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Predictors of mid-term event-free survival in adults with corrected tetralogy of Fallot

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Objectives Patients who underwent corrective surgery for tetralogy of Fallot (TOF) have increased long-term risk of cardiovascular morbidity and mortality. Yet, limited information is available on how to evaluate the risk in this population. Therefore, the aim of this study was to investigate the prognostic value of aerobic exercise capacity, along with other related parameters, at medium-term follow-up in adult patients with tetralogy of Fallot.

Methods and results Between 2000 and 2003, 92 adults (age 26.2 ± 7.8 years; 63 male) with corrected TOF or TOF-type morphology underwent a cardiopulmonary exercise test (CPET) until exhaustion and echocardiography. During a mean follow-up of 7.3 ± 1.2 years (range 0.9 to 9.3 years), 2 patients died and 26 patients required at least 1 cardiac-related intervention at a mean age of 28.9 ± 7.9 years. Event-free survival tended to be higher in patients with the classical type of TOF ($P = 0.061$).

At multivariate Cox analysis, age at CPET [hazard ratio (HR): 1.13, $P = 0.006$], age at correction (HR: 0.82, $P = 0.037$), right ventricular (RV) function (HR: 4.94, $P = 0.001$), QRS duration (HR: 1.02, $P = 0.007$), percentage of predicted peak oxygen uptake (peak VO_2%) (HR: 0.96, $P = 0.029$) and ventilatory efficiency slope (VE/VCO_2 slope) (HR: 1.13, $P = 0.021$) were significantly related to the incidence of death/cardiac-related intervention during medium follow-up.

Conclusions Early corrective surgery and a well-preserved RV are associated with a better outcome in adults with corrected TOF. Furthermore, CPET provides important prognostic information; peak VO_2% and VE/VCO_2 slope are independent predictors for event-free survival in patients with corrected TOF.

Keywords *Tetralogy of Fallot – outcome – cardiopulmonary exercise test – peak oxygen uptake – ventilatory efficiency slope.*

INTRODUCTION

Tetralogy of Fallot (TOF) is a congenital heart disease with an incidence rate of 5 in every 10,000 children. It occurs equally in boys and girls and represents 10% of all congenital heart diseases. TOF is the most common cyanotic congenital heart disease worldwide[1,2]. Since surgical correction is possible and the results of the treatment have improved, most children with this cardiac defect grow up into adulthood.

Despite therapeutical improvements during the past decades, grown-ups with congenital heart disease (GUCH) still have higher mortality rates over the mid and long term, compared to the general population[3,4]. Giardini et al. reported that sudden death due to ventricular arrhythmias, progressive heart failure and reoperation are the most important causes of death or rehospitalization in TOF patients[3]. Therefore, determining and predicting risk is an important topic to be investigated in order to improve the clinical follow-up in this patient population.

It has been abundantly reported that exercise tolerance, as reflected by several measures of cardiopulmonary exercise testing, is related to outcome in patients with cardiac disease[5]. Moreover, the prognostic value of

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peak oxygen uptake and VE/VCO_2 slope have been demonstrated in adults with TOF and in GUCH patients in general[3,4,6,7].

Recently, there has been growing interest in the use of other submaximal measures of exercise capacity, such as the oxygen uptake efficiency slope and the oxygen uptake versus exercise intensity slope[8].

Therefore, the aim of this study was to investigate the prognostic value of aerobic exercise tolerance, along with variables known to be related with outcome, at medium-term follow-up in adult patients with tetralogy of Fallot.

METHODS

Patients

Between 2000 and 2003, all adults who had received corrective surgery for TOF or Fallot-type morphology during childhood and were referred to our outpatient clinic of adult congenital heart disease for follow-up, performed a cardiopulmonary exercise test until exhaustion. Criteria for inclusion in the study were: (1) aged 16 years or older at the date of the exercise test, (2) able to understand the exercise testing protocol, and (3) able to perform a maximal graded exercise test until exhaustion. Exhaustion was defined as shortness of breath and/or fatigue of the legs. Patients with concomitant pathology were excluded. Based on these criteria, 92 patients were included. Baseline demographic and clinical data were obtained from the patients' medical records.

Cardiopulmonary exercise test and electrocardiography

Maximal exercise tests on the bicycle ergometer (Ergometrics 800S, Ergometrics, Bitz, Germany) were performed in a laboratory with a stabilized room temperature at 18 to 22°C. The initial workload of 20W was increased by 20W every minute until exhaustion. Exhaustion, based on clinical criteria, was defined as shortness of breath and/or fatigue of the legs. A 12-lead electrocardiogram (Max Personal Exercise Testing, Marquette, Wisconsin, USA) and respiratory data through breath-by-breath analysis (Oxygen AlphaR, Jaeger, Mijnhardt, Bunnik, The Netherlands) were continuously registered. Heart rate was calculated with the electrocardiogram. The gas analysers and the flow meter were calibrated before each test, according to the manufacturer's instructions. Oxygen uptake (VO_2) and carbon dioxide output (VCO_2) were determined from the continuous measurement of oxygen and carbon dioxide concentration in the inspired as well as in the expired air. The respiratory gas exchange ratio was calculated. Peak VO_2 was defined as the highest 30-second average of VO_2 at the end of the test. The first ventilatory threshold was determined according to Binder[9].

Single linear regression analysis on the respiratory data during exercise was used to calculate the ventilatory efficiency slope (VE/VCO_2 slope) [8].

Transthoracic echocardiography

Routine transthoracic echocardiography was performed with standard grayscale, and Doppler imaging examinations using a Vivid 7 or 9 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway) equipped with a 3-MHz transducer. All echocardiographic studies were performed with the participant in supine position. Qualitative assessments were used for pulmonary regurgitation (none, trivial, mild, moderate, severe, scaling from 1 to 4), right ventricular dilatation (normal, slightly, moderately, and severely enlarged, scaling from 1 to 4) and right ventricular function (normal, slightly, moderately, and severely reduced, scaling from 1 to 4).

Follow-up

All patients were regularly followed up at the outpatient clinic for cardiac-related events, in order to ensure that all events were captured. Between January and November 2011, follow-up data were collected by consulting the medical files in the outpatient clinic in order to abstract the dates and medical reasons for hospitalization as well as the survival status. Whenever the last follow-up visit dated back to at least 1 year, the patient or his/her family was contacted by phone. The end point of the study was a combination of mortality and cardiac-related hospitalization.

Statistical analysis

We used SAS statistical software version 9.1 for Windows (Sas Institute Inc, Cary, NC, USA). Data are reported as means (standard deviation) or as numbers for dichotomous variables. Cox proportional-hazards multiple regression analysis was used to assess the relation between entry characteristics and event-free survival. All statistical tests were 2-sided, at a significance level of ≤ 0.05.

RESULTS

Patients

Patient characteristics at baseline are shown in table 1. Ninety-two patients between the age of 16 and 47 years were included in the study (mean age at CPET: 26.11 ± 7.7 years). Of this group, 84 (91%) patients were

Table 1 Baseline characteristics (n = 92)

General	
Female gender	28 (30)
Age (years)	26.1 ± 7.70
Height (cm)	173 ± 9
Weight (kg)	67.7 ± 13.9
New York Heart Association class (I/II)	86/6
Heart rate at rest (beats/min)	79 ± 13
Systolic blood pressure at rest (mmHg)	125 ± 17
Diagnosis	
Tetralogy of Fallot	84 (91)
Double outlet right ventricle	6 (7)
Pulmonary atresia, VSD and patent ductus arteriosus	1 (1)
Pulmonary atresia, VSD and MAPCA	1 (1)
Palliative surgery (number (%))	
Blalock-Taussig shunt	36 (39)
Aorto-pulmonary shunt	5 (5)
Age at corrective surgery (years)	6.00 ± 4.61
Type of corrective surgery (number (%)	
Infundibulectomy and commisurotomy	41 (45)
Transvalvular patch	43 (47)
Biovalved conduit	6 (7)
Mechanical valved conduit	1 (1)
Homograft	1 (1)
Medication	
Amiodarone	2 (2)
Sotalol	1 (1)
Beta blocker	7 (8)
Digoxin/digitoxin and diuretics	1 (1)
ACE-inhibitors	1 (1)
Echocardiography	
Pulmonary regurgitation (none/mild/moderate/severe)	22/28/33/9
RV dilatation (normal/slightly/moderately/severely enlarged)	18/43/30/1
RV function (normal/slightly/moderately/severely reduced)	66/22/4/0
Exercise testing	
Peak VO_2 (ml/min/kg)	29.9 ± 7.82
Peak VO_2 (%)	74 ± 15
VE/VCO_2 slope	26.1 ± 5.51
Peak heart rate (beats/min)	169 ± 22
Peak systolic blood pressure (mmHg)	197 ± 51
Peak respiratory exchange ratio	1.13 ± 0.12

VSD: ventricular septal defect; MAPCA: major aorto-pulmonary collateral arteries; RV: right ventricular; VO_2: oxygen uptake.

born with the classical type of TOF. Sixty-four patients (70%) were males. Corrective surgery was performed in all patients at a mean age of 6 ± 4.61 years. Ninety-three percent of the patients were classified in NYHA class I, 6 patients in NYHA class II.

All patients performed the exercise test until exhaustion and no adverse events were registered during the test. ST-segment depression at peak exercise was present in one patient. Reasons for exercise test termination were muscular exhaustion (40%), dyspnoea (17%) or complete exhaustion (43%). Peak oxygen uptake was 74 ± 15% of the expected values, which is significantly lower than expected in healthy adults ($P < 0.0001$).

Survival

During a mean follow-up of 7.36 ± 1.19 years after CPET, 2 patients died and 28 patients required hospitalization for a cardiac-related intervention. Reasons for hospitalization were pulmonary valve replacement in 10 patients, EPU with ablation in 7 patients, heart catheterization with balloon dilatation in 6 patients, ICD implantation in 4 patients and pacemaker implantation in 1 patient.

Event-free survival tended to be higher in patients with the classical type of TOF ($P = 0.061$).

Based on the Cox proportional hazard multiple regression analysis (table 2), RV function, QRS duration, age at CPET, age at surgical correction, percentage of predicted peak VO_2 and VE/VCO_2 slope were all associated with the risk of death/cardiac-related hospital admission ($P < 0.05$) in the total patient group. Separate Cox analysis with the subgroup of patients with the classical type of TOF (table 3) showed that age at CPET, RV function, QRS duration and VE/VCO_2 slope were significantly related to the risk of death/cardiac-related hospital admission ($P < 0.05$).

Relation of peak oxygen uptake with death/cardiac-related hospitalization

Figure 1 is a Kaplan-Meier curve representing event-free survival of patients with normal versus subnormal peak oxygen uptake values. Exercise capacity was considered to be subnormal when peak $VO_2 < 80\%$ of the predicted value.

DISCUSSION

Our study shows that older age, older age at surgical correction, reduced RV function and RV dilatation, decreased peak VO_2 and increased VE/VCO_2 slope were all important independent predictors of hospital admission and death in patients with TOF and TOF-type morphology. Event-free survival tended to be better in patients with the classical presentation of TOF and in this subgroup older age, reduced RV function and RV dilatation and increased VE/VCO_2 slope remained independently associated with hospital admission and death.

Classical versus non-classical presentation of TOF

It has been previously shown that patients with non-classical types of TOF, such as double outlet right ventricle and pulmonary atresia variants, have a worse outcome compared to patients with a classical presentation of TOF[10]. In our study, a similar tendency was present. We therefore also investigated the smaller group of patients with classical TOF separately.

Prognostic value of the age at surgery

Older age at repair has been previously related to the risk of cardiovascular death or sustained ventricular

Table 2 Multivariate predictors of death/cardiac-related hospital admission

Variable	*p*	Hazard ratio	95% CI
Age at correction	0.037	0.82	0.68 – 0.99
Age at CPET	0.006	1.13	1.04 – 1.23
RV function	0.001	4.94	1.87 – 13.0
QRS duration	0.007	1.02	1.006 – 1.04
Peak VO_2	0.029	0.96	0.92 – 0.99
VE/VCO_2 slope	0.021	1.13	1.02 – 1.26

CI: confidence interval; CPET: cardiopulmonary exercise testing; RV: right ventricle; Peak VO_2: peak oxygen uptake; VE/VCO_2 slope: ventilatory efficiency slope.

Table 3 Multivariate predictors of death/cardiac-related hospital admission in subgroup of patients with classical type of tetralogy of Fallot (n = 84)

Variable	*p*	Hazard ratio	95% CI
Age at CPET	0.009	1.14	1.03 – 1.26
RV function	0.0004	6.82	2.34 – 19.8
QRS duration	0.004	1.03	1.009 – 1.05
VE/VCO_2 slope	0.039	1.13	1.01 – 1.27

CI: confidence interval; CPET: cardiopulmonary exercise testing; RV: right ventricle; Peak VO_2: peak oxygen uptake; VE/VCO_2 slope: ventilatory efficiency slope.

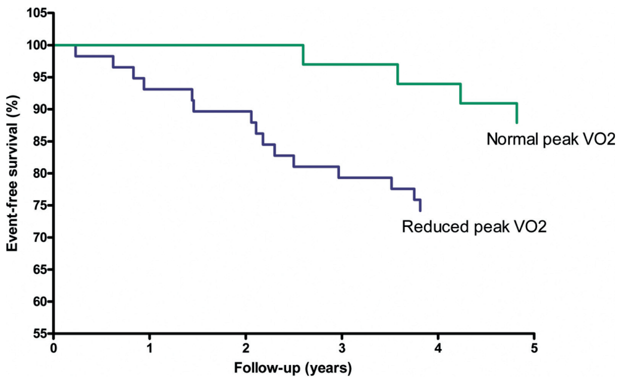

Fig 1. Kaplan-Meier curve of event-free survival according to percentage of predicted peak oxygen uptake.

tachycardia[11]. In our entire study group we showed that older age at initial correction is also related to the need for cardiovascular interventions requiring hospitalization in general. However, mean age at surgery in this patient cohort is higher than what is nowadays general practice. Moreover, many of our study subjects underwent early palliation prior to total correction. These procedures are more and more abandoned in favour of early total correction.

Furthermore, this finding might have been triggered by the subgroup of 8 patients with a non-classical presentation of TOF, since this relationship could not be confirmed in the analysis with classical TOF patients alone. The optimal age for repair of TOF and TOF-type morphology remains to be further investigated[12].

Prognostic value of RV function and dilatation

Our results demonstrate that RV function is an independent predictor of event-free survival in TOF patients. This is in line with Knauth et al., who showed that either right or left ventricular function could predict major adverse clinical events[13]. Diller et al. reported a relationship between RV function and peak VO_2 in GUCH patients. Previously, they had already suggested an indirect relationship between RV function, and hospitalization or death[6]. When the function of the right ventricle is reduced and/or the pulmonary artery is stenotic, the ejection fraction of the right ventricle will be reduced as well. Consequently, a decreased blood flow to the lungs will cause ventilation/perfusion mismatch, a decrease in oxygen uptake and reduced oxygen transport towards the muscles. This results in a decreased functional capacity of patients with a reduced RV function.

Furthermore, RV dilatation as assessed by QRS-duration was significantly related to outcome in our study. This is in line with previous investigations[11,13,14]. Gatzoulis et al. showed that a larger QRS-complex was predictive of malignant ventricular arrhythmias and sudden death[14]. Furthermore, a relationship between RV dilatation and major clinical outcomes in patients with TOF was also found by Knauth et al.[13].

Prognostic value of exercise tolerance

As our results have shown, patients with TOF commonly have a lower exercise capacity compared to the expected exercise capacity in healthy adults. This implies that patients with TOF might have a decreased functional status compared to their healthy peers. This investigation shows that peak VO_2 and, more importantly, VE/VCO_2 slope can provide valuable prognostic information in patients with TOF.

We showed that TOF patients and patients with TOF-type morphology with reduced or severely reduced peak oxygen uptake, have a substantially higher 5-year risk of death or cardiac-related rehospitalization. Other studies in GUCH patients show similar results[6]. Giardini et al. reported that peak VO_2 was an important predictor of death and hospital admission[3]. However, we could not confirm this result in our subgroup of patients with the classical type of TOF. This issue certainly needs to be further explored in larger patient cohorts. Patients with TOF can improve their exercise capacity by exercising[15]. Recommendations about sports and exercise for patients who underwent correction for TOF, have been published in order to guide clinical practitioners[16,17]. So far, cardiac rehabilitation and individual patient counselling on physical activity are rather unexplored aspects of GUCH patient care, even though they seem to be of utmost importance in order to improve long-term outcome.

Our investigation demonstrated that the VE/VCO_2 slope also has prognostic power in the studied patient groups, which is in line with other investigators[3,4,18]. The underlying mechanisms for the increased VE/VCO_2 slope in GUCH are still poorly understood. A possible explanation is that cyanosis during exercise might be related to an abnormal ventilatory response[4]. Although this might give a satisfying explanation in other patient groups, our patient group was acyanotic. Another, more likely potential mechanism that could increase VE/VCO_2 slope, is decreased right heart function[3]. If some degree of pulmonary artery stenosis is present, this might induce ventilation/perfusion mismatch. At its turn, this ventilation/perfusion mismatch can relate to an abnormal ventilatory response, and thus to an increased VE/VCO_2 slope[19].

It remains to be investigated whether exercise training can result in an improvement of the ventilatory response to exercise and constitutes an effective primary prevention measure.

Role of cardiopulmonary exercise testing in the follow-up of adults with TOF

CPET has an important role in the follow-up of adult patients with congenital heart disease in which the success of an intervention is evaluated by quality of life and functional capacity. CPET enables a broader evaluation of the function and fitness of the patients and complements clinical examination, resting and exercise ECG and echocardiography. The NYHA classification is also being used as an assessment tool of functionality in daily life. The NYHA classification in patients with TOF or other congenital heart defects gives information on the patients' perceived exercise tolerance. However, since these patients often overestimate their exercise capacity, it may not be seen as an indication of objective exercise tolerance.

In this and other studies, the strong prognostic value of cardiopulmonary exercise tolerance in adults with congenital heart disease is demonstrated[3,4,6,7]. The Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology therefore states that serial exercise testing should be a part of long-term follow-up protocols and interventional trials in adult patients with congenital heart disease[20]. This way, CPET can play an important role in the timing of interventions and re-interventions. Furthermore, CPET constitutes the perfect basis for patient counseling on physical activity in daily life in this young patient population.

Study limitations

First of all, we are aware of the fact that we cannot assure that our cohort group is free from all bias, as it is a small group and all subjects were only patients from one single tertiary care centre. Therefore, our results cannot be generalized and need to be confirmed in larger study groups. Secondly, the ventricular function was qualitatively evaluated by transthoracic echocardiography. However, this measurement tool is known to give reliable results. Since the golden standard is cardiac magnetic resonance, this tool might have given better results. Finally, in our study, we did not investigate the effect of physical training on mid-term outcome. Further studies should examine the potential benefits of physical training, as it may provide additional insights into the correlates of exercise variables and hospital admission or death.

CONCLUSION

Early corrective surgery, a well-preserved right ventricular function and shorter QRS-duration are associated with a better outcome in adult patients with corrected TOF. Furthermore, cardiopulmonary exercise testing provides important prognostic information; a higher percentage of predicted peak VO_2 and lower VE/VCO2-slope are related to lower mortality and less cardiac-related interventions requiring hospitalization in patients with corrected TOF and TOF-type morphology. Therefore, stimulating TOF patients to be physically active within the limits of their cardiac condition, seems to be an effective primary prevention measure to be taken in this patient population.

CONFLICTS OF INTERESTS: none declared.

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