The systemic right ventricle
van der Bom, T.

Citation for published version (APA):
vander Bom, T. (2014). The systemic right ventricle
CHAPTER 9

LONG-TERM BENEFITS OF EXERCISE TRAINING IN PATIENTS WITH A SYSTEMIC RIGHT VENTRICLE

Teun van der Bom
Michiel M. Winter
Jennifer L. Knaake
Elena Cervi
Leonie C.S. de Vries
Anna Balducci
Paola G. Meregalli
Petronella G. Pieper
Arie P.J. van Dijk
Marco Bonvicini
Barbara J.M. Mulder
Berto J. Bouma

International Journal of Cardiology 2014
ABSTRACT

Objectives: The aim of the present study is to determine the long-term effects of a ten-week exercise training program in adult patients with a systemic right ventricle.

Methods: All patients who participated in a 2009 randomized controlled trial were approached. At approximately three years follow-up from initial baseline, patients underwent cardiopulmonary exercise testing, filled out two quality of life questionnaires, and NT proBNP levels were measured. All examinations were performed according to the protocols of the 2009 trial. In addition, patients were asked about their current sports habits.

Results: Of the 54 patients who were randomized in the 2009-trial 40 participated in the current re-evaluation (male 50%, ccTGA 35%, age 36±10 years, intervention group n = 22, control group n = 18). After three years, no persistent effect of exercise training on $V'O_{2peak}$ training remained (-2% of predicted, 95% CI -3% to 5%; p= .56). However, patients who already participated in regular sports or exercise at baseline (n = 23/40 (58%)) showed higher $V'O_{2peak}$ of 13% of predicted (95% CI 4% to 23%; p > .01) and a decrease of 62% in plasma NT-proBNP (95% CI -115% to -10%; p > .03) during follow-up, when compared to patients who did not. Moreover, sports were associated with a lower incidence of clinical events (p = .032).

Conclusion: Short-term beneficial effects of exercise training did not persist over a three-year follow-up period. However, sports participation at baseline was associated with better exercise capacity, lower neurohormone levels, and increased event-free survival.
INTRODUCTION

The estimated prevalence of congenital heart disease (CHD) is 3 per 1000 live births, and the number of these patients that survive until adulthood is steadily increasing.\textsuperscript{1} A substantial portion of these patients has a morphological right ventricle that sustains the systemic circulation, for instance 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). The large majority of adult patients with a systemic right ventricle is faced with deteriorating right ventricular function, and decreased exercise capacity.\textsuperscript{2}

In patients with acquired congestive heart failure the European Society of Cardiology recommends patient’s participation in a multi-disciplinary care program, which includes exercise training, to reduce the risk of heart failure hospitalization.\textsuperscript{3} A study by O’Connor et al. showed an 11\% reduction in all-cause mortality or all-cause hospitalization at 30 months follow-up of a 3 month supervised training program, followed by a home-based training program.\textsuperscript{4} In our own study, ten weeks of exercise training improved exercise capacity in patients with a systemic right ventricle.\textsuperscript{5} In patients with acquired heart disease beneficial effects of exercise training are known to diminish as time from the training program progresses.\textsuperscript{6,7} However, it remains unclear whether the effects of exercise training in adult patients with a systemic right ventricle is only temporary or whether it constitutes a permanent effect, possibly due to lifestyle changes. Therefore, the primary objective of this study is to determine the long-term effects of a ten-week exercise training program in adult patients with a systemic right ventricle.

METHODS

Study design

The present study was a one-time cross-sectional re-evaluation at three years follow-up of participants of the 2009 study “The effect of exercise in adult patients with a systemic right ventricle” (http://trialregister.nl id. NTR1909)\textsuperscript{5}. 
Participants

All patients who participated in the 2009 study were eligible. These were adults with a systemic right ventricle due to congenitally or surgically corrected TGA. Patients who were mentally or physically incapable to participate in a home-based exercise program had been excluded, as were patients with experienced exercise-induced arrhythmia, 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.

Study settings

The study was conducted in the Netherlands (three sites) and Italy (one site). The study complies with the Declaration of Helsinki and was approved by the locally appointed Ethics Committee of all participating centers. Renewed informed consent was obtained from all participants prior to participation in the present re-evaluation.

Interventions

In 2009 consenting patients were randomized using unmarked opaque envelopes to an intervention group with three aerobics step training sessions per week for 10 consecutive weeks, and a control group. The detailed exercise training protocol has been published previously.\(^5\)

Sports participation

Patients were asked to indicate 1) whether they currently participated in sports or physical exercise, 2) how many times they participated in sports or exercise and 3) with what intensity (light, medium, heavy). The answers were compared to the data of the original trial. Patients who participated in sports or those who exercised at least one hour weekly in an activity that scored 5 METS or more according to the Compendium of Physical Activities\(^8\), were considered to be active in sports, while patients who scored below this threshold were not considered active in sports or exercise.
Outcomes

Cardiopulmonary exercise testing

Exercise testing was performed on an upright bicycle ergometer. After an initial calibration period of 2 minutes, workload was increased by 5-15 W/min in a stepwise manner. The exercise protocol was identical to the tests performed in 2009. Breath-by-breath analysis of minute ventilation, oxygen uptake ($\dot{V'O_2}$), carbon dioxide elimination ($\dot{V'CO_2}$), heart rate, blood pressure and electrocardiography were made.

Serum N-terminal pro-hormone of brain natriuretic peptide

Samples were analyzed locally and in a standardized fashion. N-terminal pro-hormone brain natriuretic peptide assessment kits differed between participating centers, although the same kit was used for the same patient.

Quality of life

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 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 analyzed in comparison to 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. The CHD-TAAQOL was developed as a disease specific tool for measuring health-related quality of life in adults with congenital heart defects. Scores were transformed to a 0–100 scale, with higher scores representing better quality of life.

Statistical analysis

Data are expressed as numbers with percentage, as mean with standard
deviation, or median with inter quartile range (IQR) as appropriate. Analysis was intention-to-treat. Chi-square and Students' independent t-test were performed to evaluate whether the re-recruitment process might have imbalanced the study groups, the original grouping being the result of randomization. Changes from baseline in each group were evaluated using a two-tailed paired t-test or Wilcoxon matched pairs signed ranks test where appropriate. Significance and size of the treatment effect (intervention vs control) were determined by analysis of covariance. The analysis was adjusted for baseline values and participating center (to account for stratification). In addition, a sensitivity analysis including only those patients who completed the protocol in both 2009 and 2013 was performed. A 2-tailed p-value of < 0.05 was used as a criterion for statistical significance.

**Additional analyses**

An exploratory multivariate analysis of covariance was performed to assess whether any determinants at baseline were associated with exercise capacity at follow up. Moreover, a composite endpoint of clinical events was defined similar to a previous publication.\(^9\) This included any arrhythmia, reoperation, thromboembolism, myocardial infarction, worsening heart failure, and death. Event-free survival was estimated using all available data (including chart review of non-participating patients). In patients with multiple events only the first event was used in survival analysis. Differences in the occurrence of complications were assessed using a Log Rank test.

**RESULTS**

**Recruitment**

Between January and September 2013 all but 2 (one could not be reached, one had died) of the original 54 participants were contacted by telephone. Of the 52 original study entrants who were contacted 40 consented to participate in the follow-up study and completed the full cardiopulmonary exercise test protocol (primary endpoint). Of the 40 consenting participants, four patients had not completed the full protocol in 2009. An additional three patients participated only by filling out the quality of life questionnaires. Nine original entrants refused to participate, citing no time and the distance to their tertiary
referral center as their main reasons. (Figure 1) Consequently, 22 patients who were originally assigned to the intervention group and 18 patients who were assigned to the control group were analyzed in the assessment of the primary endpoint. There were no differences in baseline parameters (age, \( V'O_2\text{peak} \), NT proBNP, medication, NYHA class) or event-rate between the 40 participants of the current follow-up study and the 14 non-participants. In 50
of the original 54 participants medical charts with complete follow-up were available leaving 50 patients for survival analysis.

**Baseline data**

Table 1 outlines the baseline characteristics of all patients who participated in the follow-up analysis. The study groups were reasonably well balanced at the present re-evaluation, although patients with Senning operation were overrepresented in the intervention group, without reaching statistical significance.

**Outcomes and estimations**

*Cardiopulmonary exercise testing*

In the overall group (n =40), $V'O_2 \text{peak}$ showed no significant change from
Baseline to three years follow-up (−0.7 ml/kg/min; 95% CI, −2.6 to 1.1 ml/kg/min; p = .43), nor were there significant changes in the two treatment groups (intervention: −1.6 ml/kg/min; 95% CI, −4.2 to 0.9 ml/kg/min; p = .96; control: −1.6 ml/kg/min; 95% CI, −4.2 to 0.9 ml/kg/min; p = .18). At three year follow-up, there were no differences in change in cardiopulmonary or hemodynamic parameters between the intervention and control groups (Table 2).

### Cardiopulmonary exercise testing

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak (ml/kg/min)</td>
<td>26.8 ± 6.6</td>
<td>26.9 ± 9.7</td>
<td>24.7 ± 5.1</td>
</tr>
<tr>
<td>VO2peak (ml/min)</td>
<td>2010 ± 471</td>
<td>2049 ± 666</td>
<td>1882 ± 445</td>
</tr>
<tr>
<td>VO2peak (% pred)</td>
<td>72 ± 17</td>
<td>73 ± 19</td>
<td>73 ± 18</td>
</tr>
</tbody>
</table>

### Hemodynamics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, rest (mmHg)</td>
<td>116 ± 11</td>
<td>113 ± 13</td>
<td>119 ± 15</td>
</tr>
<tr>
<td>Systolic blood pressure, max (mmHg)</td>
<td>162 ± 19</td>
<td>153 ± 26</td>
<td>154 ± 21</td>
</tr>
<tr>
<td>Heart rate, rest (beats/minute)</td>
<td>77 ± 15</td>
<td>72 ± 17</td>
<td>82 ± 9</td>
</tr>
<tr>
<td>Heart rate, max (beats/minute)</td>
<td>157 ± 27</td>
<td>149 ± 38</td>
<td>150 ± 35</td>
</tr>
</tbody>
</table>

### Laboratory testing

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>175 (97-308)</td>
<td>280 (104-390)</td>
<td>245 (117-338)</td>
</tr>
<tr>
<td>NT-proBNP (% change from baseline)</td>
<td>ref</td>
<td>33</td>
<td>ref</td>
</tr>
<tr>
<td>Ln NT-proBNP (ng/L)</td>
<td>5.33 ± 1.18</td>
<td>5.66 ± 1.23</td>
<td>5.33 ± 0.71</td>
</tr>
</tbody>
</table>

### Quality of Life

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 Mental health component</td>
<td>51 (48-56)</td>
<td>53 (45-56)</td>
<td>53 (48-56)</td>
</tr>
<tr>
<td>Physical health component</td>
<td>55 (44-57)</td>
<td>55 (42-60)</td>
<td>51 (39-55)</td>
</tr>
<tr>
<td>CHD-TAAQOL Symptoms</td>
<td>89 (82-96)</td>
<td>91 (80-96)</td>
<td>89 (79-96)</td>
</tr>
<tr>
<td>Worry</td>
<td>80 (75-93)</td>
<td>88 (78-94)</td>
<td>91 (76-97)</td>
</tr>
<tr>
<td>Impact</td>
<td>89 (83-94)</td>
<td>89 (79-89)</td>
<td>87 (77-92)</td>
</tr>
</tbody>
</table>

**Table 2 - Exercise response**

Data are mean ± standard deviation or median (interquartile 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.
control group (table 2). A sensitivity analysis that included only patients who completed in the protocol in both 2009 and 2013 (control n=15, intervention n= 21) yielded similar results (\(V'O_{\text{2peak}}\) 1.8 mg/kg/min (-1.8 mg/kg/min to 5.5 mg/kg/min, p = .311).

**Sports habits**

Patients in the intervention group were not more likely to change their exercise habits than patients in the control group (increase in habitual exercise: intervention 37% vs controls 24%, p = .38).

**Serum N-terminal pro-hormone of brain natriuretic peptide**

There was no significant change from baseline in NT-proBNP. Moreover, at three year follow-up there was no effect of the ten week exercise program on serum NT-proBNP (table 2).

**Quality of life**

As can be seen in table 2, no effect of the ten week exercise program on the quality of life-scores remained at three year follow-up.

**Table 3 - Multivariate analysis**

<table>
<thead>
<tr>
<th>Possible determinants</th>
<th>Univariate Effect on (V'O_{\text{2peak}})*</th>
<th>p</th>
<th>Multivariate Effect on (V'O_{\text{2peak}})*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>0.3%</td>
<td>0.303</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise training (intervention)</td>
<td>-1.6%</td>
<td>0.750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.8%</td>
<td>0.743</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA (vs ccTGA)</td>
<td>-6.7%</td>
<td>0.210</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker</td>
<td>-11.1%</td>
<td>0.057</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-blokker</td>
<td>-13.3%</td>
<td>0.033</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAAS inhibitor</td>
<td>-15.5%</td>
<td>0.006</td>
<td>-12%</td>
<td>0.026</td>
</tr>
<tr>
<td>Sports participation</td>
<td>13.1%</td>
<td>0.005</td>
<td>11.5%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* \(V'O_{2peak}\) as percentage of predicted
Ancillary analysis

An exploratory univariate analysis of baseline characteristics yielded an association between change in exercise capacity and the use of β-blockers, RAAS inhibitors, and participation in sports. In multivariate analysis, RAAS inhibitors and sports participation remained independent predictors of change in exercise capacity at follow-up (table 3). When compared to patients who did not exercise regularly (no sports group), patients who habitually exercised (sports group) had higher $V'\text{O}_{2\text{peak}}$ although this effect was no longer significant when corrected for age and sex ($V'\text{O}_{2\text{peak}}$ as percentage of predicted, table 4 and 5). Sports participation at baseline was associated with an increase of 13% (95% CI 4% to 23%) of predicted $V'\text{O}_{2\text{peak}}$ and a

Table 4 - Sports vs no sports

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sport n = 23</th>
<th>No sports n = 17</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32 ± 11</td>
<td>32 ± 8</td>
<td>0.918</td>
</tr>
<tr>
<td>Male</td>
<td>14 (61%)</td>
<td>6 (35%)</td>
<td>0.110</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24 ± 5</td>
<td>27 ± 5</td>
<td>0.067</td>
</tr>
<tr>
<td>Follow up (yrs)</td>
<td>3.4 ± 0.5</td>
<td>3.3 ± 0.7</td>
<td>0.559</td>
</tr>
<tr>
<td>TGA / ccTGA</td>
<td>12/11</td>
<td>14/3</td>
<td>0.048</td>
</tr>
<tr>
<td>TGA: Mustard / Senning</td>
<td>3/9</td>
<td>9/5</td>
<td>0.045</td>
</tr>
<tr>
<td>Exercise training</td>
<td>16 (70%)</td>
<td>6 (35%)</td>
<td>0.033</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>7 (30%)</td>
<td>6 (35%)</td>
<td>0.746</td>
</tr>
<tr>
<td>Pacemaker in situ</td>
<td>4 (17%)</td>
<td>5 (30%)</td>
<td>0.368</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B - blocker</td>
<td>3 (13%)</td>
<td>6 (35%)</td>
<td>0.096</td>
</tr>
<tr>
<td>ACE / ATII</td>
<td>8 (35%)</td>
<td>8 (47%)</td>
<td>0.433</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3 (13%)</td>
<td>3 (18%)</td>
<td>0.687</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; BMI = body mass index; ccTGA = congenitally corrected transposition of the great arteries; NYHA = New York Heart Association
decrease of 62% (95% CI -115% to 10%) in NT-proBNP, when compared to patients who did not exercise (table 5 and figure 2).

During follow up, 22 clinical events occurred in 13 patients (11 supraventricular arrhythmias, 4 episodes of worsening heart failure, 6 reoperations, 1 pulmonary embolism, 1 non-sustained VT and 1 sudden death). In patients who did exercise, 5 additional events occurred (2 episodes of worsening heart failure, 1 reoperation, 1 pulmonary embolism, 1 non-sustained VT).

Table 5 - Effects of sports

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sports Baseline</th>
<th>3 year FU</th>
<th>No sports Baseline</th>
<th>3 year FU</th>
<th>Difference (95% CI) at 3 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V'O_2\text{peak (ml/kg/min)}^*$</td>
<td>27.5 ± 6.8</td>
<td>28.4 ± 8.9</td>
<td>23.6 ± 3.8</td>
<td>20.8 ± 5.1</td>
<td>3.4 (-0.2 to 6.9)</td>
<td>.062</td>
</tr>
<tr>
<td>$V'O_2\text{peak (ml/min)}^*$</td>
<td>2047 ± 536</td>
<td>2154 ± 646</td>
<td>1862 ± 305</td>
<td>1620 ± 425</td>
<td>317 (52 to 584)</td>
<td>.021</td>
</tr>
<tr>
<td>$V'O_2\text{peak (% pred)}$</td>
<td>74 ± 17</td>
<td>80 ± 19</td>
<td>72 ± 18</td>
<td>66 ± 13</td>
<td>13 (4 to 23)</td>
<td>.006</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, rest (mmHg)</td>
<td>118 ± 12</td>
<td>118 ± 15</td>
<td>117 ± 14</td>
<td>117 ± 20</td>
<td>3 (-8 to 14)</td>
<td>.621</td>
</tr>
<tr>
<td>Systolic blood pressure, max (mmHg)</td>
<td>156 ± 20</td>
<td>146 ± 30</td>
<td>154 ± 21</td>
<td>149 ± 27</td>
<td>12 (-6 to 30)</td>
<td>.197</td>
</tr>
<tr>
<td>Heart rate, rest (beats/minute)</td>
<td>77 ± 14</td>
<td>75 ± 17</td>
<td>79 ± 12</td>
<td>68 ± 13</td>
<td>8 (-3 to 18)</td>
<td>.148</td>
</tr>
<tr>
<td>Heart rate, max (beats/minute)</td>
<td>153 ± 31</td>
<td>151 ± 38</td>
<td>154 ± 30</td>
<td>148 ± 29</td>
<td>5 (-10 to 19)</td>
<td>.523</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>238 (95-415)</td>
<td>227 (85-378)</td>
<td>158 (112-280)</td>
<td>253 (155-383)</td>
<td>-187 (-432 to 58)</td>
<td>.129</td>
</tr>
<tr>
<td>NT-proBNP (% change from baseline)</td>
<td>ref</td>
<td>-14</td>
<td>ref</td>
<td>49</td>
<td>-62 (-115 to -10)</td>
<td>.021</td>
</tr>
<tr>
<td>ln NT-proBNP (ng/L)</td>
<td>5.41 ± 1.25</td>
<td>5.27 ± 1.04</td>
<td>5.10 ± 0.76</td>
<td>5.59 ± 0.87</td>
<td>-0.60 (-1.14 to -0.05)</td>
<td>.032</td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 Mental health component</td>
<td>52 (49-56)</td>
<td>52 (40-55)</td>
<td>53 (47-56)</td>
<td>51 (48-53)</td>
<td>-2 (-9 to 4)</td>
<td>.771</td>
</tr>
<tr>
<td>Physical health component</td>
<td>56 (46-58)</td>
<td>56 (52-59)</td>
<td>43 (36-52)</td>
<td>51 (40-58)</td>
<td>3 (-3 to 6)</td>
<td>.361</td>
</tr>
<tr>
<td>CHD-TAAQOL Symptoms</td>
<td>93 (84-98)</td>
<td>93 (86-97)</td>
<td>84 (71-91)</td>
<td>87 (79-96)</td>
<td>1 (-6 to 7)</td>
<td>.884</td>
</tr>
<tr>
<td>Worries</td>
<td>86 (76-97)</td>
<td>89 (80-96)</td>
<td>84 (74-94)</td>
<td>90 (84-96)</td>
<td>0 (-7 to 8)</td>
<td>.929</td>
</tr>
<tr>
<td>Impact</td>
<td>89 (84-94)</td>
<td>89 (85-95)</td>
<td>86 (77-91)</td>
<td>87 (80-89)</td>
<td>3 (-3 to 8)</td>
<td>.312</td>
</tr>
</tbody>
</table>

* Difference between groups with p < .05 at baseline. Data are mean ± standard deviation or median (interquartile 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.
cardiac death). Whereas the 10-week exercise program had no effect on the occurrence of clinical events, patients in the sports group had better event-free survival than patients in the no-sports group (figure 3).

**Figure 2** - The effect of habitual exercise on $V'O_{2\text{peak}}$ and NT-proBNP: Blue lines indicate an increase in $V'O_{2\text{peak}}$ and a decrease in NT-proBNP; Red lines indicate a decrease in $V'O_{2\text{peak}}$ and an increase in NT-proBNP.
**DISCUSSION**

This follow-up analysis of our randomized controlled trial on the effect of exercise training in adult patients with a systemic right ventricle, demonstrates that the beneficial effects found after a 10-week exercise program do not persist over time. V'O\textsubscript{2peak}, NT-proBNP levels, and quality of life remained stable in both patients who had participated in exercise training, as well as in those who had not. On the other hand, patients who were already involved in sports at baseline, regardless of their study group, had an increase in exercise capacity, a decrease in NT-proBNP, and, more importantly, better event-free survival, as compared to those with a more sedentary lifestyle.

Current guidelines appreciate the fact that physicians have been over-conservative in their advice on sports participation, despite the growing evidence that regular exercise has a positive impact on a patient’s current status, as well as on the risk of future acquired heart disease.\textsuperscript{10} Indeed, a recent systematic review by Duppen et al. stressed the improved fitness in a large number of children and young adults with congenital heart disease who participated in an exercise training program. Moreover, in all reviewed articles the training programs had been performed without incidents.\textsuperscript{11} More...
specifically, two other recent studies demonstrated safety and efficacy of exercise in adult congenital heart disease patients. Westhoff-Bleck et al. found an improvement in exercise capacity and NYHA classification in patients with a systemic right ventricle after a 24-week training program. They found no change in right ventricular function, which could be due to small patient numbers, and short follow-up. In 146 patients with congenital heart disease, Tikkanen et al., found improved V’O_{2peak} in patients involved in regular exercise, as compared to those with a more sedentary lifestyle. Unfortunately, long-term effects of exercise could not be derived from these studies.

Our finding that beneficial effects of exercise training are short-lived in adult patients with congenital heart disease is in line with previous results published on the long-term effect of rehabilitation programs in adult patients with acquired heart disease. In patients after myocardial infarction who participated in an eight-week training program, Dorn et al. reported a diminishing effect on cardiovascular mortality as time since participation increased. Willich et al. published his findings in 2441 patients who were enrolled in a rehabilitation program after myocardial infarction, coronary artery bypass grafting, or percutaneous intervention. After an initial improvement in cardiovascular risk factors during the rehabilitation program, risk factors deteriorated in the following 12 months. In contrast, in patients with congestive heart failure, a five-year follow-up study showed less deterioration in walking distance in those patients who had participated in a 24 week rehabilitation program, compared to controls. It has to be noted, however, that the intervention group remained more physically active during follow-up. This could indicate that favorable outcome in the intervention group is not a primary result from the rehabilitation program per se, but a secondary result, as patients involved in such programs seem inclined to increase their participation in habitual exercise. These findings were confirmed by Mueller et al., who also found superior engagement in physical activity in patients with congestive heart failure who had participated in cardiac rehabilitation, compared to controls, after a six-year follow-up period.
As short-term exercise programs are no guaranty for long-term benefit, the question remains if long-term intervention is the answer for long-term improvement. Recently, Belardinelli et al., indeed found decreased deterioration of \( V'O_{\text{2peak}} \), and NT-proBNP levels in patients with chronic heart failure after a 10-year exercise-training program. More importantly, although the study was not powered for the purpose, patients who were involved in the training program had lower rates of hospital readmission, and cardiac mortality.\(^{16}\) Whether such long-term sports participation would be associated with improvement of \( V'O_{\text{2peak}} \), and NT-proBNP, and better event-free survival in our patients remains unclear. Although follow-up is relatively long, power is insufficient to draw definite conclusions.

Hence, it seems highly likely that physical exercise in itself, more than the actual intervention, results in improvement in \( V'O_{\text{2peak}} \), and decreased hospitality and mortality in patients with heart disease, independent of the etiology. The European Society of Cardiology (ESC) guidelines on prevention of cardiovascular disease recommend physical exercise as primary and secondary prevention, as it lowers the risk of hypertension and diabetes mellitus type II, and increases HDL cholesterol. ESC guidelines state that exercise decreases cardiovascular mortality in both patients with cardiovascular disease, as well as in healthy individuals.\(^{17}\) Unfortunately, less than 50% of Europeans are involved in regular exercise, which is less than in our study population (61%).\(^{18}\) Guidelines on exercise and sports in adult patients with congenital heart disease are less straightforward. As the patient group is very heterogeneous, recommendations should be based on the patient’s ability, hemodynamic status, and the risk of decompensation and arrhythmias.\(^{10}\) In our patients, the exercise-training program was executed without significant incidents. Moreover, there seems to exist a beneficial effect of habitual sports participation. Therefore, keeping patient’s ability in mind, our reticence to advice in favor of sports participation might be counterproductive.

**Limitations**

As with many studies on adult patients with congenital heart disease, our study population was relatively small. This makes the generalizability of
our results limited. However, large-scale studies do not seem feasible in this patient group. In addition, only 40 out of the original 52 patients (74%) consented to participate in the current study, as 12 patients declined for a variety of reasons. However, clinical events could be evaluated in 50 patients. Moreover, there were no differences in baseline parameters or event rate compared to the participating patients. The current study was not powered to evaluate the effect of habitual sports participation on exercise capacity, neurohormone levels, or event free survival.

CONCLUSIONS

This follow-up analysis on long-term effect of a 10-week exercise training intervention in adult patients with a systemic right ventricle, demonstrates that short-term beneficial effects of exercise training do not persist over a three-year follow-up period. On the other hand, regular sports participation at baseline was associated with better exercise capacity, lower neurohormone levels, and increased event-free survival.

REFERENCES


