Regional Ventricular Performance and Exercise Training in Children and Young Adults After Repair of Tetralogy of Fallot
Randomized Controlled Pilot Study

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Background—Public-health guidelines recommend patients with congenital heart disease to exercise. Studies have shown that patients with congenital heart disease can improve physical exercise capacity. The effect of training on regional ventricular performance has hardly been studied. We performed a pilot study to assess whether an exercise training program would result in adverse changes of regional ventricular performance in patients with corrected tetralogy of Fallot.

Methods and Results—Multicenter prospective randomized controlled pilot study in patients with tetralogy of Fallot aged 10 to 25 years. A 12-week standardized aerobic dynamic exercise training program (3 one-hour sessions per week) was used. Pre- and post-training cardiopulmonary exercise tests, MRI, and echocardiography, including tissue-Doppler imaging, were performed. Patients were randomized to the exercise group (n=28) or control group (n=20). One patient in the exercise group dropped out. Change in tissue-Doppler imaging parameters was similar in the exercise group and control group (change in right ventricle free wall peak velocity $E'$ exercise group, 0.8±2.6 cm/s; control group, 0.9±4.1; peak velocity $A'$ exercise group, 0.4±2.4 m/s; control group 4.6±18.1 cm/s).

Conclusions—This randomized controlled pilot study provides preliminary data suggesting that regional ventricular performance is well maintained during 3-month aerobic dynamic exercise training in children and young adults with repaired tetralogy of Fallot. This information might help patients adhere to current public-health guidelines.

Clinical Trial Registration—URL: http://www.trialregister.nl. Unique identifier: NTR2731.

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Key Words: echocardiography ■ exercise ■ tetralogy of Fallot

See Clinical Perspective

Exercise training in patients with ConHD has been the subject of several studies, generally in small mixed populations. Although these studies have shown that patients with ConHD can improve their physical exercise capacity, the effect of exercise training on ventricular performance has hardly been studied.

In contrast, the ventricular response to acute stress (physical or pharmacological) has been studied extensively in patients withToF demonstrating highly abnormal changes for parameters of global ventricular function. Furthermore, right ventricular regional functional abnormalities have been shown.
to occur during acute exercise in these patients. Chronic loading abnormalities have been associated with abnormal regional function at rest, abnormal mass/volume ratio, and signs of (areas of) fibrosis in many types of ConHD. These factors may contribute to abnormal ventricular wall stress that has been associated with adverse myocardial remodeling. Evidence from animal models of ConHD is limited, but abnormal right ventricular loading conditions have been associated with loading condition–dependent abnormalities in voluntary exercise.

Conventional echocardiographic parameters are widely used for the assessment of global ventricular myocardial function. In addition, regional ventricular myocardial function can be assessed with tissue-Doppler imaging (TDI). Regional ventricular performance changes have been recognized as sensitive markers of deterioration of ventricular function.

This article is the first to report a pilot study on regional cardiac changes after an exercise training program in a population of ConHD. Considering the knowledge gap with regard to the cardiac effects of exercise training, a first step to increase our knowledge would be to demonstrate a lack of adverse effects on the ventricles in response to a common and widely used type of exercise training in patients with highly abnormal loading conditions of the heart, such as in patients with ToF.

For this purpose, we performed a randomized controlled pilot study. The hypothesis was that exercise training would not lead to deterioration of regional ventricular performance. We performed a pilot study to assess whether a 12-week standardized aerobic dynamic exercise training program would result in adverse changes in regional ventricular performance in patients with ToF.

Methods
This study is a part of a broader initiative to evaluate the effects of exercise training in ConHD.

Trial Design
This study consisted of a multicenter prospective randomized controlled trial and was conducted in 5 tertiary referral centers for ConHD in the Netherlands (Amsterdam, Leiden, Rotterdam, Nijmegen, and Utrecht). The study was designed according to Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial was registered at http://www.trialregister.nl (identification number NTR2731).

Participants
Eligible participants were all children and young adults (aged 10–25 years) with corrected ToF. Surgical correction of ToF had to be performed through a transatrial–transpulmonary approach. Patients with ventricular outflow tract obstruction with a Doppler derived peak >60 mm Hg were excluded, as were all patients who were physically or mentally unable to execute a training program. Those patients, were identified by their own physician and included patients with a hemiplegia or mental retardation who were unable to follow instructions, needed to adhere to the physical exercise training sessions.

Patients were identified through the local databases of the participating hospitals. The study complied with the Declaration of Helsinki. Institutional Ethics Committees of all participating centers approved the research protocol. All participants (or their parents if required) signed a written informed consent.

Intervention
Randomization of participants was performed by an independent blinded researcher with a 2:1 allocation ratio to either the exercise training program (exercise group) or to continue normal daily life (control group). Stratification was done based on sex, congenital heart defect, and age group (10–12 years, 12–15 years, 15–18 years, and 18–25 years).

The exercise group was enrolled in a 12-week standardized aerobic dynamic exercise training program at submaximal levels, with 3 one-hour sessions per week. The training hour was divided into 40 minutes of aerobic dynamic exercise training (eg, cycling) and 10 minutes of both warming up and cooling down. Participants were given a heart rate monitor (SR400, Polar Electro the Netherlands BV, the Netherlands) to help them train within the predetermined submaximal heart rate range. This range was set at 60% to 70% of the heart rate reserve, which was determined by a cardiopulmonary exercise test before the training program.

The training program was supervised by a local physiotherapist. The physiotherapist monitored the heart rate range during sessions. An attendance list was kept to monitor adherence. A single researcher visited the participating physiotherapists before the program to ensure that it was executed in a similar way for all participants.

Cardiorespiratory Fitness
Peak workload and peak oxygen uptake (peakVO2) were assessed by cardiopulmonary exercise test. The same locally available ergometer and gas analyzers were used per patient before and after the 3-month period. A modified Bruce exercise protocol was used, with settings adjusted to age, height, and sex. All participants were encouraged to continue until exhaustion, which was defined as the inability to maintain 65 rotations per minute. The test was marked successful if a respiratory exchange ratio (RER) of at least 1.0 was attained during the maximal test phase, according to common guidelines.

Echocardiography
All participants underwent transthoracic echocardiography. This was performed by experienced technicians and supervised by the research team. Images were obtained according to a strict protocol, which was in agreement with common guidelines. An appropriate transducer was used based on age and weight. Each study was performed at rest on locally available machines. Five subsequent heart beats were recorded. Images were analyzed using offline EchoPac (GE, Horten, Norway), Xcelera and Qlab (Andover) software.

Conventional Echocardiography Parameters
All reported conventional parameters were measured 3 times and averaged. The following parameters were determined at baseline: ratio of maximum and minimum inferior vena cava dimensions; ratio of liver vein peak S and peak D flow; interventricular septum dimension in diastole; left ventricular posterior wall dimension in diastole; maximum peak flow velocities in the great arteries and across the aortoventricular valves (Doppler E and A); peak systolic (S) and peak diastolic (D) flow in the superior vena cava; and maximal mitral and tricuspid annular plane systolic excursions.

Tissue-Doppler Imaging
All reported TDI parameters were measured 3 times and averaged. TDI parameters were obtained in the apical 4-chamber view (AP4CH). Longitudinal myocardial velocity curves were obtained from the basal parts of the interventricular septum and both the left ventricle and right ventricle or dominant free walls. Peak systolic myocardial velocity (S’), peak early diastolic myocardial velocity...
(E'), peak late diastolic myocardial velocity (A'), and time to peak systolic myocardial velocity were measured. Isovolumic acceleration was assessed by tracing the slope. In addition to the E'/A' ratio, early diastolic Doppler flow/early diastolic myocardial velocity (E/E') ratio was calculated.

**Magnetic Resonance Imaging**

All participants underwent cardiac MRI on the locally available whole body MRI scanners. A multiphase, multislice volumetric data set was acquired using a fast 2-dimensional cine scan using imaging parameters and analyzed as described previously.4

**Statistical Analysis**

Differences in end points between exercise and control groups were analyzed by 2-way (repeated measures) ANOVA using complete cases only. The treatment–time interaction was estimated to assess the effect of the exercise training program on each end point. Within-subject comparisons were performed by paired Student t tests or Wilcoxon signed-rank test as appropriate, regardless the significance of this interaction. Consequently, the type I error rate for detecting significant changes from zero may be inflated, which we considered acceptable for this pilot study. We considered a P value of <0.05 (2-sided test) as statistically significant. All statistical analyses were performed using SPSS.

**Sample Size Calculation**

This pilot study was designed to detect relatively large standardized effect sizes (mean difference divided by the SD) of 1.0 for the various echocardiographic end points with 90% power (β=0.10), using 2-sided tests with α=0.05. We elected for a 2:1 randomization, with the larger number of patients randomized to the exercise training program. Then, a total of 48 (32:16) patients would be required. We finally obtained analyzable information on 47 randomized patients (27:20). Consequently, in retrospect, the power of our study was 93%, 75%, and 40% to detect effect sizes of 1.0, 0.75, and 0.5, respectively.

**Results**

**Patient Characteristics**

We invited 230 patients to participate in this study. Forty-eight patients participated (Figure, flow chart). The time-consuming nature of the study was the main reason not to participate.

No significant differences were noted between participants and those nonparticipants with regard to age at the study and age at operation. One patient in the exercise group dropped out (Figure, flow chart). Not all tests were successfully completed both before and after the 3-month (exercise training or control) period. The number of patients included in the analysis per test is given in the Figure (flow chart) under paired analysis. The characteristics of the 47 participants did not differ statistically significantly between the exercise and control groups (Table 1).

ECGs were obtained before and after the training period. Regional ischemia was not seen on the ECGs.

In accordance with the inclusion criteria, all patients had a ventricular outflow gradient <60 mm Hg. The maximal outflow gradient measured in the participating patients was 37 mm Hg. A gradient >30 was measured in 3 patients, 2 in the training group, and 1 in the control group.
increased significantly during follow-up in the ToF exercise group compared with the control group (delta exercise group 8.4±1.14 Watts; delta control group −0.1±15.9 Watts; P=0.048). PeakVO₂ at baseline was 35±6 mL/kg per minute in the exercise group and 33±8 mL/kg per minute in the control group. There was no significant difference between the change of peakVO₂ in the exercise group and that in the control group (P=0.14). In the ToF exercise group, peakVO₂ significantly increased (delta 2.9±4.0 mL/kg per minute; within-subject analysis, P=0.002), whereas in the control group, peakVO₂ did not significantly increase (delta 0.7±5.1 mL/kg per minute; within-subject analysis, P=0.54).

Echocardiography

The conventional echocardiography parameters at baseline are shown in Table 2. At baseline, the parameters did not differ between the exercise and the control groups except for MV peak A and maximal mitral annular plane systolic excursion.

TDI Echocardiography Parameters

TDI parameters in the patients with ToF before and after the exercise period are shown in Table 3.

There was no significant difference between the changes in global and regional myocardial function of the exercise group compared with the control group. None of the parameters changed after the intervention period, neither in the exercise group nor in the control group.

Magnetic Resonance Imaging

The parameters measured with MRI are shown in Table 4. Global size and function did not change after the exercise training in the exercise group compared with the control group.

Discussion

The data of this pilot study suggest that aerobic dynamic exercise training does not result in adverse changes of regional systolic and diastolic ventricular performance in children and young adults after surgical correction of ToF. As such, our preliminary data support the general health guidelines that encourage patients with ConHD to participate in sport activities and may add to the knowledge that exercise training in patients with ConHD is safe.1 From these data, it cannot be concluded that all sport activities are safe for every patient with ConHD and considering the limited power of the study the data needs to be interpreted with caution. However, although we studied patients with highly abnormal loading conditions of the heart, the information from this pilot study may encourage clinicians to prescribe an exercise training program for their patients with ConHD.16

A recent review has shown a significant lack of knowledge of alterations of ventricular performance after an exercise training program in patients with ConHD.8 A total of 29 exercise training studies have been performed in these patients. A total of 621 patients participated in these exercise training studies, which were mostly 12 weeks in duration and consisted of dynamic training 3 times per week. Interestingly, only 2 studies reported on the global cardiac status before and after the exercise training program.8 One included 6 adult Fontan patients in
a 20-week high-intensity resistance exercise training program. Four of the participants underwent cardiac MRI before and after the intervention. An improvement of global ventricular performance was seen, defined as a significant increase in cardiac output. The other included 11 pediatric patients with ToF in an 8-week aerobic dynamic exercise training program.8 An echocardiographic study was performed before and after the training period. The LV dimensions did not significantly change.

Conventional global echocardiographic parameters rely on geometric assumptions. These assumptions do not necessarily hold in patients with ConHD.17 TDI is less dependent of chamber geometry and enables assessment of global and regional ventricular performance.17 Changes in regional systolic and diastolic ventricular performance have been recognized as more sensitive markers of deterioration of function than conventional markers in patients with acquired heart disease as well as ConHD.13

Changes related to acute bouts of exercise in normal but untrained hearts may include enhanced diastolic filling velocities, as has been shown by an increase of peak diastolic velocities measured with TDI during exercise.18 The proportion of increase in stroke volume that occurs with acute bouts of exercise depends on the training status: the better trained, the more enhanced the diastolic performance, which ultimately contributes to an increase in stroke volume.18,19

Prolonged exercise training in healthy subjects (athletes) also results in changes in regional ventricular performance. This performance is enhanced as an increase in peak E′ is seen, as well as an increase in the E′/A′ ratio, both measured with echocardiography at rest. In addition, strain analysis has supported the findings of enhanced diastolic filling.20 Combined with an increase of end-diastolic volume, this contributes to enhanced stroke volume.21 Although most of the strain research in athletes has been performed in adults, the available data confirm these findings in healthy young athletes.19 Conventional echocardiographic parameters differ between athletes engaged in endurance versus strength exercise, which has not been studied for regional parameters.
In patients with ToF, the long-term effects of sequelae after correction, mainly pulmonary regurgitation, induce increased right ventricular end-diastolic volume and left-sided changes. This may cause reduced RV and LV diastolic and systolic performance. Although the RV global diastolic performance measured by Doppler blood flow in our patients with ToF was within the normal range, TDI measurements in the RV walls confirm that RV regional diastolic dysfunction exists. Van den Berg et al have shown that reduced global ventricular diastolic function seen in patients with ToF at rest is impaired to a larger extent during acute stress. In this pilot study, the data suggest that prolonged exercise training negatively affects neither regional ventricular diastolic function nor systolic performance in patients with ToF.

Limitations
The sample size in our study is relatively small. We were unable to include exactly the statistically required number of patients with ToF. This means that the current data are underpowered to detect effect sizes <0.75 SD (Statistical Analysis section). Caution is required in interpreting the results of the study, which has limited the generalizability. However, this is the first randomized exercise training trial in pediatric cardiology, and considering the complete lack of information in a potentially important and relevant area, we feel that the data are important to be available in the public domain. The data may be regarded as an initial proof of concept. We expect this study to stimulate future research in this field.

Clinical Relevance
Many patients with ConHD do not exercise, and physicians may be reluctant to advise physical activity. In this pilot study, we have provided preliminary data suggesting that a training program in patients with ToF does not influence regional ventricular performance. This information might help patients and physicians to adhere to current public-health guidelines. This pilot study warrants further investigation.

Conclusions
The preliminary data of our pilot study suggest that regional ventricular performance is well maintained during aerobic dynamic exercise training in patients with corrected ToF. However, more research is needed to confirm the findings.

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Disclosures
None.

References

CLINICAL PERSPECTIVE
Although public-health guidelines recommend patients with congenital heart disease to exercise, many patients with congenital heart disease do not, partly out of fear of peers and parents. Clinicians taking care of these patients may be reluctant to advise physical exercise as evidence to support the guidelines is flimsy. Studies have shown that congenital heart disease patients can improve physical exercise capacity. However, the effect of training on regional ventricular performance has hardly been studied. Results of our pilot study suggest that regional ventricular performance is well maintained during a 3-month aerobic dynamic exercise training program in tetralogy of Fallot patients. This information may be important for clinicians as it may be used to educate patients, reduce the reluctance to exercise and help patients to adhere to the current guidelines.
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