significantly lower exercise capacity compared with patients without.[26]

Impact of gender on exercise capacity

In the current paper, we analysed CPET data for men and women with ACHD separately and found significant differences between genders. While this may not be surprising given that peak VO_2 is generally 20–30% higher in healthy men compared with women, this difference in healthy subjects is largely explained by peripheral factors.[38] This includes a higher muscle mass, a higher haemoglobin concentration (i.e. higher oxygen carrying capacity of blood) and a better physical conditioning of males (with men being generally more physically active).[39,40] In patients with heart disease, however, it could be argued that cardiac limitations predominate, reducing, or eliminating the effect of the periphery on exercise capacity. The results of the current study in ACHD patients with simple/intermediate complexity lesions suggest that significant differences in peak VO_2 continue to exist between males and females. This finding is consistent with a study performed in patients with acquired heart failure,[40] thus highlighting the central role of the skeletal muscle abnormalities and O_2 extraction[41] even in the setting of chronic heart disease. In contrast, we

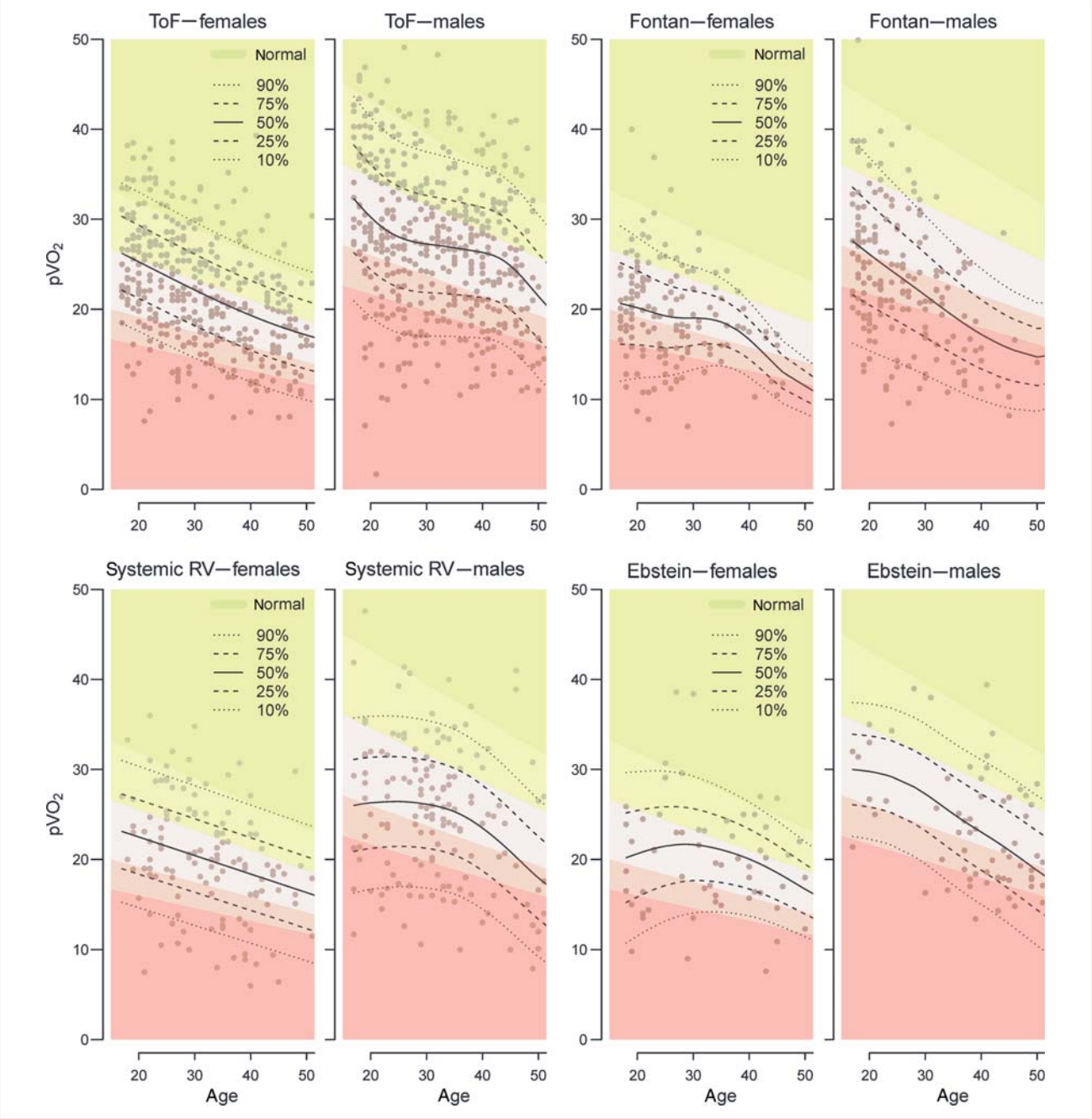

Figure 3 Centile curves for peak VO_2 (pVO_2) in mL/kg/min for patients with tetralogy of Fallot, after Fontan palliation (Fontan), a systemic right ventricle (congenitally corrected transposition of the great arteries or transposition of the great arteries after atrial switch operation) and Ebstein anomaly. Background colours represent the level of exercise impairment compared with reference values for normal individuals (green, normal; pale green, borderline reduced exercise capacity; pale red, mildly impaired exercise capacity; red, moderately impaired exercise capacity; dark red, severely impaired exercise capacity).

found no significant difference in peak VO_2 between males and females with Eisenmenger physiology (i.e. the most compromised subgroup). This suggests that disease-specific factors, such as reduced cardiac output, cyanosis, and restricted pulmonary blood flow, limit exercise tolerance in this setting. We contend that the clinical consequence of these findings is that improving exercise capacity through aerobic training is probably worthwhile in virtually all ACHD patients. In addition, the differences in peak VO_2 between men and women may impact on the ability to perform activities of daily life and be of importance for patient counselling.

According to Wassermann *et al.*,[7] predicted (normal) peak VO_2 falls slowly in a sedentary woman of average weight and height with age ($0.28\ mL \cdot kg^{-1} \cdot min^{-1}$/year) and reaches a value of $20\ mL \cdot kg^{-1} \cdot min^{-1}$ by the age of 62.[7,42] The current study

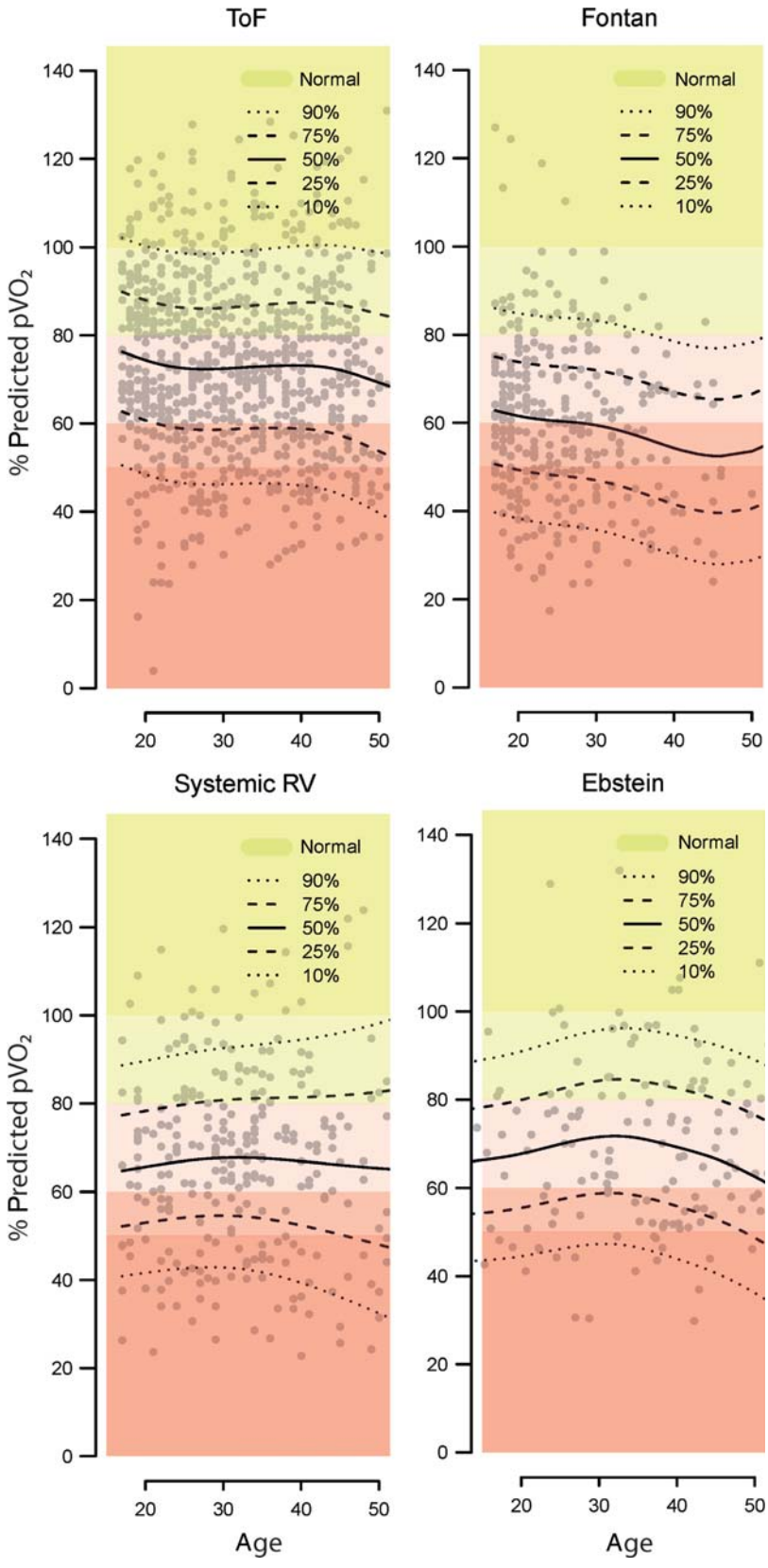

Figure 4 Centile curves for peak VO_2 (pVO_2) as percentage of predicted pVO_2 for patients with tetralogy of Fallot, after Fontan palliation (Fontan), a systemic right ventricle (congenitally corrected transposition of the great arteries or transposition of the great arteries after atrial switch operation) and Ebstein anomaly. Background colours represent the level of exercise impairment compared with reference values for normal individuals (green, normal; pale green, borderline reduced exercise capacity; pale red, mildly impaired exercise capacity; red, moderately impaired exercise capacity; dark red, severely impaired exercise capacity).

		Centiles—male					Centiles—female				
	Age	10%	25%	50%	75%	90%	10%	25%	50%	75%	90%
Arterial switch TGA	20–29	25.3	27.9	31.8	38.9	41.2	18.6	23.0	26.9	29.7	33.8
ASD	20–29	20.1	23.6	30.7	38.4	43.0	21.1	23.2	27.4	31.2	34.5
	30–39	18.5	20.5	25.3	36.6	44.2	10.7	16.6	19.5	24.1	26.8
	40–50	14.5	19.9	23.1	30.1	40.8	10.5	15.5	20.5	23.2	24.3
Atrial switch TGA	20–29	21.4	24.7	29.5	32.0	35.8	16.1	20.3	25.2	28.5	30.8
	30–39	16.1	21.9	28.3	31.5	34.4	10.3	15.5	19.2	22.2	26.2
	40–50	21.8	24.0	24.8	30.8	31.7	16.1	16.3	19.3	21.2	24.7
ccTGA	20–29	6.6	9.8	20.5	29.2	31.9	15.3	20.6	21.4	23.8	25.0
	30–39	17.4	23.2	27.6	32.5	34.0	20.9	22.2	24.1	27.0	30.2
	40–50	15.0	17.2	22.4	24.8	33.0	13.0	16.3	18.7	19.3	20.3
CoA	20–29	24.0	29.3	34.0	39.4	43.6	16.9	18.1	27.1	29.6	32.0
	30–39	20.2	21.6	24.6	32.0	38.5	11.9	18.9	21.2	22.7	25.8
	40–50	10.6	15.6	19.3	25.6	35.2	13.6	17.1	18.3	25.5	27.9
Complex	20–29	8.2	9.2	13.7	17.7	23.0	10.2	12.1	13.9	16.3	19.5
	30–39	9.8	12.5	18.3	20.0	22.4	10.1	12.2	13.2	14.9	17.0
	40–50	11.3	13.3	14.8	16.9	19.5	7.4	9.6	13.6	17.3	18.5
Ebstein	20–29	28.2	33.1	34.3	35.0	37.4	14.1	14.5	20.6	25.8	35.6
	30–39	14.1	23.0	23.4	25.7	30.8	15.2	16.6	19.9	22.3	24.5
	40–50	17.8	20.4	26.9	29.3	33.0	9.9	13.7	18.4	26.9	27.0
Eisenmenger	20–29	10.8	12.1	14.2	16.2	17.5	8.6	11.2	11.8	14.4	16.1
	30–39	6.5	8.2	12.1	13.7	16.9	9.9	11.4	13.8	15.2	19.0
	40–50	8.4	8.9	9.8	12.1	13.4	7.3	9.9	11.7	13.6	14.8
Fontan	20–29	13.4	20.2	23.7	30.5	34.6	12.6	14.8	19.2	23.3	25.6
	30–39	13.1	15.6	17.2	22.0	24.6	15.8	16.1	18.7	21.6	23.5
	40–50	11.1	12.2	14.1	14.9	15.4	11.1	11.9	14.0	16.6	17.0
ToF	20–29	17.5	23.1	27.8	33.6	39.7	17.9	19.0	25.7	29.5	32.6
	30–39	18.2	21.1	26.4	29.2	34.2	16.0	17.0	20.6	25.1	28.5
	40–50	16.1	18.4	26.7	32.4	36.1	11.4	15.2	17.7	22.9	26.5
Valvular	20–29	19.7	26.3	32.4	40.0	44.7	16.2	21.0	25.7	28.2	35.1
	30–39	20.9	26.0	30.2	36.5	39.9	14.7	18.5	22.5	25.9	28.0
	40–50	12.3	15.9	25.6	29.9	31.8	12.7	16.9	22.5	26.6	31.6
VSD	20–29	19.8	23.5	32.3	35.0	36.5	14.5	15.4	18.1	25.4	26.4
	30–39	14.6	17.2	23.5	27.6	34.4	10.7	14.7	18.1	25.3	31.6
	40–50	10.1	17.8	25.2	30.3	32.0	12.0	14.3	19.5	22.8	23.5

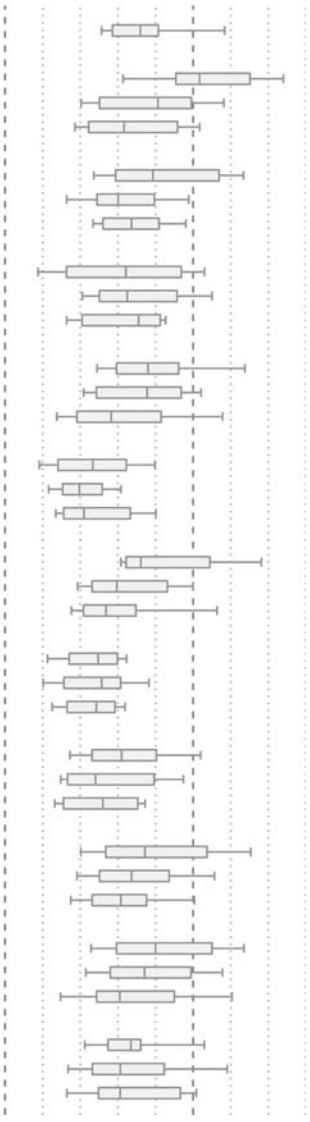

Figure 5 Centile values for peak Vo_2 (pVO_2) based on the own data and shown separately for men and women (in mL/kg/min). The Boxplots show pVO_2 as percentage of predicted pVO_2 and represent 10, 25, 50, 75, and 90 centile of predicted pVO_2.

shows that differences in peak VO_2 between genders are significant and already evident at a younger age. Applying the peak VO_2 cut-off values for light, moderate, and severely impaired exercise tolerance in heart failure as proposed by Weber *et al.* (20/16/10 mL · kg^{-1} · min^{-1}), significantly more women than men were in the more compromised groups (6/22/21/51 vs. 4/13/11/72%, respectively, $P < 0.0001$).[42] This may have practical consequences. As illustrated in *Figure 2* for many basic activities of daily life, the oxygen demand lies above 16 and 20 mL · kg^{-1} · min^{-1}, respectively. Women were found to be twice as likely as men, however, to have peak VO_2 values below these limits (odds ratio 1.7 and 2.4, respectively, $P < 0.0001$ for both).

Choice of occupation

Unemployment rates have been reported to be up to five times higher in ACHD patients compared with the general population.[43] Interestingly, the risk of unemployment was reported not to be related to the severity of the underlying cardiac lesion. Most patients with complex and cyanotic heart disease (or their parents) know that their exercise capacity is reduced and this should inform timely planning of future occupation. Many patients with less severe lesions and their parents may, however, not be aware of a reduced exercise capacity.[17,44] This may lead to inappropriate decisions regarding vocational or professional choices and may—in turn and at least in part—explain the high

unemployment rates reported among patients with less severe lesions. The data presented in the current study could be useful in advising patients in career matters. *Figure 2* provides estimates of peak VO_2 required for certain (selected) occupations. Information for additional jobs is available in the literature or on the *Compendium of Physical Activities* website.[5] Comparing the required peak VO_2 values with the distribution of oxygen uptake expected for a given condition should assist clinicians in deciding how likely it is that young patients with CHD may be able to cope with the physical demands of a job as a career.

Percentiles of exercise capacity

The percentiles of expected exercise capacity presented in *Figure 3* are one of the key deliverables of the current study. They were constructed based on CPET data from our centre to allow assessing an individual patient's peak VO_2 in relation to that of his/her peers of similar age and gender. These graphs indicate whether a patient has above or below average peak VO_2 and whether a patient's peak VO_2 lies below the expected 25 or 10th percentile.

We believe that this information is relevant to clinical decision-making; for example, when evaluating a ToF patient for surgical replacement of the pulmonary valve because of severe regurgitation. As the vast majority of ToF patients have some degree of exercise intolerance, the absolute peak VO_2 value or the percentage of predicted peak VO_2 achieved are of limited help in this case. Knowing that the patient has a 'good' or 'bad' exercise capacity *by ToF-standards* should be more helpful, however. This is analogous to nobody expecting a ToF patient with pulmonary regurgitation to have a normal sized right ventricle but too big a ventricle (compared with other ToF patients) could serve as a criterion to recommend surgery.

Limitations of the study

This was a retrospective study performed at a tertiary ACHD centre. Furthermore, published data included in the analysis were by and large from tertiary ACHD centres, too. Selection bias, therefore, with inclusion of sicker patients with more reduced exercise capacity cannot be excluded. This could, for example, account for the fact that even patients with simple defects such as atrial septal defects, ventricular septal defects, and aortic coarctation were found to have reduced exercise capacity on average. Beyond the effect of the cardiac lesion, however, extracardiac factors such as deconditioning and peripheral muscle changes could also—at least in part—account for this observation. This is a cross-sectional study and provides the best estimate of exercise capacity of contemporary ACHD patients of various ages. It was not intended to study, and the results should not be used to, estimate the change in peak VO_2 with ageing of an individual patient. This is because young patients included may have undergone different surgical/interventional procedures compared with older patients. For example, a 20-year-old Fontan patient is likely to have undergone a total cardiopulmonary anastomosis-operation, while a 40-year-old Fontan, almost certainly had a 'classic' Fontan. The decline in exercise capacity with ageing for the two patient groups, however, may be different as previously shown.[13] We acknowledge, therefore, that even within a given diagnostic ACHD subgroup, heterogeneity with regard to previous operation exists (as illustrated by the Fontan example) and, therefore, clinicians should account for this fact when using the data. Although we found no evidence of relevant differences between peak VO_2 reported in the literature and values obtained at our centre, we cannot exclude the possibility that such differences may exist for other centres. The data presented here represent a best estimate based on available information and require validation over time. The centile curves provided, despite being based on a large number of patients, are estimated based on a limited number of observations at the more extreme end of the age spectrum. This should be taken into account when interpreting the curves. In addition, further studies are required to investigate the reasons for the differences in the kinetics of the decline in exercise capacity between different diagnostic groups but also between genders. The reference values used for activities of life, sports, and occupation represent estimated average values and should not be taken as absolute cut-off values but rather be used for guidance only. In addition, other aspects of occupations or activities such as dexterity or mechanical efficiency in performing a task may be relevant but it is impossible to account for these factors in a study like ours.

Conclusions

The current study reinforces the fact that exercise capacity is reduced in ACHD patients with the lowest values seen in patients with Eisenmenger syndrome and those with complex heart disease. Albeit even patients with simpler lesions are limited compared with reference values. Based on a large number of observations, we herewith provide gender- and age-specific reference peak VO_2 centile plots for the most common lesions (ToF, systemic right ventricle, Ebstein anomaly Fontan—palliation) and relate disease-specific exercise capacity to that required for different physical activities and different occupations. This information should be useful for clinicians to guide therapy and assist advising patients on physical activity and professional or career choices.

Further studies are required to assess whether relating individual patients exercise capacity to that of other patients with the same diagnosis (i.e. normalizing for diagnosis based on the results of this study) improves the prognostic value of parameters of CPET compared with using absolute values or percentage predicted results only.

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