RBFEx
ISSN Online: 2675-1372

Revista Brasileira de Fisiologia do Exercício

Systematic review

Exercise tolerance on post-repair Tetralogy of Fallot: A systematic review with meta-analysis

Tolerância ao exercício na tetralogia de Fallot pós-reparo: uma revisão sistemática com meta-análise

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ABSTRACT

Introduction: Tetralogy of Fallot (TOF) is the most prevalent cyanotic congenital heart disease, representing around 10 to 15% of congenital heart diseases. The treatment of TOF is done through the surgical repair of cardiac anatomic anomalies. However, even after complete correction in TOF, there is a difference in cardiorespiratory capacity between people with corrected TOF and their healthy peers. **Objective:** To compare the cardiorespiratory capacity of people with and without TOF through specialized literature. **Methodology:** This is a systematic review with meta-analysis registered in Prospero under the number: CRD42020205264. Searches were carried out in the Medline databases via PubMed, PEDro and SciELO by crossing the Health Sciences Descriptors (DeCS) and Medical Subject Headings (Mesh): ((Fallot Tetralogy) AND (exercise)), without temporal or linguistic restrictions. **Results:** Seven studies were selected for the qualitative synthesis, 3 were included for the meta-analysis where there was attenuation of maximum oxygen consumption (-6.56 [95%CI: -11.24; -1.89] and heart rate maximum (-21.47 [CI95%: -40.09; -2.85]) of people with corrected TOF compared to their healthy peers. **Conclusion:** Individuals with TOF, even after surgical repair, have lower tolerance during specific exercise tests.

Keywords: Fallot tetralogy; physical exercise; congenital heart disease; exercise physiology.

RESUMO

Introdução: A tetralogia de Fallot (TOF) é a cardiopatia congênita cianótica mais prevalente, representando cerca de 10 a 15% das cardiopatias congênitas. O tratamento da TOF é feito através do reparo cirúrgico de anomalias anatômicas cardíacas. Porém, mesmo após correção completa no TOF, há diferença na capacidade cardiorrespiratória entre pessoas com TOF corrigida e seus pares saudáveis. **Objetivo:** Comparar a capacidade cardiorrespiratória de pessoas com e sem TOF por meio da literatura especializada. **Metodologia:** Trata-se de uma revisão sistemática com meta-análise registrada no Prospero sob o número: CRD42020205264. As buscas foram realizadas nas bases de dados Medline via PubMed, PEDro e SciELO por meio do cruzamento dos Descritores em Ciências da Saúde (DeCS) e Medical Subject Headings (Mesh): ((Fallot Tetralogy) AND (exercise)), sem restrições temporais ou linguísticas. **Resultados:** Sete estudos foram selecionados para a síntese qualitativa, 3 foram incluídos para a metanálise onde houve atenuação do consumo máximo de oxigênio (-6,56 [IC95%: -11,24; -1,89] e da frequência cardíaca máxima (-21,47 [IC95 %: -40,09; -2,85]) de pessoas com TOF corrigida em comparação com seus pares saudáveis. **Conclusão:** Indivíduos com TOF, mesmo após reparo cirúrgico, apresentam menor tolerância durante testes de exercício específicos.

Palavras-chave: Tetralogia de Fallot; exercício físico; cardiopáticos congênitos; fisiologia do exercício.

Received January 4, 2024; accepted March 14, 2024.

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Introduction

Tetralogy of Fallot (TOF), also known as "blue baby disease", is the most prevalent cyanotic congenital heart disease, representing around 10 to 15% of congenital heart diseases [1]. The anomalies present in TOF consist of: ventricular septal defect, aortic dextroposition, pulmonary stenosis and right ventricular hypertrophy, the latter as an adaptive response to pulmonary valve stenosis.

The main findings in the assessment of patients with TOF are cyanosis and heart murmur, both of which present with greater intensity in the first months of life. Cyanosis is a consequence of pulmonary valve stenosis, responsible for right ventricular outflow obstruction, minimizing blood flow to the pulmonary circulation, favoring hypoxemia. In addition, on cardiac auscultation, the presence of a protosystolic murmur is perceptible, resulting from valvular stenosis [2].

The treatment of TOF is performed through the surgical repair of anatomical changes, which is the safest measure to reestablish cardiovascular function, performed early. Surgical correction can be performed in the first year of life and can prevent progressive chronic hypoxemia and the risk of hypoxemic crises [3]. The presence of symptoms related to hypoxemia is an indication for surgical treatment in children, regardless of age or weight. It is estimated that at least 90% of surgically operated patients survive until the age of 30 years or more [4]. In addition, in children not surgically corrected for TOF, the risk of death in the first year is 44%, 51% up to 3 years and 76% up to 10 years [5].

When we think about survival, functional capacity, measured by tolerance to exertion, is an excellent indicator that allows measuring tolerance to activities of daily living and the risk of complications of cardiorespiratory origin [6]. Even after surgical correction, people with TOF may present limitation of cardiorespiratory capacity [7,8] and, if this finding is proven, this point will be a warning for professionals who prescribe physical exercise for this public, as failure to observe such details can result in prescription error and consequent iatrogenic effects through physical exercise. Therefore, the aim of the present review is to compare the cardiorespiratory capacity of surgically corrected TOF people and their healthy peers.

Methods

This is a systematic literature review study carried out in accordance with the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [9]. This review was registered on the PROSPERO platform with code CRD42020205264.

Searches were carried out in the following databases: MEDLINE via PubMed, PEDro and SciELO with the crossings of the Health Sciences Descriptors (DeCS) and Medical Subject Headings (Mesh): ((Fallot Tetralogy) AND (exercise)) and their synonyms as described in chart 1. There was no temporal or linguistic restriction, with the last search carried out in november 2023.

Chart 1 - Search strategy

#1	#2
(Tetralogy of Fallot) OR Tetralogy, Fallot's) OR Tetralogy, Fallot) OR Tetralogy, Fallots) OR Fallot's Tetralogy) OR Fallot Tetralogy) OR Fallots Tetralogy)	(Exercise Test) OR (Exercise Tests)) OR (Test, Exercise)) OR (Tests, Exercise)) OR (Physical Fitness Testing)) OR (Fitness Testing, Physical)) OR (Testing, Physical Fitness)) OR (Arm Ergometric Test)) OR (Arm Ergometry Tests)) OR (Ergometry Test, Arm)) OR (Ergometry Tests, Arm)) OR (Test, Arm Ergometry)) OR (Tests, Arm Ergometry)) OR (Fitness Testing)) OR (Fitness Testings)) OR (Testing, Fitness)) OR (Cardiopulmonary Exercise Test)) OR (Cardiopulmonary Exercise Tests)) OR (Exercise Test, Cardiopulmonary)) OR (Exercise Tests, Cardiopulmonary)) OR (Test, Cardiopulmonary Exercise)) OR (Tests, Cardiopulmonary Exercise)) OR (Step Test)) OR (Step Tests)) OR (Test, Step)) OR (Tests, Step)) OR (Stress Test)) OR (Stress Tests)) OR (Test, Stress)) OR (Tests, Stress)) OR (Treadmill Test)) OR (Test, Treadmill)) OR (Tests, Treadmill)) OR (Treadmill Tests)) OR (Eurofit Test Battery)) OR (Eurofit Test Batteries)) OR (Test Battery, Eurofit)) OR (EuroFit Tests)) OR (EuroFit Test)) OR (Test, EuroFit)) OR (Tests, EuroFit)) OR (European Fitness Testing Battery)) OR (Bicycle Ergometry Test)) OR (Bicycle Ergometry Tests)) OR (Ergometry Test, Bicycle)) OR (Ergometry Tests, Bicycle)) OR (Test, Bicycle Ergometry)) OR (Tests, Bicycle Ergometry)
#1 AND #2	

Selection of articles

Two experienced reviewers search the databases and select the most relevant articles from the title and abstract observing the PICOS question established in Table I. In the first screening, all studies were included and in the final selection, cases of disagreement were taken to a third independent reviewer who judged inclusion by the research question.

Table I - PICOS questions

Participants/population	Children from 6 years old, up to young adults (up to 40 years old)
Intervention	Physical exercise test, cardiopulmonary testing or ergospirometry
Comparator(s)/control	healthy people
Main Outcome(s)	VO_{2max}, Heart rate, blood pressure
Study	Cross-sectional

Eligibility criteria

Cross-sectional studies that performed an exercise test demonstrating exercise capacity in a TOF population compared to healthy controls were included. The entries of studies that present a heterogeneous sample (other congenital heart diseases) were also allowed, but that allow the identification and extraction of specific data for TOF.

Methodological quality of evidence

Again, they were examined by two independent reviewers and compared at the end of the process, differences were discussed to find consensus. As an assessment tool, the Newcastle Ottawa scale was used to assess the risk of bias in observational studies. The scale is composed of 7 items that provide a final score of 9. Among the components of the scale are the sample selection criteria, quality of comparison and outcomes.

Results

We found 375 studies, of which 7 studies involving a total of 210 with TOF and 262 controls were selected for quantitative synthesis. The study selection process is shown in Figure 1. The characteristics of the sample and ergometers used in the studies can be found in Table II.

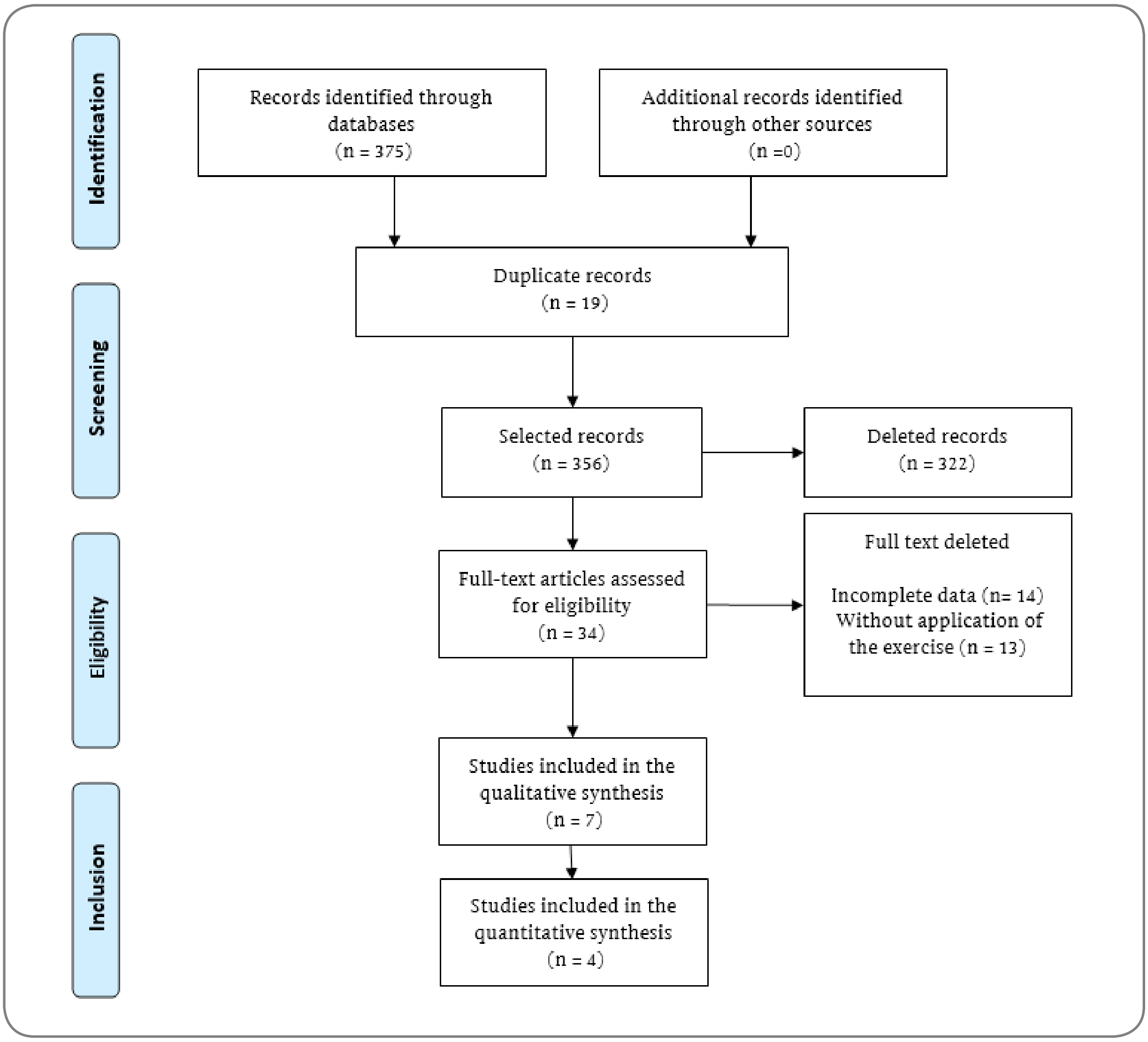


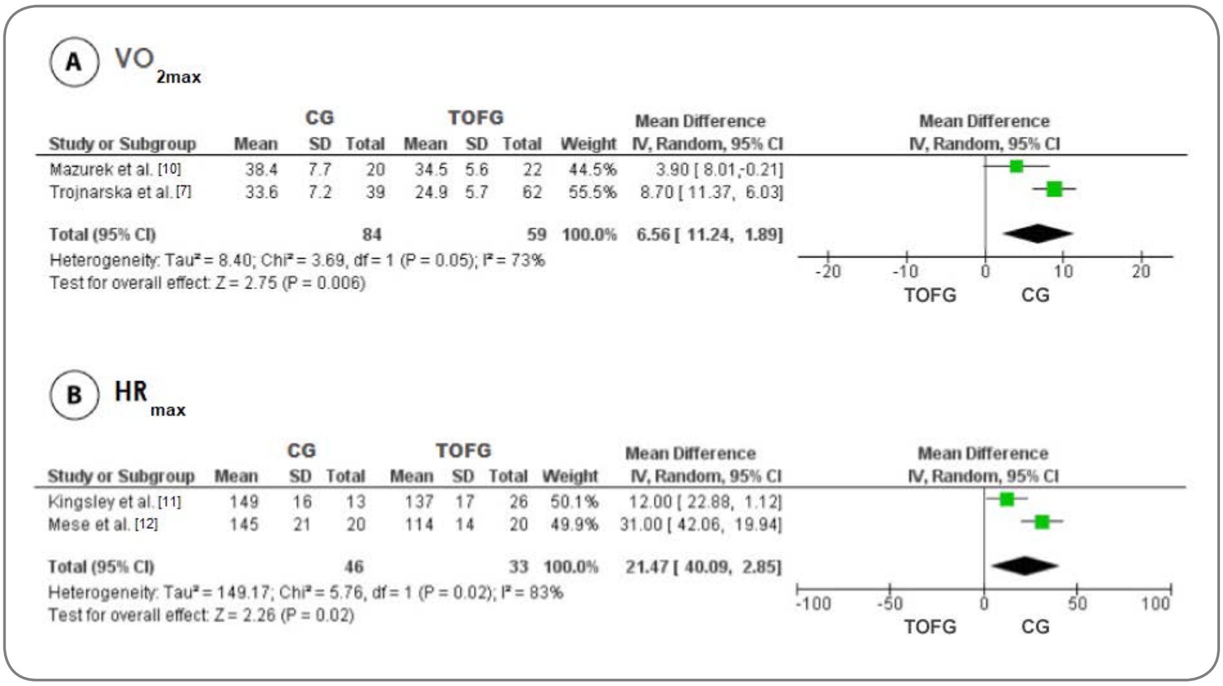
Figure 1 - Study selection flowchart

Tabele II - Characteristics and results of the studies

Author	objective	Population	Test applied	Results
Trojnarska *et al.* 2009 [7]	Assess exercise capacity and B-type natriuretic peptide in CC.	TOFG: n(62); Age: 29.7 ± 9.3 years; 30 women. CG: n(39); Age: 35.8±9.3 years; 22 women.	Bruce protocol on a treadmill, limited by symptoms.	**VO_{2max}** (mL/kg/min) (p<0.001): - TOFG 24.9 ± 5.7; - CG 33.6 ± 7.2;
Norozi *et al.* 2005[8]	To determine physical capacity of children with CC correction.	TOFG: n(23); Age: 8.2 ± 2.0; 11 women. CG: n(98); Age: 7.8 ± 1.8; 49 women.	Test on an exercise bike adapted for children, with 80rpm and progressive load (1 Watt every 10sec).	**Duration** (min) (P < 0.01): - TOFG: 8.45 (7.4-9.3); - CG: 10(9.5-10.5). **Max work** (P < 0.005): - TOFG: 63 (55-71); - CG: 78 (74-81). **Total work** (minute) (P < 0.005): - TOFG: 392 (310-474); - CG: 533 (490-577).
Mazurek *et al.* 2016 [10]	To compare exercise tolerance in children with corrected congenital heart disease.	TOFG: n(22); Age: 14.00 ± 2.72; n women not informed. CG: n(20); Age: 14.90 ± 2.48; n women not informed.	Ergospirometry on a treadmill with RAMP protocol.	**VO_{2max}** (mL/kg/min) (P = 0.041): - TOFG 34,5 ± 5,6; - GC: 38,4 ± 7,7.
Kingsley *et al.* 2018 [11]	Check RV contractility and patients with corrected TOF and pulmonary regurgitation	TOFG: n(26); Idade: 30 ± 12; 6 mulheres. GC: n(13); Idade: 29 ± 10; 11 mulheres.	Bruce protocol on treadmill.	**Duration of the test** (sec) (P = 0.02): - TOFG: 685±162; - CG: 802±108; **HRpeak** (bpm) (P = 0.016): - TOFG: 137±17; - CG: 149 ± 16.
Mese *et al.* 2017 [12]	Check ventricular strain during exercise	TOFG: n(20); Age: 13.5±0.3 years; 5 women. CG: n(20); 13.9 ± 0.3 years; 6 women.	cycle ergometer	***HR_{Max}** (bpm) (P < 0.001): - TOFG 114 ± 14bpm; - CG 145 ± 21bpm; *Not a maximum test.
YapJ *et al.* 2014 [13]	Relate exercise capacity and MRI.	TOFG: n(36); Age: 25.2 (19.5 - 31.7); 7 women. CG: n(30); Age 27.8 (21.0 - 32.8); 6 women.	Treadmill test with fixed speed and gradual incline of the treadmill to fatigue (Borg: 18/20).	**SBP peak** (mmHg) (p=0.007): - TOFG: 177(150-184); - CG: 192(168-210). **METs** (p<0.001): - TOFG 7.3(7.1-9.4); - CG 9.9(8.6-11.7); **VO_{2max}** (ml/kg/min) (p<0.001): - TOFG 29.2 (25.5-33.0); - CG: 34.5(30-41).
Marcuccio E *et al.* 2012 [14]	To assess non-invasive CI and SV during rest and exercise in children with repaired TOF	TOFG: n(21); Age: 15 (11–17) years; 8 women. CG: n(42); Age: 5 (11–17) years; 16 women.	Bruce protocol on treadmill, up to 90% of pre-dicted HRmax (220-age).	**VO_{2max}** (P não significativo): - TOFG: 35.8 (23.8–47.8); - GC: 37.4 (24.1–50.7). **Cardiac index** (p = 0.003): - TOFG: 7 (4–10); - GC: 8.3 (6.3–10.3);.

bpm = beats per minute; CC = Congenital heart disease; CG: Control group; CI: Cardiac index; HR_{max} = Maximum heart rate; METs= Metabolic equivalents; TOFG = Tetralogy Group; rpm = revolutions per minute; VO_{2max} = Maximum oxygen consumption

Two studies were included for the meta-analysis evaluating maximal oxygen consumption (VO_{2max}) and the same amount to assess maximal heart rate (HR_{max}), shown respectively in Figure 2A and 2B. The data suggest a reduction in VO_{2max} and HR_{max} achieved during exercise. However, such findings must be analyzed with caution, considering the low number of studies involved, the high degree of heterogeneity found by the inconsistency test[2] and the differences between the studies (Age of the sample, type of ergometer used and the nature of the stress test: maximum or submaximal).



CG = Control group; TOFG = Tetralogy of Fallot group

Figure 2 - (A) Meta-analysis of maximal oxygen consumption (VO_{2max}). (B) Meta-analysis of Maximum Heart Rate (HR_{max})

The methodological quality of the studies ranged from 7 to 9 points and can be consulted in the Table III.

Table III - Methodological quality: Newcastle-Ottawa Scale

Study	Trojnarska *et al.* 2009 [7]	Norozi *et al.* 2005 [8]	Mazurek *et al.* 2016 [10]	Kingsley *et al.* 2018 [11]	Mese *et al.* 2017 [12]	Yap J *et al.* 2014 [13]	Marccucio E *et al.* 2012 [14]
Research design	case control	retrospective analysis	case control	case control	prospective observational	retrospective analysis	case control
Selection							
Sample representativeness	0	0	0	0	0	0	0
Sample size	0	0	0	0	0	0	0
Selection of controls (non-respondents)	1	1	1	1	1	1	1
Determination of exposure - risk factor	2	2	2	2	2	2	2
Comparation							
Adjustment for confounders	2	2	2	2	2	2	2
Outcome							
Outcome assessment	2	2	2	2	2	2	2
Statistical test	1	1	1	1	1	1	1
Total	7/9	7/9	7/9	7/9	7/9	7/9	7/9

Discussion

This systematic review with meta-analysis of observational studies showed that individuals with TOF, even after surgical repair, have lower exercise tolerance when compared to their peers without TOF. The meta-analysis allowed us to observe attenuations in the values of VO_{2max} [7,10] and HR_{max} [11,12] during the maximum and submaximal tests. In addition, the qualitative synthesis reported shorter exercise tolerance time [8,11].

The VO_{2max} was the main indicator in the studies analyzed to assess exercise capacity, showing the body's aptitude of the control groups and the TOF group to capture, conduct and metabolize oxygen, providing objective information about the clinical condition and the factors that limit exercise tolerance. The most relevant predictors that induced poor VO_{2max} quality were: low HR_{max} at peak exercise [11], induced by insufficient chronotropic response; depressed ventilatory function; worst functional classification by the New York Heart Association (NYHA); pulmonary hypertension and cyanosis [7,10].

The study by Yap J *et al.* [13], evaluating 36 patients with corrected TOF, showed that exercise capacity is directly related to systolic stroke volumes for both ventricles. Two adaptations are possible in the face of ventricular overload: Hypertrophy or dilation of heart chambers. In the presence of dilation, the force of ventricular contraction is depressed and, in people with OFT, this finding implies a reduction in O_2 saturation. Kingsley *et al*. [11] and Trojnarska *et al*. [7] demonstrated that patients with RV dilatation were more likely to have worse RV contractile reserve and also showed that exercise tolerance time was shorter (685 ± 162 vs 802 ± 108 sec, P = 0.02).

The more complex the heart defect (generating RV overload), the greater the deficit in exercise capacity in people with TOF [8]. In this context, high-risk patients, with lower physical capacity and more symptomatic, should participate in training sessions supervised [15]. In addition to monitoring blood pressure, heart rate and perceived exertion, it is necessary that the exercise prescription be performed in a personalized way, considering the limitations pointed out in this study.

Among the limitations of this study are the scarcity of studies included in the meta-analysis, possible bias in sample selection and the high heterogeneity of the studies. The low number of research on this rare condition makes it impossible to carry out a deeper analysis, for example, of publication bias, as well as the reporting of sample selection impacts the confidence of the findings. Furthermore, we initially planned to study maximum oxygen consumption as the main outcome, however, a considerable portion did not address it, which made us monitor secondary outcomes related to cardiorespiratory capacity, such as heart rate and blood pressure. Regarding the high heterogeneity present in the meta-analysis, this result can be attributed to the difference between the evaluation protocols and age of the samples.

Furthermore, we emphasize that the scarcity of clinical trials demonstrating the effects of physical exercise programs in the medium (months) and long term (years) make it difficult for professionals to make decisions. We then reinforce the importance of such research and look to implement already known strategies (physical exercise on a treadmill and bicycle) as well as experiments such as inspiratory muscle training [16] and handgrip [17], given their importance in cardiovascular rehabilitation by promoting a reduction in of metaboreflex and cardiovascular conditioning, respectively.

Conclusion

Exercise tolerance is decreased in people with surgically corrected tetralogy of Fallot. Attenuated measures in maximal oxygen consumption, maximal heart rate and tolerance time to maximal and submaximal tests, point to worse cardiorespiratory function. Therefore, the importance of this finding in the individualization of the exercise prescription by professionals working with this group in cardiovascular rehabilitation.

Conflict of interests
The authors did not report any potential conflict of interest.

Financing
There was no funding for this work.

Author´s contribution
Conception and design of the research: Sacramento MS, Cedraz TF, Moura MS; **Data acquisition:** Cedraz TF, Moura MS; **Data analysis and interpretation:** Sacramento MS, Cedraz TF, Moura MS; **Manuscript writing:** all authors; **Critical review of the manuscript for important intellectual content:** Sacramento MS, Petto J.

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