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Surgical closure of a ventricular septal defect in early childhood leads to altered pulmonary function in adulthood: A long-term follow-up

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ABSTRACT

Background: The long-term outlook after surgical closure of ventricular septal defect (VSD) has traditionally been considered benign. However, there is an increasing awareness of not only late cardiac dysfunction, but also pulmonary abnormalities. The primary aim of this study was to describe pulmonary function in adults with a surgically repaired VSD, and secondarily to determine the effects of salbutamol on the potential abnormalities.
Methods: All patients (operated for a VSD in early childhood) and controls (age- and gender-matched) underwent static and dynamic spirometry, impulse oscillometry, multiple breath washout, diffusion capacity for carbon monoxide, and cardiopulmonary exercise testing. In a double-blinded, cross-over study, participants were randomized to inhalation of either 900 μg of salbutamol or placebo. The primary outcome was forced expiratory volume in 1 s.
Results: In total, 30 participants with a surgically closed VSD and 30 healthy controls were included. The VSD participants had a lower forced expiratory volume in 1 s (99 ± 13% vs. 111 ± 13%), $p < 0.001$, impaired forced vital capacity, (106 ± 12% vs. 118 ± 13%), $p < 0.001$, and lower peak expiratory flow, (95 ± 18% vs. 118 ± 19%), $p < 0.001$, than the control group. Also, the VSD group had a lower alveolar volume than the control group, (92 ± 10% vs. 101 ± 11%), $p < 0.001$, but there were no differences in the remaining pulmonary function parameters. Salbutamol reduced airway resistances in both groups, but exercise performance was not improved by salbutamol, however.
Conclusions: Adults who have undergone surgical closure of a VSD in early childhood have reduced pulmonary function compared with controls, which is unaffected by inhalation of salbutamol.

1. Introduction

Repair of a ventricular septal defect has a low surgical mortality, is associated with low rates of postoperative morbidity, and the long-term outcome has traditionally been considered so benign as not to require specialized adult congenital heart follow-up [1–6]. Nevertheless, several recent studies have highlighted significant late morbidity and while their focus has been towards cardiac dysfunction [7], there is also an emerging evidence of late pulmonary abnormalities [8].

The exact mechanisms of pulmonary dysfunction remain to be elucidated, however several studies have indicated that early pulmonary hyperperfusion might have a negative impact on the long-term viscoelastic properties of the lungs [9, 10], even after surgical correction [11]. Furthermore, Sulc et al. [12–14] have suggested that these patients may have increased airway resistance and our own research group showed an abnormal ventilation pattern during exercise in VSD-operated patients [15]. Consequently, a thorough investigation of VSD patients' pulmonary function on a longer-term basis with contemporary measurement techniques is warranted.

We hypothesized that adults, who had undergone surgical VSD-repair in early childhood have abnormal lung function with increased airway resistance, the latter of which can be improved with bronchodilator treatment.

2. Methods

The Danish Data Protection Agency (chart: 1-16-02-315-16), The Regional Committee on Biomedical Research Ethics of the Central Denmark Region (chart: 1-10-72-153-16), The Danish Medicines Agency (chart: 2016061269), and the European Medicines Agency (EudraCT No. 2015-005507-89) approved the study. The study was monitored by the Good Clinical Practice Unit of Aalborg and Aarhus University Hospitals, and it is registered

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[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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on clinicaltrials.gov (identifier: NCT02914652). All participants provided written informed consent prior to enrolment, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, revised in 2008.

2.1. Design

The participants were requested not to perform exhausting exercise within 24 h prior to each visit and they were asked to abstain from large meals and coffee for at least two hours before the visit. At their first visit, each participant was asked to fill in the International Physical Activity Questionnaire and bioelectrical impedance measurements were performed using the ImpediMed Ltd. Model SFB7 (ImpediMed Ltd. Brisbane, Queensland, Australia). They were then randomized to inhalation of either 900 μg of salbutamol (Ventoline®) or placebo (Evohaler®) at two separate visits with two to 14-days interval at Aarhus University Hospital, Denmark. A block randomization sequence with six participants in each block was made by the Hospital Pharmacy of Region Midtjylland, and the allocation information was concealed for all study personnel until completion of the data analyses.

After the inclusion, five different pulmonary function tests were performed. After the intervention, impulse oscillometry, dynamic spirometry, and a cardiopulmonary exercise test were performed. At the second visit, impulse oscillometry, dynamic spirometry, and a cardiopulmonary exercise test were performed after the alternate intervention. Patients and researchers were blinded to study drug, and administration of drug and placebo were randomly ordered.

2.2. Study population

Inclusion criteria were 1) operated VSD-patients who had undergone surgical closure of a congenital, isolated VSD through right atrial approach at Aarhus University Hospital between 1990 and 1997, and 2) healthy age- and gender-matched volunteer controls included through flyers and announcements on official webpages. Exclusion criteria were coexistence of congenital cardiac defects than VSD, associated syndromes, e.g. Down's syndrome, documented arrhythmia other than right bundle branch block, cardiac or pulmonary disease including any valve pathology, and missing patient chart. Details of the surgical procedures are previously described [16].

2.3. Intervention

The intervention was administered using a metered-dose inhaler containing either salbutamol (Ventoline®) or placebo (Evohaler®). The inhalations were performed in a standardized manner by use of an official, governmental instruction video and the administrations were supervised by an investigator to ensure correct inhalation. When randomized to salbutamol, the cumulative dose was 900 μg, which was administered approximately 15 min prior to the pulmonary function tests and 60 min prior to cardiopulmonary exercise testing.

2.4. Pulmonary function tests

All tests were performed by trained and experienced personnel in accordance with current guidelines from European Respiratory Society and American Thoracic Society. For each test, three reproducible maneuvers without artefacts, e.g. coughing, vocalization, swallowing, or inappropriate breath holding, were recorded in a sitting position.

2.4.1. Static and dynamic spirometry

A Jaeger MasterScreen PFT Pro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark) were used and both tests were performed according to established guidelines for standard spirometry [17].

2.4.2. Impulse oscillometry

A Carefusion Vyntus Impulse Oscillometer using SentrySuite software and a Vyntus Spirometer (IntraMedic, Gentofte, Denmark) using LabManager Version 4.67.0.1 software (CareFusion Germany GmbH, Hoechberg, Germany) were used and the test was performed according to the current guidelines [18]. A pathologically increased airway resistance was defined as >110% of the predicted value [18].

2.4.3. Multiple breath washout

An EcoMedic Exhalyzer D (IntraMedic, Gentofte, Denmark) was used and it was calibrated prior to each visit. As per established guidelines [19], the monitored tracer gas was nitrogen, whereas 100% oxygen was supplied during washout, which was considered complete when the end-tidal nitrogen concentration had decreased below 1/40th of the peak end-tidal concentration.

2.4.4. Diffusion capacity for carbon monoxide

A Jaeger MasterScreen PFT Pro Diffusion System from CareFusion (IntraMedic, Gentofte, Denmark) with LabManager Version 4.67.0.1 software (CareFusion Germany GmbH, Höchberg, Germany) was used. A gas composition consisting of 0.3% carbon monoxide, 10% helium and 21% oxygen, balanced with nitrogen, was used and the test was performed with single-breath technique according to current guidelines [20].

2.5. Cardiopulmonary exercise testing

An upright ViaSprint 150P® ergometer cycle (Ergoline, Bitz, Germany) was used, and as per current international guidelines on cardiopulmonary exercise testing, all tests were supervised by trained, experienced personnel [21]. For each participant, an individual workload protocol was chosen based on the participant's body mass, gender, and habitual activity level. The workload protocol included a baseline rest period of two minutes followed by an initial workload of 25 or 100 W, increasing with 10, 15, or 25 watts per minute. Prior to the test, the participant was instructed to keep a pedaling speed between 60 and 70 turns per minute throughout the test without standing, talking, or releasing the handlebars.

During the test, gas exchange was measured breath-by-breath using a Jaegers MasterScreen CPX® system (IntraMedic, Gentofte, Denmark). Heart rate, 12-lead electrocardiography, and arterial oxygenation were continuously monitored, whereas arterial blood pressure was measured at rest and every second minute thereafter. The participant was encouraged until complete exhaustion defined as inability to maintain the instructed pace. The test was considered valid only if the respiratory exchange ratio reached a value of 1.1 or above.

2.6. Outcomes

The primary outcome was forced expiratory volume in 1 s, and secondary outcomes were the remaining pulmonary function parameters and the peak exercise parameters in terms of minute ventilation, breath rate, oxygen uptake, and carbon dioxide excretion. Secondary outcomes also included the effects of salbutamol on both pulmonary function and peak exercise parameters.

2.7. Statistical analyses

Continuous data are presented as means ± standard deviations or medians with total ranges, as appropriate, and binary data are presented as absolute numbers and percentages of participants. Differences between groups were assessed using paired or unpaired students *t*-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data and chi-squared tests for binary data. *p*-Values < 0.05 were considered statistically significant on the primary outcome, whereas only *p*-values < 0.01 were considered statistically significant on the secondary outcomes, all *p*-values are two-sided. Descriptive data were stored in Microsoft Excel 2016 (Microsoft Corp., CA, USA) and statistical analyses were performed using Stata/IC 12.1 for Mac (Stata Corp., TX, USA).

2.7.1. Sample size justification

The sample size estimate was based on previously published data from our group [16]. In order to determine a difference between the groups on our primary outcome with a power of 80% and a significance level of 0.05 using the students *t*-test, the minimal sample size was determined to be 13 patients per group. To adjust for participant dropout, we enrolled 30 patients per group.

3. Results

In the period from October 2016 to June 2017, 30 participants with a surgically closed VSD and 30 healthy controls were enrolled as displayed in Fig. 1. In the VSD group, preoperative echocardiography had shown a mean gradient of 56 ± 25 mm Hg and a subgroup of 8 patients had underwent a cardiac catheterization with a mean Qp/Qs of 2.9 ± 0.7. The median age at surgery was 1.4 years (95% CI 0.9–2.4 years). All participants enrolled completed both study visits, but in the VSD group, 1 participant was secondarily excluded after initial enrollment due to a severe congenital scoliosis. No serious adverse events were observed. Basic characteristics and physical activity patterns for the two groups are shown in Table 1 and Supplemental Table 1, respectively as seen, the groups were generally similar including their physical activity levels.

Pulmonary function parameters are shown in Table 2. There was a lower forced expiratory volume in 1 s in the VSD group, $p < 0.001$, impaired functional vital capacity, $p < 0.001$, and peak expiratory flow, $p < 0.001$, compared with the control group. There were no differences in the remaining spirometry parameters, however the VSD operated group had a lower alveolar volume than the control group, $p < 0.001$. There were no statistical differences in mean diffusion capacity or any of the remaining pulmonary function parameters. In the VSD group, 20% of the participants had a pathologically increased airway resistance (R5), compared with 7% of the controls, 10% of the VSD participants and 7% of the controls had pathologically increased resistance in the large conducting airways (R20), and pathologically increased resistance in the small conducting airways (D5–20) was found in 20% of the VSD

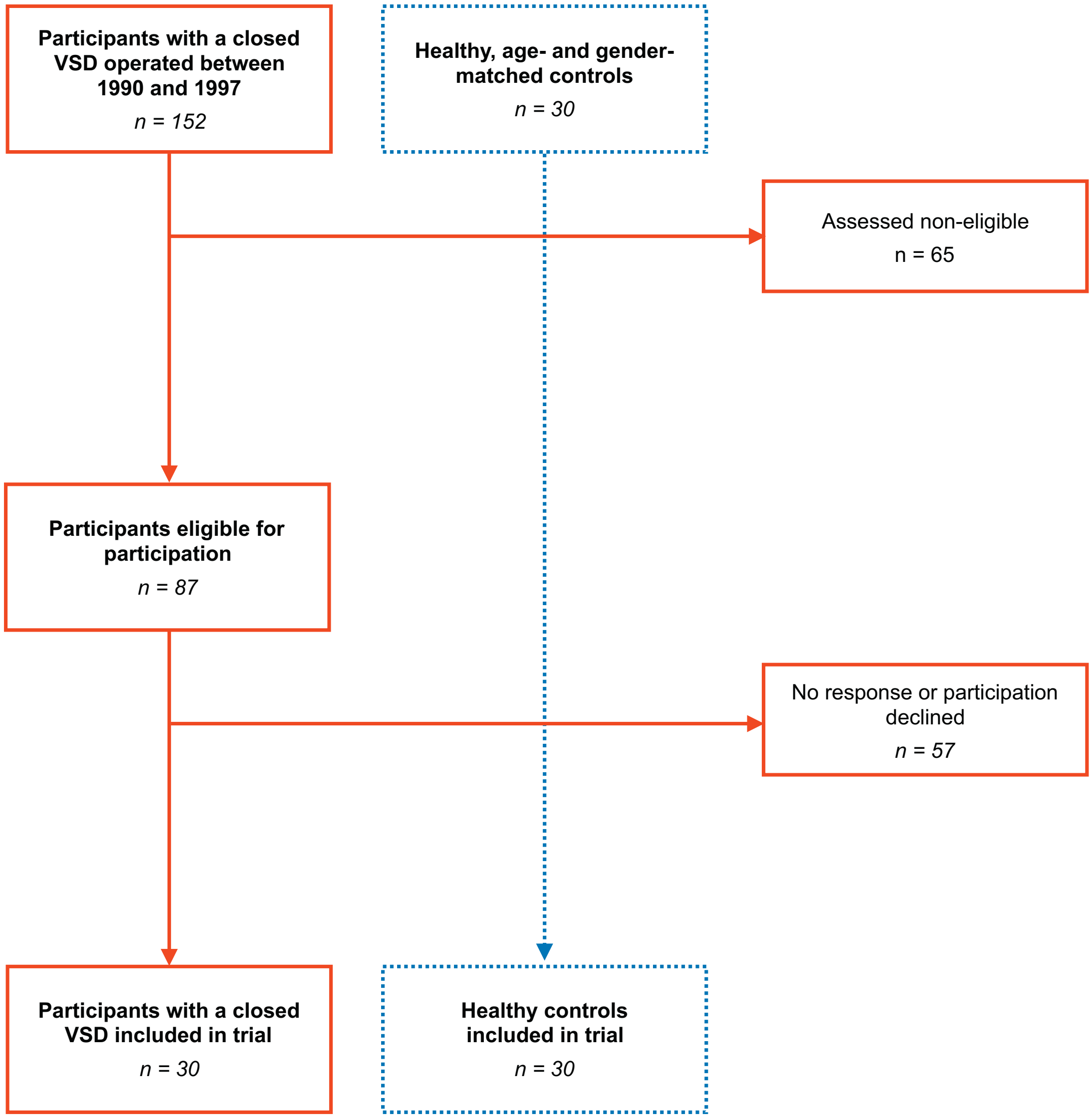

Fig. 1. Patient flow chart. Flow of VSD participants through the study period. VSD, ventricular septal defect.

participants and 10% of the controls but none of these differences reached statistical significance ($p = 0.16$, $p = 0.67$ and $p = 0.075$, respectively).

Exercise data are shown in Table 3, and the ventilatory parameters during the test session are displayed in Supplemental Fig. 2. At peak exercise, VSD participants had lower minute ventilation, $p < 0.001$, oxygen uptake, $p < 0.001$, and carbon dioxide excretion, $p < 0.001$, than the controls, but there was no difference in breath rate, $p = 0.210$, breathing reserve, $p = 0.060$, or ventilatory efficiency (VE/VCO_2-slope), $p = 0.696$, between the groups. Similarly, when compared over the entire exercise test session, minute ventilation, $p < 0.001$, oxygen uptake, $p < 0.001$, and carbon dioxide excretion, $p < 0.001$, were impaired in the VSD group compared with the control group, but again, there was no significant, although borderline, difference in breath rate, $p = 0.055$, between the groups. Also, the VSD group reached a lower maximal workload, $p < 0.001$, and had lower oxygen uptake, $p < 0.001$, and workload, $p < 0.001$, at the anaerobic threshold than the control group.

Lastly, the effects of salbutamol on pulmonary function and exercise in the VSD group are displayed in Supplemental Tables 2, 3, and Supplemental Fig. 2. As seen, salbutamol led to a decreased resistance in the conducting airways, $p = 0.005$, and a lower resistance in the large conducting airways specifically, $p = 0.003$, but there were no effects of salbutamol on any of the remaining parameters. However, except for a larger decrease in resistance in the small conducting airways in the VSD group, $p = 0.009$, there were no evidence of differences in the effects of salbutamol between the groups. In the subgroups with pathologically increased airway resistances, there were no statistically significant improvements by salbutamol either. There was no association between age at surgery and any of our outcomes.

4. Discussion

In this double-blinded, cross-over study, we demonstrate that adults operated for a VSD in early childhood have compromised pulmonary function in terms of forced expiratory volume in 1 s, forced vital capacity, peak expiratory flow, and alveolar volume compared with healthy controls. Also, as previously demonstrated, we found a reduced minute ventilation during exercise in the VSD operated participants in comparison with controls, despite similar breath rates. Lastly, while salbutamol, lowered airway resistances in both groups, we found no effects of inhaled salbutamol on exercise performance, and no evidence of differences in the effects of salbutamol between controls and VSD patients, neither in the subgroups with pathologically increased airway resistances.

Table 1
Characteristics of participants with surgically closed VSDs and healthy controls.

	Closed VSDs n = 30	Controls n = 30
Demographics		
Age, years	24 ± 2	24 ± 3
Male sex, n (%)	13 (41)	15 (50)
Weight, kg	71 ± 12	72 ± 12
Height, cm	174 ± 10	175 ± 8
Fat free mass, kg	54 ± 11	56 ± 10
Smoking status		
Non-smokers, n (%)	23 (77)	26 (87)
1–7 cigarettes/week, n (%)	3 (10)	2 (6)
8–20 cigarettes/week, n (%)	1 (3)	1 (3)
>21 cigarettes/week, n (%)	3 (10)	1 (3)

Data reported as means ± standard deviations or absolute numbers and percentages of patients. VSD, ventricular septal defect.

Until recently, the late effects of VSD and VSD closure on pulmonary function have remained almost unexplored. Nonetheless, our data are in agreement with the limited available data. Most recently, a study from Möller et al. on VSD operated patients between 30 and 45 years showed a forced expiratory volume in 1 s of 85% of predicted, a forced vital capacity of 88% of predicted, and a diffusion capacity for carbon monoxide of 89% of predicted, which, however, were all within normal ranges [22]. Binkhorst et al. [23] also found lower forced expiratory volume in 1 s and reduced forced vital capacity in VSD operated adolescents, and Sulc et al. [13] described reduced lung compliance, but unfortunately none of the studies provided a comprehensive assessment of lung function, and the data was expressed as normative rather than with directly matched controls. In comparison, we applied a broad panel of advanced pulmonary function tests and compared against a healthy, matched, control group. Alonso-Gonzalez et al. showed that abnormal lung function is prevalent across the spectrum of adults with congenital heart disease and that its severity relates to worse outcome [24]. This study identified 8% of VSD patients as having moderately to severely impaired lung function, but unfortunately, it remains unclear whether these patients were repaired or not. Clearly, however, their identification of complexity of congenital heart disease as an independent predictor of impaired lung function in surgically repaired patients is an important observation.

Table 2
Pulmonary function in participants with surgically closed VSDs and healthy controls.

	Closed VSDs n = 29	Controls n = 30	*p*-Value
Static spirometry			
Total lung capacity, %	101 ± 12	107 ± 13	0.079
Residual volume, %	101 ± 21	94 ± 25	0.266
Functional residual capacity, %	124 ± 19	136 ± 18	0.016
Specific resistance of the airways, %	70 ± 26	65 ± 21	0.421
Dynamic spirometry			
FEV_1, %	99 ± 13	111 ± 13	<0.001
FVC, %	106 ± 12	118 ± 13	<0.001
FEV_1/FVC-ratio	0.8 ± 0.1	0.8 ± 0.1	0.627
PEF, %	95 ± 18	118 ± 19	<0.001
Impulse oscillometry			
R5, %	125 ± 40	105 ± 28	0.027
R20, %	124 ± 31	113 ± 26	0.127
D5-20, %	22 ± 20	14 ± 14	0.076
Multiple breath washout			
Lung clearance index, %	102 ± 21	97 ± 9	0.266
Function of conducting airways, %	69 ± 53	62 ± 46	0.582
Function of respiratory airways, %	100 ± 85	92 ± 43	0.633
Diffusion capacity			
Diffusion capacity for carbon monoxide, %	85 ± 10	92 ± 12	0.042
Alveolar volume, %	92 ± 10	101 ± 11	0.003

Data reported as means of percentages of predicted values ± standard deviations. VSD, ventricular septal defect, FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; R5, Resistance in the conducting airways; R20, resistance in the large conducting airways; D5-20, resistance in the small conducting airways.

Table 3
Exercise data in participants with surgically closed VSDs and healthy controls.

	Closed VSDs n = 29	Controls n = 30	*p*-Value
Peak exercise parameters			
Ventilation, l/kg/min	1.7 ± 0.5	2.0 ± 0.4	<0.001
Breath rate, breaths/min	52 ± 11	55 ± 9	0.210
Oxygen uptake, ml/kg/min	38.2 ± 7.4	47.3 ± 7.4	<0.001
Carbon dioxide excretion, ml/kg/min	47.2 ± 10.4	57.2 ± 9.0	<0.001
Breathing reserve, %	24 ± 18	16 ± 14	0.060
VE/VCO_2-slope	32 ± 5	32 ± 4	0.696
Respiratory exchange ratio	1.2 ± 0.1	1.2 ± 0.1	0.301
Workload, watt/kg	3.3 ± 0.7	4.2 ± 0.7	<0.001
Heart rate, beats/min	180 ± 10	186 ± 10	0.029
Anaerobic threshold			
Oxygen uptake, ml/kg/min	26.3 ± 7.5	35.3 ± 7.1	<0.001
Workload, watt/kg	2.2 ± 0.8	3.0 ± 0.7	<0.001
Heart rate, beats/min	147 ± 27	163 ± 11	0.006

Data reported as absolute values ± standard deviations. VSD, ventricular septal defect. Breathing reserve is calculated as the difference between maximal voluntary ventilation, defined as forced expiratory volume in 1 s × 40, and peak exercise ventilation, and it is expressed as a percentage of maximal voluntary ventilation. VE/VCO_2-slope is calculated as the average ratio between minute ventilation and carbon dioxide excretion over the entire test.

Our data suggest elevated airway resistance among VSD-operated adults, but we cannot dissect the impact of the preoperative physiology versus the impact of surgery in terms of mechanism. That said the surgical procedure is a potential modifier of the viscoelastic properties of the lung and chest wall. Indeed, adults undergoing coronary artery bypass grafting also display substantial restrictive lung dysfunction [25, 26], and cardiopulmonary bypass, including mechanical ventilation, can cause immediate functional and structural injury to the lungs [27, 28]. The predominant influence of the surgical procedure is strengthened by the findings of Zaqout et al. [11], who found significantly better pulmonary outcomes after percutaneous ASD-closure than after surgery.

Nonetheless, we cannot discount the impact of preoperative pulmonary hyperperfusion, which has been shown to have a harmful impact on the viscoelastic properties [9, 10]. Enlarged or engorged pulmonary vasculature has been described in patients with high pulmonary blood flow, which may result in remodeling of the lung parenchyma and fibrotic changes [29]. Indeed, the hyperperfusion theory is strengthened by the high prevalence of increased airway resistance among VSD-operated patients. On the other hand, we found a normal VE/VCO_2-slope, which speaks against this theory as VE/VCO_2-slope has been shown to be a sensitive marker of increased pulmonary vascular resistance [30]. Investigations on adult patients with small, unrepaired defects would be of great value in order to assess potential pulmonary impairments in a non-operated group of VSD patients.

As previously described by our research group, the current study also showed reduced peak exercise minute ventilation as well as functional impairment in terms of lowered oxygen uptake throughout exercise [15, 16]. Importantly, by determining breathing reserve this study demonstrated that the functional capacity cannot be explained by abnormalities of baseline pulmonary function, and hence, abnormalities in the pulmonary vascular bed, as previously suggested [31–33], seem increasingly likely as a mechanism.

Unfortunately modification of airway resistance did not lead to improved exercise performance. Among the VSD operated adults, inhalation of salbutamol had no effects on the demonstrated impairments during exercise in the group as a whole. While disappointing, the relatively small patient group studied, obviates any definitive statement regarding the acute or chronic use of bronchodilators in subgroups of patients, and larger studies will be required to answer such questions. Also, more large-scale studies are needed in order to identify those patients with the most severely impaired lung function. However, we believe our novel data, demonstrating the important potential burden which may increase with age and additional environmental factors, provides ample justification for such studies. We also suggest that these data, and those suggesting measurable abnormalities of cardiac function, mandates continued and careful longitudinal follow-up. Most guidelines suggest that these patients do not require care in expert ACHD clinics [5, 6]. While it is premature to suggest otherwise, the data suggests that the late burden of VSD and its repair may not be completely benign and some regular assessment by knowledgeable carers is advised.

4.1. Limitations

In a contemporary cohort of VSD patients, the surgical age would clearly be expected to be lower, and so our results may be less relevant to patients being operated in the current era. Nevertheless, none of our findings were related to the age at surgery and results are relevant to the very large number of patients operated in previous era's, currently being followed by primary care physicians and cardiologists. In addition, the current study was powered based on a hypothesized difference in forced expiratory volume in 1 s, and not to show a potential effect of salbutamol on this outcome, as discussed earlier. The effects of salbutamol should therefore be interpreted carefully although there was absolutely no tendency towards effects of salbutamol. Also, we found a slight difference between the groups in terms of smoking status but importantly, only <10% of the participants in both of the groups were smoking on a daily basis. Lastly, we cannot rule the risk of selection bias since only about a third of the eligible VSD patients were included in the study.

In conclusion, in comparison with healthy controls, adults with a surgically closed VSD in early childhood have reduced forced expiratory volume in 1 s, forced vital capacity, peak expiratory flow, and alveolar volume at rest as well as lower minute ventilation during exercise. The associated lowered exercise capacity is not improved by inhalation of salbutamol. Although our findings are essentially subclinical in these young adults, they may become important later in life as the effect of environmental factors accrue, and when other lung diseases may be superimposed. We believe that these patients should remain under expert surveillance throughout their adult lives.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.06.109.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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