Accepted Manuscript

Peak Oxygen Uptake, Ventilatory Efficiency and QRS-Duration Predict Event Free Survival in Patients late after Surgical Repair of Tetralogy of Fallot

Jan Müller, Alfred Hager, Gerhard-Paul Diller, Graham Derrick, Roselien Buys, Karl-Otto Dubowy, Tim Takken, Stefan Orwat, Ryo Inuzuka, Luc Vanhees, Michael Gatzoulis, Alessandro Giardini

PII: S0167-5273(15)01278-4
DOI: doi: [10.1016/j.ijcard.2015.05.174](https://doi.org/10.1016/j.ijcard.2015.05.174)
Reference: IJCA 20644

To appear in: *International Journal of Cardiology*

Received date: 16 February 2015
Revised date: 29 May 2015
Accepted date: 30 May 2015

Please cite this article as: Müller Jan, Hager Alfred, Diller Gerhard-Paul, Derrick Graham, Buys Roselien, Dubowy Karl-Otto, Takken Tim, Orwat Stefan, Inuzuka Ryo, Vanhees Luc, Gatzoulis Michael, Giardini Alessandro, Peak Oxygen Uptake, Ventilatory Efficiency and QRS-Duration Predict Event Free Survival in Patients late after Surgical Repair of Tetralogy of Fallot, *International Journal of Cardiology* (2015), doi: [10.1016/j.ijcard.2015.05.174](https://doi.org/10.1016/j.ijcard.2015.05.174)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Peak Oxygen Uptake, Ventilatory Efficiency and QRS-Duration Predict Event Free Survival in Patients late after Surgical Repair of Tetralogy of Fallot

Jan Müller¹, MSc; Alfred Hager¹, MD, FESC; Gerhard-Paul Diller^{2,7}, MD; PhD FESC;
Graham Derrick³, MD; Roselien Buys⁴; Karl-Otto Dubowy⁵, MD; Tim Takken⁶, PhD;
Stefan Orwat⁷, MD; Ryo Inuzuka², MD; Luc Vanhees⁴, PhD, FESC; Michael
Gatzoulis², MD, PhD, FACC, FESC; Alessandro Giardini³, MD, PhD

¹ Department of Pediatric Cardiology and Congenital Heart Disease, Deutsches Herzzentrum München, Technische Universität München, Germany

² Adult Congenital Heart Center and Center for Pulmonary Hypertension, Royal Brompton Hospital and the National Heart & Lung Institute, Imperial College, London, United Kingdom

³ Cardiorespiratory Unit, Great Ormond Street Hospital for Children, London, United Kingdom

⁴ Research Centre for Cardiovascular and Respiratory Rehabilitation, Department of Rehabilitation Sciences, Katholieke Universiteit Leuven, België

⁵ Department of Paediatric Cardiology and Congenital Heart Disease, Heart and Diabetes Center of North Rhine-Westphalia, University of Bochum, Bad Oeynhausen, Germany

⁶ Child Development & Exercise Centre, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, the Netherlands

⁷ Adult Congenital and Valvular Heart Disease Center, Department of Cardiology and Angiology, University Hospital of Muenster, Muenster, Germany

Address for correspondence:

Jan Müller, Department of Pediatric Cardiology and Congenital Heart Disease
Deutsches Herzzentrum München, Technische Universität München
Lazarettstraße 36, D-80636 München, Germany
Phone: +49-89-1218-3009, Fax: +49-89-1218-3003
Email: j.mueller@tum.de, hager@dhm.mhn.de

Keywords: Tetralogy of Fallot, exercise testing, event free survival, Peak VO₂, QRS duration, ventilatory efficiency

Word count: 3312

Word count (Abstract): 248

Abstract

Objective: Patients with repaired tetralogy of Fallot (ToF) have an increased long-term risk of cardiovascular morbidity and mortality. Risk stratification in this population is difficult. Initial evidence suggests that cardiopulmonary exercise testing (CPET) may be helpful to risk-stratify patients with repaired ToF.

Methods and Results: We studied 875 patients after surgical repair for ToF (358 females, age 25.5 ± 11.7 year, range 7 – 75 years) who underwent CPET between 1999 and 2009. During a mean follow-up of 4.1 ± 2.6 years after CPET, 30 patients (3.4%) died or had sustained ventricular tachycardia (VT). 225 patients (25.7%) had other cardiac related events (emergency admission, surgery, or catheter interventions). On multivariable Cox regression-analysis, %predicted peak oxygen uptake ($\dot{V}O_2\%$) ($p=0.001$), resting QRS duration ($p=0.030$) and age ($p<0.001$) emerged as independent predictors of mortality or sustained VT. Patients with a peak $\dot{V}O_2 \leq 65\%$ of predicted and a resting QRS duration ≥ 170 ms had a 11.4-fold risk of death or sustained VT.

Ventilatory efficiency expressed as $\dot{V}_E/\dot{V}_{CO_2}$ slope ($p<0.001$), peak $\dot{V}O_2\%$ ($p=.001$), QRS duration ($p=.001$) and age ($p=0.046$) independently predicted event free survival. $\dot{V}_E/\dot{V}_{CO_2}$ slope ≥ 31.0 , peak $\dot{V}O_2\% \leq 65\%$ and QRS duration ≥ 170 ms were the cut-off points with best sensitivity and specificity to detect an unfavourable outcome.

Conclusions: CPET is an important predictive tool that may assist in the risk stratification of patients with ToF. Subjects with a poor exercise capacity in addition to a prolonged QRS duration have a substantially increased risk for death or sustained ventricular tachycardia, as well as for cardiac-related hospitalizations.

Introduction

Tetralogy of Fallot (ToF) is the most common cyanotic heart defect at birth. Surgical improvements over the past decades have lead to an excellent long term outcome.[1] Nevertheless, adults with repaired ToF continue to have residual or recurrent lesions as well as an increased risk for right and left heart failure and sudden cardiac death. The exact mechanisms for late sudden death are incompletely defined but are probably related to both, the residual hemodynamic and electrophysiological substrates that act in concert.[2, 3] Pulmonary valve replacement may be required in patients with significant pulmonary regurgitation to avoid progressive right ventricular dilation and to preserve right ventricular function,[3-7] with the ultimate aim of improving long-term survival.

In patients with congenital heart disease (CHD), cardiopulmonary exercise testing (CPET) is generally used to quantify the degree of exercise intolerance.[8-11] Beyond this application, increasing interest had been devoted at understanding the prognostic value of CPET in CHD.[5, 8, 12-14] .However, the identification of patients at higher risk for death or cardiac-related morbidity is challenging. In patients with repaired ToF, Gatzoulis et al.[3] demonstrated a relationship between prolonged QRS duration and sudden cardiac death. whereas Giardini et al.[5] demonstrated in a small cohort that peak oxygen uptake ($\dot{V}O_2$) and ventilatory efficiency could be helpful to stratify patients regarding their risk of death and hospitalization during follow-up. Recent studies[15, 16] confirmed the predictive value of hemodynamic and cardiopulmonary parameters in patients with ToF.

Both QRS prolongation and reduced exercise tolerance are thought to be related to some of the same underlying hemodynamic abnormalities. So far, there is no information on whether exercise variables provide any additional prognostic information over QRS duration, and how the information provided by the two tests

might integrate to provide a better risk stratification tool for patients with repaired ToF.

Hence, the objective of the present study was to assess the potential value of CPET variables to predict survival, as well as morbidity-free survival both independently of and in combination with QRS-duration and demographic variables in a large cohort of patients after surgical ToF repair.

Methods

Study design and study subjects

This study was designed as a multicenter retrospective investigation. In seven European tertiary institutions all consecutive patients with tetralogy of Fallot or Fallot-type morphology (double outlet right ventricle with sub-aortic ventricular septal defect and pulmonary atresia with ventricular septal defect after bi-ventricular repair) who were referred for a CPET as part of their routine clinical follow-up evaluation between 1999 and 2009 were included into the study. The study was approved by the local ethical board (project number 2992/10). J.M. and A.H. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved to the final version of the manuscript.

Cardiopulmonary exercise test (CPET)

All patients underwent a symptom limited CPET either on a bicycle ergometer in upright position (n=503) or on a treadmill (n=372) according to the institutional protocol. If more than one CPET was available the first CPET with the longest follow-up was selected.

Baseline parameters were recorded during at least two minutes at rest. Workload was increased ramp wise with the aim to reach exhaustion in 8 to 12 minutes of exercise. For those tested on a treadmill a modified Bruce protocol was used. The end of the CPET was marked by symptom limitation. A 12-lead electrocardiogram and pulse oximetry were recorded continuously throughout the whole test. Cuff blood pressure was determined every two minutes.

The exercise test featured a breath-by-breath gas exchange analysis using a metabolic chart. Peak $\dot{V}O_2$ was defined as the highest mean uptake of any 30-second time interval during exercise. Because of age related differences in the large patient cohort, reference values for age, body mass, body height, and gender, were expressed in percentage of predicted calculated as previously described[10] for children less than 18 year from Cooper & Weiler-Ravell[17] and Cooper & Storer[18] for adults. Ventilatory efficiency ($\dot{V}_E/\dot{V}_{CO_2}$ slope) was assessed by the slope of the $\dot{V}_E/\dot{V}_{CO_2}$ curve confined to the linear part, excluding values beyond the respiratory compensation point. Heart rate reserve was calculated as the difference between peak and resting heart rate (peak heart rate – resting heart rate) / (220 - age - resting heart rate) for adults older than 20 years and (peak heart rate – resting heart rate) / (200 – resting heart rate) for patients younger than 20 years. QRS duration was measured at rest in the precordial leads V_1 or V_2 .

Survival status and hospitalization

Two different end points were assessed in the present study. The primary endpoint consisted in the combination of all-cause mortality (used to eliminate the possibility of a bias arising from incorrect classification of cause of death) or occurrence of sustained ventricular tachycardia, recorded (and treated) by a resuscitation team or by an implantable cardioverter defibrillator.

The secondary endpoint consisted in the occurrence of death or of a cardiac-related event, which was defined as any hospital admission directly caused by failure of the cardiac system needing inpatient care to correct. Examples for cardiac event were cardiac surgery, interventional catheterization and symptomatic arrhythmias needing cardioversion, electrophysiological procedure or other treatments.

Patients were regularly followed up for cardiac-related events at their respective institutions, which guaranteed that all relevant events were captured. Patients' medical records were reviewed to abstract the dates and medical reasons for hospitalization and their status. Survival status was reconfirmed by phone interviews or queries of national registries.

Regarding the secondary endpoint, patients with a cardiac event less than three months after the CPET were treated as censored cases at the time of the event to eliminate a possibility of bias arising from pre-surgical or pre-interventional CPET evaluation.

Assessment of pulmonary regurgitation and right ventricular function

Pulmonary regurgitation and right ventricular function were estimated by routine transthoracic clinical echocardiography. Pulmonary regurgitation was quantified by Doppler echocardiography as none/trivial, mild, moderate or severe using published color-coded pulsed wave Doppler criteria.[19] Right ventricular function was estimated from parasternal long- and short-axis views and from an apical 4-chamber view and quantified subjectively by the investigator as normal/enhanced, slightly reduced, moderately reduced, or severely reduced.

Data analyses

Data are presented as mean $\pm$ SD, or absolute numbers (percentage). Comparisons between subgroups were performed by unpaired t-test or chi-square tests, as appropriate.

Prognostic values of variables were assessed using multivariable Cox regression. The variables tested to predict survival without sustained VT (primary endpoint) were $\dot{V}_E/\dot{V}_{CO_2}$ slope, peak $\dot{V}O_2\%$ predicted, age at CPET, and QRS duration at rest. For

the secondary endpoint of event free survival we tested exercise variables ($\dot{V}_E/\dot{V}_{CO_2}$ slope, peak $\dot{V}O_2\%$ predicted, systolic blood pressure at peak exercise, heart rate reserve, QRS duration at rest), age at CPET, palliation before repair, age at surgical repair, sex, and medications. Subsequently, a receiver-operator characteristic (ROC) curve analysis for a 5-year follow-up was used to identify the cut-offs of the variables emerged from multivariable Cox regression as being associated with the end point of interest. Cut-off values were chosen according to the highest sum of sensitivity and specificity. A non-parametric random survival forest analysis based on a log-rank splitting rule (using the random Survival Forest R-package) was used to obtain predicted 5-year outcome for various combinations of QRS-duration and $\dot{V}O_2\%$ predicted. The results are presented as contour plots with isoquants of 3-year outcome.

Analyses were performed using PASW Statistics 18.0 (SPSS Inc, Chicago, Illinois, USA) and R version 2.12.2. P-values <0.05 in a two-sided analysis were considered significant.

Results

Baseline characteristics of the 875 patients studied are presented in Table 1. All CPET were performed until maximum exhaustion resulting in a mean respiratory exchange ratio of 1.11 ± 0.16 and a mean peak $\dot{V}O_2$ of 27.7 ± 8.6 ml/kg/min, representing 76.6 ± 19.7 % predicted (Figure 1). No patient was cyanotic at rest or during peak exercise. Follow-up was completed for all patients.

Survival without sustained ventricular tachycardia

During a mean follow up of 4.1 ± 2.6 years, 30 patients met the composite primary end-point of death or survived ventricular tachycardia at a mean age of 39.6 ± 13.0 years. Four patients died postoperatively, three died suddenly, another three succumbed due to heart failure, and the cause of death could not be determined in eight patients. Another twelve patients survived sustained ventricular tachycardia and, therefore, received an ICD. Annual event rate for the primary endpoint was 0.6% per year.

At multivariate Cox regression, %predicted peak $\dot{V}O_2$ (hazard ratio [HR] 0.968, 95% confidence interval [CI] 0.948 to 0.988; $p=0.001$), QRS duration at rest (HR 1.016, CI 1.002 to 1.030; $p=0.030$) and age (HR 1.058, CI 1.032 to 1.084; $p<0.001$) emerged as independent predictors of the primary outcome.

ROC curve analysis identified a peak $\dot{V}O_2$ % ≤ 62.6 % (sensitivity 82%, specificity 63%) and QRS duration of ≥ 169.5 ms (sensitivity 53%, specificity 86%) as optimal cut-off values for 5 year freedom from death or ventricular arrhythmia in the dataset. The ROC curve for age showed no clear cut-off value but an almost linear increase of risk with age.

For clinical application, values were rounded to 65% (peak $\dot{V}O_2\%$) and 170ms (QRS duration) and Kaplan-Meier survival charts were generated. Survival curves suggest that those patients with both a peak $\dot{V}O_2\% \leq 65\%$ and QRS-duration $\geq 170\text{ms}$ are at particularly higher risk for premature death (Figure 2). Indeed when compared to patients with no or only one risk factor, the estimated survival hazard increased by 11.4-fold (95% confidence interval 5.5 - 23.7). In the first year after CPET, 13 of the 60 patients (21.6%) with both risk factors had died or had a sustained ventricular tachycardia. The random survival forest analysis (Figure 3) included both variables and confirmed that the risk of death/sustained VT is highest in those patients with both elevated QRS duration and limited peak $\dot{V}O_2\%$.

Event free survival

The secondary composite was reached by 225 (25.7%) patients after a follow up of 2.5 ± 2.3 years. Mean age was 31.2 ± 13.3 years. Annual event rate was 13.7% per year. The events are presented in detail in Figure 4.

Those patients who reached the combined secondary end-point were significantly older at surgical repair, had received more surgeries before the CPET and were older at the time of CPET. They also had more often received a palliative procedure before surgical repair. In this group peak $\dot{V}O_2\%$ and heart rate reserve were reduced, whereas $\dot{V}_E/\dot{V}_{CO_2}$ slope and QRS duration was increased (Table 1).

At multivariable Cox regression, $\dot{V}_E/\dot{V}_{CO_2}$ slope (HR 1.033, CI 1.017 to 1.049; $p < .001$), peak $\dot{V}O_2\%$ (HR 0.987, CI 0.979 to 0.995; $p = .001$), QRS duration at rest (HR 1.009, CI 1.003 to 1.015; $p = .001$) and age (HR 1.011, CI 1.010 to 1.021; $p = .046$) emerged as independent predictors for an increased risk of death or cardiac-related events.

At ROC analysis, a $\dot{V}_E/\dot{V}_{CO_2}$ slope ≥ 31.0 (sensitivity 64%, specificity 67%), a peak $\dot{V}O_2\%$ $\leq 67.9\%$ (sensitivity 73%, specificity 54%) and a QRS duration $\geq 169.5\text{ms}$ (sensitivity 31%, specificity 86%) were associated with an increased 5-year risk of reaching the secondary end point. Again, the ROC curve for age showed no clear cut-off value but an almost continuous increase of risk.

In order to improve clinical applicability, cut-off values for peak $\dot{V}O_2\%$ and QRS duration were rounded to 65% and 170ms, respectively. In addition a hazard score for the $\dot{V}_E/\dot{V}_{CO_2}$ slope cut off value of 31 was calculated. Kaplan-Meier survival charts were generated for patient's groups having none, one, two or all three of the above mentioned risk factors. The resulting survival curves show a stepwise increase in the event rate for every additional risk factor present (Figure 5). Patients with one risk factor were estimated to have a 2.7 fold hazard increased (95% confidence interval 2.0 - 3.6), compared to patients with no risk factor. If two risk factors were present, hazard increased 4.4-fold (95% confidence interval 3.1 - 6.2) and in patients with all three risk factors hazard increased by 5.4-fold (95% confidence interval 3.3 - 8.9), respectively.

For both end points, Kaplan-Meier charts showed that CPET has the best predictive ability for the first three years after CPET. Afterwards the risks of the groups are equalizing again.

Discussion

This study showed that CPET is a valuable prognostic tool in patients with repaired Tetralogy of Fallot and its prognostic value is complementary to that provided by more traditional risk factors, like QRS duration. Indeed, patients who have both a predicted peak $\dot{V}O_2 \leq 65\%$ and a resting QRS duration $\geq 170\text{ms}$ have a 11.4-fold increased risk of dying or having a sustained VT during follow-up. We also showed that significant cardiac morbidity could be predicted by a peak $\dot{V}O_2 \leq 65\%$, a $\dot{V}_E/\dot{V}_{CO_2}$ slope ≥ 31 , and a resting QRS duration $\geq 170\text{ms}$, with the risk of events increasing in a stepwise manner for every additional risk factor present.

Predictors and cut-off values for the primary endpoint

In Tetralogy of Fallot the majority of deaths are due to ventricular arrhythmias, progressive heart failure and re-operations.[4, 5, 7, 20-22] In an initial study on mechano-electrical interaction, Gatzoulis et al.[3] showed that QRS prolongation is related to increased right ventricular size and predicts malignant ventricular arrhythmias and sudden death. The study showed that all patients with documented syncope and sustained ventricular tachycardia and all patients who died suddenly had a QRS duration of 180ms or longer. In contrast, Khairy et al.[23] could not confirm a QRS duration $>180\text{ms}$ as a risk factor for appropriate shocks in patients with ToF and an implanted cardioverter/defibrillator. In the cohort studied by Khairy, however, almost half of the patients with an ICD died from heart failure and not because of malignant arrhythmias. The current study based on a large sample of ToF patient, shows that QRS duration is an important risk factor for mortality and sustained ventricular arrhythmias in this patient group. The cut-off value of 170ms estimated from ROC curve analysis in our cohort is slightly lower than the previous

threshold reported by Gatzoulis et al.[3] This could be the result of different surgical techniques adopted in our more recent cohort, such as transatrial repairs as well as limited ventriculotomies that might have been performed as a result of increased awareness of the mechanical-electrical interactions. In addition to QRS duration, our study shows that risk prediction can be substantially improved by including exercise capacity into the prognostic model. This might be explained by the fact that underlying right ventricular mechanics and ECG manifestations of the abnormal right ventricular mechanics (QRS duration) even though clearly associated, might be not proportionate to each other in terms of magnitude. For example, some patients may have a prolonged electrical intra-ventricular delay but still a good hemodynamic function that is not revealed by simple ECG, like patients with extensive ventriculotomies but substantially preserved pulmonary valve function. This group, as well as some other patients with less intra-ventricular delay but a worse hemodynamic function, like patients with residual right ventricular outflow tract obstruction, showed an almost similar risk to that of patients without risk factors. This seems to highlight that abnormal cardiac size and function needs to be associated with abnormal intraventricular conduction for the risk of death to be increased in patients with repaired ToF. Of particular importance is also the fact that the risk factors identified by the present study, both old and new, seem to be complementary, so that risk appears to be substantially higher only in patients with both prolonged QRS duration *and* reduced exercise capacity.

Peak $\dot{V}O_2$ has gained attention as a prognostic tool in adults with congenital heart disease since Diller et al.[8] originally reported that patients with a peak $\dot{V}O_2 \leq 15.5$ ml/kg/min are at increased risk of premature death. However, this single-center study was limited by the fact that different diagnostic groups had to be combined to obtain sufficient events for statistical analysis. Our cut-off value of peak $\dot{V}O_2\% \leq 65\%$ is

much higher (about 23.6 ml/min/kg) than the one observed by Diller et al.. This outlines the better exercise capacity of ToF patients as a group. It also highlights the importance of the underlying risk profile of the population studied.

Predictors and cut-off values for secondary endpoint

Our data indicate that patients with an increased ventilatory response to exercise ($\dot{V}_E/\dot{V}_{CO_2}$ slope ≥ 31.0), those with more than moderate exercise intolerance (peak $\dot{V}O_2\% \leq 65\%$) or those with a prolonged QRS duration (QRS ≥ 170 ms) are at higher risk for cardiac related events or death. We could also show that patient's hazard seems to increase stepwise when more single risk factors are present in combination. Previous studies have already shown the usefulness of CPET parameters like $\dot{V}_E/\dot{V}_{CO_2}$ slope, peak $\dot{V}O_2\%$ and heart rate response to predict event free survival in patients with CHD. These studies included patients with several different CHD,[8, 13, 14] or single diagnostic groups like in patients with ToF,[5] transposition of the great arteries after atrial repair[12] or univentricular heart after Fontan operation.[24] Again, predictive variables and thresholds for adverse outcome differed according to the underlying diagnosis and the different hemodynamic situations.

CPET has been previously used to predict cardiac-related outcomes in adults with repaired ToF[3, 5, 15]. In that study, which followed up 118 adults with repaired ToF for 5.8 ± 2.3 years, Giardini et al.[5] observed that exercise capacity and ventilatory efficiency were able to identify a subgroup of patients at increased risk of cardiac-related death and hospitalization. The present study, in comparison to the previous study included some important additional outcomes, like all cause mortality and pulmonary valve replacement. As a result of differences in the characteristics of the population studied, like the prevalence of right ventricular dysfunction, the cut-off

values observed by Giardini et al. ($\dot{V}_E/\dot{V}_{CO_2}$ slope >39 , $\dot{V}O_2\%$ $\leq 36\%$) are different from those observed in the present study. Despite these differences, our study, performed in a substantially larger patient cohort corroborates the finding that CPET is useful for risk stratification in ToF patients. Importantly, we could demonstrate that risk stratification based on the combination of CPET and QRS duration is superior to that based on a single test, with the sensitivity and specificity of the risk model that improves the more risk factors are present.

The presented risk model may assist in clinical decision-making, with particular reference to procedures aiming at preserving right ventricular size and function and minimizing the risk of late death. The beneficial effect of pulmonary valve replacement on QRS duration is only transient [25, 26], and prognosis is worse if there is no reduction in QRS duration as a result of pulmonary valve replacement.[27] The right timing for pulmonary valve replacement is very important and it was suggested that surgery should be considered early before right ventricular function deteriorates due to volume overload.[28-33] Also recent data show that percutaneous pulmonary valve implantation does not lead to any improvement if limitations in exercise capacity are mainly due to pulmonary regurgitation and right ventricular dilatation.[30, 33] Our data suggest that patients with at least moderately reduced exercise tolerance, those with elevated ventilatory response to exercise, and those with prolonged QRS duration should be investigated thoroughly to identify potentially correctable surgical or interventional target lesions.

Limitations

All patients were followed up at tertiary centers and a referral bias towards more advanced forms of the disease with more symptomatic patients cannot be excluded.

However, at the institutions involved, it is established clinical practice to test every patient with repaired ToF with CPET. Therefore, we believe that the results of our study can be generalized to the whole ToF patient population.

Cardiac MRI is the gold standard for the assessment of cardiovascular haemodynamics after repair of ToF and recent studies linked abnormal haemodynamic status measured by MRI with outcome.[34] Unfortunately, MRI data were available in only a small proportion of subjects and for this reason they were not entered in the analysis.

Conclusion

Cardiopulmonary exercise testing is a valuable tool in the long-term follow-up of patients with Tetralogy of Fallot. It has independent, additional prognostic value on top of the established risk factor of QRS duration. Exercise testing should be used in the clinical risk stratification of patients with repaired ToF.

Acknowledgment

No funding. No conflict of interest.

References

- [1] Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med*. 1993;329:593-9.
- [2] Hokanson JS, Moller JH. Adults with tetralogy of Fallot: long-term follow-up. *Cardiol Rev*. 1999;7:149-55.
- [3] Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechano-electrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation*. 1995;92:231-7.
- [4] Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet*. 2000;356:975-81.
- [5] Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Danti A, et al. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. *Am J Cardiol*. 2007;99:1462-7.
- [6] Kavey RE, Thomas FD, Byrum CJ, Blackman MS, Sondheimer HM, Bove EL. Ventricular arrhythmias and biventricular dysfunction after repair of tetralogy of Fallot. *J Am Coll Cardiol*. 1984;4:126-31.

- [7] Oechslin EN, Harrison DA, Harris L, Downar E, Webb GD, Siu SS, et al. Reoperation in adults with repair of tetralogy of fallot: indications and outcomes. *J Thorac Cardiovasc Surg.* 1999;118:245-51.
- [8] Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation.* 2005;112:828-35.
- [9] Buys R, Cornelissen V, De Bruaene AV, Stevens A, Coeckelberghs E, Onkelinx S, et al. Measures of exercise capacity in adults with congenital heart disease. *Int J Cardiol.* 2011;153:26-30.
- [10] Müller J, Christov F, Schreiber C, Hess J, Hager A. Exercise capacity, quality of life, and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection. *Eur Heart J.* 2009;30:2915-20.
- [11] Müller J, Hess J, Hager A. Exercise performance and quality of life is more impaired in Eisenmenger syndrome than in complex cyanotic congenital heart disease with pulmonary stenosis. *Int J Cardiol.* 2011;150:177-81.
- [12] Giardini A, Hager A, Lammers AE, Derrick G, Müller J, Diller GP, et al. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. *J Am Coll Cardiol.* 2009;53:1548-55.
- [13] Diller GP, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, et al. Heart rate response during exercise predicts survival in adults with congenital heart disease. *J Am Coll Cardiol.* 2006;48:1250-6.
- [14] Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV, et al. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation.* 2006;113:2796-802.
- [15] Buys R, Van De Bruaene A, De Meester P, Budts W, Vanhees L. Predictors of mid-term event-free survival in adults with corrected tetralogy of Fallot. *Acta Cardiol.* 2012;67:415-21.
- [16] Valente AM, Gauvreau K, Assenza GE, Babu-Narayan SV, Schreier J, Gatzoulis MA, et al. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Heart.* 2014;100:247-53.
- [17] Cooper DM, Weiler-Ravell D. Gas exchange response to exercise in children. *Am Rev Respir Dis.* 1984;129:S47-8.
- [18] Cooper CB, Storer TW. Exercise testing and interpretation; a practical approach. 1st ed. New York: Cambridge University Press; 2001.
- [19] Goldberg SJ, Allen HD. Quantitative assessment by Doppler echocardiography of pulmonary or aortic regurgitation. *Am J Cardiol.* 1985;56:131-5.
- [20] Nollert G, Fischlein T, Bouterwek S, Bohmer C, Kliner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol.* 1997;30:1374-83.
- [21] Nollert GD, Dabritz SH, Schmoeckel M, Vicol C, Reichart B. Risk factors for sudden death after repair of tetralogy of Fallot. *Ann Thorac Surg.* 2003;76:1901-5.
- [22] Norgaard MA, Lauridsen P, Helvind M, Pettersson G. Twenty-to-thirty-seven-year follow-up after repair for Tetralogy of Fallot. *Eur J Cardiothorac Surg.* 1999;16:125-30.
- [23] Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation.* 2008;117:363-70.
- [24] Diller GP, Giardini A, Dimopoulos K, Gargiulo G, Müller J, Derrick G, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. *Eur Heart J.* 2010;31:3073-83.
- [25] Oosterhof T, Vliegen HW, Meijboom FJ, Zwiderman AH, Bouma B, Mulder BJ. Long-term effect of pulmonary valve replacement on QRS duration in patients with corrected tetralogy of Fallot. *Heart.* 2007;93:506-9.
- [26] Therrien J, Siu SC, Harris L, Dore A, Niwa K, Janousek J, et al. Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. *Circulation.* 2001;103:2489-94.
- [27] Scherptong RW, Hazekamp MG, Mulder BJ, Wijers O, Swenne CA, van der Wall EE, et al. Follow-up after pulmonary valve replacement in adults with tetralogy of Fallot: association between QRS duration and outcome. *J Am Coll Cardiol.* 2010;56:1486-92.
- [28] Oosterhof T, van Straten A, Vliegen HW, Meijboom FJ, van Dijk AP, Spijkerboer AM, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. *Circulation.* 2007;116:545-51.
- [29] Davlouros PA, Karatza AA, Gatzoulis MA, Shore DF. Timing and type of surgery for severe pulmonary regurgitation after repair of tetralogy of Fallot. *Int J Cardiol.* 2004;97 Suppl 1:91-101.
- [30] Lurz P, Giardini A, Taylor AM, Nordmeyer J, Muthurangu V, Odendaal D, et al. Effect of altering pathologic right ventricular loading conditions by percutaneous pulmonary valve implantation on exercise capacity. *Am J Cardiol.* 2010;105:721-6.

- [31] Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *Am J Cardiol.* 2005;95:779-82.
- [32] Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of fallot: are we operating too late? *J Am Coll Cardiol.* 2000;36:1670-5.
- [33] Lurz P, Nordmeyer J, Giardini A, Khambadkone S, Muthurangu V, Schievano S, et al. Early versus late functional outcome after successful percutaneous pulmonary valve implantation are the acute effects of altered right ventricular loading all we can expect? *J Am Coll Cardiol.* 2011;57:724–31.
- [34] Knauth AL, Gauvreau K, Powell AJ, Landzberg MJ, Walsh EP, Lock JE, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. *Heart.* 2008;94:211-6.

Table 1: Study subjects

Variable	All study cohort (n=875)	Survivors without event (n=650)	Death or event (n=225)	p-value*
Female sex, n (%)	358 (40.9)	280 (43.1)	78 (34.7)	0.150
Diagnosis, n (%)				
Fallot	743 (85.0)	548 (84.3)	195 (86.7)	0.229
DORV	73 (8.3)	57 (8.8)	16 (7.1)	
PA-VSD	35 (4.0)	24 (3.7)	11 (4.9)	
PA-VSD-Mapca	24 (2.7)	21 (3.2)	3 (1.3)	
Palliation, n (%)				
None	558 (63.8)	434 (66.8)	124 (55.1)	0.002
BT-shunt	188 (21.5)	134 (20.6)	54 (24.0)	
AP-shunt	88 (10.1)	56 (8.6)	32 (14.2)	
Other	41 (4.6)	26 (4.0)	15 (6.7)	
Age at surgical repair (years)	5.3 ± 6.5	4.9 ± 6.0	6.5 ± 7.8	0.004
Type of corrective surgery	(n=688)	(n=534)	(n=154)	
Infundibulectomy/Commisurotomy	268 (38.5)	213 (39.9)	55 (35.7)	0.682
Transvalvular patch	284 (41.9)	213 (39.9)	71 (46.1)	
Unvalved conduit	36 (5.3)	28 (5.2)	8 (5.2)	
Biovalved conduit	97 (13.9)	77 (14.4)	20 (13.0)	
Mechanical valved conduit	3 (0.4)	3 (0.6)	-	
Cardiac surgeries after initial repair, but before CPET	(n=662)	(n=527)	(n=135)	
None	413 (62.0)	338 (64.1)	75 (55.6)	0.042
One	222 (33.9)	167 (31.7)	55 (40.7)	
Two or more	27 (4.1)	22 (4.2)	5 (3.7)	
Interventional heart catheter after initial repair, but before CPET	(n=875)	(n=650)	(n=225)	
None	777 (88.3)	575 (88.5)	197 (87.6)	0.864
One	81 (9.3)	60 (9.2)	21 (9.3)	
Two or more	22 (2.4)	15 (2.3)	7 (3.1)	
Electro physical procedures after initial repair, but before CPET	(n=875)	(n=650)	(n=225)	
Ablation/cardioversion	36 (4.0)	23 (3.6)	13 (5.8)	0.115
Pacer/ICD implant	19 (2.1)	12 (1.8)	7 (3.1)	
Age at CPET (years)	25.5 ± 11.7	24.3 ± 11.0	29.2 ± 12.9	<0.001
Pulmonary regurgitation	(n=853)	(n=632)	(n=221)	
Absent/trivial	227 (26.0)	192 (30.4)	35 (15.8)	<0.001
Mild	188 (21.5)	161 (25.5)	27 (12.2)	
Moderate	198 (22.6)	148 (23.4)	50 (22.6)	
Severe	240 (27.4)	131 (20.7)	109 (49.3)	
Right ventricular function	(n=858)	(n=636)	(n=222)	
Normal/enhanced	542 (61.9)	421 (66.2)	121 (54.5)	<0.001
Slightly reduced	228 (26.1)	166 (26.1)	62 (27.9)	
Moderately reduced	64 (7.3)	36 (5.7)	28 (12.6)	
Severely reduced	24 (2.7)	13 (2.0)	11 (5.0)	
Peak oxygen uptake				
ml/min/kg	27.7 ± 8.6	28.6 ± 8.6	25.2 ± 8.5	<0.001
% of predicted	76.6 ± 19.7	78.3 ± 18.6	71.8 ± 21.6	<0.001
$\dot{V}_E/\dot{V}_{CO_2}$ -slope	30.5 ± 7.3	29.8 ± 6.5	32.7 ± 9.7	<0.001

Peak systolic blood pressure, mmHg	151 ± 28	152 ± 27	149 ± 29	0.085
Heart rate reserve, %	76 ± 19	77 ± 18	74 ± 20	0.015
QRS duration at rest, ms	145 ± 27	143 ± 26	153 ± 28	<0.001
Respiratory exchange ratio	1.11 ± 0.16	1.11 ± 0.41	1.09 ± 0.11	0.248
Medication, n (%)				
Beta-blocker	55 (6.3)	39 (6.0)	16 (7.1)	0.363
Antiarrhythmic agents	49 (5.7)	23 (3.8)	26 (11.5)	<0.001
ACE inhibitors	52 (5.9)	28 (4.4)	24 (10.7)	<0.001
Diuretic	51 (5.8)	24 (3.8)	27 (12.0)	<0.001

* Comparison of the subgroups (survivors without event vs. death or event) by a t-test or Chi square test.

DORV: Double Outlet Right Ventricle, PA-VSD Pulmonary Atresia with Ventricular Septal Defect, MAPCA: Major aortopulmonary collateral artery, BT-Shunt: Blalock-Taussig shunt, AP-shunt: Aortopulmonary-shunt, CPET: cardiopulmonary exercise test, ICD: implantable cardioverter-defibrillator

Figure 1: Distribution of peak oxygen uptake expressed as percentage of predicted value in 875 patients with Tetralogy of Fallot.

Figure 2: Kaplan-Meier survival curves according to the presence or absence of peak $\dot{V}O_2 \leq 65\%$ predicted and resting QRS duration ≥ 170 ms. Results suggest that only those patients with both risk factors are at high risk for death or sustained ventricular tachycardia during follow-up.

Patients at risk

	0	1	2	3	4	5	6	7	8
VO ₂ >65%, QRS <170ms	566	525	438	337	264	213	173	128	77
VO ₂ >65%, QRS ≥170ms	76	54	49	40	36	27	24	18	13
VO ₂ ≤65%, QRS <170ms	173	139	126	89	68	54	34	22	10
VO ₂ ≤65%, QRS ≥170ms	60	48	43	27	21	16	11	6	3

Figure 3: Predicted 5-year risk of death or sustained ventricular tachycardia based on the results of a random survival forest analysis (see Methods for details).

Patients with VT or deaths are marked in black

Figure 4: Flow chart describing the types of first cardiac related event observed after cardiopulmonary exercise testing (CPET)

EPS: Intracardiac electrophysiology study, ICD: Implantable Cardioverter/Defibrillator, PPVI: Percutaneous Pulmonary Valve Implantation

Figure 5: Kaplan-Meier curve showing freedom from the secondary end point according to the numbers of risk factors (peak $\dot{V}O_2 \leq 65\%$ predicted, $\dot{V}_E/\dot{V}_{CO_2}$ slope ≥ 31 , resting QRS duration ≥ 170 ms) showing that risk increases for every additional factor present.

Patients at risk									
Follow-up (years)									
No risk factor	375	328	286	198	150	122	107	70	39
1 risk factor	322	252	187	134	94	74	52	31	10
2 risk factors	141	95	78	48	35	27	18	8	3
3 risk factors	37	19	12	8	6	4	2	2	1