CONGENITAL HEART DISEASE

Cardiovascular response to physical exercise in adult patients after atrial correction for transposition of the great arteries assessed with magnetic resonance imaging

A A W Roest, H J Lamb, E E van der Wall, H W Vliegen, J G van den Aardweg, P Kunz, A de Roos, W A Helbing

Objective: To assess with magnetic resonance imaging (MRI) cardiovascular function in response to exercise in patients after atrial correction of transposition of the great arteries (TGA).

Methods: Cardiac function at rest and during submaximal exercise was assessed with MRI in 27 patients with TGA (mean (SD) age 26 (5) years) late (23 (2) years) after atrial correction and in 14 control participants (25 (5) years old).

Results: At rest, only right ventricular ejection fraction was significantly lower in patients than in controls (56 (7)% v 65 (7), p < 0.05). In response to exercise, increases in right ventricular end diastolic (155 (55) ml to 163 (57) ml, p < 0.05) and right ventricular end systolic volumes (70 (34) ml to 75 (36) ml, p < 0.05) were observed in patients. Furthermore, right and left ventricular stroke volumes and ejection fraction did not increase significantly in patients. Changes in right ventricular ejection fraction with exercise correlated with diminished exercise capacity (r = 0.43, p < 0.05).

Conclusions: In patients with atrially corrected TGA, MRI showed an abnormal response to exercise of both systemic right and left ventricles. Exercise MRI provides a tool for close monitoring of cardiovascular function in these patients, who are at risk for late death.

PATIENTS AND METHODS

Twenty seven patients with TGA (mean (SD) age 25.7 (4.6) years) corrected at the atrial level at a mean age of 2.5 (2.2) years who were scheduled to undergo cardiac MRI examination at rest for clinical follow up of cardiovascular function and who did not have contraindications for MRI examination, such as the presence of a pacemaker, arrhythmias, claustrophobia, or the inability to perform bicycle exercise, were examined and compared with 14 control participants. The controls were normal at clinical examination and had a normal ECG at rest, no history of cardiovascular disease, and no complaints. The controls were matched for age (24.8 (5.2) years), weight, height, and body surface area (table 1). TGA had been corrected by the Mustard procedure in 11 patients and by the Senning procedure in 16 patients. Sixteen patients had additional pulmonary stenosis, ventricular septal defect, or both, which is referred to as complex TGA. All patients were in New York Heart Association (NYHA) class I or II and all were in regular cardiac rhythm (25 patients were in sinus rhythm and two patients had an atrioventricular junctional rhythm). Informed consent was obtained from all participants and the medical review board of our institution approved the study.

Exercise testing

Exercise testing was performed before the MRI examination on a separate day. A graded maximal exercise test was performed in the supine position on an MRI compatible ergometer (MRI cardiac ergometer, Lode BV, Groningen, the Netherlands).

Abbreviations: MRI, magnetic resonance imaging; NYHA, New York Heart Association; TFEPI, turbofield echo planar imaging; TGA, transposition of the great arteries.
Netherlands) with continuous recording of ECG and arterial oxygen saturation. The following parameters were measured by a gas analyser (Oxycon Record, Jaeger, Höchberg, Germany) during the exercise test: total ventilation, breathing frequency, oxygen uptake, and carbon dioxide release. Ventilatory equivalents at peak exercise for carbon dioxide (ratio of maximum total ventilation to maximum carbon dioxide release) and for oxygen (ratio of maximum total ventilation to maximum oxygen uptake) were calculated. The respiratory quotient (ratio of carbon dioxide release to oxygen uptake) at peak exercise was used as an indicator of maximum effort.

Magnetic resonance imaging
The MRI examination was done with a Philips 1.5 T ACS-NT15 magnetic resonance scanner (Philips Medical Systems, Best, the Netherlands) equipped with a Powtrak 6000 gradient system and a CPR-6 cardiac research software package (Philips Medical Systems). After scout views were obtained, MRI flow velocity was measured with retrospective electrocardiographic gating at rest in the pulmonary trunk, in the ascending aorta, at the level of both the mitral and tricuspid valves, and in the venous pathways, as previously described. At rest and during exercise, 10 consecutive slices in the left ventricular short axis orientation with a thickness of 10 mm and an interslice gap of 1 mm were used to cover the left and right ventricles from apex to base. The short axis images were obtained by a turbofield echo planar imaging (TFEPI) sequence with prospective electrocardiographic triggering. Imaging parameters were a 128 x 104 matrix, 420 x 120 mm field of view, 30° flip angle, repetition time of 14 ms, echo time of 4.8 ms, echo planar imaging factor of 5, turbo factor of 2, and temporal resolution of 31 ms. All k lines of one short axis slice were obtained during four heart beats. Two short axis slices were acquired sequentially during a breath hold of eight heart beats at end expiration.

Exercise was performed on the MRI compatible ergometer. The exercise level for the MRI examination was based on the workload corresponding to 60% of the maximum oxygen uptake measured during the preceding maximal exercise test. After reaching a steady heart rate, the participants performed a breath hold procedure and images were acquired within eight heart beats during a short exercise break. After acquisition of the images the participants continued cycling until a steady heart rate was again reached. This exercise protocol has previously been validated by Pedersen and colleagues, who used a time window of 12 heartbeats for the acquisition. Mean decrease in heart rate immediately after exercise was 4% after six heart beats and less than 14% after 11 heart beats, which was considered acceptable for the evaluation of haemodynamic changes during exercise. With our TFEPI MRI sequence we obtained two short axis slices during eight heart beats, which is within the limits used by Pedersen and colleagues. The breath hold procedure was repeated to acquire a total of 10 short axis slices.

Data analysis
MRI flow velocity measurements were analysed by the FLOW software package (Medis, Leiden, the Netherlands). Quantitative analysis of the short axis images by the MASS software package (Medis, Leiden, the Netherlands) allowed calculation of the following parameters of both ventricles: end diastolic volume, end systolic volume, stroke volume, and ejection fraction. In line with previous reports, the systemic right ventricular function of the TGA patients was compared with the right ventricular function of the control group, and the left ventricular function of the patients was compared with the left ventricular function of the controls. Abnormal right ventricular ejection fraction at rest was defined as less than 47% (± 2 SD of normal value ).

A normal ventricular response to exercise was defined as an increase in ejection fraction of more than 5%. All data were expressed as mean (SD).

Statistical analysis
An unpaired Student’s t test was used to compare the parameters of exercise performance and cardiac function between the patients with atrially corrected TGA and the matched control group. A paired Student’s t test was used to compare the parameters of cardiac function obtained at rest and during the exercise protocol. Pearson correlation analysis was used to evaluate correlation between parameters. The level of significance was p < 0.05.

RESULTS
Exercise testing
No difference in respiratory quotient at peak exercise was observed between the TGA and the control groups (table 2). All participants reached a respiratory quotient above 1.0, indicating at least near maximum effort during the graded exercise test. At peak exercise the TGA patients had a significantly lower oxygen uptake per kilogram bodyweight during exercise.

Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 14)</th>
<th>Total TGA (n = 27)</th>
<th>Mustard (n = 11)</th>
<th>Senning (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/Females</td>
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<td>15/12</td>
<td>7/4</td>
<td>8/8</td>
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<tr>
<td>Age (years)</td>
<td>24.8 (5.2)</td>
<td>25.7 (4.6)</td>
<td>29.2 (3)</td>
<td>23.3 (3.9)*</td>
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<tr>
<td>Height (m)</td>
<td>1.78 (0.06)</td>
<td>1.73 (0.09)</td>
<td>1.72 (0.11)</td>
<td>1.74 (0.08)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.8 (11)</td>
<td>71.7 (16)</td>
<td>66.8 (13)</td>
<td>75.1 (17)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 (0.2)</td>
<td>1.9 (0.2)</td>
<td>1.8 (0.2)</td>
<td>1.9 (0.2)</td>
</tr>
<tr>
<td>Simple/complex TGA†</td>
<td>NA</td>
<td>11/16</td>
<td>NA</td>
<td>7/4</td>
</tr>
<tr>
<td>Age at operation</td>
<td>NA</td>
<td>2.5 (2.2)</td>
<td>2.5 (1.1)</td>
<td>2.5 (2.7)</td>
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<tr>
<td>Balloon septostomy</td>
<td>NA</td>
<td>17</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Blalock-Hanlon septostomy</td>
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<td>9</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

All parameters are presented as mean (SD).

*p < 0.05 between TGA corrected by the Mustard procedure and by the Senning procedure; †without (simple) or with (complex) additional pulmonary stenosis or ventricular septal defect.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>TGA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory quotient (l/min)</td>
<td>1.17 (0.04)</td>
<td>1.15 (0.06)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>175 (8)</td>
<td>160 (23)*</td>
</tr>
<tr>
<td>Work load (W)</td>
<td>231 (32)</td>
<td>156 (35)*</td>
</tr>
<tr>
<td>Total ventilation (l/min)</td>
<td>105 (22)</td>
<td>79 (21)*</td>
</tr>
<tr>
<td>Breathing frequency (breaths/min)</td>
<td>46 (7)</td>
<td>48 (12)</td>
</tr>
<tr>
<td>Oxygen uptake (l/min/kg)</td>
<td>3.1 (0.3)</td>
<td>2.1 (0.6)*</td>
</tr>
<tr>
<td>Oxygen uptake per kg (ml/min/kg)</td>
<td>42 (5)</td>
<td>29 (7)*</td>
</tr>
</tbody>
</table>

*p < 0.05 TGA patients versus healthy controls.
than did the controls (29.1 (7.3) ml/min/kg v 42.0 (5.1) ml/min/kg, p < 0.01). Furthermore, peak workload of the TGA patients was lower (156 (35) W v 231 (32 W), p < 0.01). Heart rate at peak exercise was lower in the TGA group (160 (23) beats/min v 175 (8) beats/min, p < 0.05). Breathing frequency did not differ between the patients and the controls (table 2). No difference in exercise capacity was observed between patients with simple TGA and those with complex TGA or between patients who had undergone the Mustard procedure and those with the Senning procedure. The two patients who had atrioventricular junctional rhythm converted to sinus rhythm during exercise.

Cardiac function at rest
At rest, the systemic right ventricular ejection fraction was significantly lower in the patients than in controls (56 (7)% v 65 (7)%), p < 0.05). However, 24 of the 27 patients (89%) had a right ventricular ejection fraction greater than 47%. The wall mass of the right ventricle was significantly higher in the patients than in the controls (112 (43) g v 41 (7) g, p < 0.05), whereas left ventricular wall mass was significantly lower in the patients (85 (32) g v 133 (21) g, p < 0.05). All other parameters of left and right ventricular function were not significantly different between the groups (table 3). One patient was found to have a stenosis in the pulmonary venous pathway. Minimum tricuspid valve regurgitation (6 (5)%) was observed in 15 patients. No residual ventricular septal defect was observed in the patient group. In one patient high velocities (peak 210 cm/s) in the pulmonary artery suggested the presence of mild pulmonary stenosis.

Resting right ventricular ejection fraction did not correlate with exercise capacity (r = 0.1, p = 0.60) in the patients. No difference in cardiac function was observed between patients with simple TGA and those with complex TGA or between the patients who had undergone the Mustard and those who had undergone the Senning procedures.

Cardiac response to supine bicycle exercise
In response to the submaximal MRI exercise level, heart rate increased from 68 (10) beats/min to 117 (8) beats/min (p < 0.05) in the TGA patients and from 71 (9) beats/min to 121 (14) beats/min (p < 0.05) in the controls. No difference in heart rate at the MRI exercise level was observed between the TGA patients and the controls.

The response of both the left and the right ventricles to exercise was analysed for all participants (fig 1) and was significantly different between the TGA group and the controls (table 3). As expected, biventricular stroke volume and ejection fraction increased significantly in the controls. In all controls biventricular ejection fraction increased more than 5%. In the TGA patients stroke volume and ejection fraction of both ventricles did not change significantly in response to exercise. In only one patient systemic right ventricular ejection fraction increased more than 5% in response to exercise, and in 10 patients left ventricular ejection fraction increased more than 5%.

In response to exercise, volume changes of both ventricles differed significantly between the TGA patients and the controls (table 3, fig 2). Systemic right ventricular end diastolic and end systolic volumes of the TGA patients increased in response to exercise (end diastolic volume: 155 (55) to 163 (57) ml, p < 0.05; end systolic volume: 70 (34) ml to 75 (36) ml), whereas in the controls right ventricular end diastolic volume did not change and end systolic volume decreased (52 (20) ml to 37 (16) ml, p < 0.05). Left ventricular end diastolic and end systolic volumes of the TGA patients did not change significantly in response to exercise, whereas in the controls left ventricular end systolic volume decreased without a change in end diastolic volume.

In the TGA patients, systemic right ventricular ejection fraction during exercise, but not at rest, and the percentage change in right ventricular ejection fraction from rest to exercise correlated significantly with peak oxygen consumption per kilogram bodyweight (exercise right ventricular ejection fraction: r = 0.40, p < 0.05; change in right ventricular ejection fraction: r = 0.43, p < 0.05).

DISCUSSION
In the present study, cardiovascular function at rest and in response to supine exercise was evaluated with MRI in patients with TGA 23 (2) years after atrial correction and in a control group. The main finding was an abnormal response of both ventricles to exercise in the TGA patients. Despite a relatively well preserved resting ventricular function, both the right and left ventricles failed to increase stroke volume and ejection fraction in response to exercise and the systemic right ventricular end diastolic and end systolic volumes increased. The abnormal changes in right ventricular ejection fraction in response to exercise correlated with impaired exercise capacity in the patients with atrially corrected TGA.

Cardiac function at rest
At rest, the ejection fraction of the systemic right ventricle differed significantly between the controls and TGA patients.

<table>
<thead>
<tr>
<th>Table 3 Cardiac response to exercise</th>
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<tbody>
<tr>
<td><strong>Controls</strong></td>
</tr>
<tr>
<td><strong>Workload (W)</strong></td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
</tr>
<tr>
<td><strong>Right ventricle</strong></td>
</tr>
<tr>
<td>EDV (ml)</td>
</tr>
<tr>
<td>ESV (ml)</td>
</tr>
<tr>
<td>SV (ml)</td>
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<tr>
<td>EF (%)</td>
</tr>
<tr>
<td>Mass (g)</td>
</tr>
<tr>
<td><strong>Left ventricle</strong></td>
</tr>
<tr>
<td>EDV (ml)</td>
</tr>
<tr>
<td>ESV (ml)</td>
</tr>
<tr>
<td>SV (ml)</td>
</tr>
<tr>
<td>EF (%)</td>
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<tr>
<td>Mass (g)</td>
</tr>
</tbody>
</table>

*p < 0.05 TGA patients v controls; †p < 0.05 rest v exercise.
EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; SV, stroke volume.
23 (2) years after atrial correction. However, in the majority of our patients (89%) right ventricular ejection fraction was within normal limits. Lorenz and colleagues reported similar results with the use of MRI with 22 patients 16 (5) years after atrial correction of TGA. In that study, normal systemic right ventricular size, a mildly depressed right ventricular ejection fraction, increased right ventricular wall mass, and normal left ventricular function were found. In a longitudinal study, serial measurements of systemic ventricular performance showed no deterioration over time. In our study the results suggest that resting global biventricular function is relatively well preserved during follow up after atrial correction of TGA.

Quantification of tricuspid valve regurgitation showed that this was a common finding in the TGA patients, although the amount was small in most patients. The presence of tricuspid regurgitation is in concordance with earlier reports, but it is unclear whether tricuspid regurgitation is a primary phenomenon or a result of right ventricular dysfunction. Tricuspid valve regurgitation may play a part in the occurrence of atrial arrhythmias and right ventricular dysfunction. Close follow up is warranted, which can be done accurately and non-invasively with MRI.

Cardiac function in response to exercise
To evaluate the biventricular response to exercise in the TGA patients after atrial correction we used a dedicated MRI exercise protocol. This approach has already been validated in healthy young adults and in patients after correction of tetralogy of Fallot. Low intraobserver and interobserver variabilities of 4 (3)% and 8 (7)%, respectively, for the left ventricle and 5 (4)% and 9 (8)%, respectively, for the right ventricle have been obtained.

Despite the well preserved systemic ventricular function of the TGA patients after atrial correction, the right ventricular ejection fraction response to exercise was abnormal in 26 of the 27 TGA patients. Mean stroke volume and the ejection fraction of both the right and left ventricles of the TGA patients did not increase in response to exercise. Similar observations for stroke volume and ejection fraction response have been reported previously when radionuclide angiography was used. But others observed a normal response
of right ventricular ejection fraction to exercise in the majority of patients after Mustard correction of TGA.

However, for optimal interpretation of changes in stroke volume and ejection fraction in response to exercise, ventricular volumes should be quantified, which is difficult with techniques other than MRI. Using MRI measurements, we observed an increase in right ventricular end diastolic volume and end systolic volume in response to exercise, whereas both volumes of the left ventricle did not change significantly in the patients. The normal ventricular response, as observed in the control group, is characterised by no change in biventricular end diastolic volume and a decrease in biventricular end systolic volume. An increase in right ventricular end diastolic volume in response to exercise resembles the response seen in older healthy people, in patients with corrected tetralogy of Fallot with important pulmonary regurgitation, and in patients with ischaemic heart disease. In patients with coronary heart disease, exercise induced myocardial ischaemia and myocardial scar contribute to an increase in left ventricular end diastolic volume in response to supine physical exercise. In patients after atrial repair of TGA fixed and reversible myocardial perfusion defects and decreased myocardial flow reserve of the systemic right ventricle are commonly found. Therefore, our findings of an increase in right ventricular end diastolic volume and end systolic volume in response to exercise may be the result of abnormalities in myocardial perfusion in response to stress.

After atrial correction of TGA the occurrence of perfusion defects during stress is related to the duration of follow up after correction. This may explain the contrasting findings of no change or even a decrease in end diastolic volume of the right ventricle observed six to seven years after atrial correction of TGA compared with our observations of an increase in end diastolic volume in response to exercise.

The lack of increase in stroke volume observed in patients with atrially corrected TGA has been attributed to abnormalities in contractility of the systemic right ventricle, and increased exercise systemic vascular resistance. Recently, Derrick and colleagues observed an appropriate systemic right ventricular myocardial contractile reserve in patients 18 years after atrial correction of TGA by using pressure–volume loop analysis at rest and during dobutamine stress. The authors hypothesised that restricted filling through the atrial baffles is the most important factor in causing the abnormal stroke volume and ejection fraction response to physical exercise. This was also suggested by Tulevski and colleagues, who used dobutamine stress in combination with MRI. Our observations of right ventricular volume response to exercise suggest a negative influence of ischaemia and myocardial scar on contractility of the systemic right ventricle.

Differences in stress protocol and measured parameters make direct comparison of studies difficult. Various stress protocols focus on different aspects of the cardiovascular response to stress. Furthermore, cardiac response to dobutamine or physical stress is dependent on the amount of dobutamine infused and the level of exercise, respectively. Besides differences in methods, discrepancy in age at correction and duration of follow up after correction limit a direct comparison of results of various studies. The combination of exercise MRI and pressure–volume loop analysis may provide a tool to elucidate further the mechanism of cardiac dysfunction in response to physical exercise.

Exercise capacity and cardiac function

Exercise capacity of the TGA patients was diminished, as shown by significantly lower oxygen uptake and workload at peak exercise. Decreased exercise capacity is often found in this patient group. In our study, in the TGA patients we observed a significant correlation between both exercise right ventricular ejection fraction and changes in right ventricular ejection fraction with exercise on the one hand and the indexed peak oxygen uptake on the other. No direct relation.
between exercise capacity and cardiac response to exercise has been reported so far.\(^1\)\(^4\)\(^1\)

Ejection fraction is influenced by preload, contractility, afterload, and heart rate. As discussed in the previous section, abnormalities in preload\(^2\)\(^3\)\(^4\) and myocardial dysfunction\(^1\)\(^4\)\(^5\) are common findings in this patient group and may influence exercise capacity. The impaired chronotropic response to exercise observed in our patients may influence ventricular ejection fraction\(^6\) and thus exercise capacity,\(^1\) although a direct relation between chronotropic impairment and exercise capacity has not been established.\(^6\) Benson and colleagues\(^1\) did not observe abnormalities in afterload response to exercise in TGA patients after atrial correction, suggesting that afterload may play a limited part in the abnormal response of the right ventricle to physical exercise.

**Study limitations**

We studied a selected group of patients after atrial correction of TGA. NYHA functional class was I or II and regular cardiac rhythm was present. However, this is the patient group at risk for cardiac failure and arrhythmias, which are both risk factors for cardiac death.\(^7\) Therefore, this patient group should be closely monitored to detect signs of cardiac failure and abnormalities of cardiac rhythm.

Tricuspid valve flow was not evaluated during exercise because of difficulties in assessing atrioventricular valve flow at high heart rates. Therefore, valuable information on the effect of exercise on tricuspid valve regurgitation and the potential correlation with exercise capacity was not available. The development of slice tracking techniques\(^8\) may overcome this problem in the future.

During the MRI exercise protocol, the images were acquired during short exercise breaks, which is less physiological than measurement during exercise. The use of real time MRI may allow the evaluation of cardiac function during exercise.

**Conclusion**

In TGA patients late after atrial correction who had near normal cardiac function at rest, the use of exercise MRI showed an abnormal response of both the systemic right and the left ventricles. Furthermore, abnormal cardiac response to exercise, but not at rest, correlated with diminished exercise capacity in this patient group. We conclude that exercise MRI is well suited to the evaluation of biventricular function at rest and in response to exercise and provides a tool for close monitoring of cardiovascular function in TGA patients after atrial correction, who are at risk for late death.

**ACKNOWLEDGEMENTS**

The technical assistance of Robert G M van Steijn (Department of Pulmonology, Leiden University Medical Centre, the Netherlands) is gratefully acknowledged.

**REFERENCES**

FROM BMJ JOURNALS

A new form of retinopathy associated with myocardial infarction treated with percutaneous coronary intervention

N Kinoshita, A Kakehashi, T Yasu, T Katayama, M Kuroki, Y Tsurimaki, R Ono, H Yamagami, M Saito, M Kawakami

Aim: To report a new form of retinopathy that was observed in patients who had undergone percutaneous coronary intervention (PCI) following acute myocardial infarction (AMI).

Methods: Serial ophthalmological examinations were conducted in 40 patients who underwent PCI. Thirty patients were diagnosed with AMI, and another 10 had stable angina pectoris.

Results: Cotton wool spots developed in 17 (57%) patients from the group with AMI undergoing PCI (n = 30) within 2 months. Of these, 41% (seven patients) also developed superficial haemorrhages. Retinopathy was most prominent 1–2 months after AMI and then tended to become quiescent afterwards, without treatment.

Conclusion: We have identified a new form of retinopathy in patients with AMI that spontaneously subsides without treatment.

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