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CONGENITAL HEART DISEASE

Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries

THOMAS OOSTERHOF,[1] IGOR I. TULEVSKI,[1] ARNO A. W. ROEST,[2] PAUL STEENDIJK,[3] HUBERT W. VLIEGEN,[3] ERNST E. VAN DER WALL,[3] ALBERT DE ROOS,[4] JAN G. P. TIJSSEN,[1] and BARBARA J. M. MULDER, M.D.[1,*]

[1]*Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands*
[2]*Department of Pediatric Cardiology, Leiden University Medical Center, Amsterdam, The Netherlands*
[3]*Department of Cardiology, Leiden University Medical Center, Amsterdam, The Netherlands*
[4]*Department of Radiology, Leiden University Medical Center, Amsterdam, The Netherlands*

Background. In patients with an intra-atrial correction for transposition of the great arteries (TGA) an abnormal response to stress testing is common. However, hemodynamic responses may vary substantially when different stress tests are used. We compared the hemodynamic response to dobutamine stress with the response to physical exercise in patients and controls. *Methods.* Thirty-nine patients and 25 age/sex-matched control subjects underwent either dobutamine stress (15 μg/kg/min) or submaximal physical exercise cardiovascular magnetic resonance. End-systolic and end-diastolic right ventricular volumes (ESV; EDV) were determined. Five representative patients underwent both stress tests. For these patients, wall thickening reserve was calculated as systolic wall thickening during stress minus systolic wall thickening at rest. *Results.* In controls, dobutamine stress and physical exercise showed similar responses: stroke volume, cardiac output, and ejection fraction increased significantly, whereas ESV decreased significantly and EDV was unchanged. In patients, stroke volume did not increase with either dobutamine or exercise (−8.6% vs. 2.9%). Ejection fraction increased significantly with dobutamine (16%, $p < 0.001$) but tended to decrease during exercise (−2.1%, P = NS). EDV and ESV decreased during dobutamine but were unchanged during exercise (−22% vs. 5.0%, $P < 0.001$; −36% vs. 9.0%, $P < 0.01$ respectively). Wall thickening reserve was higher with dobutamine than with exercise (0.9 mm vs. −0.6 mm, P = 0.02). *Conclusion.* Dobutamine stress and physical exercise cannot be used interchangeably for assessment of systolic and diastolic function in patients with an intra-atrial correction for TGA. This may have consequences for the use of different stress CMR approaches in the clinical setting.

Key Words: Transposition of the great arteries; Cardiovascular magnetic resonance; Dobutamine stress; Physical exercise

1. Introduction

In patients with an intra-atrial correction (Mustard or Senning procedures) of transposition of the great arteries (TGA), right ventricular dysfunction is associated with adverse long-term outcome (1). Stress testing allows us to detect ventricular dysfunction (2–5), which may not be present at rest (6). Patients with an intra-atrial correction of TGA generally show an abnormal response to stress (7, 8). Possible causes for this abnormal response to stress include systolic dysfunction of the right ventricle (RV) under systemic pressure (9), filling abnormalities of the RV through rigid atrial baffles (10), and an abnormally low heart rate response (11).

Conflicting reports have been published concerning the hemodynamic response to pharmacological or physical exercise testing in this patient group (12–15). Using dobutamine stress, evidence for a decreased filling pattern but normal contractility has been reported (12, 16). On the other hand, both physical exercise and pharmacological stress may show a decreased systolic function (7, 14, 15).

The objective of this cardiovascular magnetic resonance (CMR) study was to compare the hemodynamic response to dobutamine stress with the response to physical exercise in patients with an intra-atrial correction for TGA.

2. Methods

2.1. *Patient population*

Thirty-nine patients with an intra-atrial correction (Mustard or Senning) for d-TGA (age 25.2 ± 4.4 years) underwent stress CMR. Of these patients, 12 underwent dobutamine stress

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*Address correspondence to Barbara J. M. Mulder, M.D., Department of Cardiology, Academic Medical Center, Room B2-240, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; Fax: +31-20-5666809; E-mail: b.j.mulder@amc.uva.nl

Table 1. Baseline characteristics

	Dobutamine stress		Physical exercise	
	Controls	Patients	Controls	Patients
Age	29 ± 4.6	24 ± 4.1	27 ± 4.0	26 ± 4.6
Male/Female	5/6	10/7	8/6	15/12
Mustard/Senning		15/2		11/16[a]
Simple/Complex		5/12		11/16
NYHA I/II		9/8		11/16
EDV (mL/m^2)	62 ± 17	67 ± 16	75 ± 10[a]	83 ± 22[a]
ESV (mL/m^2)	19 ± 9	28 ± 9	26 ± 7	37 ± 14[a]
SV (mL/m^2)	43 ± 10	39 ± 13	49 ± 5	46 ± 11
EF (%)	38 ± 7	32 ± 6[b]	34 ± 5	31 ± 6[b]
HR (bpm)	66 ± 12	70 ± 12	66 ± 8	68 ± 10
CI ($L/min/m^2$)	2.8 ± 0.6	2.7 ± 0.7	3.2 ± 0.4	3.0 ± 0.7

Note: EDV = end-diastolic volume, ESV = end-systolic volume, SV = stroke volume, EF = ejection fraction, HR = heart rate, and CI = cardiac index.
[a]Significant difference between dobutamine stress and physical exercise ($p < 0.05$).
[b]Significant difference vs. controls ($p < 0.05$).

CMR (age 24.2 ± 4.1 years) and 22 underwent physical exercise CMR (age 25.8 ± 4.6 years). Five additional patients underwent both dobutamine stress CMR and physical exercise CMR. Patient characteristics are summarized in Table 1. Eleven age-matched control subjects (mean age 28.9 ± 4.6 years, five male) underwent dobutamine stress CMR and 14 age-matched control subjects (mean age 26.8 ± 3.9 years, eight male) underwent physical exercise CMR. Exclusion criteria were contraindications for CMR and for dobutamine. Informed consent was obtained from all subjects and the ethical review boards of the institutions approved the study.

2.2. *Dobutamine stress CMR*

Subjects were studied using a 1.5 Tesla CMR scanner with high power gradients (Vision, Siemens, Erlangen, Germany) in the Academic Medical Center. After obtaining standard scout views of the short-axis stack of 12–14 contiguous images with a slice thickness of 10 mm and 0-mm slice gap from the valve plane to the apex was created using an ultra-fast turbo field echo imaging sequence with the following parameters: repetition time (TR) = R − R interval, echo time (TE) 4.8 ms, imaging matrix 256 × 256, field of view 350 mm, flip angle 20°. Dobutamine was administered through an intravenous line by a digital infusion pump with an initial dose of 5 μg/kg/min and after 3 minutes, dobutamine infusion was increased by 5 μg/kg/min up to a maximum of 15 μg/kg/min. Three minutes after reaching the maximal dose the CMR protocol was repeated. Electrocardiogram, heart rate, and blood pressures were monitored continuously throughout the protocol.

2.3. *Physical exercise CMR*

Subjects were studied using a Philips Gyroscan ACS/NT 1.5 Tesla MR scanner (Philips Medical Systems, Best, The Netherlands) equipped with a Powertrack 6000 gradient system (Philips Medical Systems) in the Leiden University Medical Center. Exercise was performed on an MR-compatible bicycle ergometer. After obtaining standard scout views of the heart, MR velocity mapping measurements were obtained in a plane perpendicular to the ascending aorta. Volumetric indexes of the systemic ventricle were obtained from a short axis stack of 10 images with a slice thickness of 10 mm and 1-mm slice gap, using an ultra fast, turbo field echo planar imaging MR technique with the following parameters: TR 14 ms, TE 4.8 ms, EPI factor of 5, flip angle 30°, 128 × 40 matrix, field of view 420 × 120. The protocol was repeated during submaximal exercise. The submaximal exercise level for the MR examination was calculated at 60% of peak oxygen consumption, which was obtained from an exercise test performed 1 day prior to the MR examination (16).

2.4. *Data analysis*

Unix workstations were used for analysis of the MR images. MASS image analysis software (Medis, Leiden, The Netherlands) was used for the short axis images to calculate end-diastolic volumes (EDV), end-systolic volumes (ESV), stroke volume (SV), and ejection fraction (EF). For internal validation purposes, stroke volume obtained from multislice-multiphase images was compared with stroke volume obtained from velocity mapping of the ascending aorta. Only measurements with comparable data were used in the analysis.

Five patients, who were representative of the entire population, underwent both dobutamine and physical exercise. Furthermore, in these patients systolic wall thickening was determined using the modified centerline method (17) both at rest and during stress. Endocardial and epicardial borders were drawn in all phases of one short axis slice at the midventricular level of the systemic ventricle, which was divided into four segments: inferior, free wall, anterior, and septal wall (15). For these segments systolic wall thickening was calculated by subtracting end-diastolic wall thickness from end-systolic wall thickness in rest and during stress. Systolic wall thickening reserve was calculated as systolic wall thickening during stress minus systolic wall thickening at rest (18).

2.5. *Statistical analysis*

Data are described as frequencies and means with standard deviations. Difference between baseline characteristics and the hemodynamic response to stress were sought with Chi-squared test and independent samples T-test. Differences in hemodynamic parameters in rest vs. stress and the comparison of hemodynamic response of five patients who underwent both stress tests were analyzed using a paired Student's t-test. A Pearson's correlation coefficient was used for comparison of wall thickening reserve and change in EF to stress. A p-value < 0.05 was considered statistically significant.

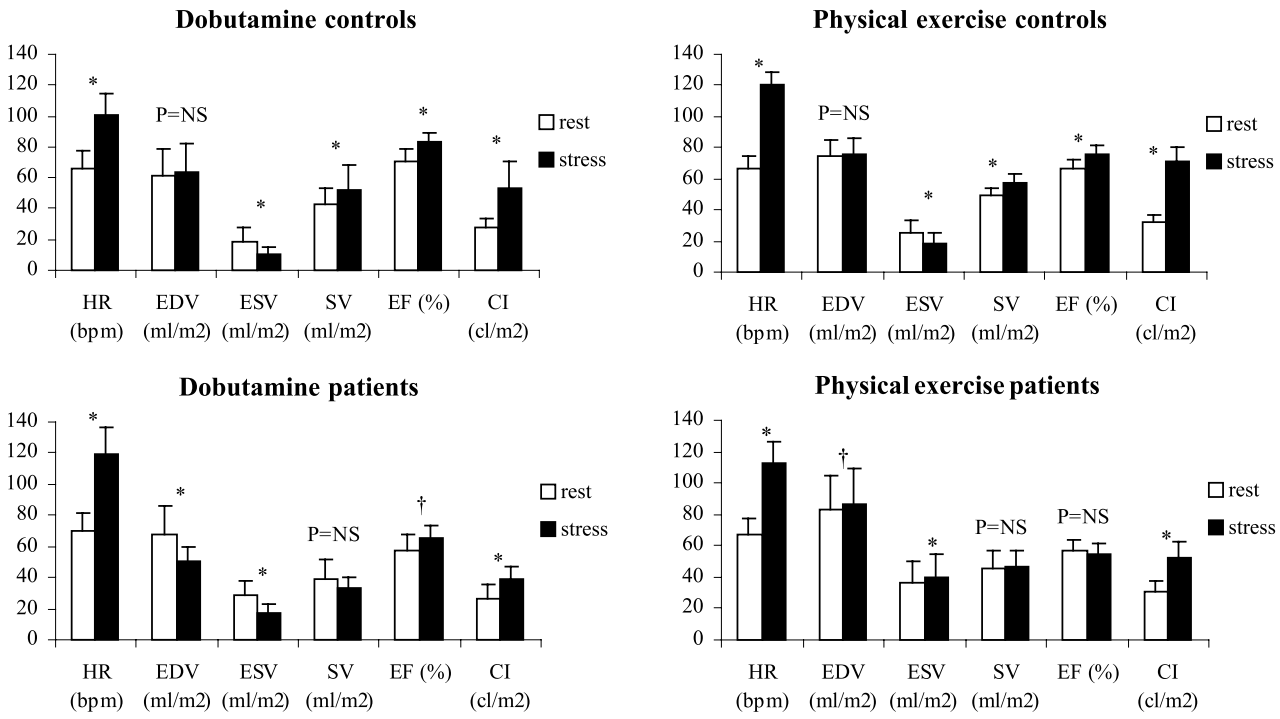

Figure 1. Cardiovascular response to dobutamine and physical exercise CMR in controls and patients with transposition of the great arteries. White bars show baseline values, black bars show stress values. CI indicates cardiac index; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; SV, stroke volume. * = Significant difference between rest and stress of $P < 0.001$. † = Significant difference between rest and stress of $P < 0.01$.

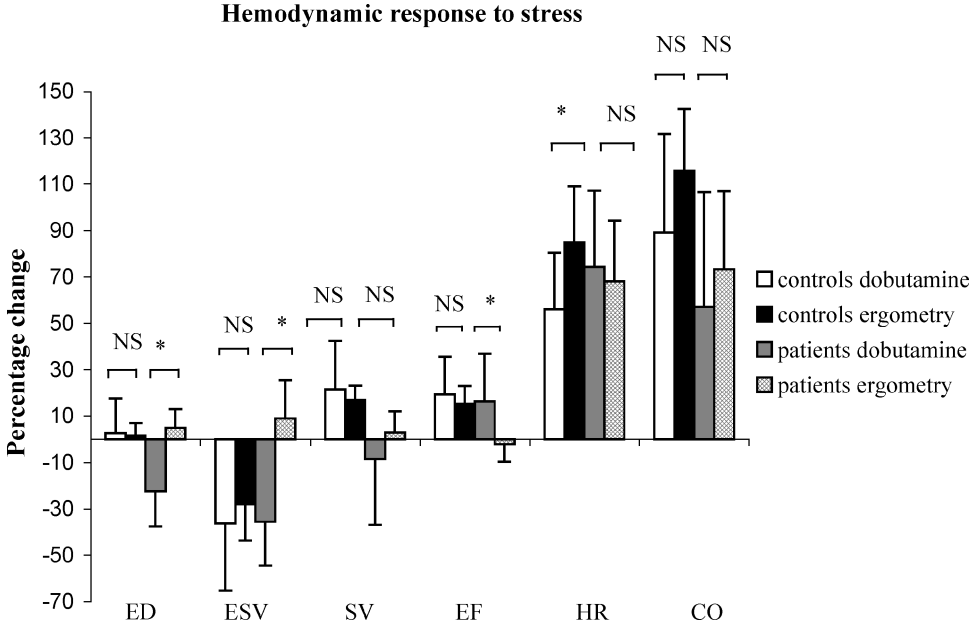

Figure 2. Differences in cardiovascular response in control subjects and patients with an intra-atrial correction for TGA between physical exercise and dobutamine stress. CO indicates cardiac output; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; SV, stroke volume. * = Significant difference in dobutamine vs. physical exercise of $P < 0.05$.

3. Results

3.1. *Response to stress in control subjects*

Baseline characteristics are depicted in Table 1. During dobutamine and physical exercise, controls showed a similar increase in stroke volume (21% vs. 17%, P = NS) and EF (19% vs. 15%, P = NS), ESV was decreased (– 37% vs. – 28%, P = NS), and EDV did not change (2.6% vs. 1.5%, P = NS; Figs. 1 and 2). Compared to dobutamine stress, a greater increase in heart rate was observed during physical exercise in controls (56% vs. 85%, P = 0.007) with a comparable increase in cardiac output (89% vs. 116%, P = NS).

3.2. *Response to stress in patients with TGA*

Heart rate and cardiac index increased significantly and to a similar extent with both dobutamine and physical exercise (74% vs. 68%, P = NS; 57% vs. 74%, P = NS, respectively). In patients we observed an inappropriate response to dobutamine stress and physical exercise, demonstrated by the failure to increase stroke volume (– 8.6% vs. 2.9%, P = NS, respectively).

An abnormal systolic response was observed in patients during physical exercise, shown by an increase in ESV (9.0% vs. – 28% in controls, P < 0.001), and a slight decrease in EF (– 2.1% vs. 15% in controls, P < 0.001) (Figs. 1 and 2). However, during dobutamine stress a

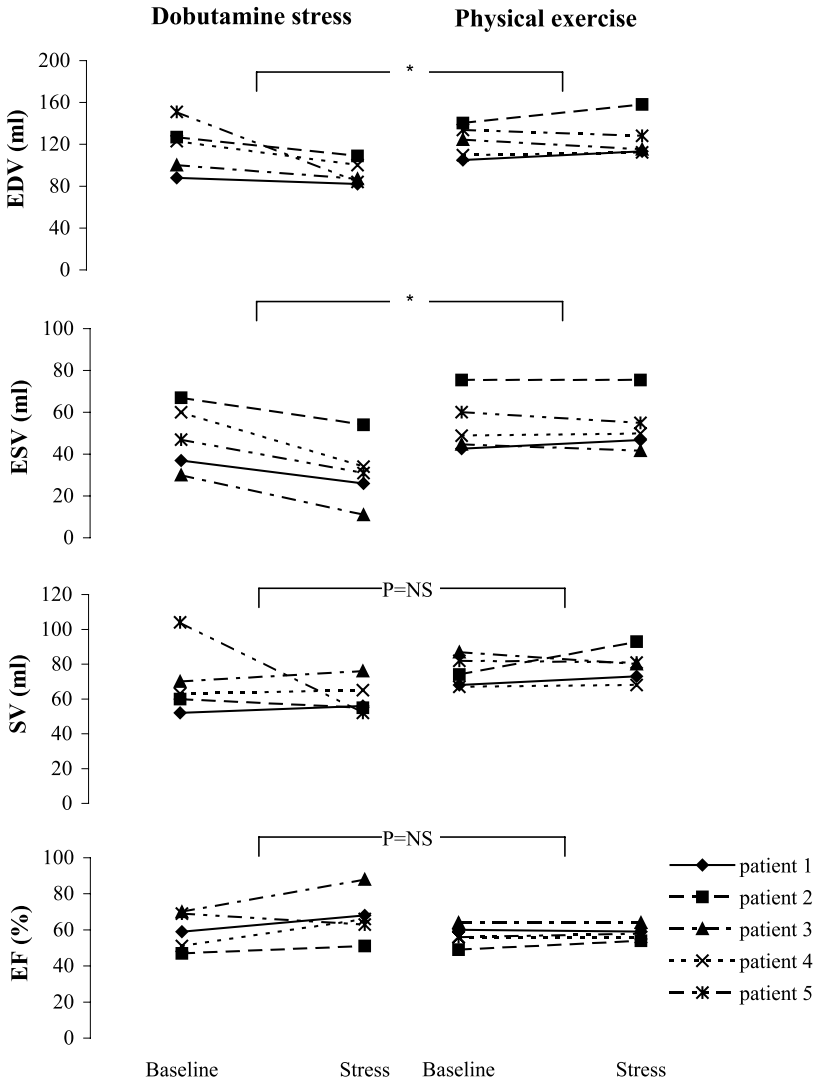

Figure 3. Effect of dobutamine stress and physical exercise on volumetric indices in five patients, who underwent both dobutamine stress and physical exercise. The five patients generally show a similar response to dobutamine stress and physical exercise in comparison to the entire patient group. EDV indicates end-diastolic volume; EF, ejection fraction (%); ESV, end-systolic volume and SV, stroke volume. * = Significant difference (P < 0.005) in the change of the hemodynamic parameter to stress in dobutamine vs. physical exercise.

Table 2. Wall motion abnormalities

	Dobutamine stress CMR (n = 5)	Physical exercise CMR (n = 5)	P-value
Systolic wall thickening in rest (mm)			
Inferior	4.1 ± 2.5	5.8 ± 2.6	0.68
Free wall	2.7 ± 1.2	3.3 ± 1.5	0.37
Anterior	2.1 ± 1.6	2.6 ± 1.3	0.91
Septal	2.0 ± 0.5	1.5 ± 0.5	0.11
Mean	*2.7 ± 1.7*	*3.3 ± 2.2*	*0.27*
Wall thickening reserve (mm)			
Inferior	1.8 ± 1.6	− 1.3 ± 2.6	0.14
Free wall	0.5 ± 2.4	− 0.6 ± 1.8	0.18
Anterior	1.0 ± 0.8	0.3 ± 2.2	0.58
Septal	0.2 ± 1.3	− 0.7 ± 0.4	0.21
Mean	*0.9 ± 1.6*	*− 0.6 ± 1.9*	*0.02*

relatively normal systolic response was observed (Figs. 1 and 2).

On the other hand, a decrease in EDV was observed during dobutamine stress (−22% vs. 2.6% in controls, $P < 0.001$), whereas during physical exercise no significant EDV change was observed (5.3% vs. 1.5%, P = NS). No significant differences in hemodynamic parameters between male vs. female and NYHA 1 vs. 2 were found.

3.3. *Wall motion abnormalities*

In the subgroup of five patients who underwent both dobutamine stress and physical exercise, we analyzed systolic wall thickening both at rest and during stress. Note that the hemodynamic responses to both stress tests in this subgroup showed similar findings as seen in the entire patient group (Fig. 3). Systolic wall thickening at rest is shown for dobutamine and physical exercise in Table 2. During dobutamine stress, mean systolic wall thickening increased significantly (2.7 mm to 3.6 mm, P = 0.03), whereas during physical exercise systolic wall thickening did not increase significantly (3.3 mm to 2.7 mm, P = NS). Wall thickening reserve was higher during dobutamine stress compared to physical exercise (0.9 ± 1.6 mm vs. − 0.6 ± 1.9 mm, P = 0.02, respectively). Global wall thickening reserve correlated well with change in EF during stress (R = 0.67, P = 0.03).

4. Discussion

The present study revealed disparity between results obtained by dobutamine stress and physical exercise in patients with an intra-atrial correction for TGA. Systolic dysfunction (unchanged EF and wall thickening during stress) was a limiting factor during physical exercise, whereas during dobutamine stress a relatively normal systolic response was observed along with a decreased diastolic filling. To our knowledge, a direct comparison between the effects of dobutamine stress and physical exercise has not been performed before.

4.1. *Normal response to dobutamine stress and physical exercise*

The hemodynamic responses of control subjects to both stress tests were similar, observed by an increase in SV and EF, a decrease in ESV, and no change in EDV. These findings represent a normal physiological response and are consistent with previous studies using radionuclide angiography and echocardiography (19–21).

4.2. *Stroke volume and cardiac output response to stress in tga patients*

In patients with an intra-atrial correction for TGA, an inappropriate hemodynamic response to stress (failure to increase stroke volume) is almost a consistent finding (7, 8, 14). The cause of this inappropriate response to stress has been sought in an abnormal chronotropic response, restricted flow through the atrial baffles, or systolic dysfunction. In the present study no abnormal chronotropic response was observed, but patients with a pacemaker were excluded from the study due to CMR incompatibility.

4.3. *Systolic dysfunction*

In the present study, the increase in end-systolic volume and no significant change in ejection fraction during physical exercise is likely the result of systolic RV dysfunction. The reduced wall thickening reserve during physical exercise, demonstrated in a subgroup of patients, further supports this finding.

The presence of systolic dysfunction in these patients is consistent with previous studies, which showed that myocardial perfusion defects with concordant wall motion abnormalities and a decreased myocardial flow reserve were reported (15, 23).

In our study, a normal systolic response was observed during dobutamine stress. The direct effect of dobutamine resulted in a normal decrease in ESV and a normal increase in EF. This is supported by Derrick et al. (12), who reported a normal response in RV contractility to dobutamine infusion (10 μg/kg/min) measured with conductance catheters. In both studies, the reason for the absence of systolic dysfunction was the low dobutamine infusion rate.

During physical exercise an abnormal contractility response was observed with a slight increase in EDV. We feel it is likely that blood volume recruitment during exercise explains the maintained EDV in this group. The lower threshold for systolic dysfunction during physical exercise (at 60% of V02 max) in comparison to dobutamine stress (at 15 μg/kg/min) probably is the result of differences in pre- and

afterload (peripheral arterial resistance). Furthermore, it has been emphasized that physical exercise causes greater severity of ischemia as assessed by ECG patterns and ventricular dilatation in patients with coronary artery disease (23).

4.4. *Diastolic function in patients with TGA*

In patients with an intra-atrial correction for TGA, Derrick et al. (12) reported a failure to increase the filling rate of RV. The decrease in EDV during dobutamine stress reported in our study is in agreement with these findings.

4.5. *Clinical implications*

In patients with an intra-atrial correction for TGA, stress-induced hemodynamic changes may vary dependent on the used stress modality. This is important when interpreting stress test results in clinical practice. These differences may also be present in other patient groups and it might also apply for the detection of coronary artery disease (24, 25). Further investigation is needed to clarify these dissimilarities for different patient categories.

4.6. *Study limitations*

Direct comparison was only possible in five patients. Larger studies should be undertaken in different patient categories. However, not many patients are willing to undergo both stress CMR approaches within a short time.

5. Conclusion

In the present study we demonstrated that using CMR, control subjects showed a uniform response to physical exercise and dobutamine stress, whereas the responses were different for patients with an intra-atrial correction for TGA. During both stress tests an inadequate stroke volume response was observed. Our data suggest that systolic dysfunction was a limiting factor for an appropriate response during physical exercise. During dobutamine stress, on the other hand, a relatively normal systolic response was observed with decreased diastolic filling. Therefore, physical exercise and dobutamine stress tests do not produce interchangeable results, which may have consequent implications for clinical practice.

Abbreviations

CO	cardiac output
EDV	end-diastolic volume
EF	ejection fraction
ESV	end-systolic volume
HR	heart rate
RV	right ventricle
SV	stroke volume
TGA	transposition of the great arteries

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