Cardiopulmonary fitness in children with congenital heart diseases versus healthy children

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ABSTRACT

Objective We aimed to compare the cardiopulmonary fitness of children with congenital heart diseases (CHD) with that of age-adjusted and gender-adjusted controls. We also intended to identify clinical characteristics associated with maximum oxygen uptake (VO_{2max}) in this population.

Methods and results We included in a cross-sectional multicentre study a total of 798 children (496 CHD and 302 controls) who underwent a complete cardiopulmonary exercise test (CPET). The association of clinical characteristics with VO_{2max} was studied using a multivariate analysis. Mean VO_{2max} in the CHD group and control represented $93\pm 20\%$ and $107\pm 17\%$ of predicted values, respectively. VO_{2max} was significantly lower in the CHD group, overall (37.8 ± 0.3 vs 42.6 ± 0.4 mL/kg/min, $P<0.0001$) and for each group ($P<0.05$). The mean VO_{2max} decline per year was significantly higher in CHD than in the controls overall (-0.84 ± 0.10 vs -0.19 ± 0.14 mL/kg/min/year, $P<0.01$), for boys (-0.72 ± 0.14 vs 0.11 ± 0.19 mL/kg/min/year, $P<0.01$) and for girls (-1.00 ± 0.13 vs -0.55 ± 0.21 mL/kg/min/year, $P=0.05$). VO_{2max} was associated with body mass index, ventilatory anaerobic threshold, female gender, restrictive ventilatory disorder, right ventricle systolic hypertension, tricuspid regurgitation, the number of cardiac catheter or surgery procedures, and the presence of a genetic anomaly.

Conclusions Although the magnitude of the difference was not large, VO_{2max} among children with CHD was significantly lower than in normal children. We suggest performing CPET in routine follow-up of these patients.

Trial registration number ClinicalTrials.gov NCT01202916; Post-results.

paediatric cardiologists prescribe a CPET in the regular follow-up of their patients. Yet there is a growing number of children and adolescents living with CHD,⁵ and their increase in life expectancy should also lead to a better quality of life. This includes the ability to engage in normal physical activity, which is a main quality of life parameter.⁶ Indeed, we recently pointed out a correlation between quality of life and VO_{2max} in a large cohort of children with CHD.⁷ However, we need more data in regard to aerobic physical activity in children with CHD. Indeed, most studies focused on a specific group of CHD, such as single ventricles,⁸ tetralogy of Fallot⁹ or coarctation of the aorta.¹⁰ Therefore, the use of a large CHD group in comparison with a control group, rather than an exclusive reliance on prediction equations, would provide unique features on children from across the spectrum of CHD.

We thus planned, for the first time, to compare the cardiopulmonary fitness of a large cohort of children with CHD with that of age-adjusted and gender-adjusted normal controls. We also intended to identify associations between VO_{2max} and clinical determinants in this specific population.

METHODS

Study design

This cross-sectional study was carried out from November 2010 to September 2015 in two paediatric CPET laboratories (centre 1: M3C Regional Paediatric and Congenital Cardiology Centre, Montpellier University Hospital, France; centre 2: Paediatric Cardiology and Rehabilitation Centre, Institut-Saint-Pierre, Palavas-Les-Flots, France). Four regional tertiary care paediatric cardiology centres participated in this study.

Patient population

Children aged 5–18 years old were recruited in one of the two CPET laboratories after a regular paediatric cardiology outpatient visit. Children with absolute contraindications for CPET were not eligible (fever, uncontrolled asthma, respiratory failure, acute myocarditis or pericarditis, uncontrolled arrhythmias causing symptoms or haemodynamic compromise, uncontrolled heart failure, acute pulmonary embolus or pulmonary infarction, and children with mental impairment leading to inability to cooperate).

INTRODUCTION

In 1980, the WHO stated that functional capacity explorations best reflect the impact of a chronic disease on the quality of life.¹ Indeed, in adults with chronic heart failure, maximum oxygen uptake (VO_{2max}) correlates with both quality of life and prognosis.² Therefore, in adult cardiology, the cardiopulmonary exercise test (CPET) has become the ‘gold standard’ to quantify disease severity.³ These results have also been found in adults with congenital heart diseases (CHD), and CPET is now recommended in the follow-up of this particular population.⁴

Such recommendations about CPET do not exist in paediatric cardiology, while more and more

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Two groups were identified: children with CHD and the control children.

1. The CHD group consisted of children followed in one of the four centres and referred by their paediatric cardiologists to one of the two CPET laboratories after their annual medical check-up. The anatomical and clinical classification of congenital heart diseases was used to define the type of malformation.¹¹ Patients with CHD were categorised into three severity classes, on the 32nd Bethesda classification: mild, moderate and severe heart defects.¹² The following clinical data were collected: gender, age, weight (kg), size (cm), body mass index (BMI, kg/cm²), medical treatments, the number and type of cardiac surgical and catheter procedures, and genetic anomalies (Down, DiGeorge, Noonan and Williams syndromes). The following echocardiographic data were collected: systemic ventricle systolic ejection fraction (altered if <55%), right ventricle hypertension (right ventricle systolic pressure greater than one-third of systemic systolic pressure), left and/or right outflow tract obstacle (peak and mean Doppler velocity), valvular regurgitation (mild, moderate or severe), and/or stenosis (peak and mean Doppler velocity).
2. The control group consisted of children referred for a non-severe functional symptom linked to exercise (murmur, palpitation or dyspnoea) or for a medical sports certificate. These children were classified in the control group only after a completely normal check-up, including physical examination, ECG, echocardiography and spirometry. Children with any chronic disease, medical condition (cardiac, neurological, respiratory, muscular or renal), or medical treatment and those requiring any further specialised medical consultation were not eligible.

CPET procedures

CPET procedures in both centres were harmonised before the study started. Both CPET laboratories used the same technical devices: paediatric face masks (Hans Rudolph, Shawnee, Kansas, USA), a calibrated gas analyser (Oxycon Pro, Jaeger, Erich Jaeger, Hoechberg, Germany), breath-to-breath measurement software (Windows V.98, Jaeger), 12-lead ECG equipment (CardioSoft, GE Healthcare, Little Chalfont, UK), a pulse oximeter (Nellcor, Medtronic, Fridley, Minnesota, USA) and a manual sphygmomanometer with adapted paediatric cuffs. Spirometry using a common gas device (Oxycon Pro, Jaeger, Erich Jaeger) was systematically performed before the exercise test with a flow volume curve and measurement of forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC) and the FEV₁/FVC ratio (FEV₁%), with normalisation to theoretical values.¹³

Both centres used the same CPET paediatric cycle ergometer protocol adapted to CHD children¹⁴ to obtain a homogeneous incremental overall duration between 8 and 12 min: a 1 min rest; a 3 min warm-up (10–20 W) in increments of 10, 15 or 20 W each minute; a pedalling rate of 60–80 revolutions per minute; a 3 min active recovery (20 W); and a 2 min rest. The CPET was considered as maximal when three out of the following four criteria were reached: respiratory exchange ratio ($RER = VCO_2 / VO_2$) ≥ 1.1 , maximum heart rate >85% of maximal age-predicted heart rate, limit of the child’s tolerance despite verbal encouragement, and plateau of VO_2 (VO_{2max}) despite the increasing exercise intensity. When the VO_{2max} did not reach a plateau, the peak VO_2 was informed, as usual in paediatrics.^{15 16} The same investigator coordinator manually calculated the VO_{2max} and the ventilatory anaerobic threshold (VAT) using Beaver’s method.¹⁷ VO_{2max} and

VAT values were normalised in a percentage of the predicted VO_{2max} using normal values from Wasserman and Cooper.^{18 19} We considered that a VAT value below 50% of predicted VO_{2max} was in favour of muscular deconditioning, in reference with reported values in adults and children.^{20 21}

Formal aspects

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. It belongs to a multicentre European research programme dedicated to quality of life among children with CHD and registered on ClinicalTrials.gov (NCT01202916). Informed consent was obtained from all parents.

Statistics

The study population was described using means and SD for quantitative variables and with frequencies for qualitative variables. The continuous variable distributions were tested using the Shapiro-Wilk test. Quantitative variables were compared using Student’s t-test when the distribution was Gaussian and using the Mann-Whitney test otherwise. For qualitative variables, groups were compared using the χ^2 test or Fisher’s exact test.

The normality of the measured VO_{2max} was tested in the control group. The agreement between this measure and the predicted VO_{2max} from Cooper and Wasserman^{18 19} was studied using a Bland-Altman plot.

Depending on the distribution of variables, correlations were performed using Pearson’s or Spearman’s coefficients.

In the comparison between all CHD cases and controls, generalised linear models adjusted on gender and age were performed, the number of controls being not sufficient for matching.

Foreach type of CHD, gender-matched and age-matched control comparisons were performed. For a given CHD case, all the controls with the same gender and age (exact year of age) were used. The case with his (or her) matched controls were considered as a cluster. Therefore mixed models were performed in which the clusters were introduced as a random effect.

To assess, globally and in each CHD group, the variation of VO_{2max} per year, a linear model adjusted on gender was used. The interaction age and case–control group being significant, the VO_{2max} variation was estimated separately in CHD and control groups. These results were illustrated with box plots in each group and according to age.

A multiple linear regression was used to identify the explanatory factors for VO_{2max} among the children with CHD (all types of CHD combined). The clinically relevant variables with a P value ≤ 0.2 in the univariate analysis were included in the model. The final model was obtained using an upward selection based on the Akaike information criterion and with an exit threshold of 0.10. The normality of residues in the final model was tested using the Shapiro-Wilk test.

The statistical significance was set at 0.05 and analysed using SAS V.9.

RESULTS
Population

During the 5-year study period, 2007 CPET were performed in the two laboratories (centre 1: n=904, centre 2: n=1103). During this period, 798 children were included in the study, 496 in the CHD group and 302 in the control group (figure 1). No families refused to participate. Both groups were similar in terms of demographic data (table 1). Similarly, we found no demographic differences between the two centres, except for the

Figure 1 Flow chart. CHD, congenital heart diseases.

CHD group with a slightly younger age and smaller height in centre 1 compared with centre 2 (11.5 ± 3.4 vs 12.3 ± 3.3 years, $P=0.04$ and 146.8 ± 17.0 cm vs 151.7 ± 17.5 cm, $P=0.02$, respectively). No side effects or complications during the exercise tests were reported.

The anomalies of the ventricular outflow tracts represented the largest group, with 53.6% of the CHD cohort. In greater detail, the most frequent types of CHD were in the following order: coarctation of the aorta ($n=76$, 15.3%), tetralogy of

Fallot ($n=93$, 18.8%), ventricular septal defect (VSD) ($n=46$, 9.3%), bicuspid aortic valve ($n=52$, 10.5%) and Ebstein’s anomaly ($n=27$, 5.4%). The smallest samples were congenital anomalies of coronary arteries ($n=6$), complex anomalies of atrioventricular connections ($n=5$) and heterotaxy ($n=3$).

The numbers of cardiac surgeries and cardiac catheter procedures are detailed in online supplementary table 1.

Children with genetic syndromes ($n=21$) were equally distributed between mild ($n=11$) and moderate or severe ($n=10$) CHD (online supplementary table 2). They all performed a peak exercise test.

	CHD	Controls	P value
n	496	302	
Age (years)	12.2 ± 3.3	11.1 ± 2.6	<0.001
Height (cm)	150.9 ± 17.5	150.0 ± 16.0	0.4
Weight (kg)	44.1 ± 15.8	42.2 ± 13.3	0.2
BMI (kg/m ²)	18.7 ± 3.6	18.3 ± 2.9	0.3
Sex ratio (male/female)	1.4	1.3	0.7
Peak heart rate (beats per minute)	174.7 ± 18.8	187.5 ± 11.1	<0.001
Percentage of predicted peak heart rate (%)	83.4 ± 11.7	89.8 ± 5.5	<0.001
Maximum load (W)	105.2 ± 71.6	111.5 ± 73.9	0.3
Peak RER	1.13 ± 0.11	1.12 ± 0.12	0.7
% FEV ₁	97.4 ± 16.2	106.9 ± 13.3	<0.001
% FVC	94.8 ± 17.7	104.3 ± 14.9	<0.001
% FEV ₁ /FVC	102.9 ± 10.8	102.9 ± 9.4	0.2

BMI, body mass index; CHD, congenital heart diseases; CPET, cardiopulmonary exercise test; % FEV₁, normalised forced expiratory volume in 1 s; % FVC, normalised forced vital capacity; % FEV₁/FVC, normalised Tiffeneau index; RER, respiratory exchange ratio.

CPET results

Both groups were similar in terms of maximum load, RER and Tiffeneau index, using univariate comparisons. In the CHD group, the maximum heart rate, the FEV₁ and the FVC were significantly lower than in the control group (table 1). The VAT was lower in the CHD group, globally (26.1 ± 6.2 vs 29.1 ± 6.4 mL/kg/min, $P<0.0001$) and in terms of percentage of predicted VO_{2max} (64 ± 15 vs $71\% \pm 14\%$, $P<0.0001$). Deconditioning ($VAT \leq 50\%$ of the predicted VO_{2max}) affected more CHD children than controls (18% vs 6%, $P<0.0001$, respectively). Children with univentricular hearts had the lowest VAT (53.4% $\pm$ 2.9%), but we also observed a lower VAT in simple CHD, such as atrial septal defect (ASD) and VSD, and more complex CHD, such as tetralogy of Fallot and transposition of the great arteries (TGA) (table 2).

In the control population, the mean VO_{2max} (43.5 ± 7.5 mL/kg/min) represented 107% $\pm$ 17% of the predicted values according to Wasserman and Cooper and had a normal distribution. Moreover, VO_{2max} correlated well to the predicted values ($r=0.89$, $P<0.0001$) (figure 2A). The concordance between the measured

Table 2 VAT in CHD and controls

			VAT (mL/kg/min)		P*	% of predicted VAT			
			Mean±SD			Mean±SD			
			n _{CHD} /n _{Controls}	CHD	Controls	P*	CHD	Controls	P*
Total			496/302	26.1±6.2	29.1±6.4	<0.0001	64±15	71±14	<0.0001
ACC-CHD group			n _{CHD} /n _{Controls}	CHD	Controls	P†	CHD group	Controls	P†
1	Heterotaxy	3/36	32.6±3.6	30.2±6.5	0.55	77±11	71±17	0.67	
2	Anomalies of the venous return	13/147	26.9±5.3	30.7±6.1	0.08	66±15	72±15	0.16	
3	Anomalies of the atria and interatrial communications	29/194	25.6±5.6	28.0±6.5	0.06	66±14	72±14	0.03	
4	Anomalies of the atrioventricular junctions and valves	27/185	24.8±6.1	29.4±6.3	<0.01	61±15	71±14	<0.01	
5	Complex anomalies of atrioventricular connections	5/64	24.9±5.8	27.0±6.3	0.40	60±19	67±13	0.27	
6	Functionally univentricular hearts	25/221	22.6±5.8	30.2±6.3	<0.0001	53±13	72±15	<0.0001	
7	Ventricular septal defects	46/259	26.2±5.7	29.1±6.5	<0.01	63±13	71±14	<0.01	
8.1	Transposition of the great arteries	72/261	27.8±6.5	29.6±6.4	<0.01	64±17	71±14	<0.001	
8.2	Tetralogy of Fallot; truncus arteriosus; pulmonary atresia; double outlet right ventricle	93/299	25.5±5.6	29.0±6.4	<0.0001	63±14	71±14	<0.0001	
8.5	Aortic valve stenosis; Shone syndrome	52/285	24.7±6.6	29.2±6.4	<0.0001	62±16	71±14	<0.0001	
8.6	Pulmonary valve stenosis	49/281	27.5±6.7	29.2±6.4	0.25	70±14	71±14	0.48	
9	Anomalies of the extrapericardial arterial trunks	76/289	27.0±6.3	29.0±6.5	<0.01	65±16	71±14	<0.01	
10	Congenital anomalies of the coronary arteries	6/72	23.8±7.2	28.4±6.6	0.06	60±19	71±15	0.05	

*Comparisons of VAT (mL/kg/min) between CHD and the controls after adjustment for age and gender.

†Comparisons of VAT (mL/kg/min) between CHD and the controls matching for age and gender (random cluster).

ACC-CHD, anatomical and clinical classification of congenital heart diseases; CHD, congenital heart diseases; VAT, ventilatory anaerobic threshold.

value and the predicted value was illustrated on the Bland-Altman plot. Among the 302 controls, only 6 had values below the CI and 13 were above (figure 2B). Moreover, 14 athlete children, referred for a medical sports certificate, were included in the control group (mean %predicted VO_{2max} of 117%).

In the CHD group, the mean VO_{2max} (38.1±8.1 mL/kg/min) represented 93%±20% of the predicted values. The %predicted VO_{2max} was over 85% for all children with CHD, except for complex anomalies of atrioventricular connections (80%±20%) and functionally univentricular hearts (76%±16%) (figure 3). The VO_{2max} was not related to the severity of the CHD, when using the Bethesda classification (P=0.73).

VO_{2max} comparison between CHD and controls

Overall, the CHD children had a lower VO_{2max} than the controls (P<0.001). We found similar results after adjustment for age and gender (37.8±0.3 vs 42.6±0.4 mL/kg/min, P<0.0001, respectively). Specifically, VO_{2max} was significantly lower than the controls in all of the CHD groups except for the two smallest groups (heterotaxy and anomalies of the coronary arteries), in which numbers and thus power to detect a significant difference were lower (table 3). After removal of children with single ventricles (ie, the most severe subgroup) from the statistical analyses, comparisons between CHD and controls remained significantly different, overall and in each one of the other subgroups.

VO_{2max} decreased significantly faster with age in the CHD group than in the controls, overall (P<0.01), in boys (P<0.01) and in girls (P=0.05). Overall, at each year of age, the children with CHD lost 0.84 mL/kg/min of gender-adjusted VO_{2max}. This coefficient was 0.72 mL/kg/min per year in boys (figure 4A) and 1 mL/kg/min per year in girls (figure 4B), corresponding to 1.5% and 2.6% of the predicted values per year, respectively. Children with ASD and pulmonary valve stenosis had the lowest mean decrease rate of VO_{2max} per year of age. Children with anomalies

of the atrioventricular junctions and valves had the highest mean decrease rate of VO_{2max} per year of age.

Clinical determinants of VO_{2max} in the CHD group

The following determinants affected VO_{2max} in both univariate and multivariate analyses: BMI, VAT, female gender, restrictive ventilatory disorder, right ventricle systolic hypertension, tricuspid regurgitation, existence of a genetic anomaly, the number of cardiac catheter procedures and the number of cardiac surgical procedures. The final multivariate model explained 77% of the variability of VO_{2max} in the CHD group (table 4).

DISCUSSION

This multicentre study of a large cohort of nearly 800 children presented the values and the clinical determinants of VO_{2max} of 496 children with CHD compared with 302 controls.

We found that in children with CHD, VO_{2max} was weakly impaired with a mean overall value of 93% when expressed as a percentage of predicted values. This good level of oxygen uptake in a large paediatric CHD cohort is very encouraging and appears to be directly in line with medical and surgical progress in paediatric cardiology over the past two decades.⁵ Indeed, the so-called ‘changing epidemiology’ transferred from paediatrics to adulthood the mortality and, to a less extent, the morbidity.²²

We recently found a correlation between VO_{2max} and the quality of life of children with CHD.⁷ The ‘physical well-being’ dimension in health-related quality of life instruments stands as a significant patient-related outcome in the young cardiac population.²³

Therefore, most of these children with CHD are assumed to have a satisfactory quality of life, with normal physical activity, including sports. Although physical activity and sports are in most cases authorised under an individual paediatric cardiologist’s prescription,²⁴ children with CHD are often hovered over by

Figure 2 Correlation and concordance between VO_{2max} and predicted VO_{2max} in the control group. (A) Correlation between measured VO_{2max} and predicted VO_{2max} from Wasserman and Cooper (mL/min). (B) Concordance between the measured VO_{2max} value and the predicted VO_{2max} value from Wasserman and Cooper (mL/min) with a Bland-Altman plot. VO_{2max} , maximum oxygen uptake.

their parents, stigmatised by their teachers and eventually remain on the sidelines.²⁵ In this context, our results with mostly normal or subnormal VO_{2max} may participate in promoting self-confidence to the child, reassuring his or her family and motivating them to engage the young patient in physical activity.²⁶ Evaluating the degree of VO_{2max} alteration in a CHD paediatric cohort based only on results expressed as a percentage of

predicted values may cause some misinterpretation. Indeed, the predicted values were based on a reference population evaluated with different equipment and cycle ergometer protocols and came from a different country with different daily levels of physical activity, which are highly dependent on cultural habits.¹⁸ Therefore, using a control population was fundamental to avoid these biases. In our control population, we used a similar CPET

Figure 3 VO_{2max} for each ACC-CHD group. The numbers above the density lines indicate percentage of VO_{2max} values for the 25th, 50th (bold) and 75th percentiles. Histograms represent the distribution of the %predicted VO_{2max} values for each ACC-CHD group. The density lines above the histograms and the numbers to the right of the graph relate to all patients for each ACC-CHD group. Groups 1, 5 and 10 (small cohorts) were not represented. ACC-CHD, anatomical and clinical classification of congenital heart diseases; ASD, atrial septal defect; TGA, transposition of the great arteries; VO_{2max}, maximum oxygen uptake; VSD, ventricular septal defect.

	n _{CHD} /n _{Controls}	VO _{2max} (mL/kg/min)		P†	% of predicted VO _{2max}		P‡	VO _{2max} variation (per year)*		P‡
		CHD	Controls		CHD	Controls		CHD	Controls	
Total	496/302	38.1±8.1	43.5±7.5	<0.0001	93±20	107±17	<0.0001	−0.84±0.10§	−0.19±0.14	<0.001
Gender										
Male	290/172	40.5±8.1	47.1±6.3	–	91±22	106±16	–	−0.72±0.14§	0.11±0.19	<0.001
Female	206/130	34.7±6.8	38.7±6.4	–	96±16	108±17	–	−1.00±0.13§	−0.55±0.21§	0.05
ACC-CHD group	n _{CHD} /n _{Controls}	CHD	Controls	P¶	CHD	Controls	P¶	CHD	Controls	P‡
1 Heterotaxy	3/36	42.6±4.9	44.6±7.3	0.65	101±16	104±17	0.68	–	–	–
2 Anomalies of the venous return	13/147	39.4±6.3	45.6±7.0	<0.01	97±18	107±17	0.03	−0.96±0.35§	−0.14±0.20	0.14
3 Anomalies of the atria and interatrial communications	29/194	37.9±6.6	41.8±7.5	<0.01	98±18	108±16	<0.01	−0.35±0.41	−0.31±0.19	0.95
4 Anomalies of the atrioventricular junctions and valves	27/185	35.4±9.4	43.6±7.3	<0.0001	88±23	106±16	<0.0001	−1.87±0.45§	0.17±0.19	<0.001
5 Complex anomalies of atrioventricular connections	5/64	33.5±5.2	42.2±7.9	<0.01	80±20	104±17	<0.01	–	–	–
6 Functionally univentricular hearts	25/221	32.3±7.2	45.0±7.4	<0.0001	76±16	106±17	<0.0001	−0.55±0.38	−0.25±0.17	0.47
7 Ventricular septal defects	46/259	38.2±7.5	43.6±7.6	<0.0001	92±16	106±17	<0.0001	−0.44±0.35	−0.25±0.18	0.53
8.1 Transposition of the great arteries	72/261	40.5±7.7	44.2±7.5	<0.0001	93±20	106±17	<0.0001	−0.94±0.26§	−0.08±0.15	<0.01
8.2 Tetralogy of Fallot; truncus arteriosus; pulmonary atresia; double outlet right ventricle	93/299	36.7±7.7	43.4±7.5	<0.0001	91±20	107±16	<0.0001	−0.63±0.21§	−0.12±0.14	0.07
8.5 Aortic valve stenosis; Shone syndrome	52/285	36.7±8.0	43.6±7.5	<0.0001	92±19	106±16	<0.0001	−0.78±0.29§	−0.12±0.14	0.04
8.6 Pulmonary valve stenosis	49/281	40.2±7.6	43.8±7.5	<0.01	102±15	107±17	0.03	−0.31±0.26	−0.13±0.15	0.39
9 Anomalies of the extrapericardial arterial trunks	76/289	39.9±8.8	43.4±7.6	<0.0001	95±21	107±17	<0.0001	−0.97±0.26§	−0.22±0.15	0.01
10 Congenital anomalies of the coronary arteries	6/72	36.4±11.8	42.6±8.2	0.07	93±30	106±17	0.09	–	–	–

* Gender-adjusted regression coefficient for a variation of 1 year of age (mL/kg/min/year)
† Comparisons of VO_{2max} (mL/kg/min) between all CHD and the controls after adjustment for age and gender.
‡ Age×group interaction test.
§ Significant VO_{2max} variation (β coefficient) according to age (P<0.05).
¶ Comparisons, in each CHD group, of VO_{2max} (mL/kg/min) between CHD and the age-matched and gender-matched controls (random cluster).
ACC-CHD, anatomical and clinical classification of congenital heart diseases; CHD, congenital heart diseases; VO_{2max}, maximum oxygen uptake.

Figure 4 Box plots of VO_{2max} as a function of age (years). (A) Boys and (B) girls. The bottom and top of the box represent the first and third quartiles, the band inside the box represents the second quartile (median), and the end of the whiskers represents the minimum and maximum values. Data not included between the whiskers were plotted as outliers with small circles (controls) and crosses (CHD), and the linear curves represent the mean VO_{2max} variation with age. CHD, congenital heart diseases; VO_{2max} , maximum oxygen uptake.

protocol and the same equipment and measured VO_{2max} at mean 107% of predicted values. Therefore, from a scientific and clinical perspective, the most important and relevant comparison should be of the groups' %predicted values. Consequently, in our study, the %predicted VO_{2max} (93%) of patients with CHD was in fact only 87% of the control subjects'. Moreover, we found that VO_{2max} compared with a control population coming from the same centres was significantly lower than the controls, with a mean loss of 5.4 mL/kg/min (−12.4%).

Not surprisingly, VO_{2max} in mL/kg/min was lower in children with high BMI. Indeed, adipose tissue does not consume oxygen but will lower weight-normalised VO_{2max} . Similarly, the fact that girls had lower VO_{2max} than boys is well known and is related to gender differences in muscle mass and adipose tissue, especially postpuberty.²⁷

In regard to each specific CHD group, VO_{2max} was significantly impaired compared with matched controls, except for the two smallest groups (heterotaxy and anomalies of the coronary arteries), probably because of low sample sizes. We observed that the alteration of VO_{2max} was more prevalent in the most complex CHD, such as single ventricles and complex anomalies of atrioventricular connections. VO_{2max} was also associated with the existence of a right ventricle systolic hypertension and a tricuspid regurgitation, which probably stand as the common denominator of many cases of right heart complex CHD. Indeed, left heart failure is less common in paediatrics: in our cohort, the impaired left ejection fraction correlated to a lower VO_{2max} only in the univariate analysis, as few patients with left heart failure were included in this study. Similarly, we showed that VO_{2max} was altered in the most severe CHD commonly associated with numerous surgical or catheter procedures and pulmonary restrictive syndrome. These results are consistent with previous results from smaller or non-controlled cohorts from the literature,^{28–31} where, to our knowledge, no multivariate analysis had been performed to identify the clinical determinants of VO_{2max} in cardiac children. We recently emphasised the impact of these clinical severity variables on the quality of life of children with CHD.⁶ In paediatric cardiology, CPET could therefore contribute to assess disease severity and its impact on daily living, as in adults with CHD.^{4 32}

An important result of our study is the existence of a greater VO_{2max} decline over time in the children with CHD than in the controls. Few data about this VO_{2max} decline from longitudinal studies are available in the paediatric literature. Fernandes *et al*³⁰ showed that the %predicted VO_{2max} decline started in adolescence in children with single ventricles. Previous studies also showed that Fontan completion at a younger age was associated with better exercise performance in adolescents.^{28 33} Similarly, in a cohort of 53 teenagers and young adults with single ventricles, Giardini *et al* found an overall VO_{2max} decline of $2.6\% \pm 2.7\%$ per year.³⁴ This accelerated decline of oxygen uptake with age in children with CHD continues into adulthood: Müller *et al* reported a slow decline of $1\% \pm 6.8\%$ per year in exercise capacity within the natural history of 522 adult patients with CHD.³⁵ It has also been observed in non-severe CHD such as repaired ventricular and atrial septal defects.³²

The VAT in our CHD cohort was rather good, with an overall mean value of 64% of predicted VO_{2max} . The VAT values were above 60% in all CHD subgroups, but single ventricles. In the current era, children with CHD are more likely to engage in sports and are not limited by any submaximal exercise performance, as reported by Müller *et al*.³⁶ However, the VO_{2max} was associated with the decrease in VAT, which reflects muscular deconditioning, present in 18% of the children with CHD of our cohort, that is, three times more than in the control group. Unsurprisingly, children with single ventricles had the lowest VAT. However, we also observed a lower VAT in lesser complex CHD such as tetralogy of Fallot or TGA, or even in simple CHD such as ASD and VSD. Therefore, the follow-up of children with CHD with an annual CEPT is a good tool for the early selection of those who will benefit from cardiac rehabilitation programme to stop or slow down the decline of their oxygen uptake.^{37 38} Although paediatric cardiac rehabilitation seems to positively impact the oxygen uptake and the quality of life in children with CHD, selection criteria for cardiac rehabilitation in the paediatric population are currently unclear and structured paediatric structures are scarcely available.³⁹ Therefore, VO_{2max} change with age should be a main parameter to identify patients with CHD eligible for cardiac rehabilitation, especially during educational transition programme, from adolescence.⁴⁰

Table 4 VO_{2max} explanatory variables in the CHD group

Variables	Description	Univariate analysis	Multivariate analysis (AIC selection model) (n=391)
	r	P value	P value
Age (years)*	−0.35	<0.0001	–
BMI (kg/m ²)*	−0.51	<0.0001	<0.0001
VAT (mL/kg/min)*	0.84	<0.0001	<0.0001
Mean VO _{2max} ±SD (mL/kg/min)			
		P value	P value
Gender*			
Girls	34.7±6.8	<0.0001	<0.0001
Boys	40.5±8.1		
Restrictive ventilatory disorder*			
No	38.4±8.0	0.02	<0.0001
Yes	36.1±8.1		
Obstructive ventilatory disorder*			
No	38.0±8.0	<0.01	–
Yes	28.0±5.9		
Altered systolic ejection fraction*			
No	37.9±8.2	0.06	–
Yes	33.4±3.6		
Right ventricle systolic hypertension*			
No	38.0±8.2	0.10	0.08
Yes	36.2±7.7		
Right outflow tract obstacle*			
No	37.5±8.1	0.14	–
Yes	39.4±8.0		
Left outflow tract obstacle			
No	37.9±8.2	0.36	–
Yes	36.5±6.8		
Mitral regurgitation			
No	37.8±8.1	0.31	–
Yes	35.4±9.6		
Aortic regurgitation*			
No	38.0±8.2	0.08	–
Yes	37.5±7.0		
Tricuspid regurgitation*			
No	37.9±8.0	0.12	0.06
Yes	34.9±10.1		
Pulmonary regurgitation			
No	37.8±8.3	0.86	–
Yes	37.6±7.4		
Genetic anomalies*			
No	38.1±8.0	<0.001	<0.01
Yes	32.1±7.9		
Number of cardiac surgical procedures*			
0	38.7±8.0	<0.01	0.01

Continued

Table 4 Continued

	Mean VO _{2max} ±SD (mL/kg/min)	P value	P value
1	38.7±8.2	<0.001	0.02
≥2	35.4±7.6	–	–
Number of cardiac catheter procedures*		0.01	<0.01
0	38.3±8.2	<0.01	0.02
1	38.5±7.8	<0.01	0.34
≥2	33.5±7.3	–	–
Beta blockers*			
No	38.3±8.1	0.04	–
Yes	35.3±7.7		

*Candidate variables for multivariate analysis.
AIC, Akaike information criterion; BMI, body mass index; VAT, ventilatory anaerobic threshold; VO_{2max}, maximum oxygen uptake.

Study limitation

This study was performed in tertiary care centres and may not represent CHD in the general population. Indeed, complex CHD, such as the anomalies of the ventricular outflow tracts, was over-represented (54% vs 20% in the French CHD EPICARD registry¹¹), and simple CHD, such as VSD, was under-represented (9% vs 52% in EPICARD). Similarly, only 5% of our patients with CHD had a genetic anomaly (14% in EPICARD). In our study, VO_{2max} was associated with the presence of a genetic anomaly. Indeed, performing a CPET on cycle ergometer requires a good understanding of the instructions, which is not always easy in these patients.

CPET in very severe types of CHD (severe heart failure, pulmonary hypertension, acute arrhythmia and severe left outflow tract obstacle) is not routinely performed, especially in children, mostly for safety reasons. Therefore this study did not analyse VO_{2max} in this population.

The control group was recruited at the hospital and may not be considered as healthy as if they were recruited from the general

Key messages

What is already known on this subject?
The cardiopulmonary exercise test (CPET) is recommended in the follow-up of adults with congenital heart diseases (CHD) but not yet in children with CHD.

What might this study add?
This multicentre cross-sectional study of a large cohort of nearly 800 children showed that maximum oxygen uptake (VO_{2max}) was weakly impaired in children with CHD but decreased with age faster than controls, especially for the most complex CHDs.

How might this impact on clinical practice?
We suggest performing CPET in routine follow-up of children with CHD. In most cases, CPET will be normal and therefore will contribute to promote physical activity in these young patients. Further work should be done to determine whether VO_{2max} change with age should be a main parameter to identify children with CHD eligible for cardiac rehabilitation.

population. We thus called them the control children. Moreover, no physical activity questionnaire was administered to this population. However, this bias seems very limited, considering the very good correlation of their $\text{VO}_{2\text{max}}$ values with the predicted normal values and the supramaximal $\text{VO}_{2\text{max}}$ values obtained in our control population.

The association between age and $\text{VO}_{2\text{max}}$ is limited by the design of this cross-sectional study. Therefore, we plan to follow this cohort to confirm that $\text{VO}_{2\text{max}}$ declines with age in children with CHD.

CONCLUSIONS

This comparative CPET study provided, for the first time, relevant values of $\text{VO}_{2\text{max}}$ and their clinical determinants in a large cohort of children with CHD compared with a control group. We observed that $\text{VO}_{2\text{max}}$ in children with CHD was weakly altered when expressed as a percentage of predicted values. However, $\text{VO}_{2\text{max}}$ in this paediatric CHD cohort was significantly lower than in age-adjusted and gender-adjusted control children, and we observed a mean overall $\text{VO}_{2\text{max}}$ decline of 0.84 mL/kg/min per year, more pronounced in the most complex types of CHD. Moreover, deconditioning affected three times more children with CHD than controls. We suggest performing CPET in routine follow-up of children with CHD. In most cases, CPET will be normal and therefore will contribute to promote physical activity in these young patients. Further work should be done to determine whether $\text{VO}_{2\text{max}}$ change with age should be a main parameter to identify children with CHD eligible for cardiac rehabilitation.

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