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Abnormal ventilatory response to exercise in young adults operated for ventricular septal defect in early childhood: A long-term follow-up☆

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ABSTRACT

Background: Ventricular septal defects (VSDs) are normally closed in early childhood, and postsurgical physical capacity is generally considered normal. Despite an increasing understanding of late cardiac morbidity among these patients, long-term pulmonary function remains to be investigated. Therefore, the aim of this prospective follow-up study was to describe ventilatory function during exercise in VSD-repaired adults operated in early life.
Methods: We tested cardiopulmonary exercise capacity in 27 patients and 30 healthy control subjects on an ergometer cycle. Each test was preceded by a standard spirometry, and the exercise test was performed as a maximal incremental test. Pulmonary ventilation and gas exchange were simultaneously measured breath-by-breath with minute ventilation at peak exercise as our main endpoint.
Results: In the VSD-group the median surgical age was 1.9 (95% CI 1.1–2.8 years) and the mean age at time of examination was 21.1 ± 3.1 years in the VSD-group vs. 21.2 ± 2.5 years in the control group. Mean minute ventilation at peak exercise was significantly lower in the VSD-group compared with the controls: 1.4 ± 0.4 L/kg/min vs. 1.8 ± 0.4 L/kg/min, $p < 0.01$. Likewise, mean oxygen uptake was reduced: 38.0 ± 8.2 ml/kg/min in the VSD-cohort vs. 47.9 ± 6.5 ml/kg/min among controls, $p < 0.01$. In terms of breath rate and ventilatory equivalents (O_2 and CO_2) there were no differences between the groups.
Conclusions: Patients with a surgically closed VSD have a markedly abnormal ventilatory response to exercise with significantly reduced minute ventilation despite a similar breath rate. With a follow-up of almost two decades our finding most certainly reflects an unknown but persisting abnormality.

1. Introduction

Surgical closure of the most common congenital heart anomaly, ventricular septal defect (VSD) [1], is a procedure with low rates of mortality and post-operative morbidity [2]. Post-surgically the outcome for this patient group has therefore widely been considered as benign [3,4], but the understanding of late morbidity is rapidly evolving with late cardiovascular disease as the main focus [5–7].

In addition, there is a growing interest in late pulmonary abnormalities in these patients with 'simple' congenital heart disease, and several studies have demonstrated residual pulmonary dysfunction after surgical closure of an atrial septal defect (ASD) [8–10]. The most frequent findings are lung volume restriction [8,10], airway obstruction [8,10], and changes in lung elasticity [8,9], but a number of questions remain unanswered. Firstly, there have been no studies conducted on VSD-patients, who differ from ASD-patients in terms of preoperative pathophysiology and mainly age at surgery. Secondly, no studies have evaluated pulmonary function more than a few years after surgery, wherefore one may speculate that these impairments normalize over time. Lastly, data on ventilatory mechanics in response to exercise are highly warranted in order to further describe the clinical significance of these findings.

Therefore, the aim of this prospective, controlled, long-term follow-up was to establish whether there are demonstrable alterations in ventilatory function during exercise in adults operated in infancy or early childhood for VSD.

2. Methods

This Danish Data Protection Agency (chart: 2010-41-5600) and The Regional Committee on Biomedical Research Ethics of the Central Denmark Region (chart: 20110078) approved the study, which conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study is listed on clinicaltrials.gov (identifier: NCT01480908) and according to Danish law, written informed consent was obtained for each study participant or his/her guardian.

☆ 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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2.1. Design

From 1990 to 1995, a total of 182 consecutive patients underwent surgical closure of a congenital VSD at Aarhus University Hospital: a cohort treated by the same team of doctors. Surgical procedures were performed on cardiopulmonary bypass with a cross-clamp on the aorta, cold crystalloid cardioplegia, and moderate hypothermia of 25–32 °C. The defects were closed by either direct suture or insertion of a dacron or pericardial patch.

After a thorough review of all charts, 117 patients were excluded from participation. Criteria for exclusion were coexistence of other congenital heart defects (n = 89), associated syndromes, e.g. Down's (n = 14), operation through a ventricular approach (n = 7), missing chart (n = 6), and documented arrhythmia requiring pacemaker (n = 1). The remaining 65 patients were invited to participate, and in the period from November 2011 to November 2012, 30 patients and 30 healthy controls were enrolled. Controls were matched by age and gender, and were randomly recruited with flyers in our local area. All participants, patients as well as controls, also underwent cardiac magnetic resonance imaging (CMR) and echocardiography as described elsewhere [5,6]. Peak exercise data are previously described [7].

2.2. Measurements

Data collection protocol is previously described in detail [7]. In brief, all tests were preceded by calibration of the gas-analysing system with defined gas mixtures, determination of body mass and height under standardized conditions, and assessment of exercise habits by a validated questionnaire (IPAQ, International Physical Activity Questionnaire). Prior to the cardiopulmonary exercise test, Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV_1), and Peak Expiratory Flow (PEF) were measured by a standard spirometry. An individual and gradually incremented workload protocol was chosen based on the subject's body mass, gender and exercise habits. Each participant was thoroughly instructed to maintain a cycling speed of 60 to 70 rounds/min, not to talk or stand up in the pedals during testing, and to keep pedalling until complete exhaustion.

During the test gas exchange parameters were simultaneously measured breath-by-breath, averaged for 15-second intervals, and expressed as minute values. The participant was strongly encouraged throughout the entire test to ensure complete exhaustion, and the test was only considered valid if either oxygen uptake (VO_2) or heart rate was levelling off (plateau). Data were collected using Jaeger MasterScreen® CPX (CareFusion, San Diego, CA, USA) and a Lode Corival® ergometer cycle (Lode Corival Ergometer, Groningen, The Netherlands).

2.3. Statistical analysis

For statistical analyses and graphical description we used Stata/IC 12.1 for Mac (StataCorp, TX, USA) and Graph Pad Prism 6 (GraphPad Software, La Jolla, CA, USA). Continuous, normally distributed variables are reported as mean ± standard deviation (SD), and compared using unpaired Student's *t*-tests with either equal or unequal variance if assumptions were met; otherwise with Mann–Whitney–Wilcoxon rank sum test. A significance level of 0.05 was applied. Correlations were checked applying simple linear regression analyses, and by unpaired Student's *t*-tests on subgroups.

3. Results

All the tests were completed according to the predefined criteria; 24 participants levelled off on oxygen uptake and 36 participants levelled off on heart rate. However, post hoc three patients were secondarily excluded from different reasons: 1) Pregnancy in the first trimester, 2) Henoch–Schönlein purpura requiring daily anti-inflammatory treatment, and 3) discovery of an atrial tumour on the day of examination. Therefore, 27 patients and 30 healthy controls were enrolled in the study.

3.1. Perioperative data

The median age at VSD repair was 1.9 (95% CI 1.1–2.8 years) in the operated group (N = 27). A subgroup of 5 patients had previously undergone pulmonary artery banding by a left-sided thoracotomy. These bandings were removed at the time of VSD closure. None of the patients suffered from preoperative pulmonary hypertension evaluated by echocardiography or right-sided catheterization.

3.2. Follow-up data

Demographics and clinical characteristics at the time of follow-up are displayed in Table 1. There were no differences between the groups in terms of age, height, weight, gender distribution, or basic hemodynamic parameters prior to exercise. As previously described [7], we demonstrated no difference in terms of high intensity exercise habits between the two groups. However, the operated patients were more physically active in terms of low and moderate intensity exercises.

3.2.1. Spirometry test

Standard spirometry data prior to exercise has previously been published [7]. In brief, the absolute values, but not the standard ones, were significantly different between the groups. FEV_1 was 3.8 ± 1.0 L in the operated group vs. 4.5 ± 0.8 L in the control group, $p = 0.01$ (98 ± 15% of predicted vs. 104 ± 16% of predicted, $p = 0.21$). PEF was 6.3 ± 2.2 ml/s among the operated patients vs. 8.1 ± 1.8 ml/s among the controls, $p < 0.01$ (76 ± 21% of predicted vs. 86 ± 15% of predicted, $p = 0.07$). For the remaining spirometric parameters no differences were demonstrated. FVC was 5.3 ± 1.4 L among the patients vs. 5.9 ± 1.3 L among controls, $p = 0.07$ (115 ± 19% of predicted vs. 115 ± 22% of predicted $p = 0.98$). Likewise, there was no difference in FEV_1/FVC, 73 ± 10% in the operated group vs. 76 ± 8%, $p = 0.22$.

3.2.2. Exercise test

In the operated group peak exercise heart rate was 182 ± 8.8 beats/min vs. 188 ± 9.0 beats/min in the control group, $p = 0.03$. Peak exercise mean arterial blood pressures were 99.6 ± 10.0 mm Hg among patients vs. 92.0 ± 20.2 mm Hg among controls, $p = 0.08$.

As displayed in Fig. 1A there was no difference in breath rate during the test; mean peak breath rate (BR_{peak}) in the patient group was 50.5 ± 6.7 breaths/min compared with 50.5 ± 7.9 in the control group, $p = 0.95$. The patients had a significantly lower mean peak exercise minute ventilation (MV_{peak}) as visualized in Fig. 1B: 1.4 ± 0.4 L/kg/min in the patient group vs. 1.8 ± 0.4 L/kg/min in the control group, $p < 0.01$.

As displayed in Fig. 2, we found no differences in terms of ventilatory equivalents (O_2 and CO_2), and likewise, peak exercise RERs were similar in the groups: mean 1.23 ± 0.14 in the patient cohort vs. 1.24 ± 0.14 in

Table 1
Demographics and clinical characteristics.

	Patients (n = 27)	Controls (n = 30)
Age at examination, years	21.1 (3.1)	21.2 (2.5)
Body surface area, m^2	1.8 (0.2)	1.8 (0.2)
Height, cm	175.0 (11.3)	177.1 (9.3)
Weight, kg	70.6 (12.2)	68.4 (11.0)
HR, beats/min	82.0 (14.5)	84.5 (13.9)
MAP, mm Hg	99.6 (10.0)	92.0 (20.2)
BR, 1/min	18.2 (3.3)	16.8 (1.8)
Males, %	55.6 (15/27)	63.3 (19/30)

HR, heart rate prior to exercise; MAP, mean arterial blood pressure prior to exercise; BR, breath rate prior to exercise.