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Assessing Late Cardiopulmonary Function in Patients with Repaired Tetralogy of Fallot Using Exercise Cardiopulmonary Function Test and Cardiac Magnetic Resonance

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Background: Patients with repaired tetralogy of Fallot (TOF) usually experience progressive right ventricle (RV) dysfunction due to pulmonary regurgitation (PR). This could further worsen the cardiopulmonary function. This study aimed to compare the changes in patient exercise cardiopulmonary test and cardiac magnetic resonance imaging, and consider the implication of these changes.

Methods: Our study examined repaired TOF patients who underwent cardiopulmonary exercise test (CPET) to obtain maximal (peak oxygen consumption, peak VO_2) and submaximal parameters (oxygen uptake efficiency plateau, oxygen uptake efficiency plateau (OUEP), and ratio of minute ventilation to carbon dioxide production, V_E/VCO_2 slope). Additionally, the hemodynamic status was assessed by using cardiac magnetic resonance. Criteria for exclusion included TOF patients with pulmonary atresia, atrioventricular septal defect, or absence of pulmonary valve syndrome.

Results: We enrolled 158 patients whose mean age at repair was 7.8 ± 9.1 years (range 0.1-49.2 years) and the mean patient age at CPET was 29.5 ± 12.2 years (range 7.0-57.0 years). Severe PR (PR fraction ≥ 40%) in 53 patients, moderate in 55, and mild (PR fraction < 20%) in 50 patients were noted. The mean RV end-diastolic volume index (RVEDVi) was 113 ± 35 ml/m^2, with 7 patients observed to have a RVEDVi > 163 ml/m^2. The mean left ventricular ejection fraction (LVEF) was 63 ± 8%, left ventricular end-diastolic volume index (LVEDVi) was 65 ± 12 ml/m^2, and LVESVi was 25 ± 14 ml/m^2. CPET revealed significantly decreased peak VO_2 (68.5 ± 14.4% of predicted), and fair OUEP (90.3 ± 14.1% of predicted) and V_E/VCO_2 slope (27.1 ± 5.3). PR fraction and age at repair were negatively correlated with maximal and submaximal exercise indicators (peak VO_2 and OUEP). Left ventricular (LV) function and size were positively correlated with peak VO_2 and OUEP.

Conclusions: The results of CPET showed that patients with repaired TOF had a low maximal exercise capacity (peak VO_2), but a fair submaximal exercise capacity (OUEP and V_E/VCO_2 slope), suggesting limited exercise capability in high intensity circumstances. PR, LV function and age at total repair were the most important determinants of CPET performance.

Key Words: Cardiac magnetic resonance • Cardiopulmonary exercise function • Pulmonary regurgitation • Surgical age • Tetralogy of Fallot

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INTRODUCTION

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease, with an incidence ranging from 0.36-0.63/1000 live births.[1] The first reported repair of TOF in the world and in Taiwan was in 1955 and in 1965, respectively.[2,3] Taiwan is an island country with a national child health index similar to the US.[4] Our previous studies have shown that total cardiac repair in TOF resulted in low early mortality and high survival 30 years after operation.[3,5] Although they have good postoperative survival, progressive right ventricular (RV) dysfunction is a major concern throughout the lives of these patients, which can contribute to low cardiopulmonary exercise capacity and poor prognosis.

Cardiopulmonary exercise test (CPET) has been applied in predicting prognosis in patients with repaired TOF.[6,7] CPET parameters could be derived from both maximal and submaximal exercise. The peak oxygen consumption (peak VO_2) is obtained from maximal exercise, and the oxygen uptake efficiency plateau (OUEP) and ratio of minute ventilation to carbon dioxide production (V_E/VCO_2 slope) are obtained from submaximal exercise.[8] Peak VO_2 is determined by the cellular O_2 demand and the maximal rate of O_2 transport. It is limited by the amount of O_2, which is delivered to muscles from the cardiopulmonary system. Peak VO_2 is a useful predictor of early surgical mortality in pulmonary valve replacement (PVR) in repaired TOF patients.[6] It is also related to a need for re-intervention and death in long-term follow-up TOF patients.[7]

V_E (minute ventilation) rises linearly in proportion with VCO_2 during a progressive exercise test, such that the ventilatory efficiency slope (V_E/VCO_2 slope) is steady during the exercise period. The V_E/VCO_2 slope is equivalent to the number of liters of air that must be breathed out to eliminate 1 L of CO_2. A high value of V_E/VCO_2 slope indicates poor cardiopulmonary reserve and poor ventilation-perfusion matching. The V_E/VCO_2 slope should be < 28 in the pediatric group.[9] Similar to the peak VO_2, V_E/VCO_2 slope is also a useful predictor for the early mortality in surgical PVR,[6] and the need for re-intervention and death in long-term follow-up TOF patients.[7]

OUEP is an index of cardiopulmonary reserve derived from the logarithmic relationship between oxygen uptake (VO_2) and minute ventilation during incremental exercise. OUEP had been used as a poor prognostic indicator in patients with pulmonary arterial hypertension[10] and Fontan patients.[11]

This study sought to assess the cardiopulmonary functional reserve using CPET (both the maximal and submaximal exercise parameters), and to investigate the relationship between exercise data and ventricular function evaluated by cardiac magnetic resonance (CMR) in a Taiwanese cohort of patients with repaired TOF.

MATERIALS AND METHODS

The institutional review committee of the National Taiwan University Hospital approved this study, and informed consent was obtained from all patients enrolled. Eligible patients were those who received total repair of the TOF between 1970 and 2011 in this institution. All preoperative, surgical, and postoperative data were obtained from medical records and clinical visits. Patients with pulmonary atresia, atrioventricular septal defect, or absence of pulmonary valve syndrome were excluded. All patients received echocardiography, CMR and CPET. Only patients who had an interval between CPET and CMR less than 12 months were enrolled.

Cardiac magnetic resonance assessment

Magnetic resonance scans were performed with a 1.5-T system (Sonata, Siemens, Erlangen, Germany). We have previously described the detailed methods that were employed.[12] CMR imaging was derived by a short-axis contiguous stack of electrocardiography (ECG)-gated balanced steady-state free-precession cine images. We acquired CMR images from the atrioventricular ring to the apex. The following parameters were measured and indexed for body surface area: biventricular end-diastolic volume index (EDVi), end-systolic volume index (ESVi), and ejection fraction (EF). We calculated pulmonary regurgitation (PR) fraction, which was graded as mild (PR fraction < 20%), moderate (PR fraction ≥ 20% and < 40%), and severe (PR fraction ≥ 40%).[13]

Cardiopulmonary exercise test assessment

The symptom-limited CPET was conducted on a cycle ergometer (Corival; Lode BV, Zernikepark 16, Groningen, the Netherlands). Patients were in an upright position, and used a rampwise increase of load depending on the expected individual physical capacity.

Peak oxygen consumption was presented as a percentage of predicted value. The predicted value was determined by age, gender, body height, and body weight.[14] Patients were considered to have achieved maximal exercise intensity only if the respiratory exchange ratio ≥

1.09. Some patients could not achieve maximal exercise because of leg soreness, shortness of breath or arrhythmia, so peak VO_2 could not be obtained. In contrast to peak VO_2, V_E/VCO_2 slope and OUEP could be calculated for all participants regardless of maximal exercise effort. OUEP was then expressed as the percentage of predicted values. The predicted value of OUEP was determined by OUEP (mL/L) = 42.18 – 0.189 × age (years) + 0.036 × body height (cm) in men, OUEP (mL/L) = 39.16 – 0.189 × age (years) + 0.036 × body height (cm) in women.[15]

Electrocardiogram and echocardiogram assessment

Every patient received resting ECG to obtain QRS duration. Echocardiography was also used to assess right ventricular outflow tract (RVOT) gradient, and residual shunt in all patients.

Statistics

We used the Statistical Package for the Social Sciences (SPSS) software version 17.0 for statistical analysis. Continuous variables were presented with mean ± 1 standard deviation. Differences of categorical variables were compared using the Fisher's exact and Chi-square tests. Student's t test was used to determine if two sets of continuous variables were significantly different than each other.

Multivariate linear regression analysis was used to identify factors related to exercise parameters (peak oxygen consumption, OUEP, V_E/VCO_2 slope). Variables included in this analysis were sex, RVOT gradient, PR fraction, age at total repair, age at CPET, right ventricular end-diastolic volume (RVEDV) index, right ventricular end-systolic volume (RVESV) index, right ventricular ejection fraction (RVEF), right ventricular (RV) mass index, left ventricular end-diastolic volume (LVEDV) index, left ventricular end-systolic volume (LVESV) index, right ventricular ejection fraction (LVEF), left ventricular (LV) mass index and QRS duration on EKG. If a p value < 0.1 was reached in univariate analysis, the variable was selected for entering the multivariable analysis by stepwise method. A p value < 0.05 was considered statistically significant.

RESULTS

Preoperative clinical characteristics

We enrolled 158 repaired TOF patients (male/female = 81/77). The mean age at total repair was 7.7 ± 9.0 years (range 0.1-49.2 years), with 92 patients undergoing repair before 5 years of age, 31 patients between 5 and 10 years of age, and 35 patients over 10 years old. Systemic-to-pulmonary shunt surgery had been performed before total repair in 32 patients. Surgical methods were classified as non-transannular patch (non-TAP) and trans-annular patch (TAP) across the pulmonary valve, and 81 patients underwent TAP method. Two patients had associated chromosome anomaly, which was CATCH-22 syndrome and Down syndrome, respectively.

Postoperative clinical follow-up

The mean age at follow-up, which was also the age of performing CPET and CMR, was 29.5 ± 12.2 years (range: 7.0-57.0 years).

Resting cardiac function by CMR

Severe PR was found in 53 (33.5%) patients, while 55 (34.8%) patients and 50 (31.7%) patients had moderate and mild PR, respectively.

Table 1 demonstrated the detailed CMR results. The mean RVEDVi was 113 ± 35 ml/m^2, and the mean RVESVi was 69 ± 26 ml/m^2. Based on the Lee et al. study, RVEDVi > 163 ml/m^2 or RVESVi of > 80 ml/m^2 was indicated for pulmonary valve replacement.[16] Seven patients were noted to have an RVEDV index > 163 ml/m^2, and 33 patients had an RVESV index > 80 ml/m^2. Since RVEF < 45% and QRS duration ≥ 160 msec demonstrated persistent RV dysfunction,[17] 39 patients had both RVEF < 45% and QRS duration ≥ 160 msec.

Exercise cardiopulmonary function

Cardiopulmonary exercise test of the 158 patients revealed decreased peak VO_2 (68.5 ± 14.4%), fair OUEP (90.3 ± 14.1%) and V_E/VCO_2 slope (27.1 ± 5.3) (Table 1). Among the 134 patients who achieved respiratory exchange ratio ≥ 1.09, 26 (19.4%) patients had peak VO_2 > 80%, whereas 72 patients (53.4%) had 60-80%, and 36 patients (26.8%) were ≤ 60%. In the measurement of submaximal exercise parameters, 103 (65.2%) patients presented OUEP > 80%, and 55 patients (34.8%) ≤ 80%. One hundred and twenty-three patients (91.2%) had V_E/VCO_2 slope < 30, whereas 35 patients (8.8%) had V_E/VCO_2 slope ≥ 30. The distribution of peak VO_2, OUEP, and V_E/VCO_2 slope with age is shown in Figures 1-3. We

Table 1. Summary of the cardiac MR imaging and the exercise cardiopulmonary function in 158 patients with repaired tetralogy of Fallot

	Mean ± SD (range)
Pre-op saturation (%)	82 ± 4 (53-98)
Pre-op hemoglobin (g/dL)	14.8 ± 4.6 (11.3-20.8)
Age at repair (years old)	7.7 ± 9.0 (0.1-49.2)
Age of CPET (years old)	29.5 ± 12.2 (7.0-57.0)
RVOT gradient (mmHg)	18 ± 16 (0-71)
Body height (cm)	161 ± 10
Body weight (kg)	58 ± 14
QRS duration (msec)	150 ± 23 (78-198)
CMR data	
PR fraction %	32 ± 19 (1.1-86)
RVEDV index (ml/m^2)	113 ± 35 (55-297)
RVESV index (ml/m^2)	69 ± 26 (27-203)
RVEF %	40 ± 7 (17-58)
LVEDV index (ml/m^2)	65 ± 12 (31-104)
LVESV index (ml/m^2)	25 ± 14 (9-63)
LVEF %	63 ± 8 (26-82)
CPET data	
Predicted peak VO_2 (%)	68 ± 14 (39-119)
Predicted OUEP (%)	90 ± 14 (62-131)
V_E/VCO_2 slope	27 ± 5 (15-42)

CPET, cardiopulmonary exercise test; CMR, cardiac magnetic resonance; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, magnetic resonance; OUEP, oxygen uptake efficiency plateau; PR, pulmonary regurgitation; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVOT, right ventricular outflow tract; SD, standard deviation.

found that the distribution of all these parameters was not correlated to age in the CPET.

Relation between CMR and CPET parameters

With multivariable regression model, both PR fraction and surgical age had a negative impact on peak VO2 and OUEP independently. LVEF and LV volume were also parameters that positively correlated with the peak VO_2 and OUEP (Table 2).

Univariate analysis revealed surgical age, age at CPET, sex, PR fraction, RVEDVi, RVESVi, and RVMi were related to V_E/VCO_2 slope. However, multivariable regression disclosed only RV mass index and sex had influence on V_E/VCO_2 slope. RV mass index ($p < 0.001$) was positively correlated with the value of V_E/VCO_2 slope. It was noted that the male sex had lower V_E/VCO_2 slope (95% CI -4.140 – -0.842) (Table 2).

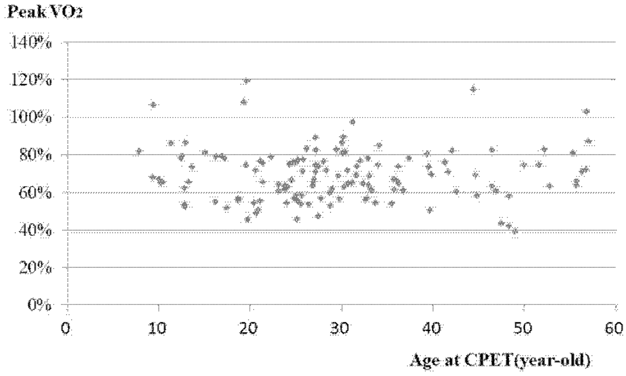

Figure 1. *The relationship between peak VO_2 and age at CPET. Abbreviations are in Table 1.*

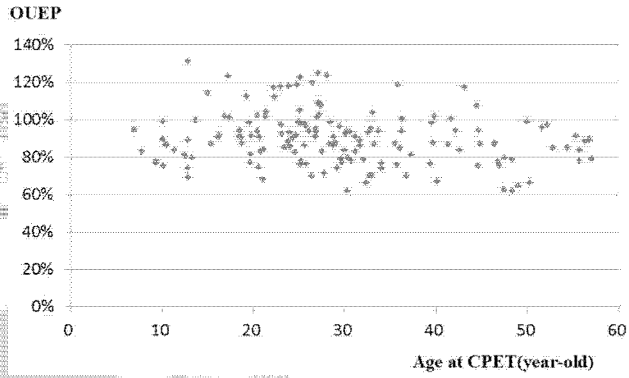

Figure 2. *The relationship between OUEP and age at CPET. Abbreviations are in Table 1.*

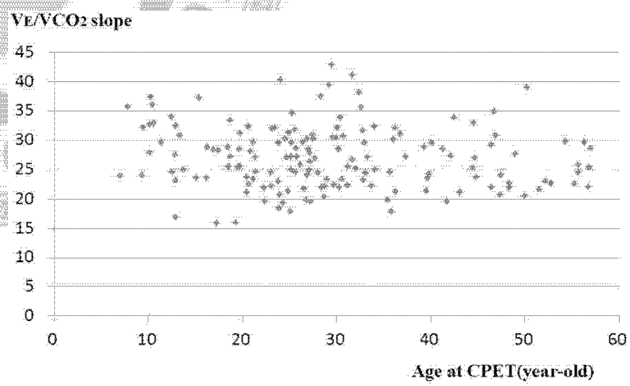

Figure 3. *The relationship between V_E/VCO_2 slope and age at CPET. Abbreviations are in Table 1.*

DISCUSSION

By assessing the CPET and CMR in patients with repaired TOF in this study, we found that: 1) peak VO_2 (mean 68.5 ± 14.4%), which is a maximal exercise parameter, decreased significantly in repaired TOF patients; 2) OUEP and V_E/VCO_2 slope, which are submaximal exercise parameters, were mildly decreased in repaired TOF patients; 3) PR fraction and age at repair were negatively associated with maximal and submaximal exercise indicators (peak VO_2, OUEP); and 4) LV systolic function and size also influenced the result of peak VO_2 and OUEP.

There have been several western studies that described the changes of CPET in repaired TOF. We summarized their results and our own in Table 2. The peak VO_2 mostly ranged from 51-83% of predicted (Table 3).[7,18-23] Although there are some data from studies involving other populations, data focusing on CPET from studies of Asian TOF patients are still rare. Except for a previous study[12] from our research team, only one other study based on a Singapore cohort of 36 patients had ever summarized the peak VO_2, which was 83 ± 18% of predicted.[23] In the present study, most patients (108 out of 134 patients) had a peak VO_2 lower than 80% of the predicted value. Such observation was similar to previous western reports. This implied that TOF patients had unsatisfactory exercise performance while they were doing high intensity exercise. Determinants on diminished peak VO_2 in TOF patients included the PR severity,[24,25] RV and LV function,[19] older age at total repair,[20,21] age at CPET,[20] residual shunt,[21] peak exercise heart rate,[21] pulmonary arterial hypertension,[21] FEV_1,[21] and indexed LV and RV end-diastolic volumes.[23] In our study, we found that PR fraction, and age at repair and LV function were the most important determinants on the decreased peak VO_2.

Kipps et al. had also described their longitudinal follow-up study of the peak VO2 in TOF patients.[22] They found that the mean peak VO_2 in TOF patients might decrease with follow-up. In the cross-sectional study at age 27.8 ± 15 years (range: 8.2 to 61.4), the percentage of predicted peak VO_2 was 78 ± 19%.[22] After mean follow-up of 2.7 ± 1.5 years, the mean peak VO_2 decreased to 73 ± 16% of the predicted value. They suggested that the peak VO_2 decreased over time in individuals with TOF.[22] However, the same study did not show the changes in submaximal exercise parameter, V_E/VCO_2 slope, during this follow-up. Although our present study is a cross-sectional study in design, we did not document the association between peak VO_2 and age at CPET, or

Table 2. Multivariate linear regression for CPET parameters

	Beta	95% of confidence interval	p value
Determinants of peak VO_2			
LVEF (%)	0.341	0.303–0.923	< 0.001
LVEDV index (ml/m²)	0.255	0.096–0.481	0.004
PR (%)	-0.199	-0.270–-0.028	0.016
Surgical age (year)	-0.176	-0.530–-0.019	0.035
Determinants of OUEP			
LVESV index (ml/m²)	0.197	0.050–0.354	0.010
PR (%)	-0.240	-0.288–-0.068	0.002
Surgical age(year)	-0.259	-0.629–-0.169	0.001
Determinants of VE/VCO_2 slope			
Gender	-0.235	-4.140–-0.842	0.003
RV mass index (g/m²)	0.293	0.130–0.424	< 0.001

* Variables included sex, RVOT gradient, surgical age, age at CPET, PR fraction, RVEDV index, RVESV index, RVEF, RV mass index, LVEDV index, LVESV index, LVEF, LV mass index, QRS duration. Abbreviations are in Table 1.

Table 3. Summary of CPET work-up from different studies in repaired TOF patients

Author	Nation	No.	Age at CPET (years)	Peak VO_2 (% of predicted)	V_E/VCO_2 slope
Yang et al., current study	Taiwan	158	29.5 ± 12.2	68 ± 14%	27.1 ± 5.3
Buys et al., 2011[18]	Belgium	98	25.6 ± 7.7	74 ± 15%	26.2 ± 5.5
Samman et al., 2008[19]	Canada	99	34 ± 11	66 ± 13%	NA
Fredriksen, et al, 2002[20]	Canada	168	NA	51%	NA
Diller et al., 2005[21]	U.K.	107	31 ± 11	56 ± 20%	NA
Kipps et al., 2011[22]	USA	70	27.8 ± 15	78 ± 19%	28.2 ± 4.6
Yap et al., 2013[23]	Singapore	36	30 ± 10	83 ± 18%	NA
Giardini et al., 2007[7]	Italy	118	24 ± 8	58 ± 17%	31.1 ± 4.6

CPET, cardiopulmonary exercise test; NA, not available.

association between V_E/VCO_2 slope and age at follow-up. There was no association between another submaximal exercise parameter, OUEP, and age at CPET either. The difference between Kipps' study and our study in the relationship between peak VO_2 and age could be attributed to different study design. Nonetheless, it is possible that the submaximal exercise parameters may not change significantly with age. Longitudinal study with longer follow-up is mandatory to substantiate our findings.

V_E/VCO_2 slope is one of the commonly used CPET parameters, and is related to severity of congestive heart failure. In normal individuals, mean V_E/VCO_2 slope is 20.8, whereas mean V_E/VCO_2 slope goes up to 30.6 and 40.7 in patients with mild and moderate heart failure, respectively.[26] Previous reports revealed that V_E/VCO_2 slope in repaired TOF patients ranged from 26 to 31.[7,18,22] Mean V_E/VCO_2 slope in our study cohort was 27.1 ± 5.3. Some studies even showed that there was no significant difference in V_E/VCO_2 slope between TOF and an age-matched normal population.[8,23] In addition, the OUEP in our study patients were nearly normal compared to normal predicted values. Collectively, these results suggested that although TOF patients have worse exercise capacity and cardiopulmonary performance during high intensity exercise, their exercise capacity during moderate to low intensity exercise is relatively preserved.

Study limitation

This study is the first report regarding CPET performance of TOF patients in Taiwan, and the study cohort is relatively large. However, the present study cohort may not represent the entire spectrum of patients with repaired TOF, at least in part because of the exclusion of patients with pacemakers and implantable defibrillators. The patient enrollment process did not explore those patients lost to follow-up, and thus might also result in patient selection bias.

CONCLUSIONS

Results from CPET showed that patients with repaired TOF had low maximal exercise capacity (peak VO_2), and fair submaximal exercise capacity (OUEP and V_E/VCO_2 slope), suggesting limited exercise capability in high intensity circumstances. The most important determinants of CPET performance were PR fraction, LV function and age at repair, which could influence both maximal exercise capacity and submaximal exercise capacity.

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