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Abstract

Purpose: This study aimed at evaluating (1) right ventricular (RV) mean power during exercise, (2) the contribution of flow and pressure to RV mean power, and (3) the impact of pulmonary artery pressure on RV function during exercise. **Methods:** Fifty patients with atrial septal defect (ASD) type secundum (20 open, 30 closed) were enrolled. All underwent standard echocardiography, a bicycle stress echocardiography, and symptom-limited cardiopulmonary exercise testing. RV mean power was calculated as the product of RV cardiac output and mean pulmonary artery pressure (mPAP). RV function was assessed using RV fractional area change (FAC) at rest and at peak exercise.

Results: RV mean power was linearly related with oxygen uptake (VO_2) in patients with open ($R^2 = 0.88$; $p < 0.0001$) and closed ASD ($R^2 = 0.90$; $p < 0.0001$). The increase in RV mean power was steeper in open than in closed ASD patients ($p < 0.0001$). The change in RV cardiac output (7.1 ± 3.4 vs. 5.7 ± 2.4 l/min; $p = 0.132$) was not statistically different, but the change in mPAP (21.7 ± 9.6 vs. 12.8 ± 4.6 mmHg; $p < 0.0001$) and RV mean power (0.97 ± 0.56 vs. 0.53 ± 0.22 W; $p = 0.009$) were higher in patients with an open ASD. The change in RV FAC from rest to peak exercise was related to peak mPAP in open ($R = -0.589$; $p = 0.010$) and closed ($R = -0.450$; $p = 0.021$) ASD patients.

Conclusion: RV mean power during exercise is higher in patients with an open than in patients with a closed ASD. The workload of the RV in patients with an open ASD is higher at rest due to a left-to-right shunt, at peak exercise due to an additional increase in mPAP. A higher increase in afterload may affect RV function during exercise.

Keywords

Atrial septal defect, exercise, pulmonary circulation, right ventricular function

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Introduction

Atrial septal defect (ASD) type secundum is a common congenital heart defect with an estimated birth prevalence of 1.43 per 1000 births and an expected probability of survival into adulthood of 97%.^{1,2} Because of a higher compliance and therefore lower end-diastolic pressure in the right ventricle (RV), these patients initially present with a left-to-right shunt causing what is considered to be a pure volume overload of the RV and pulmonary circulation.³ This volume overload causes a dilatation of the RV and will eventually lead to RV systolic dysfunction.⁴

The energy used by the RV to pump blood in the pulmonary circulation is called the extrinsic hydraulic power and consists of oscillatory power and mean power. Although oscillatory power in the pulmonary circulation is considerable and proportional to mean power, it does not contribute to blood flow.⁵

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Mean power is the energy per time expended to produce a steady flow and is the product of mean pulmonary artery pressure (mPAP) and mean flow.^{6,7} Little is known about mean power of the RV in patients with open ASD at rest and during exercise.

The RV is able to sustain a volume load for a long period of time, but poorly tolerates increases in afterload. Patients with an open ASD or an ASD closed later in life present with a steeper increase in PAP during exercise,⁸ which may translate into increases in wall stress, coronary perfusion, and oxygen extraction in the RV.⁹ Although a few studies have evaluated RV function during exercise,^{10–13} they failed to address whether this is influenced by different changes in afterload.

This study aimed at evaluating (1) right ventricular (RV) mean power during exercise, (2) the contribution of flow and pressure to RV mean power, and (3) the impact of pulmonary artery pressure on RV function during exercise.

Materials and methods

Study population

In total, 20 patients with open ASD, all scheduled for repair (10 males and 10 females, mean age 39.3 ± 17.5 years) and 30 with closed (seven males and 23 females, mean age 42.4 ± 16.8 years, mean age at repair 35.6 ± 20.0 years) ASD type secundum gave informed consent to participate in the study. Patients were consecutively enrolled in the outpatient clinic of congenital heart disease of the University Hospitals of Leuven. Patients younger than 17 years and patients with known coronary artery disease, significant valvular diseases other than mild tricuspid or mitral regurgitation, pulmonary disease, a history of pulmonary embolism, or concomitant congenital heart disease were excluded from the study. Patients with a history or current arrhythmias were also excluded. The University Hospitals Leuven Institutional Review Board approved the study and informed consent was obtained from all patients.

Transthoracic echocardiography

Echocardiography was performed with a Vivid 7 or 9 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway) equipped with a 3-MHz transducer and tissue Doppler imaging technology. Before exercise, a complete resting echocardiography study was performed in the supine position in all standard views. Two-dimensional, Doppler, and tissue Doppler images were digitized for off-line analysis

using dedicated software (EchoPac BT08; General Electric Vingmed Ultrasound).

Bicycle stress echocardiography

Exercise echocardiography was performed on a semi-supine ergometer (Easystress, Ecogito Medical, Liège, Belgium). The exercise table was tilted laterally by $20 - 30^\circ$ to the left. The protocol started at 25 W with an increment of 25 W at every 2-min stage, until the maximum tolerated load. Blood pressure and 12-lead electrocardiogram were recorded at rest and at every 2 min during exercise. A single observer performed the on-line and the off-line analyses. All measurements were made in triplicate and results are presented as means.

Hemodynamic calculations

Right ventricular (RV) and left ventricular (LV) stroke volume and cardiac output were calculated from the outflow tract diameter and flow velocity time integral in the outflow tract of both ventricles respectively. The diameter of the outflow tract was assumed to remain constant throughout exercise. Systolic pulmonary artery pressure (sPAP) was calculated from tricuspid regurgitant velocities using the simplified Bernoulli equation ($4 \times \text{velocity squared}$) without addition of right atrial pressure estimates. During exercise echocardiography, RV cardiac output was recorded at each stage. sPAP was measured with contrast enhancement using agitated geloplasma as previously validated at rest and during exercise.^{14–16} RV mean power was calculated as the product of mean RV cardiac output and mPAP. For the purpose of calculating RV mean power, mPAP was calculated as $0.6 \times \text{systolic PAP} + 2$.¹⁷ Power was expressed in Watts, with $1 \text{ W} = 7.5 \times 10^3 \text{ mmHg.ml/s}$. RV fractional area change (FAC) was obtained by tracing the RV end-diastolic area (DA) and end-systolic area (SA) in the apical 4-chamber view using the formula $(\text{DA} - \text{SA}) / \text{DA} \times 100$.¹⁸

Cardiopulmonary exercise test

Supine exercise testing was performed on a bicycle ergometer (Ergometrics 800S; Ergometrics, Bitz, Germany) with the room temperature stabilized at $18 - 22^\circ\text{C}$. The initial workload of 20 W was increased by 20 W every minute until exhaustion. A 12-lead electrocardiogram (Max Personal Exercise Testing, Marquette, Wisconsin, USA) and respiratory data through breath-by-breath analysis (Oxygen AlphaR; Jaeger, Mijndhardt, Bunnik, The Netherlands) were continuously registered. Cuff blood pressure measurements

Table 1. Clinical and standard echocardiographic parameters

	Open ASD (n = 20)	Closed ASD (n = 30)	p-value
Age (years)	39.3 ± 17.5	42.4 ± 16.8	0.527
Male gender (%)	50	23	0.051
Defect size (mm)	18.2 ± 7.1	16.8 ± 4.9	0.447
Qp:Qs invasive	1.8 ± 1.0	1.8 ± 0.8 ^a	0.999
Qp:Qs echo	1.6 ± 0.7	–	–
BMI (kg/m ²)	25.1 ± 4.7	26.0 ± 5.0	0.503
SBP (mmHg)	117 ± 16	120 ± 16	0.573
DBP (mmHg)	76 ± 10	72 ± 11	0.176
HR (bpm)	76 ± 12	71 ± 12	0.217
sPAP (mmHg)	23.8 ± 6.0	22.5 ± 6.2	0.492
Mean PAP (mmHg)	19.3 ± 3.6	18.5 ± 3.7	0.492
TAPSE (mm)	29.0 ± 5.9	23.6 ± 5.0	0.001
RV end-diastolic area index (cm ² /m ²)	16.4 ± 5.0	12.7 ± 2.3	0.005
RV end-systolic area index (cm ² /m ²)	10.7 ± 2.5	8.5 ± 1.4	0.002
RV FAC (%)	53.0 ± 19.0	48.8 ± 12.5	0.348
RV SV index (ml/m ²)	49.8 ± 13.9	39.2 ± 10.0	0.003
RV CI (l/min/m ²)	3.4 ± 1.0	2.4 ± 0.5	<0.0001
LV EF (%)	60 ± 5	62 ± 6	0.226
Peak VO ₂ (%pred)	78 ± 18	88 ± 17	0.072

Values are mean ± SD. ^aShunt ratio before ASD repair. BMI, body mass index; CI, cardiac index; DBP, diastolic blood pressure; FAC, fractional area change; HR, heart rate; LVEF, left ventricular ejection fraction; (s)PAP: (systolic) pulmonary artery pressure; Qp:Qs, shunt ratio; RV, right ventricular; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; SV, stroke volume; TAPSE, tricuspid annular systolic excursion; VO₂, oxygen uptake.

were obtained at 2-min intervals during exercise, at peak exercise and at 2 and 4 min after exercise. Oxygen saturation was monitored by pulse oximetry throughout the study. Prior to each test, spirometric measurements were obtained. The exercise testing was calibrated before each test. Oxygen uptake (VO₂) was determined from continuous measurement of oxygen in the inspired and expired air. Peak oxygen consumption (peak VO₂) was obtained and expressed as percentage of the predicted value according to age, gender, and size.¹⁹

Statistical analysis

We analysed the data using SPSS for Windows version 16 (SPSS, Chicago). Descriptive data for continuous variables are presented as means ± SD or as medians with ranges, when appropriate. Descriptive data for discrete variables are presented as frequencies or percentages. Continuous variables were evaluated between subgroups using independent Student's t-test.

Proportions were evaluated between subgroups using chi-squared analysis.

For linearity assessment between VO₂, RV cardiac output, and RV mean power, a Poon-adjusted mean slope for each subgroup was calculated, allowing for similar linear or mildly non-linear data from different subjects to be grouped together while effectively minimizing intersubject variabilities.²⁰ For each measure, there were at least three values from which to derive a linear regression. Slope values were then used for between group comparisons (independent t-test) and the mean values are quoted for each relationship.

Open and closed ASD patients were stratified into two groups according to the median change in RV FAC from rest to peak exercise. All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. Four patients with open ASD and eight patients with closed ASD were taking beta-blockers. There tended to be less female patients in the control group when compared to patients with a closed ASD. Invasive haemodynamic measurements showed no evidence of pulmonary hypertension at rest.

Relation between oxygen uptake (VO₂) and haemodynamic parameters during exercise

There was a strong linear relation between RV cardiac output and VO₂ in patients with an open ASD ($R^2 = 0.88$; $p < 0.0001$) and a closed ASD ($R^2 = 0.90$; $p < 0.0001$). However, the slope of the relation was significantly different in patients with a open ASD ($p = 0.001$) when compared to patients with a closed ASD, indicating that RV cardiac output increases more rapidly with increasing VO₂ in patients with an open ASD (Figure 1). A linear relationship between mPAP and VO₂ was present in patients with an open ($R^2 = 0.86$; $p < 0.0001$) and a closed ($R^2 = 0.88$; $p < 0.0001$) ASD. Patients with an open ASD had a significantly steeper slope when compared to patients with a closed ASD ($p = 0.002$). There was a highly linear relationship between RV mean power and VO₂ in patients with an open ASD ($R^2 = 0.88$; $p < 0.0001$) and a closed ASD ($R^2 = 0.90$; $p < 0.0001$). However, RV mean power increased more rapidly in patients with an open ASD than in patients with a closed ASD ($p < 0.0001$). Figure 2 indicates that in order to increase oxygen uptake to 11 l/min, the RV had to develop 0.53 W in patients with a closed ASD and 0.86 W in patients with an open ASD.

Figure 1. Relationship between right ventricular (RV) cardiac output and VO_2 in patients with an open or closed atrial septal defect (ASD). Blue, open ASD; Red, closed ASD. The full line represents the mean value of the regression lines of each individual patient. The mean slope in open ASD patients is significantly higher than in closed ASD patients ($p = 0.001$).

Figure 2. Relation between right ventricular (RV) mean power and VO_2 in patients with an open or closed atrial septal defect (ASD). Blue, open ASD; Red, closed ASD. The full line represents the mean value of the regression lines of each individual patient. The mean slope in open ASD patients is significantly higher than in closed ASD patients ($p = 0.001$).

Figure 3. Delta right ventricular RVFAC is related with peak VO_2 in patients with open and closed atrial septal defect (ASD).

Figure 4. If right ventricular RVFAC increases $\leq 5\%$ from rest to peak exercise, open and closed atrial septal defect (ASD) patients present with a significantly higher mean pulmonary artery pressure (mPAP) at peak exercise.

Contribution of RV cardiac output and mPAP to the mean power

At rest, patients with an open ASD had a higher RV cardiac output (6.8 ± 2.3 vs. 4.4 ± 1.0 l/min; $p < 0.0001$), a similar mPAP (19.7 ± 3.9 vs. 18.4 ± 3.7 mmHg;

$p = 0.237$), resulting in a significantly higher mean power (0.30 ± 0.14 vs. 0.18 ± 0.05 W; $p = 0.001$) when compared to patients with a closed ASD. At peak exercise, patients with an open ASD had a higher RV cardiac output (14.2 ± 4.3 vs. 10.1 ± 2.8 l/min; $p = 0.002$) and a higher mPAP (41.3 ± 10.2 vs. 31.4 ± 5.4 mmHg;

$p < 0.0001$), resulting in a higher mean power (1.276 ± 0.58 vs. 0.71 ± 0.25 W; $p = 0.002$) when compared to patients with an closed ASD. Whereas the change in RV cardiac output (7.1 ± 3.4 vs. 5.7 ± 2.4 l/min; $p = 0.132$) was not statistically different, the change in mPAP (21.7 ± 9.6 vs. 12.8 ± 4.6 mmHg; $p < 0.0001$) and RV mean power (0.99 ± 0.58 vs. 0.54 ± 0.22 W; $p = 0.009$) were significantly higher in patients with an open ASD when compared to patients with a closed ASD.

RV function during exercise and peak mPAP

In open ASD patients, RV FAC increased from rest to peak exercise (43.8 ± 6.2 to $48.4 \pm 9.7\%$; $p = 0.020$). The change in RV FAC was related to mPAP at peak exercise ($R = -0.589$; $p = 0.010$) and peak VO_2 ($R = 0.517$; $p = 0.033$), but not with RV mean power at peak exercise ($R = -0.027$; $p = 0.926$). In closed ASD patients, RV FAC increased from rest to peak exercise (42.6 ± 7.1 to $48.7 \pm 8.4\%$; $p < 0.0001$). The change in RV FAC was related to mPAP at peak exercise ($R = -0.450$; $p = 0.021$) and peak VO_2 ($R = 0.635$; $p < 0.0001$), but not with RV mean power at peak exercise ($R = 0.076$; $p = 0.724$) (Figure 3). Open and closed ASD patients who increase RV FAC with $\leq 5\%$ present with a significantly higher mPAP at peak exercise when compared to patients with an increase in RV FAC $> 5\%$ (Figure 4).

Discussion

This study showed that (1) RV mean power increased more rapidly with increasing oxygen uptake in patients with an open ASD than in patients with a closed ASD, (2) the increase in RV mean power during exercise in patients with an open ASD was higher than in patients with a closed ASD, mainly caused by a higher increase in mPAP during exercise in patients with an open ASD, and (3) change in RV FAC is inversely related with peak mPAP.

Relation between oxygen uptake and haemodynamic variables during exercise

The strong linear relation between cardiac output and VO_2 has been shown before.^{21,22} The slope of the relation is lower in patients with an open ASD because of the presence of a left-to-right shunt. Moreover, the linear relation between RV cardiac output and VO_2 in patients with an open ASD as shown in Figure 1 indicates that the size of the shunt decreases during exercise which is consistent with earlier published reports,²³ but in contrast with other studies.²⁴ The ratio of both slopes (1.34) is lower than the mean value of the

invasively measured shunt ratio (1.8), although differences may be present because the shunt ratios were measured under general anaesthesia before ASD closure.²⁵ There was a weaker linear relationship between VO_2 and mPAP in patients with an open and closed ASD. Exercise-induced pulmonary hypertension has been recognized as a clinical entity,²⁶ but is not included in the current pulmonary hypertension practice guidelines.²⁷ Indeed, whether the increase in mPAP in some patients with an open ASD is due to the inability to further decrease pulmonary vascular resistance at high RV cardiac output or due to the development of pulmonary vascular lesions is hard to determine.⁸

The VO_2 -work relation describes how much work is performed by the RV in relation to how much oxygen is utilized by the exercising subject. Compared with patients with a closed ASD, the increase in oxygen uptake is considerably lower in patients with an open ASD than the increase in oxygen uptake in patients with a closed ASD. Figure 2 indicates that in order to increase oxygen uptake to 1 l/min, the RV had to develop 0.49 W in patients with a closed ASD in contrast to 0.86 W in patients with an open ASD.

Contribution of RV cardiac output and mPAP to RV mean power

The higher RV mean power at rest in patients with an open ASD is mainly determined by a higher RV cardiac output due to left-to-right shunting. However, there is a larger increase in RV mean power from rest to peak exercise in patients with an open ASD than in patients with a closed ASD. As the increase in RV cardiac output is almost similar, the larger increase in RV mean power in patients with open ASD is also determined by the larger increase in mPAP. Using the slopes of the regression lines, it can be estimated that cardiac output and mPAP are responsible for 77% and 23% respectively of the additional workload on the RV in patients with and open ASD. Therefore, there is not only a volume load of the RV in patients with an open ASD, but also a pressure overload during exercise.

Change in RV function and peak mPAP during exercise

Our study indicated that the change in RV FAC was related to peak mPAP and exercise capacity. The behaviour of, and interaction between, the right ventricle and pulmonary circulation during exercise has gained interest.²⁸ It has been shown that the impact of exercise is greatest on the RV, with structural changes being related to haemodynamic stressors during exercise.^{9,29,30} We previously showed that

patients with an open ASD or an ASD closed later in life present with a steeper increase in PAP during exercise.⁸ A steeper and higher increase in PAP during exercise may be clinically relevant as the RV poorly tolerates increases in afterload. Indeed, Holverda et al.³¹ showed RV stroke volume response to exercise is related to PAP increase during exercise. Moreover, in heart failure patients, Lewis et al.³² showed that a steep increment in PAP was related with reduced exercise capacity and reduced survival. However, failure to augment PAP (after a steep initial PAP increase; suggestive of RV dysfunction) was related with the worst prognosis. So, although the work requirement of the RV of open ASD patients is higher mainly due to a left-to-right shunt (volume load), the additional increase in PAP (pressure load) may be the main cause of a decreased RV contractile reserve (and exercise capacity) in some patients, which should be taken into account when advising on physical activity.³³

The supplementary files (available online only) give more information on a male aged 64 years with closed ASD and a female aged 40 years with open ASD. The patient with the open ASD develops a higher PAP during exercise. However, in contrast to the patient with the closed ASD, there is no increase in RV function as measured by TAPSE and RV FAC.

Limitations

It is important to underline a few limitations of the study. First, we used non-invasive echocardiographic parameters that have been validated against invasive measurements at rest and during exercise.^{14,34} In order to enhance tricuspid regurgitation Doppler signals, we used agitated geloplasma. Pulmonary artery pressure was measured without assessment of right atrial pressures. Second, RV FAC is an imperfect measure of RV function and dependent on the image quality obtained. Third, RV outflow tract diameter was considered constant during exercise.

Conclusion

RV mean power during exercise is higher in patients with an open than in patients with a closed ASD. The workload of the RV in patients with an open ASD is higher at rest due to a left to right shunt, at peak exercise due to an additional increase in mPAP. A higher increase in afterload may affect RV function during exercise.

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Conflict of interest

The authors confirm there is no conflict of interest.

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