HHS Public Access

Author manuscript

Pediatr Cardiol. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Pediatr Cardiol. 2019 January ; 40(1): 71–78. doi:10.1007/s00246-018-1962-0.

Determinants of Exercise Performance in Children and Adolescents with Repaired Tetralogy of Fallot Using Stress Echocardiography

Shivani M. Bhatt, **Okan U. Elci**, **Yan Wang**, **Elizabeth Goldmuntz**, **Michael McBride**, **Stephen Paridon**, and **Laura Mercer-Rosa**

Children's Hospital of Philadelphia, Philadelphia, PA

Abstract

Objective: Exercise performance is variable and often impaired in patients with repaired tetralogy of Fallot (rTOF). We sought to identify factors associated with exercise performance by comparing high to low performers on cardiopulmonary exercise testing (CPET) in patients with rTOF.

Study Design: We conducted a cross sectional study of subjects presenting for CPET who underwent echocardiograms at rest and peak exercise. Patients with pacemakers and arrhythmias were excluded. Right ventricular (RV) global longitudinal strain was used as a measure of systolic function. Pulmonary insufficiency (PI) was assessed with the Diastolic Systolic ratio and the Diastolic Systolic Time Velocity Integral ratio by Doppler interrogation of the pulmonary artery. CPET measures included percent-predicted maximum VO2 (%mVO2), percent-predicted maximum work and oxygen pulse. High versus low performers were identified as those achieving %mVO2 of at least 80% or falling below, respectively. Differences in echocardiographic parameters from rest to peak exercise were examined using mixed-effects regression models.

Results: Compared to the low performers (n=17), high performers (n=12), were younger (12.8 ± 3.3 years vs 18.3 ± 4.8 years), had normal chronotropic response (peak heart rate >185bpm) with greater heart rate reserve and superior physical working capacity. High performers also had a greater reduction in PI at peak exercise, despite greater PI severity at rest. Oxygen pulse was comparable between groups. For both groups, there was no association of PI severity and RV systolic function at rest with exercise parameters. There was no group difference in the magnitude of change in RV strain and diastolic parameters from rest to peak exercise.

Conclusions: Chronotropic response to exercise appears to be an important parameter with which to assess exercise performance in rTOF. Chronotropic health should be taken into

Corresponding Author: Shivani M. Bhatt, MD, Division of Cardiology, Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia PA 19104, Phone: 215-590-3548, Fax: 215-590-5825, bhatts@email.chop.edu.

Funding: This study was supported by CHOP Cardiac Center Grant (Mercer-Rosa, Bhatt), Matthew's Hearts of Hope Grant (Bhatt), NIH K01HL125521 (Mercer-Rosa), NIH 5T32HL007915 (Bhatt) and NIH F32HL139042 (Bhatt).

Conflict of interest The authors declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

consideration in this population, particularly given that RV function and PI severity at rest were not associated with exercise performance.

Keywords

Congenital Heart Disease; Tetralogy of Fallot; Stress Echocardiography; Cardiopulmonary exercise testing

Introduction:

Despite improved survival into adulthood due to successful surgical repair, patients with tetralogy of Fallot are known to have impaired exercise capacity with abnormally low percent-predicted maximal oxygen consumption (VO2max) that appears to worsen over time.[1-5] [4,5] However, abnormal indices of exercise performance on cardiopulmonary exercise testing (CPET) can vary significantly from patient to patient. Deciphering the factors that contribute to exercise capacity in this population is challenging and the determinants of exercise performance are not fully understood.

Diminished exercise performance in patients with rTOF is associated with worse health status and quality of life in children and adolescents, and also a predictor of mortality. [6-9] However, the individual factors associated with exercise performance after repair of tetralogy of Fallot remain to be completely explained and are likely multifactorial. [10] Possible contributing factors for exercise capacity in rTOF include pulmonary regurgitation, ventricular dysfunction, chronotropic impairment, abnormal lung function, and pulmonary artery distortion. [11-15] Habitual exercise is also associated with exercise performance, independently of a direct correlation between ventricular function and exercise parameters. [16] Due to this multifactorial interaction, discriminating individual contributors to exercise performance in rTOF is challenging. We sought to further discern these factors by comparing children and adolescents with rTOF based on their exercise performance. We used stress echocardiography to compare clinical and functional parameters between high versus low exercise performers with rTOF.

Methods:

Study population

We conducted a cross-sectional study with prospective data collection of patients with rTOF presenting to our institution for clinically indicated CPET from May 2015 to June 2016. Subjects with history of surgically repaired TOF, ages eight years and above were included, based upon the youngest age at which subjects are generally able to complete a CPET. All anatomic subtypes of rTOF were included (pulmonary stenosis, pulmonary atresia, absent pulmonary valve). Subjects with pacemakers and those using beta blockers were excluded. Study subjects were divided into high and low performers, defined by a mVO2% cutoff value of 80%. [17] The study was approved by the Institutional Review Board for the Protection of Human Subjects and subjects provided written informed consent prior to participating in the study.

CPET and Exercise Stress Echocardiography

Standard cardiopulmonary exercise testing using an electronically braked cycle ergometer or 1-min incremental treadmill protocol was performed. A respiratory exchange ratio greater than 1.10 (VCO2/VO2) was used to define aerobic effort. [18] Breath-by-breath expired gas analysis on metabolic cart was used to obtain ventilatory and metabolic data (Carefusion, Yorba Linda, CA). According to normative values for age, gender and body size, the percent of predicted maximum VO2 (%mVO2) was calculated for each subject. [19-21] Oxygen pulse, calculated as maximum VO2 divided by the peak heart rate and indexed for body surface area (ml/O2/beat/m^2), was used as a surrogate of stroke volume. The slope of minute ventilation versus CO2 production (VE/VCO2 slope), an index gas exchange efficiency was measured. [22,23] A normal VE/VCO2 slope in pediatric patients is less than 28. [24] Heart rate reserve was calculated as the difference between maximum heart rate and resting heart rate. A heart rate greater than 185 beats per minute at peak exercise was defined as normal chronotropic response.[17,23]

A focused, protocol-based echocardiogram was performed immediately prior to CPET (rest) and repeated at peak exercise immediately upon completion of the CPET. Echocardiographic parameters included peak RV global longitudinal strain (systolic function), tricuspid inflow and myocardial velocities (diastolic function), and the ratio of the diastolic to systolic time velocity integral, or DSTVI (PI). Image acquisition for offline RV longitudinal strain measurements included an apical four chamber view optimizing settings for strain analysis. Based on normative RV strain data from our institution for children ages eight and above with normal cardiac structure and function, RV GLS was considered normal if the absolute value was greater than 26%. RV contractile reserve was defined as the change in RV global longitudinal strain (i.e. difference between rest and peak exercise value).

Myocardial velocities of the RV free wall were obtained with tissue Doppler imaging (TDI). The early filling (e′), late filling (a′) and systolic (s′) waves of the right ventricle were recorded. Pulse wave Doppler interrogation of the tricuspid inflow was performed and the early and atrial contraction velocities were recorded. Pulse-wave Doppler tracing of the main pulmonary artery was used to obtain time-velocity integrals of diastolic and systolic flows in the MPA. To quantify PI, offline measurements of the regurgitant (diastolic) and antegrade (systolic) time velocity integrals and a ratio of those was calculated (diastolic to systolic time-velocity integral ratio, or DSTVI). [25,26] Standard pediatric transthoracic echocardiographic views were obtained on a Phillips IE33 machine (Phillips, Andover, MA, USA) using appropriate sized transducers by a sonographer trained on the study's protocol. Images were digitally stored and measurements were performed offline by a single observer using Syngo Dynamics software (Siemens, Ann Arbor, MI, USA) and Cardiac Performance Analysis Software (TomTec, Germany). Using speckle tracking software (Cardiac Performance Analysis Software, TomTec, Germany) right ventricular longitudinal strain curves were obtained.

Statistical Methods:

Descriptive statistics are presented as mean ± standard deviation or median (minimum-maximum) for continuous variables and frequency counts (percentages) for categorical

variables. Baseline characteristics and exercise parameters were compared between low and high performers using the chi-square test or Fischer's exact test for categorical variables and t-test or Wilcoxon rank sum test as appropriate for continuous variables. Mixed-effects linear regression models with identity link were used to examine the changes in echocardiographic parameters from rest to peak exercise within and between the performer groups. Mixed-effects models implemented via maximum likelihood account for correlations arising from the repeated measures obtained at rest and at peak exercise and allow using all measurements obtained from each subject. The model for the predictor RVGLS was adjusted for DSTVI ratio to account for changes in RVGLS that are independent of changes in PI. Sensitivity analyses were performed to examine potential outliers and influential points. These measurements were assessed by visual examination of histograms and normal probability plots of residuals from each model. Statistical analyses were conducted using Stata 14.1 (StataCorp, College Station, TX) and the significance level was set at 0.05 for all tests.

Results:

Baseline Characteristics

The high performers had a median mVO2% of 97.5% (IQR 90.5, 110.5) with mean maximal VO2 of 41.2 ml/kg/min while the low performers had a median mVO2% of 68% (IQR 66, 76) and mean maximal VO2 of 30 ml/kg/min. In comparison to low performers (n=17), the high performers (n=12), were younger upon testing, and had lower body surface area (BSA). There was no difference between the two groups by genetic syndrome, type of tetralogy of Fallot, type of surgical repair, age at complete repair, or history of pulmonary valve replacement. (Table 1 & 2)

Echocardiographic Parameters

RVGLS was abnormal in both groups at baseline measuring 16% (range 8-27) in the low performers and 17.5% (range 12.5-27) in the high performers. RVGLS decreased from rest to peak exercise in both high and low performers. There was no significant difference in the magnitude of change in RVGLS or in diastolic parameters from rest to peak exercise between the groups. There was a significant decrease in degree of PI from rest to peak exercise in both groups. The high performers had a greater reduction in PI at peak exercise, despite greater PI severity at rest by DS ratio (Table 3 and Figure 1)

Exercise Parameters

High performers had a greater peak heart rate and heart rate reserve [median 114 (range 97-136)] in comparison to the low performers [100 (range 41-142)]. Oxygen pulse and VE/VCO2 slope were comparable between groups. (Table 1, Figure 1)

Discussion:

In this small but prospectively conducted study, we sought to investigate the factors associated with exercise performance in patients with rTOF using CPET and stress echocardiography. Our main findings were that subjects in the high performer group were

younger upon CPET, had greater physical work rate capacity and heart rate reserve, and, despite greater PI at rest, demonstrated a greater reduction in PI at peak exercise compared to low performers. The groups were comparable in terms of RV contractile reserve and ventilatory efficiency.

Studies have reported that exercise performance in patients with rTOF declines with age. [1,3] We found that subjects in the high performer group were younger compared to the low performers, but the low performers themselves were relatively young (adolescents). Only longitudinal assessment of these groups will allow us to ascertain whether their exercise performance will decline with age.

The baseline characteristics including age at repair or type of surgical repair was comparable between the high and low performers. This suggests clinical factors that are often thought to have negative prognostic implications in rTOF may not necessarily influence exercise capacity. Similar to our findings, Sarubbi et al. found patients with rTOF had reduced peak work rate in comparison to healthy controls irrespective of type of surgical repair and age at surgery. [27] Others have also reported that age at repair, type of surgical repair and history of previous shunt palliation are not associated with indices of exercise function or the decrease of exercise performance over time. [15,2,3] Therefore, it is reasonable to search for factors other than those anatomic or surgery-related that could explain variability in exercise performance from one individual with rTOF compared to another.

We report that the high performers had a normal heart rate response and better heart rate reserve as compared to the low performers. This does not appear to be due to any difference in effort during the exercise testing between the two study groups. Both groups consisted only of subjects achieving a maximal effort and their RER at peak exercise was similar indicating a comparable level of metabolic acidosis and effort. In healthy children, the maximum heart rate achieved during exercise is an important determinant of VO2max. [28] Compared to healthy peers, patients with rTOF have been shown to have significantly reduced heart rate at peak exercise despite normal resting heart rate.[29,30] Chronotropic incompetence with depression of maximal heart rate is common in patients with CHD after cardiac surgery. [18,31,32] However, the mechanisms underlying reduced chronotropic response and its contribution to decreased exercise performance in rTOF are not fully understood. [27,30] In the adult congenital and heart failure populations, it has been proposed that chronotropic incompetence may relate to autonomic dysfunction, neurohormonal activation and cardiac arrhythmias. [33-38] There was no evidence of arrhythmia in either group. Longitudinal follow-up of this cohort is needed to elucidate the changes in chronotropic response over time in rTOF as well as factors that may influence heart rate reserve, such as habitual exercise.

Given that there was no difference in stroke volume at peak exercise (measured by oxygen pulse) between groups in our study, the ability to increase heart rate may be a significant contributor to augmentation of cardiac output and exercise performance. Studies in adults with rTOF have shown that heart rate reserve can be used to stratify patients at higher risk of mortality. [33,34] This is in part a reflection of a higher resting heart rate in the higher risk population as a result of their impaired resting volume. In children, however, the prognostic

implications of heart rate reserve have not yet been investigated. Exercise training in adults with stable heart failure has been shown to improve chronotropic response and exercise capacity. [39] In children with repaired CHD, exercise rehabilitation has shown to improve heart rate recovery after peak exercise. [40] Therefore, it is possible that interventions to improve heart rate response, such as exercise rehabilitation programs, may improve exercise capacity in this population.

There was a significant decrease in PI at peak exercise in both groups. However, high performers had a greater reduction in PI at peak exercise despite greater PI severity at rest compared to low performers. Greater PI severity at rest in the high performers may be related to the fact they were younger and therefore presumably had less stiff RVs compared to the low performers. Important determinants of chronic PI, increasing RV stiffness and consequent increase in RV diastolic pressure potentially decreases the gradient for PI. Therefore, it is possible that low performers who were older and may have had increasing RV stiffness overtime related to fibrosis or hypertrophy leading to less PI at rest in this group in our study. [41,42]

The decrease in PI at peak exercise is likely related to a shorter diastolic time with an increased heart rate. Therefore, it is possible that, independently of PI severity at baseline, the ability to increase heart rate at peak exercise (and as a result, reduce PI) could be a significant contributor to exercise performance. Similar to our findings, O'Meagher et al. demonstrated an increase in RV output during exercise in adults with rTOF facilitated by increase in heart rate and decrease in PI regurgitant fraction on CMR. [43] We propose that chronotropic response in addition to RV contractile response and change in PI is an important yet underappreciated contributor to exercise performance in rTOF.

We found that both high and low performers had abnormal resting RVGLS and abnormal contractile reserve, with comparable magnitude of change in RV strain from rest to peak exercise, indicating that exercise capacity in this group of children and adolescents with rTOF may not be influenced by ventricular performance (systolic or diastolic). Similarly to this finding, others have also shown a lack of relationship between RV functional parameters and exercise performance.[44] It is possible there is an adaptive mechanism to exercise in rTOF, such as greater contribution of chronotropic response, which may compensate for the role of ventricular function in augmenting cardiac output during exercise.

Lastly, both groups had an abnormal ventilatory response to exercise (VE/VCO2 slope). However, there was no significant difference between groups, suggesting that the ventilatory response in this small group is not a significant determinant of exercise performance. Other studies have shown that the ventilatory response is negatively correlated with exercise capacity and is a predictor of %mVO2 in rTOF [45] It is a powerful predictor of mortality in adults with rTOF and is proportional to maldistribution of pulmonary blood flow, possibly related to pulmonary artery distortion. [12] [7,33] We did not find a significant difference in this index of gas exchange efficiency, which may be but one of many factors contributing to exercise performance in this population

Limitations:

We conducted a small study using exercise stress echocardiography to evaluate changes in function and pulmonary insufficiency from rest to peak exercise. However, we conducted prospective data collection that allowed us to assess PI and RV function at peak exercise. We included a relatively young population with rTOF and most subjects had TOF with pulmonary stenosis as well as primarily pulmonary regurgitation with minimal residual pulmonary outflow tract obstruction. Therefore, our findings are not generalizable to all patients with rTOF. This was a cross sectional analysis and as such, we were not able to ascertain changes in exercise performance over time. Finally, it is possible that patients are restricted from performing exercise, and therefore we are not able to comment on whether younger patients could have performed better because of increased habitual exercise or lower exercise restriction.

Conclusions:

Preserved chronotropic response, rather than contractile reserve, is an important contributor to augmentation of cardiac output and exercise performance in this group of rTOF patients, possibly through augmentation of cardiac output. The effect of higher heart rate on PI at peak exercise is a possible mediator of this association. Chronotropic health can be a possible target for intervention and future studies.

Abbreviations:

rTOF	Repaired Tetralogy of Fallot
CPET	Cardiopulmonary exercise test
PI	Pulmonary insufficiency
RVGLS	Right Ventricular Global Longitudinal Strain
DSTVI	Diastolic Systolic Time Velocity Integral

References

1. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA (2005) Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 112 (6):828–835. doi:10.1161/CIRCULATIONAHA.104.529800 [PubMed: 16061735]
2. Mahle WT, McBride MG, Paridon SM (2002) Exercise performance in tetralogy of Fallot: the impact of primary complete repair in infancy. Pediatr Cardiol 23 (2):224–229. doi:10.1007/s00246-001-0054-7 [PubMed: 11889543]
3. Kipps AK, Graham DA, Harrild DM, Lewis E, Powell AJ, Rhodes J (2011) Longitudinal exercise capacity of patients with repaired tetralogy of fallot. Am J Cardiol 108 (1):99–105. doi:10.1016/j.amjcard.2011.02.349 [PubMed: 21529748]
4. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M (2014) Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation 130 (9):749–756. doi:10.1161/CIRCULATIONAHA.113.008396 [PubMed: 24944314]

5. Bacha EA, Scheule AM, Zurakowski D, Erickson LC, Hung J, Lang P, Mayer JE, Jr., del Nido PJ, Jonas RA (2001) Long-term results after early primary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 122 (1):154–161. doi:10.1067/mtc.2001.115156 [PubMed: 11436049]
6. Goldmuntz E, Cassedy A, Mercer-Rosa L, Fogel MA, Paridon SM, Marino BS (2017) Exercise Performance and 22q11.2 Deletion Status Affect Quality of Life in Tetralogy of Fallot. J Pediatr 189:162–168. doi:10.1016/j.jpeds.2017.06.049 [PubMed: 28734657]
7. Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Donti A, Formigari R, Bonvicini M, Picchio FM (2007) Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. Am J Cardiol 99 (10):1462–1467. doi:10.1016/j.amjcard.2006.12.076 [PubMed: 17493481]
8. Muller J, Hager A, Diller GP, Derrick G, Buys R, Dubowy KO, Takken T, Orwat S, Inuzuka R, Vanhees L, Gatzoulis M, Giardini A (2015) Peak oxygen uptake, ventilatory efficiency and QRS-duration predict event free survival in patients late after surgical repair of tetralogy of Fallot. Int J Cardiol 196:158–164. doi:10.1016/j.ijcard.2015.05.174 [PubMed: 26114442]
9. Dean PN, Gillespie CW, Greene EA, Pearson GD, Robb AS, Berul CI, Kaltman JR (2015) Sports participation and quality of life in adolescents and young adults with congenital heart disease. Congenit Heart Dis 10 (2):169–179. doi:10.1111/chd.12221 [PubMed: 25196468]
10. O'Meagher S, Munoz PA, Alison JA, Young IH, Tanous DJ, Celermajer DS, Puranik R (2012) Exercise capacity and stroke volume are preserved late after tetralogy repair, despite severe right ventricular dilatation. Heart 98 (21):1595–1599. doi:10.1136/heartjnl-2012-302147 [PubMed: 22869677]
11. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN (1995) Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. Circulation 91 (6):1775–1781 [PubMed: 7882487]
12. Rhodes J, Dave A, Pulling MC, Geggel RL, Marx GR, Fulton DR, Hijazi ZM (1998) Effect of pulmonary artery stenoses on the cardiopulmonary response to exercise following repair of tetralogy of Fallot. Am J Cardiol 81 (10):1217–1219 [PubMed: 9604951]
13. Samman A, Schwerzmann M, Balint OH, Tanous D, Redington A, Granton J, Siu SC, Silversides CK (2008) Exercise capacity and biventricular function in adult patients with repaired tetralogy of Fallot. Am Heart J 156 (1):100–105. doi:10.1016/j.ahj.2008.02.005 [PubMed: 18585503]
14. Fredriksen PM, Therrien J, Veldtman G, Ali Warsi M, Liu P, Thaulow E, Webb G (2002) Aerobic capacity in adults with tetralogy of Fallot. Cardiol Young 12 (6):554–559 [PubMed: 12636004]
15. Rowe SA, Zahka KG, Manolio TA, Horneffer PJ, Kidd L (1991) Lung function and pulmonary regurgitation limit exercise capacity in postoperative tetralogy of Fallot. J Am Coll Cardiol 17 (2):461–466 [PubMed: 1991905]
16. O'Byrne ML, Mercer-Rosa L, Ingall E, McBride MG, Paridon S, Goldmuntz E (2013) Habitual exercise correlates with exercise performance in patients with conotruncal abnormalities. Pediatr Cardiol 34 (4):853–860. doi:10.1007/s00246-012-0556-5 [PubMed: 23104594]
17. Rowland TW (1993) Pediatric Laboratory Exercise Testing: Clinical Guidelines. Human Kinetics Publishers, Champaign.
18. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li JS, Margossian R, Mital S, Russell J, Rhodes J, Pediatric Heart Network I (2008) A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. J Am Coll Cardiol 52 (2):99–107. doi:10.1016/j.jacc.2008.02.081 [PubMed: 18598887]
19. Ross RM (2003) ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167 (10):1451; author reply 1451. doi:10.1164/ajrccm.167.10.952 [PubMed: 12738602]
20. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K (1984) Aerobic parameters of exercise as a function of body size during growth in children. J Appl Physiol Respir Environ Exerc Physiol 56 (3):628–634 [PubMed: 6706770]
21. Howley ET, Bassett DR, Jr., Welch HG (1995) Criteria for maximal oxygen uptake: review and commentary. Med Sci Sports Exerc 27 (9):1292–1301 [PubMed: 8531628]
22. Wasserman K (1999) Principles of exercise testing & interpretation : including pathophysiology and clinical applications. 3rd edn. Lippincott Williams & Wilkins, Philadelphia

23. Rowland TW, American College of Sports Medicine, North American Society for Pediatric Exercise Medicine (2018) Cardiopulmonary exercise testing in children and adolescents
24. Rhodes J, Ubeda Tikkanen A, Jenkins KJ (2010) Exercise testing and training in children with congenital heart disease. Circulation 122 (19):1957–1967. doi:10.1161/CIRCULATIONAHA.110.958025 [PubMed: 21060085]
25. Mercer-Rosa L, Yang W, Kutty S, Rychik J, Fogel M, Goldmuntz E (2012) Quantifying pulmonary regurgitation and right ventricular function in surgically repaired tetralogy of Fallot: a comparative analysis of echocardiography and magnetic resonance imaging. Circ Cardiovasc Imaging 5 (5):637–643. doi:10.1161/CIRCIMAGING.112.972588 [PubMed: 22869820]
26. Bhat M, Goldmuntz E, Fogel MA, Rychik J, Mercer-Rosa L (2017) Longitudinal Validation of the Diastolic to Systolic Time-Velocity Integral Ratio as a Doppler-Derived Measure of Pulmonary Regurgitation in Patients with Repaired Tetralogy of Fallot. Pediatr Cardiol 38 (2):240–246. doi:10.1007/s00246-016-1505-5 [PubMed: 27837302]
27. Sarubbi B, Pacileo G, Pisacane C, Ducceschi V, Iacono C, Russo MG, Iacono A, Calabro R (2000) Exercise capacity in young patients after total repair of Tetralogy of Fallot. Pediatr Cardiol 21 (3):211–215. doi:10.1007/s002460010041 [PubMed: 10818175]
28. Godfrey S (1974) Exercise testing in children; applications in health and disease. Saunders, London, Philadelphia, Saunders, London.
29. Cumming GR (1979) Maximal supine exercise haemodynamics after open heart surgery for Fallot's tetralogy. Br Heart J 41 (6):683–691 [PubMed: 465243]
30. Wessel HU, Paul MH (1999) Exercise studies in tetralogy of Fallot: a review. Pediatr Cardiol 20 (1):39–47; discussion 48. doi:10.1007/s002469900393 [PubMed: 9861075]
31. Reybrouck T, Weymans M, Stijns H, Van der Hauwaert LG (1986) Exercise testing after correction of tetralogy of Fallot: the fallacy of a reduced heart rate response. Am Heart J 112 (5):998–1003 [PubMed: 3776826]
32. Norozi K, Wessel A, Alpers V, Arnhold JO, Binder L, Geyer S, Zoege M, Buchhorn R (2007) Chronotropic incompetence in adolescents and adults with congenital heart disease after cardiac surgery. J Card Fail 13 (4):263–268. doi:10.1016/j.cardfail.2006.12.002 [PubMed: 17517345]
33. Inuzuka R, Diller GP, Borgia F, Benson L, Tay EL, Alonso-Gonzalez R, Silva M, Charalambides M, Swan L, Dimopoulos K, Gatzoulis MA (2012) Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation 125 (2):250–259. doi:10.1161/CIRCULATIONAHA.111.058719 [PubMed: 22147905]
34. Diller GP, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, Bayne S, Poole-Wilson PA, Sutton R, Francis DP, Gatzoulis MA (2006) Heart rate response during exercise predicts survival in adults with congenital heart disease. J Am Coll Cardiol 48 (6):1250–1256. doi:10.1016/j.jacc.2006.05.051 [PubMed: 16979014]
35. Davos CH, Francis DP, Leenarts MF, Yap SC, Li W, Davlouros PA, Wensel R, Coats AJ, Piepoli M, Sreeram N, Gatzoulis MA (2003) Global impairment of cardiac autonomic nervous activity late after the Fontan operation. Circulation 108 Suppl 1:II180–185. doi:10.1161/01.cir.0000087946.47069.cb [PubMed: 12970229]
36. Colucci WS, Ribeiro JP, Rocco MB, Quigg RJ, Creager MA, Marsh JD, Gauthier DF, Hartley LH (1989) Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization. Circulation 80 (2):314–323 [PubMed: 2546698]
37. Ellestad MH (1996) Chronotropic incompetence. The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?). Circulation 93 (8):1485–1487 [PubMed: 8608613]
38. Ohuchi H, Watanabe K, Kishiki K, Wakisaka Y, Echigo S (2007) Heart rate dynamics during and after exercise in postoperative congenital heart disease patients. Their relation to cardiac autonomic nervous activity and intrinsic sinus node dysfunction. Am Heart J 154 (1):165–171. doi:10.1016/j.ahj.2007.03.031 [PubMed: 17584572]
39. Keteyian SJ, Brawner CA, Schairer JR, Levine TB, Levine AB, Rogers FJ, Goldstein S (1999) Effects of exercise training on chronotropic incompetence in patients with heart failure. Am Heart J 138 (2 Pt 1):233–240 [PubMed: 10426833]

40. Singh TP, Curran TJ, Rhodes J (2007) Cardiac rehabilitation improves heart rate recovery following peak exercise in children with repaired congenital heart disease. Pediatr Cardiol 28 (4): 276–279. doi:10.1007/s00246-006-0114-0 [PubMed: 17530324]

41. Chaturvedi RR, Redington AN (2007) Pulmonary regurgitation in congenital heart disease. Heart 93 (7):880–889. doi:10.1136/hrt.2005.075234 [PubMed: 17569817]

42. d'Udekem Y, Ovaert C, Grandjean F, Gerin V, Cailteux M, Shango-Lody P, Vliers A, Sluysmans T, Robert A, Rubay J (2000) Tetralogy of Fallot: transannular and right ventricular patching equally affect late functional status. Circulation 102 (19 Suppl 3):III116–122 [PubMed: 11082373]

43. O'Meagher S, Munoz PA, Muthurangu V, Robinson PJ, Malitz N, Tanous DJ, Celermajer DS, Puranik R (2014) Mechanisms of maintained exercise capacity in adults with repaired tetralogy of Fallot. Int J Cardiol 177 (1):178–181. doi:10.1016/j.ijcard.2014.09.008 [PubMed: 25499372]

44. Menon SC, Kaza AK, Puchalski MD (2012) Effect of ventricular size and function on exercise performance and the electrocardiogram in repaired tetralogy of Fallot with pure pulmonary regurgitation. Ann Pediatr Cardiol 5 (2):151–155. doi:10.4103/0974-2069.99617 [PubMed: 23129904]

45. Clark AL, Gatzoulis MA, Redington AN (1995) Ventilatory responses to exercise in adults after repair of tetralogy of Fallot. Br Heart J 73 (5):445–449 [PubMed: 7786660]

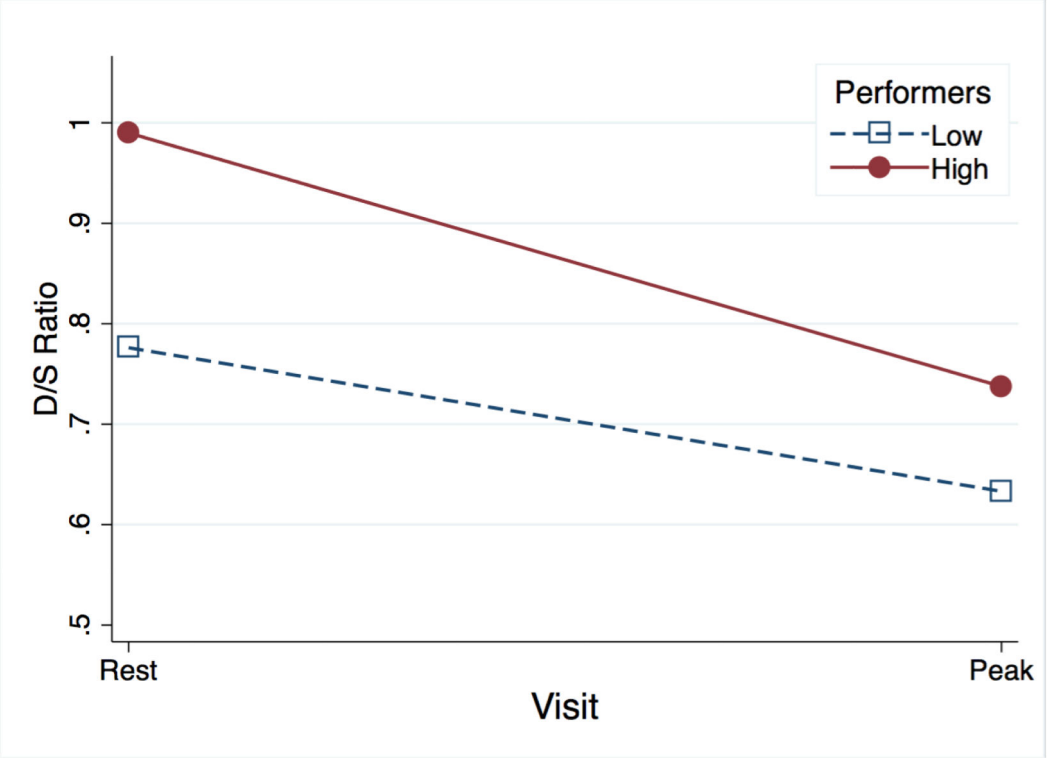

Figure 1:
Change in Diastolic Systolic Ratio from rest to peak exercise by group, in High performers (solid line) and Low Performers (dashed line) *Circles* and *squares* represent the mean Diastolic Systolic Ratio at rest and peak exercise in high performers and low performers, respectively.

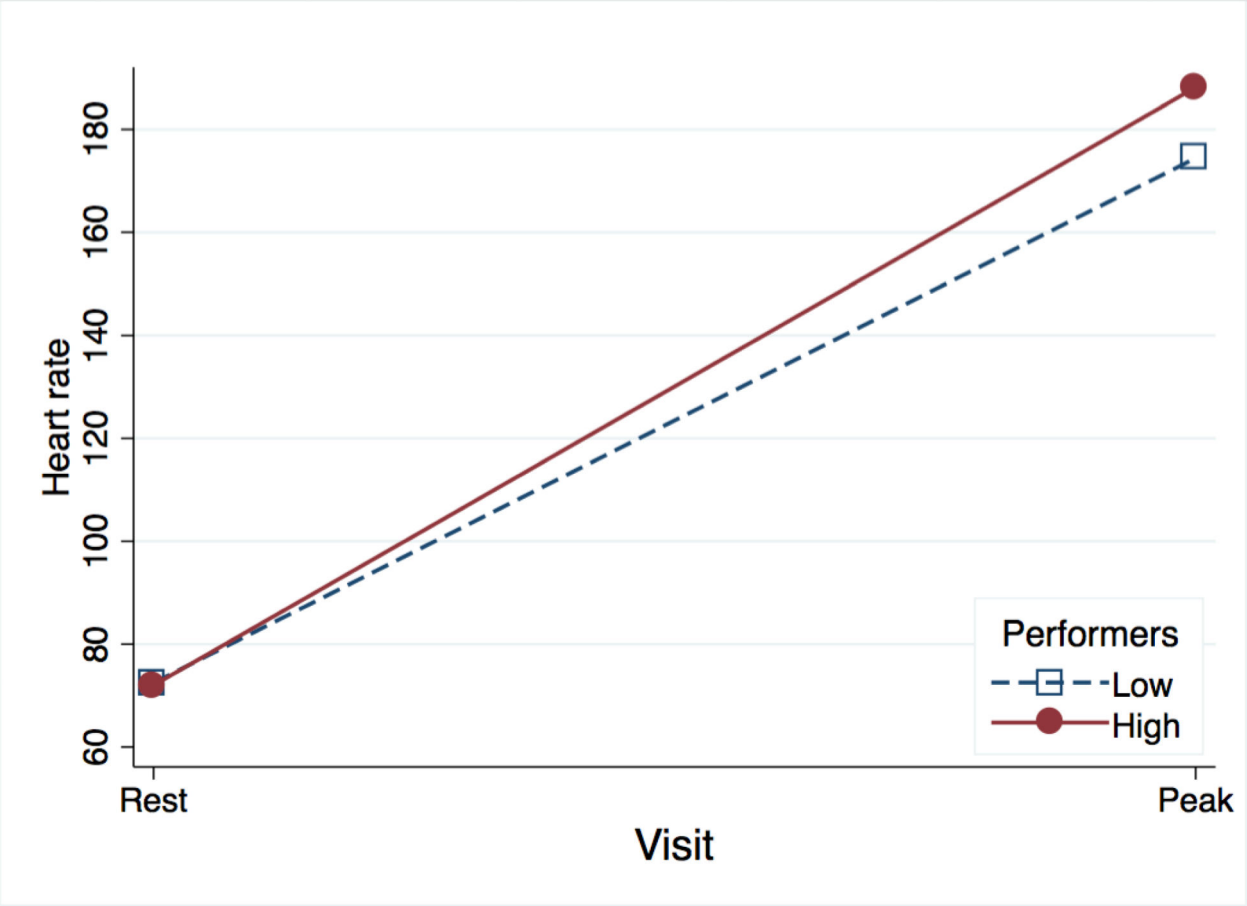

Figure 2:
Change in heart rate from rest to peak exercise by group, in High performers (solid line) and Low Performers (dashed line) *Circles* and *squares* represent the mean heart rate at rest and peak exercise in high performers and low performers, respectively.

Table 1.

Baseline Characteristics and Exercise Parameters

	Low Performer (n=17)	High Performer (n=12)	P
Demographics			
Gender, Male, n (%)	11 (64.7)	8 (66.7)	0.913
Race, White, n (%)	8 (47.1)	9 (75.0)	0.132
Age at testing, years	18.3 ± 4.83	12.8 ± 3.26	**0.002**
Weight, kg	62.7 ± 15.55	47.5 ± 18.77	**0.025**
Height, cm	164.4 ± 14.1	154.6 ± 18.0	0.111
Body Surface Area, m^2	1.7 ±0.28	1.4 ±0.36	**0.027**
Genetic Syndrome	2 (11.7)	0	
Exercise parameters			
Mode of CPET			
Treadmill, n(%)	1 (6%)	1 (8%)	
Cycle Ergometer, n(%)	16 (94%)	11 (92%)	
Heart rate, bpm			
Rest	72 (51-93)	71.5 (54-93)	0.929
Peak	176 (109-206)	190 (166-203)	**0.017**
Heart Rate Reserve	100 (41-142)	114 (97-136)	**0.051**
Percent predicted maximum work, %	61.9 ± 18.73	88.3 ± 16.15	**0.001**
Oxygen Pulse, ml/beat/m^2	5.8 (4.7-8.8)	7.1 (4.4-10.2)	0.132
VE/VCO2 Slope	31 (25 - 36)	30 (22 - 46)	0.456
Respiratory Exchange Ratio (RER) *	1.26 ± 0.11	1.22 ±(0.09)	0.43
Oxygen Saturation at rest (%)	97.3 ±3.4%,	95 ± 7.9 %	0.29

Data are reported as Mean ± Standard Deviation or Median (Range) unless indicated.

P values comparing Low Performers with High Performers using Chi-square test for categorical variables and t-test for continuous variables were reported.

* Maximum effort on CPET was defined as RER ≥1.1

Table 2.

Cardiac Diagnosis and History

	Low Performer (n=17)	High Performer (n=12)	P
Cardiac Diagnosis:			
Pulmonary Stenosis	14 (82%)	11 (92%)	
Pulmonary Atresia	3 (18%)	0	0.146
Absent Pulmonary Valve	0	1 (8%)	
Age at complete repair (months)	4.2 (0.1-26)	3.7 (0.1-60)	0.757
Type of Repair:			
Transannular patch	14 (82%)	9 (75%)	
Right Ventricular conduit	1 (6%)	1 (8%)	0.99
Pulmonary valvotomy	1 (6%)	0	
Non-Transannular patch	1 (6%)	2 (17%)	
History of Pulmonary Valve Replacement	3 (19%)	1 (8%)	0.613

Data are reported as n (%) or Median (Range) unless indicated.

P values comparing Low Performers with High Performers using Fischer's exact test for categorical variables and Wilcoxon rank-sum test for age at complete repair were reported.

Table 3.

Echocardiographic Parameters

Echocardiographic Parameters	Low Performer (n=17)	P1	High Performer (n=12)	P2	P3
Diastolic to Systolic Velocity Ratio					
Rest	0.73 (0.47-1.22)	**<0.001**	1.05 (0.42-1.43)	**<0.001**	**0.053**
Peak Exercise	0.62 (0.37-1.25)		0.72 (0.32-1.32)		
Systolic Time Velocity Integral (cm)					
Rest	58.4 (34.3-119)	0.912	56.3 (34.9-79.8)	0.135	0.225
Peak Exercise	57.8 (30.8-129)		50.5 (28.8-78.1)		
Diastolic Time Velocity Integral (cm)					
Rest	47.3 (0-79.0)	**<0.001**	54.6 (23.4-75.3)	**<0.001**	**0.043**
Peak Exercise	31.4 (0-67.0)		34.0 (18.9-44.4)		
Diastolic Systolic Time Velocity Integral Ratio					
Rest	0.73 (0-1.61)	**0.001**	0.97 (0.38-1.38)	**<0.001**	0.183
Peak Exercise	0.59 (0-1.21)		0.67 (0.32-1.30)		
*RV Global Longitudinal Strain (%)					
Rest	16 (8-27)	**0.023**	17.5 (12.5-27)	0.097	0.862
Peak Exercise	14 (5-18.5)		13.0 (10.5-28)		
Pulmonary outflow peak velocity (m/sec)					
Rest	2.74 (1.75 - 4.8)	**<0.001**	2.30 (2.17 - 3.18)	**<0.001**	0.266
Peak Exercise	4.23 (3.35 - 6.2)		3.20 (1.64 - 4.56)		
Tricuspid-Peak S Velocity					
Rest	0.10 (0.06-0.78)	0.972	0.09 (0.07-0.13)	0.200	0.331
Peak Exercise	0.13 (0.06-0.20)		0.16 (0.10-0.20)		
Tricuspid-Peak E Velocity					
Rest	0.09 (0.06-0.18)	**0.001**	0.10 (0.07-0.16)	**<0.001**	0.660
Peak Exercise	0.13 (0.07-0.28)		0.16 (0.10-0.27)		
Tricuspid-Peak A Velocity					
Rest	0.07 (0.03-0.61)	0.673	0.05 (0.04-0.48)	0.635	0.943
Peak Exercise	0.10 (0.06-0.19)		0.11 (0.05-0.20)		

P1 and P2 are p values referring to visit effect (change from Rest to Peak exercise) within the low and high performers, respectively. P3 is testing whether change from Rest to Peak exercise is different between the Low and High performers (Performers by Visit interaction effect).

*Model adjusted for change in DSTVI