Does exercise training improve cardiopulmonary fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan circulation? A randomized controlled trial

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Background Many patients with congenital heart disease do not meet current public health guidelines to participate in moderate-to-vigorous physical activity for ≥60 minutes per day. They are less fit than their healthy peers. We hypothesized that exercise training would increase cardiopulmonary fitness and daily physical activity in these patients. We therefore assessed effects of an exercise training program on cardiopulmonary fitness and daily physical activity in patients with corrected tetralogy of Fallot (ToF) or Fontan circulation.

Methods In a multicenter prospective controlled trial, patients with ToF or Fontan circulation (age 10-25 years) were randomized, 56 patients to the exercise group and 37 to the control group. The exercise group participated in a 12-week standardized aerobic exercise training program. The control group continued lifestyle as usual. Cardiopulmonary exercise testing and activity measurements were performed before and after 12 weeks.

Results Peak oxygen uptake increased in the exercise group by 5.0% (1.7 ± 4.2 mL/kg per minute; \( P = .011 \)) but not in the control group (0.9 ± 5.2 mL/kg per minute; \( P = \) not significant). Workload increased significantly in the exercise group compared with the control group (6.9 ± 11.8 vs 0.8 ± 13.9 W; \( P = .047 \)). Subgroup analysis showed a significant increase in pre-to-post peak oxygen uptake in the exercise group of ToF patients but not in the exercise group of Fontan patients. Percentage of measured time spent in moderate-to-vigorous activity at baseline was 13.6% ± 8.6%, which did not significantly change after training.

Conclusions Aerobic exercise training improved cardiopulmonary fitness in patients with ToF but not in patients with Fontan circulation. Exercise training did not change daily physical activity. (Am Heart J 2015;0:1-9.)

Current public health guidelines suggest ≥60 minutes of moderate-to-vigorous physical activity daily for children and adults.\(^1\) Increasing physical activity can improve cardiopulmonary fitness, and a better cardiopulmonary fitness may promote more physical activity.\(^2\) Among other factors such as diagnosis, New York Heart Association (NYHA) class, age at surgery, and peak heart rate (peakHR), poor cardiopulmonary fitness is a risk factor for hospitalization and death in patients with congenital heart disease (ConHD).\(^3\) Patients with corrected tetralogy of Fallot (ToF patients) or Fontan circulation (Fontan patients) are among those with the highest risk for late deterioration of cardiac function.\(^4\) These patients are advised to engage in physical activities in concordance with the current public health guidelines.\(^5\)

Several studies have examined the effect of physical exercise training programs in patients with ConHD. Training programs that successfully improved cardiopulmonary fitness had an average duration of 12 weeks, an aerobic intensity level and a minimal training frequency of twice a week for 1 hour.\(^6\) Peak oxygen uptake (peakVO\(_2\)) was the most frequently used outcome measure.
parameter to assess improvement in physical exercise capacity. These studies, often with small sample sizes and including different ConHD diagnoses as well as ages from 4 up to 40 years, reported a mean increase in peakVO2 of 2.6 mL/kg per minute. However, a randomized controlled trial design was seldom used.

Previous studies that measured activity levels objectively demonstrated that only a minority of children with ConHD were moderately to vigorously physically active for ≥60 minutes per day. Only 2 studies included accelerometry assessments to evaluate changes in daily physical activity after an exercise training program. These studies suggested a positive effect of exercise training on daily physical activity in a heterogeneous group of ConHD patients. This contributes to the suggestion that an interaction between daily physical activity and cardiopulmonary fitness exists.

We aimed to assess the effects of a standardized 12-week exercise training program on cardiopulmonary fitness and daily physical activity in children and young adults with corrected ToF or Fontan circulation. Both groups were selected to create a homogenous study population, all at risk for late deterioration of cardiac function. The duration of the exercise training program was based on the results of previous studies. We hypothesized that exercise training would increase cardiopulmonary fitness, measured as peakVO2 and daily physical activity level, measured in metabolic equivalent.

Methods

Trial design

A multicenter prospective randomized controlled trial was designed according to Consolidated Standards of Reporting Trials guidelines. Five university hospital congenital cardiology centers in the Netherlands participated (Amsterdam, Leiden, Rotterdam, Nijmegen, and Utrecht).

Participants

Patients were identified through local databases of participating hospitals. Tetralogy of Fallot or Fontan patients between 10 and 25 years were eligible. Correction of ToF, using the transatrial-transpulmonary approach, had to be performed before the age of 3.5 years. The Fontan circulation had to be completed before the age of 6 years. All participants had to be able, both mentally as well as physically, to adhere to a training program. Patients with a ventricular outflow obstruction >60 mm Hg were excluded as were patients with general contraindications for cardiac magnetic resonance imaging (MRI).

The study complied with the Declaration of Helsinki. Local ethics committees approved of the research protocol. All participants and/or their parents if required signed a written informed consent. The trial was registered at www.trialregister.nl, identification number NTR2731.

Randomization, allocation, and blinding

Participants were randomized in a 2:1 ratio to the exercise group or control group. Randomization was performed by an independent blinded researcher. Stratification was based on gender, ConHD, and age group (10-12, 12-15, 15-18, and 18-25 years). The protocol included cardiac MRI and MRI at rest with dobutamine stress. Not all patients consented in dobutamine stress MRI. Randomization took place irrespective of the consent whether to participate in stress MRI. Only if the entire imaging procedure could be finished within the allocated scan time of 90 minutes did we perform dobutamine stress MRI. Logistics of MRI and stress tests was managed by personnel unaware of the randomization.

Intervention

Based on previous studies, a 12-week standardized aerobic exercise training program was used. The training program consisted of three 1-hour exercise sessions per week, which were added to normal daily life activity. The exercise sessions consisted of 40 minutes aerobic dynamic cardiovascular training, 10 minutes warming up, and 10 minutes cooling down. Participants were given a HR monitor (SR400; Polar Electro the Netherlands BV, Almere, the Netherlands) to help them train within the predetermined submaximal HR range, which was set at the resting HR plus 60% to 70% of the HR reserve, determined at the baseline cardiopulmonary exercise test. The training program was executed and supervised by a local physiotherapist. An attendance list was kept to monitor adherence to the training sessions. A single researcher visited the participating physiotherapists before the program to ensure uniform use for all participants.

The control group was instructed to continue their normal daily life.

Outcome assessments

The outcome assessments took place at the university hospital that followed up the patient. The following assessments were made in a period of 2 weeks before and 2 weeks after the exercise training.

Cardiopulmonary fitness. Cardiopulmonary fitness was assessed by cardiopulmonary exercise testing. The same locally available ergometer and gas analyzers were used per patient. The protocol started with 1 minute of unloaded cycling with a cadence of 65 to 75 repetitions per minute. Thereafter, load increased by 10, 15, or 20 W per minute, depending on height (<150, >150-180, and >180 cm). All participants were encouraged to continue cycling until exhaustion, defined as the inability to maintain the preset repetition rate. The test was marked as maximal effort if the respiratory exchange ratio (RER) during the test phase was higher than 1.0, according to widely accepted guidelines. The following parameters were determined: peakVO2 (milliliters per kilogram per
minute), averaged over the final 30 seconds of exercise; peak workload (Watt), averaged over the final 60 seconds of exercise; peak minute ventilation (peakVE) (liter per minute), averaged over the final 30 seconds of exercise; peakHR (beat/min), highest HR measured during exercise; peak oxygen pulse (peakO2Pulse) (milliliters per beat), peakVO2 divided by peakHR; peak RER, highest measured RER during exercise; ventilatory anaerobic threshold (VAT) VO2 (milliliters per kilogram per minute), VO2 at VAT; minute ventilation to carbon dioxide production slope (VE/VCO2 slope) (measured from the start of exercise up until the respiratory compensation point); and oxygen uptake efficiency slope (OUES). \[^{15-15}\]

**Stroke volume.** Each participant underwent cardiac MRI before and after the intervention period on the locally available whole body MRI. A multiphase, multislice volumetric data set was acquired with either breath holds (ToF patients) or averaging 3 heart beats to eliminate the effect of respiration (Fontan patients). \[^{16}\] Low-dose dobutamine stress images were only acquired when logistically possible and if the patient consented. \[^{16}\] Analysis was performed with software package QMass (Medis Medical Imaging Systems BV, Leiden, the Netherlands). Stroke volume (SV) was indexed for body surface area. If a second ventricle existed in Fontan patients, its SV was added to that of the systemic. Experienced observers analyzed the data according to previously described methods. \[^{17}\]

**Daily physical activity.** Daily physical activity was measured with an Actigraph GT3X triaxial accelerometer, which has been validated. \[^{18}\] The subjects wore the accelerometer on their waist for 5 consecutive days, including weekend days. The tool was removed only for swimming, showering, and sleeping. Accelerometer data were only included in analysis in case of a minimum of wear time of 3 days and per day of 8 hours. Data were analyzed with ActiLife 6 software. Counts per minute were converted to metabolic equivalent using age specific formulas by Freedson et al. \[^{19}\] Metabolic equivalent values of 3, 6, and 9 were used as lower limits for moderate, vigorous, and very vigorous activity, respectively. \[^{19}\] The subjects’ level of physical activity was interpreted as the amount of time spent at each activity level, expressed as percentage of the total measured time and as the average metabolic equivalent.

**Statistical analysis**

Sample size calculation was based on the primary end point of change in peakVO2. We calculated that 90 patients were required to obtain 88% power to detect a difference of 20% of peakVO2 (from 37 ± 10 to 44 ± 10 mL/kg per minute) between the intervention and control group, considering a randomization ratio of 2:1 and a 2-sided α of .05.

Data were tested for normality with Kolmogorov–Smirnov test. Normally distributed data are expressed as mean (±SD), nonparametric data as median (interquartile range).

Between-subject comparisons were analyzed by 2-way analysis of variance (ANOVA); within-subject comparisons were analyzed by paired Student t test or Wilcoxon signed rank test if appropriate. Correlation was analyzed using linear regression. Analysis was performed using SPSS statistical software package version 21.

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**Results**

**Patients characteristics**

Three hundred sixty-two patients were contacted to participate in this study (flow chart [Figure 1]). The time-consuming nature of the study was the main reason for patients not to participate. Age at the time of the study and age at operation did not significantly differ between the participants and nonparticipants. A total of 93 patients participated in the study. Three patients (3.2%), randomized to the exercise group, dropped out. The baseline characteristics did not significantly differ between the exercise group and the control group (Table I). 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.

**Training adherence**

Fifty-three participants in the exercise group completed the study protocol. On average, 4 training sessions in 12 weeks were missed. Adherence to the training session in the program was 89% (median; interquartile range 79%-100%). To assess adherence to the training intensity level, a random sample of recorded HR during exercise training was reviewed (n = 11). In all these patients, HR was within the set limits.

**Cardiopulmonary fitness**

All but 3 participants underwent cardiopulmonary exercise testing twice (Table II). Peak values are only presented for patients who successfully completed the test twice with a RER >1.0. Submaximal values are presented for all patients.

**All participants, a comparison of the exercise and control groups.** In the exercise group peakVO2 increased with 5.0% after the exercise training program (P = .011), whereas the control group did not show an increase in peakVO2. The increase of peakVO2 was not significantly different between groups. Workload and ventilation (peakVE) significantly increased in the exercise group compared with the control group. Peak
The oxygen pulse in the exercise group increased ($P = .001$), whereas the control group showed no increase. The increase of peak $\text{O}_2$Pulse was not significantly different between groups (Table II). The changes in submaximal parameters, $\text{VO}_2$ at VAT, $\text{VE}/\text{VCO}_2$ slope, and OUES, did not significantly differ between the exercise group and the control group (Table II).

The changes in blood pressures from the baseline measurements to the postintervention measurements from rest (113 ± 13/73 ± 11 mm Hg) to peak exercise (165 ± 31/71 ± 14 mm Hg) and from peak exercise to recovery (135 ± 22/68 ± 14 mm Hg) did not significantly change, nor differ between the exercise group and the control group.
Tetralogy of Fallot patients. Peak oxygen uptake in the ToF patients allocated to the exercise group increased with 8.3% after the exercise training program ($P = .002$), whereas peakVO$_2$ in the control group did not increase. The increase in peakVO$_2$ was not significantly different between groups. Workload and ventilation (peakVE) significantly increased in the exercise group compared with the control group. Peak oxygen pulse in the exercise group increased ($P < .001$), whereas peakO$_2$Pulse in the control group did not increase. The increase in peakO$_2$-Pulse was not significantly different between groups. The changes in submaximal parameters, VAT VO$_2$, VE/VCO$_2$ slope, and OUES, did not significantly differ between the exercise group and the control group.

Fontan patients. Peak oxygen uptake did not significantly increase after the exercise training program in the Fontan patients in the exercise group as well as the control group. The change in peakVO$_2$, peak load, peakVE, and peakO$_2$-Pulse after the exercise training program did not significantly differ between the exercise group and the control group (Table II). Within the submaximal parameters, VO$_2$ at VAT and OUES significantly changed between the exercise group and the control group, whereas VE/VCO$_2$ slope did not significantly change between the groups.

Stroke volume

Indexed SVs (SV$_i$), as assessed with MRI, are shown before and after the exercise training program in Figure 2. Tetralogy of Fallot patients (regardless of randomization) had an SV$_i$ before the exercise training program at rest of 50.2 ± 6.5 mL/m$^2$, which significantly increased with dobutamine stress to 61.0 ± 9.0 mL/m$^2$. After the exercise training program, SV$_i$ at rest was 48.0 ± 7.8 mL/m$^2$, which significantly increased at dobutamine stress to 59.9 ± 11.4 mL/m$^2$. The exercise training program did not affect the SV$_i$ or SV$_i$ increase from rest to dobutamine stress.

Fontan patients (regardless of randomization) had an SV$_i$ before the exercise training program at rest of 51.1 ± 8.8 mL/m$^2$ and at dobutamine stress of 53.3 ± 13.0 mL/m$^2$. After the exercise training program the SV$_i$ at rest was 50.0 ± 9.2 mL/m$^2$ and at dobutamine stress, 51.4 ± 12.4 mL/m$^2$. Indexed SVs did not significantly increase in the exercise group or control group in Fontan patients, either from rest to dobutamine stress or from pre–exercise training program to post–exercise training program.

Daily physical activity

Twenty-eight patients in the exercise group and 18 patients in the control group were included in daily physical activity analyses (Table III). Time spent sedentary or in moderate-to-very-vigorous activity measured at baseline did not significantly differ between the exercise group and control group, nor did it change after the intervention period. Time spent in moderate-to-very-vigorous activity at baseline, regardless of randomization was 13.6% ± 8.6% of the registered time, which was 104 ±
Table II. Results: cardiopulmonary exercise tests

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>ToF</th>
<th>Fontan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise group (n = 43)</td>
<td>Control group (n = 30)</td>
<td>Exercise group (n = 24)</td>
</tr>
<tr>
<td><strong>Maximal tests</strong></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>PeakVO₂ (mL/kg per minute)</td>
<td>34.2 ± 6.4</td>
<td>35.9 ± 7.4*</td>
<td>33.3 ± 8.6</td>
</tr>
<tr>
<td>Peak workload (W)</td>
<td>151 ± 54</td>
<td>157 ± 51</td>
<td>148 ± 48</td>
</tr>
<tr>
<td>PeakVE (L/min)</td>
<td>70.6 ± 22.6</td>
<td>78.3 ± 28.9</td>
<td>71.2 ± 21.2</td>
</tr>
<tr>
<td>PeakO₂Pulse (mL/beat)</td>
<td>10.9 ± 2.9</td>
<td>11.9 ± 3.6*</td>
<td>10.4 ± 3.3</td>
</tr>
<tr>
<td>PeakHR (beats/min)</td>
<td>175 ± 16</td>
<td>175 ± 15</td>
<td>178 ± 19</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.12 ± 0.06</td>
<td>1.14 ± 0.08</td>
<td>1.14 ± 0.08</td>
</tr>
</tbody>
</table>

| **Submaximal tests**    |                                |                                |                                |                                |                                |                                |
|-------------------------|                                |                                |                                |                                |                                |                                |
|                         | Exercise group (n = 46) | Control group (n = 31) | Exercise group (n = 24) | Control group (n = 19) | Exercise group (n = 22) | Control group (n = 12) |
| VAT                     | 22.2 ± 7.9 | 20.9 ± 5.9 | 20.6 ± 6.0 | 20.6 ± 6.2 | ns | 20.8 ± 7.2 | 22.4 ± 6.5 | 20.2 ± 6.3 | 19.8 ± 6.2 | ns | 23.8 ± 8.5 | 19.3 ± 4.7 | 21.2 ± 5.7 | 21.9 ± 6.3 | 0.038 |
| VO₂ (mL/kg per minute)  |                                |                                |                                |                                |                                |                                |
| VE/VO₂                 | 28.8 ± 5.1 | 29.5 ± 6.4 | 29.6 ± 6.6 | 29.3 ± 6.5 | ns | 26.5 ± 4.0 | 27.7 ± 5.0 | 26.2 ± 3.7 | 26.3 ± 4.5 | ns | 31.3 ± 5.2 | 31.4 ± 7.4 | 35.1 ± 6.5 | 34.3 ± 6.2 | ns |
| slope                  |                                |                                |                                |                                |                                |                                |
| OUES                   | 2196 ± 616 | 2180 ± 615 | 2049 ± 603 | 2175 ± 676 | ns | 2431 ± 656 | 2513 ± 599 | 2289 ± 567 | 2397 ± 639 | ns | 1937 ± 455 | 1814 ± 388 | 1670 ± 459 | 1823 ± 597 | 0.009 |

Abbreviation: ns, Not significant.
Within-group analysis with paired t-tests, *P < .05; between-group analysis with 2-way ANOVA.
65 minutes per day. At baseline, 30% of all patients did not meet the guidelines of 60 minutes of moderate-to-vigorous activity, which did not change significantly after the training program.

Discussion

This randomized controlled trial demonstrated that 12 weeks of exercise training significantly increased peak VO2 in ToF patients, although this did not significantly differ from the control group. However, the significant increase in workload and ventilation in the ToF exercise group in comparison with the control group points in the direction of improved cardiopulmonary fitness. In contrast, the Fontan patients did not increase their cardiopulmonary fitness after training. In addition, we demonstrated that exercise training did not alter daily physical activity in any of the groups.

Cardiopulmonary fitness

Strict supervision and monitoring of the training sessions and of training intensity level assured that the required training effort was delivered. This is reflected in our below average drop out percentage (3%) in comparison with a mean of 16% in previous exercise studies in ConHD. Compared with previous studies, training adherence in our participants (89%) was above the reported average of 80%.

The significant increase in peakVO2 of 3 mL/kg per minute (5%) in our ToF patients is in the same range as reported in a pilot study with adult ToF patients as well as in other exercise studies among heterogeneous groups of ConHD patients and exercise studies in healthy adolescents (5%-6%). In contrast, 2 previous exercise studies involving children with ToF were unable to demonstrate a significant increase in peakVO2. This may have been related to the small number of participants (<12) included in those studies as well as a less vigorous training program.

Our data on the changes in SV with dobutamine stress and on peakO2Pulse indicate that ToF patients can increase HR as well as SV when exercise demands an increased cardiac output. This may have contributed to the increased cardiopulmonary fitness in response to aerobic exercise training.

In contrast to the ToF patients, Fontan patients did not increase their peakVO2 after exercise training. This observation is in contrast with most previous exercise studies in adult Fontan patients as well as in 3 of 4 exercise studies in younger Fontan patients. The most likely explanation for these contrasting findings may be related to the low baseline peakVO2 of 25 to 28 mL/kg per minute in previous studies compared with a baseline peakVO2 of 33 mL/kg per minute in our study. A relatively high baseline of physical exercise capacity may hamper an increase in cardiopulmonary fitness by training. In a cross-sectional study in our institutions, a similar peakVO2 of 33 ± 8 mL/kg per minute was observed in Fontan patients. We, therefore, think inclusion bias for our exercise study toward the fitter patients is unlikely.

The data on the changes in SV with dobutamine stress indicate that Fontan patients were not able to increase SV, which was not altered by the exercise training intervention. The lack of increase in SV most likely relates to preload impairment in the Fontan circulation. This suggests that when exercise demands an increased cardiac output, this will result in a limited increase in SV and therefore limitation of exercise capacity in Fontan patients. We, therefore, speculate that Fontan patients may reach a plateau in their capability to enhance SV and thus cardiac output, which may reduce the potential increase in peakVO2 with aerobic exercise training.

Daily physical activity

Seventy percent of our patients were moderately to vigorously active for >60 minutes per day at baseline, which is in concordance with the reported 76% of moderately to vigorously active ConHD patients by Muller et al. Other studies have reported much lower percentages. This observation may in part explain the difference in baseline physical fitness between our study and previous studies. Physical activity may be related to geographic location and associated cultural differences; for instance, in the Netherlands many, if not all, adolescents ride a bicycle as means of transport to and from school.

Morrison et al noted an increase in activity levels after exercise intervention, which was accompanied by psychologic motivational techniques. Because it is well
known that changing lifestyle is difficult, a multidisciplinary approach may be required to successfully change daily physical activity levels.\textsuperscript{32} Based on the results of our study, with already 70\% of patients adhering to ≥60 minutes of daily activity, a change in activity level cannot be achieved by an exercise training program alone in children and young adults ToF or Fontan patients. An increase in cardiorespiratory fitness, like in the ToF exercise group, does not directly result in an increase in daily physical activity.

Limitations

Because this was a multicenter trial, we had to use different setups for exercise testing in our study. However, we do not think that this has affected our main outcome measures because all centers used the same protocol; had state of the art equipment; and, moreover, patients served as their own controls. In the present study, we focused on aerobic exercise training. Considering our results, aerobic exercise is adequate to improve physical fitness in ToF patients. In Fontan patients, other types of exercise may require further study. The geographic location of the study may have influenced the activity level results, as Dutch children commonly commute by bicycle, which is not custom in most other countries. Although we did not find major differences between participants and nonparticipants in the study, we cannot rule out inclusion bias toward more fit patients. Patients with irregular heart rhythm were excluded from MRI because this is a general contraindication for cardiac MRI. However, the presence of arrhythmias may have limited inclusion of subjects into the study in general. Age may be a factor in the effects of exercise training. Our study lacks statistical power to demonstrate an age effect.

Contrary to the situation in adults with CongHD, there is no consensus on the optimal RER value to determine maximal exercise in exercise testing.\textsuperscript{33} Different cutoff values of the RER have been used in various studies that have focused on the change of peak\textsubscript{vo2} due to an exercise training program in children. In these studies, RER cutoff values have varied from 1.1.\textsuperscript{34,35} The results of our study did not change if we used an RER of 1.05 or 1.1.

Conclusion

Twelve weeks of aerobic exercise training improved physical performance in ToF patients but not in Fontan patients, whereas it did not alter daily physical activity in both groups.

References


