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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

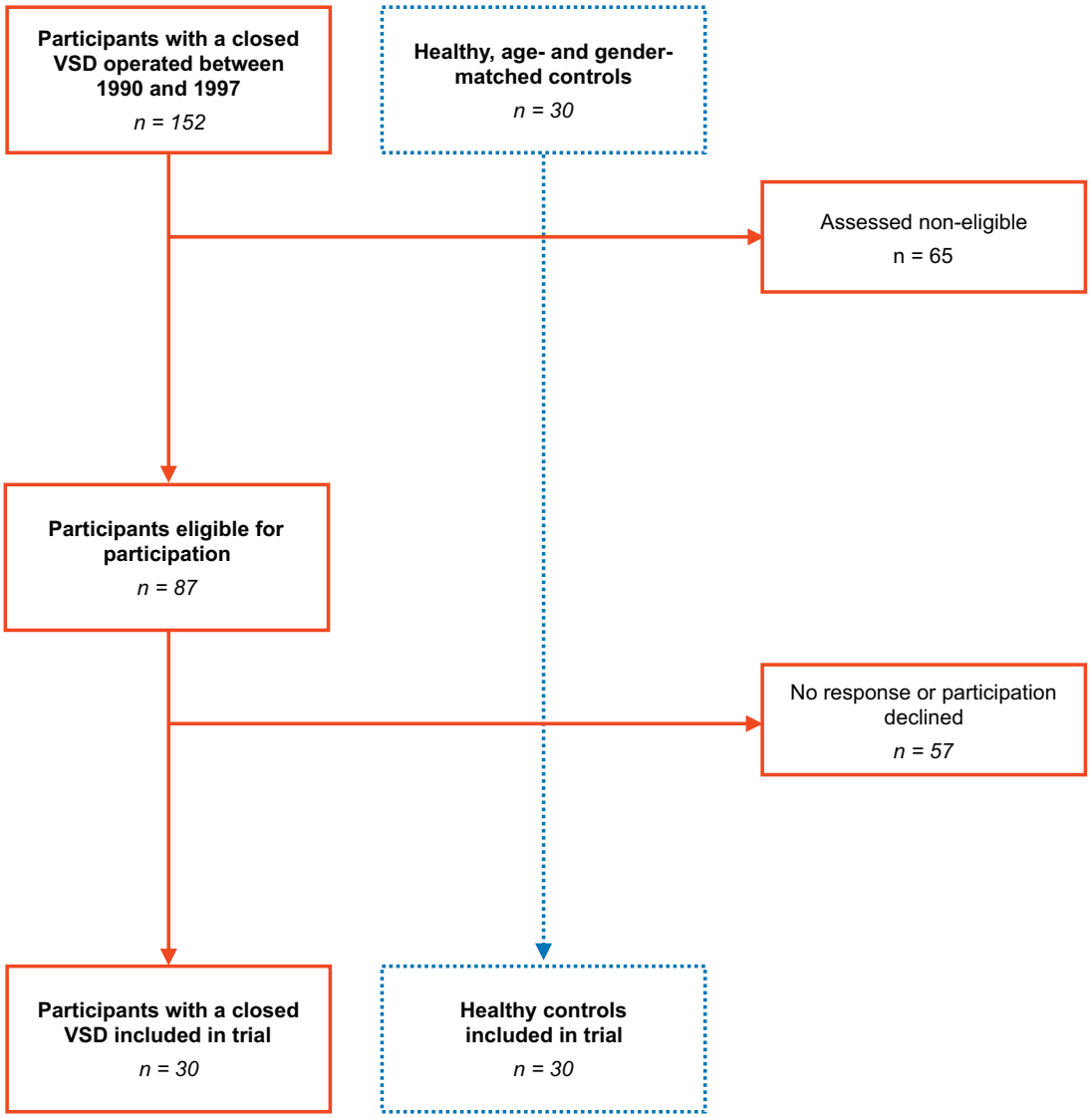

Fig. 1. Patient flow chart. Flow of VSD participants through the study period. VSD, ventricular septal defect.

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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Cardiopulmonary dysfunction in adults with a small, unrepaired ventricular septal defect: A long-term follow-up

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ABSTRACT

Background: There are increasing reports of cardiac and exercise dysfunction in adults with small, unrepaired ventricular septal defects (VSDs). The primary aim of this study was to evaluate pulmonary function in adults with unrepaired VSDs, and secondly to assess the effects of 900 μg salbutamol on lung function and exercise capacity.

Methods: Young adult patients with small, unrepaired VSDs and healthy age- and gender-matched controls were included in a double-blinded, randomised, cross-over study. Participants underwent static and dynamic spirometry, impulse oscillometry, multiple breath washout, diffusion capacity for carbon monoxide, and ergometer bicycle cardiopulmonary exercise test.

Results: We included 30 patients with VSD (age 27 ± 6 years) and 30 controls (age 27 ± 6 years). Patients tended to have lower FEV_1, 104 ± 11% of predicted, compared with healthy controls, 110 ± 14% ($p = 0.069$). Furthermore, the patient group had lower peak expiratory flow (PEF), 108 ± 20% predicted, compared with the control group, 118 ± 17% ($p = 0.039$), and showed tendencies towards lower forced vital capacity and increased airway resistance compared with controls. During exercise, the patients had lower oxygen uptake, 35 ± 8 ml/min/kg (vs 47 ± 7 ml/min/kg, $p < 0.001$), minute ventilation, 1.5 ± 0.5 l/min/kg (vs 2.1 ± 0.3 l/min/kg, $p < 0.001$) and breath rate, 48 ± 11 breaths/min (vs 55 ± 8 breaths/min, $p = 0.008$), than controls.

Conclusion: At rest, young adults with unrepaired VSDs are no different in pulmonary function from controls. However, when the cardiorespiratory system is stressed, VSD patients demonstrate significantly impaired minute ventilation and peak oxygen uptake, which may be early signs of parenchymal dysfunction and restrictive airway disease. These abnormalities were unaffected by the inhalation of salbutamol.

1. Introduction

Large ventricular septal defects (VSDs) are surgically closed at an early age, while smaller VSDs either close spontaneously during childhood or are considered haemodynamically insignificant with excellent 'long-term' outcomes. However, several recent studies have suggested that outcomes are not completely benign, with significant cardiac morbidity described later in life [1–3]. Our group recently demonstrated an impaired pulmonary function at rest and a lower ventilation during exercise in young adults with surgically corrected VSDs [4], but it remains unclear whether this reduced ventilation is related to the surgical procedure or the long-term effects. We recently showed that adults with small VSD's had abnormal exercise function [5], but the underlying mechanism was not explored. Larger septal defects are associated with morphological changes in the lungs and airways [6–8] and late ventilatory dysfunction has been observed in patients after early VSD closure [9–12]. We therefore hypothesized that adults with small, unrepaired VSD's will also display abnormal resting and dynamic pulmonary function, and that these abnormalities would be improved by inhaled salbutamol.

2. Methods

2.1. Ethics and approvals

The study was conducted in accordance to Danish law and the Helsinki Declaration of 1975, revised in 2013, for research involving

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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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human subjects. Approvals were obtained from the Danish Data Protection Agency (chart: 1-16-02-315-16), the Danish (chart: 2016061269) and the European (EudraCT No. 2015-005507-89) Medicines Agency, and the Committee on Biomedical Research Ethics of the Central Denmark Region (chart: 1-10-72-153-16). The project is listed on clinicaltrials.gov (identifier: NCT02914652) and was continuously monitored by The Good Clinical Practice Unit at Aalborg and Aarhus University. All participants gave informed consent prior to study inclusion.

2.2. Study population

Adults between 18 and 40 years of age with an isolated, small, unrepaired VSD, followed at our local clinic or a regional outpatient clinic with echocardiographic follow-ups and healthy, age- and gender-matched controls were included. A small VSD was defined in childhood as a defect with a shunt ratio below 1.5 estimated by echocardiography and in borderline cases, assessed by cardiac catheterization. Controls were recruited through announcements on official webpages. Exclusion criteria were coexistence of other cardiac abnormalities, pulmonary disease, associated syndromes e.g. Downs', current pregnancy or breastfeeding, and metabolic disorders e.g. hyperthyroidism. Physicians from the department were responsible for enrolment of participants and assignment to interventions.

2.3. Study design

In a double-blinded, cross-over cohort study, participants inhaled either salbutamol or placebo in a randomised order on two separate visits at Aarhus University Hospital, Denmark. A block randomization sequence with six participants per block was made by the Hospital Pharmacy of the Central Denmark Region and the allocation information was concealed for all study personnel until completion of all data analyses. Each participant received an identification number which was linked with the participant's intervention containers. To ensure comparable conditions and sufficient physical recovery, the two visits were performed with an interval of two to fourteen days. Participants were requested not to perform exhausting exercise 24 h prior to either visit, and they were asked to abstain from large meals, alcohol, and coffee for at least 2 h before the visit.

An overview of the investigations performed during the study period is outlined in Fig. 1. At visit 1, a questionnaire on weekly physical activity was filled in, and afterwards, bioelectrical impedance measurements using an ImpediMed Ltd. model SFB7 (ImpediMed Ltd. Brisbane, Queensland, Australia), 5 pulmonary function tests, and a cardiopulmonary exercise test were performed. At visit 2, participants performed 2 pulmonary function tests and a cardiopulmonary exercise test.

2.4. Intervention protocol

Salbutamol and placebo were administered using identical metered dose-inhalers and an official, governmental instruction video was shown at both visits to ensure standardized administration. Between 10 and 15 min before the interventional pulmonary function tests, 8 doses of either 100 μg salbutamol (Ventoline®) or Placebo (Evohaler®) were administered. An additional dose of 100 μg salbutamol (Ventoline®) or Placebo (Evohaler®) was given 60 min before the exercise test to ensure maximal effect during the test. Consequently, a cumulative dose of 900 μg salbutamol was administered.

2.5. Pulmonary function tests

The pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society [13–16]. In a sitting position, 3 reproducible maneuvers without artefacts (e.g. coughing, swallowing, vocalization, or inappropriate breath holding) were recorded for each test and all equipment was calibrated before each visit.

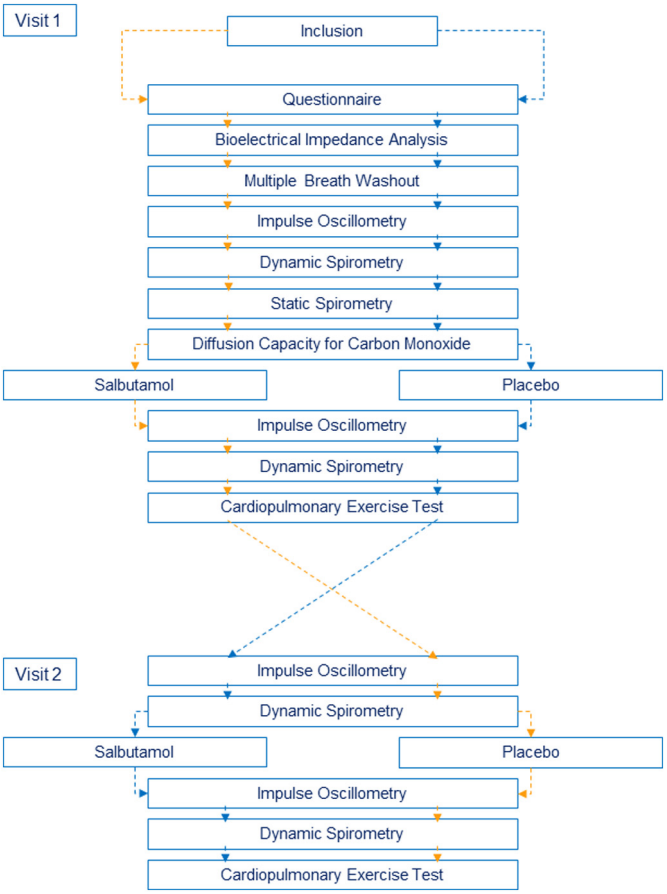

Fig. 1. Investigation order at first and second trial visit. The orange and blue lines represent the randomization order. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.5.1. Static and dynamic spirometry

For static and dynamic spirometry measurements an IntraMedic Jaeger MasterScreen PFTpro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark) were used.

2.5.2. Impulse oscillometry

A Carefusion Vyntus Impulse Oscillometer using SentrySuite Software and Vyntus Spirometer (IntraMedic, Gentofte, Denmark) with LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechberg, Germany) were used for impulse oscillometry examination.

2.5.3. Multiple breath washout

Multiple breath washout was performed using an EcoMedic Exhalyzer D (IntraMedic, Gentofte, Denmark). The monitored tracer gas was nitrogen, whereas 100% oxygen was supplied during washout, which was deemed complete when the end-tidal nitrogen concentration had decreased below 1/40th of the peak end-tidal concentration.

2.5.4. Diffusion capacity for cabon monoxide

For diffusion capacity for carbon monoxide measurements, an IntraMedic Jaeger MasterScreen PFTpro Diffusion System from CareFusion (IntraMedic, Gentofte, Denmark) with software LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechberg, Germany) was used. The single-breath technique was used, with a gas composition of 0.3% carbon monoxide, 10% helium and 21% oxygen, balanced with nitrogen.

2.6. Cardiopulmonary exercise test

The cardiopulmonary exercise tests were performed by trained and experienced personnel in accordance to current guidelines [17] on an upright ViaSprint 150P® ergometer cycle (Ergoline, Bitz, Germany). An individual workload protocol was chosen based on the participant's body mass, gender, and habitual activity level. Workload protocols included a baseline rest period of 2 min followed by an initial workload of 25 or 100 watts, increasing with 10, 15, or 25 watts per minute. Jaegers MasterScreen CPX® system (IntraMedic, Gentofte, Denmark) was used for breath-by-breath gas measurements with results condensed over 15-seconds intervals. Heart rate, 12-lead electrocardiography, and arterial oxygenation were continously monitored, whereas arterial blood pressure was measured at rest and every 2 min during the test. Participants were instructed to maintain a pedaling speed between 60 and 70 rpm throughout the test without standing, talking or releasing the handlebars, and they were encouraged to exercise until complete exhaustion defined as inability to maintain instructed pace. Tests were considered vaild if the respiratory exchange ratio (RER) reached a value of 1.1 or above [17].

2.7. Endpoints

The primary endpoint was forced expiratory volume in 1 s (FEV_1) whereas secondary endpoints were resistance in the small airways, diffusion capacity, anaerobic threshold, peak oxygen uptake, peak exercise minute ventilation, and breathing reserve index. Resistance in the small airways was evaluated through impulse oscillometry and multiple breath washout measurements. Peak oxygen uptake was defined as the highest oxygen uptake per kilogram body mass per minute reached during active pedaling. The anaerobic threshold was determined noninvasively by the V-slope method [18]. Maximal voluntary ventilation was estimated using the FEV_1 multiplied by 40, from which the breathing reserve index at maximum exercise was calculated as 100 × (maximal voluntary ventilation − maximum ventilation at peak exercise) / maximal voluntary ventilation [19]. The minute ventilation versus the carbon dioxide output ratio at the anaerobic threshold was used to noninvasively assess ventilatory efficiency [20].

2.8. Statistical analyses

Data analyses was performed with STATA/IC 12.1 for Mac (StataCorp, Texas, United States of America) and descriptive data were stored in Microsoft Excel 2016 (Microsoft Corp., CA, USA). Continuous data were, if appropriate, reported as mean with standard deviation, and compared using paired or unpaired student's *t*-tests if normally distributed. The Mann Whitney-Wilcoxon rank-sum test was used for non-normal distributed data. Binominal data are presented as absolute numbers and percentages of participants, and compared applying the χ^2 test. We considered p-values <0.05 statistically significant, all p-values are two-sided.

2.8.1. Sample size justification

Our sample size justification was based on previously published data from our group [21] and the minimal sample size was determined to be 13 patients per group, based on a power of 80% and a significance level of 0.05 using the students *t*-test. We enrolled 30 participants per group to account for potential dropouts.

3. Results

3.1. Participant characteristics

Between October 2016 and June 2017, a total of 30 participants with small, unrepaired VSD's and 30 healthy controls were included at Aarhus University Hospital, Denmark, as seen in Fig. 2. All enrolled

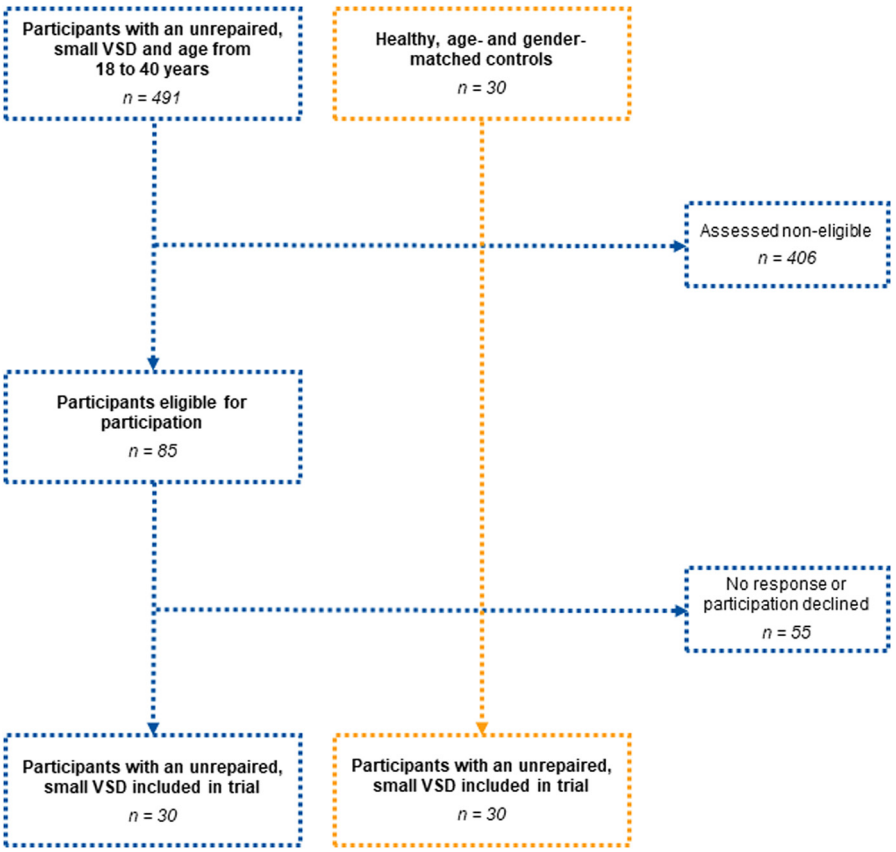

Fig. 2. Participant flowchart. VSD, ventricular septal defect.

Table 1
Demographics and clinical characteristics of patients with small, unrepaired ventricular septal defects and healthy controls.

	Patients (n = 30)	Controls (n = 30)	p-value
Age at examination, years	27 ± 6	27 ± 6	0.742
Sex distribution, ♂/♀	17/13	17/13	1.000
Time between visit 1 and 2, days	7 ± 3	7 ± 3	0.827
Weight, kg	75 ± 13	72 ± 12	0.326
Height, cm	174 ± 9	176 ± 9	0.503
Body mass index, kg per m^2	25 ± 4	23 ± 3	0.058
Fat free mass, %	74 ± 8	79 ± 7	0.019
Smokers, n		4	0.244
≤20 cigarettes per week	5	3	0.373
>20 cigarettes per week	1	1	0.627
Systolic blood pressure, mmHg	122 ± 13	119 ± 10	0.290
Diastolic blood pressure, mmHg	71 ± 9	71 ± 7	0.777
Heart rate, beats per minute	66 ± 13	64 ± 15	0.571
Ventricular septal defect type			
Muscular/perimembranous/inlet/outlet	8/20/1/1	–	NA

Data are reported as means with standard deviation, number of participants, or median with total ranges.

participants completed both study visits and no serious adverse events were observed. Demographics and clinical characteristics are displayed in Table 1. As shown, the groups were comparable in terms of age at examination, body composition, sex distribution, and smoking status. None of the VSD patients received prescribed anti-congestive or anti-arrhythmic medication. Two VSD patients and three controls received prescribed drugs: Antidepressants (n = 2), attention deficit hyperactivity disorder medication (n = 1), biological anti-rheumatic drug (n = 1), and disease-modifying anti-rheumatic drug (n = 1).

3.2. Pulmonary function tests

Extended pulmonary function tests at baseline are shown in Table 2. Patients displayed a tendency towards lower FEV_1, 104 ± 11% of pred., compared with healthy controls, 110 ± 14%, $p = 0.069$, and had a peak expiratory flow of 108 ± 20% of predicted, which was lower than 118 ± 17% among the controls, $p = 0.039$. We were unable to demonstrate a difference in resistance in the small airways or in diffusion capacity for carbon monoxide. At baseline, 10% of the VSD patients displayed pathologically increased airway resistance in the larger airways, in contrast to 0% of the controls ($p = 0.076$). Pulmonary function after intervention are presented in Table 3. As illustrated, the effect from salbutamol intervention on pulmonary function in VSD patients were equivalent to the response of the healthy control group.

Table 2
Extended pulmonary function tests at baseline in patients with small, unrepaired ventricular septal defects and healthy controls.

	Patients (n = 30)	Controls (n = 30)	p-value
Static pulmonary function			
TLC (%)	103 ± 11	105 ± 12	0.491
RV (%)	98 ± 18	93 ± 24	0.400
FRC (%)	127 ± 21	133 ± 18	0.190
sR_{aw} (%)	62 ± 23	60 ± 18	0.744
Dynamic pulmonary function			
FEV_1 (%)	104 ± 11	110 ± 14	0.069
FVC (%)	111 ± 11	116 ± 13	0.099
FEV_1/FVC-ratio	0.80 ± 0.07	0.81 ± 0.05	0.780
PEF (%)	108 ± 20	118 ± 17	0.039
Impulse oscillometry			
R5 (%)	112 ± 26	101 ± 22	0.079
R20 (%)	122 ± 28	109 ± 22	0.124
D5–20 (%)	16 ± 17	13 ± 13	0.558
Multiple breath washout			
LCI (%)	95 ± 6	96 ± 7	0.590
S_{cond} (%)	86 ± 50	64 ± 46	0.089
S_{acin} (%)	122 ± 118	96 ± 50	0.272
Diffusion capacity for carbon monoxide			
DLCO (%)	92 ± 13	91 ± 13	0.742
V_A (%)	95 ± 11	100 ± 10	0.085

Data are reported as mean percentage of predicted values ± standard deviation. D5–20, resistance in the small conducting airways; DLCO, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; LCI, lung clearance index; PEF, peak expiratory flow, R5, resistance in the conducting airways; R20, resistance in the large conducting airways; RV, residual volume; S_{acin}, function of respiratory airways; S_{cond}, function of conducting airways; sR_{aw}, specific resistance of the airways; TLC, total lung capacity; V_A, alveolar volume.

Table 3
Pulmonary function tests after intervention in patients with small, unrepaired ventricular septal defects and healthy controls.

	Patients (n = 30)		Controls (n = 30)		
	Placebo	Salbutamol	Placebo	Salbutamol	p-value[a]
Dynamic pulmonary function					
FEV_1 (%)	104 ± 11	110 ± 11*	109 ± 13	116 ± 14*	0.448
FVC (%)	110 ± 11	111 ± 11	115 ± 12	117 ± 12*	0.696
FEV_1/FVC-ratio	0.82 ± 0.07	0.84 ± 0.07*	0.80 ± 0.05	0.84 ± 0.06*	0.433
PEF (%)	108 ± 22	115 ± 23*	118 ± 15	122 ± 15*	0.771
Impulse oscillometry					
R5 (%)	105 ± 20	88 ± 20*	98 ± 26	84 ± 20*	0.727
R20 (%)	114 ± 22	94 ± 17*	106 ± 24	90 ± 18*	0.877
D5–20 (%)	12 ± 14	15 ± 17	12 ± 13	13 ± 12	0.049

Data are reported as mean percentage of predicted values ± standard deviation. 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.
* Significant difference between placebo and intervention with $p < 0.05$.
[a] Difference in effect from intervention between patients and controls.

3.3. Exercise outcomes

All exercise tests were considered valid according to above mentioned criteria with no premature test terminations. VSD patients reached a mean RER at peak exercise of 1.26 ± 0.1 and the group of healthy controls reached 1.22 ± 0.1. Baseline exercise outcomes are outlined in Table 4. VSD patients displayed lower oxygen uptake, $p < 0.001$, workload, $p < 0.001$, minute ventilation, $p < 0.001$, and breath rate, $p = 0.008$, at peak exercise compared with healthy controls. At ventilatory anaerobic threshold, oxygen uptake, $p < 0.001$, and workload, $p < 0.001$, were inferior in the patient group compared with the control group. We observed no difference in breathing reserve index between groups. Oxygen uptake, $p < 0.001$, and carbon dioxide excretion, $p < 0.001$, were lower among patients during the entire test compared with controls, as illustrated in Fig. 3A and Fig. 3B, respectively. Furthermore, as displayed in Fig. 3C and Fig. 3D, breath rate, $p < 0.001$, and minute ventilation, $p < 0.001$, were lower in the patient group compared with the control group. The relationship between peak oxygen uptake (ml/kg/min) and workload (watts/kg), peak oxygen uptake (ml/kg/min) and fat free mass (% of total body weight) and peak minute ventilation (l/min/kg) and fat free mass (% of total body weight) is illustrated in Fig. 5 in the supplementary material.

Exercise outcomes after intervention are presented in Appendix 1, in the supplementary material. Salbutamol neither affected the peak oxygen uptake nor peak ventilation in the patient group. The difference in breath rate during exercise under placebo condition was abolished with salbutamol intervention; nevertheless, the lower minute ventilation in patients persisted. The effect from intervention on exercise parameters did not differ between groups. Oxygen uptake, carbon dioxide production, breath rate and minute ventilation as percentage of maximal workload in patients under salbutamol condition are outlined in Fig. 4, in the supplementary material. Ventilatory anaerobic threshold parameters were unaffected by salbutamol intervention in the patient group, whereas workload and oxygen uptake dropped in the control group. The response to salbutamol on oxygen uptake at

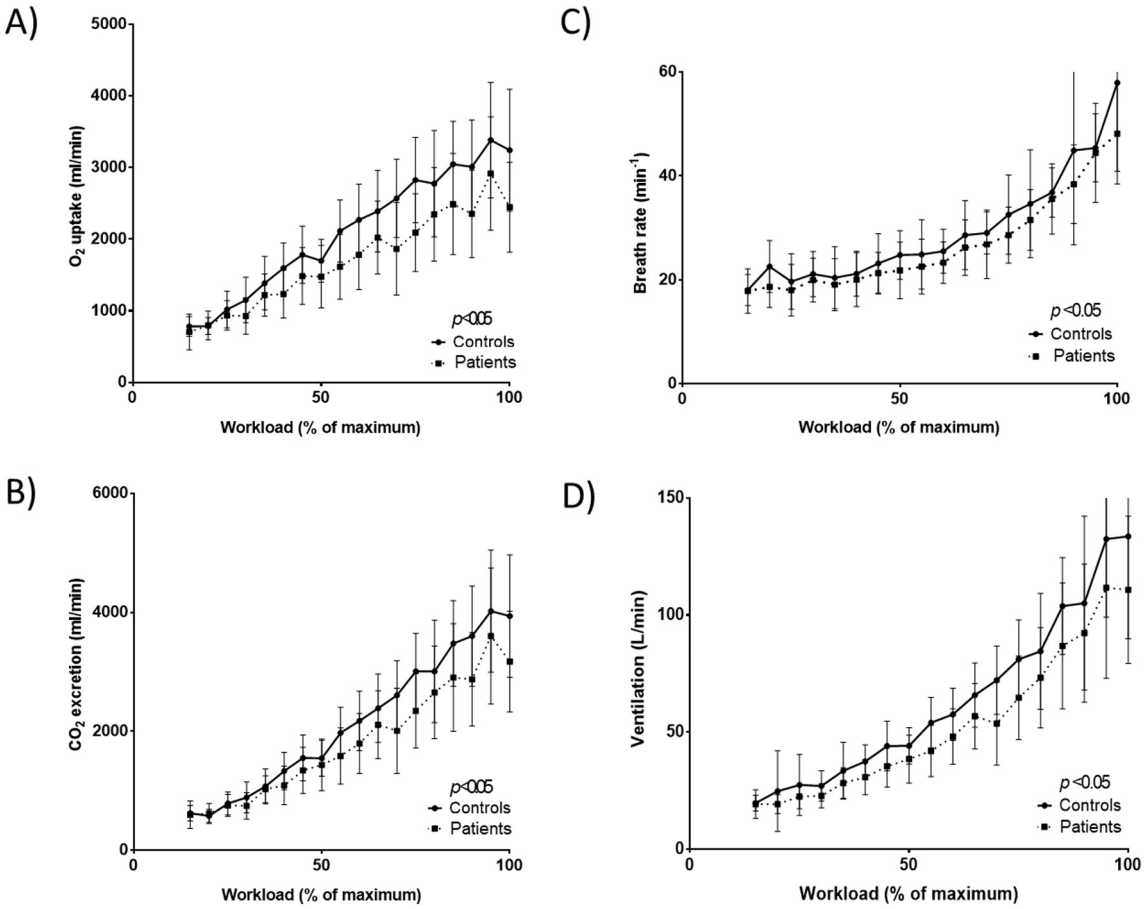

Fig. 3. Exercise outcome curves in patients with small, unrepaired ventricular septal defects and healthy controls. A. Oxygen uptake in relation to workload during bicycle ergometry. B. Carbon dioxide excretion in relation to workload during bicycle ergometry. C. Breath rate in relation to workload during bicycle ergometry. D. Minute ventilation in relation to workload during bicycle ergometry.

anaerobic threshold tended to be different between groups. Patients slightly increased their oxygen uptake while the controls decreased, outlined in Appendix 1. We were unable to demonstrate a relation between the degree of pulmonary dysfunction to the degree of exercise dysfunction.

Table 4
Peak exercise data at baseline in patients with small, unrepaired ventricular septal defects and healthy controls.

	Patients (n = 30)	Controls (n = 30)	p-value
Maximal workload, watt per kg	3.0 ± 0.8	4.1 ± 0.6	<0.001
Peak oxygen uptake, milliliters per kg per minute	35 ± 8	47 ± 7	<0.001
Peak heart rate, beats per minute	183 ± 14	184 ± 11	0.618
Peak systolic blood pressure, mmHg	198 ± 43	200 ± 33	0.962
Peak diastolic blood pressure, mmHg	87 ± 19	98 ± 22	0.473
Peak breath rate, breaths per minute	48 ± 11	55 ± 8	0.008
Peak ventilation, liters per minute per kg	1.5 ± 0.5	2.1 ± 0.3	<0.001
Respiratory exchange ratio at peak exercise	1.26 ± 0.1	1.22 ± 0.1	0.050
Ventilatory anaerobic threshold			
Workload, watt per kg	1.9 ± 0.8	2.9 ± 0.6	<0.001
Oxygen uptake, milliliters per kg per minute	25 ± 8	35 ± 7	<0.001
Heart rate, beats per minute	149 ± 26	161 ± 14	0.033
Oxygen pulse, milliliters per minute per heart beat	14.4 ± 3.8	18.3 ± 4.3	<0.001
Breathing reserve (%)	31 ± 17	15 ± 12	<0.001
Ventilatory efficiency, V_E/V_{CO_2}	32 ± 5	33 ± 4	0.795

Data are reported as mean ± standard deviation. V_{CO_2}, carbon dioxide output, V_E, ventilation.

4. Discussion

This double-blinded, randomised, controlled, cross-over study of young adult patients with small unrepaired VSDs generated several important findings. First, unrepaired VSD patients experience lower breath rate and minute ventilation during exercise and a tendency towards lower pulmonary function at rest compared with healthy controls. Second, adults with unrepaired VSD's had a 25% reduction in ventilation at peak exercise compared with healthy controls. Third, peak oxygen uptake among unrepaired VSD patients is reduced compared with their healthy peers. The latter findings confirm our previous results in another cohort of VSD patients and healthy controls [5]. Finally, these abnormalities are not reversible with inhaled salbutamol.

Early observational studies suggested that cardiopulmonary capacity in adults with small, unrepaired VSD's is comparable to that of healthy individuals [22–24]. However, the studies lacked a reference group of healthy controls, and had a relatively short follow-up time and more recent papers report adverse late cardiovascular performance among these patients [1–3,25] supporting the notion that these defects may not be as benign as previously thought. Our prior results [5] showing lower exercise capacity in these patients may be important, as cardiorespiratory fitness is a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women [26]. However, in the previous cardiopulmonary exercise study, we did not assess potential mechanisms, or reversibility, of any cardiopulmonary compromise that may underpin these abnormalities.

The present data are clear in this regard. Resting and dynamic pulmonary abnormalities are common in patients with an unoperated VSD that is considered hemodynamically unimportant, the pulmonary

abnormalities are unrelated to the amount of exercise dysfunction, and they are not reversed by salbutamol. While these data provide possible insights into the compromised maximal exercise performance, the mechanism for the pulmonary and airway disease is not clear. Nonetheless, our novel findings of impaired ventilation during exercise are in line with the suggestion in a systematic review of pulmonary abnormalities in older patients with left to right shunts [12]. Importantly, however, it is clear that the reduction in peak exercise capacity cannot be explained by the observed alterations in pulmonary function alone, as VSD patients revealed an oxygen pulse inferior to that of their peers with no difference in peak heart rate. Hence, the pathophysiology behind the lower oxygen uptake in VSD patients is probably not uniform, but consists of both a respiratory and a cardiac component. For instance, pulmonary hyperperfusion may also play a significant role in the pathophysiology as previously suggested [5]. The tendencies towards lower dynamic pulmonary function and increased airway resistance, and the significant impaired minute ventilation when the cardiorespiratory system is stressed may be early signs of parenchymal dysfunction and restrictive airway disease. The lack of reversibility with salbutamol suggests that the latter is not 'reactive', however.

Anatomically, the pulmonary arterioles and the bronchi, and further distally the alveoli and the capillaries, lie in close proximity to each other. Thus, it is conceivable that morphological changes in the pulmonary vascular bed also affect the respiratory system. Prolonged exposure to high pulmonary blood flow may have a harmful impact on the viscoelastic properties of the pulmonary vasculature seen as smooth muscle hypertrophy [6,7], increased respiratory system resistance [6], and reduced lung compliance in infants with large left-to-right shunts [8]. There is emerging evidence that these abnormalities persist into adult life, despite early closure of large VSD's. We recently demonstrated impaired pulmonary function at rest in adults who underwent surgical closure of VSD more than two decades earlier [4]. Whether this mechanism is responsible for some or all of our findings in adults with persistent small left-to-right shunts will require a much larger group of patients, relating QpQs (potentially measured by MRI) to pulmonary dysfunction, as exercise dysfunction can be negatively correlated to the size of the shunt [27]. In that way, it might be possible to demonstrate subgroups that may benefit from VSD closure later in life, despite having apparently 'insignificant' defects. Our data cannot be used as justification for closure of small defects, as it is unknown whether the abnormalities we describe herein would be modified for the better or worse by open heart surgery.

4.1. Limitations

We identified 85 patients with an isolated VSD eligible for study participation of which 30 participated. The generalizability of the patients we have studied can be flawed by an overrepresentation of patients with below average functional capacity. However, it could also be the opposite, i.e. that our group is overrepresented by well-functioning patients who sign in to the project to have their functional capacity tested. Since the dropout does not have an association to the exposure, we believe the study population is representative of patients with a simple VSD deemed hemodynamically insignificant.

It is not uncommon that patients with a congenital heart defect do not want to go to their limits during an exercise test, however, we are certain all participants performed until maximum exhaustion as the group of VSD patients reached a mean RER at peak exercise of 1.26 ± 0.1 and the group of healthy controls 1.22 ± 0.1. We gently but nonetheless firmly reject that the difference between patients and controls can be explained by simple deconditioning by referring to the anaerobic threshold. The anaerobic threshold clearly illustrates the real difference in oxygen uptake between VSD patients and controls as it is independent of maximal effort. Echocardiography- or MRI-based shunt estimation would have been valuable, in order to estimate the extent of pulmonary hyperperfusion and furthermore, correlate shunt size with minute ventilation and pulmonary function. Finally, sample size calculation was based on surgically closed VSDs, whereas we examined a cohort of patients with small open VSDs. Even though we enrolled more than twice the number supposed to be needed, to help overcome a too small sample size, we are not in a position to rule out the possibility that the sample size was insufficient.

In conclusion, at rest, young adults with unrepaired VSDs are no different in pulmonary function from controls. However, when the cardiorespiratory system is stressed, VSD patients demonstrate significantly impaired minute ventilation and peak oxygen uptake, which may be early signs of parenchymal dysfunction and restrictive airway disease. These abnormalities may be caused by irreversible morphological changes as they were not reversed by inhaled salbutamol. However, the reduced peak oxygen uptake is not necessarily caused by reduced ventilatory function. Our findings are the latest in a growing number of studies revealing that the outcome for repaired and unrepaired VSD's is not completely benign, and that continuous follow-up for decades will be required before their full implications are understood.

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CRediT authorship contribution statement

Filip Eckerström: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Visualization, Project administration. **Christian Emil Rex:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - review & editing, Project administration. **Marie Maagaard:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision, Project administration. **Johan Heiberg:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing, Supervision, Project administration. **Sune Rubak:** Conceptualization, Methodology, Validation, Resources, Writing - review & editing, Supervision, Funding acquisition. **Andrew Redington:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Vibeke Elisabeth Hjortdal:** Conceptualization, Methodology, Validation, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Heart rate variability is impaired in adults after closure of ventricular septal defect in childhood: A novel finding associated with right bundle branch block

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ABSTRACT

Background: Ventricular septal defects (VSDs) generally have benign long-term prognoses, but recent studies have indicated increased pulmonary vascular resistance. A potential tool for monitoring pulmonary artery pressure is heart rate variability, and therefore, the aim of this study was to assess heart rate variability in adults with a surgically repaired or unrepaired VSD.

Methods: In a long-term, follow-up study, three groups were included; VSD-patients operated in early childhood, patients with an open VSD, and controls. For each patient, 24-hour Holter monitoring was performed and heart rate variability was assessed.

Results: In total, 30 participants with a surgically closed VSD, 30 participants with an unrepaired VSD, and 36 controls were included. In the closed VSD group, there was a higher proportion of participants, who had low sNN50 ($p = 0.005$) and low sNN6% ($p = 0.017$) than in the other two groups. Similar differences were found when sNN50 was divided into increases and decreases ($p = 0.007$ and $p = 0.005$, respectively) as well as sNN6% ($p = 0.014$ and $p = 0.014$, respectively). Lastly, there was a higher proportion of patients in the closed VSD group with low rMSSD than in the other two groups ($p = 0.005$). For the closed VSD group, the proportion of participants with low total sNN50 ($p = 0.046$) and low total sNN6% ($p = 0.046$) were higher among participants with a complete right bundle branch block (RBBB) than among participants with no or an incomplete RBBB.

Conclusions: Adults who had surgical VSD closure in early childhood had impaired heart rate variability and, particularly, participants with complete RBBB had lower heart rate variability.

1. Introduction

Ventricular septal defect (VSD) is the most common congenital heart defect [1], and while around a third close spontaneously in the first years of life, the rest either undergo surgical closure or are considered hemodynamically insignificant. For both of the latter two groups, the long-term implications have traditionally been considered to be benign [2–6]. However, there is emerging evidence of late morbidity in adults with a surgically closed VSD [7–11] and also in patients with small, open defects [12–15].

In particular, studies on adults operated for VSD have indicated ncreased pulmonary vascular resistance, especially during exercise [9, 10, 16, 17]. Right ventricular thickening and an abnormal right ventricular strain pattern have also been demonstrated [9], which themselves may be adaptive to increased pulmonary hemodynamics. Most recently, our own study group has shown an abnormal right ventricular force-frequency relationship, which was directly correlated to exercise capacity [10].

It has long been known that severe left ventricular dysfunction is associated with abnormal heart rate variability (HRV) and that the degree of impaired HRV carries prognostic implications [18]. However, even relatively minor abnormalities of right ventricular function have been

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associated with abnormalities of HRV [19, 20]. For example, Tadic et al. demonstrated that minimal right ventricular remodeling was associated with impaired HRV in patients with systemic hypertension [19]. The same group showed that abnormal right ventricular strain was associated with abnormal HRV in diabetic patients [20]. There is also evidence of abnormal HRV in patients with congenital heart disease. For example, patients with atrial and ventricular septal defects have decreased HRV prior to surgical closure [21, 22], which is thought to be due to pressure and volume overload of the right ventricle altering the homeostasis of the pulmonary and systemic circulation. Whatever the mechanism, HRV has been shown to improve after transcatheter or surgical closure of atrial septal defects, for example [23].

Little is known regarding HRV in the long-term follow-up of patients with VSD, however. We hypothesized that adults, who had undergone surgical VSD-repair in early childhood and adults with small, open VSDs have abnormal HRV as a consequence of the recently demonstrated abnormalities of RV function. Therefore, the aim of this prospective cohort study was to assess HRV in adults with either a surgically repaired or a small, open VSD.

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

2.1. Design

In a long-term, follow-up study, participants were included at Aarhus University Hospital, Denmark. This report presents a substudy of a double-blinded, cross-over trial in which participants inhaled 900 μg of salbutamol (Ventoline®) or placebo (Evohaler®) in a randomized order at two separate visits with 2 to 14-days interval. In the original study, the aim was to assess ventilatory function in VSD-patients, including the potential effects of inhaled salbutamol. As a substudy, participants were equipped with a Holter monitor, and hence, this report only includes placebo data none of which have been presented elsewhere.

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, 2) patients from 18 to 40 years of age with a small, unrepaired VSD followed at our local or a regional outpatient clinic with echocardiographic follow-ups, 3) a healthy control group consisting of age- and gender-matched controls enrolled through flyers and announcements on government, official webpages. Exclusion criteria were coexistence of other congenital cardiac defects than VSD, associated syndromes, e.g. Down's syndrome, documented arrhythmia, cardiac or pulmonary disease including any valve pathology, and missing patient chart. Details of the surgical procedures are previously described [7].

2.3. Holter monitoring

At each visit, the participant was equipped with a 2-channel Holter monitor (Lifecard CF Digital Holter Recorder, Spacelabs Healthcare, WA, US), which was worn for 48-hours after the first visit and 24 h after the second visit. The recordings were analyzed using Pathfinder SL software (Spacelabs Healthcare, WA, US) and all measurements were expressed as 24-hour values.

The Holter recordings were analyzed for presence of arrhythmic events including premature ventricular contractions, supraventricular and ventricular tachyarrhythmia (defined as ≥1 runs of ≥3 beats), sinus arrest (defined as pauses of ≥2 s), and atrioventricular block (defined as PQ intervals of ≥0.22 s). Right bundle branch block (RBBB) was subdivided into *complete RBBB* defined as RSr' or RSR' configuration in leads V_1 or V_2 and a QRS duration ≥120 ms in leads I, II, III, aVL, and aVF and *incomplete RBBB* (QRS duration <120 ms) [24].

HRV analyses were performed for the first 24 h after each visit and included the following parameters: **1**) number of pairs of adjacent NN intervals differing by >50 ms per 24 h, standardized for invalid intervals (sNN50); **2**) number of pairs of adjacent NN intervals differing by >6% per 24 h, standardized for invalid intervals (sNN6%); **3**) standard deviation of all normal sinus intervals (SDNN); **4**) standard deviation of all normal sinus intervals for all 5 min segments (SDNNi); **5**) standard deviation of the averaged normal sinus intervals for all 5 min segments (SDANN); **6**) root mean square of the successive normal sinus interval difference (rMSSD); **7**) integral of the density distribution divided by the maximum of the density distribution i.e. total number of NN intervals divided by number of NN intervals in the modal bin (triangular index).

2.4. Endpoints

Our primary endpoint was low sNN50 defined as the proportion of participants with a sNN50 lower than a predefined threshold (mean value in the control group − 1 standard deviation). Secondary endpoints were similarly defined as the proportions of participants with low sNN6%, low SDNN, low SDNNi, low SDANN, low rMSSD, and low triangular index.

2.5. Statistical analyses

Continuous data are presented as means ± standard deviations or median with 95% confidence intervals (CI), as appropriate, and binary data are presented as absolute numbers and percentages of participants. Differences between groups were assessed using one-way analyses of variance (ANOVA) or Students *t*-tests, as appropriate, for continuous data and chi-squared tests for binary data. *p*-Values < 0.05 were considered statistically significant, 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).

2.5.1. Sample size justification

The sample size was determined by the number of participants included in the original study, wherefore no formal sample size calculation was performed for this substudy.

3. Results

In the period from November 2016 to June 2017, 96 participants were enrolled of which 30 participants had a surgically closed VSD, 30 participants had an unrepaired VSD and 36 participants were healthy controls as detailed in Fig. 1. In the operated group, the median age at surgery was 1.4 years (95% CI 0.9–2.4 years). All participants completed both study visits and no serious adverse events were observed. In the closed VSD group, 9 participants had complete RBBB and 21 participants had either no or incomplete RBBB, whereas there were no participants in either the open VSD group or in the control group with complete RBBB. Basic characteristics for all the enrolled participants are shown in Table 1, there was no significant difference between the groups.

Heart rate variations and arrhythmic events over 24 h are displayed in Table 2.There was a higher proportion of participants in the closed VSD group with a high number of premature ventricular contractions than in the two other groups ($p < 0.001$), but there were no differences between the three groups in terms of heart rate variations or proportions of participants with supraventricular tachycardia ($p = 0.128$), ventricular tachycardia ($p = 0.708$), sinus pause ($p = 0.553$), or atrioventricular block ($p = 0.174$).

HRV for the three groups is shown in Table 3. There was a higher proportion of patients in the closed VSD group with low total sNN50 ($p = 0.005$) and low total sNN6% ($p = 0.017$) than in the other two groups. A similar pattern was observed when sNN50 was divided into increases and decreases ($p = 0.007$ and $p = 0.005$, respectively) as well as sNN6% ($p = 0.014$ and $p = 0.014$, respectively). We also found a higher proportion of patients in the closed VSD group with low rMSSD than in the other two groups ($p = 0.005$), but there were no differences between the groups in terms of SDNN ($p = 0.400$), SDNNi ($p = 0.059$), SDANN ($p = 0.602$), or triangular index ($p = 0.400$).

For the closed VSD group, HRV was then analyzed according to the presence of a complete RBBB (Supplementary Table 1). The proportion of participants with low total sNN50 ($p = 0.046$) and low total sNN6% ($p = 0.046$) was higher among patients with complete RBBB compared to those with no or incomplete RBBB. There were no differences between these two subgroups in terms of rMSSD, SDNN, SDNNi, SDANN, or triangular index.

Participants with a closed VSD without complete RBBB were then compared with the control group (Supplementary Table 2). A higher proportion of participants with a closed VSD without complete RBBB had low sNN50 (decreases) compared with the control group, but otherwise there were no differences in HRV between these two groups. As seen, 38% and 17%, respectively, had low total sNN50 ($p = 0.070$), and 38% and 19%, respectively, had low total sNN6% ($p = 0.198$).

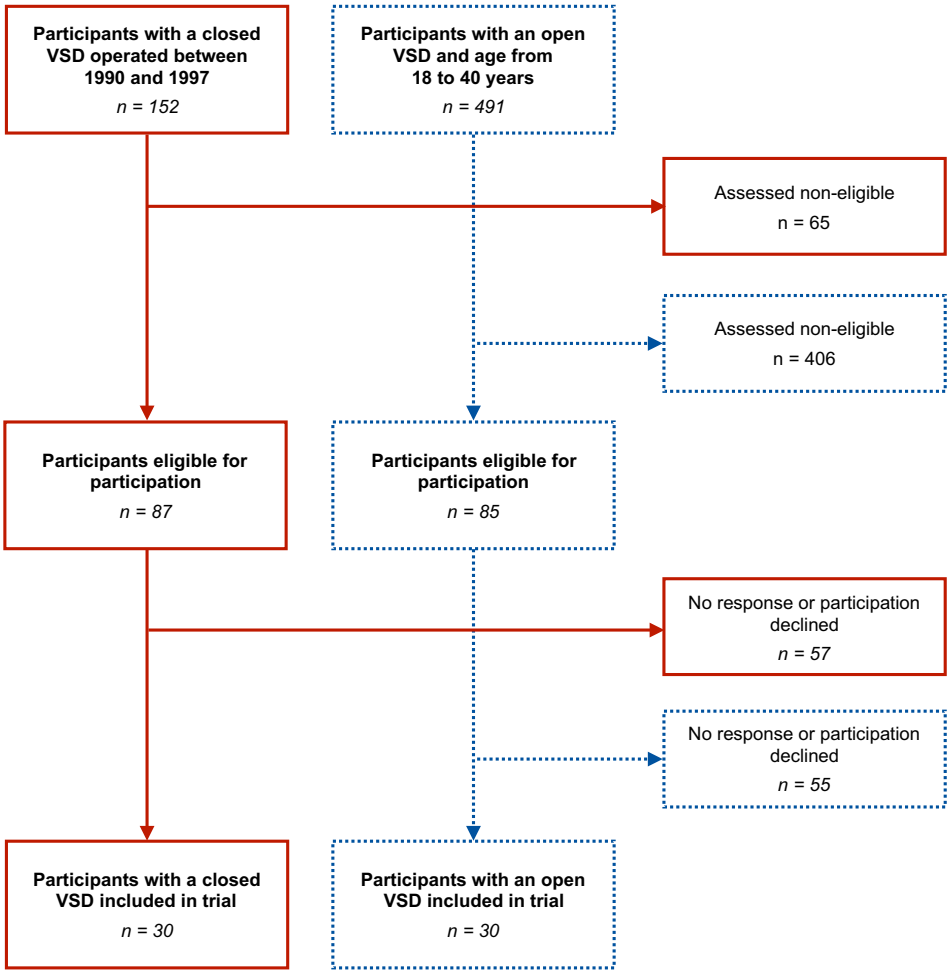

Fig. 1. Patient flow chart Flow of VSD participants through the study period. VSD, ventricular septal defect.

4. Discussion

In this long-term follow-up study, adults who had surgical VSD closure in early childhood have a significantly impaired HRV compared with adults with small, hemodynamically insignificant VSDs and healthy controls. It was also clear that HRV impairment is more pronounced in patients with complete RBBB compared to those with no or incomplete RBBB, although HRV in the latter group was still impaired compared to unoperated patients and healthy controls. These novel findings add to the increasing number of reports suggesting that surgical repair of VSD, even when performed decades earlier, is associated with measurable abnormalities of cardiopulmonary performance and challenge the notion that the long-term outcome of such surgery is benign. Indeed, given that anticipated survival of these patients may span many decades, it is perhaps premature to suggest that they do not require specialist follow-up [25–27].

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

	Closed VSDs n = 30	Open VSDs n = 30	Controls n = 36
Demographics			
Age, years	24 ± 2	27 ± 6	26 ± 5
Male sex, n (%)	17 (57)	17 (57)	18 (50)
Weight, kg	71 ± 12	75 ± 13	71 ± 11
Height, cm	174 ± 10	174 ± 9	175 ± 8
Body mass index, kg/m^2	24 ± 3	25 ± 3	23 ± 3
Fat free mass, kg	54 ± 11	56 ± 12	56 ± 10
Smoking status			
Non-smokers, n (%)	23 (77)	24 (80)	32 (89)
1–7 cigarettes/week, n (%)	3 (10)	2 (7)	2 (6)
8–20 cigarettes/week, n (%)	1 (3)	3 (10)	1 (3)
>21 cigarettes/week, n (%)	3 (10)	1 (3)	1 (3)

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

While this proof-of-principle study was not designed to explore mechanisms, our data suggest possible areas for future investigation. As discussed above, we showed that postoperative RBBB has a negative, independent effect on HRV. Our group has previously shown that postoperative RBBB is associated with a blunted heart rate response to exercise [28], and in a recently conducted review, chronotropic incompetence was found to be more common in operated patients with postoperative RBBB than in those without [29]. While it is possible that there is a causal relationship between RBBB and these outcomes, it is perhaps more likely that RBBB is a surrogate for other pathophysiologic processes e.g. greater RV damage, worse RV function, and abnormal HRV is, in turn, a reflection of underlying dysfunction rather than a consequence of disturbed conduction. Indeed, there is increasing evidence that even subtle degrees of RV dysfunction, in the absence of conduction disturbance, is associated with abnormal HRV [19, 20]. Going along with this hypothesis, we also showed impaired HRV in patients with no or incomplete RBBB. While clearly, we cannot address the mechanisms underlying this suggestion, it is noteworthy that impaired

Table 2
Heart rate variations and events over 24 h for participants with surgically closed VSDs, open VSDs and healthy controls.

	Closed VSDs n = 30	Open VSDs n = 30	Controls n = 36	P-value
Heart rate variations				
Minimum heart rate, beats/min	49 ± 8	51 ± 7	50 ± 9	0.879
Mean heart rate, beats/min	72 ± 8	75 ± 10	73 ± 9	0.555
Maximum heart rate, beats/min	140 ± 23	141 ± 25	150 ± 26	0.212
Events				
High number of PVCs, n (%)	9 (30)	2 (7)	0 (0)	<0.001*
Supraventricular tachyarrhythmia, n (%)	6 (20)	1 (3)	4 (11)	0.128
Ventricular tachyarrhythmia, n (%)	2 (7)	2 (7)	1 (3)	0.708
Sinus pause, n (%)	3 (10)	1 (3)	2 (6)	0.553
Atrioventricular block, n (%)	3 (10)	2 (7)	0 (0)	0.174

Data reported as means ± standard deviations or absolute numbers and percentages of patients.
High number of PVCs was defined as >200 over 24 h. Supraventricular and ventricular tachyarrhythmia were defined as ≥1 runs of ≥3 beats, sinus pause was defined as pauses of ≥2 s, and atrioventricular block was defined as PQ intervals of ≥0.22 s.
VSD, ventricular septal defect; PVC, premature ventricular contractions.
* Marks a statistically significant difference.

HRV, characteristic of congestive heart failure, is associated with modulation of vagal tone [30] and abnormalities of adrenoreceptor responses to endogenous stimulation [31]. We cannot exclude a more direct effect of surgery however. A number of studies, have shown that surgical VSD closure is associated with persisting chronotropic impairment [32–34] and this, in turn, has been ascribed to autonomic denervation in the proximity of the aorta [35, 36].

No matter what the cause, impaired HRV can now be added to the list of subtle, but potentially important, abnormalities that are seen in the late follow-up of patients who have undergone repair of VSD in early childhood. While the functional implications of these abnormalities are minimal at present (the vast majority of patients are entirely asymptomatic] it is unclear what impact these modest hemodynamic burdens may have both cumulatively and when present over the lifetime of our patients. Current recommendations suggest that these patients do not require specialist follow-up [25–27]. However, we would suggest that, on the basis of current evidence, these patients do warrant continued (albeit intermittent) follow-up in adult congenital heart clinics, not only for clinical surveillance, but also to facilitate ongoing studies of the mechanisms of their potentially modifiable pathophysiology.

Table 3
Heart rate variability over 24 h for participants with surgically closed VSDs, open VSDs and healthy controls.

	Closed VSDs n = 30	Open VSDs n = 30	Controls n = 36	P-value
Mean RR, ms	816 ± 93	803 ± 100	805 ± 85	0.857
Low sNN50 (total), n (%)	15 (50)	6 (20)	6 (17)	0.005*
Low sNN50 (increases), n (%)	14 (46)	6 (20)	5 (14)	0.007*
Low sNN50 (decreases), n (%)	15 (50)	8 (27)	5 (14)	0.005*
Low sNN6% (total), n (%)	15 (50)	6 (20)	8 (22)	0.017*
Low sNN6% (increases), n (%)	14 (47)	5 (17)	7 (19)	0.014*
Low sNN6% (decreases), n (%)	14 (47)	6 (20)	6 (17)	0.014*
Low SDNN, n (%)	6 (20)	7 (23)	4 (11)	0.400
Low SDNNi, n (%)	11 (37)	5 (17)	5 (14)	0.059
Low SDANN, n (%)	6 (20)	5 (17)	4 (11)	0.602
Low rMSSD, n (%)	13 (43)	5 (17)	4 (11)	0.005*
Low triangular index, n (%)	7 (23)	6 (20)	4 (11)	0.400

Data reported as means ± standard deviations or absolute numbers and percentages of participants with heart rate variability lower than a predefined threshold (mean value in the control group − 1 standard deviation).
VSD, ventricular septal defect; sNN50, number of pairs of adjacent NN intervals differing by >50 ms per 24 h, standardized for invalid intervals; sNN6%, number of pairs of adjacent NN intervals differing by >6% per 24 h, standardized for invalid intervals; SDNN, standard deviation of all normal sinus intervals; SDNNi, standard deviation of all normal sinus intervals for all 5 min segments; SDANN, standard deviation of the averaged normal sinus intervals for all 5 min segments; rMSSD, root mean square of the successive normal sinus interval difference; triangular index, integral of the density distribution divided by the maximum of the density distribution i.e. total number of NN intervals divided by number of NN intervals in the modal bin.
* Marks a statistically significant difference.

4.1. Limitations

The median surgical age is higher then would be expected in contemporary cohorts, but nevertheless reflective of practice 25 years ago and relevant to the large number of patients operated in that era. No sample size calculation was performed for this substudy, hence, there is a risk of reporting statistically significant but clinically irrelevant results. However, we found a prevalence of low HRV that was more than twice as high in the operated group than in the two other groups. Similarly, due to the missing sample size calculation there is a risk of type 2 errors, therefore, we urge caution in statistical interpretation, particularly of the subdivision of VSD operated patients.

In conclusion, adults who had surgical VSD closure in early childhood have a significantly impaired HRV compared with adults with small, hemodynamically insignificant VSDs and healthy controls. Long-term surveillance for possible clinically relevant sequalae, and future studies of underlying mechanisms, with higher patient numbers and longer period of follow-up, appears to be warranted.

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Conflict of interest

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

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