Exercise limitations in various forms of pulmonary hypertension
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Mechanisms For Cardiac Output Augmentation
In Patients With A Systemic Right Ventricle

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ABSTRACT

Background: Conflicting data have been published on the differences in cardiac response to exercise between patients with an atrially switched transposition of the great arteries (TGA), and patients with a congenitally corrected TGA (ccTGA). The purpose of our study was to evaluate the differences in cardiac response to exercise in these 2 patient groups with a systemic right ventricle (RV).

Methods: Thirty four patients (62% male; mean 35, range 21-69 years) with a systemic RV (20 with an atrially switched TGA and 14 with a ccTGA) were included. Exercise test with Portapres® measurements were performed to assess maximal exercise capacity (V’O2-peak), cardiac index, stroke volume index, and heart rate augmentation. Cardiac function was assessed by Cardiovascular Magnetic Resonance or Computed Tomography, and serum NT-proBNP levels.

Results: We found that both groups were able to significantly augment cardiac index during exercise. Cardiac index augmentation during exercise was positively related to V’O2-peak (r=0.37, p<0.05), and independent of resting cardiac function. Although the increase in cardiac index during exercise was similar in both patients with TGA and with ccTGA, mechanisms to achieve this increase differed between groups. ccTGA patients increased both stroke volume and heart rate during exercise. Atrially switched TGA patients augmented heart rate during exercise, but failed to increase stroke volume.

Conclusion: Mechanisms to achieve cardiac output augmentation differ between ccTGA patients and TGA patients. We suggest that therapeutic approaches should be tailored to the specific patient group to avoid counterproductive effects.
INTRODUCTION

Advances in treatment strategies have caused a steady increase in the prevalence of adult patients with a congenital heart defect (1). A substantial portion of these patients have a morphologic right ventricle (RV) supporting the systemic circulation, for example patients with a transposition of the great arteries (TGA) who have undergone an atrial switch procedure (Mustard or Senning operation), and patients with a congenitally corrected TGA (ccTGA). These patients are known to develop systemic right ventricular dysfunction, have an abnormal cardiac response to stress, and a reduced exercise capacity (2;3).

Maximal exercise capacity is an important prognostic factor for patients with a systemic right ventricle (2). Maximal exercise capacity is directly related to the ability to increase cardiac output during exercise, which is done by increasing stroke volume, heart rate or both. Conflicting data have been published on the different mechanisms used to achieve cardiac output augmentation between atrially switched TGA patients and patients with a ccTGA (3-7). Therefore, the aim of our study was to evaluate cardiac response to exercise in patients with a systemic RV, and to evaluate the differences in cardiac response between ccTGA and TGA patients. Moreover, we determined the relation between resting cardiac function and cardiac response to exercise in both patient groups.

MATERIALS AND METHODS

Patient characteristics

A cross-sectional study was performed in 34 consecutive patients with a systemic RV. The Institutional Review Board of the participating tertiary referral center approved the study protocol, which conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation in the study.

Cardiopulmonary exercise test

For the assessment of exercise capacity we performed a symptom limited cardiopulmonary exercise test according to the guidelines of the American Thoracic Society (8). Patients were placed on a cycle ergometer in the upright position and continuous measurements were made of minute ventilation, oxygen consumption (V'O2), carbon dioxide production (V'CO2), heart rate, blood pressure and electrocardiography (Jaeger Oxycon pro, Wuerzburg, Germany). Work load was increased by 5 to 15 Watt in a stepwise manner, depending on the individually predicted maximum exercise capacity and in such a way that calculated maximal effort should be attained in approximately 10-15 minutes. All patients were exercised to their maximum exercise capability. V'O2-peak was determined 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, and reported as percentages of predicted (9). Calibration of the system was done prior to every test according to manufacturer specifications.
Heart rate, stroke volume and cardiac output

The Portapres® model 2 device (TNO-TPD Biomedical Instrumentation, the Netherlands) continuously measured heart rate, and beat-to-beat arterial pressure through a cuff wrapped around the left middle finger (10;11). In short, a pressure waveform is constructed by clamping the finger volume through servo-loop-controlled photoplethysmography, from which systolic, diastolic and mean arterial blood pressure are calculated. Modelflow® (TNO-BMI) (12). Calculations provided changes in stroke volume, cardiac output and total peripheral resistance, and were derived using the Beatscope Software for Windows, version 1 (TNO-TPD Biomedical Instrumentation) (12). Thirty second averages of stroke volume, heart rate, and cardiac output were used for calculations. Cardiac output and stroke volume were corrected for body surface area; cardiac index (L/min/m²) and stroke volume index (ml/m²).

Cardiovascular Magnetic Resonance (CMR)

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 chose end-diastole and end-systole. Trabeculations and papillary muscles were considered part of the ventricular cavity (13). 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 [(end-diastolic volume - end-systolic volume) / end-diastolic volume] X 100%.

Multidetector Row Computed Tomography

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 kVolt; 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.
Serum NT-proBNP
Venous blood samples were drawn prior to the performance of the cardiovascular exercise test. NT-proBNP measurements are subsequently quoted as plasma concentrations (ng/L) (14;15).

Statistical analysis
For statistical analyses SPSS 16.0 (SPSS Inc., Chicago, Illinois) for Windows was used. P values < 0.05 were considered statistically significant. The descriptive data are presented as mean with standard deviation if normally distributed or as median with range as appropriate. A logarithmic transformation was performed for NT-proBNP levels. 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. Changes within groups in heart rate, stroke volume (index), cardiac output and cardiac index at rest and in response to exercise were analyzed using a paired-samples t test. The relation between cardiac response and maximum exercise capacity activity was assessed by linear regression analysis, as was the predicting value of resting cardiac function on cardiac response to exercise. Multivariate analysis was performed to assess the influence of age and gender on differences found within and between groups.
RESULTS

Patient characteristics

Thirty four consecutive patients (62% male, 34.7 ± 12.0 years old) with a systemic RV (14 with a ccTGA and 20 with an atrially switched TGA) were included in the study. Eleven patients had a permanent pacemaker at the time of inclusion. Pacing modes were DDD-R in 5 patients, VVI in 3 patients, and AAI in 2 patients. One patients had an Implantable Cardioverter Defibrillator. Patient characteristics are summarized in Table 1.

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients* (n=34)</th>
<th>TGA* (n=20)</th>
<th>ccTGA* (n=14)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 (21 - 69)</td>
<td>30 (21 - 39)</td>
<td>41 (23 - 69)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>21 (62%)</td>
<td>16 (80%)</td>
<td>5 (36%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>124±14</td>
<td>123±15</td>
<td>125±12</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>82±12</td>
<td>83±13</td>
<td>80±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>6 (18%)</td>
<td>3 (15%)</td>
<td>3 (21%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Other cardiac medication</td>
<td>11 (32%)</td>
<td>7 (35%)</td>
<td>4 (29%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Pacemaker in situ</td>
<td>11 (32%)</td>
<td>6 (30%)</td>
<td>5 (36%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Log NT-pro BNP (ng/L)</td>
<td>2,4±0,5</td>
<td>2,5±0,6</td>
<td>2,4±0,4</td>
<td>N.S.</td>
</tr>
<tr>
<td>Maximal exercise capacity - ml/min</td>
<td>1952±581</td>
<td>2076±572</td>
<td>1775±569</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>26±7</td>
<td>27±8</td>
<td>24±7</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>79±26</td>
<td>73±16</td>
<td>87±35</td>
<td>N.S.</td>
</tr>
<tr>
<td>Systemic right ventricular ejection fraction</td>
<td>38±7</td>
<td>36±7</td>
<td>40±8</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

* Data are mean value ± standard deviation, as median (range), or as number of patients (percent).

ccTGA = congenitally corrected transposition of the great arteries; TGA = transposition of the great arteries; % predicted = percentage of predicted.

Cardiac function

Cardiac volumes and function were assessed by means of CMR in 21 patients, and by means of CT-scan in 13 patients (11 patients with a permanent pacemaker, 1 patient with a Implantable Cardioverter Defibrillator, and 1 metal worker respectively). We found no differences in right ventricular ejection fraction between the CMR group and the CT-scan group.

Exercise capacity and cardiac response

Symptom limited cardiopulmonary exercise tests could be performed without complications in all patients. One patient’s exercise test was aborted prematurely by the attending physician due to the development of an atrial arrhythmia; after the initiation of anti-arrhythmic drugs the
exercise test was repeated successfully 2 weeks later (8).

Mean cardiac output increased significantly during exercise in both patient groups, and there were no differences in cardiac output augmentation between patients with ccTGA and patients with an atrially switched TGA (Table 2). Mean stroke volume at rest was significantly lower in patients with a ccTGA, compared to patients with an atrially switched TGA. However, this difference was mainly due to the fact that, compared to the atrially switched TGA group, the ccTGA group consisted of significantly more female patients (p < 0.05); the contribution of the underlying congenital heart defect was statistically non-significant (p = NS) (16). Although patients with a ccTGA showed a statistically significant stroke volume augmentation during exercise, no such change was seen in the atrially switched TGA group. Both patient groups showed a statistically significant increase in heart rate during exercise. However, this increase was significantly higher in patients with an atrially switched TGA, compared to patients with a ccTGA. Individual cardiac response to exercise is visualized in Figure 1. None of the above mentioned parameters were significantly influenced by differences in age or gender between the 2 patient groups, except for resting stroke volume as mentioned above. Moreover, we found no significant differences in stroke volume, heart rate, and cardiac output augmentation between patients with and without permanent pacemakers (independent of the mode of pacing or the underlying arrhythmia), nor between patients on β-blockers or other cardiac medication and those without medication.

Table 2  Cardiac response to exercise in patients with a systemic RV

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients* (n=34)</th>
<th>TGA* (n=20)</th>
<th>ccTGA* (n=14)</th>
<th>p Value †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD p Value</td>
<td>Mean±SD p Value</td>
<td>Mean±SD p Value</td>
<td></td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>4±1</td>
<td>4±1</td>
<td>4±1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Exercise</td>
<td>9±2</td>
<td>9±2</td>
<td>8±2</td>
<td>N.S.</td>
</tr>
<tr>
<td>Change</td>
<td>5±2 &lt; 0.001</td>
<td>5±2 &lt; 0.001</td>
<td>4±2 &lt; 0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>SVI (ml/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>55±18</td>
<td>60±17</td>
<td>47±16</td>
<td>&lt; 0.05 ‡</td>
</tr>
<tr>
<td>Exercise</td>
<td>66±18</td>
<td>68±17</td>
<td>63±20</td>
<td>N.S.</td>
</tr>
<tr>
<td>Change</td>
<td>11±20 &lt; 0.01</td>
<td>8±23 N.S.</td>
<td>16±15 &lt; 0.01</td>
<td>N.S.</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>76±15</td>
<td>70±14</td>
<td>83±13</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Exercise</td>
<td>137±21</td>
<td>140±23</td>
<td>133±18</td>
<td>N.S.</td>
</tr>
<tr>
<td>Change</td>
<td>62±24 &lt; 0.001</td>
<td>70±25 &lt; 0.001</td>
<td>50±19 &lt; 0.001</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

* Data are mean values ± standard deviations; † p Value of difference between TGA and ccTGA patients; ‡ gender differences are of statistically significant influence on p value.

bpm = beats per minute; ccTGA = congenitally corrected transposition of the great arteries; CI = cardiac index; HR = heart rate; L/min = litres per minute; ml = millilitre; RV = right ventricle; SVI = stroke volume index; TGA = transposition of the great arteries
Figure 1  Cardiac response to exercise in patients with a systemic RV.
Caption: Individual heart rate, stroke volume index, and cardiac index response to exercise of patients with an atrially switched TGA and with a ccTGA. Indicates mean value in rest and during exercise.
Overall, cardiac output augmentation was found to correlate with \( V'O_2\)-peak (ml/kg/min) (Figure 2).

**Ventricular function and cardiac index augmentation.**
We found no relation between RV ejection fraction at rest and cardiac index augmentation, nor between serum NT-proBNP levels at rest and cardiac index augmentation. These findings were applicable to the entire group of patients with a systemic RV, as well as to the separate patient groups.

![Figure 2](image)

**Figure 2**  Relation between change in cardiac output and during exercise and exercise capacity in patients with a systemic right ventricle.  
Caption: Patients with a systemic right ventricle who have the ability to increase CO during exercise, have a better exercise capacity.
DISCUSSION

The ability to increase cardiac output during exercise is positively associated with $V'O_2$-peak in patients with a systemic RV, and seems independent of resting cardiac function. Although cardiac output augmentation during exercise is similar among patients with a systemic RV, the mechanisms used to achieve this increase differ between patient groups. In patients with a ccTGA, cardiac output augmentation was achieved by an increase in stroke volume as well as in heart rate. On the other hand, in patients with an atrially switched TGA cardiac output augmentation was primarily achieved by an increase in heart rate during exercise, as many of these patients failed to increase stroke volume.

Conflicting data have been published on the hemodynamic response to exercise in patients with a ccTGA. Some authors found an increase in heart rate during exercise comparable to healthy controls (4;6), whereas others found an inability to achieve sufficient increase in heart rate in these patients (5;17). Our present findings are in agreement with the former 2 authors, as we found an appropriate heart rate response to exercise in patients with a ccTGA. Although heart rate response to exercise was less in ccTGA patients, compared to atrially switched TGA patients, this does not necessarily indicate an inability to further increase heart rate. As stroke volume increases significantly during exercise in patients with a ccTGA, a further increase in heart rate could be unnecessary to obtain sufficient cardiac output augmentation.

Similar equivocal results have been published on the hemodynamic response to exercise in patients with an atrially switched TGA. Although most articles describe a normal heart rate response during exercise (3;6;18-19), Ohuchi et al. found a significantly lower peak heart rate in atrially switched TGA patients compared to healthy controls (17). Failure to augment stroke volume during exercise is a more consistent finding in this patient group (3;6;18-20), and is known to be progressive over time (21). Several mechanisms are found to contribute to the decreased stroke volume augmentation in patients with an atrially switched TGA. Preload restrictions caused by the atrial baffle hamper adequate ventricular filling in these patients. Moreover, myocardial blood flow is frequently impaired, and coronary flow reserve decreased, which could importantly contribute to inadequate SV augmentation (22-24). Although we found no echocardiographic evidence of atrial baffle obstruction in any of our patients, and did not further investigate myocardial blood flow, our findings are consistent with the above mentioned results; most atrially switched TGA patients fail to increase stroke volume during exercise, and cardiac output augmentation is primarily caused by the increase in heart rate.

It is known that $V'O_2$-peak is positively associated with prognosis and with wellbeing in patients with a systemic RV (25). As cardiac output augmentation during exercise is directly related to $V'O_2$-peak, the importance of cardiac output augmentation preservation is evident. The differences in cardiac output augmentation between ccTGA and atrially switched TGA patients indicate that the diagnostic and therapeutic approach should be tailored to the specific patient group.
Limitations
Our study is limited by low patient numbers. However, found differences between the 2 patient groups are of such extend that it suggests overall applicability.

CONCLUSIONS
Patients with a systemic RV have the capability to augment cardiac output during exercise. This cardiac output augmentation is positively related with exercise capacity, and appears unrelated to resting cardiac function. However, the mechanisms by which cardiac output augmentation is achieved differs importantly between patient groups. Therefore, diagnostic and therapeutic approach should be tailored to the specific patient group to avoid undesirable and counterproductive effects.
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