The systemic right ventricle
Winter, M.M.

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Relation of physical activity, cardiac function, exercise capacity, and quality of life in patients with a systemic right ventricle

Michiel M Winter, Berto J Bouma, Arie PJ van Dijk, Maarten Groenink, Pythia T Nieuwkerk, Mart N van der Plas, Gertjan T Sieswerda, Thelma C Konings, Barbara JM Mulder

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Exercise is recommended in patients with left ventricular failure. Although right ventricular failure is common in patients with a systemic right ventricle (RV), no data are available on the effect of physical activity in these patients. The aim of this study was to evaluate the relation of physical activity and cardiac function, exercise capacity and quality of life in patients with a systemic RV. Forty-seven patients (64% male, mean age 35, range 21-69 years) with a systemic RV (31 with an atrially switched transposition of the great arteries (TGA) and 16 with a congenitally corrected TGA) were included. Cardiac function was assessed by Cardiovascular Magnetic Resonance or Computed Tomography, exercise tests and serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels. Habitual physical activity was assessed using the SQUASH questionnaire, and quality of life using the SF-36. Mean systemic right ventricular ejection fraction was impaired (36.8±7.8%), as was maximal exercise capacity (78.5±23.9% of predicted). NT-proBNP level was increased (median 269, range 34-4476 ng/L). Mean SQUASH score was 6808±3241, indicating a decreased level of habitual physical activity. Although patients’ scores on mental quality of life domains were comparable to the general population, scores on most physical quality of life domains were significantly lower. SQUASH scores were found to be a significant predictor for exercise capacity (p<0.01) and physical quality of life (p<0.001). However, we found no relation between SQUASH scores and right ventricular ejection fraction or NT-proBNP. In conclusion, physical activity in patients with a systemic RV is positively associated with exercise capacity and quality of life, irrespective of cardiac performance.
INTRODUCTION
The American Heart Association recommends patients with left ventricular failure to participate in exercise training.¹ Not only does physical activity improve exercise capacity and quality of life in these patients, it also decreases heart failure related morbidity and mortality.²⁻⁶ These improvements seem to be irrespective of a patient’s cardiac function at the time exercise training is commenced.⁴ Despite these improvements seen with exercise in patients with left ventricular failure, available data on the effect of physical activity in adult patients with systemic right ventricular failure are limited. The prevalence of patients with a systemic right ventricle (RV) has increased steadily over the last decades to 0.04 per 1,000 living adults in 2000,⁷ and right ventricular dysfunction is a common complication in these patients.⁸ Currently, a large number of patients with a systemic RV leads a sedentary lifestyle caused by overprotection by their parents and physicians. This reticence could have unintentional counterproductive effects. In children with congenital heart defects physical activity has a proven beneficial effect, both on exercise capacity and on a psychosocial level.⁹, ¹⁰ These results could well be applicable to adult patients with a systemic RV. The present study evaluates the relation of habitual physical activity and cardiac function, exercise capacity and quality of life in patients with a systemic RV.

METHODS
A cross-sectional study was performed among 47 patients with a systemic RV. The Institutional Review Boards of all participating institutions approved the study protocol. Written informed consent was obtained from all patients prior to participation in the study.

Cardiovascular Magnetic Resonance Imaging was performed to assess systemic right ventricular function. A 1,5 Tesla scanner (Siemens Avanto, Erlangen, Germany), with retrospective electrocardiographic triggering was used with a standard steady-state free-precession sequence with the following parameters: flip angle: 50-70 degrees; repetition time: 3-4 msec; echo time: 1-2 msec;
temporal resolution: 40 msec, 1-2 X 1-2 mm / pixel in-plane spatial resolution, 8 mm slice thickness, and 4 mm interslice gap. For image analysis MASS Analytical Software System (Medis, Leiden, the Netherlands) was used. Cine loops were used to choose end-diastole and end-systole. Trabeculations and papillary muscles were considered part of the ventricular cavity. The slices at the base of the heart were considered to be in the ventricle if the blood was at least half surrounded by ventricular myocardium. End-diastolic volumes and end-systolic volumes were used to calculate stroke volume and ejection fraction. Stroke volume was defined as end-diastolic volume - end-systolic volume, and ejection fraction as \[
\frac{[(end-diastolic volume - end-systolic volume)]}{end-diastolic volume}\] X 100%.\(^{11}\)

For the assessment of right ventricular function of patients unsuitable for cardiovascular magnetic resonance imaging, Multidetector Row Computed Tomography was used. A Philips Brilliance-64 Computed Tomography scanner (120 kVp; average 500 mAs) was used to obtain cardiac images. Axial images of 20 cardiac phases were obtained in steps of 10% of the RR-interval. To cover the whole heart 60-80 slices were made, each with a 2 mm thickness and no interslice gap. Short-axis reconstructions were made after the Multidetector Row Computed Tomography was performed. For Multidetector Row Computed Tomography image analysis MASS Analytical Software System (Medis, Leiden, the Netherlands) was used. For contour tracing and end-diastolic volume, end-systolic volume and ejection fraction calculations we used the cardiovascular magnetic resonance imaging protocols.

Blood samples for N-terminal prohormone brain natriuretic peptide (NT-proBNP) assessment were drawn into vacuum-sealed containers containing heparin gel (Becton Dickinson, NJ, USA) and immediately centrifuged using a PK110 centrifuge (ALC, Winchester, VA, USA), and stored at -80°C. NT-proBNP analysis was performed on an Modular E170 bench top analyser utilising a chemiluminescent assay with a coefficient of variation < 5% (Roche Diagnostics, Lewes, UK). NT-proBNP measurements are subsequently quoted as plasma concentrations (ng/L).\(^{12, 13}\)
Cardiopulmonary exercise tests were performed to assess maximal exercise capacity, according to the guidelines of the American Thoracic Society. Patients were placed on a cycle ergometer and continuous measurements were made of minute ventilation, oxygen consumption (V'O\textsubscript{2}), carbon dioxide production, heart rate, blood pressure and electrocardiography (Jaeger Oxycon pro, Wuerzburg, Germany). Work load was increased by 5 to 15 Watt, depending on the predicted maximum exercise capacity and in such a way that maximal effort was attained within approximately 10-15 minutes. Exercise tests were considered valid if the patient reached anaerobic threshold, defined as having a respiratory exchange ratio > 1.0. In case of uncertainty whether the anaerobic threshold was reached, the venous lactate level was determined. Patients with a venous lactate level > 4.0 mmol/L were also considered to have reached anaerobic threshold. 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.

Patient's habitual physical activity was assessed using the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH). The SQUASH was developed by the Dutch National Institute of Public Health and the Environment and contains questions on habitual activities with respect to occupation, leisure time, household, transportation means and other daily activities. Patients were requested to fill out the number of days per week, the average time per day and the intensity in which the activity was performed. Based on a patient’s self reported effort an individual activity score is calculated by multiplying the intensity of the activity (Ainsworth’s compendium of Physical activities) with the number of minutes the activity was performed per week. Patients’ SQUASH scores were compared with published population norms.

Health related quality of life was assessed by means of the Dutch translation of the Medical Outcomes Study Short Form 36 item health survey (SF-36). 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 Dutch reference population norms.

For statistical analyses SPSS 12.0.1 (SPSS Inc., Chicago, Illinois) for Windows was used. The descriptive data are presented as mean with standard deviation if normally distributed or as median with range as appropriate. Comparison of continuous variables between groups were made by unpaired Student’s t-tests. In case of skewed distribution, the Mann-Whitney U test was used. P values < 0.05 were considered statistically significant. The relation between Physical Activity, Cardiac Function, Exercise Capacity, and Quality of Life was assessed by linear regression analysis. Multivariate analysis was performed to evaluate the influence of age and gender on the above mentioned analyses. The 8 dimensions of the SF-36 scores were converted to standard scores on the basis of the scores of an age- and gender- matched representative reference sample of the Dutch population. A standard score indicates how many standard deviations the observed SF-36 score falls below or above the score from the reference population. Consequently the score of the reference population is set at 0.19 The study population was compared with reference values from the literature, to elaborate the differences between the scores of the SF-36 and the SQUASH.16,18

RESULTS
Between September 2006 and February 2008, 47 patients were included in this study. Baseline characteristics are presented in table 1.

Thirty-one patients were eligible to undergo cardiovascular magnetic resonance imaging for the evaluation of cardiac volumes and function. In 16 patients we performed computed tomography scans. Cardiac function was impaired in almost all patients with a systemic RV. There were no significant
differences in age and gender, nor in mean right ventricular ejection fraction between the cardiovascular magnetic resonance and the computed tomography-scan group.

Symptom limited cardiopulmonary exercise tests were performed successfully (mean respiratory exchange ratio 1.1 ± 0.1) and without complications in all patients. One patient’s exercise test was aborted prematurely due to the development of an atrial arrhythmia. Anti-arrhythmic drugs were initiated and the exercise test was repeated successfully 2 weeks thereafter. Overall, maximal exercise capacity as a percentage of predicted (V’O\textsubscript{2peak} % predicted) was decreased in patients with a systemic RV.\textsuperscript{14}

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients* (n=47)</th>
<th>TGA* (n=31)</th>
<th>ccTGA* (n=16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 (21 - 69)</td>
<td>30 (21 - 41)</td>
<td>43 (23 - 69)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>30 (64%)</td>
<td>23 (74%)</td>
<td>7 (44%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 15</td>
<td>77 ± 17</td>
<td>73 ± 13</td>
<td>N.S.</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>125 ± 14</td>
<td>125 ± 15</td>
<td>125 ± 12</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>81 ± 11</td>
<td>81 ± 11</td>
<td>79 ± 11</td>
<td>N.S.</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B - blockade</td>
<td>9 (19%)</td>
<td>7 (23%)</td>
<td>2 (13%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>ACE inhibitor / Angiotensin Receptor Blocker</td>
<td>11 (23%)</td>
<td>7 (23%)</td>
<td>4 (26%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Anti-arrhythmic medication</td>
<td>6 (13%)</td>
<td>4 (13%)</td>
<td>2 (13%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Anti-coagulant</td>
<td>8 (17%)</td>
<td>6 (19%)</td>
<td>2 (13%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2 (4%)</td>
<td>1 (3%)</td>
<td>1 (6%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Pacemaker in situ</td>
<td>15 (32%)</td>
<td>10 (32%)</td>
<td>5 (31%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>N-terminal prohormone brain natriuretic peptide (ng/L)</td>
<td>269 (34 - 4476)</td>
<td>258 (49 - 2265)</td>
<td>377 (34 - 4476)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Maximal exercise capacity - % predicted</td>
<td>79 ± 24</td>
<td>76 ± 16</td>
<td>84 ± 34</td>
<td>N.S.</td>
</tr>
<tr>
<td>- ml/kg/min</td>
<td>26 ± 7</td>
<td>27 ± 7</td>
<td>24 ± 7</td>
<td>N.S.</td>
</tr>
<tr>
<td>SQUASH</td>
<td>6808 ± 3240</td>
<td>7241 ± 3090</td>
<td>5997 ± 3461</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

\* Data are mean value ± standard deviation, as median (range), or as number of patients (percent).  
ACE = Angiotensin Converting Enzyme; ccTGA = congenitally corrected transposition of the great arteries; SQUASH = short questionnaire to assess health-enhancing physical activity; TGA = transposition of the great arteries; % predicted = percentage of predicted.

Patients with a systemic RV had a mean SQUASH score of 6808 ± 3241, which is significantly lower compared to the general Dutch population (mean SQUASH score 7850 ± 3066); p < 0.05.\textsuperscript{16} However, not all patients scored below average; 17 patients had SQUASH scores over 7850.
Generally, patients perceived similar quality of life compared to the general Dutch population on mental health domains, but scored significantly lower on physical health domains. Strikingly, scores on the domain of bodily pain were significantly higher in patients, signifying less pain, compared to the general population (figure 1).

Linear regression analysis showed that patient’s self reported habitual physical activity (SQUASH score) was an independent predictor for $V'\text{O}_2\text{peak}$ and for the Physical Component Summary, adjusted for age and gender. These findings were not influenced by right ventricular ejection fraction or serum NT-proBNP levels. There was no statistically significant relation between patient’s SQUASH score and right ventricular ejection fraction and serum NT-proBNP levels. The SQUASH score was not related to a patient’s mental health status, as determined by Mental Component Summary (figure 2).

**Figure 1.** Health related Quality of Life.
The 8 domains of the 36 item Short Form compared with general population norms in 47 patients with a systemic right ventricle. BP = bodily pain; GH = general health; MH = mental health; PF = physical functioning; RE = role functioning emotional; RP = role functioning physical; SF = social functioning; VT = vitality. * Significant difference with the general population of $p < 0.001$; † Significant difference with the general population of $p < 0.05$. Data are presented as mean ± 2 SD.
Figure 2. The relation between habitual physical activity and 1a. exercise capacity as percentage of predicted; 1b. right ventricular ejection fraction; 1c. serum NT-proBNP level; and 2a. physical component summary; 2b. mental component summary. * SQUASH: Short Questionnaire to ASsessment Health-enhancing physical activity.

1a. $r^2 = 0.40 \quad p < 0.01$
1b. $r^2 = 0.20 \quad p = N.S.$
1c. $r^2 = 0.10 \quad p = N.S.$

2a. $r^2 = 0.41 \quad p < 0.001$
2b. $r^2 = 0.12 \quad p = N.S.$
DISCUSSION

Patients with a systemic RV who are physically active in daily life have an enhanced exercise tolerance and experience favourable physical wellbeing, compared to those who are physically less active. These advantages are irrespective of a patient’s cardiac function as determined by cardiovascular magnetic resonance imaging or computed tomography scan and serum NT-proBNP levels.

To our knowledge, this is the first study to evaluate the influence of physical activity in patients with a systemic RV. Although habitual physical activity was significantly lower in patients with a systemic RV compared to the general population, we found a positive association between physical activity and a patient’s exercise capacity and quality of life.

Exercise tests were performed with only 1 minor complication, strengthening the hypothesis that physical activity is not only beneficial, but can generally be performed safely in patients with complex congenital heart defects like TGA. However, the complexity of the congenital cardiac condition and the heterogeneity of the patient group makes the need for individual evaluation, before exercise recommendations are given, indisputable. Contact sports should be avoided in patients with a potential harmful effect of trauma (e.g. patients with mechanical valves or a permanent pace-maker). Holter registration and exercise tests can rule-out potentially malignant arrhythmias. Exercise tests were performed with only 1 minor complication, strengthening the hypothesis that physical activity is not only beneficial, but can generally be performed safely in patients with complex congenital heart defects like TGA. However, the complexity of the congenital cardiac condition and the heterogeneity of the patient group makes the need for individual evaluation, before exercise recommendations are given, indisputable. Contact sports should be avoided in patients with a potential harmful effect of trauma (e.g. patients with mechanical valves or a permanent pace-maker). Holter registration and exercise tests can rule-out potentially malignant arrhythmias. Moreover, our study was not specifically designed to address safety issues, and larger patient numbers are required to definitely establish safety of exercise in this patient group.

For the present study, ccTGA patients and patients with an atrially switched TGA were considered as 1 group. However, ccTGA patients differ from atrially switched TGA patients, as they often not diagnosed until adulthood, and remain asymptomatic until a later age. Moreover, associated anomalies are frequent and differ between ccTGA and the atrially switched TGA patients. Although we found no differences in RV ejection fraction, serum NT-proBNP levels
and $\text{V'O}_{2\text{peak}}$ between the 2 patient groups, this could be due to small patient numbers, differences in age, or in pathophysiology.

The absent relation between ejection fraction and exercise capacity suggests that maximal exercise capacity might be determined by various other physical variables. Many patients with a systemic RV are pacemaker dependent, or have some degree of tricuspid valve regurgitation. To determine the influence of these parameters, larger patient numbers are required. The positive effects of a physically active lifestyle on exercise capacity and quality of life could be the other way around: patient’s who have good exercise tolerance and who experience an enhanced quality of life could automatically be more active in daily life. However, the known positive results of exercise in patients with left ventricular failure, strengthens our interpretation of the found data in patients with a systemic RV. An exercise intervention study is needed to definitely confirm our findings.

In conclusion, physical activity in patients with a systemic RV is positively associated with enhanced exercise capacity and favourable quality of life, irrespective of a patient’s cardiac function.
Reference List


