Alterations in ventricular pumping in patients with atrial septal defect at rest, during dobutamine stress and after defect closure

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Summary

Background Regional ventricular pumping mechanisms in patients with volume-loaded right ventricles (RV) are altered, but the cause is unknown. The aim was to determine whether these changes in ventricular pumping mechanisms are influenced by the RV dilatation itself or the aetiology behind it.

Methods Seventeen patients with atrial septal defects (ASD) and 10 healthy controls underwent cardiovascular magnetic resonance (CMR) at rest and during dobutamine/atropine stress. Sixteen patients underwent transcatheter ASD closure. Follow-up CMR at rest was performed the following day. Thirty patients with RV overload due to pulmonary regurgitation (PR) underwent CMR at rest. Cine images were used to measure left ventricular (LV) and RV volumes as well as septal, longitudinal and lateral contributions to LV and RV stroke volume (SV).

Results At rest, septal contribution to LVSV was lower in ASD patients than controls (1% versus 7%, P<0.05), but there was no difference in longitudinal or lateral contribution to SV. Patients with PR had lower longitudinal contribution to RV with increased lateral and septal contribution. During dobutamine stress, longitudinal contribution to LV and RVSV decreased and lateral contribution increased for ASD patients and controls. The day after ASD closure, septal contribution to LVSV was 6%, longitudinal contribution had increased for RVSV (P<0.05) and decreased for LVSV (P<0.01).

Conclusion Pumping mechanisms in patients with RV volume overload depend on the aetiology for the RV dilatation and not the size of the RV.

Introduction

The thin-walled right ventricle (RV) is compliant and reacts to volume load with enlargement (Laks et al., 1967). Enlarged RV end-diastolic volume is an indication for intervention for haemodynamically significant atrial septal defects (ASD) and pulmonary regurgitation (PR) in patients with tetralogy of Fallot (TOF) (Warnes et al., 2008). Cardiac pumping is affected in the enlarged RV, but it is unknown whether the mechanisms for the altered pumping physiology are due to the RV dilatation itself or the different aetiologies of RV dilatation.

Longitudinal systolic shortening seen as atrioventricular plane displacement (AVPD) generates 80% of RV stroke volume in the healthy heart. The systolic movement of the AV plane towards the apex acts as a piston and thereby simultaneously causes atrial filling (Steding-Ehrenborg et al., 2013a). In a previous study, we showed that pulmonary regurgitation (PR) in patients with TOF leads to adaptation in pumping mechanics, including decreased longitudinal contribution to RV stroke volume (SV) (Stephensen et al., 2014). This is compensated by increased septal contribution to the RVSV and consequently increased contribution of the lateral wall to LVSV. In contrast to patients with PR, patients with atrial septal defect (ASD) have a volume-loaded RV because of left-to-right shunting across the ASD. The discontinuation of left-to-right shunting with transcatheter ASD closure leads to instant decrease in the RV volume load, but the reverse remodelling process takes time (Schoen et al., 2006). Studies before and early after ASD closure thereby offer a possibility to differ between the effect of RV volume load and...
remodelling. Furthermore, it is not known how increased workload affects longitudinal pumping in patients with ASD. Administration of dobutamine–atropine lowers the left-to-right shunt in ASD patients and subsequently the degree of RV volume overload (Stephensen et al., 2017). Thus, studies in ASD patients with dobutamine–atropine may elucidate if the mechanisms of altered RV pumping physiology in the volume-overloaded state is caused by the RV dilatation itself or if the different aetiologies of RV dilatation lead to different responses in pumping physiology. An increased understanding of how RV pumping is affected may help to better guide treatment in these patient groups. Therefore, we aimed to quantify pumping mechanics in patients with ASD before and after transcutaneous closure and during dobutamine–atropine stress and compare the results to a previously studied cohort with RV volume load secondary to PR (Stephensen et al., 2014), as well as healthy controls.

Methods

Study population

The study was approved by the Regional ethics committee in Lund, Sweden. Written informed consent was obtained by patients and controls. Nineteen patients (13 females) with haemodynamically significant ASD, based on clinical findings, echocardiography and CMR were included. Of these, 17 patients underwent dobutamine–atropine stress CMR as described below and 16 patients underwent follow-up CMR after transcutaneous closure of the defect. In addition, 10 healthy controls (three females) matched for age were included. Patients with atrial fibrillation were not considered for inclusion. A previously published cohort of patients with RV volume load secondary to PR (Stephensen et al., 2014) was included for comparison with ASD patients at rest (Stephensen et al., 2014).

CMR

All ASD and control subjects underwent CMR at rest and during dobutamine stress. An intravenous infusion of 10 μg kg⁻¹ min⁻¹ of dobutamine for 3 min followed by 20 μg kg⁻¹ min⁻¹ 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. CMR was performed in the supine position, and images were acquired during end-expiratory breath hold. A 1·5T CMR scanner was used for all studies (Philips Achieva, Best, The Netherlands).

Steady-state free precession cine images were acquired at rest and during dobutamine in three long-axis planes and a short-axis stacks covering the whole heart. Typical cine imaging parameters were as follows: retrospective ECG triggering with acquired temporal resolution of 47 ms reconstructed to 30 time phases per cardiac cycle, repetition time 3 ms, echo time 1·4 ms, flip angle 60°, slice thickness of 8 mm with no slice gap. Breath-hold times were typically 10 s.

Flow velocity mapping of the aorta and pulmonary trunk was acquired at rest and during stress using a retrospective ECG-triggered fast-field echo velocity encoded sequence, acquired during free breathing. Typical imaging parameters were as follows: repetition time 10 ms, echo time 5 ms, flip angle 15°, slice thickness 8 mm, acquired in-plane resolution 2·4 × 2·4 mm reconstructed to 1·3 × 1·3 mm, number of acquisitions 1, no parallel imaging and a velocity encoding gradient (VENC) of 200 cm s⁻¹. The VENC was increased to 280 cm s⁻¹ during dobutamine, if needed. The flow sequence had an acquired temporal resolution of 20 ms during the cardiac cycle reconstructed to 35 phases per heart cycle and a typical scan time of 2 min at rest. In the 16 patients that underwent transcutaneous ASD closure, CMR was done at rest the following day using the same imaging parameters as described above.

Imaging analysis

All image analysis was performed using Segment, v 2.0 (http://segment.heiberg.se) (Heiberg et al., 2010). Left and right ventricular volumes and stroke volumes (SV) were obtained by delineating the endocardial borders of both ventricles in all slices of the short-axis stack in end-diastole (ED) and end-systole (ES). The time phases for ED and ES were chosen based on the largest (ED) and smallest (ES) LV volumes. Flow images were used to calculate cardiac output (CO) in the aorta and pulmonary trunk in controls and ASD patients (Carlsson et al., 2012). In PR patients, systemic CO was obtained from planimetry images.

Quantification of longitudinal contribution to stroke volume

Atrioventricular plane displacement (AVPD) was measured as previously described (Fig. 1) (Carlsson et al., 2007a,b). The position of the AV plane was determined using eight location points in three long-axis views: two-chamber, three-chamber and four-chamber views. AVPD during the cardiac cycle was calculated by subtracting the position of the AV plane in ES from that in ED in each of the three long-axis views. The short-axis area was calculated using the epicardial delineation of the LV and the RV in ED. As the AVPD was larger than the slice thickness, the mean of the two largest areas of the LV and the three largest areas of the RV was calculated. This area was multiplied by the AVPD for each ventricle to calculate the volume contributed by the AVPD to SV (longitudinal contribution to SV).

Quantification of radial contribution to stroke volume

The septal and lateral contribution to SV, representing the radial motion, was quantified as previously described (Fig. 2)
The ventricular septum was defined by the LV epicardial border and the RV insertion points. The epicardial contours of the LV in ED were copied to the corresponding images in ES in all slices from the base to the apex. This generated an area (diagonal lines in Fig. 2) that represents the volume contributed by the septal motion to either left or right SV, depending on the direction of the septal motion (septal contribution to SV).

(Carlsson et al., 2007a; Stephensen et al., 2014). The ventricular septum was defined by the LV epicardial border and the RV insertion points. The epicardial contours of the LV in ED were copied to the corresponding images in ES in all slices from the base to the apex. This generated an area (diagonal lines in Fig. 2) that represents the volume contributed by the septal motion to either left or right SV, depending on the direction of the septal motion (septal contribution to SV).
Correspondingly, the lateral contribution to LVSV, demarcated by the lateral LV epicardial contours in ED and ES and the RV insertion points, was calculated. This lateral area (dotted arrows in Fig. 2) represents the volume contributed by the lateral motion of the LV to LVSV. Likewise, the contribution of the RV lateral motion to RVSV was calculated using the RV insertion points and epicardial contours of the RV (solid arrows in Fig. 2). Total heart volume was measured by delineating the pericardium including the ventricles, atria and the proximal parts of the aorta and the pulmonary trunk in short-axis stacks. Total heart volume was obtained in ED and ES by summation of all slices. Total heart volume variation (THVV) was calculated as the difference between THV at ED and ES divided by THV at ED.

Statistical analysis

All statistical analysis was performed using GraphPad Prism v7.0. Continuous variables are presented as means ± SD. Pearson’s correlation was used to examine the relationship between right ventricular volumes, left-to-right shunt volume and the different contributors to SV. Mann–Whitney and Wilcoxon tests were used to test whether continuous variables (e.g. longitudinal, lateral and septal contribution to SV) differed among the groups. Chi-square test was used to test whether New York Heart Association (NYHA) functional class and the dichotomous variables of gender differed between groups. Results with a two-sided P-value of less than 0.05 were considered statistically significant. Interobserver variability was calculated as bias ± SD according to Bland–Altman in nine ASD patients and six healthy controls for LVSV, RVSV, LVAVPD and RVAVPD at rest and during dobutamine stress.

Results

Subject characteristics

Age, gender, body surface area (BSA) and NYHA class are presented in Table 1. Heart rate, systemic and pulmonary cardiac index, ejection fraction (EF), left and right ventricular volumes indexed to BSA and longitudinal, and lateral and septal contribution to SV are presented in Table 2. Three patients had moderate tricuspid regurgitation (TR) and the others had mild or no TR.

ASD patients and PR patients

Longitudinal contribution to SV was higher in ASD patients compared to PR patients for both LV (P<0.05) and RV (P<0.001; Fig 3). Lateral contribution to SV was lower in ASD patients than in PR patients for both LV (P<0.001) and RV (P<0.001). The contribution of ventricular septal movement to RVSV was larger in PR patients than in ASD patients (P<0.001). Total heart volume variation was higher in PR patients than ASD patients (P<0.001). The longitudinal contribution to RVSV was not related to RV end-diastolic volume (EDV) indexed to BSA in either ASD patients or PR patients (Fig 4a). In ASD patients, a negative correlation (r = −0.51) was found between longitudinal contribution to RVSV and RVSV indexed to BSA (Fig 4b) but not in PR patients. Thus, lower longitudinal contribution to RVSV was found in PR patients irrespective of RVEDV and RVSV.

ASD patients and healthy controls at rest

At rest, the systolic function of both left and right ventricle was intact in ASD patients (Table 2). There was no difference in AVPD or longitudinal contribution to stroke volume between ASD patients and healthy controls in either the LV (P = 0.95) or RV (P = 0.39; Fig 5). There was a small difference in the lateral contribution to SV between ASD patients and controls for the LV (P<0.05) but not for the RV (P = 0.93). The septum movement contributed to RVSV in ASD patients and to LVSV in controls (P<0.05). There was no difference in THVV at rest between ASD patients and controls (P = 0.72). The left-to-right shunt in 1 min⁻¹ did not correlate with longitudinal contribution to SV (P = 0.80 for LV and P = 0.28 for RV), and the same was true for the septal (P = 0.07) and lateral contribution to SV (P = 0.07 for LV and P = 0.57 for RV).

Dobutamine stress

Atrial septal defects patients and controls responded in a similar manner to dobutamine stress (Table 2). In both groups, longitudinal contributions to LVSV and RVSV were lower and lateral contributions higher during stress. AVPD for LV did not differ between ASD patients and controls (P = 0.11), but longitudinal contribution to LVSV was larger in ASD patients compared to controls (P<0.01) (Fig. 6). This is explained by a lower LVSV in patients than in controls, making the AVPD relatively larger. On the right side, AVPD did not differ between ASD patients and controls (P = 0.59) during dobutamine stress and neither did longitudinal contribution to RVSV (P = 0.97).
### Table 2  Left and right ventricular size and function and various contributions to stroke volume in ASD patients and healthy controls at rest and during dobutamine stress

|                        | ASD patients, rest (n = 17) | ASD patients, dobutamine stress (n = 17) | Controls, rest (n = 10) | Controls, dobutamine stress (n = 10) | PR patients, rest (N = 30) |
|------------------------|-----------------------------|------------------------------------------|-------------------------|--------------------------------------|-----------------------------|
| HR (bpm)               | 73 ± 11                     | 121 ± 14***                             | 66 ± 8                  | 134 ± 13***                          | 72 ± 13                     |
| Systemic CI (l min⁻¹ m⁻²) | 2.8 ± 0.5***                | 5.1 ± 1.3***                            | 3.5 ± 0.5***            | 5.8 ± 1.2**                          | 3.5 ± 0.7                  |
| Pulmonary CI (l min⁻¹ m⁻²) | 6.1 ± 2.1**                 | 8.0 ± 2.6***                            | 3.6 ± 0.7***            | 5.6 ± 1.4***                         | 3.0 ± 0.2**                |
| LVEDVI (ml m⁻²)        | 82 ± 12**                   | 75 ± 15**                               | 103 ± 14***             | 93 ± 18†                             | 92 ± 14§                   |
| LVESVI (ml m⁻²)        | 35 ± 11†                    | 24 ± 9***                               | 48 ± 8†                 | 31 ± 7‡                              | 43 ± 9                     |
| LVEDVI (ml m⁻²)        | 47 ± 5†                     | 50 ± 10†                                | 56 ± 11†                | 62 ± 12†                             | 49 ± 8                     |
| LVSV (%)               | 58 ± 8**                    | 68 ± 10***                              | 54 ± 7‡                 | 67 ± 2**                             | 53 ± 6                     |
| RVESVI (ml m⁻²)        | 177 ± 53                    | 131 ± 42***                             | 102 ± 13***             | 87 ± 15***                           | 163 ± 38***               |
| RVESVI (ml m⁻²)        | 85 ± 29                     | 50 ± 24***                              | 46 ± 7***               | 26 ± 4***                            | 93 ± 29†                  |
| RVEF (%)               | 93 ± 31†                    | 81 ± 26†                                | 57 ± 10†                | 61 ± 13†                             | 70 ± 16†                  |
| LVAVPD (mm)            | 52 ± 7†                     | 63 ± 11***                              | 56 ± 6†                 | 71 ± 4***                            | 44 ± 8†                    |
| RVAVPD (mm)            | 16 ± 3†                     | 15 ± 3*                                 | 16 ± 2                  | 13 ± 3†                              | 12 ± 2†                    |
| Longitudinal contribution to LVSV (%) | 63 ± 11†                  | 54 ± 9*                                 | 62 ± 8                  | 44 ± 7***                            | 54 ± 11†                  |
| Lateral contribution to LVSV (%) | 74 ± 15†                  | 59 ± 9**                                | 79 ± 9                  | 59 ± 10**                            | 47 ± 10***                |
| Lateral contribution to RSV (%) | 40 ± 11†                  | 48 ± 13***                              | 30 ± 8†                 | 47 ± 6***                            | 63 ± 14***                |
| Septal contribution to LVSV (%) | 31 ± 7†                   | 36 ± 7**                                | 30 ± 7                  | 44 ± 11***                           | 40 ± 7†                    |
| Septal contribution to RSV (%) | -1 ± 13†                  | -5 ± 12†                                | 7 ± 4†                  | 2 ± 6**                              | -12 ± 8***                |
| THV (%)                | 6 ± 2†                      | 8 ± 4*                                  | 6 ± 2                   | 9 ± 2**                              | 15 ± 3†                    |

Continuous variables are presented as mean±SD. HR, heart rate; CI, cardiac index; LVEDVI, left ventricular end-diastolic volume indexed to body surface area (BSA); LVESVI, left ventricular end-systolic volume indexed to BSA; LVSV, left ventricular stroke volume indexed to BSA; LVEF, left ventricular ejection fraction; RVEDVI, right ventricular end-diastolic volume indexed to BSA; RVESVI, right ventricular end-systolic volume indexed to BSA; RVSV, right ventricular stroke volume indexed to BSA; RVEF, right ventricular ejection fraction; LVAVPD, left ventricular atrioventricular plane displacement; RVAVPD, right ventricular atrioventricular plane displacement; THVV, total heart volume variation.

*P<0.05, **P<0.01, ***P<0.001 when comparing rest and dobutamine-atropine stress, †P<0.05, ‡P<0.01, §§P<0.001 when comparing ASD patients and controls, ††P<0.05, ‡‡P<0.01, ‡‡‡P<0.001 when comparing PR patients and controls at rest, †††P<0.05, ‡‡‡‡P<0.01, ††††P<0.001 when comparing PR patients and ASD patients at rest.

The lateral contribution to SV was lower in ASD patients than controls for the RV (P<0.05) during dobutamine stress, but not for the LV (P = 0.94), and the septal contribution to LVSV did not differ. THVV increased during dobutamine stress in both ASD patients and controls as a result of the decreased longitudinal and increased lateral contribution to SV.

**ASD patients before and after ASD closure**

Closure of the ASD resulted in a decrease in RVSV by 27 ± 20% (P = 0.001), and there was an insignificant increase in LVSV by 9 ± 20% (P = 0.07). This was accompanied by a decrease in longitudinal contribution to LVSV (P<0.01) and increase in longitudinal contribution to RVSV (P<0.05) compared to before closure. Septal movement during systole shifted from right to left and contributed to LVSV after closure instead of RVSV pre-intervention (P<0.001; Table 3; Fig. 7). There was still a small residual shunt the day after ASD closure with QP/QS 1.3 ± 0.2 (Table 3).

**Internal control of contributions to stroke volume**

The sum of the longitudinal, lateral and septal contribution to SV in healthy controls at rest was 99 ± 12% for LVSV and 102 ± 10% for RVSV. In ASD patients at rest, the sum was 102 ± 9% for LVSV and 104 ± 12% for RVSV. During dobutamine stress, the sum was 93 ± 6% for LVSV and 102 ± 9% for RVSV in controls and 97 ± 12% for LVSV and 98 ± 9% for RVSV in patients. This serves as an internal control of the results, since the sum of the derived measurements in theory
should be 100%. Interobserver variability was 6 ± 4% for LSV and 1 ± 3% for RVSV at rest and 1 ± 2% for LSV and 2 ± 2% for RVSV during dobutamine stress. The interobserver variability for LVAVPD was 1 ± 1% and 0 ± 1% for RVAVPD at rest and 2 ± 2% for LVAVPD and 0 ± 2% for RVAVPD during dobutamine stress.

**Discussion**

This study offers mechanistic insights showing that the pumping physiology differs in patients with right ventricular dilatation depending on the aetiology and not the RV volume overload itself. Patients with ASD had higher longitudinal contribution to both LV and RV stroke volume compared to patients with PR. Conversely, lateral contribution to LV and RV stroke volume was higher in patients with PR. Septal contribution to stroke volume in ASD patients was around zero but in PR patients the septum contributed to RVSV. *P<0.05***

TOF patients with PR where the contribution to RV longitudinal shortening is replaced by radial shortening (lateral and septal) (Stephensen et al., 2014). The day after ASD closure – with near equalization of LV and RV stroke volumes but remaining RV dilatation – the longitudinal and septal contributions to SV had changed. Furthermore, dobutamine stress caused decreased longitudinal contribution and increased lateral contribution to both LV and RVSV in both ASD patients and controls. Thus, it is imperative in the assessment of RV function clinically and during development of new treatment strategies for RV dysfunction, to take into account the cause of RV dilatation.

**Different aetiology of RV dilatation and effect on RV pumping**

Our previous study revealed that patients with PR have lower AVPD and decreased contribution of longitudinal shortening...
Continuous variables are presented as mean±SD. Longitudinal, lateral and septal contribution to stroke volume at rest in patients with atrial septal defect (ASD) before and after closure and healthy controls. HR, heart rate; CI, cardiac index; LVSV, left ventricular stroke volume; RVSV, right ventricular stroke volume.

*P<0.05, **P<0.01, ***P<0.001 when comparing ASD patients before and after closure. †P<0.05, †††P<0.001 when comparing healthy controls and ASD patients after closure.
to altered contractile pattern (Mercer-Rosa et al., 2013). Our findings support the conclusion of less longitudinal pumping in patients with PR and RV volume load after TOF repair. Decreased TAPSE is often seen secondary to cardiac surgery in the immediate postoperative period (Hanséus et al., 2002). A study on paediatric patients after surgical closure of ventricular septal defects by Klitsie et al. (2013) measured TAPSE up to 20 months postoperatively. This study showed gradual recovery in TAPSE over time, even though the values were still lower at 20 months follow-up than in controls. The two cohorts in our study differ in that the PR patients have all undergone cardiac surgery and the ASD patients not. Also, the progress of RV dilatation in patients with ASD and PR may differ. In patients with PR, the progression has been shown to be mild, if detectable at all (Wald et al., 2015). In ASD patients, one study has shown increased RVEDV/LVEDV proportion with time in children with medium-sized ASD (Saito et al., 2012), but data on progression rates of RV dilatation in adults are more scarce. However, in a recent study, we have shown support for the theory that the PR per se can be the source for decreased longitudinal function and that it is not only a by-product of the surgical repair of TOF as suggested by Riesenkampff et al. (2014). We showed a decrease in RV longitudinal pumping in a porcine model with PR in the absence of surgery which was restored after transcatheter treatment of the PR (Kopic et al., 2017). It is therefore imperative, when using TAPSE to evaluate RV function, to understand the aetiology and pathophysiology behind the changes seen in different disease states and, with this knowledge, be able to decide whether the findings represent RV dysfunction or a physiological adaptation to abnormal volume condition. A decreased longitudinal contribution from TAPSE can be expected in a patient with PR, but a normal contribution from TAPSE should be expected in ASD patient with a well-functioning RV.

**Cardiac pumping in ASD patients compared to controls**

In healthy subjects, RV longitudinal systolic motion generates the atrial reservoir volume and is thereby the main contributor of right atrial filling from the caval veins (Steding-Ehrenborg et al., 2013a). Normal right atrial filling thus predominantly occurs in systole, and the reservoir volume is larger than the conduit volumes (Carlsson et al., 2004). This is due to the AVPD working as a piston (Lundbäck, 1986; Carlson et al., 2007a) when pumping the blood into the great arteries, resulting in a near constant total heart volume during the cardiac cycle at rest (Bowman & Kovács, 2003; Carlson et al., 2004). In patients with ASD, however, right atrial filling also originates from the left atrium. A larger AVPD could thus hypothetically cause a larger left-to-right shunt, but we saw no correlation between AVPD and shunt volume. This may be explained by the fact that most of the left-to-right shunting occurs when the pressure gradient between left and right atrium is at its highest, namely in late systole and early diastole as well as during atrial contraction (Levin et al., 1968).

**Cardiac pumping after ASD closure**

The reverse remodelling process towards normalized ventricular volumes had already begun the day after ASD closure, as demonstrated by the increased LV and decreased RVEDV. These findings are in concordance with previous studies (Thilén & Persson, 2006). The decrease in left-to-right shunting after ASD closure caused significant changes in pumping physiology with a decreased septal contribution to RVSV and corresponding increased septal contribution to LSVS. AVPD decreased for both ventricles but resulted in increased longitudinal contribution to RVSV, due to a lower RVSV, and lower longitudinal contribution to LSVS due to the higher LSVS. The pumping mechanisms in patients with RV overload due to left-to-right shunting thus adjust when the stroke volumes equalize, which may be driven by the changing movement of the ventricular septum during the heart cycle. The explanation for the decreased LV longitudinal pumping after ASD closure might also be an effect of LV diastolic dysfunction that becomes unmasked with the increased LV preload after ASD closure (Sato et al., 1996). Apart from RV volume load, LV pressure likely affects the septal contour in ASD patients. The effect of ASD closure on LV end-diastolic pressure (EDP) is thought to be age-dependent, where a larger increase in LVEDP can be expected in older patients, with decreased myocardial relaxation and compliance, as LV preload increases after ASD closure (Giardini et al., 2005). We do not have invasive pressure data immediately after ASD closure, and with a wide age range in the patient group (27–81 years), it is difficult to interpret the effect of LV pressure on radial and
longitudinal motion in this study. The small residual shunt seen after ASD closure (QP/QS) is expected to subside with time.

**Effect of dobutamine stress on pumping physiology in ASD patients and controls**

During dobutamine stress, left-to-right shunting volume decreased which resulted in more balanced stroke volumes in the left and right ventricle (Stephensen et al., 2017) and a larger increase in systemic compared to pulmonary cardiac index. Thus, during dobutamine stress, there was a greater increase in trans-mitral flow compared to trans-septal flow. During dobutamine stress, SV is generated more from lateral and less from longitudinal motion. This means that a smaller proportion of atrial filling from the caval and pulmonary veins occurs during systole and a larger proportion during diastole. Also there is a mismatch in inflow and outflow from the heart and a deviation from the near constant volume of the pericardial sac, presenting as increased total heart volume variation as was observed during dobutamine stress in both ASD patients and controls. The results are in line with our previous findings in healthy volunteers during supine exercise (Steding-Ehrenborg et al., 2013b) where longitudinal contribution to LVSV was reduced, but not to RVSV. The difference may be explained by a lower maximum heart rate reached during supine exercise compared to dobutamine stress (94 ± 2 bpm vs 130 ± 12 bpm in healthy controls) or by differences in systemic venous return between physical exercise and dobutamine stress.

**Limitations**

There was a higher degree of females in the patient group compared to controls, although not statistically significant, and this may influence the results. The PR patients were also younger than the ASD patients. The control group was therefore not entirely matched to the patient group. The PR patients had lower RVEF than the ASD patients indicating worse systolic function in the PR group. This does not influence the main interpretation of the findings as the decrease in longitudinal contribution was seen in PR patients irrespective of RV dilatation and RYSV. Also, the patients with ASD had higher NYHA score, indicating higher degree of clinically symptomatic heart failure compared to the PR patients. Dobutamine infusion was used to imitate the chronotropic and inotropic changes seen during supine exercise, but it is not known whether the two methods can be used interchangeably in this context. However, both types of stress have been shown to cause increase in heart rate, stroke volume and ejection fraction (Oosterhof et al., 2005).

**Conclusion**

In patients with ASD and RV volume overload, longitudinal and lateral contribution to SV is comparable to healthy subjects. This differs from patients with RV volume load due to PR. Pumping mechanisms thus differ depending on the aetiology rather than the degree of RV dilation or stroke volume. Improvements in pumping mechanism are present already the day after transcutaneous closure with normalization of the paradoxical septum movement, increase in longitudinal RV pumping and decrease in longitudinal LV pumping. These findings are important because they imply that the assessment of RV function must take into account the cause of RV volume overload both in the clinical setting and in the development of new treatment strategies for RV dysfunction.

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**Conflict of interest**

Einar Heiberg is the founder and owner of Medviso AB, the producer of software for medical image analysis called Segment.

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