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Original research

Exercise capacity in patients with repaired Tetralogy of Fallot aged 6 to 63 years

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ABSTRACT

Objectives This study aimed to provide a perspective for the interpretation of exercise capacity (peakVO_2) in patients with repaired Tetralogy of Fallot (patients with rTOF) by describing the course of peakVO_2 from patients aged 6–63 years.

Methods A retrospective study was performed between September 2001 and December 2016 in the German Heart Centre Munich, Germany, and in the University Medical Centre Groningen, the Netherlands. A total of 1175 cardiopulmonary exercise tests (CPETs) were collected from 586 patients with rTOF, 46% female. Maximal exertion was verified using a respiratory exchange ratio ≥1.00. PeakVO_2 was modelled using time-dependent multilevel models for repeated measurements (n=889 in 300 patients), and compared with subject-specific reference values calculated by the models of Bongers *et al* and Mylius *et al*.

Results The peakVO_2 of patients with rTOF was reduced at all ages. At the age of 6, the peakVO_2 was 614 mL/min (70% of predicted (95% CI 67 to 73)). The reduced increase in peakVO_2 during adolescence resulted in a significant lower maximum peakVO_2 of 1209 mL/min at 25 years (65% predicted, p<0.001). A linear decline after 25 years was observed in patients and references, although patients showed an accelerated decline, with a -0.24% point of predicted (95% CI 0.11 to 0.38) per year without differences between sexes (p=0.263).

Conclusions This study provides a context for peakVO_2 across ages in patients with rTOF under contemporary treatment strategies. It showed that the reduction in peakVO_2 originates from childhood and declines over time. Sex differences in patients with rTOF were similar to natural existing sex differences.

INTRODUCTION

Serial exercise testing using cardiopulmonary exercise tests (CPETs) is an emerging strategy to monitor patients with congenital heart disease (CHD). Measuring exercise capacity (maximal oxygen consumption, peakVO_2) is increasingly advocated as a diagnostic and prognostic tool to recognise clinical deterioration early in the course of the disease.[1–3] The CPET has been adopted in international guidelines to support treatment decisions, including valve replacement interventions in patients with repaired Tetralogy of Fallot (rTOF).[3–7] Such recommendations are predominantly based on cross-sectional studies, whereas cohort studies with repeated measures over time are scarce.

Ageing has been shown to affect peakVO_2.[8] In healthy children, peakVO_2 increases associated with a growth-related increase in height and weight.[9–11] During adolescence, weight gain is predominantly determined by increased skeletal muscle mass, most pronounced in boys.[10–12] After reaching adulthood, peakVO_2 gradually declines during life.[13] This decline is partially explained by a loss of muscle mass and a decrease of chronotropic response.[8 12 14]

Previous cross-sectional studies in patients with rTOF reported a reduced peakVO_2 of 60%–80% of predicted.[15–18] Longitudinal studies assessing the peakVO_2 course in patients with rTOF are rare, especially in children. These studies are mainly small studies in adults.[19 20] A slow attrition of peakVO_2, about 1% point per year, is described under contemporary treatment strategies.[19 20]

To adequately interpret serial CPETs in individual patients, knowledge of the peakVO_2 course across a wide age range is essential. The peakVO_2 course, and its variation between sexes, will put an individual's result in a more proper perspective. It will provide better insight into when the deviations of patients with rTOF from the healthy references occur. This allows for customised and more optimally timed interventions, including lifestyle advice and physical training programmes. This study aimed to show the peakVO_2 course from childhood to the ageing adult.

METHODS

Design, setting and patients

This multicentre cohort study included consecutive CPETs of patients with rTOF followed in the German Heart Centre Munich, Germany, or in the University Medical Center Groningen, the Netherlands. Patients were retrospectively included between September 2001 and December 2016. Clinical and demographic data were collected from medical records. Patients or the Public were not involved in the design, conduct, reporting or dissemination plans of our research.

Cardiopulmonary exercise test

All patients performed symptom-limited upright sitting CPET with an incremental protocol on a bicycle ergometer with breath-by-breath analysis, according to international guidelines and recommendations.[21 22] The CPETs performed on

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a treadmill were excluded, since treadmill exercise is a weight-bearing form of physical activity, while cycling is not. By using only cycling tests, the effects of weight fluctuations over time were minimised.[23]

In short, a patient started the CPET with a resting and warming-up phase, followed by a progressive incremental workload protocol, adapted to the individual patient, aiming for an exercise duration of 8–12 min for both children and adults. The workload protocol was determined based on age, height and subjective fitness of the patient. The test ended when the patient could not maintain the pedal cycle rhythm, or if any arrhythmias occurred. CPETs were considered valid if the VO_2 reached a plateau (>1 min) despite increasing workload (only scarce in adults) and/or a complementary respiratory exchange ratio (RER) ≥1.00 combined with the presence of subjective signs of maximal effort (facial flushing, sweating, unwillingness to continue despite encouragement).[21 22] Additional analyses of the peakVO_2 course in adults who reached RER ≥1.00 but RER <1.1, vs those with a RER ≥1.1 showed no significant difference in slope nor intercept. Therefore, all were included.

Outcome

The primary outcome value was peakVO_2, either expressed in absolute mL/min, or as percentage of predicted.[13 24] PeakVO_2 was defined as the mean VO_2 of the last 30 s of the incremental protocol. The absolute peakVO_2 was compared with subject-specific references based on two prediction models. The model of Bongers *et al* was used in girls until the age of 13, and boys until the age of 15.[24] For participants above those ages, weight and height contributed to their peakVO_2 and therefore reference values reported by Mylius *et al* were used.[9–13]

Statistical analyses

Patient characteristics were described using means and SD or median with IQR depending on the distriubtion. All variables were visually checked and tested for normality using histograms, PP and QQ plots and the Kolmogorov-Smirnov test. To depict the age-related distribution of the population, the population was divided into age-based quartiles at initial measurement. Differences between sexes were tested using t-test for normally distributed variables, Mann-Whitney U test for skewed variables and χ^2 test was used for dichotomous variables. Deviations from the reference values were tested by combining subject-specific references and patients measurements into one time-dependent model.

Modelling peakVO_2 course

The peakVO_2 of all initial measurements were plotted in a box plot with age-based quartiles to show the distribution across ages. Scatterplots of the repeated measurements were used to visualise the peakVO_2 course, for the individual within-person variation (see online supplemental file). The models' lines including 95% CIs (dotted lines) were plotted over the scatterplots. This was used to visually assess the fit of the model.

Time-dependent multilevel models for repeated measures using an unstructured covariance structure with maximum likelihood estimation were used to calculate the course over time using repeated measures (n=889, in 300 patients).[25] This model was suitable for an unbalanced dataset, including various waves (eg, visits), non-identical spacing and different starting points. Assumptions of the model were: (1) linearity checked by empirical growth plots and scatterplots, and (2) normality and homoscedasticity of the residuals checked by normal probability plots for residuals and scatterplots of the residuals against age. The statistical best fit was checked by using the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC). The best model had the lowest BIC and AIC. For detailed information about the statistical methods and model building methods, see online supplemental file. Statistical analyses were performed using SPSS version 26 and STATA version 15. A p value of <0.05 was considered significant for determinants.

RESULTS

Baseline characteristics

A total of 586 individual patients (46% female patients) were included in the study, and 1175 valid CPETs were available for analyses. In 300 patients (51%), at least two measurements were available for analyses, and in 141 patients (24%) three or more measurements were available (n=889). Characteristics at initial measurement of all patients divided based on age quartiles are shown in figure 1 and table 1. At initial measurement, the median age was 21 (IQR 15–30) years. The youngest patient was 6 and the oldest 63 years of age. Almost half of the patients (42%) were 18 years or younger (n=247) at initial measurement. The median interval between the initial and follow-up CPET was 24 (IQR 12–38) months, with a maximal interval of 11 years. There was no significant difference in baseline characteristics between the single measurement sample and the repeated measurement sample, besides the morphology (table 2).

PeakVO_2 course in patients with rTOF

The absolute peakVO_2 course (mL/min) in the 300 patients with repeated measures and their subject-specific references[13 24] is depicted in figure 2A. Additionally, the relative peakVO_2 course (%-predicted) is shown in figure 2B. The indexed peakVO_2 course (mL/min/kg) is shown in figure 3 (AIC 14.725; BIC 14.771) and figure 4 stratified for sex (AIC 14.235; BIC 14.344).

The cubic prediction model was the best fit to describe the absolute peakVO_2 course (AIC 26.054; BIC 26.098). The absolute peakVO_2 at age 6 (intercept of the model) seemed lower in patients (614 mL/min) compared with subject-specific references (637 mL/min), however, not significant, p=0.764. Thereafter, the peakVO_2 increased faster in references (280 mL/min per year) compared with children with rTOF (167 mL/min per year), p<0.001. The course was described by the model for patients' peakVO_2 (mL/min)=614+167×(age-6)–6×(age-6)^2+0.06×(age-6)^3 vs the model for references' peakVO_2 (mL/min)=637+280×(age-6)–10×(age-6)^2+0.10×(age-6)^3; p<0.001. The maximal peakVO_2 was reached around 20–25 years of age in both patients and references. Thereafter, there was a gradual decline over the years. This is also visible in the relative peakVO_2 course (figure 2).

The linear model was used to describe the relative peakVO_2 course (BIC 6.910; AIC 6.882). The relative peakVO_2 of patients with rTOF at age 6 was 70% (95% CI 67 to 73). Patients showed a reduced peakVO_2 at all ages, and an accelerated decline compared with references with 0.24% points of predicted (95% CI 0.11 to 0.38) per year.

Sex-related differences in exercise capacity in patients with rTOF

The absolute peakVO_2 (mL/min) modelled and stratified for sex is depicted in figure 5. Again, the cubic model was the best fit (AIC 25.547; BIC 25.652). No significant difference between male and female patients at the age of 6 (p<0.906) was observed. Both sexes showed a lower peakVO_2 than the references at age 6

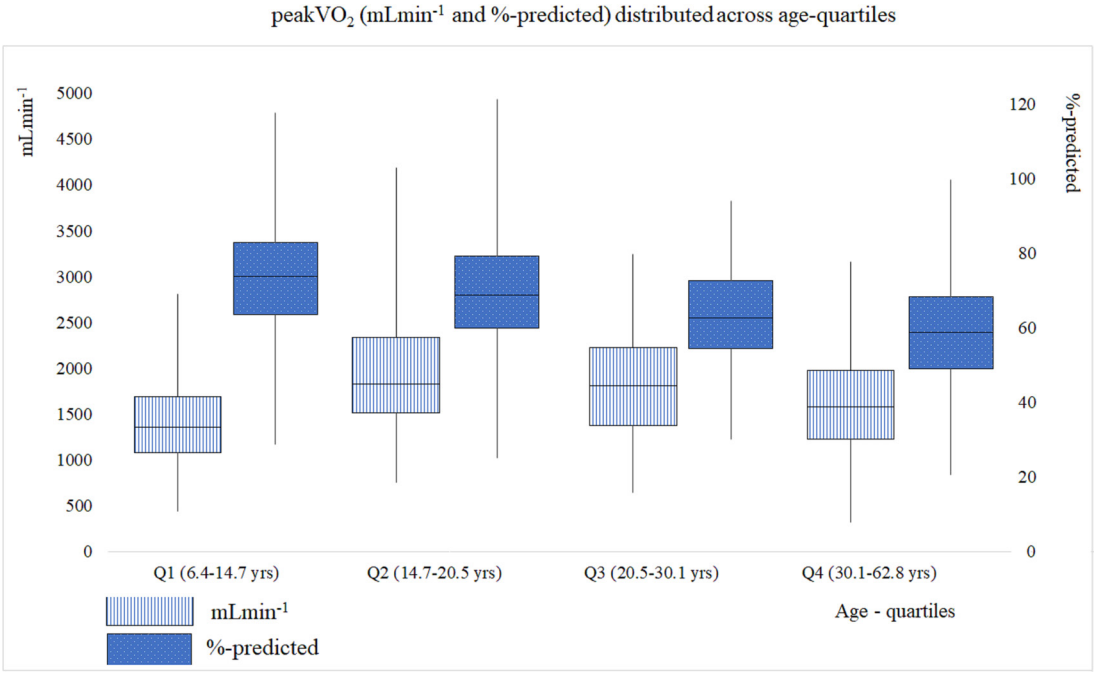

Figure 1 Box plot of the absolute and relative peakVO$_2$ at intial cardiopulmonary exercise test of all 586 individual patient, divided by age quartiles to show the age distribution and effect of age. The left boxes represent the absolute peakVO$_2$ (mL/min) corresponding to the left y-axis. The right boxes represent the relative peakVO$_2$ (%-predicted) corresponding to the right y-axis.

($p<0.001$). The steep and linear increase in peakVO$_2$ is accelerated in boys compared with girls ($p<0.001$). The model for female patients' peakVO$_2$ (mL/min)$=922+167\times$(age-6)$-5.3\times$(age-6)$^2+0.05\times$(age-6)^3 vs the model for male patients' peakVO$_2$ (mL/min)$=935+322\times$(age-6)$-9.7\times$(age-6)$^2+0.09\times$(age-6)^3; $p<0.001$. All effects for male and female patients are significantly lower compared with the subject-specific references (figure 5, $p<0.001$), also appreciated in figure 6, which shows the percentage of predicted.

The linear model was the best fit to model relative peakVO$_2$ (AIC 6.885; BIC 6.923). The relative peakVO$_2$ at age 6 was not significantly different between boys and girls ($p=0.389$). The annual decline in comparison to the subject-specific references was not significantly different between sexes ($p=0.263$).

DISCUSSION

This study showed the peakVO$_2$ course in 300 patients with rTOF aged 6 to 63 years (n=889 CPETs). The peakVO$_2$ was reduced at all ages and deteriorated significantly faster in patients compared with healthy reference values with -0.24% of predicted point per year. Female patients had a lower peakVO$_2$ than male patients,

Table 1 Overview of 586 patients with rTOF divided into age-based quartiles at initial visit

	Q1		Q2		Q3		Q4	
Patient characteristics	n=146		n=146		n=147		n=147	
Age range, years	6.4–14.7		14.7–20.5		20.5–30.1		30.1–62.8	
Age, years	11.6	(9.8–13.4)	16.8	(15.6–18.4)	25.2	(23.0–27.4)	37.1	(33.6–43.5)
Female sex, n	53	36%	63	43%	81	55%	72	49%
Morphology								
TOF	104	71%	110	75%	104	71%	125	85%
PAVSD	36	25%	27	19%	27	18%	19	13%
DORV	6	4%	9	6%	16	11%	3	2%
Functional assessment								
CPET, n	1.44	±0.8	1.85	±1.2	2.2	±1.7	2.2	±1.4
Body weight, kg	41	(30–51)	61	(54–72)	65	(57–76)	69	(58–81)
Body height, cm	150	(138–161)	169	(162–178)	170	(163–175)	170	(163–177)
BMI, kg/m^2	18.3	±3.6	21.7	±3.2	23.2	±4.0	24.7	±4.4
PeakVO$_2$, mL/min	1358	(1082–1696)	1828	(1513–2342)	1813	(1377–2227)	1584	(1233–1976)
PeakVO$_2$, %-predicted*	73	±16	69	±16	63	±13	59	±15
PeakVO$_2$, mL/min/kg	35.8	(29.3–42.1)	31.7	(26.4–37.4)	26.8	(22.2–31.4)	22.0	(18.4–28.1)

Baseline characteristics for all patients at initial visit. Values are expressed as median (IQR), counts (percentage) or mean±SD.
*Predicted values were based on the model by Bongers *et al* for girls until 13 years, for boys until 15 years and the model by Mylius *et al* for girls >13 years and boys >15 years.
Age quartiles were constructed to show the age distribution in the population Q1 (first 25%, n=146), Q2 (25%–50%, n=146), Q3 (50%–75%, n=147) and Q4 (last 25%, n=147).
BMI, body mass index; CPET, cardiopulmonary exercise test; DORV, double outlet right ventricle; PAVSD, pulmonary atresia/ventricular septal defect; TOF, Tetralogy of Fallot.

Table 2 Baseline characteristics of 586 patients with rTOF

	Single measurements		Repeated measurements		P value
Patient characteristics	n=286		n=300		
Age, years	20.0	(14.7–31.5)	21.5	(14.7–28.7)	0.815*
Female sex, n	128	45%	141	47%	0.099¥
Morphology					
TOF	229	80%	214	71%	0.019¥
PAVSD	40	14%	69	23%	
DORV	17	6%	17	6%	
Functional assessment	n=286		n=300		
CPET, n	1	±0	2.3	±1.4	<0.001$
Body weight, kg	60	(49–73)	60	(51–72)	0.512*
Body height, cm	165	(158–174)	167	(158–175)	0.261*
BMI, kg/m^2	22.0	±4.9	21.9	±4.1	0.690$
PeakVO$_2$, mL/min	1633	(1307–2069)	1628	(1251–2008)	0.501*
PeakVO$_2$, %-predicted†	67	±17	65	±15	0.153$
PeakVO$_2$, mL/min/kg	29.2	(22.0–36.5)	28.7	(23.1–33.8)	0.493*

Baseline characteristics for all patients at initial visit. Values are expressed as median (IQR), counts (percentage) or mean±SD.
*P<0.05 was considered significant between the populations, based on Mann-Whitney (*) or Student's t-test ($) or χ^2 test (¥).
†Predicted values were based on the model by Bongers *et al* for girls until 13 years, for boys until 15 years and on the model by Mylius *et al* for girls >13 years and boys >15 years.
BMI, body mass index; CPET, cardiopulmonary exercise test; DORV, Double Outlet Rigth Ventricle; PAVSD, Pulmonary Atresia/Ventricular Septal Defect; TOF, Tetralogy of Fallot.

as is expected compared with the references (and so, the healthy population). Compared with male patients, female patients did not show significant different rates of decline in peakVO$_2$.

The physiological effect of age on peakVO$_2$

The growth and maturation of children and adolescents, and the gradual decline of the cardiopulmonary system and muscle mass in adulthood have a substantial effect on physical fitness.[10–12] In early childhood, body compositions are similar in boys and girls; however, during adolescence this changes dramatically.[12] As adolescence proceeds, the weight gain is predominantly determined by an increase in skeletal muscle mass, which is most pronounced in boys.[12] Therefore, it is only logical to incorporate more than just age as a predictor of peakVO$_2$ in older children, healthy or diseased. A linear increase related to age is assumed in boys until the age of 15 and in girls until the age of 13.[10–12] After

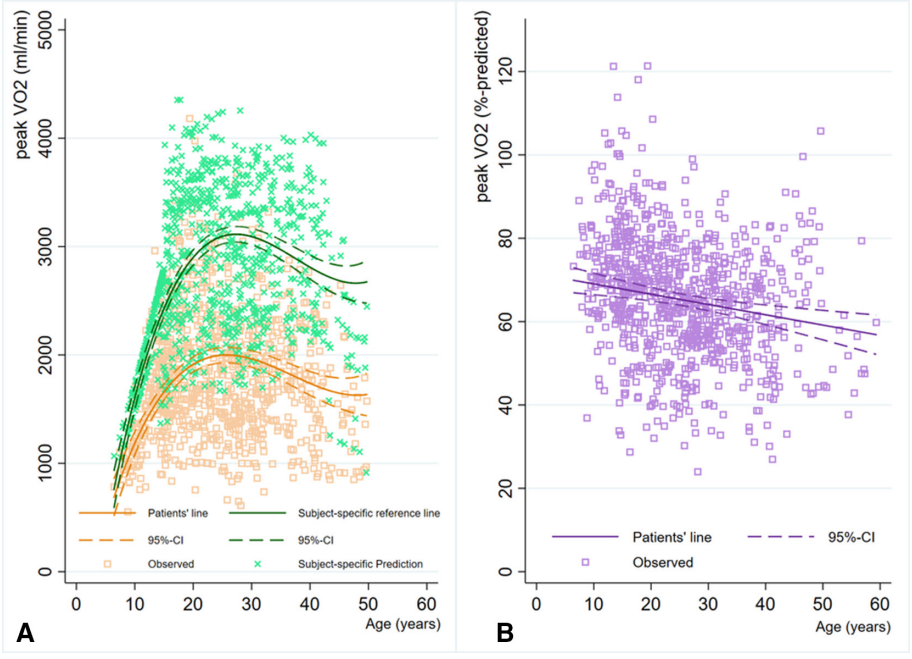

Figure 2 (A) The scatterplot represents repeated peakVO$_2$ measurements (n=889) (orange) and the subject-specific reference peakVO$_2$ (green) in the dataset. The time-dependent model is shown by the line including the 95% CI (dotted line) (AIC 26.054; BIC 26.098). Model 1A—orange (*patients*): peakVO$_2$ (mL/min)=614+167×(age-6)–6×(age-6)^2+0.06×(age-6)^3. Model 1A—green (*references*): peakVO$_2$ (mL/min)=637+280×(age-6)–10×(age-6)^2+0.10×(age-6)^3. (B) The scatterplot represents calculated percentage of predicted based on the subject-specific references (purple). The time-dependent model is show by the line. Including the 95% CI (dotted line) (AIC 6.882; BIC 6.910). Model 1B—purple (*patients*): peakVO$_2$ (%-predicted)=70–0.24×(age-6). AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

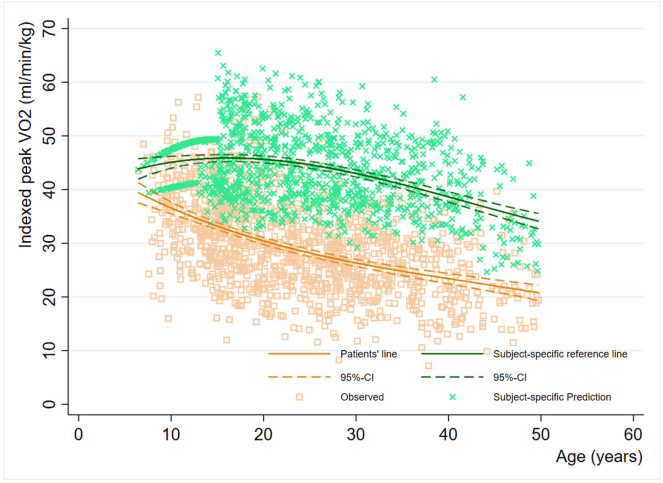

Figure 3 The scatterplot represents repeated indexed peakVO$_2$ measurements (n=889) (orange) and the subject-specific reference indexed peakVO$_2$ (green) in the dataset. The time-dependent model is shown by the line including the 95% CI (dotted line) (AIC 14.725; BIC 14.771). Model 2—orange (*patients*): peakVO$_2$ (mL/min/kg)=38.9–0.9×(age-6)+0.02×(age-6)^2–0.0002×(age-6)^3. Model 2—green (*references*): peakVO$_2$ (mL/min)=42.7+0.5×(age-6)–0.03×(age-6)^2+0.0002×(age-6)^3. AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

these ages, body composition influences exercise performance.[12] Figure 2 shows a combination of the predictions of Bongers *et al*[24] and Mylius *et al*.[13] The linear increase suggested by Bongers *et al* for the first 18 years of a child's life is not necessarily true, especially not for girls.[10 24] In girls, from 13 years of age body weight and height are important factors in addition to age. From this age onwards, girls accumulate more fat, whereas boys do increase their muscle mass.[12 26] This partly explains the natural difference in peakVO$_2$ between sexes.[12 26 27]

Cross-sectional studies in healthy, active adult people described a percentage rate of change of about 1% points per year.[28 29] The deterioration of exercise capacity is related to ageing, reduced physical activity, natural weight gain and increased fat mass during life with subsequent sarcopenia starting at 40 years of age.[29]

The peakVO$_2$ course with a cardiac lesion

While growing and ageing, physiological changes should be considered when assessing and interpreting peakVO$_2$ of patients with rTOF.[5–7] We found a peakVO$_2$ at age 6 of 70% (95% CI 67 to 73) of predicted in the current study. This result is comparable to the cross-sectional studies in children with rTOF in the literature.[15–18] The models combined with the scatterplots showed that there is a significant variation in exercise capacity. Roughly, a range from 25% until 120% of predicted at a young age, and 25% until 80% of predicted at older age, also shown in the indexed peakVO2 course (mL/min/kg).

At a young age, there is no significant difference between sexes yet. Probably because the natural difference between sexes is not yet expressed too.[10–12] Both male and female patients show a similar relative peakVO$_2$ compared with the subject-specific reference values. The peakVO$_2$ in young patients with rTOF does not rise as fast as in references (figure 2A). This is also shown in figure 2B, where the predicted percentage declined linearly from the beginning. The reduced increase during childhood and adolescence might be the reason why patients reach a critical point of exercise limitation, at which daily life is affected, faster than a healthy peer. This peakVO$_2$ course in patients with rTOF suggests that the limitation in exercise performance described in adults with rTOF originates mainly in childhood and adolescence. In this period of life, the musculoskeletal

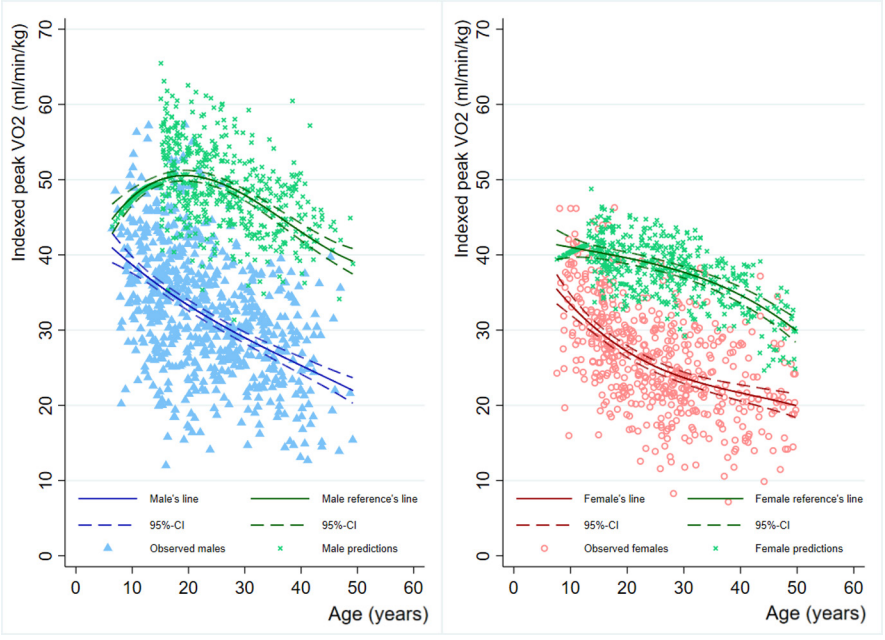

Figure 4 The scatterplot represents repeated indexed peakVO$_2$ measurements (n=889) (red for female patients, blue for male patients) and the subject-specific reference indexed peakVO$_2$ (green) in the dataset. The time-dependent model is shown by the line, including the 95% CI (dotted line) (AIC 14.235; BIC 14.344). Model 5—blue (*male patients*): peakVO$_2$ (mL/min/kg)=40.8–0.8×(age-6)+0.01×(age-6)^2–0.0001×(age-6)^3. Model 5—red (*female patients*) peakVO$_2$ (mL/min/kg)=35.9–2.7×(age-6)+0.07×(age-6)^2–0.0007×(age-6)^3. AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

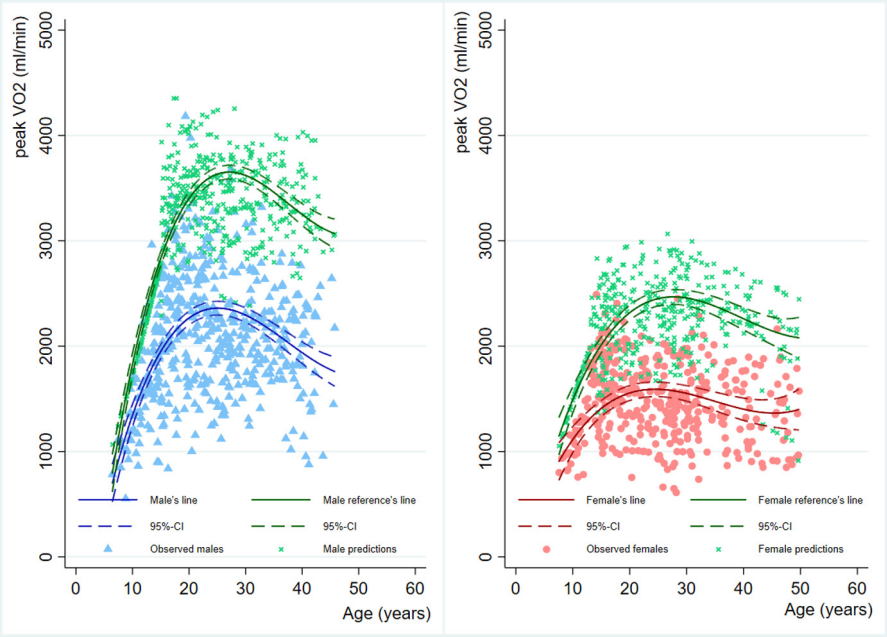

Figure 5 The scatterplot represents repeated peakVO$_2$ measurements (n=889) (red for female patients, blue for male patients) and the subject-specific reference peakVO$_2$ (green) in the dataset. The time-dependent model is shown by the line, including the 95% CI (dotted line) (AIC 25.547; BIC 25.652). Model 3—blue (*male patients*): peakVO$_2$ (mL/min)=935+322×(age-6)–9.7×(age-6)^2+0.09×(age-6)^3. Model 3—red (*female patients*): peakVO$_2$ (mL/min)=922+167×(age-6)–5.3×(age-6)^2+0.05×(age-6)^3. AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

system normally grows and matures.[13 14] These children do have residual lesions; however, they do not (yet) suffer from major cardiac problems, such as right ventricular dysfunction or dilatation, requiring pulmonary valve replacement.[18] Besides affecting the heart, muscle development is failing in a young patient with rTOF.[30] Future assessment of patients should also implement more unconventional variables, such as muscle function.

Two studies in the literature do show a longitudinal assessment of peakVO$_2$ in patients with CHD. Müller *et al* described a slow decline of −1.01% point predicted per year in peakVO$_2$ in patients with CHD, based on the references of Gläser *et al*.[31] A total of 116 patients with rTOF were included in the group of 522 patients with CHD. Patients with simple and more complex CHD were also included, no differences in the rate of change of the relative peakVO$_2$ were observed between CHD subgroups. There was no distinction based on sex.[19] The rate of decline was slower in our population, with 0.24% of predicted points per year. We did not observe a difference between sexes, except for the natural existing difference between boys and girls. Our study showed the peakVO$_2$ course, which provides more insight in the overall peakVO$_2$ of a patient with rTOF than just a difference between two measures.

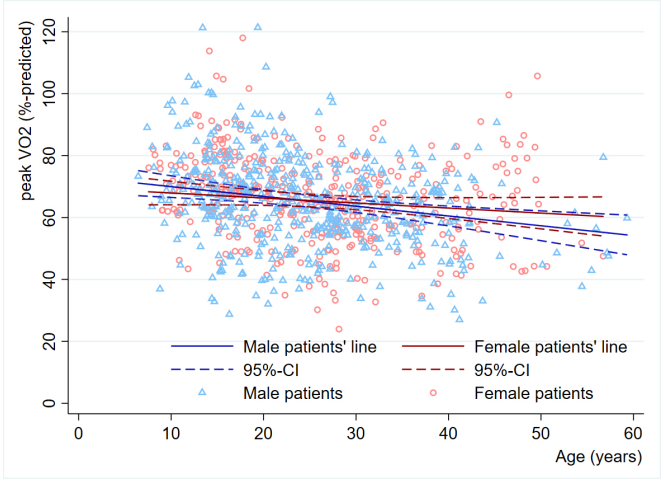

Figure 6 The scatterplot represents calculated percentage of predicted based on the subject-specific predictions (red for female patients, blue for male patients). The time-dependent model is shown by the line, including the 95% CI (dotted line) (AIC 6.885; BIC 6.923). Model 4—blue (*male patients*): peakVO$_2$ (%-predicted)=71–0.32×(age-6). Model 4—red (*female patients*): peakVO$_2$ (%-predicted)=69–0.16×(age-6). AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Kipps *et al* also described peakVO$_2$ over time in sole patients with rTOF, and included 70 patients with at least two measures (n=179). They showed a detailed change in peakVO$_2$ as percentage of predicted for the individual patient, based on the references of Cooper *et al*.[32] The individual trajectories provide a detailed overview of the peakVO$_2$ of the patient with rTOF; however, it also shows its diversity.[20] By using a statistical model to average the peakVO$_2$ course, we were able to zoom out. Our study provides a stronger context for individual patients by acknowledging and addressing the natural existing difference between sexes concerning peakVO$_2$.

In the light of explaining peakVO$_2$, there were no associations between clinical or demographic variables at baseline and the deterioration of peakVO$_2$.[20] Furthermore, the cardiac function at rest, measured by cardio magnetic resonance, was not associated with a decline in peakVO$_2$. Thus, it seems to be hard to predict which patients would deteriorate faster than the other with conventional methods.[20] To explain the differences between a well-performing patient with rTOF and a deteriorating patient with rTOF, future studies and assessment of patients should implement objective measurements of fitness and daily activities or leisure-time sports. Besides cardiopulmonary fitness,

the muscle status and lung function at a young age should be addressed as well.

Strengths and limitations

To our knowledge, this is the largest study to describe the peakVO$_2$ of sole patients with rTOF in a wide age range. Our study included a relatively young cohort with at least 42% children and adolescents (<18 years) at baseline, from two centres. The statistical model made it possible to create a representative model of the peakVO$_2$ course. All CPETs included were performed on a cycle ergometer, which eliminates the fluctuations in weight over time on the modality of exercise.[23] The peakVO$_2$ course of reference values and patients provide clinicians with a clear context for their interpretation of CPETs. Furthermore, up-to-date prediction models were used to address the difference with the references.

A limitation of this study is the retrospective design. Our dataset was unbalanced, it did not include follow-up measurements for every patient. We chose to compute the model with repeated measurements, which ensured a modelled course over time. Selection bias was minimal, since there was no difference between the single measurement sample and the repeated sample. In addition, the policy in both hospitals was not to perform the CPET only on indication, but as a part of routine follow-up. Furthermore, there was a discrepancy between the absolute versus the predicted models due to averaging by the mathematical model. This happened in the crude model (with only peakVO$_2$ and age), not when stratified for sex. Therefore, this discrepancy was explained by averaging out the sex effect in the patient group. Individual cardiac functional imaging, such as echocardiography or cardio magnetic resonance, was not available for analysis. Our mathematical models describing the course of peakVO$_2$ did not include explanatory factors (such as re-operations, sports activities, etc). Including these factors would have made the mathematical model too complex to interpret. Further studies are warranted to investigate whether re-operations affect the lifetime trajectories of peakVO$_2$ in patients with rTOF.

Key messages

What is already known on this subject?

- Cross-sectional studies in children and adults show reduced peakVO$_2$ in patients with repaired tetralogy of Fallot (rTOF).
- Two longitudinal studies including patients with rTOF (n=70, n=116) show the same trend.
- Both studies describe the exercise capacity either as a difference between two points in time or as differences that occur in the individual patient.

What might this study add?

- Our study is the largest study to date that encompasses 300 patients with rTOF and describe the course of peakVO$_2$ across a wide age range from 6 to 63 years.
- Also, this study for the first time includes a young population with 42% aged 18 years or younger and addresses sex differences.

How might this impact on clinical practice?

- This study provides a context for interpreting peakVO$_2$ in patients with rTOF.
- A clinician can apply this to compare the patient with healthy reference values and a contemporary cohort of patients with rTOF.

CONCLUSION

This multicentre study showed that the reduction in peakVO$_2$ in patients with rTOF originates already from childhood. The peakVO$_2$ is reduced at all ages. Particularly, the magnitude of the rise in peakVO$_2$ during adolescence is smaller, while the decline in adulthood is accelerated compared with healthy references.

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