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Serial pulmonary vascular resistance assessment in patients late after ventricular septal defect repair

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ABSTRACT

Background: The long-term evolution of pulmonary vascular resistance (PVR) after ventricular septal defect (VSD) repair is unknown. This study serially evaluated resting and exercise PVR after VSD repair in childhood.
Methods: Patients were enrolled from the outpatient Adult Congenital Heart Disease clinic of the University Hospitals Leuven and compared to age- and gender-matched controls. Participants underwent resting and exercise echocardiography and cardiopulmonary exercise testing at baseline and follow-up. Total PVR was calculated as the ratio of mean pulmonary artery pressure (mPAP) to cardiac output (CO). The slope of the mPAP-CO curve (exercise PVR) was obtained using linear regression analysis.
Results: Twenty-seven patients (mean age 31 ± 7 years, 70% male) and 18 controls were included. At baseline, patients had larger right ventricular (RV) end-diastolic areas (10 ± 2 vs 9 ± 1 cm^2/m^2, $p = 0.001$) and lower tricuspid annular plane systolic excursion (TAPSE) (17 (17–19) vs 26 (22–28) mm, $p < 0.001$). After 1.1 (1.0–1.5) years follow-up, similar differences in RV areas and TAPSE were found. Patients reached lower peak workload and cardiac index compared to controls at each time point. Peak total PVR was higher (Baseline: 2.7 ± 0.8 vs 2.2 ± 0.3 mm Hg/L/min, $p = 0.005$; Follow-up: 2.9 ± 0.9 vs 2.1 ± 0.3 mm Hg/L/min, $p < 0.001$) and the mPAP-CO slope was steeper (Baseline: 2.2 ± 0.8 vs 1.7 ± 0.3 mm Hg/L/min, $p = 0.008$; Follow-up: 2.5 ± 0.9 vs 1.6 ± 0.3 mm Hg/L/min, $p < 0.001$) in patients. The mPAP-CO slope in patients correlated inversely with peak oxygen uptake ($R = -0.41$ and -0.45, $p = 0.036$ and 0.022, baseline and follow-up, respectively).
Conclusion: Despite repair, VSD patients seem to show altered pulmonary hemodynamics and RV impairment at rest and exercise, supporting life-long follow-up.

1. Introduction

Ventricular septal defect (VSD) is one of the most common congenital heart defects, with 2.6 per 1000 live births [1]. Pulmonary vascular disease (PVD) in patients with VSD usually develops secondary to chronic volume and pressure overload of the pulmonary circulation following left-to-right shunt [2]. This pressure overload of the right heart is related to morbidity and mortality [3]. Long-term follow-up after shunt repair is necessary to detect late complications such as exercise intolerance, increased pulmonary vascular resistance (PVR) and arrhythmias [2,4,5]. Development of pulmonary arterial hypertension (PAH) after timely shunt repair is rare. However, if PAH develops, it is often detected late, when symptoms and increased PVR are already present.

Bicycle stress echocardiography has been proposed as a method to detect early PVD [6–8]. Studies showed that pulmonary vascular function can be evaluated non-invasively during exercise [9,10]. Evidence is accumulating to define a reference range for pulmonary artery pressure (PAP) relative to cardiac output (CO) during exercise [8,9,11]. In patients with atrial septal defect, a steeper slope of the PAP-CO curve relates to morphometric changes of the right heart, such as more severe

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tricuspid regurgitation and greater right atrial (RA) dilatation [12,13]. Some suggest that this "early PVD" may be progressive, being a precursor of PAH [14].

This study aimed at evaluating (1) pulmonary hemodynamics at rest and during exercise, (2) its relationship with exercise capacity, (3) whether its potential differences change over time, and (4) its value for risk stratification in patients late after VSD repair.

2. Methods

2.1. Patient selection

Adults with isolated VSD repair in childhood were identified through the local database of Pediatric and Congenital Heart Disease (CHD). Patients were consecutively enrolled in the outpatient CHD clinic of the University Hospitals Leuven from October 2014 to December 2015. Patients with associated heart defects, significant valve disease, right ventricular (RV) outflow tract obstruction or pulmonary disease were excluded. An age- and gender-matched healthy control group was composed. Healthy was defined as absence of heart and lung disease, based on careful history, physical examination, electrocardiography, spirometry and transthoracic echocardiography. Each participant signed informed consent. The study protocol was approved by our hospital ethics committee (protocol number B322201420877).

2.2. Review of patient records

Catheterization data prior to VSD repair and details on defect closure were analysed. The PAP was measured and shunt ratio (Qp/Qs) calculated through series of oxygen saturations by the Fick method. Pulmonary hypertension (PH) at baseline was defined as mean PAP (mPAP) ≥25 mm Hg [3].

2.3. Resting and bicycle stress echocardiography

All participants underwent transthoracic echocardiography at rest in supine position, followed by bicycle stress echocardiography, performed with a Vivid 9 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway). Analyses were done according to current guidelines [15]. Systolic PAP (sPAP) was calculated from the RV – RA pressure difference using the simplified Bernoulli equation ($4\times[\text{tricuspid regurgitation velocity (TRV)}]^2$). No RA pressure was added as those estimates are not validated during exercise [16]. The mPAP was calculated with the Chemla formula [17]: $\text{mPAP} = (0.61 \times \text{sPAP}) + 2$ mm Hg. This formula can be used as the relationship between sPAP and mPAP remains linear throughout exercise [10]. Left ventricular cardiac output (LVCO) was derived from the Doppler-estimated stroke volume (SV) using the velocity time integral of flow through the LV outflow tract (LVOT), together with LVOT area. Total PVR was calculated as mPAP over LVCO.

Bicycle stress echocardiography was performed in semi-supine position on a cycle ergometer (Baseline: Easystress, Ecogito Medical sprl, Liège, Belgium; Follow-up: eBike EL, General Electric Company, Freiburg, Germany), with the exercise table tilted 20–30 degrees to the left. Participants cycled at 60 rpm. The initial workload of 25 watts (W) was increased by 25 W every 2 min until exhaustion. The slope of the mPAP-CO curve was obtained for each participant using linear regression analysis of the measurement points of all workloads, since a consistent nearly linear relationship between changes in PAP and CO during exercise was reported [11,18]. Blood pressure (BP) was continuously measured using finger cuff technology (Nexfin®). A single observer performed on-line and off-line analyses using Echopac® software. All measurements were repeated 3 times and mean values were used for data analysis.

2.4. Cardiopulmonary exercise testing (CPET)

Upright CPET was performed on a bicycle ergometer (Ergometrics 800S, Ergometrics, Bitz, Germany), 1.5 h after ending the exercise echocardiography. Participants cycled at 60 rpm. Initial workload of 20 W was increased by 20 W/min until exhaustion. Patients with excellent exercise capacity followed a 50 W + 25 W protocol, patients with lower exercise capacity a 10 W + 10 W protocol. A 12-lead electrocardiogram, BP and respiratory data through breath-by-breath ventilation analysis (Oxycon Pro®, Jaeger, Mijnhardt, Bunnik, the Netherlands) were continuously registered [19]. Oxygen saturation was monitored by pulse oximetry. Oxygen and carbon dioxide concentration were continuously measured in inspired and expired air to determine oxygen uptake (VO_2) and carbon dioxide production (VCO_2). The ventilatory anaerobic threshold (VAT) was determined by the ventilatory equivalents method [19]. Peak VO_2 was defined as the highest 30s-average of VO_2. Peak O_2 pulse was calculated as peak VO_2/peak heart rate. The slope of the minute ventilation (V_E)/VCO_2 curve was determined using linear regression analysis.

2.5. Serial testing

Patients were firstly tested at baseline, secondly recalled and re-tested (follow-up). Retesting was done to evaluate whether similar potential differences between controls and VSD patients at baseline could be confirmed.

2.6. Statistical analysis

Statistical analyses were performed using SPSS (version 24.0, Chicago, USA). Continuous variables are reported as mean ± SD if data are normally distributed, otherwise as median(interquartile range). Discrete variables are presented as frequencies and/or proportions. Comparison of two means was done by a Student's *t*-test, comparison of two medians by a Mann-Whitney *U* test. Proportions were compared using Fischer's Exact test. Correlations were estimated with Pearson's or Spearman's Correlation Coefficient, where applicable. Linear regression analysis was performed to identify predictors of total PVR at follow-up. Only variables that were statistically significant ($p < 0.05$) in univariate analysis were included in the multivariate analysis. In case of collinearity ($r > 0.40$), only one of the collinear variables was retained. Intra- and interobserver variability testing was performed for resting and peak mPAP and LVCO measurements. Intraobserver variability was assessed by repeated analysis of 10 data sets (5 patients - 5 controls) at least 2 months after and blinded to the initial analysis. Interobserver variability was assessed by a second blinded observer. The agreement between the 2 observers was determined as the mean bias ± 1.96SD and visualized using Bland-Altman plots. Moreover, intra- and interobserver reliability was assessed using the intraclass correlation coefficient (two-way mixed model) [20]. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient selection

Thirty-eight patients with VSD repair and 19 controls participated. Two patients were excluded because of RV outflow tract obstruction and one because of severe aortic valve regurgitation. Eight patients and one control subject were excluded because of insufficient quality of the TRV measurements during exercise. Data from the remaining 27 patients and 18 controls were analysed. There were no significant differences in VSD characteristics, age and type of repair, age, body mass index, gender, exercise capacity, LV and RV function and tricuspid regurgitation severity between the included and excluded patients.

3.2. Patient characteristics

Twenty-seven patients with median VSD defect size of 10 (8–14) mm and median Qp/Qs ratio of 2.5 (1.7–4.0) were studied. Median age at VSD repair was 3.3 (0.6–5.1) years. Fifteen (56%) patients had PH before closure. Twenty-six patients underwent surgical VSD repair: 3 (12%) primary closures, 22 (85%) patch closures, 1 unspecified. One patient underwent percutaneous closure with an Amplatzer Septal Occluder Device (St. Jude Medical, Minnesota, USA) in that time period.

After a median follow-up time of 1.1 (1.0–1.5) years, 25 patients and 18 controls were retested. One patient dropped out because of pregnancy, one because of emigration. There were no significant differences in demographic and clinical characteristics between VSD patients and controls, except that baseline diastolic BP was lower in VSD patients (72 ± 8 vs 79 ± 9 mm Hg, $p = 0.014$) (Supplementary Table 1).

3.3. Resting and bicycle stress echocardiography

Patients had larger RV areas and lower tricuspid annular plane systolic excursion (TAPSE) compared to controls at baseline and after follow-up (Table 1).

During bicycle stress echocardiography, VSD patients reached lower peak workload and peak LVCO than controls (Table 1). Peak TAPSE and RV FAC were lower and peak total PVR was higher. Both groups could significantly lower total PVR during exercise (Fig. 1), although the decrease in total PVR was lower in VSD patients (Table 1). The low E/e′ ratios measured at peak exercise exclude an important increase of left atrial (LA) pressure during exercise.

The mean mPAP-CO slope was steeper in patients compared to controls (Baseline: 2.2 ± 0.8 vs 1.7 ± 0.3 mm Hg/L/min, $p = 0.008$; Follow-up: 2.5 ± 0.9 vs 1.6 ± 0.3 mm Hg/L/min, $p < 0.001$) (Fig. 2). Individual mPAP-CO slopes for each participant can be consulted in the Supplementary Fig. 1. There was a strong correlation between all slopes at baseline and follow-up ($R = 0.70$, $p < 0.001$).

3.4. Predictive value of the mPAP-CO slope

Bivariate correlation analysis showed a strong correlation between the mPAP-CO slope and resting total PVR, female gender and SV index at peak exercise (Supplementary Table 2).

The mPAP-CO slope at baseline was the only independent predictor of follow-up resting total PVR (Beta coefficient 0.628, 95% CI [0.060–1.195]) (Supplementary Table 3). Age at repair, Qp/Qs ratio and PH before repair did not predict follow-up resting total PVR.

3.5. Intra- and interobserver variability

There was good agreement in LVCO and mPAP measurements between two blinded observers. Mean bias ± limits of agreement for LVCO measures were 0.08 ± 0.27 L/min at rest and 0.07 ± 0.77 L/min at peak exercise. Mean bias ± limits of agreement for mPAP measures were 0.53 ± 1.79 mm Hg at rest and 1.52 ± 5.10 mm Hg at peak. Bland-Altman plots for rest and peak measures combined can be consulted in the Supplementary Fig. 2. The interobserver intraclass correlation coefficient was 0.987 (95% CI 0.942–0.997) for LVCO at rest and 0.994 (95% CI 0.976–0.998) for LVCO at peak exercise. The interobserver intraclass correlation coefficients for mPAP were 0.951 (95% CI 0.801–0.988) at rest and 0.888 (95% CI 0.596–0.971) at peak exercise. Intraobserver variability for rest and peak measurements combined was 0.04 ± 1.25 L/min for LVCO and − 0.16 ± 4.35 mm Hg for mPAP. Intraobserver intraclass correlation coefficient for rest and peak measurements combined was 0.995 (95% CI 0.987–0.998) for LVCO and 0.978 (95% CI 0.946–0.991) for mPAP.

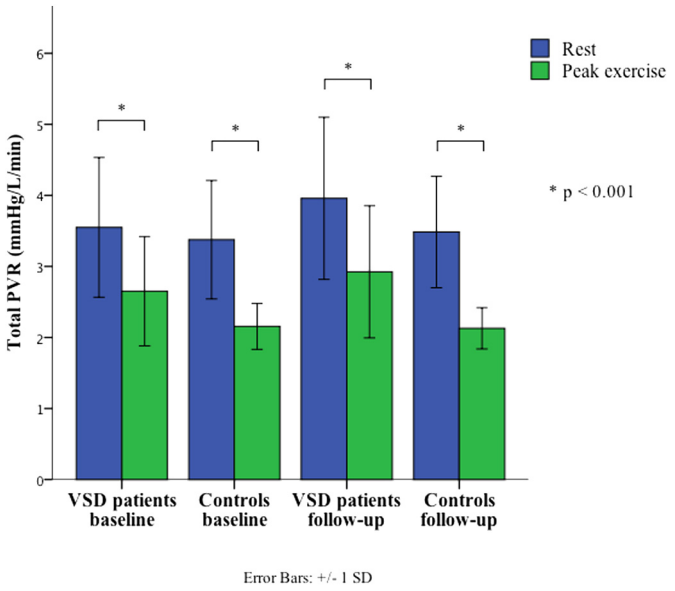

Fig. 1. Change in total PVR from rest to peak exercise. PVR, pulmonary vascular resistance; SD, standard deviation.

3.6. Cardiopulmonary exercise testing correlates with mPAP-CO slope

At baseline, peak workload, peak VO_2 and peak O_2 pulse were lower in VSD patients (Table 2). At follow-up, VO_2 at VAT was lower in VSD

Table 1
Resting and bicycle stress echocardiography (data at peak exercise).

	Baseline			Follow-up		
	VSD (n = 27)	Controls (n = 18)	p-Value	VSD (n = 25)	Controls (n = 18)	p-Value
Resting echo						
Biplane LV EDV (mL)	129 ± 35	127 ± 24	0.832	120 ± 24	124 ± 18	0.502
Biplane LV ESV (mL)	54 ± 19	51 ± 12	0.556	49 ± 12	46 ± 10	0.306
Biplane LV EF (%)	59 ± 5	60 ± 4	0.490	59 ± 4	63 ± 4	**0.002**
E/e′	4.8 ± 0.9	4.5 ± 0.7	0.330	4.7 ± 1.0	3.9 ± 0.5	**0.001**
TAPSE (mm)	17 (17–19)	26 (22–28)	<**0.001**	18 ± 2	26 ± 3	<**0.001**
RV EDAi (cm^2/m^2)	10 ± 2	9 ± 1	**0.001**	12 ± 2	9 ± 2	<**0.001**
RV ESAi (cm^2/m^2)	6 ± 1	5 ± 1	**0.022**	7 ± 1	5 ± 1	<**0.001**
RV FAC (%)	45 ± 5	44 ± 6	0.410	40 ± 6	47 ± 5	<**0.001**
mPAP (mm Hg)	17 ± 4	16 ± 2	0.091	17 ± 3	16 ± 2	0.191
SV (mL/beat)	74 (67–82)	76 (70–81)	0.705	71 ± 13	79 ± 14	**0.048**
SV index (mL/m^2/beat)	40 ± 8	39 ± 5	0.716	37 ± 7	40 ± 6	0.101
LVCO (L/min)	5.0 ± 1.0	4.8 ± 0.8	0.520	4.4 ± 0.8	4.7 ± 1.1	0.296
LVCI ($L/min/m^2$)	2.6 ± 0.5	2.5 ± 0.3	0.263	2.3 ± 0.4	2.4 ± 0.4	0.545
Total PVR at rest (mm Hg/L/min)	3.5 ± 1.0	3.4 ± 0.8	0.542	3.8 (3.1–4.3)	3.4 (3.0–4.3)	0.266
Bicycle stress echo						
Peak workload (W)	158 ± 47	204 ± 47	**0.002**	174 ± 50	208 ± 52	**0.035**
Duration of test (min)	13.1 ± 3.9	16.5 ± 4.0	**0.007**	14.2 ± 4.0	16.5 ± 4.2	0.078
Peak SBP (mm Hg)	172 ± 21	197 ± 20	<**0.001**	187 ± 18	200 ± 20	**0.042**
Peak DBP (mm Hg)	97 ± 12	108 ± 10	**0.006**	104 ± 13	106 ± 15	0.595
Peak heart rate (bpm)	149 ± 20	157 ± 15	0.160	156 ± 17	163 ± 13	0.196
Peak mPAP (mm Hg)	37 ± 6	37 ± 5	0.796	38 ± 5	35 ± 4	**0.019**
Peak SV (mL/beat)	100 ± 21	111 ± 17	0.076	90 ± 21	103 ± 20	**0.042**
Peak SV index (mL/m^2/beat)	52 ± 9	56 ± 6	0.057	47 ± 8	53 ± 8	**0.022**
Peak LVCO (L/min)	14.9 ± 3.6	17.4 ± 3.1	**0.019**	14.2 ± 4.0	16.8 ± 3.3	**0.026**
Peak LVCI ($L/min/m^2$)	7.7 ± 1.5	8.9 ± 1.3	**0.011**	7.3 ± 1.5	8.6 ± 1.5	**0.012**
Peak total PVR (mm Hg/L/min)	2.7 ± 0.8	2.2 ± 0.3	**0.005**	2.9 ± 0.9	2.1 ± 0.3	<**0.001**
Decrease in total PVR from rest to peak (%)	24 ± 14	34 ± 12	**0.028**	26 ± 12	37 ± 13	**0.008**
Peak RV FAC (%)	–	–	–	49 ± 6	57 ± 7	**0.001**
Increase in RV FAC from rest to peak (%)	–	–	–	16 (12−20)	20 (15–25)	**0.034**
Peak TAPSE (mm)	26 ± 5[a]	39 ± 5	<**0.001**	25 (22–28)	39 (36–40)	<**0.001**
Peak E/e′	5.0 ± 0.8[a]	5.5 ± 0.9	0.123	5.3 ± 1.0	5.5 ± 0.8	0.509

LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricular; EDAi, end-diastolic area indexed for body surface area; ESAi, end-systolic area indexed; FAC, fractional area change; mPAP, mean pulmonary artery pressure; SV, stroke volume; LVCO, left ventricular cardiac output; LVCI, left ventricular cardiac index; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure.
The p-values indicated in bold are the significant p-values, meaning $p < 0.05$.
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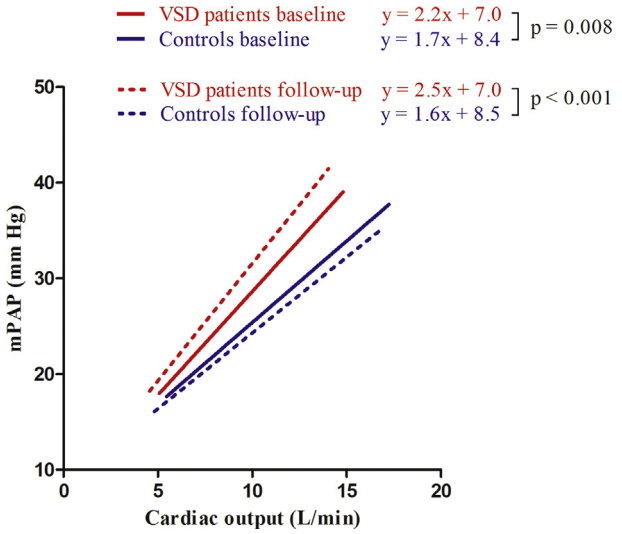

Fig. 2. Mean mPAP-CO slope of VSD patients versus controls. mPAP, mean pulmonary artery pressure; CO, cardiac output.

patients. The V_E/VCO_2 slope ranged from 20 to 39 in patients, from 18 to 31 in controls. Similar values of peak V_E as a percentage of predicted maximal voluntary ventilation (63 ± 15 vs 69 ± 16%, p = 0.224) rule out a relevant pulmonary limitation to exercise. The mPAP-CO slope correlated strongly with peak VO_2 and peak O_2 pulse at baseline and after re-testing (Supplementary Table 2).

4. Discussion

The present study is the first to serially investigate pulmonary hemodynamics in repaired VSD patients. Echocardiography-derived pulmonary hemodynamics and RV function during exercise seem to be altered in VSD patients. Patients had lower exercise capacity that correlated inversely with the mPAP-CO slope. Despite the short follow-up period, the mPAP-CO slope at baseline was an independent predictor of follow-up resting total PVR.

4.1. Pulmonary hemodynamics and RV function during exercise seem to be altered

The pulmonary circulation has a low resistance. Consequently, PVR during exercise cannot lower that much. In PAH, alterations in pulmonary vascular structure and function (with less nitric oxide and prostacyclin and upregulated endothelin production) result in a blunted decrease in PVR [21]. Similarly, this could explain why peak total PVR and the mPAP-CO slope were repeatedly higher in the VSD group. Despite VSD closure, subclinical alterations in the pulmonary vasculature might persist [22]. Herve et al. suggested to define a pathological hemodynamic response of the pulmonary circulation during exercise as the combination of mPAP > 30 mm Hg and total PVR > 3 mm Hg/L/min [23]. According to this definition, 10/25 patients but no control subjects had a pathological response.

VSD patients had lower TAPSE and RV FAC at rest, compared to controls. This could indicate incomplete RV remodeling after VSD repair or be related to the surgical intervention with opening of the pericardium and RA with subsequent scarring [24,25]. However, it could also result from increased ventricular afterload due to early PVD. With increasing exercise-induced PAP, the RV has to work harder to sustain CO necessary for the level of exertion [21]. This impairment of RV output could explain why in VSD patients SV index did not increase to the same level as in controls [22,26]. The strong correlation between peak VO_2 and RV S-velocity at peak heart rate observed in another VSD patient group supports this hypothesis of impaired RV contractility [27]. Furthermore, recurring pressure overload of the RV with exercise could further damage RV function. The hypothesis of RV impairment based on echocardiographic data will need to be confirmed by more detailed imaging techniques as magnetic resonance imaging.

4.2. Patients have lower exercise capacity that correlates with the mPAP-CO slope

Patients reached lower peak workload and peak VO_2 compared to controls, as described before [25]. There are theoretically 3 main reasons to explain the lower exercise capacity: patients do not reach maximal effort, they are deconditioned, or they present a cardiac and/or circulatory limitation to exercise.

As both groups reached similar peak heart rates on both exercise tests, they achieved the same level of effort. The high respiratory exchange ratios suggest that both groups reached truly maximal effort [28].

At follow-up, a lower VO_2 at VAT in patients could indicate deconditioning, but could also indicate PVD [19]. Moreover, deconditioning does not explain the higher V_E/VCO_2 slopes in patients. The V_E/VCO_2 slope describes the ventilatory efficiency during effort and normal values range between 20 and 30 [28], whereas the V_E/VCO_2 slope in the VSD group ranged from 20 to even 39.

Last, the VSD patients seem to be unable to increase LVCO to the level of controls. The difference in peak LVCO was mostly due to a difference in peak SV. The lower SV could result from decreased LV function

Table 2
Cardiopulmonary exercise testing.

	Baseline			Follow-up		
	VSD (n = 27)	Controls (n = 18)	p-Value	VSD (n = 25)	Controls (n = 18)	p-Value
Heart rate before start (bpm)	84 ± 11	80 ± 14	0.295	81 ± 13	78 ± 10	0.438
Peak workload (W)	200 (180–250)	275 (215–300)	**0.006**	200 (160–250)	250 (195–288)	0.085
Peak SBP (mm Hg)	175 ± 18	199 ± 22	**<0.001**	189 ± 18	207 ± 21	**0.005**
Peak DBP (mm Hg)	79 (70–93)	85 (71–96)	0.793	87 ± 9	91 ± 11	0.143
Peak heart rate (bpm)	178 ± 12	180 ± 10	0.721	178 ± 13	176 ± 10	0.511
Peak VO_2 (mL/kg/min)	32 ± 6	39 ± 9	**0.005**	34 (29–37)	37 (32–47)	0.188
VO_2 at VAT (mL/kg/min)	21 ± 7	25 ± 8	0.067	20 (17–22)	25 (19–29)	**0.038**
Peak VCO_2 (mL/kg/min)	37 ± 7	45 ± 10	**0.002**	40 ± 9	46 ± 11	0.065
Peak O_2 pulse (mL/beat)	14 ± 3	17 ± 4	**0.010**	15 ± 4	17 ± 4	0.072
Peak O_2 saturation (%)	–	–	–	98 (97–99)	98 (97–100)	0.240
RER	1.13 ± 0.07	1.15 ± 0.05	0.413	1.14 ± 0.06	1.17 ± 0.05	0.107
Peak V_E (L/min)	86 ± 21	106 ± 26	**0.007**	90 ± 26	103 ± 30	0.145
V_E/VCO_2 slope	29 ± 4	27 ± 3	0.108	28 ± 3	26 ± 3	**0.044**

VAT, ventilatory anaerobic threshold; SBP, systolic blood pressure; DBP, diastolic blood pressure; VO_2, oxygen uptake; VCO_2, carbon dioxide production; RER, respiratory exchange ratio; V_E, minute ventilation.
The p-values indicated in bold are the significant p-values, meaning p < 0.05.

(due to long-standing volume overload before VSD closure and/or septal dyskinesia after VSD closure) [26], but may also be due to impaired RV function with reduced LV preload, as discussed earlier. This is supported by our data that show an inverse correlation between the mPAP-CO slope and peak VO_2.

4.3. The mPAP-CO slope at baseline predicts resting total PVR at follow-up

The mPAP-CO slope at baseline was an independent predictor of follow-up resting total PVR. This could make the mPAP-CO slope a promising tool for PVD risk stratification in VSD patients, but future studies are needed to confirm this.

5. Limitations

The present study was monocentric with a rather limited patient number. However, other studies investigating pulmonary hemodynamics during exercise in VSD patients have similar patient numbers. The median follow-up time was short. It was determined by study protocol to validate the technique of bicycle stress echocardiography (reproducibility of the mPAP-CO slopes). However, it is intended to follow these patients with repeated testing in future. The technique of bicycle stress echocardiography is not feasible in every patient [27]. Nine out of 54 (17%) participants were excluded because of inaccurate TRV measurements during exercise. On the other hand, our data show a good test-retest reproducibility of the mPAP-CO slopes. Furthermore, LA pressure was not taken into account for the calculation of PVR, a known limitation of exercise echocardiography [9]. However, the low E/e′ ratios measured at peak exercise exclude an important increase of LA pressure during exercise. Moreover, the current findings of pulmonary hemodynamics are based on echocardiography, whereas the gold standard for PVR, mPAP and CO measurements is catheterization. Our data will need to be confirmed by catheterization in a next step. However, in this study we aimed at evaluating a non-invasive screening tool, to create awareness of possible alterations in pulmonary vascular function. Furthermore, a training effect cannot be excluded as both groups are more confident with the exercise testing at follow-up. Finally, RV FAC during exercise and O_2 saturation during CPET were no predefined measurement goals at baseline, but were implemented during follow-up.

6. Conclusions

The present study is the first to serially investigate pulmonary hemodynamics in repaired VSD patients. Our data suggest that the lower exercise capacity and peak LVCO in VSD patients may be explained by alterations in the pulmonary vasculature and RV impairment, potentially resulting from VSD-related pressure overload. Future studies are needed to confirm this hypothesis. Our data support life-long follow-up of VSD patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.044.

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Declarations of interest

None.

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