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In patients after Fontan completion exercise capacity is significantly reduced. Although peak oxygen consumption (VO_{2peak}) is a strong prognostic factor in many cardiovascular diseases, it requires the achievement of a maximal effort. Therefore, submaximal exercise parameters such as oxygen uptake efficiency slope (OUES) may be of value. In the present observational study we evaluated the exercise capacity with maximal and submaximal parameters in a group of Fontan patients with an extracardiac conduit and determined their prognostic value. Sixty Fontan patients followed up in the Leiden University Medical Center who have performed an exercise test were included in this retrospective study. Exercise tests were performed at a median age of 11 years. Fontan patients showed on average lower values for all exercise parameters compared to reference values from a healthy dataset as shown by the %predicted values: VO_{2peak}%:mean 66%(95%CI:64 to 74) and OUES%:mean 72%(95%CI:67 to 77). Twenty percent of the patients were not able to achieve an RER>1.0. RER showed a moderate positive correlation with VO_{2peak} but not with OUES. There was a deterioration of VO_{2peak}% and OUES% over time. OUES was significantly lower in patients with cardiac events in the follow up period. Fontan patients have an impaired exercise performance even at young ages and it deteriorates with age. An important percentage of Fontan patients is not able to reach maximal effort so the use of submaximal parameters, like OUES, should be considered as part of the evaluation. Moreover, OUES could have a prognostic value in this group of patients. **(Am J Cardiol 2021;154:92−98)**

The Fontan procedure, as surgical palliation for patients with single ventricle physiology, has significantly developed from the original atriopulmonary connection to the use of a total cavopulmonary connection (TCPC) with either an intracardiac tunnel (ILT) or extracardiac conduit (ECC). In the current era, survival of these patients at 10 years is up to 95%,[1] but longevity and morbidity at mid and long-term follow-up remain a challenge.[1,2] In adult Fontan patients decreased exercise capacity is associated with increased morbidity,[2-4] and also a decline in exercise capacity is a risk factor for major cardiovascular events.[5,6] Exercise capacity is mostly determined by the maximal cardiopulmonary exercise test (CPET) parameter peak oxygen consumption (VO_{2peak}) and it is decreased and deteriorates over time in even asymptomatic Fontan patients.[1,3,4,7-9] However, it requires a maximal effort for its correct interpretation, which is often difficult in patients after TCPC. Therefore, submaximal exercise parameters such as the OUES have been developed but it has only been used in a small number of studies with young Fontan patients.[7,10] We hypothesize that OUES, as a submaximal exercise parameter, could be useful to determine exercise capacity in young Fontan patients and could be of prognostic value for future cardiac events.

Methods

All Fontan patients with an ECC from the Leiden University Medical Center who had performed a CPET between 2010 -2019 were included in this retrospective study. Information regarding the clinical and echocardiographic aspects were acquired from the electronic medical history, both at the time the CPET was performed and during the follow-up period. The study was approved by the institutional review board and the need for individual consent for this retrospective study was waived.

If patients performed more than one CPET, the first in time was evaluated. Only tests in which oxygen consumption was measured were included. The CPET's were performed on an electronically braked cycle ergometer (Jaeger ER900, Viasys Healthcare GmbH, Höchberg, Germany). A facemask (Hans Rudolph, Kansas City, MO, USA) connected to a flowmeter (Triple V volume transducer) and a

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computerized gas analyser (Jaeger MasterScreen CPX, CareFusion GmbH, Hoechberg, Germany; or Vyntus CPX, Vyaire Medical GmbH, Hoechberg, Germany) were used to do the analysis. A breath-by-breath minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide production (VCO_2) and respiratory exchange ratio (RER, defined as the ratio VCO_2/VO_2) was calculated in 10 second intervals. Heart rate (HR) was continuously monitored through a twelve-lead electrocardiogram and blood pressure was determined every 2 minutes by sphygmomanometry. Weight and height were obtained and body surface area (BSA) and body mass index (BMI) were calculated by using the Dubois equation.

A 3 minute warm-up phase (unloaded cycling) was followed by a continuous incremental bicycle protocol with a work rate increment of 10, 15 or 20 W/min depending on the height (<125cm, 125-150cm or >150cm) according to the Godfrey protocol.[11] The patients had to maintain a pedalling rate between 60 and 65 revolutions/min and were encouraged to perform to exhaustion. The CPET was ended by the patient in case of discomfort or by the supervising physician in case of ECG changes, an excessive breathing pattern or otherwise.

The peak RER (RER_{peak}) was calculated as the average of 2 highest consecutive achieved RER values in 10 sec during peak work rate (WR_{peak}). WR_{peak} was defined as the maximum work rate achieved and finished (1 min completed) and the % of the predicted value was calculated as previously described.[12]

HR at rest (HR_{rest}) was measured after at least 3 min in a seated position and the HR peak at exercise (HR_{peak}) was calculated as the highest value achieved during WR_{peak}. Then the %predicted value was calculated with the formula [200-age(in years)], being abnormal <85%.[13] HR reserve ($HR_{reserve}$) was defined as $HR_{peak}-HR_{rest}$. HR was also recorded at 1 and 2 minutes after cessation of the CPET (HR01' and HR02'). HR recovery ($HR_{recovery01}$,and $HR_{recovery02}$,) was calculated as the difference between HR_{peak} and HR01' and HR_{peak} and HR02'. The relative decrement in HR (HR01% and HR02%) was calculated as ($HR_{recovery}/HR_{reserve}$) x100%.

VO_{2peak} was calculated as the average of 2 highest consecutive achieved VO_2 values in 10 sec during WR_{peak}. It was expressed in absolute values (ml/min), per body weight (ml/kg/min) and as the % of the predicted value adjusted for age, gender and weight (VO_{2peak}).[12,13]

VE/VCO_2 and VO_2/WR slopes were calculated. The O_2 pulse is the VO_2 divided by HR, and the maximal O_2 pulse (O_2pulse_{max}) was calculated as the average of the highest two consecutive O_2 pulse values during WR_{peak}. The data of Ten Harkel et al[12] was used to calculate the % predicted values of O2 pulse.

OUES was calculated by the linear least squares regression of the VO_2 on the common logarithm of the VE by the equation VO_2 = a log (VE) + b, where the constant 'a' is the regression coefficient OUES.[14] Absolute values, % of predicted values and values per body weight were represented. The %predicted values of OUES (OUES%) were determined using the previously described formulas based on reference normal values.[15]

Follow-up data were collected until November 2019. Patients with at least 2 years of follow-up after the CPET were considered for this analysis. The medical records were reviewed to determine cardiac events (morbidity and mortality). Cardiac morbidity was defined as the need of cardiac-related hospitalization including medical or surgical management of any complications derived from heart failure, arrhythmias, protein losing enteropathy or plastic bronchitis. Overall mortality and the need for heart transplantation were noted as well.

SPSS Statistics software (version 25.0 IBM SPSS, Chicago, IL) was used to perform data analysis. Variables were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous data were expressed as mean ± standard deviation (SD) or as median with first to third quartile [Q1-Q3] where suitable. Patient values were expressed relatively to the reference values as % of predicted value (100% would mean equal to reference value) and represented as mean with 95% of confidence interval (CI). P value < 0.05 was considered statistically significant. The independent samples t-test or the Mann-Whitney test, in case of non-normality, were used to assess differences in CPET parameters between gender, ventricular dominance, ventricular function and medication at the time CPET was performed and with the cardiac events during the follow-up period. Correlations between the different CPET parameters with clinical parameters (age, years after Fontan, $SatO_2$) as well as correlation between VO_{2peak} and OUES were calculated as Pearson or Spearman correlation coefficient depending on data distribution. The Kaplan-Meier method was used to construct an outcome-free of cardiac morbidity survival curve after Fontan procedure. To test whether the CPET values of patients differed from their reference values, the one sample t-test was used to evaluate the % predicted values.

Results

General characteristics of the study group are shown in Table 1. Sixty patients with a functional univentricular heart after Fontan palliation were included; 31 of them (52%) had a dominant left ventricle and 29 had a dominant right ventricle. All patients had undergone an ECC Fontan

Table 1
Characteristics of study population

Variable	n = 60
Men	38 (63%)
Dominant left ventricle	31 (52%)
Age at CPET (years)	11 [10-13]
Years after Fontan	8 [7-10]
Weight (kg)	37 [30-50]
Body Surface Area (m^2)	1.22 [1.07-1.51]
Body Mass Index (kg/m^2)	16.87 [15.36-19.19]
$SatO_2$	96 [94-97]
Cardiac medications	
Anticoagulants/antiplatelet	60 (100%)
ACEI	6 (10%)
β-blocker	1 (1.7%)
Sildenafil	1 (1.7%)
Diuretics	1 (1.7%)

Data shown as number (%), mean ± SD or median [Q1-Q3]
CPET: cardiopulmonary exercise test, *ACEI*: angiotensin-converting enzyme inhibitors.

Table 2
Cardiopulmonary exercise test results

Variable	All patients	Male	Female	p-value
SBP basal (mmHg)	120 ± 16	120 ± 16	121 ± 16	0.60
SBP peak (mmHg)	159 ± 27	159 ± 27	158 ± 26	0.85
RER_{peak}	1.06 ± 0.11	1.05 ± 0.10	1.06 ± 0.12	0.70
Maximal exercise	N = 48	N= 30	N = 18	
Work $Rate_{peak}$ (W)	90 [80-100]	80 [79-123]	93 ± 16	0.357
WR_{peak}%	70 (65-74)	68 (62-74)	72 (66-78)	0.448
(W/kg)	2.3 ± 0.6	2.3 ± 0.7	2.2 ± 0.4	0.573
Heart $Rate_{peak}$ (bpm)	170 ± 18	163 ± 18	180 ± 14	**0.002**
HR_{peak}%	90 (87-93)	87 (83-91)	96 (92-100)	0.002
VO_{2peak} (ml/min)	1187 [1079-1377]	1152 [1046-1468]	1234 ± 213	0.749
VO_{2peak}%	69 (64-74)	68 (61-75)	70 (63-76)	0.744
(ml/kg/min)	31.1 ± 8.4	31.6 ± 8.7	30.2 ± 8.2	0.580
VO_{2peak}% / kg	70 (64-75)	68 (61-76)	72 (62-82)	0.546
O_2 $pulse_{max}$ (ml/beat)	7.3 [6.5-8.3]	7.5 [6.9-8.8]	7 ± 1	0.069
O_2 $pulse_{max}$%	59 (56-62)	61 (57-65)	54 (50-59)	0.013
Submaximal exercise	n = 60	n = 38	n = 22	
VE/VCO_2 slope (L/min)	35.9 [32.7-39.5]	35.9 [32.8-39]	37 ± 5.8	0.81
OUES (ml/min/log(L/min))	1350 ± 376	1385 ± 417	1288 ± 293	0.34
OUES%	72 (67-77)	70 (64-78)	74 (65-83)	0.59
OUES/kg	35.4 ± 11.1	36.7 ± 11.7	33.2 ± 9.9	0.25
OUES% / kg	76 (70-82)	75 (67-83)	79 (68-89)	0.51

Data shown as mean ± SD or median [Q1-Q3]. The %predicted values were shown as mean(95%CI).
p: Independent samples T test or Mann-Whitney U.
HR_{peak}%: % of the predicted values of heart rate at peak exercise; *O_2 $pulse_{max}$*: maximal O_2 pulse; *OUES*: oxygen uptake efficiency slope; *OUES%*: % of the predicted values of OUES; *RER_{peak}*: respiratory exchange ratio at peak exercise; *SBP basal*: systolic blood pressure at rest; *SBP peak*: systolic blood pressure at peak exercise; *VCO_2*: carbon dioxide production; *VE*: minute ventilation; *VO_{2peak}*: oxygen uptake at peak exercise; *VO_{2peak}%*: % of the predicted values of VO_{2peak}; *WR_{peak}*: peak work rate; *WR_{peak}%*: % of the predicted values of peak work rate.

procedure. The median [Q1-Q3] age at which the CPET was performed was 11[10-13] years, 8[7-10] years after Fontan completion. The subjective function of the dominant ventricle as assessed by echocardiography was good in 83% of the patients and reasonable in the other patients. The general condition of patients at the time of the CPET was good in 88%; 3 patients had a pacemaker because of sinus node dysfunction, 1 patient had plastic bronchitis and 1 patient had protein losing enteropathy.

Table 2 depicts the CPET results**.** Twenty percent of the patients were not able to achieve an RER > 1.0. There were no adverse events, such as arrhythmia or (near) syncope during the exercise tests. Maximal exercise test parameters were calculated only in patients who achieved RER>1.0. Patients showed on average lower values for all CPET parameters compared to reference values from a healthy dataset,[12,13,15] as reflected by % predicted values (mean VO_{2peak}% 69% (95%CI: 64-74), p <0.001; and mean OUES% 72% (95%CI: 67-77), p <0.001). Male patients had lower HR_{peak} and HR_{peak}%, as compared to female subjects, no other significant differences in CPET parameters were found between males and females. There were no differences in exercise performance between patients with reasonable or good ventricular function. When analysing the differences in CPET performance between the left or right dominant ventricle, only OUES% was significantly lower in left dominant ventricles (LV mean OUES%: 65%(95%CI 59-72) vs RV mean OUES%: 79%(70-88); p = 0.011).

Table 3
Difference in cardiopulmonary exercise test parameters regarding the treatment or the clinical status patients had when the test was performed

	Treatment		
	Only antiaggregant/ anticoagulant	+ other cardiac drugs	p
Maximal exercise	n = 40	n = 8	
Heart $Rate_{peak}$	173 ± 17.8	155 ± 14.3	0.010
Heart $Rate_{peak}$%	92 (89-95)	82 (76-88)	0.011
Submaximal exercise	N=51	n = 9	
OUES%	75 (69-81)	57 (46-68)	0.017
OUES/kg	37 ± 12	29 ± 6	0.011
OUES% / kg	79 (72-86)	60 (51-69)	0.001
	Clinical status		
	Good	Other	p
Submaximal exercise	n = 53	n = 7	
VE/VCO_2 slope	27.5 [25.66-29.9]	24.1 [22.8-26.8]	0.021
OUES	1388 ± 358	1055 ± 410	0.026
OUES%	75 (69-80)	53 (44-61)	0.009

Data shown as mean ± SD, median [Q1-Q3] or the % predicted values as mean (95%CI). p: Independent samples T test or Mann-Whitney U. Only significant results are depicted in this table. The cardiac drugs that were used are specified in Table 1.
HR_{peak}%: % of the predicted values of the maximal heart rate at peak exercise; *OUES*: oxygen uptake efficiency slope; *OUES%*: % of the predicted values of the oxygen uptake efficiency slope; *VCO_2*: carbon dioxide production; *VE*: minute ventilation; *VO_{2peak}*: oxygen uptake at peak exercise; *VO_{2peak}%*: % of the predicted values of the VO_{2peak}.

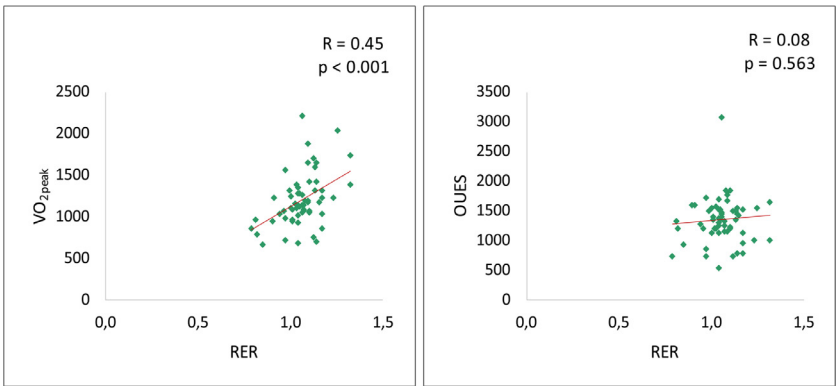

Figure 1. **Correlation between oxygen uptake efficiency slope and oxygen uptake peak with RER** *VO_{2peak}*, oxygen uptake peak; *OUES*, oxygen uptake efficiency slope; *RER*, expiratory exchange ratio.

Patients in good clinical condition or taking only anticoagulant/antiplatelet medication performed better on several CPET parameters (specially submaximal exercise test parameters) as compared to patients with worse general condition or that were having more than anticoagulant/antiplatelet medication (Table 3).

A moderate positive correlation was shown between RER and VO_{2peak} but not between RER and OUES (Figure 1). Both the age and the number of years after Fontan completion were negatively correlated to the % predicted values of VO_{2peak} and OUES (Figure 2). Figure 3 shows a strong positive correlation between the VO_{2peak} and OUES, for both the absolute and the adjusted for body weight data.

Thirty six (60%) patients had a follow up period of ≥ 2 years after CPET. For them the median follow-up after CPET was 4.8 years [Q1-Q3: 3.5-5.8]. There were no deaths or heart transplantations during the follow up period and 10 patients (28%) had a cardiac-related problem. Table 4 shows the cardiac related morbidity after Fontan.

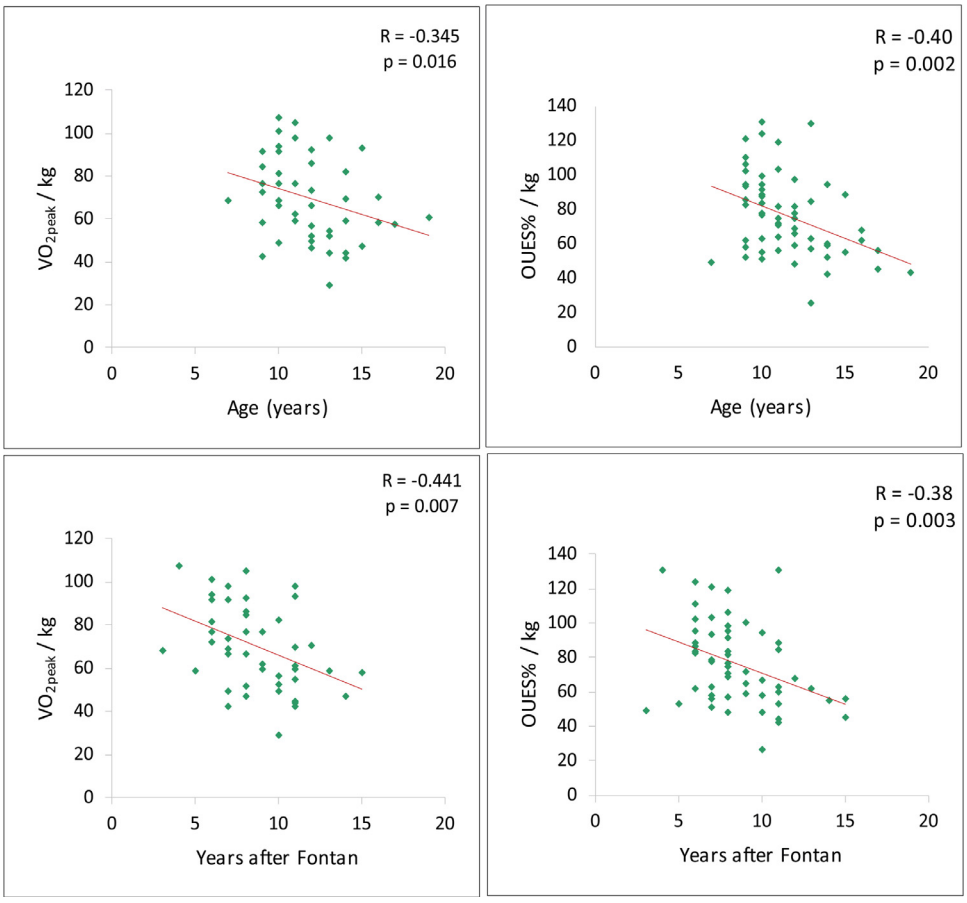

Figure 2. **Correlation between cardiopulmonary exercise test parameters with age (years) and years after Fontan procedure.** *VO_{2peak}*, oxygen uptake peak; *OUES*, oxygen uptake efficiency slope.

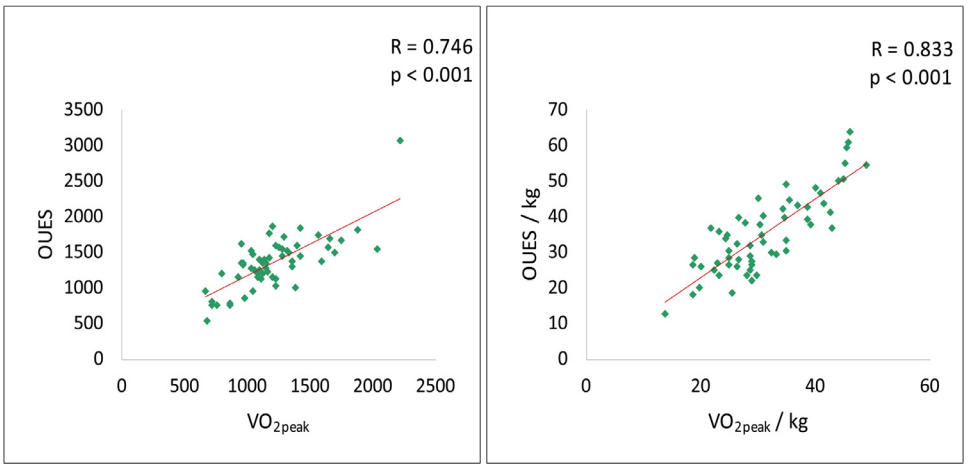

Figure 3. **Relationship between oxygen uptake efficiency slope with oxygen uptake peak.** *VO_{2peak}*, oxygen uptake peak; *OUES*, oxygen uptake efficiency slope.

Table 4
Morbidity after Fontan procedure

	n = 10
Cardiac catheterization	
Left pulmonary artery stenting	3
Extracardiac conduit stenting	1
Collateral closure	3
Heart rhythm disorders	1
Sinus node dysfunction	1
Supraventricular tachycardia	1
Heart surgery	
Extracardiac conduit replacement	

The median follow-up time after cardiopulmonary exercise test was 3 [0.5-7] years (period 2010-2018).

Both, the absolute OUES and the OUES% values where lower in the patients that had a cardiac event than the ones without events: mean OUES 1499 ± 404 in no events versus 1096 ± 337 in events, p = 0.007; mean OUES% 85% (95%CI 77-92) in no events versus 67% (95%CI 52-82) in events, p = 0.002. No significant difference was seen in other CPET parameters. In Figure 4 is depicted the Kaplan-Meier outcome-free survival curve after Fontan procedure

Discussion

This study showed that exercise capacity is impaired in paediatric Fontan patients with an ECC as determined by both maximal and submaximal parameters, and it deteriorates with age. Furthermore, an excellent correlation was found between VO_{2peak} and OUES. Only VO_{2peak} was correlated with the RER_{peak} whereas OUES was not. Lastly, OUES was significantly lower in patients that had a cardiac event during the follow-up period.

In the present study of mostly asymptomatic young paediatric Fontan patients, a VO_{2peak}% of 69% and OUES% of 72% was found. Both parameters were also negatively correlated with age and years after Fontan completion suggesting a deterioration of exercise capacity over time. Previous investigations, although predominantly in adult patients, also

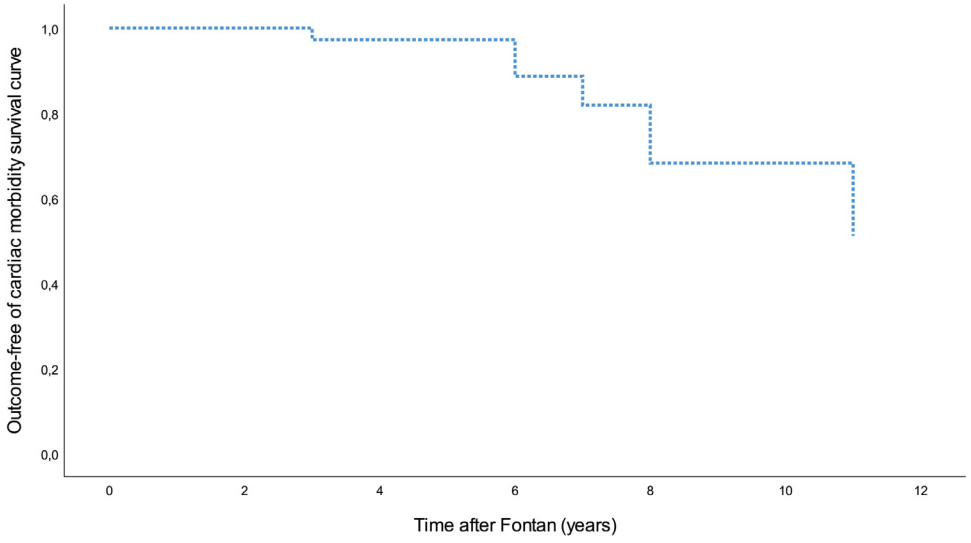

Figure 4. Outcome-free of cardiac morbidity survival curves in patients with ≥ of 2 years of follow up after Fontan procedure.

showed a reduced exercise capacity in Fontan patients, with a level of reduced VO_{2peak} below 60%.[1-7,9] In these studies a deterioration of exercise performance over time was also reported.[1,3,4,9] In contrast to our patient group with only Fontan-ECC patients, these patient cohorts usually have different types of Fontan completion in the same study.

The Fontan procedure has undergone several technical modifications since its introduction in 1971. The most commonly used modifications currently are the ILT and the ECC. Bossers et al studied the difference between the two techniques and found that both the VO_{2peak}% and OUES% were significantly higher in the ECC group.[7] On the contrary, other studies found no differences in VO_{2peak} between both techniques.[4,9,16] This is the first study that include a homogenous group of paediatric ECC Fontan patients and indicates that a decline of exercise capacity over time already starts during childhood in this group of patients.

Twenty percent of patients in this study were not able to reach maximal exercise as defined by an RER>1.0. In other studies this inability of Fontan patients to reach an RER>1.0 was as high as 20-40%.[6,7,10] It is therefore of importance that in our Fontan patients an excellent correlation was found between the maximal CPET parameter VO_{2peak} and the submaximal CPET parameter OUES, for both absolute values and % predicted values. Hence, OUES is a very useful parameter to evaluate CPET in Fontan patients. The usefulness of this submaximal exercise parameter is further underscored by the fact that its value is independent of the RER reached. These findings extend the previous use of OUES in healthy subjects and patients with a biventricular congenital heart disease to univentricular Fontan patients.[15,17-19] The OUES% of 72% in our group was comparable to the OUES% reported by Bossers et al, who studied children after Fontan palliation as well.[7] Most other studies evaluated adult Fontan patients and found even lower OUES% values of 57%.[7,10]

Several factors have been shown to limit the increase of cardiac output, and therefore VO_{2peak}, during exercise in Fontan patients. The stroke volume index is significantly decreased near the end of maximal exercise and it is the most important hemodynamic factor limiting exercise capacity in this patients.[20,21] An impaired chronotropic response is also common in Fontan patients, but it is not clear whether it is a physiological response to the lack of preload rather than a pathological process as higher HR frequencies reduce the diastolic filling time.[20-22] The HR_{peak} in our study was similar to the healthy dataset (90% of the predicted value). A lower maximal exercise capacity has also been correlated to an impaired systolic ventricular function[23] but we found no correlation between ventricular function and CPET parameters.

The prognostic value of VO_{2peak} in Fontan patients is controversial. Fernandes et al. found that lower VO_{2peak} was a risk factor of midterm morbidity and mortality whereas several other studies were not able to demonstrate this.[2-6,10] Recently, the decrease of the VO_{2peak} over time (decline in VO_{2peak}% ≥3 percentage points/year) has been pointed as a good predictor of risk of cardiac events.[5,6] We did find an association between OUES and cardiac events, but an association with VO_{2peak} was lacking. This difference in prognostic value between OUES and VO_{2peak} might be explained by the high percentage of Fontan patients who did not achieve maximal effort. This again underscores the value of OUES as an important submaximal exercise parameter in Fontan patients. Similarly, Chen and colleagues conclude in their work that OUES can provide superior prognostic information in predicting cardiac morbidity in Fontan patients than maximal CPET parameters, establishing a OUES% ≤ 45% as an optimal threshold.[10] As OUES is an effort independent parameter it may be a better prognostic parameter to use in TCPC patients, that often are not able to reach maximal effort.

This study involves a young population, with good general condition and all had been palliated with an ECC, so they may not represent the overall group of Fontan patients. Nonetheless, it represents a homogeneous group of TCPC patients with one of the most current techniques. Furthermore, we could not include all the patients in our study to analyse the prognostic value of the CPET parameters due to the short period of follow-up. We consider that a longitudinal study with longer follow-up period and a greater number of patients would be necessary to corroborate our findings and to determine the decrement of OUES per year.

In conclusion, this is the first study of the exercise capacity in a homogenous group of patients after TCPC with an ECC and at a young age, and we found an impaired exercise performance with a negative correlation with age. As we demonstrated an excellent correlation between VO_{2peak} and OUES and an important percentage of Fontan patients is not able to reach the maximal effort during a CPET, the use of submaximal parameters such as OUES should be considered as part of the evaluation of exercise tests in these patients. Moreover, in our study only OUES has demonstrated to have a prognostic value as it was related to cardiac-related hospitalization.

Competing Interest

The authors declare that they have no competing interests.

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