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Only slow decline in exercise capacity in the natural history of patients with congenital heart disease: A longitudinal study in 522 patients

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Abstract

Objective: Exercise studies in patients with congenital heart disease (CHD) suggest that exercise capacity declines progressively. This study aims to assess the natural history of exercise capacity in patients with CHD from serial cardiopulmonary exercise tests (CPETs) and to identify factors that are associated with the rate of decrease.

Patients and methods: From July 2001–August 2012 we included all patients with CHD who had two CPETs separated by at least six months. Patients with any kind of intervention (surgery, catheter intervention, or change in medication) between the two tests were excluded.

Results: In 522 patients (24.8 ± 10.2 years, 215 female) peak oxygen uptake ($\dot{V}O_2$) was reduced to $80.0 \pm 20.7\%$ predicted and declined significantly during a mean follow-up of 2.5 ± 1.8 years to $78.1 \pm 20.4\%$ predicted ($p < 0.0001$). The annual declining rate of peak $\dot{V}O_2$ was only $-1.01 \pm 6.83\%$ points per year. Higher peak oxygen pulse (% predicted) ($r = -0.230$; $p < 0.0001$), higher peak $\dot{V}O_2$ (% predicted) ($r = -0.213$; $p < 0.0001$) at baseline testing and the presence of a pacemaker ($r = -0.095$; $p = 0.031$) were only weakly associated with a more rapid decline in peak $\dot{V}O_2$ (% predicted) over time. The decline was independent from diagnosis, heart defect severity, systemic ventricular morphology and age.

Conclusions: There was a progressive, but slow, decline in the natural history of exercise capacity in all kind of patients with CHD. Except for having a pacemaker, we could not find any factors associated with this decline.

Keywords

Congenital heart disease, natural history, exercise capacity, peak oxygen uptake, exercise testing, serial study

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Introduction

Exercise capacity of patients with congenital heart disease (CHD) is reduced[1–5] and recent reports have demonstrated that variables derived from cardiopulmonary exercise tests (CPETs) are of predictive value regarding long term mortality and morbidity in this cohort.[4,6–9] Therefore, CPETs became a powerful tool in the evaluation of current physical status, prognosis and treatment progress of patients with CHD. However, most of those studies were cross-sectional and conclusions drawn from a single CPET are probably of limited value. Era effects from improvements in therapy, the training status and the daily performance of the individuals might have biased the data and made interpretation difficult.

Currently, there is little knowledge about the natural history of exercise capacity in patients with CHD. It has been suggested that there is a progressive decline of exercise capacity in patients after Fontan surgery,[10–14] with repaired tetralogy of Fallot,[10,15] in patients with aortic stenosis[10] and with native conditions of Ebstein's anomaly.[16] Larger studies that have

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investigated both the more simple defects and the more complex ones do not exist.

Therefore, the aim of the present study was to assess how fast exercise capacity in patients with CHD deteriorates, and to identify factors that influence this decrease in exercise capacity.

Patients and methods

Study subjects

We retrospectively reviewed our institutional database of CPETs performed between July 2001–August 2012. Almost all of our patients underwent CPET as part of their routine follow-up examination in our outpatient department. The others underwent CPETs for the evaluation of new symptoms.

All patients with two exercise tests separated by at least six months were included in the study. Patients who had undergone cardiac surgery or interventional catheterization during that period of time were excluded, as well as patients who underwent an electrophysiological procedure or changes in medical treatment. We further excluded patients with a CPET less than six months after cardiac surgery or interventional catheterization, to avoid bias arising from an incomplete recovery after intervention. From those eligible 589 patients with two examinations we excluded 67 patients that terminated exercise at the first or the second CPET before reaching their cardiovascular limit. This was defined as previously described [12,16] as respiratory exchange ratio at peak exercise <1.05 or heart rate at peak exercise $<85\%$ predicted.

Patients were categorized into eight subgroups: isolated shunts (pre- and post-tricuspid), left outflow obstructions (including 44 patients with coarctation and 90 patients with aortic stenosis), pulmonary valve dysfunction (including 116 patients with repaired tetralogy of Fallot, 15 patients with repaired common arterial trunk, and 24 patients with isolated pulmonary stenosis), Ebstein anomaly, transposition of the great arteries (including those after atrial redirection and congenitally corrected), Fontan circulation (including various modifications), cyanotic (including Eisenmenger and various defects with pulmonary stenosis and prestenotic right-to-left shunt) and miscellaneous conditions. Heart defect severity was defined as simple, moderate or complex according to the American College of Cardiology (ACC) guidelines.[17]

CPET

All patients underwent a symptom-limited CPET on a bicycle ergometer in upright position according to international guidelines and as previously described.[1,18–20] Fifteen patients with a rate-adaptive pacemaker were tested on a treadmill.

The exercise test featured a breath-by-breath gas exchange analysis using a metabolic chart (Vmax 229, SensorMedics, Viasys Healthcare, Yorba Linda, California, USA). Peak oxygen uptake ($\dot{V}O_2$) was defined as the highest mean uptake of any 30 s time interval during exercise. Reference values for age, body mass, body height, and gender, expressed as '% predicted' were calculated as previously described.[21] Ventilatory efficiency was displayed as minute ventilation-to-carbon dioxide output ($\dot{V}_E/\dot{V}CO_2$) slope confined to the linear part of the curve, excluding values beyond the respiratory compensation point.

Peak O_2 pulse was calculated as peak $\dot{V}O_2$ divided by peak heart rate. The reference value was estimated from the peak $\dot{V}O_2$ reference value divided by the expected peak heart rate.[20] Expected peak heart rate was calculated $(220–age)\times0.925$ according to Rhodes et al.[22]

Data analyses

Gauss' normal distribution of the primary outcome variable change in peak $\dot{V}O_2$ was approved by a Shapiro-Wilk test. All descriptive data were, therefore, expressed as mean $\pm$ standard deviation (SD).

Baseline values were compared with follow-up data using a paired Student's *t*-test. Subgroup comparisons of changes in peak $\dot{V}O_2$ were done by unpaired Student's *t*-tests and one-way analysis of variance. Univariate associations of changes in peak $\dot{V}O_2$ (% points per year) and baseline parameters were assessed using Pearson correlation. Afterwards a multivariate, stepwise regression model was performed with all of the seven diagnostic subgroups and all parameters that show an univariate association to the changes in peak oxygen uptake (% points per year).

Values of $p < 0.05$ in a two-sided analysis were considered significant. All analyses were performed using SPSS 20.0 software (IBM Inc, Armonk, New York, USA).

Results

Peak $\dot{V}O_2$ was reduced to $80.0 \pm 20.7\%$ predicted and declined significantly during a mean follow-up of 2.50 ± 1.81 years to $78.1 \pm 20.4\%$ predicted ($p < 0.0001$). The annual decline in peak $\dot{V}O_2$ was $-1.01 \pm 6.83\%$ points per year, respectively. The indexed work load (Watt per kg body weight), peak oxygen pulse (% predicted), and peak heart rate declined, respectively (Table 1).

There was a decline in peak $\dot{V}O_2$ in all diagnostic subgroups (Table 2). The amount of decline did not differ significantly between the seven diagnostic groups ($p = 0.871$).

Table 1. Comparison of study characteristic and exercise variables at baseline and follow-up examination

Variable		*n*	Baseline	Follow-up	Change	*p*-value[a]	Change per year[b]
Sex	M/F	522	307/215	307/215	–	–	–
Age	years	522	24.8 ± 10.2	27.3 ± 10.4	2.50 ± 1.81	–	–
BMI	kg/m^2	522	22.2 ± 3.8	23.0 ± 3.8	0.76 ± 1.65	*<0.0001*	0.35 ± 0.92
Peak $\dot{V}O_2$	ml/min/kg	522	30.0 ± 9.3	28.3 ± 9.2	−1.75 ± 4.42	*<0.0001*	−0.75 ± 2.46
	%	522	80.0 ± 20.7	78.1 ± 20.4	−1.92 ± 10.87	*<0.0001*	−1.01 ± 6.83
Peak O_2 pulse	%	522	86.6 ± 21.2	85.3 ± 21.1	−1.34 ± 13.44	*0.023*	−0.75 ± 8.33
Peak work load	watts	503	159.6 ± 57.2	159.1 ± 59.5	0.00 ± 22.79	0.999	1.10 ± 12.78
	watts/kg	503	2.53 ± 0.73	2.39 ± 0.75	−0.13 ± 0.34	*<0.0001*	−0.05 ± 0.19
$\dot{V}_E/\dot{V}CO_2$ slope		492	29.7 ± 5.9	29.7 ± 6.4	0.08 ± 3.70	0.594	0.15 ± 2.37
Peak heart rate	bpm	522	167.4 ± 22.1	164.1 ± 22.9	−3.38 ± 15.4	*<0.0001*	−1.49 ± 11.11
	%	522	92.7 ± 8.5	91.9 ± 11.4	−0.73 ± 8.85	0.059	−0.37 ± 6.47
Peak SBP	mm Hg	512	165.2 ± 31.0	164.7 ± 29.7	−0.43 ± 21.00	0.648	−0.11 ± 14.90

BMI: body mass index; bpm: beats per minute; SBP: systolic blood pressure. Values are presented as mean ± standard deviation (SD).
[a]Comparing baseline values with follow-up by a paired *t*-test; [b]Change per year is displayed in absolute values or in case of '%' displayed as '% points per year'.
p-values < 0.05 are displayed in italic.

Table 2. Comparison of study characteristic and exercise variables at baseline and follow-up examination

Diagnostic group	*n*	Peak $\dot{V}O_2$ (%) baseline	Peak $\dot{V}O_2$ (%) follow-up	Length of follow-up (years)	Change in peak $\dot{V}O_2$ (% points per year)
Isolated shunts	25	90.7 ± 17.8	87.4 ± 17.8	2.0 ± 1.0	−2.07 ± 7.01
Left outflow obstruction	127	92.1 ± 19.6	90.1 ± 21.3	2.0 ± 1.3	−1.26 ± 7.82
Pulmonary valve dysfunction	145	81.5 ± 18.3	79.3 ± 17.7	2.5 ± 1.8	−1.12 ± 7.10
Ebstein anomaly	37	79.8 ± 19.9	77.2 ± 14.7	2.4 ± 1.7	−1.64 ± 7.27
TGA[b] and ccTGA	84	70.7 ± 16.5	68.7 ± 15.6	3.5 ± 2.4	−0.67 ± 6.20
Fontan circulation	55	63.2 ± 16.3	62.6 ± 18.2	2.6 ± 1.7	−0.01 ± 5.55
Cyanotic	21	58.8 ± 16.3	57.6 ± 15.1	2.9 ± 2.1	−0.86 ± 2.94
Miscellaneous	28	84.9 ± 16.2	84.2 ± 13.6	2.2 ± 1.8	−0.77 ± 6.37

TGA: transposition of the great arteries. Values are presented as mean ± standard deviation (SD); ccTGA: congenital corrected Transposition of the Great Arteries. *p*-values < 0.05 are displayed in italic; [b]TGA after atrial redirection (Senning or Mustard).

In bivariate analysis, higher peak oxygen pulse (% predicted) ($r = -0.230$; $p < 0.0001$), higher peak oxygen uptake (% predicted) ($r = -0.213$; $p < 0.0001$) at baseline testing and the presence of a pacemaker ($r = -0.095$; $p = 0.031$) were weakly associated with a more rapid decline in peak $\dot{V}O_2$ (% predicted) over time (Table 3).

In multivariate regression analyze only peak oxygen pulse ($p < 0.0001$) and the presence of a pacemaker ($p = 0.040$) were of independent predictive value (Table 4).

However, the decline in peak $\dot{V}O_2$ was independent from ACC severity classes ($p = 0.732$), age ($p = 0.326$), in patients with a systemic right ventricle ($p = 0.456$) or in patients with native conditions ($p = 0.357$, Table 5).

Discussion

This study showed that there is a progressive, but only slow, decline of exercise capacity in the natural history of patients with CHD. Except for patients with a pacemaker, none of our investigated variables could be associated with this progressive decline in exercise capacity.

Exercise capacity is depressed throughout all diagnostic subgroups of patients with CHD.[2–7,11,15,16,18,20] In most of those studies, there was evidence that peak $\dot{V}O_2$ was lower in patients with older age. But solely from cross sectional studies, it could not be supposed that there is a progressive decline in exercise capacity. Interventions, changes in therapeutic management, other era effects, patients' selection, survival bias, and the natural decline of peak $\dot{V}O_2$ of approximately 0.7% per year have to be considered. Thus the only way to detect a progressive change in peak $\dot{V}O_2$ is serial exercise testing.

These serial studies aiming on the natural decline of exercise capacity were limited to small patient numbers[10] and existed only in subgroups with Ebstein

Table 3. Bivariate association between the changes in peak oxygen uptake (% points per year) and baseline parameters

Bivariate association	*r*	*p*-value*
Age (years)	0.038	0.387
Sex	−0.022	0.609
Body mass index (kg/m^2)	−0.028	0.527
Peak oxygen uptake (%)	*−0.213*	*<0.0001*
Peak oxygen pulse (%)	*−0.230*	*<0.0001*
$\dot{V}_E/\dot{V}CO_2$slope	−0.057	0.210
Peak heart rate (%)	−0.004	0.934
Systolic blood pressure at peak exercise (mm Hg)	0.061	0.170
Severity of the heart defect (simple, moderate, complex)	0.022	0.624
Systemic ventricle (left, right)	−0.030	0.497
Pacemaker (yes, no)	*−0.095*	*0.031*
Surgery for congenital heart defect (yes, no)	0.040	0.357

p-values < 0.05 are displayed in italic.

Table 4. Multivariate association between the changes in peak oxygen uptake (% points per year) and baseline parameters

Variable	Regression coefficient	SE	Beta	*p*-value	r^2 change (%)
Peak oxygen pulse (%)	−0.073	0.014	−0.228	<0.0001	5.3
Presence of pacemaker	−2.707	1.312	−0.088	0.040	0.8

SE: standard error of the mean.
p-values < 0.05 are displayed in italic.

anomaly,[16] tetralogy of Fallot[15] and with Fontan circulation.[11–14] All of these studies reported a progressive decline in exercise capacity. Our study confirmed those results for all of the examined diagnostic subgroups of patients with CHD, but we found considerably lower decline rates in peak $\dot{V}O_2$ per year than previous studies.[11–16] The reasons for this are very speculative. The most obvious one is a referral bias to the tertiary center that performed the studies. This means, that the indication for a repeated CPET was slightly clinically driven. This might have increased the number of deteriorating patients and hampers generalization to the total group of patients with congenital heart defects. Maybe we have a more representative study group in our outpatient department where we see more than 7000 patients a year. However, another reason for the more favorable results in the present study could also be that our follow-up management includes a very liberal attitude towards sport activities and even promotion of an active lifestyle. This might have stabilized exercise capacity at a higher level.[23]

Nevertheless, the decline in peak $\dot{V}O_2$ was highly variable and weakly predictable from our examined variables and not attributable to a specific diagnostic subgroup. In accordance with reports of patients with tetralogy of Fallot,[15] with Ebstein's anomaly,[16] and of patients after Fontan procedure,[11,12] a higher baseline peak $\dot{V}O_2$ was associated with a higher decrease in peak $\dot{V}O_2$ during the follow-up period. These studies concluded that the exercise performance of patients with CHD is not sustained in the long term, which is also reflected in the faster deterioration of the peak oxygen pulse, a surrogate for the forward stroke volume. However, the other side of the correlation, that those patients with the worst baseline values showed the least deterioration or even an improvement, is hard to explain, if there is no surgery or intervention. The explanation becomes more comprehensive, if we consider a statistical phenomenon called 'regression to the mean'. Patients, tested with higher baseline values (peak $\dot{V}O_2$ and peak oxygen pulse) are more likely to decrease in the second test, and vice versa. Thus we have doubts whether a high peak oxygen pulse at baseline is a real risk factor for a progressive reduction in peak oxygen pulse. The same holds true for peak $\dot{V}O_2$.

Only the presence of a pacemaker seemed to contribute not only to a lower peak $\dot{V}O_2$ at baseline, but also to a faster decline in peak $\dot{V}O_2$. This is in accordance to cross-sectional cohorts studies,[4,6] in which patients with CHD and a pacemaker showed lower peak $\dot{V}O_2$ values than CHD patients without pacemaker. Even rate-responsive pacing did not improve exercise capacity in patients with a systemic right ventricle.[24] According our data, it seems that pacing cannot maintain the normal performance of the heart and the declining stroke volume over time leads to a progressive decrease in exercise capacity compatible with some kind of subtle pacemaker cardiomyopathy.

Conclusion

In general, there is only a slow decline of exercise capacity in the natural history of patients with CHD. For the patients' management this means that if a patient substantially declines in his/her regular exercise test then this finding should not be neglected with the excuse that this is fairly normal in the natural history of CHD. Those patients should be carefully re-evaluated for new hemodynamic impairment.

Limitations

This was a retrospective study with a heterogeneous group of patients with all kinds of congenital heart defects. The next steps are to carry out prospective

Table 5. Comparison of study characteristic and exercise variables at baseline and follow-up examination

Subgroup	Peak $\dot{V}O_2$ (%) baseline	Change in peak $\dot{V}O_2$ (% points per year)	p-value[a]
Whole study group ($n = 522$)	80.0 ± 20.7	-1.01 ± 6.83	
ACC severity class			
Simple ($n = 53$)	96.9 ± 17.6	-1.71 ± 7.35	0.732
Moderate ($n = 176$)	85.6 ± 18.8	-0.89 ± 7.25	
Complex ($n = 293$)	73.5 ± 19.6	-0.97 ± 6.45	
Age at baseline			
<18 years ($n = 154$)	84.0 ± 20.8	-1.48 ± 7.11	0.326
≥ 18 years ($n = 368$)	78.3 ± 20.4	-0.82 ± 6.70	
Surgery			
Yes ($n = 445$)	78.2 ± 20.0	-0.90 ± 6.87	0.357
No ($n = 77$)	90.2 ± 21.7	-1.68 ± 6.56	
Pacemaker			
No ($n = 495$)	80.4 ± 20.7	-0.87 ± 6.73	*0.031*
Yes ($n = 27$)	73.4 ± 19.4	-3.78 ± 8.08	
Systemic ventricle			
Left ($n = 427$)	82.4 ± 20.7	-1.11 ± 7.00	0.456
Right ($n = 93$)	69.0 ± 16.8	-0.58 ± 6.02	

Values are presented as mean $\pm$ standard deviation (SD)
[a]Comparing differences in the subgroups by Student's t-test, or analysis of variance.
p-values < 0.05 are displayed in italic.

long-term follow-up studies with clearly defined and representative cohorts to exclude a referral and a survival bias. These studies should include the role of physical activity and sport participation to determine whether the decline in exercise capacity is due to simple deconditioning or progression of the disease. In addition, the predictive value of the change in exercise capacity in patients with CHD regarding morbidity and mortality has to be evaluated. Probably trends in peak $\dot{V}O_2$ or $\dot{V}_E/\dot{V}CO_2$ slope are more predictive than the results from a single exercise test.

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Conflict of interest

None declared.

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