The systemic right ventricle
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Exercise training is beneficial and safe in adult patients with a systemic right ventricle

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Submitted
ABSTRACT

Aims. The aim of this prospective, randomized trial was to evaluate whether exercise training in adult patients with a systemic right ventricle (RV) improves exercise capacity, serum NT-proBNP levels and quality of life.

Methods and results. Fifty-four adult patients (46% male; age 33±10 years) with a systemic RV, were randomized to an intervention group (n=28) with 3 training sessions per week for 10 consecutive weeks, and a control group (n=26). At baseline, and follow-up, we determined maximal exercise capacity (VO$_{2peak}$), serum NT-proBNP levels, and quality of life by means of the SF-36, and the TAAQOL Congenital Heart Disease questionnaires. Paired samples t-tests demonstrated that VO$_{2peak}$ increased with 7%, from 27±7 to 29±7 ml/kg/min; p=0.01, in the intervention group, and remained unchanged in the control group (26±9 versus 26±8 ml/kg/min; p=N.S). No significant changes in serum NT-proBNP levels were found in the intervention group (416±636 versus 400±623 ng/L, p=N.S.), nor in the control group (319±419 versus 301±371 ng/L, p=N.S.). Quality of life remained unchanged in the intervention group, as well as in the control group. None of the patients in the intervention group had to discontinue the training program due to adverse events.

Conclusions: In adult patients with a systemic RV exercise training improves exercise capacity, and can be performed safely. We recommend to revise restrictive guidelines, and to encourage patients to become physically active.
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, i.e. 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.

The American Heart Association recommends patients with acquired heart disease to engage in physical exercise, as it is safe, increases exercise capacity and improves quality of life in these patients. Few small studies have demonstrated similar beneficial effects of exercise training in heterogeneous groups of patients with CHD, especially in children and adolescents. 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. 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

Patient characteristics

The study was an multi-centre prospective, randomized, controlled trial, and was set-up to evaluate the effect of exercise training on exercise capacity, serum NT-proBNP levels and quality of life in adult patients with a systemic RV.

In the Netherlands, the study population was identified through the CONgenital COR vitia (CONCOR) database, the national database and DNA-bank for adult CHD,\(^\text{14}\) and, in Italy, through the echocardiography database of the Paediatric Cardiology and Adult Congenital Unit, at the University Medical Center in Bologna. Exclusion criteria were mental or physical incapable to participate in a home-based exercise training program, the presence of exercise-induced arrhythmias, symptomatic myocardial ischemia, 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.

Sample size calculation was based on the primary endpoint of change in \(V'O_{2\text{peak}}\) (ml/kg/min) as determined by cardiopulmonary exercise test.\(^\text{15, 16}\) 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 \(V'O_{2\text{peak}}\) between the two treatment groups after 10 weeks with a 2 sided \(\alpha\) of 0.05.

One hundred forty one patients were eligible to participate in the study, and were contacted by telephone by a member of the research team. Patient inclusion was conducted in the Netherlands (\(n=105\)) in April and May 2009, in Italy (\(n=36\)) in September and October 2009. The study complies 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.
Exercise training program
Consenting patients were randomized, stratified by sex, and country, to a). commence with an exercise training protocol for the duration of 10 consecutive weeks (the intervention group), or b). refrain from this exercise training protocol for the duration of 10 consecutive weeks (the control group). Patients started the training protocol within one week after all baseline procedures had been performed. The training protocol was home-based, and consisted of 3 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 minutes at 60% of maximal heart rate, as determined by baseline cardiopulmonary exercise testing, before starting a 32 minute interval training. The interval training consisted of 5 times 4 minutes of steps aerobics, starting at 75% and incrementing to 90% of maximal heart rate during the 10 week training protocol, alternated with 4 times 3 minutes of steps aerobics at 60% of maximal heart rate. Each training session was terminated by a 5 minute cool-down period at 60% of maximal heart rate.\(^{16}\) 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 program and contact a physician if they experienced chest pain, palpitations, dizziness or other distressing symptoms.

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. Patients were placed on an upright cycle ergometer and breath-by-breath analysis were made of minute ventilation, oxygen uptake ($VO_2$), carbon dioxide elimination ($V'CO_2$), heart rate, blood pressure and electrocardiography (Jaeger Oxycon pro, Wuerzburg, Germany). Work load was increased by 5 to 15 Watt/minute in a stepwise manner, depending on the individually predicted maximum exercise capacity and in such a way that calculated maximal effort was attained in approximately 10-15 minutes. All patients were exercised to their maximum exercise capability. We averaged $VO_2$ using a 10 second time interval to determine $VO_2_{peak}$ as the largest value in the terminal phase of exercise. Measured cardiopulmonary exercise test parameters were compared with predicted normal values from Wasserman and co-workers. Calibration of the system occurred prior to every test according to manufacturer specifications.

**Serum NT-proBNP**

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 analyzed locally, and in a standardized fashion.

**Quality of Life**

Quality of life was assessed prior to randomization, and after a 10 week follow-up period using 2 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. The SF-36 is a generic multi-item questionnaire comprising of 36 questions on 8 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. The 8 domains were combined into 2 higher-ordered clusters; the Physical
Component Summary and the Mental Component Summary. Patients’ SF-36 scores were compared with published age- and gender-matched reference population norms.

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.\textsuperscript{22} The CHD-TAAQOL was developed as a disease specific tool for measuring health-related quality of life in adults with congenital heart defects.\textsuperscript{22} 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 4-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.\textsuperscript{22}

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 toward sports participation. Patients were subsequently asked whether they had engaged in sports in the year prior to inclusion in the study.

**Statistical analysis**

For statistical analyses SPSS 16.0 (SPSS Inc., Chicago, Illinois) for Windows was used. A 2-tailed probability 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. Chi-squared 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 who completed both baseline and follow-up investigations, using a two-tailed paired \( t \) test.

**RESULTS**

**Patient characteristics**

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

**Compliance and safety**

In total, 8 patients did not complete the protocol, 4 in the intervention group, 4 in the control group. Two patients underwent pacemaker battery replacement during follow-up. Two patient withdrew from the study due to personal circumstances, 4 other patients decided to withdraw from the study after a few weeks without apparent reason. There were no differences in baseline characteristics between patients who withdrew from the study, compared to those who completed the study.
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 hours later. As stated above, one patients developed ventricular bigeminy in the recovery phase, and was excluded from participating in the study. During the training protocol, one patient sustained calf injury during exercise, and had to discontinue the protocol for two weeks. No other complaints and/or complications were reported.

**Cardiopulmonary exercise tests**

At baseline, we found no differences in hemodynamic and exercise parameters between the intervention and the control group. At baseline, no differences were observed between the Dutch and the Italian patient population. The intervention group showed a 7% increase in $\text{V'\text{O}_{2}\text{peak}}$ (27±7 to 29±7 ml/kg/min; $p=0.01$) during the 10 week follow-up period, whereas $\text{V'\text{O}_{2}\text{peak}}$ remained unchanged in the control group. Figure 1. Resting systolic blood pressure decreased during follow-up in the intervention group ($p=0.01$). We found no changes in any of the hemodynamic and exercise parameters during follow-up in the control group (table 2).

**Laboratory tests**

At baseline, there were no differences in serum NT-proBNP levels between the intervention and the control group, nor between the Dutch and Italian patient population. No significant changes in serum NT-proBNP levels were observed during follow-up in the intervention and the control group (table 2).

**Quality of life**

At baseline, there were no differences in quality of life between the intervention and the control group. The Dutch patients were less worried about their disease (TAAQOL-CHD), compared to their Italian peers (NL: 86.7±10.5 vs. IT: 76.9±13.2; $p=0.004$). As can be readily seen in table 2, quality of life remained unchanged during follow-up in intervention and the control group.
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 (73%) patients who had been consulted, had received positive advise, and 26 (48%) 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 V'O_2peak and serum NT-proBNP levels, compared to patients who had not engaged in sports.
participation. However, at baseline, sporting patients had increased physical quality of life (SF-36) and less worries (TAAQOL-CHD), compared to non-sporting patients. We found no differences in the number of patients who had received advise, 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.

**Figure 1.** Changes in maximal exercise capacity at baseline and follow-up.
Changes in maximal exercise capacity (\(\text{V}^{'\text{O}_2}\text{peak}\)) for the training (left panel), and the control (right panel) group, at baseline and after 10 weeks.

![Graph showing changes in VO2peak](image)

**DISCUSSION**
This randomized controlled trial demonstrates that exercise training increases exercise capacity in adult patients with a systemic RV. Moreover, high-intensity exercise training can be performed safely in these patients. Serum NT-proBNP levels, and quality of life remained unchanged during 10 consecutive weeks of exercise training.
Table 2. Exercise response

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention (n=24)</th>
<th>Control (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>p-value</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, rest (mmHg)</td>
<td>115 ± 12</td>
<td>109 ± 7</td>
<td>.024</td>
</tr>
<tr>
<td>Systolic blood pressure, max (mmHg)</td>
<td>159 ± 21</td>
<td>163 ± 24</td>
<td>N.S.</td>
</tr>
<tr>
<td>Heart rate, rest (beats/minute)</td>
<td>75 ± 15</td>
<td>70 ± 12</td>
<td>N.S.</td>
</tr>
<tr>
<td>Heart rate, max (beats/minute)</td>
<td>155 ± 28</td>
<td>160 ± 29</td>
<td>N.S.</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO2max (ml/kg/min)</td>
<td>2043 ± 558</td>
<td>2119 ± 547</td>
<td>.009</td>
</tr>
<tr>
<td>VO2max (% pred)</td>
<td>70 ± 18</td>
<td>76 ± 20</td>
<td>.009</td>
</tr>
<tr>
<td>VCO2max (ml/min)</td>
<td>2240 ± 731</td>
<td>2457 ± 619</td>
<td>.042</td>
</tr>
<tr>
<td>Ventilation (L/min)</td>
<td>7.4 ± 1.9</td>
<td>8.0 ± 1.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>416 ± 636</td>
<td>400 ± 623</td>
<td>N.S.</td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 Mental health component</td>
<td>-0.04 ± 0.85</td>
<td>-0.16 ± 0.80</td>
<td>N.S.</td>
</tr>
<tr>
<td>Physical health component</td>
<td>0.08 ± 0.81</td>
<td>0.21 ± 0.68</td>
<td>N.S.</td>
</tr>
<tr>
<td>CHD-TAQOL Symptoms</td>
<td>87 ± 9</td>
<td>89 ± 11</td>
<td>N.S.</td>
</tr>
<tr>
<td>CHD-TAQOL Worries</td>
<td>81 ± 12</td>
<td>81 ± 15</td>
<td>N.S.</td>
</tr>
<tr>
<td>CHD-TAQOL Impact</td>
<td>87 ± 8</td>
<td>86 ± 8</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation; L/min = litre per minute; ml/kg/min = millilitre per kilogram per minute; ml/min = millilitre per minute; % pred = percentage of predicted.

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, 6, 10, 23-26 However, results on serum NT-proBNP levels and quality of life are equivocal. Arad et al. found NT-proBNP levels to remain unchanged after 4.5 months of exercise training, whereas others describe a significant decrease of these levels, after nine months of training with a similar protocol.27, 28 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. 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, V'O_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. Furthermore, similar to healthy individuals, V'O_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 V'O_2peak, a decrease in resting systolic blood pressure, but no significant change in serum NT-proBNP levels. 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. 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, as well as with CHD. However, it is known that, in general, quality of life in adult patients with CHD is excellent, and comparable to the standard population. We found similar high quality of life scores, which do not allow for much improvement. Moreover, power calculation was performed based on the primary outcome measure (V'O_2peak), which could have led to insufficient power to observe changes in quality of life.

Whether exercise training decreases cardiac morbidity and mortality remains controversial. Belardinelli et al. found significantly lower mortality in the
trained, compared to the untrained patients with left-sided congestive heart failure. In addition, a recent paper by Giardini et al. demonstrated that increased $V'O_{2\text{peak}}$ was positively associated with event-free survival in adult patients with a systemic RV.\textsuperscript{34} These data suggest that an increase in patients’ $V'O_{2\text{peak}}$ through exercise could have a subsequent positive effect on event-free survival. On the other hand, a recent paper by O’Conner et al. describe no such differences between groups in a similar patient population.\textsuperscript{5, 35} 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 program 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 enroll consenting patients in a 10-week, high-intensity, home-based, interval exercise training protocol. Recent studies have proven a superior cardiovascular effect of interval training, in comparison to continuous training in patients with congestive heart failure.\textsuperscript{26, 36} Wisløff et al. found that patients enrolled in the high-intensity interval training were more motivated to perform the training, and showed a greater increase in $V'O_{2\text{peak}}$, and quality of life, and a more significant decrease in pro-BNP levels, compared to those in the continuous training program.\textsuperscript{26} Moreover, a study by Meyer et al. demonstrated superior cardiac output increase in the interval training group, compared to the continuous training group.\textsuperscript{36} It is known that home-based exercise training protocols can be performed safely and successfully.\textsuperscript{37, 38} In addition, we expected a home-based training program 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.\textsuperscript{4} On the other hand, the European Society of Cardiology states that, as literature on exercise and sports participating in patients with CHD is limited, a restrictive attitude seems wise in these patients.\textsuperscript{13} Notwithstanding the restrictive guidelines, 63% of participation patients had received advise on sports participation, of whom 73% positive, by
their treating cardiologist. Moreover, 48% of patients had already engaged in sports participation. Results from the current study suggest that restrictive guidelines could have unintentional counterproductive effects. Further research is warranted to obtain information on the effect of exercise training in patients with other congenital cardiac conditions, as alleviation of restrictive guidelines seems to be appropriate.

**Limitations**

As in many studies on adult patients with a systemic RV, the number of patients included in this study was relatively small. 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$_{2\text{peak}}$. Power calculations based on the secondary endpoints could have resulted in a higher number of patients required for this study, and could have increased the likelihood to identify significant changes in serum NT-proBNP levels and quality of life. 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.$^{37, 38}$ 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 enroll 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.
CONCLUSION

The results of this longitudinal study, demonstrate that exercise training improves exercise capacity in adult patients with a systemic RV. Moreover, the current study showed that high-intensity exercise training can be performed safely. Patients with a systemic RV should be encouraged to engage in regular exercise, and restrictive guidelines should be re-evaluated.


