INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Exercise training in patients with corrected tetralogy of Fallot: A protocol for systematic review and meta-analysis

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Review question / Objective: **In this study, we will conduct a systematic review and meta-analysis to evaluate the effectiveness and safety of exercise training on patients with corrected ToF.**
Condition being studied: **Previous studies have compared the effects of exercise on cardiopulmonary function in patients with ToF. These original studies show that daily physical exercise in children with ToF has a positive effect, and there is an interaction between daily physical activity and cardiopulmonary adaptation. However, the effects of exercise training on vascular function and cardiac autonomic nervous system are still elusive. Whether exercise will lead to adverse cardiac remodeling, which will lead to cardiac enlargement and cardiac function decline. In addition, the specific effects of different intensities of exercise training are not yet supported by definite synthesis evidence.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 May 2021 and was last updated on 01 May 2021 (registration number INPLASY202150006).

INTRODUCTION

Review question / Objective: **In this study, we will conduct a systematic review and meta-analysis to evaluate the effectiveness and safety of exercise training on patients with corrected ToF.**

Rationale: **The birth prevalence of congenital heart disease (CHD) had gradually risen to the current 9.4 cases per 1000 live births, with an increase of 10% over ten years ago. Improvements in surgical practice and intervention had resulted in a significant reduction in CHD mortality. The number of deaths due to**

CHD in 2017 was estimated with a decrease of 34.5% from the estimated in 1990. The decline in mortality had also led to an estimated 12 million patients with CHD worldwide in 2017, an increase of 18.7% from 1990. In recent years, the long-term prognosis of patients with CHD has been greatly increased. With all improvements in care, it might be predicted that adults with CHD will eventually grow to an estimated 75 000 patients per ten million residents. Current public health guidelines recommend that children and adults perform moderate to vigorous exercise for ≥60 minutes a day, even in patients with CHD after surgery. Exercise-based cardiac rehabilitation is widely used in patients with acquired ischemic heart disease or dilated cardiomyopathy, and has been shown to improve aerobic exercise capacity, relieve symptoms, reduces the long-term risks associated with heart failure, and improve the survival rate of these patients. However, many patients with congenital heart disease do not exercise. This may be partly due to concerns about the negative effects of exercise on their hearts and the overprotection of these children by their parents. In addition, physicians who care for these patients are reluctant to encourage these patients to exercise, and often ignore the discussion of this issue. These patients have limited understanding of adverse cardiac events during exercise and the impact of exercise on cardiac remodeling, which may hinder the implementation of these public health guidelines. Among all patients with CHD, those with tetralogy of Fallot (ToF) are most likely to develop heart failure, and it can be considered to benefit most from exercise training. Patients with ToF can live a relatively normal life and grow to adulthood after surgical repair in childhood. Many studies have reported that in patients with modified ToF, their exercise capacity, blood vessel and cardiac autonomic nerve function are still damaged, and their health-related quality of life may be reduced. Compared with healthy peers, these patients have lower aerobic exercise ability. Residual cardiopulmonary disease, sedentary, avoidance of physical activity, and a lack of physical activity lifestyle are thought to be responsible for these differences. Exercise training can be expected to offset these damages.

Condition being studied: Previous studies have compared the effects of exercise on cardiopulmonary function in patients with ToF. These original studies show that daily physical exercise in children with ToF has a positive effect, and there is an interaction between daily physical activity and cardiopulmonary adaptation. However, the effects of exercise training on vascular function and cardiac autonomic nervous system are still elusive. Whether exercise will lead to adverse cardiac remodeling, which will lead to cardiac enlargement and cardiac function decline. In addition, the specific effects of different intensities of exercise training are not yet supported by definite synthesis evidence.

METHODS

Search strategy: #1 "Heart Defects, Congenital" [Mesh] OR "Tetralogy of Fallot" [Mesh] #2 "congenital heart defect" [Title/Abstract] OR "congenital heart disease" [Title/Abstract] OR "heart abnormality" [Title/Abstract] OR "congenital heart defects" [Title/Abstract] OR "congenital heart diseases" [Title/Abstract] OR "heart abnormalities" [Title/Abstract] #3 ("tetralogy" [Title/Abstract] OR "trilogy" [Title/Abstract] OR "syndrome" [Title/Abstract]) AND "fallot*" [Title/Abstract] #4 #1 OR #2 OR #3 #5 "Exercise" [Mesh] OR "Exercise Therapy" [Mesh] OR "Exercise Movement Techniques" [Mesh] OR "Physical Exertion" [Mesh] OR "Physical Fitness" [Mesh] OR "Physical Therapy Modalities" [Mesh] OR "Physical Endurance" [Mesh] OR "Resistance Training" [Mesh] OR "rehabilitation" [Mesh] OR "Walking" [Mesh] OR "Bicycling" [Mesh] #6 "rehabilitation" [Title/Abstract] OR "exercise*" [Title/Abstract] OR "physical therap*" [Title/Abstract] OR "physical training" [Title/Abstract] OR "physiotherap*" [Title/Abstract] OR "resistance training" [Title/Abstract] OR "fitness" [Title/Abstract] OR "aerobic*" [Title/Abstract] OR

"endurance" [Title/Abstract] OR "treadmill*" [Title/Abstract] OR "walking" [Title/Abstract] OR "bicycling" [Title/Abstract] OR "quality of life" [Title/Abstract] #7 #5 OR #6 | #8 #4 AND #7.

Participant or population: Patients after surgical repair of ToF, regardless of gender and age. Patients with ventricular outflow tract obstruction with a Doppler derived peak >60 mmHg were excluded.

Intervention: The intervention group was defined as receiving exercise-based cardiac rehabilitation training. According to previous studies, exercise rehabilitation needs to meet three times a week, at least one hour of planned aerobic exercise each time, and persist for two months. We do not impose other restrictions on higher-intensity exercise training programs.

Comparator: The control group did not receive an exercise-based cardiac rehabilitation training program, and just chose a normal daily lifestyle.

Study designs to be included: Randomized and nonrandomized controlled studies will be both included, and related systematic reviews or meta-analysis will be also attended for retrieving their applicable reference.

Eligibility criteria: Patients after surgical repair of ToF, regardless of gender and age. Patients with ventricular outflow tract obstruction with a Doppler derived peak >60 mmHg were excluded. The intervention group was defined as receiving exercise-based cardiac rehabilitation training. According to previous studies, exercise rehabilitation needs to meet three times a week, at least one hour of planned aerobic exercise each time, and persist for two months. We do not impose other restrictions on higher-intensity exercise training programs. The control group did not receive an exercise-based cardiac rehabilitation training program, and just chose a normal daily lifestyle. Randomized and nonrandomized controlled studies will be both included, and related systematic reviews or meta-analysis will be also attended for retrieving their applicable reference.We will include studies with language of English or Chinese, and there will be no restrictions on the year of publication and publication status.

Information sources: We will perform a systematic search via PubMed, EMbase, the Cochrane Library, Web of Science, CBM, CNKI, WanFang Data, and VIP. Besides, the reference lists of included studies and other relevant articles will be retrieved for supplement.

Main outcome(s): The outcomes of our study including cardiopulmonary fitness, disease-specific biomarkers (lipid status, N terminal pro B type natriuretic peptide, and fibrinogen levels), cardiac autonomic function (heart rate variability and post-exercise heart rate recovery), and health-related quality of life.

Data management: The retrieved articles from the databases will be exported to EndNote X9 Thomson Reuters (Scientific) LLC Philadelphia, PA) software for duplicate removal and further categorization. Two authors will independently screen the titles and abstracts, than to determine the preliminary inclusion of systematic reviews according to the eligibility criteria. While insufficient data are available or where there is any uncertainty in the abstract, the full-text will be retrieved. Any differences in selection will be resolved through discussion to reach a consensus or by adjudicating with a third reviewer. We will record the excluded articles and the reasons for their exclusion. If necessary, we will get additional information for unclear or doubtful data from the corresponding authors by email.

Quality assessment / Risk of bias analysis: We assessed risk of bias of included randomized studies according to the Cochrane 'Risk of bias' assessment tool version 2 (RoB2), including 1) bias arising from the randomization process, 2) bias due to deviations from intended interventions, 3) bias due to missing

outcome data, 4) bias in measurement of the outcome, and 5) bias in selection of the reported result. We will assess risk of bias as low, high, or unclear risk of bias. The risk of bias of included nonrandomized studies will be assessed according to the tool named Risk Of Bias in Non-randomized Studies - of Interventions (ROBINS-I), which is divided into seven domains including 1) bias due to confounding (preintervention), 2) bias in selection of participants into the study (preintervention), 3) bias in classification of interventions (at intervention), 4) bias due to deviations from intended interventions (postintervention), 5) bias due to missing data (postintervention), 6) bias in measurement of outcome (postintervention), and 7) bias in selection of the reported result (postintervention), while finally with an assessment of overall risk of bias. The risk of bias will be evaluated as low, moderate, serious, critical risk of bias, and no information. The risk of bias assessment will be completed by two independent reviewers, and disagreements will be resolved by a third reviewer.

Strategy of data synthesis: We processed data in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. Revman 5.4 (Nordic Cochrane Centre, Denmark) will be used to complete the meta-analysis and generate forest plots. We expressed dichotomous outcomes as risk ratios (RR), and calculated 95% confidence intervals (CI) for each study. For continuous variables, we compared net changes (that is intervention group minus control group differences) and calculated mean difference (MD) and 95% CI for each study. We sought missing data from investigators to obtain key information or missing numerical outcome data where possible. If SDs for outcomes were not reported and were not provided by study authors, then we imputed these values from data within the trial using methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

Subgroup analysis: In this study, year of publication, country of corresponding author, type of study design, mean age, training intensity, and length of exercise-training time will be considered and designed for subgroup analysis to find the possible sources significant heterogeneity.

Sensitivity analysis: We need to solve heterogeneity because it is only when the included studies have the least heterogeneity, the credibility of the synthesized effect size is high, and sensitivity and subgroup analyses are the most common approaches used to solve heterogeneity. If the results of meta-analysis are positive and the number of included studies is over three, we will analyze the sensitivity using STATA 15.0 software. The sensitivity analysis is performed by excluding study one by one. The sensitivity is low and the results are of stability and reliability if there are no significant changes that appear in the results before and after the exclusion; if not, it indicates a high sensitivity and unstable result.

Language: We will include studies with language of English or Chinese.

Country(ies) involved: China.

Keywords: exercise training; tetralogy of Fallot; congenital heart disease; systematic review; meta-analysis.

Dissemination plans: The results of this systematic review and meta-analysis will be submitted to a peer-reviewed journal for publication.

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