

ORIGINAL RESEARCH

# Functional Capacity Past Age 40 in Patients With Congenital Ventricular Septal Defects

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**BACKGROUND:** Ventricular septal defects (VSD), when treated correctly in childhood, are considered to have great prognoses, and the majority of patients are discharged from follow-up when entering their teens. Young adults were previously found to have poorer functional capacity than healthy peers, but the question remains whether functional capacity degenerates further with age.

**METHODS AND RESULTS:** A group of 30 patients with surgically closed VSDs (51±8 years) with 30 matched, healthy control participants (52±9 years) and a group of 30 patients with small unrepaired VSDs (55±12 years) and 30 matched control participants (55±10 years) underwent cardiopulmonary exercise testing using an incremental workload protocol and noninvasive gas measurement. Peak oxygen uptake was lower in participants with closed VSDs than matched controls (24±7 versus 34±9 mL/min per kg,  $P<0.01$ ) and with unrepaired VSDs than matched controls (26±5 versus 32±8 mL/min per kg,  $P<0.01$ ). Patients demonstrated lower oxygen uptake from exercise levels at 20% of maximal workload compared with respective control groups ( $P<0.01$ ). Peak ventilation was lower in patients with surgically closed VSDs than control participants (1.0±0.3 versus 1.4±0.4 L/min per kg,  $P<0.01$ ) but similar in patients with unrepaired VSDs and control participants ( $P=0.14$ ). Exercise capacity was 29% lower in older patients with surgically closed VSDs than healthy peers, whereas younger patients with surgically closed VSDs previously demonstrated 18% lower capacity compared with peers. Older patients with unrepaired VSDs reached 21% lower exercise capacity, whereas younger patients with unrepaired VSDs previously demonstrated 17% lower oxygen uptake than healthy peers.

**CONCLUSIONS:** Patients with VSDs demonstrate poorer exercise capacity than healthy peers. The difference between patients and control participants increased with advancing age—and increased most in patients with operated VSDs—compared with previous findings in younger patients. Results warrant continuous follow-up for these simple defects.

**Key Words:** adult congenital heart disease ■ functional capacity ■ long-term outcome ■ ventricular septal defects

The isolated ventricular septal defect (VSD) belongs to the simple types of congenital cardiac defects, with good surgical results for hemodynamically significant lesions and subsequent discharge from further follow-up.<sup>1,2</sup> Treatment of patients with small, insignificant defects is conservative, and following visits in outpatient-clinics for the first two decades of life, patients are usually discharged from further follow-up although no clear consensus on this area exists.<sup>3</sup> According to some earlier guidelines, neither surgically closed nor small unrepaired defects require

continuous follow-up at specialized centers, reflecting that late outcome is generally considered benign.<sup>4-7</sup> However, there is a paucity of data investigating long-term outcomes in these patients. The true burden of late morbidity may not become manifest until later in life.

Our research group has previously demonstrated a number of abnormal outcomes when young adults with congenital VSDs were compared with healthy peers. Young adults with surgically closed VSDs display impaired ventricular contractility,<sup>8</sup> compromised ventilatory

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## CLINICAL PERSPECTIVE

### What Is New?

- People with congenital ventricular septal defects, surgically closed or unrepaired, in their mid-50s demonstrate 20% to 30% lower functional capacity than healthy peers, with markedly lower oxygen uptake evident at 20% of maximal effort.
- Comparative exercise studies in younger people with ventricular septal defects demonstrate that aging seems to have an accelerated impact on functional capacity when matched with healthy peers—most in those with operated ventricular septal defects.

### What Are the Clinical Implications?

- Our results warrant continuous follow-up for patients with either successfully closed or unrepaired congenital ventricular septal defects, as functional capacity seems to deteriorate further with age compared with healthy peers.

## Nonstandard Abbreviations and Acronyms

<b>RBBB</b>	right bundle-branch block
<b>RV</b>	right ventricle
<b>VSD</b>	ventricular septal defect

response,<sup>9</sup> and reduced cardiac output<sup>10</sup> during exercise, as well as decreased heart rate variability<sup>11</sup> and altered pulmonary function<sup>12</sup> at rest. Moreover, both surgically closed and unrepaired VSDs have demonstrated lower functional capacity<sup>13–16</sup> and abnormal biventricular morphology<sup>17</sup> during exercise. An increasing number of studies, both clinical and register-based, likewise note a significant burden of cardiovascular events in patients with a congenital VSD.<sup>18–20</sup> Perhaps consequently, the latest updates in a set of international guidelines now recommend continuing follow-up of these simple defects.<sup>21</sup> However, the question remains whether these findings in young adulthood are static, will normalize, or will degenerate as patients get older and could potentially need either surgical or medical intervention in the future. In this study, we set out to investigate exercise capacity in a group of patients, all aged >40 years, with surgically closed or unrepaired VSD.

## METHODS

### Ethics

This study protocol complies with the ethical standards of the Regional Committee on Biomedical Research

Ethics of the Central Denmark Region (chart 1-10-72-185-18), the regional data protection bank (*Region Midts fortegnelse over forskningsprojekter*, chart 1-16-02-290-18), and the Helsinki Declaration of 1975, revised in 2008. The project is registered on ClinicalTrials.gov (identifier NCT03684161). Following written and oral information, all participants gave written informed consent before study inclusion, consistent with Danish law. The data that support the findings of this study are available from the corresponding author on reasonable request.

### Study Population

At Aarhus University Hospital, Denmark, adults aged 40 to 75 years who were born with a VSD were included in a cross-sectional study with healthy age- and sex-matched controls. Inclusion criteria were either a surgically closed VSD or an unrepaired VSD that had previously been deemed hemodynamically insignificant by echocardiography or cardiac catheterization. Patients were identified by searching hospital records using the diagnosis code for a VSD (DQ210). At the time of inclusion, patients underwent auscultation and echocardiography to exclude spontaneous defect closure in the unrepaired VSDs and significant residual VSD in the surgically closed group. Exclusion criteria included coexistence of serious congenital cardiac lesions, associated syndromes (eg, Down syndrome), or severe pulmonary disease. For comparison, flyers and announcements on an official webpage ([www.forsoegsperson.dk](http://www.forsoegsperson.dk)) invited healthy people to participate in the study as controls, and participants were included in an ad hoc manner throughout the study period to match the patients for age and sex. Patients and control participants were included in random order.

### Cardiopulmonary Exercise Test

Height and weight were measured, and body composition, defined as lean body mass as a percentage of total body weight, was determined by bioelectrical impedance analysis (SFB7 analyzer; ImpediMed) before the cardiopulmonary exercise test. Participants were asked to fill out the International Physical Activity Questionnaire<sup>22</sup> to assess the amount of weekly physical activity, distinguishing between levels of high-, moderate-, and low-intensity exercise. Participants were requested not to perform any exhausting exercise sessions 24 hours before the test date and to abstain from large meals and coffee for at least 2 hours before the test. The exercise test was conducted on an upright ViaSprint 150P ergometer cycle (Ergoline), and gas exchange was measured using a breath-by-breath technique (Jaeger MasterScreen CPX) and averaged for 15-second

intervals. Before each test, the ambient-, flow-, and gas-analyzing systems were calibrated with standardized calibration tools.

An individual workload ramp protocol was chosen based on each participant's body mass, sex, and habitual activity level. The incremental workload protocol had 5 levels, with the first 4 levels starting at 25 W and increasing 5, 10, 15, or 25 W/min, and the fifth level starting at 100 W and increasing 25 W/min. Each test lasted between 8 and 12 minutes. During testing, continuous 12-lead ECG and pulse oximetry monitoring were conducted, along with blood pressure measurements at rest and every second minute during exercise testing. Participants were meticulously instructed to maintain a pedaling speed between 60 and 70 rounds/min without talking, standing, or releasing the handlebars during the tests. Participants were encouraged to exercise until complete exhaustion, and the test was considered valid if the respiratory exchange ratio, calculated as volume of carbon dioxide divided by the volume of oxygen uptake, was  $>1.1$ .<sup>23</sup>

### End Points

The primary end point was peak oxygen uptake defined as the highest value of oxygen uptake per kilogram of body mass per minute reached during the exercise test. The peak oxygen uptake was chosen because it is considered the gold standard for functional capacity assessment.<sup>23</sup> The secondary end point was ventilatory anaerobic threshold, an effort-independent measure of aerobic capacity defined as the point at which lactic acids start to accumulate in the blood stream. The value was automatically calculated by the Jaeger MasterScreen CPX software system using the V-slope method.<sup>24</sup>

### Comparative Studies

We assessed raw data from 2 previously published studies from our group<sup>12,14,25</sup> collected from identical upright bicycle tests of patients between ages 18 and 30 years with either a surgically repaired or small unrepaired VSD. Exercise tests were performed under conditions similar to those of the current study with healthy age- and sex-matched controls, and the criteria for a valid test were identical to those of the current study. Peak exercise values and exercise curves were examined and compared with those of the currently studied older patients to assess possible changes in functional capacity.

### Statistical Analysis

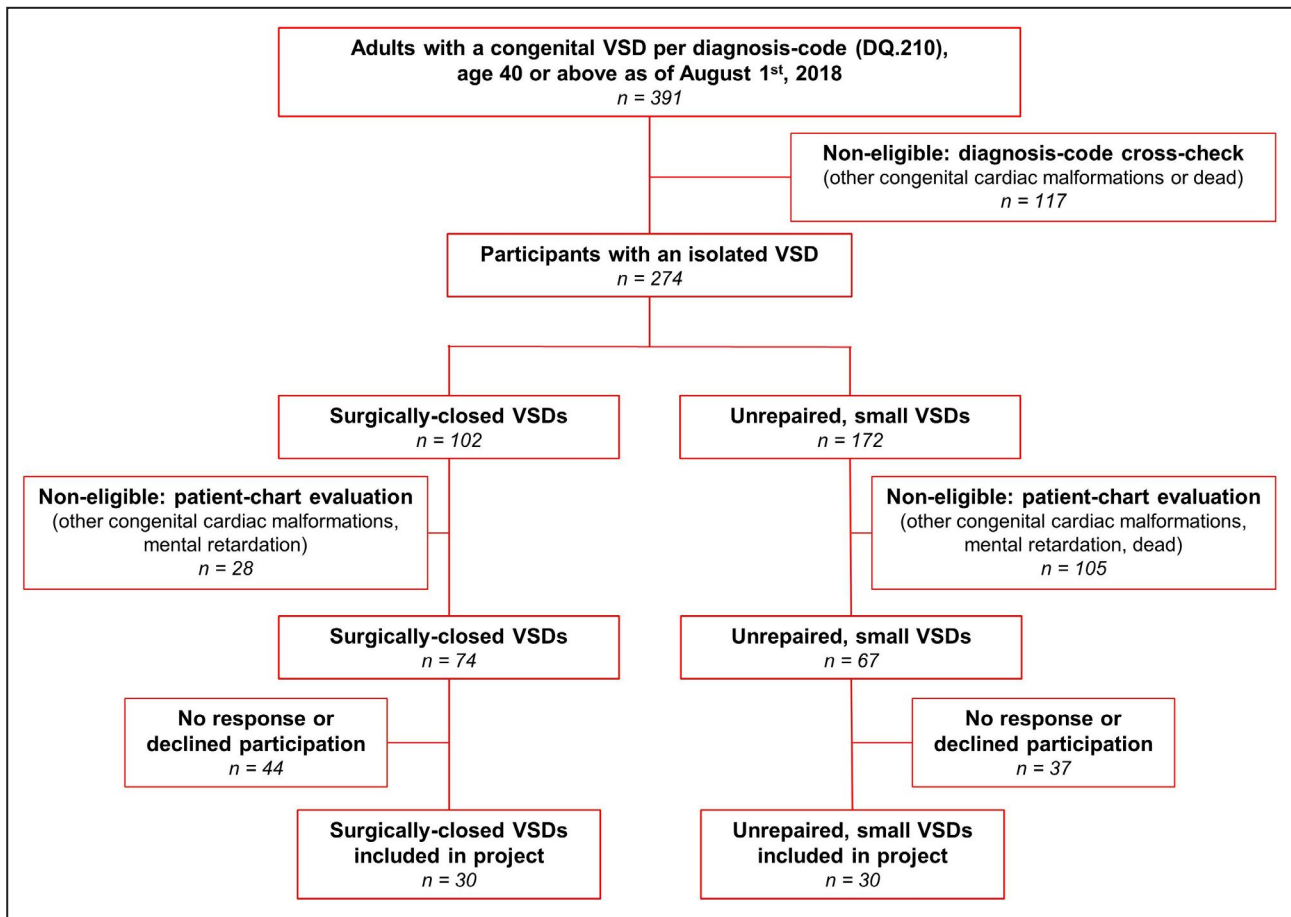
Continuous data were presented as mean $\pm$ SD, as appropriate. Outcomes not normally distributed were

presented as medians with total ranges. Normally distributed data were tested using the unpaired Student *t* test with either equal or unequal variance, which was tested using the variance-comparison test as appropriate, whereas the Wilcoxon rank sum test was used for nonnormally distributed data. The number of participants needed was determined based on power calculation of peak oxygen uptake based on findings from a similar study of patients with surgically closed VSD conducted by Heiberg et al.<sup>13</sup> This approach was chosen because both the study setup and the primary end point were comparable. We expected a difference in peak oxygen uptake between patients and healthy controls that was 80% of the previously found difference with the same standard deviations, with a statistical power of 90% and a significance level of 5%. The estimated sample size for 2-sample comparison of means was at least 19 participants, and to account for dropouts and post hoc excluded values, 30 participants were included in each group. Correlation analyses were made using the Pearson sample correlation *r*.  $P < 0.01$  was considered statistically significant. Descriptive data were collected, stored, and managed using Microsoft Excel 2010 (Microsoft Corp) and REDCap hosted at Aarhus University Hospital, Denmark.<sup>26</sup> Statistical analyses and drawing of plots were performed using StataC 11.2 (StataCorp) and GraphPad Prism 7 (GraphPad Software).

## RESULTS

### Study Population

In total, 391 patients aged  $>40$  years with a congenital VSD were found through a search by diagnosis code; 74 patients with surgically closed VSDs and 67 patients with small unrepaired VSDs were eligible for inclusion, as shown in Figure 1. Between September 2018 and August 2019, 30 patients with surgically closed VSDs and 30 healthy matched control participants and 30 patients with small unrepaired VSDs and 30 healthy matched control participants were included at Aarhus University Hospital. Patient groups and respectively matched control groups displayed similar demographics, as presented in Table 1. No sex- or ethnicity-based differences were present. Cardiovascular comorbidities were more prevalent in patients than controls. Regarding comorbidities of patients with surgically closed VSDs, 5 patients had arrhythmias and 8 had hypertension compared with hypertension in 4 control participants. Among patients with unrepaired VSDs, 9 had hypertension, 1 had diabetes mellitus, 1 had stroke, 1 had retinal artery occlusion, and 4 had arrhythmia compared with hypertension in 6 control participants.



**Figure 1.** Flowchart illustrating the inclusion process of adults with a congenital VSD, aged ≥40 years. VSD indicates ventricular septal defect.

Regarding the different arrhythmias, 4 patients in the surgically closed group had atrial fibrillation and 1 had sick sinus syndrome; in addition, 1 had first-degree atrioventricular block and 2 had multifocal ventricular extrasystole. In the group with unrepaired VSDs, 3 patients had atrial fibrillation and 1 had atrioventricular nodal reentry tachycardia; in addition, 1 had first-degree atrioventricular block and 3 had supraventricular extrasystole. The usage of  $\beta$ -blockers and calcium channel blockers was distributed evenly among the groups of patients and control participants with no statistical difference in exercise capacity between users and nonusers in any group. For the group with surgically closed VSDs, all patients were operated at Aarhus University Hospital between 1967 and 2015 except 1 patient who was operated in Alberta, Canada, in 1964 at age 5 years. All procedures were performed through median sternotomy on cardiopulmonary bypass with a cross-clamp on the aorta. Closure of the defect was performed with either a Dacron- or pericardial patch or by direct suture through a right atrial or ventricular approach. Median age at surgical closure was 6.3 years (range, 1.4–54

years) with all patients initially discharged after closure. Further information on surgery and anatomical position of VSDs, as classified into 4 types by Jacobs et al,<sup>27</sup> is displayed in Table 2. None of the surgically closed VSDs had residual shunting except in 1 patient in whom an insignificant jet could be visualized by echocardiography. Overall, 53% of patients with surgically closed VSDs were initially discharged at age <10 years (median age, 6.5 years; range, 2–8 years) and 47% were ≥10 years (median age, 19 years; range, 14–53 years). Following discharge, 60% were eventually referred again for check-up in outpatient clinics ≥1 time, with the most common cause being palpitations (33% of patients). Currently, 2 patients with surgically closed VSDs are followed with regular visits because of a mechanical aortic valve and a marginally dilated right ventricle (RV). Regarding the unrepaired VSDs, none were spontaneously closed and 83% had been discharged from further follow-up at a median age of 19 years (range, 6–24 years). However, following discharge, 80% were referred back ≥1 time with the most frequent reasons being chest pain (47% of patients) and palpitations (27% of

**Table 1. Demographics in Patients With Either Surgically Closed or Small Unrepaired VSDs and Healthy Age- and Sex-Matched Control Participants**

	Closed VSD n=30	Healthy Controls n=30	Open VSD n=30	Healthy Controls n=30
Age, y	51±8	52±9	55±12	55±10
BMI	28±4	26±4	27±7	26±4
Height, cm	173±9	174±9	171±9	172±8
Weight, kg	84±15	80±15	78±24	76±17
BSA, m <sup>2</sup>	2.0±0.2	2.0±0.2	1.9±0.3	1.9±0.2
Male, % (n)	50 (15)	50 (15)	43 (13)	43 (13)
Lean body mass, %	72±8	75±6	72±8	74±5
Systolic BP, mm Hg	122±19	129±24	129±17	128±17
Diastolic BP, mm Hg	80±11	86±17	82±11	85±18
HR, beats/min	75±15	73±16	72±10	77±21
Smoking habits				
Current/former/never, n	2/11/17	2/13/15	3/9/18	2/14/14
Cardiac comorbidities, n	9	4	9	6
NYHA class I/II/III, n	21/7/2	29/1/0	23/7/0	29/1/0
Prescription medicine, n	15	9	18	12
Antihypertensive	6	4	9	6
Anticoagulants	4		6	
Antiarrhythmic	1		2	
High-intensity exercise, min/wk	0 (0–2880)	28 (0–1680)	0 (0–1800)	10 (0–1680)
Moderate-intensity exercise, min/wk	90 (0–4800)	60 (0–1050)	90 (0–1680)	60 (0–1050)
Low-intensity exercise, min/wk	210 (10–5040)	308 (0–2940)	300 (0–1680)	315 (0–2940)

Data presented as mean±SD, median (range), or percentage (number). BMI indicates body mass index; BP, blood pressure; BSA, body surface area; HR, heart rate; NYHA, New York Heart Association; and VSD, ventricular septal defect.

patients). Currently, 7 patients with unrepaired VSDs are followed at intervals of 3 to 5 years. Age, sex distribution, and age at time of surgical closure were comparable for eligible patients included in the study and patients who were eligible for inclusion but either declined the invitation or did not respond. The cardiopulmonary exercise test was performed on the same day that the participants performed extensive lung function tests, as reported elsewhere.<sup>16</sup>

### Cardiopulmonary Exercise Test

Outcomes of cardiopulmonary exercise tests in patients with either surgically corrected or small unrepaired VSDs and respective matched control participants are displayed in Table 3. For peak oxygen uptake, patients with surgically corrected VSDs reached values 29% lower than those of matched peers ( $P<0.01$ ), whereas patients with unrepaired VSDs reached 21% lower peak oxygen uptake than healthy peers ( $P<0.01$ ). Regarding aerobic capacity, those with surgically closed VSDs demonstrated 35% lower oxygen uptake than control participants ( $P<0.01$ ), whereas those with small unrepaired VSDs reached 21% lower uptake than matched control

participants ( $P<0.01$ ). Both patient groups reached lower oxygen uptake throughout the exercise tests compared with respectively matched control groups, as seen in Figure 2. At exercise levels as low as 20% of maximal workload, patients demonstrated lower oxygen uptake than healthy peers, for both patients with surgically closed VSDs compared with control participants (4.2±1 versus 6.2±2 mL/min per kg,  $P<0.01$ ) and those with small unrepaired VSDs compared with control participants (4.6±2 versus 6.1±2 mL/min per kg,  $P<0.01$ ). Considering previous pulmonary banding in the surgically closed VSDs, no difference was found in peak oxygen uptake when those with banded VSDs were compared with those with nonbanded VSDs (26.3±6 versus 22.1±8 mL/min per kg,  $P=0.18$ ) or in anaerobic threshold (16.7±5 versus 14.3±8 mL/min per kg,  $P=0.33$ ). The potential relationship between right bundle-branch block (RBBB) and both chronotropic impairment and decreased functional capacity was investigated for the patients with surgically closed VSDs, but no difference was found between 14 patients with complete and 16 patients with incomplete or no RBBB. This is further illustrated in Figure 3. Regarding exercise outcomes in relation to cardiac surgery, no differences

**Table 2. Clinical Characteristics of Patients With Either Surgically Closed or Small Unrepaired VSDs**

	Closed VSD n=30	Open VSD n=30
Type of VSD, n		
Perimembranous	18*	17
Muscular	1	7
Inlet	1	4
Outlet	4	2
QpQs	2.1±0.5 <sup>†</sup>	1.3±0.1 <sup>†</sup>
Cardiac catheterization, times 1/≥2, n	5/19	11/9
Other congenital abnormality, n	9 <sup>‡</sup>	2 <sup>‡</sup>
Banding, yes/no, n	10/11 <sup>§</sup>	0/30
Age at banding, mo	3.7 (1.6–30)	NA
Age at surgical closure of defect, y	6.3 (1.4–54)	
<10 y of age, 20 patients	5.5 (1.4–8.6)	
≥10 y of age, 10 patients	31 (17–54)	NA
Sternotomy, n	21 <sup>  </sup>	NA
Surgical type; atriotomy/ ventriculotomy, n	5/16 <sup>  </sup>	NA
Patch/direct suture, n	20/6	NA
Cardiopulmonary bypass time, min	88±29	NA
Aortic occlusion time, min	59±28	NA
Days until discharge	15±5	NA
Causes of readmission, No. of patients		
Chest pain or dyspnea	4	17
Palpitations	10	8
Syncope	2	3
Aortic insufficiency		1
Infectious endocarditis, n	4	5
RBBB, complete/incomplete, n	14/7	

Data presented as mean±SD, median (range), or percentage (number). NA indicates not available; QpQs, pulmonary-to-systemic ratio; RBBB, right bundle-branch block; and VSD, ventricular septal defect.

\*Missing information on type of VSD in 6 patients with surgically closed VSDs.

<sup>†</sup>Corresponds to preoperative measurements, missing information on QpQs in 15 patients with surgically closed VSDs. For patients with unrepaired VSDs, QpQs is calculated from old catheterization reports, some >30 years old. Information was missing for 14 patients with unrepaired VSD.

<sup>‡</sup>Surgically corrected VSDs: persistent ductus arteriosus (n=3, closed), minor atrial septal defect (n=4, closed), aortopulmonic fistula (n=1, closed), mitral valve disease (n=1), aortic insufficiency (n=1), bicuspid aortic valve (n=1, mechanic valve). Unrepaired VSDs: bicuspid aortic valve (n=1), subvalvular membrane (n=1).

<sup>§</sup>Information missing for 9 patients with surgically closed VSDs.

<sup>||</sup>Information missing on operation type for 9 patients with surgically closed VSDs.

were found on any exercise parameters between patients with surgically closed VSDs and patients with small unrepaired VSDs.

## Correlation Analyses

Associations between patient data and exercise outcome were tested. None were found between peak oxygen uptake and pulmonary-to-systemic ratio, age

at operation, time spent in hospital following operation, aortic occlusion time, or cardiopulmonary bypass time. For unrepaired VSDs, no relations were found between peak oxygen uptake and type of VSD, age at discharge, or pulmonary-to-systemic ratio information taken from previous catheterization reports.

## Comparative Studies

Raw data from 2 studies<sup>12,14,25</sup> on exercise capacity in patients with congenital VSDs aged 20 to 30 years, 30 patients with surgically closed VSDs (mean age, 24±2 years) and matched peers (mean age, 24±2 years) and 36 patients with unrepaired VSD (mean age, 24±4 years) and 36 matched peers (mean age, 24±2 years) were included for comparison of results of the current older cohort. Young patients with surgically closed VSDs reached peak oxygen uptake of 38.4±8 mL/min per kg and control participants reached 47.1±8 mL/min per kg ( $P<0.01$ ). Patients with unrepaired VSDs reached 35.8±10 mL/min per kg, whereas control participants reached 46.3±8 mL/min per kg. Exercise capacity was 29% lower in the currently tested older patients with surgically closed VSDs compared with healthy peers, whereas younger patients surgically closed VSDs demonstrated 18% lower exercise capacity compared with peers. Older patients with unrepaired VSDs reached 21% lower exercise capacity, whereas younger patients with unrepaired VSDs demonstrated 17% lower oxygen uptake than healthy peers. In Figure 4, curves of oxygen uptake throughout the bicycle test are illustrated for younger and older patients with surgically closed and unrepaired VSDs and their respective matched control participants.

## DISCUSSION

With improvements in treatment and diagnostic tools over the past decade, the population of adults with congenital cardiac defects is greater today than that of children with congenital cardiac defects.<sup>28,29</sup> Nevertheless, there is a lack of data documenting the long-term outcomes in this growing pool of adult patients. The novel findings in the current study of functional capacity past age 40 years in isolated patients with VSDs emphasize the importance of focusing on the long-term outcomes in this steadily increasing population. Our study reveals 3 important findings. First, functional capacity is lower by 20% to 30% in people aged >40 years with congenital VSDs compared with healthy, matched peers. Second, compared with young patients with VSDs, the functional capacity of older patients with VSDs is not normalized but rather remains decreased, with an

**Table 3. Exercise Test Outcomes in Patients With Either Surgically Corrected or Small Unrepaired VSDs and Healthy, Respectively Matched Control Participants**

	Closed VSD n=30	Healthy Controls n=30	P Value	Open VSD n=30	Healthy Controls n=30	P Value
Resting values						
Vo <sub>2</sub> kg, mL/min/kg	3.5±0.8	4.1±1.0	0.02	4.0±1.0	4.6±3.0	0.36
BF, breaths/min	16±4	15±5	0.44	15.3±4	16.0±4	0.49
Ventilation, L/min/kg	0.1±0.04	0.1±0.03	0.14	0.1±0.04	0.2±0.09	0.39
HR, beats/min	75±15	73±16	0.63	72±10	77±21	0.28
Systolic BP, mm Hg	122±19	129±24	0.21	129±17	128±17	0.80
Diastolic BP, mm Hg	80±11	86±17	0.17	82±11	85±18	0.49
Peak exercise values*						
Test time, min	12.2±4	12.5±3	0.72	10.7±2	12.0±2	0.07
Workload protocol, 1–5	3±1	3±1	0.20	3±1	3±1	0.47
Peak workload, W/kg	2.1±0.7	3.1±1.0	<0.01	2.3±0.6	2.8±0.9	0.01
Peak Vo <sub>2</sub> kg, mL/kg/min	24.3±6.8	34.2±8.9	<0.01	26.0±6	32.9±8.2	<0.01
RER	1.2±0.1	1.2±0.1	0.13	1.2±0.1	1.2±0.1	0.85
Peak BF, breaths/min	42±7	43±9	0.84	41.2±8	42.2±10	0.67
Peak ventilation, L/min/kg	1.0±0.3	1.4±0.4	<0.01	1.2±0.3	1.3±0.4	0.13
Peak HR, beats/min	160±21	168±16	0.10	160±18	165±15	0.24
Peak systolic BP, mm Hg	185±30	198±37	0.15	198±25	195±35	0.73
Peak diastolic BP, mm Hg	102±34	103±25	0.86	101±26	100±22	0.94
VE/Vco <sub>2</sub>	35.5±4	33.3±4	0.05	35.7±5	33.3±4	0.04
Anaerobic threshold						
Workload, W/kg	1.2±0.5	1.9±0.9	<0.01	1.3±0.6	1.8±0.8	<0.01
Vo <sub>2</sub> kg, mL/kg per min	15.5±5	23.8±8	<0.01	17.9±5	22.5±7	<0.01
HR, beats/min	116±24	131±25	0.03	122±23	131±25	0.15

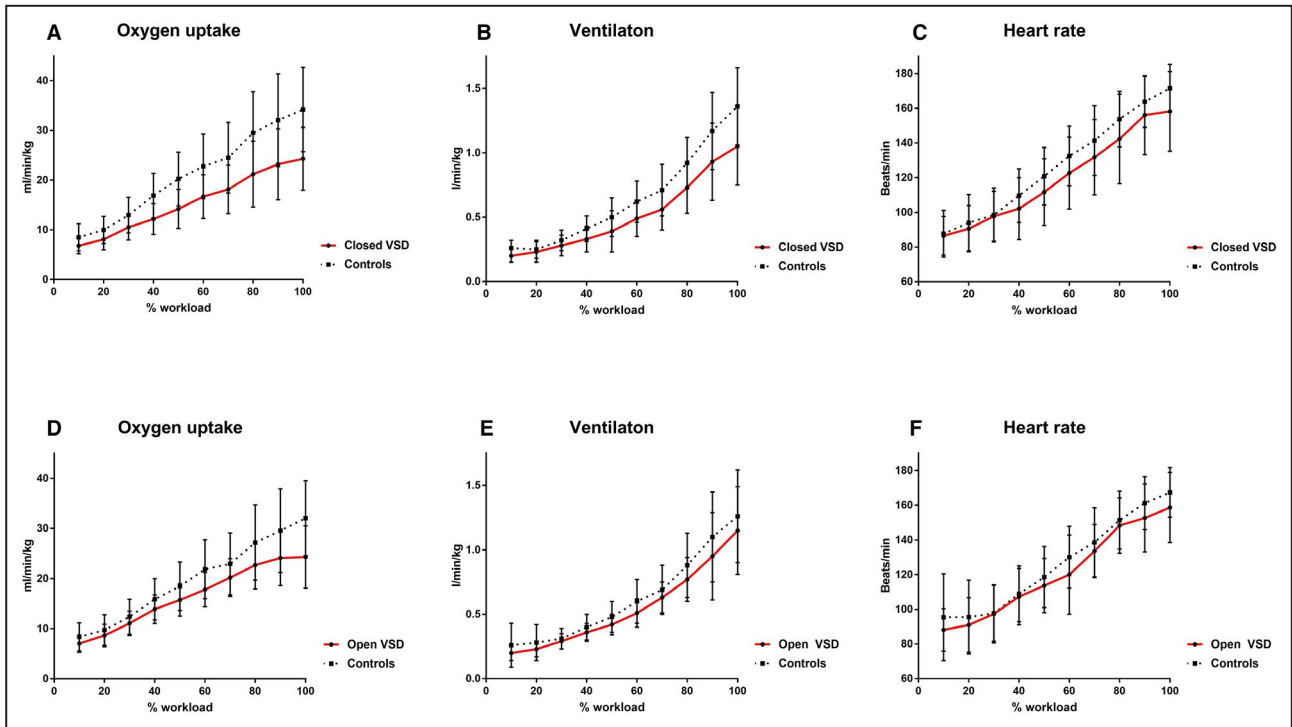
Data presented as mean±SD, median (range), or percentage (number). BF indicates breath frequency; BP, blood pressure; HR, heart rate; RER, respiratory exchange ratio; VE/Vco<sub>2</sub>, minute ventilation/carbon dioxide production; Vo<sub>2</sub>kg, mL oxygen uptake per kilogram; and VSD, ventricular septal defect.

\*For peak exercise values, 2 male control participants matched with patients with surgically closed VSDs were dropped, along with 1 female patient with unrepaired VSD and 2 matched controls (male) because of peak RER <1.1 with no significant changes.

even larger difference compared with corresponding healthy peers; the difference is greatest for those with surgically closed VSDs. Third, both patients with surgically closed VSDs and those with unrepaired VSDs exhibit lower functional capacity detectable at only 20% of their maximal effort compared with their healthy peers.

The mechanisms of lower functional capacity can be multifaceted. One theory is that the VSDs exhibit exercise-induced increased pulmonary vascular resistance. It is hypothesized that the hyperperfusion of the pulmonary vascular bed—either in large quantities for a short time period in surgically closed VSDs or in small continuous quantities for a longer period in unrepaired VSDs—will trigger endothelial remodeling in the pulmonary vascular wall that ultimately results in vessel hypertrophy and stiffness. This causes a rise in resistance and, eventually, increased pulmonary pressure. An indirect sign of this could be the 16% higher oxygen uptake at peak activity of patients with surgically closed VSDs who previously had their pulmonary artery banded compared with those who

did not. Although the results are not statistically significant, a simple explanation could be that the results are underpowered given the small study sample; it would be interesting to investigate this tendency in a larger study population. Other studies have previously supported the theory of increased pulmonary vascular resistance. Moller et al found that one-third of younger patients with surgically closed VSDs and those with unrepaired VSDs demonstrated increased RV systolic pressure during exercise, as estimated by echocardiography.<sup>30</sup> At rest, all patients were found to have normal RV systolic pressure. In a newer magnetic resonance imaging study of young adults with surgically corrected VSDs, a progressive pulmonary retrograde flow was demonstrated with increasing exercise workloads compared with healthy peers.<sup>10</sup> Furthermore, lower cardiac output during maximal exercise was also established in patients compared with controls. Additional signs of increased RV afterload are larger RV volume, which was seen recently in young adults with either surgically closed or unrepaired VSD.<sup>17</sup> Another consequence of

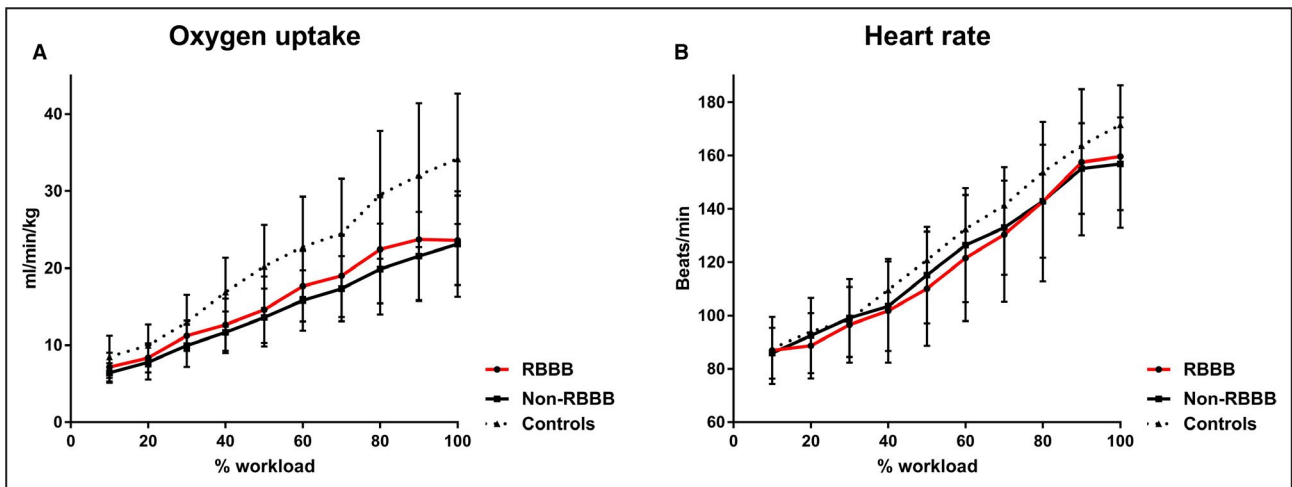


**Figure 2.** Curves of oxygen uptake, ventilation, and heart rate at rest and during the exercise test in patients with surgically closed VSDs and their matched controls (A through C) and in patients with unrepaired VSDs and matched controls (D through F).

VSD indicates ventricular septal defect.

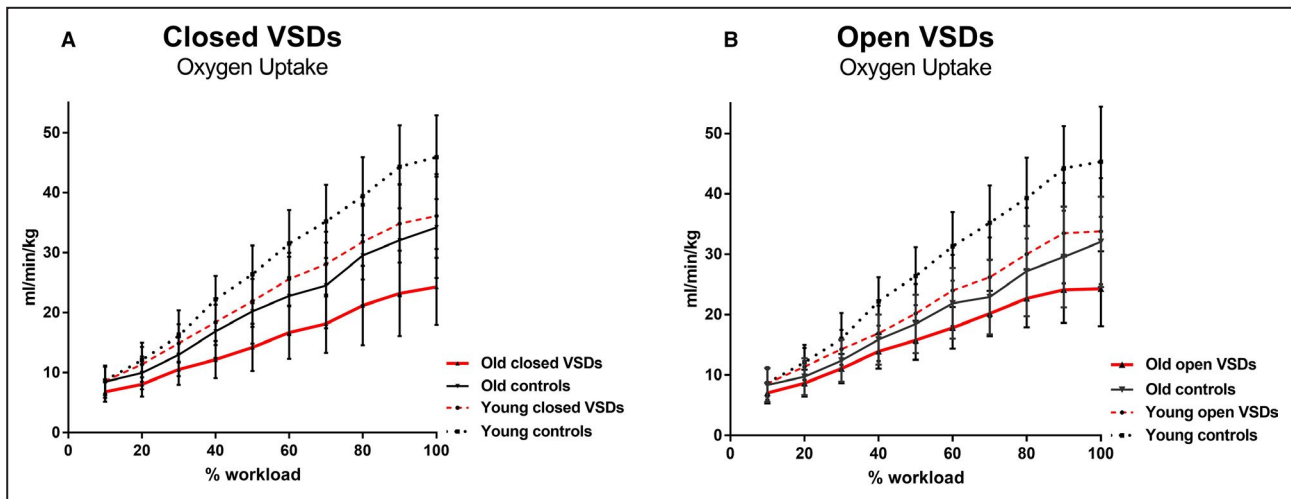
increased afterload could be changed RV function, which Menting et al<sup>18</sup> described with abnormal RV fractional area change in 14% of 49 adults with surgically closed VSDs in a large long-term follow-up study. Interestingly, Menting et al also described an age-related increase in the number of patients with impaired RV systolic function, going from 1% to 17% over an 11-year period. Another theory for the lower

functional capacity could be that patients have abnormal ventricular contractility with a lower reserve at physical activity than healthy peers. This has been demonstrated recently with echocardiography during exercise in young adults with either surgically closed or unrepaired VSD.<sup>8,31</sup> Although both ventricles contract markedly slower at higher exercise levels than those of healthy peers, the difference is particularly



**Figure 3.** Curves of oxygen uptake (A) and heart rate (B) at rest and during exercise in patients with surgically closed VSDs with complete or incomplete or with no right bundle-branch block, as well as healthy age and sex-matched controls. RBBB indicates right bundle-branch block; and VSD, ventricular septal defect.





**Figure 4.** Curves of oxygen uptake at rest and during exercise in younger and older patients with surgically-closed VSDs (A) or unrepaired VSDs (B) and in their respectively matched controls. VSD indicates ventricular septal defect.

prominent in the RV. Abnormal contractility, larger RV volumes, and larger pulmonary retrograde flow may all reflect increased RV afterload as the consequence of the hypothesized exercise-induced increased pulmonary vascular resistance in patients with VSDs.

Another mechanism of decreased oxygen uptake during physical activity could be abnormal pulmonary function in the patients. In the patients with surgically closed VSDs in this study, ventilation at peak exercise was found to be lower than in healthy peers. In a newly published study of the same study cohort performed on the same day of the bicycle test, those with surgically closed VSDs were found to have impaired dynamic pulmonary function, increased airway resistance in the small airways, and reduced diffusion capacity compared with healthy peers.<sup>16</sup> Patients with unrepaired VSDs were largely comparable to healthy peers for both dynamic and static parameters. This primarily points toward the previous surgery, with subsequent disruption of the normal physiology of the thorax as the main cause of impaired pulmonary function. Nevertheless, the consecutively lower curve of ventilation throughout the exercise test in the patients with unrepaired VSDs, as seen in Figure 2, emphasizes that a previous surgical intervention cannot explain everything. Interestingly, from the pulmonary function investigation, those with unrepaired VSDs did not demonstrate increased diffusion capacity, which would be anticipated with the persistent shunt. Instead, values were in the normal ranges, which may support the hypothesis of increased pulmonary vascular resistance, as it could imply an alveolar–capillary membrane dysfunction.

A possible theory to be explored as an explanation for lower functional capacity is that a degree of chronotropic impairment might be present. Although peak

heart rates do not differ between groups, Figure 2 shows that the heart rate curve of the patients is consecutively below that of the healthy peers. This effect is most pronounced in the patients with surgically closed VSDs; consequently, the potential role of RBBB was investigated, given the high proportion of patients with complete RBBB in the current cohort. Nevertheless, the substudy did not yield further explanation because RBBB did not seem to play a role in heart rate during exercise or oxygen uptake, as seen in Figure 4. In a study of patients with surgically closed VSDs in their mid-20s, Heiberg et al<sup>32</sup> found that postoperative RBBB predicted lower peak heart rate during the upright bicycle test. In a larger recently published study by our research group, patients with surgically closed VSDs in their mid-20s, particularly those with complete RBBB, were found to have impaired heart rate variability.<sup>11</sup> Whether a similar or even more disrupted pattern could be established in older patients has yet to be determined and necessitates further clinical research in this area.

An entirely different theory could simply be that these patients are less physically active and thus reach lower peak oxygen uptake. Two cases could be made against this assumption. First, the patients and their matched controls in this study both filled out a subjective questionnaire on habitual physical activity level, and no differences were found. Furthermore, objective measurements such as lean body mass as measured with bioimpedance, body mass index, and weight did not differ either. A second argument against this viewpoint is that both patient groups yielded lower ventilatory threshold than their respective control groups; this threshold is not bound to physical exertion and participant motivation and thus is independent of potential deconditioning. Along these lines, it could be

emphasized that both patient groups demonstrated markedly lower oxygen uptake at 20% of their individual maximal efforts compared with peers.

Clinical studies have previously investigated young adult patients with isolated VSDs and reported lower-than-expected functional parameters,<sup>12–14,25</sup> but not to the same extent as the current findings. Although we compared different patient cohorts rather than conducting a follow-up study over a number of years, the equipment used and the research personnel performing the tests were unchanged, which strengthens the comparison of data. We may not be able to conclude indisputably that our findings reflect the true evolution of functional capacity in isolated VSDs, however; they clearly suggest further deterioration of parameters with increasing age—an effect that is more pronounced in patients than in age-matched healthy controls. In the literature, only 1 long-term, follow-up study including exercise testing on VSDs exists. In a Dutch follow-up study from 2015, 69 patients with surgically corrected VSDs and a mean age of 40 years were followed with 10-year intervals with exercise testing among other measurements.<sup>18</sup> Median oxygen uptake was 87% of expected compared with undocumented reference values. In this cohort, exercise capacity decreased from 100% of expected values in 1990 to 91% of expected values in 2001.<sup>33</sup> In the newest study in 2015, 48% of patients demonstrated decreased exercise capacity. Furthermore, cumulative survival in the cohort of patients with surgically closed VSDs was 86% at 40 years (excluding in-hospital operative mortality), which was slightly lower than in the background population. Interestingly, in more than half of cases, late mortality was cardiac related. In the newest set of guidelines,<sup>21</sup> the survival rate for small unrepaired VSDs at age 25 was 96%; however, this was based on a study from 1977.<sup>34</sup> No nationwide study has investigated survival rate in adults with isolated VSDs. A similar and “simple” defect, the atrial septal defect, was recently investigated in a Danish nationwide study in which overall mortality in participants with either repaired or unrepaired atrial septal defect was found to be higher, with an adjusted hazard ratio of 1.7.<sup>35</sup> Interestingly, examining the graphical outline of overall survival probability, the atrial septal defects seem to decrease at a steeper slope from ages in the late 30s to the early 60s compared with the background population. In another Danish register-based study, patients with simple congenital heart defects (VSDs, atrial septal defects, pulmonary stenosis, and patent ductus arteriosus) diagnosed between 1963 and 1975 were compared with a background population and followed to a median age of 47.4 years.<sup>36</sup> Mortality was increased overall for the group, with an adjusted hazard ratio of 2.08 specifically for VSDs (both surgically closed and unrepaired).

Reduced functional capacity of 20% to 30% constitutes an interesting clinical finding and has consequences for patients. A quarter of patients with surgically closed VSDs placed themselves in New York Heart Association (NYHA) class II and 7% in NYHA class III when contemplating daily symptoms, as seen in Table 1. For those with unrepaired VSDs, 23% placed themselves in NYHA class II, with none in class III. For comparison, only 1 healthy control chose NYHA class II; the rest placed themselves in NYHA class I. The high proportion of patients placing themselves in class II or III could also be interpreted as reflected in the bicycle results, with patients having markedly lower oxygen uptake at 20% of maximal exercise output. This level of exercise corresponds with minor daily physical activities, implying that these patients would experience daily impairment if compared with people without a congenital VSD. This result underscores the clinical implication of the finding and helps in understanding why younger patients have previously described lower physical functioning compared with norm-based scores in the self-reported, health-related quality-of-life questionnaire Short Form-36 (SF-36).<sup>13,14</sup> Good cardiorespiratory fitness is known to be related to lower risk of all-cause mortality in healthy people.<sup>37</sup> Low cardiorespiratory fitness, typically defined as the lowest quartile or quintile on an exercise test, is associated with 2- to 5-fold increases in cardiovascular events or all-cause mortality, independent of other cardiovascular risk factors. Recognizing the importance of physical performance, the newest set of guidelines not only recommend routine follow-up visits for patients with either unrepaired or surgically closed VSD but also include exercise testing among the tests suggested for the visits.<sup>21</sup>

## Limitations

A limiting factor is the lack of contemporary catheterization data, especially for the unrepaired VSDs. Only half of the patients previously underwent cardiac catheterization, for which the calculated pulmonary-to-systemic ratio is outdated and could have changed in our patients with unrepaired VSDs. The number of participants in each group is small; therefore, broader applicability of our results is limited. In addition, the study design was cross-sectional, whereas an accurate reflection of the age-related change in exercise capacity in isolated patients with congenital VSDs requires a longitudinal design. Nevertheless, these findings could form the basis of multicenter studies with larger numbers of patients or longitudinal studies investigating long-term outcomes in terms of hemodynamics in the isolated VSD. Another limitation is the lack of updated, internationally accepted reference values for bicycle ergometry. Consequently, it cannot be clarified

whether our patients are within the normal range or below. Overall, our study is greatly strengthened by the individually matched control participants included and the highly significant results for both our primary and secondary end points.

Those with surgically corrected VSDs underwent surgical closure at older ages than would be expected in a contemporary cohort. Furthermore, pulmonary artery banding is currently performed only rarely, and the advances in surgical and anesthesiology techniques and improvements in perioperative care have greatly reduced perioperative mortality. In addition, the care during follow-up is better organized today. Therefore, these early results are not readily applicable to patients who underwent surgery in more recent years. However, our results still reflect a large cohort of adults living with the long-term consequences of a congenital VSD, underscoring the importance of these findings.

## CONCLUSIONS

This study clearly emphasizes that living with a congenital VSD, surgically closed or unrepaired, is not a static state with outcomes comparable to those of healthy peers. Not only do patients with either surgically closed or small unrepaired VSD demonstrate poorer exercise capacity compared with matched control participants; their exercise capacity does not seem to normalize but rather deteriorates further with increasing age. Our novel findings warrant attention for aging patients with congenital VSDs and suggest continuous follow-up in specialized cardiology clinics.

## ARTICLE INFORMATION

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None.

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