Right ventricular volume load and function in congenital heart defects

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Changes in blood volume shunting in patients with atrial septal defects: assessment of heart function with cardiovascular magnetic resonance during dobutamine stress

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Background

The purpose of this study was to determine the effect of stress on left-to-right shunting in patients with atrial septal defect (ASD) and to investigate if the degree of shunting, cardiac output (CO), and right ventricular (RV) volumes are related to exercise capacity.

Methods

Twenty-six patients with a secundum ASD and 16 healthy volunteers were studied with rest/stress cardiac magnetic resonance using 20 μg/kg/min dobutamine and 0.25–0.75 mg atropine to quantify CO, pulmonary to systemic flow ratio (QP/QS), and left ventricular (LV) and RV volumes. Peak oxygen uptake (VO2peak) was determined on ergospirometry.

Results

In patients with ASD the QP/QS decreased from 2.0 ± 0.2 at rest to 1.5 ± 0.1 (P < 0.001) during dobutamine stress (n = 20) and shunt volume per heartbeat decreased from 70 ± 9 to 38 ± 9 mL (P < 0.001). However, absolute shunt volume per minute was unchanged (5.1 ± 0.8 vs. 4.5 ± 1.0 L/min, P = 0.32) explained by a higher increase in systemic CO during stress (90 ± 11%) compared with pulmonary CO (43 ± 7%, P < 0.001). In ASD patients, VO2peak correlated with aortic CO during stress (r = 0.77) and QP/QS at rest (r = −0.48) but not during stress (P = 0.09). VO2peak did not correlate with RV volumes in patients.

Conclusion

Pulmonary to systemic flow ratio and shunt volume per heartbeat decrease during stress in ASD patients. This may be explained by an enhanced LV diastolic function during stress and may have implications to detect disturbances in LV compliance in ASD patients. A high systemic CO during stress is a strong predictor of exercise capacity.

Introduction

Patients with atrial septal defects (ASDs) often have decreased exercise capacity, shortness of breath and palpitations.1 ASD closure is recommended in all patients with left-to-right shunts larger than 1.5:1, dilation of the right atrium or ventricle and pulmonary vascular resistance <5 Wood units. Patients with paradoxical embolism should also be considered for intervention.1 Pulmonary cardiac output (CO) (QP) divided by systemic CO (QS) is used to quantify the degree of left-to-right shunting (QP/QS). The magnitude of left-to-right shunting has been related to the size of the ASD4 and the compliance of the ventricles.3 However, the effect of exercise on left-to-right shunting is less well known. Two previous invasive studies have found decreased pulmonary to systemic flow ratio during exercise but with different responses in absolute shunt volumes. Bay et al. showed increased absolute shunt volume during exercise4
while Nielsen et al. found decreased shunt volume during exercise. An invasive study using rapid atrial pacing showed increased aortic blood flow but not pulmonary blood flow in sedated children with ASD. It is therefore not clear if and how the shunt volume changes with increased heart rate and systemic stroke volume (SV). Also, the mechanisms for these changes during stress are relatively unknown.

Quantification of left-to-right shunting in ASDs with cardiac magnetic resonance (CMR) is highly accurate. Flow measurements with CMR have proved to be superior to invasive cardiac catheterization besides the advantages of CMR being non-invasive. Dobutamine infusion can be used to simulate stress in the MR scanner and enables quantification of cardiac function during stress. Dobutamine increases heart rate through stimulation of β-1 receptors and SV through α-1 stimulation with the net result of increased CO.

Exercise capacity is often used as a marker of the impact of the ASD because it is quantitative and less prone to bias compared with reported symptoms. Several studies have found improved exercise capacity after surgical or transcatheter closure of the ASD, even though impaired results have also been described in a subset of patients. The relationship between exercise capacity and the size of the defect or the degree of shunting (QP/QS) is not straightforward. In this study, we hypothesized that exercise capacity in patients with ASD has a stronger relationship to QP/QS during stress compared with rest.

The purpose of the study was therefore to (i) determine if left-to-right shunting changes during stress, (ii) investigate the mechanisms for these changes and (iii) determine if the pulmonary to systemic flow ratio (QP/QS), systemic and pulmonary flow and RV volumes during stress are related to exercise capacity in ASD patients.

Methods

Study population
The study was approved by the Regional ethics committee in Lund, Sweden. Written informed consent was obtained by patients and controls. In total, 26 patients with a secundum ASD were included, 18 patients (13 females) with a large ASD and indication for transcatheter closure of the defect, and 8 patients (3 females) with a small ASD not eligible for transcatheter closure. In addition, 16 healthy controls (3 females) were included. Patients with uncontrolled atrial fibrillation were excluded. Detailed information on methodology, i.e. CMR sequence parameters, can be found in the Supplementary data online, Appendix.

Cardiovascular magnetic resonance imaging
CMR was performed at rest and during dobutamine stress. An intravenous infusion of 10 μg/kg/min of dobutamine for 3 min followed by 20 μg/kg/min dobutamine was administered and 0.25–0.75 mg atropine was added to reach a target of 70% of age-predicted maximal heart rate determined as 220 minus the patient’s age. Cine imaging in the left ventricular (LV) short-axis and long-axis views and phase contrast flow velocity mapping in the aorta and pulmonary trunk was performed at rest, at an infusion rate of 10 μg/kg/min of dobutamine and when target heart rate was reached.

Image analysis
All image analysis was performed using Segment, v1.9 (http://segment.heiberg.se). Left and right ventricular (RV) volumes and SVs were obtained at rest and at max heart rate by delineating the endocardial borders of both ventricles in all slices in end-diastole (ED) and end-systole (ES). Flow images were used to calculate CO in the aorta and pulmonary trunk as well as the QP/QS as earlier described and validated.

Ergospirometry
Peak oxygen uptake (VO2 peak) was determined using an exercise test with continuous gas analysis. VO2 peak per cent of predicted value was calculated according to the Hansen/Wasserman equation.

Catheterization and transoesophageal echocardiography
Eighteen patients underwent cardiac catheterization under conscious sedation (n = 16) or general anaesthesia (n = 2) and ASD diameters were measured in two planes using transoesophageal echocardiography. Invasive pressure recordings were obtained in 17 patients using 5F MPA catheter in the right and left atrium, right ventricle, and pulmonary trunk.

Statistical analysis
Statistical analysis was performed using Graphpad Prism v 6.0. Continuous variables are reported as means ± SEM. Pearson’s correlation was used to examine the relationship between VO2 peak, and systemic and pulmonary CO, QP/QS, and ASD size. Mann–Whitney and Wilcoxon tests were used to test if results differed (Table 2). Results with a P-value of < 0.05 were considered statistically significant.

Results

Patient characteristics
Two patients did not undergo dobutamine stress due to technical reasons and one patient did not reach target heart rate. Three patients were excluded from the flow measurements due to background phase errors, leaving 20 patients for analysis at both rest and stress. Characteristics for the 20 patients and 16 controls are presented in Table 1. Results from CMR including ventricular volume and stroke volume are presented in Table 2.

| Subject characteristics of the ASD patients and controls that underwent CMR both at rest and during dobutamine stress |
|-----------------|-----------------|-----------------|
|                  | ASD patients    | Healthy controls |
|                  | n = 20          | n = 16          |
| Mean age and range | 47 ± 4 (24–81)** | 35 ± 3 (21–62) |
| Females, n (%)     | 15 (75)         | 3 (19)          |
| BSA, mean and range (m²) | 1.8 ± 0.0 (1.5–2.4) | 1.9 ± 0.0 (1.7–2.3) |
| VO2 peak (mL/kg/min) | 27.6 ± 9.0***   | 46.0 ± 2.0      |
| VO2 peak per cent of predicted value (%) | 103 ± 6**          | 130 ± 6         |
| PAP, mean and range (mmHg) | 20 ± 1 (14–31) | 20 ± 1 (14–31) |
| LAP, mean and range (mmHg) | 7 ± 1 (2–14) | 7 ± 1 (2–14) |

Continuous variables are presented as mean ± SEM.
BSA, body surface area; VO2 peak, peak oxygen uptake; PAP, pulmonary artery pressure; LAP, left atrial pressure.

**P < 0.05, ***P < 0.01, ****P < 0.001.
Table 2  Results at rest and during dobutamine stress

<table>
<thead>
<tr>
<th></th>
<th>ASD patients, rest (n = 20)</th>
<th>ASD patients, dobutamine (n = 20)</th>
<th>Controls, rest (n = 16)</th>
<th>Controls, dobutamine (n = 16)</th>
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</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>71 ± 3***</td>
<td>122 ± 3</td>
<td>67 ± 3***</td>
<td>127 ± 3</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120 ± 5***</td>
<td>147 ± 5</td>
<td>122 ± 3***</td>
<td>158 ± 5</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>72 ± 3*</td>
<td>81 ± 3</td>
<td>74 ± 2***</td>
<td>87 ± 3</td>
</tr>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>88 ± 4***++++</td>
<td>80 ± 4+</td>
<td>108 ± 4**</td>
<td>96 ± 4</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>39 ± 3***++++</td>
<td>27 ± 2</td>
<td>50 ± 2***</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>LSVI (mL/m²)</td>
<td>50 ± 2++</td>
<td>53 ± 2++</td>
<td>58 ± 3**</td>
<td>65 ± 3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57 ± 2***</td>
<td>68 ± 2</td>
<td>54 ± 2***</td>
<td>68 ± 1</td>
</tr>
<tr>
<td>RVEDVI (mL/m²)</td>
<td>164 ± 13***+++++++</td>
<td>123 ± 10++</td>
<td>109 ± 4***</td>
<td>92 ± 4</td>
</tr>
<tr>
<td>RVESVI (mL/m²)</td>
<td>77 ± 7***+++++</td>
<td>44 ± 5+++</td>
<td>50 ± 3***</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>RVSVI (mL/m²)</td>
<td>87 ± 7***++++</td>
<td>79 ± 6++</td>
<td>59 ± 2</td>
<td>64 ± 3</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>53 ± 1***</td>
<td>65 ± 2++</td>
<td>56 ± 1***</td>
<td>70 ± 1</td>
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<tr>
<td>Systemic CI (L/min/m²)</td>
<td>2.9 ± 0.1***+++</td>
<td>5.4 ± 0.3</td>
<td>3.6 ± 0.2***</td>
<td>6.1 ± 0.3</td>
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<tr>
<td>Pulmonary CI (L/min/m²)</td>
<td>5.7 ± 0.5***+++</td>
<td>7.9 ± 0.5++</td>
<td>3.6 ± 0.2**</td>
<td>5.9 ± 0.3</td>
</tr>
<tr>
<td>Shunt per heartbeat (mL)</td>
<td>70 ± 9***</td>
<td>38 ± 9</td>
<td></td>
<td></td>
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<tr>
<td>Absolute shunt volume (L/min)</td>
<td>5.1 ± 0.8</td>
<td>4.5 ± 1.0</td>
<td>1.02 ± 0.02</td>
<td>0.97 ± 0.02</td>
</tr>
<tr>
<td>QP/QS</td>
<td>2.04 ± 0.17***+++</td>
<td>1.54 ± 0.13***+++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR, heart rate; LVEDVI, left ventricular end-diastolic volume indexed to body surface area (BSA); LVESVI, left ventricular end-systolic volume indexed to BSA; LSVI, left ventricular stroke volume indexed to BSA; LVEF, left ventricular ejection fraction; RVESVI, right ventricular end-diastolic volume indexed to BSA; RVSVI, right ventricular end-systolic volume indexed to BSA; RVEF, right ventricular ejection fraction; QP/QS, pulmonary to systemic flow ratio. Continuous variables are presented as mean ± SEM.

Comparing subjects at rest to subjects during dobutamine stress, †P < 0.05, ‡P < 0.01, §P < 0.001.

Comparing patients to controls, either at rest or during dobutamine stress, *P < 0.05, **P < 0.01, ***P < 0.001.

Ventricular systolic volume, systemic and pulmonary output, and QP/QS are presented in Table 2.

Haemodynamic changes during dobutamine stress

Typical aortic and pulmonary flow curves at rest and during dobutamine are shown in Figure 1. Systemic and pulmonary CI at rest and during dobutamine stress is shown in Figure 2. Dobutamine stress increased heart rate in both patients (76% increase) and healthy subjects (94%). In patients, left ventricular stroke volume (LVSV) had a non-significant increase of 7% during stress, and RV stroke volume (RVSV) had a non-significant decrease of 6%, leading to a decreased shunting volume per heartbeat by 28% during stress (P < 0.001), Table 2. This resulted in an increase in systemic CO during stress by 90 ± 11% and a concomitant lower increase in pulmonary CO, 43 ± 7% compared with rest (P < 0.001 for both), Figure 3. Thus, the pulmonary to systemic flow ratio was lower during stress (1.5 ± 0.1) compared with rest (2.0 ± 0.2, P < 0.001). However, there was no difference in the mean absolute left-to-right shunt flow at rest and during stress per minute (5.1 ± 0.8 vs. 4.5 ± 1.0 L/min, P = 0.32). Absolute shunt flow decreased in 12 patients, increased in 7 patients, and was unchanged in one patient during dobutamine stress. Only 2 patients out of 20 had increased shunting volume per heartbeat. There were no significant differences between patients with increased and decreased shunt flow in terms of indexed RV or LV volumes, indexed ASD size, shunt volume at rest, right atrial pressure (RAP), LAP or PAP, VO2 peak or VO2% of predicted value. Mean ASD diameter was 15.3 ± 1.3 mm and mean cross-sectional area indexed to BSA was 1.0 ± 0.2 cm²/m². The latter did neither correlate to absolute shunt flow (L/min/BSA) at rest (r = 0.47, P = 0.07) nor during dobutamine stress (r = 0.44, P = 0.09), Figure 4A. However, ASD size correlated to QP/QS and shunting volume per heartbeat (mL/BSA) both at rest (r = 0.75, P < 0.001 and r = 0.70, P < 0.01, respectively) and during dobutamine stress (r = 0.50, P < 0.05 and r = 0.60, P < 0.05, respectively), Figure 4B and C. Also, there was an inverse correlation between indexed ASD size and systemic CI at rest (r = −0.50, P < 0.05) but no correlation during dobutamine stress (P = 0.38). Of note, there was no correlation between indexed ASD size and pulmonary CI at rest (P = 0.21) or during stress (P = 0.25). The change in absolute shunting volume per heartbeat from rest to dobutamine stress did not differ in patients with restrictive ASD defined as <0.9 cm²/m² (44 ± 12%) compared with patients with larger ASD sizes (44 ± 11%, P = 0.99).

Pressure measurements

The mean pulmonary artery pressure (PAP) measured invasively during cardiac catheterization was 20 ± 1 mmHg (range 14–31), left atrial pressure (LAP) was 7 ± 1 mmHg, and right atrial pressure (RAP) was 5 ± 1 mmHg. There was no correlation between PAP, LAP or RAP and absolute shunt flow or QP/QS at rest or during dobutamine stress (P = ns). There was no correlation between absolute shunt flow and pressure recordings in either patients with restrictive or non-restrictive ASD.
Relations to exercise capacity

There was a moderate correlation between VO$_2$ peak and aortic and pulmonary CO during dobutamine stress in controls, Figure 5A. In contrast, VO$_2$ peak in patients did not correlate with pulmonary CO during dobutamine stress ($r = 0.25$, $P = 0.29$), but there was a strong correlation with aortic CO ($r = 0.77$, $P < 0.001$) (Figure 5B). There was an inverse correlation between VO$_2$ peak and QP/QS at rest ($r = -0.48$, $P < 0.05$) but not during dobutamine stress in ASD patients ($r = -0.39$, $P = 0.09$), Figure 5C. VO$_2$ peak correlated with RV end-diastolic and end-systolic volume during stress in controls ($P < 0.001$ and $P < 0.01$, respectively) but not in patients ($r = 0.14$, $P = 0.59$ and $r = 0.14$, $P = 0.58$, respectively). There was no correlation between VO$_2$ peak and LAP or PAP at rest ($P = 0.63$ and $P = 0.41$, respectively). There was no correlation between absolute shunt flow and exercise capacity in either patients with restrictive or non-restrictive ASD.
Discussion

This study has demonstrated that the pulmonary to systemic flow ratio (QP/QS) decreases during stress due to a higher increase in systemic compared with pulmonary CO. Thus, flow across the septal defect does not increase in relation to increased systemic flow. Even though the mean absolute shunt volume per minute did not change between rest and dobutamine stress, results differed...
between individual patients. In the majority of the patients, the shunt volume per minute decreased, but in a large minority, the shunt volume per minute increased. Interestingly, the absolute shunting volume with each heartbeat decreased during stress. Thus, with increased heart rate and shorter diastole, less volume is shunted from left to right with each heartbeat. The size of the ASD indexed to BSA was strongly related to QP/QS at rest but to a lesser degree during stress. Independently of the ASD size the QP/QS was unchanged or decreased in all patients during stress. This indicates that with increased flow, the ASD size per se has less impact on left-to-right shunting. More likely, the degree of shunting during stress is determined by the relationship between diastolic compliance of the LV and RV. The normal relationship between peak oxygen uptake and CO in both the systemic and pulmonary circulation during stress is disrupted in ASD patients, where peak oxygen uptake has a strong correlation with systemic CO at rest and during stress, but no correlation with pulmonary CO or RV volumes.

**Physiological explanations for changes in shunting during exercise**

With increased heart rate and flow during dobutamine stress, we found a relatively larger increase in CO from the left than the right ventricle compared with rest. Thus, during stress the increase in transmural flow per heartbeat is larger than the increase in the left-to-right flow through the ASD. This was seen in all but two patients during stress. Possible explanations for the decrease in shunting fraction and differences in response with respect to shunting volume include: (i) the ASD becomes more restrictive with increased flow, limiting the left-to-right shunt; (ii) the LV diastolic pressure gradient decreases with stress due to increased LV compliance; (iii) decreased RV compliance during stress; (iv) the diastolic movement of the ventricular septum towards the left ventricle decreases during stress and therefore does not impair LV filling; (v) the recruitment of pulmonary vasculature has been maximized at rest and further increase in pulmonary flow leads to increased pulmonary pressure; and (vi) the kinetic energy of left atrial blood increases during stress, driving the flow towards the left ventricle.

(i) A small sized ASD is often described as restrictive to the shunting volume, but this is affected by body surface area and CO. The correlation coefficients between ASD size and QP/QS at rest varies between studies, and studies on the correlation between ASD size and shunt ratio during stress are lacking. An ASD of 10 mm in diameter may be non-restrictive at rest but restrictive during exercise with increased flow. Our study showed decreased QP/QS in all patients at stress, independent of ASD size. There was no relation between the ASD size and whether the absolute shunting volume increased or decreased during stress. Thus, in our study, the decrease of shunting fraction does not seem to be explained by restrictive ASD.

(ii) With improved LV compliance, more blood will be drawn into the left ventricle in diastole, thus limiting the shunting volume and shunting fraction. The left-to-right shunting occurs predominantly in late systole and early diastole as well as during atrial contraction. In healthy subjects, the pulmonary capillary wedge pressure, representing LAP, increases with exercise and LV end-diastolic pressure increases or is unchanged between rest and supine exercise. However, the nadir of diastolic pressure is lower during exercise than at rest due to enhanced LV relaxation and elastic recoil. This leads to increased atrioventricular pressure gradient and enhanced flow across the mitral valve during exercise.

(iii) A decreased RV compliance during stress would also cause decreased shunting in the same way increased LV compliance during stress would lower QP/QS. There is limited data on RV diastolic function during stress in ASD patients. Further studies will have to elucidate the differences in diastolic function of the LV and RV in ASD patients and investigate if the decrease in shunting flow during stress is a marker of bi-ventricular compliance.

(iv) The filling of the left ventricle in patients with ASD is not only affected by the left-to-right shunting across the ASD but also from the volume overload of the right ventricle. The normal septal movement is disrupted in patients with right volume overload with systolic movement to the right side of the heart. This leads to a diastolic movement towards the left and bulging of the interventricular septum into the left ventricle in diastole. This may cause impaired filling of the left ventricle and decreased SV. There may be changes in septal motion during stress in these patients that can affect LV filling and limit ASD shunting, but this remains to be studied.

(v) It has been shown that systolic pulmonary artery pressure increases during exercise in adult patients with ASD but not in controls. This affects systemic CO and exercise tolerance in ASD patients. The mechanism for increased pulmonary artery pressure may be that total pulmonary vascular capacity is already used at maximum level at rest and further increases in pulmonary blood flow will thus increase the pressure. However, increased pulmonary artery pressure would only result in lower ASD shunting if RV filling pressure increased concurrently.

(vi) Atrial kinetic energy contributes to ventricular filling due to the inertia of the rotating blood generated by systolic contraction and the position of the veins. This ‘flywheel’ mechanism is probably of minor importance at rest but during stress the kinetic energy plays a larger part in heart filling. Thus, the increase in kinetic energy may contribute to increased transmural flow during stress in ASD patients.

In summary, the most likely explanation for the decreased shunting fraction during dobutamine stress is improved compliance of the LV and less pronounced bulging of the ventricular septum towards the LV in diastole.

**ASD and exercise capacity**

In contrast to our hypothesis, exercise capacity was not significantly related to shunting during stress. Furthermore, pulmonary flow and RV volumes during stress were not related to exercise capacity. The strongest relationship was found between exercise capacity and systemic flow during stress. This is probably explained by the fact that the body is dependent on a high systemic outflow to perform exercise. Whether this happens during a high or low degree of shunting does not seem to be relevant to the exercising body, as long as systemic CO is delivered at an appropriate rate. These findings support the current guidelines where athletes with ASD and no pulmonary artery hypertension (PAH) are allowed to participate in all sports. The increase in SV and heart rate seen during stress can be compared with the haemodynamic changes seen during pregnancy. Our findings thus suggest that shunt size during pregnancy in women...
with ASD and no PAH does not increase and the haemodynamic changes should be well tolerated in pregnant ASD patients.28

Stress studies may help in the assessment of patients who do not fully meet the criteria for ASD closure. Further studies on the outcome of ASD closure are needed to assess the clinical benefit of stress studies.

Previous studies, that have evaluated the exercise capacity of patients with ASD, often show significantly impaired VO₂peak during stress studies. A previous CMR study showed that VO₂peak of predicted values.14,29–32 In these studies, VO₂peak was reported between 13.1 and 23.5 mL/min/kg and VO₂peak of predicted values ranging from 50 to 91%. The patients in our study had peak oxygen consumption of 27.6 mL/min/kg or 103% of predicted value, which implies that our group of patients were relatively fit compared with cohorts in previous studies. Ten patients had a shunt of less than 2:1 and 8 patients had moderate-sized shunts between 2:1 and 3:1.

Limitations
Subjects were stressed to 70% and not 100% of age-predicted maximum heart rate because of problems to obtain good image quality at high heart rates. Thus, we do not have CMR data on volumes and flows at heart rates comparable with the ones at peak oxygen uptake on ergospirometry. New developments in CMR have enabled the improved imaging of ventricular function at high heart rates and these techniques can be used in future studies.

Dobutamine stress was used as a surrogate to supine exercise, but whether the two methods are comparable regarding the response of LV and RV flow and pressure is not entirely clear. However, one study using dobutamine stress found a decrease in both LV mean and end-diastolic pressure.33 Both physical exercise and dobutamine infusion cause increased heart rate and β-adrenergic stimulation, with enhanced LV relaxation. Also, a previous CMR study showed similar results using dobutamine infusion and physical exercise on SV, CO, and ejection fraction.34 Our results in controls with decreased LV and RV volumes during dobutamine stress and increased SVs, although not significant for the RV, are similar to our previous findings using supine moderate exercise in the CMR scanner.35

Conclusion
Pulmonary to systemic flow ratio and shunt volume per heartbeat decrease during stress in ASD patients. This may be explained by an enhanced LV diastolic function during stress and may have implications to detect disturbances in LV compliance in ASD patients. A high systemic CO during stress is a strong predictor of exercise capacity.

Supplementary data
Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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Conflict of interest: none declared.

References


