Exercise training improves exercise capacity in adult patients with a systemic right ventricle: a randomized clinical trial

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Objective
To assess whether exercise training in adult patients with a systemic right ventricle (RV) improves exercise capacity and quality of life and lowers serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels.

Design
Multi-centre parallel randomized controlled trial.

Participants
Patients with a systemic RV due to congenitally or surgically corrected transposition of the great arteries.

Methods
Fifty-four adult patients with a systemic RV, were randomized using unmarked opaque envelopes to an intervention group (n = 28) with three training sessions per week for 10 consecutive weeks, and a control group (n = 26). Randomization was stratified by participating centre. At baseline, and follow-up, we determined maximal exercise capacity (V'O2peak), serum NT-proBNP levels, and quality of life by means of the SF-36, and the TAAQOL Congenital Heart Disease questionnaires. The final analysis was performed by linear regression, taking into account the stratified randomization.

Results
Forty-six patients were analysed (male 50%, age 32 ± 11 years, intervention group n = 24, control group n = 22). Analysis at 10 weeks showed a significant difference in V'O2peak (3.4 mL/kg/min, 95% CI: 0.2 to 6.7; P = 0.04) and resting systolic blood pressure (−27.6 mmHg, 95% CI: −14.0 to −1.3; P = 0.03) in favour of the exercise group. No significant changes were found in serum NT-proBNP levels or quality of life in the intervention group or in the control group nor between groups. None of the patients in the intervention group had to discontinue the training programme due to adverse events.

Conclusion
In adult patients with a systemic RV exercise training improve exercise capacity. We recommend to revise restrictive guidelines, and to encourage patients to become physically active. (Trial registration: The study was registered at http://trialregister.nl. Identifier: NTR1909.)

Keywords
Exercise • Transposition of the great arteries • Right ventricle

Introduction
The prevalence of congenital heart disease (CHD) in the adult population has increased steadily over the last decades. A substantial portion of these patients has a morphological right ventricle (RV) that sustains the systemic circulation, like patients with a transposition of the great arteries (TGA) after a Mustard or Senning operation, and patients with a congenitally corrected
transposition of the great arteries (ccTGA). Currently, the large majority of patients with a systemic RV survive until adulthood. However, these patients often have decreased ventricular function, and reduced exercise capacity in comparison to their peers.\(^{2,3}\)

The American Heart Association recommends patients with acquired heart disease to engage in physical exercise,\(^{4}\) as it is safe, increases exercise capacity, and improves quality of life in these patients.\(^{5–9}\) Few small studies have demonstrated similar beneficial effects of exercise training in heterogeneous groups of patients with CHD, especially in children and adolescents.\(^{10–11}\) Despite the positive effect of exercise training in these patient groups, there are no data on the effect of exercise training in adult patients with a systemic RV. Positive results in children with CHD should not be adopted indiscriminately to the complex population of adult patients with a systemic RV, as complications primarily occur in adulthood. On the other hand, positive results as described above, combined with the benefits of exercise training in adult patients with congestive heart failure, suggest that patients with a systemic RV could benefit from exercise. Currently, European guidelines on exercise and sports participation are restrictive, due to the limited availability of literature.\(^{12,13}\) This could lead to physicians’ reluctance to advise patients with a systemic RV to engage in physical activity, with possibly counterproductive effects.

The primary aim of our study was to determine whether exercise training improves maximal exercise capacity in adult patient with a systemic RV. Additionally, we aimed to determine whether exercise training decreases serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels and improves quality of life in these patients.

**Methods**

**Trial design**

The study was a multi-centre prospective, randomized, controlled parallel group trial, conducted in the Netherlands (three sites) and Italy (one site).

**Participants**

Eligible participants were adults with a systemic RV due to a congenitally or surgically corrected TGA. Exclusion criteria were mental or physical incapability to participate in a home-based exercise training programme, the presence of exercise-induced arrhythmia, symptomatic myocardial ischaemia, a resting systolic blood pressure > 200 mmHg and/or diastolic blood pressure > 110 mmHg, New York Heart Association (NYHA) class III or IV, pregnancy during the training period, and non-cardiac co-morbidity that could affect exercise performance or that could aggravate by exercise.

**Study settings**

In the Netherlands, the study population was identified through the CONgenital COR vita (CONCOR) database, the national database and DNA-bank for adult CHD,\(^{14}\) and, in Italy, through the echocardiography database of the Paediatric Cardiology and Adult Congenital Unit, at the University Medical Center in Bologna. The study complied with the Declaration of Helsinki, locally appointed Ethics Committees have approved the research protocol and informed consent was obtained from the subjects prior to their participation in the study. The study was registered at http://trialregister.nl. Identifier: NTR1909.

**Interventions**

**Exercise training programme**

Consenting patients were randomized to (i) commence with an exercise training protocol for the duration of 10 consecutive weeks (the intervention group), or (ii) refrain from this exercise training protocol for the duration of 10 consecutive weeks (the control group). Patients started the training protocol within 1 week after all baseline procedures had been performed. The training protocol was home-based, and consisted of three sessions of steps aerobics per week for the duration of 10 consecutive weeks. The training sessions were set up as follows: all patients warmed-up for 5 min at 60% of maximal heart rate, as determined by baseline cardiopulmonary exercise testing, before starting a 32 min interval training. The interval training consisted of five times 4 min of steps aerobics, starting at 75% and incrementing to 90% of maximal heart rate during the 10 week training protocol, alternated with four times 3 min of steps aerobics at 60% of maximal heart rate. Each training session was terminated by a 5 min cool-down period at 60% of maximal heart rate.\(^{15}\) Participating patients, both in the intervention and the control group, were requested to continue habitual daily activities, even if these included regular physical exercise.

To obtain the desired exercise intensity, all patients randomized to the exercise training protocol received a Cresta Metal Line PM-233 (Sabre, the Netherlands) heart rate wrist watch, to monitor their heart rate during the training sessions. To improve compliance with the training protocol and to ensure safety, each patient received a weekly email asking them about their progress. Patients who did not respond to this email were contacted by telephone. All patients were instructed to immediately cease the exercise programme and contact a physician if they experienced chest pain, palpitations, dizziness, or other distressing symptoms.

**Outcomes**

**Cardiopulmonary exercise tests**

Cardiopulmonary exercise tests were performed twice in all patients, once prior to randomization, and a second time after the 10-week follow-up period. Cardiopulmonary exercise tests were performed to assess maximal exercise capacity, and maximal heart rate, according to the guidelines of the American Thoracic Society.\(^{16}\) Patients were placed on an upright cycle ergometer and breath-by-breath analysis were made of minute ventilation, oxygen uptake (\(V'O_2\)), carbon dioxide elimination (\(V'CO_2\)), heart rate, blood pressure, and electrocardiography (Jaeger Oxycon pro, Wuerzburg, Germany). Work load was increased by \(5–15\) W/min in a stepwise manner, depending on the individually predicted maximum exercise capacity and in such a way that calculated maximal effort was attained in \(10–15\) min. All patients were exercised to their maximum exercise capability.

We averaged \(V'O_2\) using a \(10\) s time interval to determine \(V'O_2\)peak as the largest value in the terminal phase of exercise. Measured cardiopulmonary exercise test parameters were compared with predicted normal values from Wasserman et al.\(^{17}\) Calibration of the system occurred prior to every test according to manufacturer specifications. Single linear regression was performed on respiratory data to determine oxygen uptake efficiency slope (OUES) and \(V'E/V'CO_2\) slope. Respiratory data were averaged every \(30\) s. The OUES was determined by the method of Baba et al.\(^{18}\) The \(V'E/V'CO_2\) slope was calculated as linear regression function, excluding the non-linear part after the ventilatory compensation point.\(^{19}\)
Serum N-terminal prohormone brain natriuretic peptide
Blood samples for NT-proBNP assessment were drawn twice, once prior to randomization, and a second time after a 10-week follow-up period. Samples were analysed locally, and in a standardized fashion. 20,21 N-terminal prohormone brain natriuretic peptide assessment kits differed between participating centres, although the same kit was used for the same patient.

Quality of life
Quality of life was assessed prior to randomization, and after a 10-week follow-up period using two different quality of life questionnaires. Health-related quality of life was assessed by means of the Dutch and Italian translations of the Medical Outcomes Study Short Form 36 item (SF-36) health survey. 22 The SF-36 is a generic multi-item questionnaire comprising of 36 questions on eight domains (physical functioning, role functioning physical, bodily pain, general health perception, vitality, social functioning, role functioning emotional, and mental health). Scores range from 0 to 100, with higher scores representing better quality of life. Patients’ SF-36 scores were analysed against published age- and gender-matched reference population norms, after which the eight domains were combined into two higher-ordered clusters; the physical component summary and the mental component summary.

In addition, quality of life was assessed by means of the Dutch and Italian translations of the CHD-TNO/AZL Adult Quality of Life (CHD-TAAQOL) questionnaire. 23 The CHD-TAAQOL was developed as a disease specific tool for measuring health-related quality of life in adults with congenital heart defects. 23 It contains 26 items covering three subscales: symptoms or limitations during the previous month, worries during the previous month, and impact of the medical examinations. Each item consists of two questions. First, the presence (1: no; 2: yes) or frequency (1: never; 2: occasionally; 3: often) of occurrence of each complaint or limitation during the last month is scored. If a problem occurred, the degree it bothers the respondent is assessed on a four-point scale (1: not at all to 4: very much). The scores were transformed to a 0–100 scale, with higher scores representing better quality of life. Convergent and discriminate validity showed satisfactory coefficients. 23

All patients were asked whether they had been consulted by their treating cardiologist in regard to sports participation, and whether they had been advised positively or negatively towards sports participation. Patients were subsequently asked whether they had engaged in sports in the year prior to inclusion in the study.

Sample size
Sample size calculation was based on the primary endpoint of change in $\text{VO}_2\text{peak}$ (mL/kg/min) as determined by cardiopulmonary exercise test. 15,24 Based on a standard deviation of 2.5, we calculated that 52 patients were required to obtain 80% power to detect a difference of 2 mL/kg/min in $\text{VO}_2\text{peak}$, between the two treatment groups after 10 weeks with a two-sided $\alpha$ of 0.05.

Randomization
Randomization was performed using sealed envelopes. Each participant chose an opaque envelop from a shuffled stack which contained either ‘yes’, which allocated him to the treatment group or ‘no’ which allocated him to the control group. Randomization was stratified by participating centre.

Statistical analysis
Analyses were intention to treat. For statistical analyses SPSS 16.0 (SPSS, Inc., Chicago, IL, USA) for Windows was used. A two-tailed $P$-value of $< 0.05$ was used as a criterion for statistical significance. The descriptive data are presented as numbers with percentage, or as mean with standard deviation, or median with range, as appropriate. Fisher’s exact test and unpaired t-tests, or Mann-Whitney U tests if appropriate, were performed to assess differences in baseline characteristics between the intervention, and the control group, and between the Dutch, and Italian patients, in categorical and continuous variables, respectively. Changes in exercise capacity, serum NT-proBNP levels, and quality of life during follow-up were assessed for all patients in the intervention and the control group, using a two-tailed paired t-test or Wilcoxon test if appropriate. Differences in the main outcome variables (change in exercise capacity, serum NT-proBNP levels, and quality of life) between the training and the control group were assessed by linear regression. As randomization was stratified, the participating centre was included as an independent variable in the linear regression model in order to obtain the correct standard error.

Results
Recruitment
Between April and May 2009 (the Netherlands, $n = 105$) and September and October 2009 (Italy, $n = 36$) patients with a systemic RV were contacted by telephone by a member of the research team. Fifty-five patients (45% male; mean age 32.6 ± 9.9 years) consented to participate in the study. One patient was excluded from participation after baseline procedures had been performed, as she developed ventricular bigeminy during the recovery phase of the baseline exercise test. Subsequently, 54 patients (46% male, mean age 32.5 ± 9.9, of whom 36 in the Netherlands (47% male; mean age 33.6 ± 9.3 years), and 18 in Italy (44% male; mean age 30.1 ± 11.1 years) were randomized. Twenty-eight participants were assigned to the intervention group and twenty-six participants to the control group.

In total, eight patients did not complete the protocol, four in the intervention group, and four in the control group. Two patients underwent pacemaker battery replacement during follow-up. Two patients withdrew from the study due to personal circumstances, four other patients decided to withdraw from the study after a few weeks without apparent reason (figure 1). There were no differences in baseline characteristics between patients who withdrew from the study, compared with those who completed the study.

Baseline data
The intervention ($n = 28$) and control group ($n = 26$) were well balanced on baseline characteristics, including age, type of condition, type of corrective surgery, NYHA classification, presence of pacemaker, and medicinal use. Baseline characteristics are summarized in Table 1. There were no changes in the use of medications during the study period in any of the participating patients. There were no significant differences in baseline characteristics between the Dutch and the Italian patient population, except for
At baseline, no differences in outcome variables were observed between the Dutch and the Italian patient population, except for the TAAQOL-CHD questionnaire. The Dutch patients were less worried about their disease (TAAQOL-CHD), compared with their Italian peers [NL: 89(64–100) vs. IT: 77(60–100); P = 0.013].

**Numbers analysed**

The primary analysis was intention-to-treat and involved all patients who were randomly assigned except those who were lost to follow-up.

**Outcomes and estimations**

Table 2 shows the primary and secondary outcome measurements at baseline and at 10-week follow-up. Changes in outcome parameters (between baseline and follow-up), from which the treatment effects were calculated (difference in change between intervention and control), were distributed symmetrically and fulfilled the assumptions of the linear regression models.

**Cardiopulmonary exercise tests**

The intervention group showed a 7% increase in \( \text{VO}_2\text{peak} \) the 10-week follow-up period (2.2 mL/kg/min, 95% CI: 0.5–3.9; \( P = 0.01 \)), whereas \( \text{VO}_2\text{peak} \) remained unchanged in the control group (\( -0.5 \text{ mL/kg/min, 95% CI: } -2.9 \text{ to } 3.9; P = 0.75 \)). Analysis at 10 weeks showed a significant difference in \( \text{VO}_2\text{peak} \) (3.4 mL/kg/min, 95% CI: 0.2–6.7; \( P = 0.04 \)) and resting systolic blood pressure (\( -7.6 \text{ mmHg, 95% CI: } -14.0 \text{ to } -1.3; p = 0.03 \)) in favour of the exercise group. The OUES also improved in the exercise group (170, 95% CI: 105–236; \( P < 0.001 \)). We found no statistically significant changes in any of exercise parameters during follow-up in the control group.

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**Figure 1** Study enrolment and randomization.

**Table 1** Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 46)</th>
<th>Control (n = 22)</th>
<th>Intervention (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32 ± 11</td>
<td>34 ± 11</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>Male (%)</td>
<td>23 (50)</td>
<td>14 (63)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.18</td>
<td>1.90 ± 0.2</td>
<td>1.90 ± 0.2</td>
</tr>
<tr>
<td>TGA/ccTGA</td>
<td>28/18</td>
<td>11/11</td>
<td>17/17</td>
</tr>
<tr>
<td>TGA: mustard/senning</td>
<td>15/13</td>
<td>5/12</td>
<td>8/3</td>
</tr>
<tr>
<td>TGA: age at repair (months)</td>
<td>7 (1–56)</td>
<td>7 (2–48)</td>
<td>7 (1–56)</td>
</tr>
<tr>
<td>NYHA class I/II</td>
<td>31/15</td>
<td>13/9</td>
<td>18/6</td>
</tr>
<tr>
<td>Pacemaker in situ (%)</td>
<td>11 (24)</td>
<td>6 (27)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Medication (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>12 (27)</td>
<td>7 (35)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>ACE/ATII</td>
<td>17 (39)</td>
<td>8 (40)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>8 (18)</td>
<td>5 (25)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs</td>
<td>4 (9)</td>
<td>2 (10)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>No medication</td>
<td>21 (46)</td>
<td>9 (41)</td>
<td>12 (50)</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation; median (range); number of patients (percentage); number of patients/number of patients. ACE, angiotensin-converting enzyme inhibitor; ATII, angiotensin II receptor antagonist; BSA, body surface area; ccTGA, congenitally corrected transposition of the great arteries; NYHA, New York Heart Association functional class; TGA, transposition of the great arteries. There were no significant differences between intervention and control groups.

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the age at repair [NL: median 8 (2–57) months vs. IT: median 6 (1–10) months; \( P = 0.05 \)].

At baseline, these were no significant differences in any of the outcome variables between the intervention and control group.
As can be readily seen in Table 2, quality of life remained unchanged during follow-up in the intervention and the control group, nor a difference in change between the control and the intervention group, were observed (Table 2).

**Quality of life**
As can be readily seen in Table 2, quality of life remained unchanged during follow-up in the intervention and the control group.

**Sports consultation**
The majority of patients (n = 34; 63%) had been consulted by their cardiologist on sports participation, whereas 13 (24%) had not been consulted, and 7 (13%) could not remember. Twenty-five (74%) patients who had been consulted, had received positive advice and 26 (48%) of all patients stated that they had engaged in any form of sports participation in the year prior to participating in the current study. The latter patient group had similar baseline $\text{VO}_{2\text{peak}}$ and serum NT-proBNP levels compared with patients who had not engaged in sports participation. Moreover, at baseline, sporting patients had increased physical quality of life (SF-36) and less worries (TAAQOL-CHD), compared with non-sporting patients. We found no statistically differences in changes of outcome parameters between patients that had and patients that had not engaged in sports participation. We found no differences in the number of patients who had received advice, and who stated that they had engaged in sports participation between the intervention and the control group, nor between the Dutch, and the Italian patients.

**Harms**
Exercise tests could be performed without complications in all patients. One baseline exercise test was aborted due to nausea of the patient, but was repeated successfully 6 h later. As stated above, one patient developed ventricular bigeminy in the recovery phase, and was excluded from participation in the study. During the training protocol, one patient sustained calf injury during exercise, and had to discontinue the protocol for 2 weeks. No other complaints and/or complications were reported.

**Discussion**
This randomized controlled trial demonstrates that exercise training increases exercise capacity in adult patients with a systemic RV. Moreover, high-intensity exercise training was performed safely in these patients. Serum NT-proBNP levels, and quality of life remained unchanged during 10 consecutive weeks of exercise training.

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**Table 2  Exercise response**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention Baseline</th>
<th>Follow-up</th>
<th>Control Baseline</th>
<th>Follow-up</th>
<th>Difference (95% CI) at 10 weeks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiopulmonary exercise testing</strong></td>
<td></td>
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<tr>
<td>$\text{VO}_{2\text{peak}}$ (mL/kg/min)</td>
<td>27 ± 7</td>
<td>29 ± 7</td>
<td>26 ± 9</td>
<td>26 ± 8</td>
<td>3.4 (0.2 to 6.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>$\text{VO}_{2\text{peak}}$ (mL/min)</td>
<td>2043 ± 558</td>
<td>2219 ± 547</td>
<td>1973 ± 740</td>
<td>1920 ± 650</td>
<td>283 (22 to 544)</td>
<td>0.03</td>
</tr>
<tr>
<td>$\text{VO}_{2\text{peak}}$ (% pred)</td>
<td>70 ± 18</td>
<td>76 ± 20</td>
<td>73 ± 18</td>
<td>74 ± 19</td>
<td>5.2 (−0.9 to 11.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>V/E/VCO$_2$ slope</td>
<td>30 ± 5</td>
<td>30 ± 4</td>
<td>31 ± 8</td>
<td>31 ± 8</td>
<td>−1.3 (−4.9 to 2.4)</td>
<td>0.48</td>
</tr>
<tr>
<td>OUES</td>
<td>1931 ± 431</td>
<td>2101 ± 452</td>
<td>2203 ± 855</td>
<td>2193 ± 594</td>
<td>94 (−229 to 417)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Haemodynamics</strong></td>
<td></td>
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</tr>
<tr>
<td>Systolic blood pressure, rest (mmHg)</td>
<td>115 ± 12</td>
<td>109 ± 7</td>
<td>120 ± 15</td>
<td>119 ± 14</td>
<td>−7.6 (−14.0 to −1.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic blood pressure, max (mmHg)</td>
<td>159 ± 21</td>
<td>163 ± 24</td>
<td>159 ± 23</td>
<td>165 ± 27</td>
<td>−0.9 (−15.2 to 13.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>Heart rate, rest (beats/minute)</td>
<td>75 ± 15</td>
<td>70 ± 12</td>
<td>79 ± 10</td>
<td>77 ± 14</td>
<td>−6.6 (−15.0 to 1.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart rate, max (b.p.m.)</td>
<td>155 ± 28</td>
<td>160 ± 29</td>
<td>147 ± 37</td>
<td>148 ± 32</td>
<td>5.5 (−3.3 to 14.2)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Laboratory testing</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>166 (25–2816)</td>
<td>183 (29–2778)</td>
<td>227 (25–1696)</td>
<td>222 (5–1521)</td>
<td>109 (−6 to 224)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Quality of life</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SF-36</td>
<td></td>
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<tr>
<td>Mental health component</td>
<td>−0.04 ± 0.85</td>
<td>−0.16 ± 0.8</td>
<td>0.07 ± 0.86</td>
<td>0.16 ± 0.72</td>
<td>−0.2 (−0.5 to 0.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Physical health component</td>
<td>0.08 ± 0.81</td>
<td>0.21 ± 0.68</td>
<td>−0.24 ± 0.95</td>
<td>−0.25 ± 0.99</td>
<td>0.2 (−0.1 to 0.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>CHD-TAAQOL</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>89 (69–100)</td>
<td>91 (58–100)</td>
<td>88 (53–100)</td>
<td>86 (60–100)</td>
<td>2.0 (−2.0 to 6.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Worries</td>
<td>80 (60–100)</td>
<td>84 (40–100)</td>
<td>92 (60–100)</td>
<td>92 (54–100)</td>
<td>−3.3 (−9.6 to 3.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Impact</td>
<td>89 (71–97)</td>
<td>85 (69–97)</td>
<td>87 (60–100)</td>
<td>86 (69–100)</td>
<td>−0.2 (−3.8 to 3.4)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or median (range); 95% CI, 95% confidence interval; L/min, litre per minute; mL/kg/min, millilitre per kilogram per minute; mL/min, millilitre per minute; % pred, percentage of predicted; ng/L, nanogram per litre; OUES, oxygen uptake efficiency slope.

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Laboratory tests
No significant changes in serum NT-proBNP levels during follow-up in the intervention and the control group, nor a difference in change between the control and the intervention group, were observed (Table 2).
Limitations
As in many studies on adult patients with a systemic RV, the number of patients included in this study was relatively small. Small patient numbers make accurate subgroup analyses difficult, which raises concerns about generalizability. Moreover, a significant number of patients (39%) refused participation, which could have lead to the collection of a selected patient group. Larger-scaled studies should be pursued to definitely establish the value of our findings. Power calculation was performed based on our primary endpoint, a change in VO\textsubscript{2peak}. Consequently, the study might not have had sufficient power to identify significant changes the secondary endpoints NT-proBNP levels and quality of life. Furthermore, no central core laboratory was used for NT-proBNP assessment. No complications occurred during the 10 weeks high-intensity exercise training protocol. Although the study is probably underpowered to draw conclusions on safety, these data represent the best available evidence concerning safety of high-intensity training in patients with a systemic RV, as much larger cohorts are unlikely given the low prevalence of CHD. The exercise training protocol was home based, which makes verification of compliance difficult. Previous studies had established that home-based exercise can be performed successfully.25,26 In addition, all patients were contacted on a weekly basis to verify and secure compliance. Patients in NYHA functional class III and IV were excluded from participating in the study. We are the first to enrol patients with a systemic RV in a (home-based) training protocol, and somewhat restrictive inclusion criteria seemed appropriate. On the other hand, as exercise training is found to be safe in adult patients with advanced congestive heart failure, one would not expect major safety issues in adult patients with systemic RV failure.

Generalizability
A significant number of eligible patients were not included or did not complete the protocol. The large majority of patients that refused participation did so because they considered the protocol to be too time-consuming, and incompatible with their daily life activities. This suggests that our patient group is not necessarily more active, or healthier in comparison to non-consenting patients. In addition, there were no differences in baseline characteristics between these patients who did, and those who did not complete the protocol, suggesting that participants did not quit because they were in worse condition (e.g. VO\textsubscript{2peak} 26.6 mL/kg/min; \(P = 0.41\)). Consequently, we consider our data to be representative.

Interpretation
To our knowledge, this is the first trial to demonstrate the benefits of physical exercise in adult patients with a systemic RV. Previous studies have universally demonstrated that exercise training increases exercise capacity.5,8,10,27–30 However, results on serum NT-proBNP levels and quality of life are equivocal. Arad et al.31,32 found NT-proBNP levels to remain unchanged after 4.5 months of exercise training, whereas others describe a significant decrease of these levels, after 9 months of training with a similar protocol. Our study showed no decrease in serum NT-proBNP levels after 10 weeks of training in adult patients with a systemic RV. Although systemic RV dysfunction is the most frequently seen complication in the adult systemic RV population, levels are generally not elevated to the extent of left-sided heart failure patients. This could significantly decrease the value of NT-proBNP as a marker of ventricular dysfunction. In addition, serum NT-proBNP levels are usually elevated during exercise, especially in patients with ventricular dysfunction.33 A relative elevation in our intervention group, who experience an increased level of daily physical activity, could have blurred our results on a potential positive effect of exercise on the myocardium.

In general, VO\textsubscript{2peak} is limited in adult patients with a systemic RV. This is primarily due to their inability to increase cardiac output during exercise, caused by an incompetent chronotropic response, inadequate ventricular filling through the atrial baffle, and decreased coronary flow reserve.34 Furthermore, similar to healthy individuals, VO\textsubscript{2peak} is determined by peripheral factors (i.e. endothelial function, muscle mass, muscle oxygenation, etc.). Improvements in our patient population seem predominantly peripheral, with an increase in VO\textsubscript{2peak}, a decrease in resting systolic blood pressure, but no significant change is serum NT-proBNP levels.8 Further investigation is warranted to obtain information on how peripheral improvements are achieved.

At baseline, we found that patients who had stated that they were engaged in sports participation had increased quality of life. This is in line with previous findings by our group.29 However, it remained unclear whether sports participation increased quality of life, or whether increased quality of life motivated patients to engage in sports participation. The 10-week training protocol did not result in an improvement in quality of life in adult patients with a systemic RV. These findings are contrary to the overall perception on the effect of exercise on quality of life. Most authors describe an improvement in quality of life after exercise training, both in patients with acquired heart disease,5,29,35 as well as with CHD.15,27 However, it is known that, in general, quality of life in adult patients with CHD is excellent, and comparable with the standard population.36,37 We found similar high quality of life scores, which do not allow for much improvement.

Whether exercise training decreases cardiac morbidity and mortality remains controversial. Belardinelli et al. found significantly lower mortality in the trained, compared with the untrained patients with left-sided congestive heart failure. In addition, a recent paper by Giardini et al.38 demonstrated that increased VO\textsubscript{2peak} was positively associated with event-free survival in adult patients with a systemic RV. These data suggest that an increase in patients' VO\textsubscript{2peak} through exercise could have a subse-quent positive effect on event-free survival. On the other hand, a recent paper by O’Conner et al.5,39 describes no such differences between groups in a similar patient population. To evaluate the effect of exercise training on cardiac morbidity and mortality in adult patients with a systemic RV, a large-scaled study with a long-term exercise training programme is warranted. However, feasibility of such a study is questionable, as patient numbers are low, and major cardiac events, and (cardiac) death are relatively rare.

We chose to enrol consenting patients in a 10-week, high-intensity, home-based, interval exercise training protocol. Recent studies have proved a superior cardiovascular effect of interval
training, in comparison to continuous training in patients with congestive heart failure.30,40 Wisløff et al.10 found that patients enrolled in the high-intensity interval training were more motivated to perform the training, and showed a greater increase in VO_2peak and quality of life, and a more significant decrease in pro-BNP levels, compared with those in the continuous training programme. Moreover, a study by Meyer et al.40 demonstrated superior cardiac output increase in the interval training group, compared with the continuous training group. It is known that home-based exercise training protocols can be performed safely and successfully.25,26 In addition, we expected a home-based training programme to increase willingness to participate in the study, and to improve compliance in this relatively young and socially active patient population.

The American Heart Association recommends exercise training for patients with left ventricular failure, as it safe and beneficial.4 The European Society of Cardiology states that, as literature on exercise and sports participation in patients with CHD is limited, a restrictive attitude towards competitive sports seems wise in these patients.1 A more recent position paper by an international expert panel appointed by the European Society of Cardiology suggests a more liberal attitude towards leisure sports (as opposed to competitive sports) and advises moderate to low-intensity dynamic exercise in patients with surgically and congenitally corrected TGA.12 In our study, 63% of participating patients had received advice from their treating cardiologist on sports participation, of whom 73% positive. Moreover, 48% of patients had already engaged in sports regularly. Results from the current study suggest that exercise training is beneficial for patients with a systemic RV and should not only be permitted but actively recommended. In order to generalize this advice for all CHD patients, further research is warranted to obtain information on the effect of exercise training in patients with other congenital cardiac conditions.

Conclusion

This randomized trial demonstrates that exercise training improves exercise capacity in adult patients with a systemic RV. Patients with a systemic RV should be encouraged to engage in regular exercise.

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References


