Journal Pre-proof

Cardiopulmonary Exercise Test (CPET) in patients with repaired Tetralogy of Fallot (rTOF); A Systematic Review

S. Alborikan, MSc, B. Pandya, MD, K. Von Klemperer, M.D, F. Walker, MD, S. Cullen, MD, S. Badiani, MRCP, S. Bhattacharyya, MD, G. Lloyd, MD

PII: S2666-6685(20)30050-1

DOI: https://doi.org/10.1016/j.ijcchd.2020.100050

Reference: IJCCHD 100050

To appear in: *International Journal of Cardiology Congenital Heart Disease*

Received Date: 9 September 2020

Accepted Date: 27 October 2020

Cardiopulmonary Exercise Test (CPET) in patients with repaired Tetralogy of Fallot (rTOF); A Systematic Review.

Alborikan S, MSc,[a,b,c] Pandya B, MD,[d] Von Klemperer K, M.D,[d] Walker F, MD,[d] Cullen S, MD,[d] Badiani S, MRCP,[a,b] Bhattacharyya S MD,[a,b,e] Lloyd G, MD[a,b,e]

a) Barts Heart Centre, St Bartholomew's Hospital, London, United Kingdom
b) William Harvey Research Institute, QMUL, London, United Kingdom
c) King Fahad Specialist Hospital, Cardiac department, Dammam, Saudi Arabia
d) Grown-up Congenital Heart Disease Services, Barts Heart Centre, St. Bartholomew's Hospital, London, UK
e) Institute of Cardiovascular science, UCL, London, UK

Corresponding author

Sahar Alborikan: Sahar.borikan@nhs.net
Telephone number: +447482474733
Address: Echocardiography Laboratory, Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London, Greater London EC1A 7BE, United Kingdom.

Manuscript word count: 4534 (including references and figure legends)

Disclosures: The authors have nothing to disclose.

Funding: This review receives no external funding.

Ethical Consideration: No ethical approval was required.

Abstract

Background:
Cardiopulmonary exercise testing (CPET) provides a comprehensive objective assessment in patients with repaired Tetralogy of Fallot (rTOF). However, the evidence underpinning this practice is scanty as are the mechanisms which drive exercise ability.

Objectives:
To describe the current evidence linking CPET data and prognosis in addition to review the most important determinants of exercise.

Methods:
The preferred reporting items (PRISMA) guidelines were followed. A systematic search of CPET studies, with/without echocardiography was carried out on PubMed MEDLINE, EBM review-Cochrane Database, Wiley Online library and EBM reviews.

Results:
Of 400 studies identified, 21 met the inclusion criteria. 17 articles (81%) were reported in young adults, and 4 articles (19%) in younger group. The sample size ranged from 15 to 875, and the publication year ranged from 2002 to 2019. Mean age was 25±7 years. Overall mean predicted VO_2 peak was 68±2.8% (95% CI.62.3-74%). There was no difference in mean predicted VO_2 between older and younger groups (68±2.7vs 69±2.9,%, p>.05). Peak predicted VO_2 was found to be higher in contemporary studies than historic investigations (76±6vs 59±13,%, p.001). Submaximal measures were rarely reported. Determinants of exercise capacity were reported in 9 studies (43%). Prognostic findings qualitatively suggested that mild exercise intolerance with preserved ventilatory-equivalent for carbon dioxide is associated with better outcomes and lower mortality rate.

Conclusions:
The literature showed a high degree of heterogeneity which limited comparability. Marked reduction in functional capacity in patients with repaired TOF seems to be more dependent on surgical selection and developing technique than advancing age.

Key words: Tetralogy of Fallot; Cardiopulmonary exercise; pulmonary regurgitation; respiratory exchange ratio; ventilatory-equivalent for carbon dioxide; predicted VO_2 peak.

Abbreviation and Acronyms

rTOF= repaired Tetralogy of Fallot

CPET= cardiopulmonary exercise test

VO_2 peak (%)= maximum predicted oxygen uptake

RER= respiratory exchange ratio

VE/VCO2= ventilatory-equivalent for carbon dioxide

VT= ventilatory threshold

OUES= oxygen uptake efficiency slope

PR= pulmonary regurgitation

Unstructured Abstract

This systematic review was conducted to review the evidence linking CPET data and prognosis in patients with repaired TOF. A literature review provided 21 studies that investigated exercise capacity in these patients. There was a marked reduction in exercise capacity with no difference between age groups. Submaximal effort data, determinants of exercise capacity and predictors of adverse outcomes were rarely reported. We concluded that marked reduction in exercise capacity in these patients seems to be more dependent on surgical selection and technique used. These findings should trigger more investigation into how CPET can aid the clinician's decision making for intervention.

Introduction

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease (CHD) and accounts for 10 percent of all forms of CHD (1). The population of adult patients with surgically repaired TOF is increasing and knowledge about how objective exercise assessment can predict adverse late clinical outcomes is still evolving. Although the hemodynamic sequelae after primary repair are often well tolerated during childhood and adolescence, exercise intolerance, arrhythmias, heart failure and premature death are seen frequently in adulthood (2,3). The majority of patients with TOF have been shown to have exercise limitation which worsens overtime (4). Subjective evaluation of symptoms may be a poor guide of exercise intolerance, so exercise testing is routinely performed for an objective assessment (2,3,4,5). There are however no interventional or randomised trials to specifically support this practice. Exercise intolerance in this population is multifactorial and has been shown to relate to pulmonary regurgitation (PR), impaired lung function, chronotropic impairment and ventricular dysfunction (6-11). To what extent each of these factors is responsible for exercise intolerance remains poorly understood (12).

We therefore undertook a systematic review evaluating determinants of cardiopulmonary exercise test performance in this patient group and based on current literature how it can best be used to predict clinical outcomes and plan intervention.

Material and Methods

Systematic review analysis

This review was performed in accordance with the preferred reporting items for systematic reviews (PRISMA) guidelines. The flow diagram in figure 1 demonstrates the literature search based on the PRISMA guidelines.

Inclusion and exclusion criteria

This review was limited to studies published in English. Inclusion criteria were (a) prospectively or retrospectively conducted cohort, cross sectional, single and multicenter studies and (b) CPET included in methodology; (c) both adult and adolescent patients with repaired TOF. Studies excluded from the review were those: (a) without CPET data; (b) other types of exercise test (e.g. Dobutamine exercise); (c) not published in English; (d) non rTOF.

Information sources and search strategy

A comprehensive retrospective search of the literature was conducted using databases including MEDLINE, Pubmed, EBM review- Cochrane Database of systematic review, Wiley Online library and EBM reviews, utilising a combination of the following search keywords: "Tetralogy of Fallot'", "Stress echocardiography", "cardiopulmonary exercise test in TOF with severe pulmonary regurgitation“,” Exercise capacity in TOF “, “Severe pulmonary regurgitation and functional capacity”. There was no limitation on age. The search included all studies between 1990 and 2019.

Study selection and Eligibility criteria

The following steps were performed (figure 1). (1) Identification of titles through database searching. (2) Removal of duplicates. (3) Titles and abstracts screening. (4) Full text sources for further screening. Eligible studies were either retrospective or prospective studies.

Data Extraction

Data collected by one reviewer (S.A) who determined the eligibility of the studies by screening the titles and abstracts of all identified literature and verified by a second reviewer (G.L). To prevent bias, the screening was performed independently. The following data were extracted: first author’s name, country, year of publication, number of patients included, study design, age at CPET, predicted VO_2 peak (%), respiratory exchange ratio (RER), CPET protocol, ventilatory-equivalent for carbon dioxide (VE/VCO2), ventilatory threshold (VT) and oxygen uptake efficiency slope (OUES) when available and the conclusion together with main findings of the study. Because of the wide ranges of age included in the study and many of selected studies have reported oxygen uptake as a percentage of predicted (%), we have chosen to report oxygen uptake as a percentage of predicted VO_2. Older group was defined as studies with participants who were older than 18 years old and younger group who were under that age. Contemporary studies were defined as those published between 2011 to present and historic studies prior 2008.

Statistical Analysis

Studies were divided into (i) those that reported in an adult population and (ii) those reported in a population younger than 18 years old. For the continuous outcome variables, data were presented as mean differences (MD) ± standard deviation. The overall mean of age and different reported exercise parameters in 21 studies were calculated. The overall mean of different exercise parameters in older and younger groups were calculated independently**.** Comparison of mean exercise parameters was evaluated by paired student t-test with $p<.05$, level of significance. Statistical analyses were conducted using SPSS statistics version 23 (IBM corp, London, United Kingdom).

Results

Literature search outcomes

The literature search identified a total of 400 potentially eligible studies. After the exclusion of irrelevant studies, 273 were screened thoroughly though abstract and/or full text. 93 articles were excluded due to duplication. Of 180 articles, 60 articles were excluded, as they did not meet the inclusion criteria. Full text article assessment was performed for 120 articles and 99 articles were further excluded, leading to a total of 21 articles included in this review. Figure 1 shows the PRISMA flow chart for the systematic selection of studies during the literature search.

Characteristics of selected studies

Of the 21 articles, 17 (81%) were reported in adult survivors of TOF(10,11,13-27), while 4 studies (19%) were reported in younger group (5,8,28,29) . 8 studies (38%) were cross-sectional studies(13,19,21,23-27). 12 studies (57%) were cohort studies (5,8,10,11,14-16, 18,20,22,28,29). 6 studies (29%) were conducted prospectively (8,13,16,28,29) and 10 studies (48%) were conducted retrospectively (5,10,11,14,15,17,19,20,22,23). Sample size ranged from 15 to 875, and the publication year ranged from 2002 to 2019. Mean age of included participants ranged from 12 to 34 years. All included studies were single center designed except one big multicenter study with retrospective evaluation (17).

Bicycle ergometry protocol was the most frequently used protocol. Baseline characteristics of the included studies and CPET parameters are shown in table 1.

Cardiopulmonary Exercise Testing Parameters

In total, data was collected on 2239 young patients with repaired TOF with a mean age of 25±7 years. Mean age of older group was 27±4 years in 17 studies in young adults and the mean age of younger group was 13±2 years in 4 studies in adolescents. All 21 articles have reported maximal exercise effort data as predicted VO_2 peak (%). Higher proportion of population had undergone transannular patch repair in 10 studies (48%)(relatively less frequent surgical approach in recent years) (5,8,10,13,16,17,22,26,27,29). Respiratory exchange ratio (RER) was reported in 13 studies (61%) with a mean of 1.18±.09 (5,8,10,13,14,16,17-19,20-23,29). 19 studies (90%) have used a bicycle ergometer protocol in their exercise methodology while only 2 (10%) studies have used treadmill protocol. An overview of the included 21 studies is provided in table 2.

Maximum Oxygen Uptake (VO_2)

Overall mean peak predicted VO_2 in patients with repaired TOF was 68 ± 2.8%, ranged from 40 to 85 %. Despite small individual studies showing a relationship with age (5,11,13,22,28), there was no overall difference in mean predicted VO_2 between older and younger participants (68±2.7 vs 69±2.9, %, $p>.05$) (table 1). Contemporary studies (13-

22,28,29) have demonstrated higher peak predicted VO_2 comparing to historic investigations (5,8,10,11,23-27) (76 ±6 vs 59±13 %, p .001). Among all studies, lower exercise performers were reported in populations where transannular patch (TAP) was used as a surgical approach (reported in 10 studies (48%)) (5,8,10,13,16,17,22,26,27,29). Distribution of exercise capacity in TAP and non-TAP studies (other type of surgery or unknown) is shown in figure 2.

Moderate exercise intolerance (when max VO_2 40 to < 65% of predicted), was observed in 6 studies (29%) (8,10,11,25-27). Mild exercise intolerance (when max VO_2 65 to 80 % of predicted) was observed in 13 studies (62%) (5,13-18,20,22-24,28,29). Borderline exercise intolerance (when max VO_2 81 to 85 % of predicted) was observed in 2 studies (9%) (19,21). The highest mean predicted VO_2 peak was reported in only one study performed by O'Meager et al., 2012 who showed that preserved oxygen consumption in young adults with repaired TOF with mean predicted VO_2 of 85 % (21) (table 2).

Exercise parameters as a predictor of death, arrhythmias and the need of reintervention

The use of CPET to predict cardiac related mortality and the need for reintervention was reported only in two studies included in this review (10%) (17,25). Peak oxygen uptake and V_E/VCO_2 were reported as the most powerful predictors of cardiac related mortality and hospitalisation (25). Poor exercise capacity was associated with increased the risk for death and sustained ventricular arrhythmias (17). Peak oxygen uptake < 36% of predicted value was found to have the highest sensitivity and specificity to predict cardiac-related outcomes and death (sensitivity 89% and specificity 99%) (25). While a cut off value of peak predicted VO_2 of 62 % was identified as an optimal cut -off value for 5-year freedom from death or ventricular arrhythmia (sensitivity 82% and specificity 63%) (17). No studies evaluated whether intervention could influence objective exercise performance.

Sub maximal exercise effort data

Only one study in this review reported OUES in adult patients with repaired TOF with a normal mean value of 90.3 % (normal >80%) (16,30). Minute ventilation (V_E) to carbon dioxide production (VCO_2) slope was reported in ten studies (48%); one in younger group and 9 studies in adults (43%) (13,14,16,17,20-22,35,26,28). The observed mean V_E/VCO_2 slope was normal with a mean value of 29±2.2 (normal < 30) (31). In two studies, V_E/VCO_2 was used as a predictive tool to determine outcomes following pulmonary re-intervention (17,25). A value of V_E/VCO_2 >39 has higher sensitivity to predict cardiac -related mortality and the need for reintervention in this group of patients (sensitivity 89% and specificity 99%) (25). While a value of V_E/VCO_2 >31 are at highest risk of cardiac related events or death (sensitivity 82% and specificity 63%) (17). These values were proposed as a risk model guidance for surgical intervention. Ventilatory threshold (VT) was reported only in two studies (19,20). Minute of ventilation (VE) was reported in five studies (23%) (10,14,24-26).

Determinants of exercise capacity

Hemodynamic determinants of exercise performance were reported in 9 studies (43%). These studies used echocardiography in addition to CPET. Impaired exercise tolerance was mainly explained by a variety of different measured echocardiographic parameters at rest and augmentation during exercise (13-16,19,22,23,26,27). At rest, severe PR and left ventricle (LV)/ right ventricle (RV) dysfunction were reported the most important determinants of exercise capacity in some studies (16,23,26), although this was not observed in all (13-15,19). Reduced LV stroke volume at peak exercise was related to more exercise deterioration in one study (22), while peak RV systolic pressure was associated with exercise impairment in two reports (15,27).

Discussion

CPET has entered routine clinical cardiovascular practice as a reduced VO_2 peak has been associated with poor prognosis in both ischemic heart disease and heart failure assessment (11). This has also been applied to patients with congenital heart disease and in particular those with repaired TOF patients, where CPET is used to predict early mortality and to provide clinically relevant data to determine optimal timing of pulmonary valve replacement (PVR)(11,17,25,32). However, the literature remains unclear about the extent of limitation, the causes of any limitation and there is scant data demonstrating an improvement in exercise performance after PVR.

It has been extensively reported that asymptomatic rTOF patients have exercise intolerance (17,26,27,29,33). Identification of early functional impairment by CPET is intuitively important even though the underlying mechanisms may not be well understood (2,4,5). Most studies included in this review were single-centre cohort studies and few were originally designed for assessing the functional status in these patients. There were significant methodological weaknesses or limitations; for instance, predicted VO_2 values were reported but infrequently with the associated RER. It cannot therefore be verified that these were maximal effort scans; other submaximal measures such as OUES, VT and V_E/VCO_2 were rarely reported. Finally, the majority of the tests were performed using a bicycle ergometer protocol, and although this allows for more accurate blood pressure, electrocardiogram and other physiological measures, treadmill protocol produces higher maximum oxygen uptake (34,35). This finding of rare documentation of submaximal effort in the current evidence was highlighted also in a big recent systematic review in cardiopulmonary exercise test in healthy subjects (30). A summary of CPET studies and their findings in patients with repaired TOF is shown in table 2.

Overall a marked reduction in exercise tolerance and functional capacity was noted in patients with repaired TOF with an overall mean peak predicted VO_2 of 68± 2.8% (95% CI. 62.3- 74 %). 17 adult (81%) studies have shown impaired functional capacity with a mean peak of predicted VO_2 of 68± 2.7% (ranging from 51 to 85 %). 16 of these were single-center studies with either prospective or retrospective design (10,11,13-16,18-27). Mild exercise intolerance was the most reported level of functional capacity in this review (13 studies, 62%). This was in keeping with the only multicenter study that performed by Muller et al., 2015 who have reported mild exercise intolerance with an overall peak of predicted VO_2 of 76 % (17).

Exercise performance in patients with repaired TOF is thought to decline with age, however, we found no difference in mean predicted VO_2 between populations drawn from older and younger age groups suggesting that young patients are equally affected by functional limitation (68± 2.7 vs 69±2.9, %, p>.05)(11, 22). Similar findings were reported in two adolescents' studies included in this review as they have demonstrated an exercise intolerance of 66 and 40% (8, 29). However, Bhatt et al found that in their small but prospectively conducted recent study; there was a better functional capacity with higher performance in younger patients (13). This also has been reported in other two contemporary studies in adolescents (5, 28). In this review, more contemporary studies have shown higher predicted VO_2 peak comparing to historic investigations irrespective of age and this is most likely to be related to an era of more careful surgical selection and contemporary technique used to repair TOF(13-22,28,29) (figure 2). Because of the high level of heterogeneity it is difficult to draw firm conclusions, but our analysis suggests that subsequent exercise tolerance is more a function of surgical technique than a function to age.

Determinants of exercise capacity in patients with Repaired TOF

Due to multifactorial interaction behind the progressive exercise intolerance in adult survivors of TOF, determining the precise relationship between each facet of heart function exercise intolerance is challenging; consequently, the major determinants of exercise capacity in patients with repaired TOF are not yet completely understood (13,23,26,36,37). It has been found that the main determinants of diminished peak VO_2 are: RV/LV function, degree of PR severity (23,26,36), older age at total repair (10,11), age at cardiopulmonary exercise test (10), residual shunt (11), pulmonary arterial hypertension (11), peak heart rate (11), and indexed LV and RV end-diastolic volumes (19). Approximately half of studies, 9 articles (43%) have used echocardiography in addition to CPET. In the literature, there is limited evidence to support the use of stress echocardiography and CPET to better understand RV and LV function in relation to exercise intolerance (37-43). Some studies have demonstrated the limited impact of RV dilation on exercise performance when the biventricular function is preserved (44,45), in contrast to current clinical understanding. Others found that severe PR and RV dysfunction were not predictors of exercise capacity in this population (13,15). These findings are consistent with previous reports that found no relationship between exercise intolerance and pulmonary regurgitation fraction (4,9,46,47). However, these were low powered cross-sectional studies.

Study limitations

Review limitations include cross-sectional cohorts, heterogeneity in reporting functional capacity and the absence of reporting standards. Quality data can be further improved by performing reliability and reproducibility analyses. Large, longitudinal, prospective and randomised studies are needed to determine whether CPET is a valuable investigation for these patients.

Conclusions

We have demonstrated that despite the widespread use of CPET in clinical practice the literature shows a high degree of heterogeneity. It is clear that there is a marked reduction in exercise capacity in young adults with rTOF with a mean peak predicted VO_2 of 68 %. This seems to be more dependent on surgical selection and technique than advancing age. The comparability of the literature was limited by variable techniques and reported parameters. We strongly recommend that to allow comparison of data sets including RER, OUES, V_E/VCO_2 and VT in addition to peak VO_2. Moderate decline in peak VO_2 and high ventilatory-equivalent for carbon dioxide were the best predictors of adverse outcomes. However, despite its widespread use, further investigation into how CPET can aid the clinician's decision making for intervention is needed.

Clinical Implication

The use of CPET to identify patients who are at greater risk for adverse outcomes is clinically relevant. However, only two studies have demonstrated the importance of CPET testing in which the primary end point was VO_2 and V_E/VCO_2 in the other (17,25). For clinical application, these findings from this systematic review suggest that a value of less than 62 % is associated with higher risk of adverse outcomes.

An elevated V_E/VCO_2 in adult survivors of TOF could be associated with higher risk of mortality and hospitalisation (17,22,25). The potential reasons for enhanced ventilatory response in this population to exercise are poorly understood. However, the possible factors that contribute to this slope elevation in these patients are pulmonary blood flow mal-distribution, numerous surgical sternotomies and thoracotomies, and the presence of ventilatory/perfusion mismatch (48). Although the objective value of submaximal measures and their relation to exercise intolerance have been evaluated, these studies are relatively small cross-sectional studies that cannot be generalised (16,17,20,22,25).

Acknowledgment

Funding: This review receives no external funding.

Conflict of interest: The authors declare no conflict of interest.

Ethical consideration: Since this was a systematic review, no ethical approval was required.

References

1. Perloff JK, Marelli AJ. Clinical recognition of congenital heart disease: Elsevier Health Sciences; 2012.
2. Wessel H, Cunningham W, Paul M, Bastanier C, Muster A, Idriss F. Exercise performance in tetralogy of Fallot after intracardiac repair. The Journal of Thoracic and Cardiovascular Surgery. 1980;80(4):582-93.
3. Frigiola A, Hughes M, Turner M, Taylor A, Marek J, Giardini A, et al. Physiologic and phenotypic characteristics of late survivors of tetralogy of fallot repair who are free from pulmonary valve replacement. Circulation. 2013:CIRCULATIONAHA. 113.001600.
4. Rowe SA, Zahka KG, Manolio TA, Horneffer PJ, Kidd L. Lung function and pulmonary regurgitation limit exercise capacity in postoperative tetralogy of Fallot. Journal of the American College of Cardiology. 1991;17(2):461-6.
5. Mahle W, McBride M, Paridon S. Exercise performance in tetralogy of Fallot: the impact of primary complete repair in infancy. Pediatric cardiology. 2002;23(2):224-9.
6. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Circulation. 1995;91(6):1775-81.
7. Sutton NJ, Peng L, Lock JE, Lang P, Marx GR, Curran TJ, et al. Effect of pulmonary artery angioplasty on exercise function after repair of tetralogy of Fallot. American heart journal. 2008;155(1):182-6.

8. Roest AA, Helbing WA, Kunz P, van den Aardweg JG, Lamb HJ, Vliegen HW, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of Fallot repair. Radiology. 2002;223(1):204-11.
9. Meadows J, Powell AJ, Geva T, Dorfman A, Gauvreau K, Rhodes J. Cardiac magnetic resonance imaging correlates of exercise capacity in patients with surgically repaired tetralogy of Fallot. The American journal of cardiology. 2007;100(9):1446-50.
10. Fredriksen PM, Therrien J, Veldtman G, Warsi MA, Liu P, Thaulow E, et al. Aerobic capacity in adults with tetralogy of Fallot. Cardiology in the young. 2002;12(6):554-9.
11. Diller G-P, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, et al. Exercise intolerance in adult congenital heart disease. Circulation. 2005;112(6):828-35.
12. Mueller GC, Sarikouch S, Beerbaum P, Hager A, Dubowy K-O, Peters B, et al. Health-related quality of life compared with cardiopulmonary exercise testing at the midterm follow-up visit after tetralogy of Fallot repair: a study of the German competence network for congenital heart defects. Pediatric cardiology. 2013;34(5):1081-7.
13. Bhatt SM, Elci OU, Wang Y, Goldmuntz E, McBride M, Paridon S, et al. Determinants of Exercise Performance in Children and Adolescents with Repaired Tetralogy of Fallot Using Stress Echocardiography. Pediatric Cardiology. 2019;40(1):71-8.

14. Dłużniewska N, Podolec P, Miszalski-Jamka T, Krupiński M, Banyś P, Urbańczyk M, et al. Effect of ventricular function and volumes on exercise capacity in adults with repaired Tetralogy of Fallot. Indian heart journal. 2018;70(1):87-92.

15. Meierhofer C, Tavakkoli T, Kühn A, Ulm K, Hager A, Müller J, et al. Importance of non-invasive right and left ventricular variables on exercise capacity in patients with tetralogy of fallot hemodynamics. Pediatric cardiology. 2017;38(8):1569-74.

16. Yang M-C, Chen C-A, Chiu H-H, Chen S-Y, Wang J-K, Lin M-T, et al. Assessing late cardiopulmonary function in patients with repaired tetralogy of fallot using exercise cardiopulmonary function test and cardiac magnetic resonance. Acta Cardiologica Sinica. 2015;31(6):478.

17. Müller J, Hager A, Diller G-P, Derrick G, Buys R, Dubowy K-O, et al. 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;196:158-64.

18. Eindhoven JA, Menting ME, van den Bosch AE, Cuypers JA, Ruys TP, Witsenburg M, et al. Associations between N-terminal pro-B-type natriuretic peptide and cardiac function in adults with corrected tetralogy of Fallot. International journal of cardiology. 2014;174(3):550-6.

19. Yap J, Tan R, Gao F, Le T, Zhong L, Go Y, et al. Exercise capacity correlates with ventricle size in adult operated tetralogy of Fallot. European Heart Journal. 2013;34(suppl_1):126.

20. Buys R, Cornelissen V, Van De Bruaene A, Stevens A, Coeckelberghs E, Onkelinx S, et al. Measures of exercise capacity in adults with congenital heart disease. International journal of cardiology. 2011;153(1):26-30.
21. O'Meagher S, Munoz PA, Alison JA, Young IH, Tanous DJ, Celermajer DS, et al. Exercise capacity and stroke volume are preserved late after tetralogy repair, despite severe right ventricular dilatation. Heart. 2012;98(21):1595-9.
22. Kipps AK, Graham DA, Harrild DM, Lewis E, Powell AJ, Rhodes J. Longitudinal exercise capacity of patients with repaired tetralogy of fallot. The American journal of cardiology. 2011;108(1):99-105.
23. Samman A, Schwerzmann M, Balint OH, Tanous D, Redington A, Granton J, et al. Exercise capacity and biventricular function in adult patients with repaired tetralogy of Fallot. American heart journal. 2008;156(1):100-5.
24. Izbicki G, Fink G, Algom A, Hirsch R, Blieden L, Klainman E, et al. Lung function and cardiopulmonary exercise capacity in patients with corrected tetralogy of Fallot. Isr Med Assoc J. 2008;10(8-9):564-7.
25. Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Donti A, et al. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. The American journal of cardiology. 2007;99(10):1462-7.
26. Giardini A, Specchia S, Coutsoumbas G, Donti A, Formigari R, Fattori R, et al. Impact of pulmonary regurgitation and right ventricular dysfunction on oxygen uptake recovery kinetics in repaired tetralogy of Fallot. European journal of heart failure. 2006;8(7):736-43.

27. Norozi K, Buchhorn R, Kaiser C, Hess G, Grunewald RW, Binder L, et al. Plasma N-terminal pro-brain natriuretic peptide as a marker of right ventricular dysfunction in patients with tetralogy of Fallot after surgical repair. CHEST Journal. 2005;128(4):2563-70.
28. Hock J, Häcker A-L, Reiner B, Oberhoffer R, Hager A, Ewert P, et al. Functional outcome in contemporary children and young adults with tetralogy of Fallot after repair. Archives of disease in childhood. 2019;104(2):129-3
29. Fernandes FP, Manlhiot C, Roche SL, Grosse-Wortmann L, Slorach C, McCrindle BW, et al. Impaired left ventricular myocardial mechanics and their relation to pulmonary regurgitation, right ventricular enlargement and exercise capacity in asymptomatic children after repair of tetralogy of Fallot. Journal of the American Society of Echocardiography. 2012;25(5):494-503.
30. Ramos RP, Ota-Arakaki JS, Alencar MC, Ferreira EV, Nery LE, Neder JA. Exercise oxygen uptake efficiency slope independently predicts poor outcome in pulmonary arterial hypertension. European Respiratory Journal. 2014;43(5):1510-2.
31. Dallaire F, Wald RM, Marelli A. The Role of Cardiopulmonary Exercise Testing for Decision Making in Patients with Repaired Tetralogy of Fallot. Pediatric Cardiology. 2017:1-9.
32. Babu-Narayan SV, Diller G-P, Gheta RR, Bastin AJ, Karonis T, Li W, et al. Clinical outcomes of surgical pulmonary valve replacement after repair of tetralogy of Fallot and potential prognostic value of preoperative cardiopulmonary exercise testing. Circulation. 2014;129(1):18-27.

33. Clark AL, Gatzoulis MA, Redington AN. Ventilatory responses to exercise in adults after repair of tetralogy of Fallot. Heart. 1995;73(5):445-9.

34. Astrand P. Measurement of maximal aerobic capacity. Canadian Medical Association Journal. 1967;96(12):732.

35. Pescatello LS, Riebe D, Thompson PD. ACSM's guidelines for exercise testing and prescription: Lippincott Williams & Wilkins; 2014.

36. Cetin I, Tokel K, Varan B, Örün UA, Gökdemir M, Cındık N, et al. Evaluation of right ventricular functions and B□type natriuretic peptide levels by cardiopulmonary exercise test in patients with pulmonary regurgitation after repair of tetralogy of fallot. Journal of cardiac surgery. 2008;23(5):493-8.

37. Cifra B, Dragulescu A, Border WL, Mertens L. Stress echocardiography in paediatric cardiology. European Heart Journal-Cardiovascular Imaging. 2015;16(10):1051-9.

38. Apostolopoulou SC, Laskari CV, Tsoutsinos A, Rammos S. Doppler tissue imaging evaluation of right ventricular function at rest and during dobutamine infusion in patients after repair of tetralogy of Fallot. The International Journal of Cardiovascular Imaging (formerly Cardiac Imaging). 2007;23(1):25-31.

39. Parish V, Valverde I, Kutty S, Head C, Qureshi SA, Sarikouch S, et al. Dobutamine stress MRI in repaired tetralogy of Fallot with chronic pulmonary regurgitation: a comparison with healthy volunteers. International journal of cardiology. 2013;166(1):96-105.

40. Baspinar O, Alehan D. Dobutamine stress echocardiography in the evaluation of cardiac haemodynamics after repair of tetralogy of Fallot in children: negative effects of pulmonary regurgitation. Acta cardiologica. 2006;61(3):279-83.

41. Roche SL, Grosse-Wortmann L, Redington AN, Slorach C, Smith G, Kantor PF, et al. Exercise induces biventricular mechanical dyssynchrony in children with repaired tetralogy of Fallot. Heart. 2010;96(24).
42. Ait-Ali L, Siciliano V, Passino C, Molinaro S, Pasanisi E, Sicari R, et al. Role of stress echocardiography in operated Fallot: feasibility and detection of right ventricular response. Journal of the American Society of Echocardiography. 2014;27(12):1319-28.
43. Frigiola A, Giardini A, Taylor A, Tsang V, Derrick G, Khambadkone S, et al. Echocardiographic assessment of diastolic biventricular properties in patients operated for severe pulmonary regurgitation and association with exercise capacity. European Heart Journal–Cardiovascular Imaging. 2012;13(8):697-702.
44. Davlouros PA, Kilner PJ, Hornung TS, Li W, Francis JM, Moon JC, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. Journal of the American College of Cardiology. 2002;40(11):2044-52.
45. Silvilairat S, Wongsathikun J, Sittiwangkul R, Pongprot Y, Chattipakorn N. Effects of left ventricular function on the exercise capacity in patients with repaired tetralogy of Fallot. Echocardiography. 2011;28(9):1019-24.
46. Wald RM, Haber I, Wald R, Valente AM, Powell AJ, Geva T. Effects of regional dysfunction and late gadolinium enhancement on global right ventricular function and exercise capacity in patients with repaired tetralogy of Fallot. Circulation. 2009;119(10):1370-7.

47. Marx GR, Hicks RW, Allen HD, Goldberg SJ. Noninvasive assessment of hemodynamic responses to exercise in pulmonary regurgitation after operations to correct pulmonary outflow obstruction. The American journal of cardiology. 1988;61(8):595-601.

48. Yang M-C, Chiu S-N, Wang J-K, Lu C-W, Lin M-T, Chen C-A, et al. Natural and unnatural history of tetralogy of Fallot repaired during adolescence and adulthood. Heart and vessels. 2012;27(1):65-70.

Figure Legends

Figure 1. The PRISMA flow chart for the systematic selection of studies

Figure 2. Distribution of exercise capacity in TAP and non-TAP studies

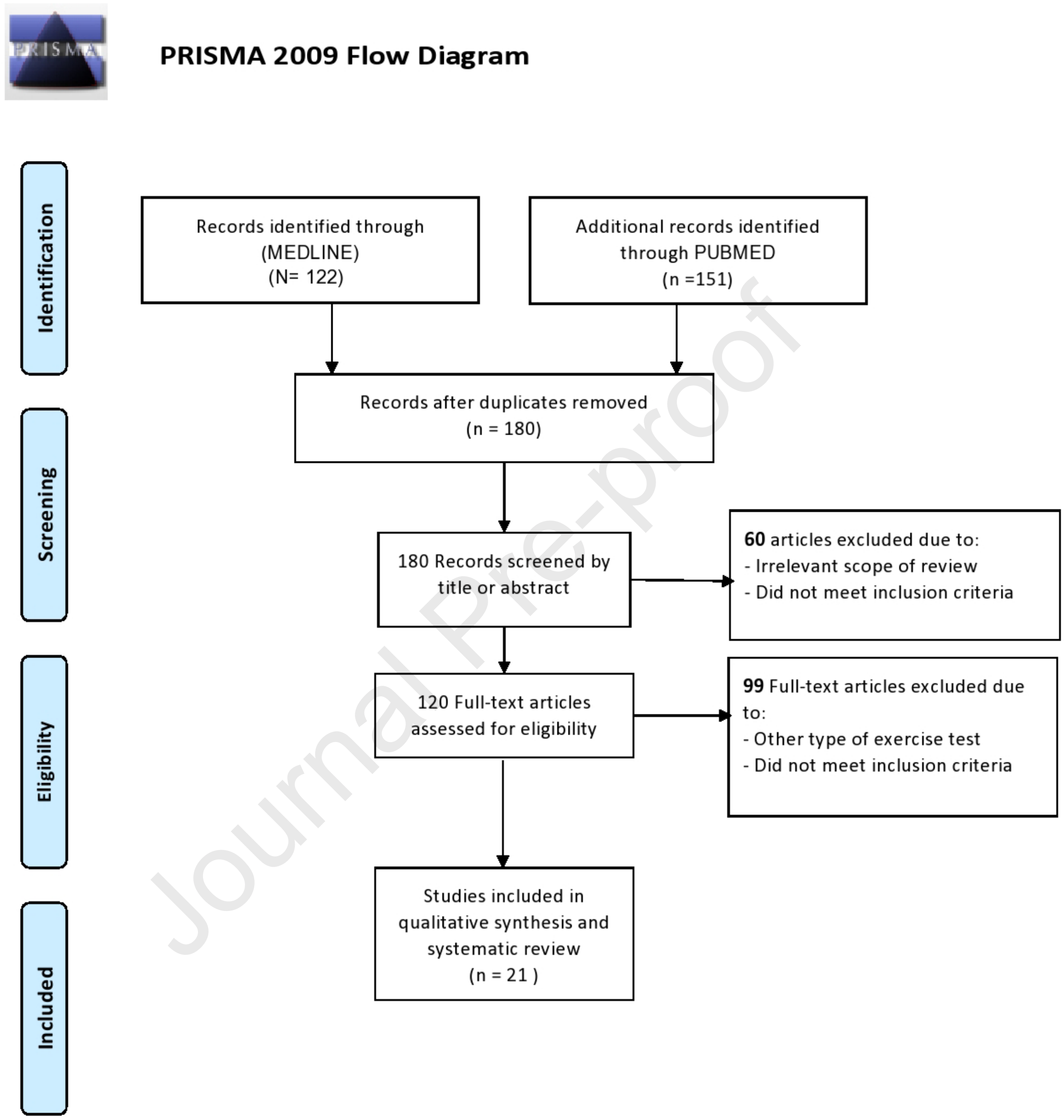
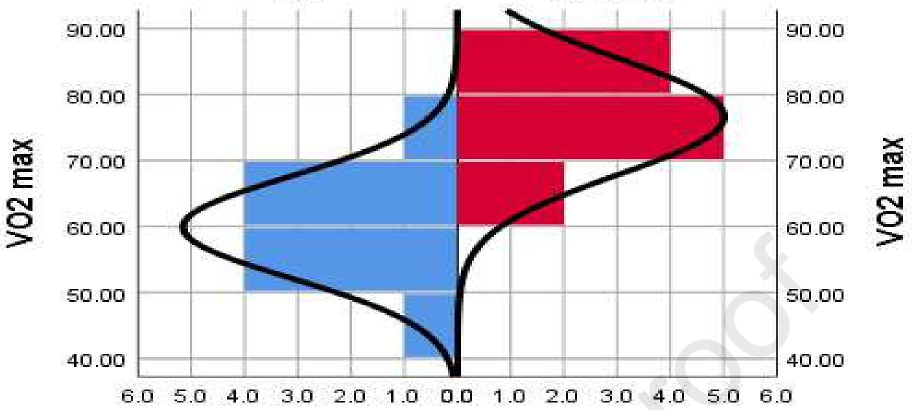

PRISMA 2009 Flow Diagram
Identification
Screening
Eligibility
Included
Records identified through (MEDLINE) (N= 122)
Additional records identified through PUBMED (n =151)
Records after duplicates removed (n = 180)
180 Records screened by title or abstract
60 articles excluded due to:
- Irrelevant scope of review
- Did not meet inclusion criteria
120 Full-text articles assessed for eligibility
99 Full-text articles excluded due to:
- Other type of exercise test
- Did not meet inclusion criteria
Studies included in qualitative synthesis and systematic review (n = 21)

Figure 1



TAP = studies with transannular patch; non-TAP = studies with other type of surgery (e.g. pulmonary valvotomy) or not known.

Figure 2

Table 1. Baseline characteristics of the included studies and CPET parameters

Baseline characteristics	N= 2239*	Older n=17?	Younger n=4?	P value
Mean age±SD , years	25±7	27±4	13±2	**p >.05**
Study type	20, Single Centre One, multicentre	-	-	-
CPET parameters				
Peak predicted VO_2 (% pred)	68±2.8 % CI.(62.3-74%)	68 ± 2.7 %	69±2.9%	**p >.05**
RER max	1.18±.09	1.2±.1	1.1±.1	**p >.05**
VE/VCO_2	29±2.2	29±2.4	29.6#	**p >.05**
OUES (% pred)	90.3 %?	90.3	-	-
Mode of CPET				
Bicycle ergometry protocol (n, %)	19 (90%)	-	-	-
Treadmill (n, %)	2 (10%)	-	-	-

VO_2 (% pred) = maximum predicted oxygen uptake; RER = respiratory exchange ratio; VE/VCO_2 = ventilator-equivalent; OUES = oxygen uptake efficiency slope**.**
*Total number of patients in all studies.
? Number of studies in young adult survivors of TOF repair.
? Number of studies in younger group.
? OUES derived from one adult study.
VE/VCO_2 derived from one study in younger group.

Table 2. Summary of CPET studies and their findings in patients with repaired TOF included in this review.

Author	Country	Study type	N*	Age at CPET (Years)	Peak Vo_2 (%)	RER	VE/VCO_2	OUES	Conclusion
Hock et al., 2019	Germany	Single-centre, prospective cohort	55	13.5±3.8	80.4±16.8	n/a	29.6±3.6	n/a	-Limited exercise capacity -No predictive analysis
Bhatt et al., 2019	USA	Single-centre, cross sectional Prospective	29	18.3± 4.83	75±10	1.24	31±4.2	n/a	-There was low and high exercise performers -Chronotropic response was a predictor of exercise capacity, neither RV or PR
Dluzniewska et al., 2018	Poland	Single-centre, retrospective cohort	52	29±8.9	67.2±16.7	1.1±.2	25.8± 6.2	n/a	-Markedly reduced exercise tolerance -Impaired RV function was associated with exercise intolerance
Meierhofer et al., 2017	Germany	Single-centre, retrospective cohort	132	29±11	77.5±19.3	n/a	n/a	n/a	-Limited exercise capacity -RVSP predicts functional capacity (not RV or PR)
Yang et al., 2015	Taiwan	Single-centre, Prospective cohort	158	29.5± 12.2	68±14	1.09	27.1± 5.3	90.3± 14.1	-Impaired exercise capacity -Normal submaximal measures -PR fraction, LV function and age at repair were the most important exercise determinants
Muller et al., 2015	Germany	Multicentre, retrospective	875	25.5± 11.7	67.6±19.7	1.11±. 16	30.5± 7.3	n/a	-Impaired exercise capacity -Poor exercise capacity was associated with poor outcomes(death and arrhythmias)
Eindhoven et al., 2014	Australia	Single-centre, prospective cohort	177	34±11.8	77±12	1.37	n/a	n/a	-Impaired exercise capacity -No predictive analysis
Yap et al., 2013	Singapore	Single-centre, cross sectional retrospective	36	30±10	83±18	1.1	n/a	n/a	-Near normal exercise capacity -Indexed RV and LV volume were associated with exercise capacity -No predictive analysis
Fernandes et al., 2012	Canada	Single-centre, prospective cohort	124	12±3	66±15	1.01	n/a	n/a	-Impaired exercise capacity -No predictive analysis
Buys et al., 2011	Netherland	Single-centre, retrospective	98	25.6±7.7	74±15	1.13	26.2± 5.5	n/a	-Impaired exercise capacity -Exercise duration and chronotropic response were predictors of all-cause mortality and hospitalisation
O'Meagher et., 2012	England	Single centre, cross sectional	55	26±8.8	85±15	1.27±. 12	28±4	n/a	-Preserved exercise capacity -No predictive analysis

Kipps et al., 2011	USA	Single-centre, retrospective	[illegible]	[illegible]	[illegible]	n/a	[illegible]	n/a	-Low exercise capacity that decline overtime -No predictive analysis
Samman et al.,2008	Canada	Single-centre, cross sectional retrospective	99	34±11	66±13	1.1	n/a	n/a	-Impaired exercise capacity -RV/ LV function were associated with exercise intolerance
Izbicki et al., 2008	Israel	Single-centre, cross sectional	50	29 ±11	75±7	n/a	n/a	n/a	-Mild limitation of exercise capacity -No predictive analysis
Giardini et al.,2007	Italy	Single-centre, cross sectional	118	24±8	58±17	n/a	31.1±4.6	n/a	-Impaired exercise capacity -Peak VO_2 and VE/VCO_2 were the most important predictors for poor outcomes and plan intervention
Giardini et al.,2006	Italy	Single-centre, cross sectional	61	23.1±12.1	54±18	n/a	32±7	n/a	-Impaired exercise capacity -CPET could be used to guide intervention -Severe PR and RV dysfunction were associated with exercise intolerance
Norozi et al.,2005	Germany	Single-centre, cross sectional	50	30.5±1.6	64±3	n/a	n/a	n/a	-Impaired exercise capacity -RV dysfunction was associated with exercise intolerance
Diller et al., 2005	England	Single-centre, retrospective	107	31±11	56±20	n/a	n/a	n/a	-Impaired exercise capacity -Chronotropic response and pulmonary artery pressure were the most important exercise determinants
Fredriksen et al.,2002	Canada	Single-centre, retrospective	168	32±15	51±12	1.1± .10	n/a	n/a	-Impaired exercise capacity -No predictive analysis
Roest et al., 2002	Netherland	Single-centre, prospective cohort	15	17.5±2.5	40±12	1.16±. 05	n/a	n/a	-Impaired exercise capacity -First exercise with MRI -PR and RV Dysfunction were not associated with exercise intolerance
Mahle et al., 2002	USA	Single-centre, retrospective	57	12.5±3.2	80±10	1.12±. 07	n/a	n/a	-Nearly normal exercise capacity

VO_2 (% pred) = maximum predicted oxygen uptake; RER = respiratory exchange ratio; VE/VCO_2 = ventilatory-equivalent; OUES = oxygen uptake efficiency slope; RV = right ventricle; LV = left ventricle; PR= pulmonary regurgitation; RVSP= right ventricular systolic pressure. *N= number of patients in each stud; n/a = not available

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The authors declare no conflict of interest