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ORIGINAL ARTICLE

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Small unrepaired atrial septal defects display impaired exercise capacity compared with healthy peers

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Abstract

Objective: Adult patients with small, unrepaired atrial septal defects have an increased risk of pneumonia, atrial fibrillation, and stroke. Furthermore, they have higher late mortality than the background population. The functional capacity is unknown in these patients. Therefore, our objective was to determine exercise capacity in adult patients diagnosed with an unrepaired atrial septal defect compared to healthy controls.

Design: A cross-sectional study.

Patients: Adult patients with small, unrepaired atrial septal defects, aged 18-65, diagnosed between 1953 and 2011.

Interventions: Cardiopulmonary exercise test was performed using an incremental bicycle test and gas exchange was measured using breath-by-breath technique.

Outcome measures: Primary outcome was peak oxygen uptake, secondary outcome was maximal workload and ventilatory anaerobic threshold.

Results: We included 32 patients previously diagnosed with a small, unrepaired atrial septal defect and 16 healthy, age- and gender-matched controls (age 36.3 ± 13 years). Patients were divided into two groups based on whether the atrial septal defect was open (age 36.3 ± 11 years) or spontaneously closed (age 36.8 ± 14 years) since time of diagnosis. No differences in demographic characteristics or weekly exercise levels were found. Both patient groups reached lower peak oxygen uptake (open: 31.7 ± 11 mL/kg/min; spontaneously closed: 29.7 ± 6.9 mL/kg/min) compared with controls (42.6 ± 6.1 mL/kg/min; $P = .0001$). Workload (open: 2.6 ± 1.0 watt/kg; spontaneously closed: 2.5 ± 0.6 watt/kg) and aerobic capacity (open: 21.4 ± 8.7 mL/kg/min; spontaneously closed: 22.5 ± 6.5 mL/kg/min) was also poorer in patients compared to controls (workload: 3.5 ± 0.5 watt/kg; $P = .0006$, aerobic capacity: 31.3 ± 6.8 mL/kg/min; $P = .0007$).

Conclusion: Adult patients with a diagnosis of small, unrepaired atrial septal defect have significantly impaired exercise capacity when compared to healthy controls. The impairment was present even if, by the time of assessment, the defect had closed spontaneously. The pathophysiological mechanisms behind the impaired exercise capacity demonstrated in these patients remain unexplained and will be a target for future work.

KEYWORDS
cardiopulmonary exercise test, exercise capacity, grown-up with congenital heart disease (GUCH), simple lesions, small atrial septal defect

1 | INTRODUCTION

Atrial septal defect (ASD) is a common congenital cardiac lesion with a total prevalence of 1.1 per 1000 live births in Denmark.[1] Approximately 70% of these defects close spontaneously in early childhood.[1] The remaining defects are either closed or considered too small to be a significant left-to-right shunt.

Controversies remain regarding the management and clinical implications of these small unrepaired ASD.[2] Generally, they are untreated and follow-up varies since their natural history and prognosis is predominantly thought to be benign.[2-4] However, novel studies have instigated a revived interest in an otherwise overlooked patient group. A study by Nyboe et al, demonstrated that patients with a small, unrepaired ASD have an increased mortality when compared with the general population, thereby emphasizing a need for long-term medical follow-up even with these simple small defects. Adults living with small, unrepaired ASD also have an increased risk of several comorbidities such as pneumonia, stroke, and atrial fibrillation.[5,6]

Exercise impairment is well known in adult patients with a hemodynamically significant ASD.[7,8] In contrast to patients with large open or closed ASD, the functional capacity in small, unrepaired ASD patients is still unknown. The general perception is that they are as healthy and fit as the general population. Nevertheless, a similar perception was disproved for patients with small, unrepaired ventricular septal defects demonstrating a significantly impaired exercise capacity.[9]

Our primary objective was to determine functional capacity in adult patients diagnosed with a small, isolated, and unrepaired ASD compared to healthy, age-, and gender matched controls. Secondary objectives include evaluating aerobic capacity, maximal workload, and peak ventilation in these patients.

2 | METHODS

2.1 | Study design and participants

This cross-sectional study is part of a larger ongoing nationwide descriptive study of patients with small, unrepaired ASD, with all participants included between May 2016 and January 2018 at Aarhus University Hospital, Denmark. All patients were previously identified through the Danish National Patient Registry,[5,6] identifying all patients in Denmark diagnosed with an unrepaired ASD. Two independent clinicians validated the ASD diagnosis through review of hospital records. Patients with pulmonary arterial hypertension and Eisenmenger syndrome were excluded, thus presumably leaving only small and hemodynamically insignificant ASDs. In Denmark, an ASD is normally categorized as small when Q_p/Q_s is less than 1.5 and without dilatation of the right atrium or ventricle at the time of diagnosis. All our patients underwent transthoracic echocardiography and cardiac MRI (cMRI) prior to inclusion. Heart chamber areas were assessed by echocardiography in apical 4-chamber view. cMRI was used to determine the pulmonary to systemic flow ratio (Q_p:Q_s) and to verify if the ASD was spontaneously closed. Patients were then divided into two groups: (1) Patients where the defect was still open. (2) Patients where the defect was spontaneously closed since time of diagnosis. If there was any doubt on the cMRI whether the defect was spontaneously closed or not, a transesophageal echocardiography was performed. For comparison, healthy controls, matched on age and gender, were included through flyers and announcements on official webpages. The three groups of participants were included in purposely order by investigator during the study period. Chamber measurements and measurement of Q_p/Q_s were done in a blinded fashion. Inclusion criteria were as follows: Patients diagnosed with unrepaired, atrial septal defect. Exclusion criteria were coexistence of other congenital cardiac defects than atrial septal defect (including persistent foramen ovale), age <18 and >65 years, and significant cardiac or pulmonary disease.

All participants gave written informed consent at the beginning of the study. The project protocol complies to the ethical guidelines of The Regional Committee on Biomedical Research Ethics of the Central Denmark Region, The Danish Data Protection Agency and with the 1975 Helsinki Delectation, and the study was approved by the ethics committee of the institution.

2.2 | Cardiopulmonary exercise test

The subject was requested not to perform any exhausting exercise sessions 24 hours prior to the visit and was to abstain from large meals and coffee for at least 2 hours before the test. Exercise data were collected using the Jaegers MasterScreen CPX system (IntraMedic, Gentofte, Denmark). Before each test, the ambient-, flow-, and gas-analyzing systems were calibrated with standardized calibration tools. During testing, continuous 12-lead electrocardiographic and pulse oximetry monitoring were made along with blood pressure measurements at rest, and every second minute during exercise testing. Gas exchange was measured using breath-by-breath technique and averaged for 15 seconds intervals. Exercise tests were performed on an electronically braked Sprint 150P ergometer cycle (Ergoline, Bitz, Germany). Before each exercise test, an individual ramp workload protocol was chosen based on the subject's body mass, gender, and habitual activity level. The incremental workload protocol started at either 25 or 100 W and increased with 10, 15, or 25 W/min. Each test aimed at lasting between 8 and 12 minutes.

The participants were meticulously instructed to maintain a pedalling speed between 60 and 70 rounds per minute 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 and at least 85% of age predicted maximal heart rate (207−[age*0.7]) was reached.[10] Each participant also filled out questions from The Danish National Health Survey in order to assess the weekly amount of physical activity.[11]

2.3 | Outcome measures

The primary outcome was peak oxygen uptake. We defined it as the highest amount of oxygen uptake per minute per kilogram during exercise. Peak oxygen uptake (mL O_2/kg/min) was chosen for functional capacity assessment.[10]

Secondary outcome was: Workload, minute ventilation, heart rate reserve, heart rate at peak exercise, ventilatory anaerobic threshold (VAT), and fitness category. VAT was defined as the point at which lactic acid accumulate in the blood stream and signifies an effort-independent measurement of aerobic capacity. The Jaegers MasterScreen CPX system automatically calculated VAT using the v-slope method according to Beaver et al.[12] Heart rate reserve was calculated as the difference between peak and resting heart rates.[13] Fitness categories were based on normative data values for age and gender.[14]

2.4 | Statistical analysis

We used power calculations to determine the needed number of participants based on findings from the similar studies on VSD patients.[9,15] Continuous, normally distributed data were reported as means with standard deviation. Differences in echocardiographic data between patient groups were analyzed with unpaired students *t* test. Categorical variables were summarized by percentages. Comparisons of categorical baseline characteristics were performed by Fisher's exact test. For comparative statistics, continuous variables were evaluated between the three groups using 1-way ANOVA with Bonferonni post hoc testing if normally distributed. Statistical significances were considered with *P* values below .05. All analyses were performed using Stata IC 15.1 (StataCorp LP, College Station, Texas).

3 | RESULTS

3.1 | Patient characteristics

A total of 32 patients, 16 in each group, were enrolled. All patients were asymptomatic. For comparison, 16 age- and gender-matched controls were included. Demographic and clinical characteristics of the 3 groups are summarized in Table 1.

As displayed, the groups were generally comparable. In the open ASD group, 3 patients smoked between 7 and 17 cigarettes each day, while 1 patient in the spontaneously closed group smoked 3 cigarettes a day. None of our controls smoked. A larger proportion of patients self-assessed their physical function poorer than the controls. Weekly exercise habits were not different between the groups. The Q_p:Q_s was measured in all patients with an open ASD. The mean is presented in Table 1. No differences in age, time of diagnosis, or comorbidities were found when comparing included patients and patients who did not respond to the invitation letter. Four patients had transesophageal echocardiography, however, no patients were reassigned.

3.2 | Cardiopulmonary exercise test

Exercise data are presented in Table 2. Neither respiratory exchange ratio at peak exercise or test duration differed between the 3 groups, nor was any test terminated prematurely. As a result, we considered all tests valid. Peak oxygen uptake was significantly lower in both patient groups when compared with controls, both at rest, VAT and at peak exercise. Actually, both patient groups had lower oxygen uptake during the entire exercise test, as shown in Figures 1 and 2. At no time-point was there difference between

TABLE 1 Patient characteristics

	Open ASD (*n* = 16)	Closed ASD (*n* = 16)	Controls (*n* = 16)	*P* value
Age (years)	36.3 ± 11	36.8 ± 14	36.3 ± 13	.9927
Males (%)	31.3	31.3	31.3	1.000
Weight (kg)	72 ± 20	73 ± 17	69 ± 10	.6747
Height (cm)	169 ± 7	169 ± 8	172 ± 8	.5953
Body mass index	25.0 ± 4.2	25.6 ± 5.9	23.2 ± 2.3	.2551
Poor self-assessed physical function (%)	38	25	6.3	.040
30 Min exercise ≥3 days a week (%)	63	50	69	.560
Q_p:Q_s ratio	1.25 (range 0.99-1.57)	–	–	–

Note. Data presented as mean with standard deviation or percentage. *P* value derived from ANOVA.

TABLE 2 CPET variables

Variable	Open ASD (*n* = 16)	Closed ASD (*n* = 16)	Controls (*n* = 16)	*P* values
Rest				
Oxygen uptake, mL/kg/min	4.1 ± 1.2	3.9 ± 1.1	5.1 ± 1.1	.0099
Heart rate, beats/min	81 ± 14	90 ± 21	86 ± 12	.2616
Ventilation, mL/min	10.6 ± 3.4	10.3 ± 3.1	12.1 ± 3.5	.2855
O_2 pulse, mL O_2/heart beat	3.8 ± 1.2	3.3 ± 1.2	4.1 ± 1.1	.1713
Peak				
Peak oxygen uptake, mL/kg/min	31.7 ± 11.0	29.7 ± 6.9	42.6 ± 6.1	.0001
Maximal workload, W/kg	2.6 ± 1.0	2.5 ± 0.6	3.5 ± 0.5	.0006
Peak heart rate, bpm	175 ± 21	175 ± 16	183 ± 10	.3306
Peak systolic blood pressure, mm Hg	180 ± 38	186 ± 31	176 ± 26	.6314
Peak diastolic blood pressure, mm Hg	94 ± 18	84 ± 31	95 ± 20	.3735
Respiratory exchange ratio at peak exercise	1.24 ± 0.1	1.24 ± 0.1	1.17 ± 0.1	.2601
Peak ventilation, L/kg/min	1.4 ± 0.6	1.3 ± 0.3	1.8 ± 0.3	.0044
Heart rate reserve, bpm	97 ± 23	88 ± 15	100 ± 13	.1781
Ventilatory anaerobic threshold				
Oxygen uptake, mL/kg/min	21.4 ± 8.7	22.5 ± 6.5	31.3 ± 6.8	.0007
Workload, W/kg	1.6 ± 0.8	1.7 ± 0.6	2.4 ± 0.6	.0013
Heart rate, bpm	131 ± 26	151 ± 32	159 ± 21	.0168
Exercise duration, min	10.0 ± 2.0	10.3 ± 2.5	12.0 ± 1.5	.0136

Note. Data presented as mean with standard deviation. *P* value derived from ANOVA.

the two patient groups. Peak exercise ventilation and maximal workload were lower in both patient groups compared with controls. Peak oxygen saturation was within normal limits for all three groups during the entire exercise test. At VAT, heart rate was also lower in patients with open defects. Lastly, hemoglobin concentrations were normal for all three groups.

Table 3 display which fitness category each participant belongs to, clearly showing that the majority of patients have reduced exercise capacity.

3.3 | Echocardiography

The echocardiography based on visual estimation by an interventional paediatric cardiologist only disclosed right-sided dilatation in 4 patients. Interestingly, the quantitative observer-blinded measurements illustrated in Figure 3 shows, that there was a significantly larger right ventricle when comparing patients with open ASDs with patients whose defect was spontaneously closed. Right atrium tended to be larger in open ASDs compared with spontaneously closed ASD.

There was no difference in left atria or left ventricular size, see Figure 4.

4 | DISCUSSION

We have provided strong evidence, that adults with a small unrepaired ASD have significantly impaired exercise capacity when compared with healthy age- and gender-matched controls. This impairment corresponds well with patients´ poor self-assessed physical function. Surprisingly, we also found a reduced exercise capacity in patients with a spontaneously closed defect.

Patients with significant ASDs are known to have substantially impaired exercise capacity.[7,8,16] Even if asymptomatic, ASD patients are found to have an impairment more than 25% below normal.[17] A favorable impact of ASD closure on exercise capacity has since been clearly demonstrated.[18-21] Helber et al found a slight increase in oxygen uptake 4 months after surgical ASD repair, with normalized cardiopulmonary exercise capacity 10 years after surgery.[18] Several device closure series have described similar findings. Brochu et al reported a 15% increase in peak oxygen uptake 6 months after device closure. All patients in Brochu's study had sizable ASD, however the authors concluded that the same degree of improvement was observed regardless of the baseline Q_p:Q_s being above or below 2.[19] Even patients with peak VO_2 values within the normal range had significant improvements to levels above normal. Giardini et al

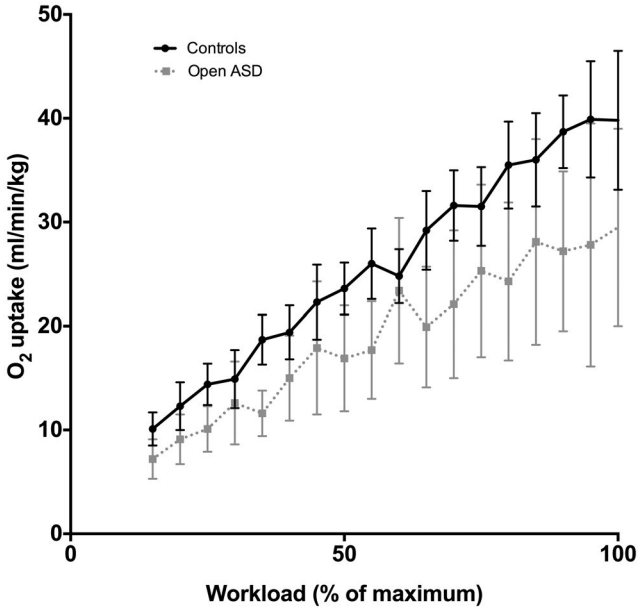

FIGURE 1 Oxygen uptake in relation to workload during incremental cardiopulmonary exercise test in patients with small, unrepaired atrial septal defects and healthy controls. Abbreviation: ASD, atrial septal defect

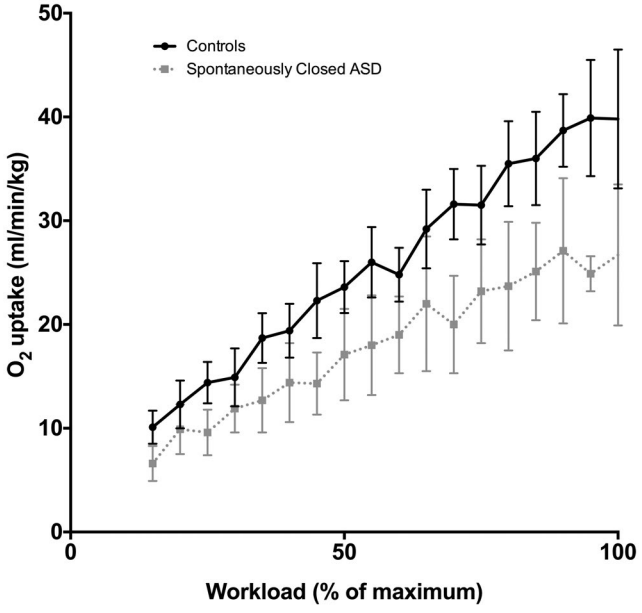

FIGURE 2 Oxygen uptake in relation to workload during incremental cardiopulmonary exercise test in patients with spontaneously closed atrial septal defects and healthy controls. Abbreviation: ASD, atrial septal defect

concluded that peak oxygen uptake was within normal range in 79% of ASD patients 3 years after device closure.[21]

As concluded in a literature review, doubt remains if asymptomatic patients with very small shunts would improve exercise function following ASD closure.[22] These patients who have been diagnosed with a small ASD in early life and later discharged without further follow-up have never been examined systematically until now. The lack of follow-up is primarily because the defects are believed to close spontaneously and patients are considered completely healthy. Our study shows that asymptomatic patients with small defects have significantly impaired oxygen uptake. Both at rest, at VAT and at peak exercise. Data from Kempny et al (n = 128, age = 44.8) demonstrated a mean peak VO_2 of 22.4 ± 8.4 mL O_2/kg/min in significant ASDs scheduled for closure. Our patients had slightly higher peak VO_2, adjusting for our patients younger age. This was to be expected given our patients' smaller defects and smaller shunts. Compared with other patients in the spectrum of adults with congenital heart disease, the exercise impairment found in our patients is comparable with the ones in patients with coarctation of the aorta and collective of patients with various valvular lesions.[8]

We believe the pathophysiological mechanisms behind the lower functional capacity in patients with small, open defects might be similar to those in larger defects: Volume overload of the right ventricle and pulmonary hyper-perfusion.[23] Disrupted right ventricular contractility during exercise could explain our findings, as it did in surgically repaired ventricular septal defects.[24] Another possible explanation is diminished left ventricular function. It has been proven that, the mechanism responsible for improving exercise capacity after device ASD closure is improved left ventricular volume loading with concomitant improvement in left ventricular output.[17]

Impaired exercise values were also found in patients whose defect had spontaneously closed since time of diagnosis, with results identical to patients with small, open ASDs. This is somewhat counterintuitive given that several studies have demonstrated an improvement in exercise capacity after ASD closure. It is fair to assume that patients with a spontaneously closed defect would have had defects with small shunts (Q_p:Q_s < 2). Jategaonkar et al demonstrated that closure of ASDs with small shunts did not significantly improve exercise function in elderly patients.[25] Another study indicated that patients with smaller shunts would benefit least from closure.[17] In contrast, Brochu et al stated that the observed improvement in exercise capacity was irrespective of baseline shunt.[19] Even though spontaneous closure happened at an unknown time point, we must assume that patient have had time to "recover" given that approximately 70% of defects close spontaneously before 5 years of age.[1] An explanation for the impaired exercise capacity in patients with a spontaneously closed defect could be low habitual physical activity level since their weekly exercise tended to be lower than the healthy controls. However, the poor functional capacity demonstrated in these patients despite a discernible defect, may be attributed to the late consequences of the subtle effects of the ASD earlier in life, thereby, perhaps suggesting that even small ASD might benefit from closure in early childhood. Our findings could be explained by an irreversible altered pulmonary system, given that pulmonary vascular obstructive disease was present in 5-10% of adults with unrepaired atrial septal defects.[26] While speculative, these alterations might be related to the increased frequency of recurrent chest infections demonstrated in patients with ASD, which only normalizes 5 years after closure.[5] The pathophysiological mechanisms behind the

TABLE 3 Peak VO_2 reference groups for each participant based on normative data

Age	Poor	Fair	Good	Excellent	Superior
Open ASD					
20-29	IIII		I		
30-39	III	I			I
40-49	II				I
50-65	II	I			
Spontaneously closed ASD					
20-29	IIII	I	I		
30-39	II	I			
40-49	IIII				
50-65	I	I	I		
Healthy controls					
20-29		II	I	III	
30-39			II	I	I
40-49			I	II	
50-65	I				II

pulmonary vascular obstructive disease are, however, not fully understood and genetic predisposition could be a contributing factor. Clearly, the pathophysiologic basis of this unexpected finding needs to be explored in future research.

5 | LIMITATIONS

Enrolling both patients and healthy controls will always cause a concern ensuring good matching between the groups. It is impossible to guarantee zero degree of selection bias, since exercise tests may be more appealing to controls interested in their physical capacities. It should be noted that peak exercise capacity in our control group is almost identical to that found in the study by Maagaard et al[9] and Heiberg et al.[15] Furthermore, selection bias in the control group do not explain why most ASD patients are in the "poor" reference category (Table 3). Four patients with a small, open ASD had dilatation of the right ventricle, thereby per definition making them a significant ASD.[23] However, results did not differ when excluding these patients, since 2 were the only patients in the superior category. A logic explanation is that both are competitive athletes (triathlete and

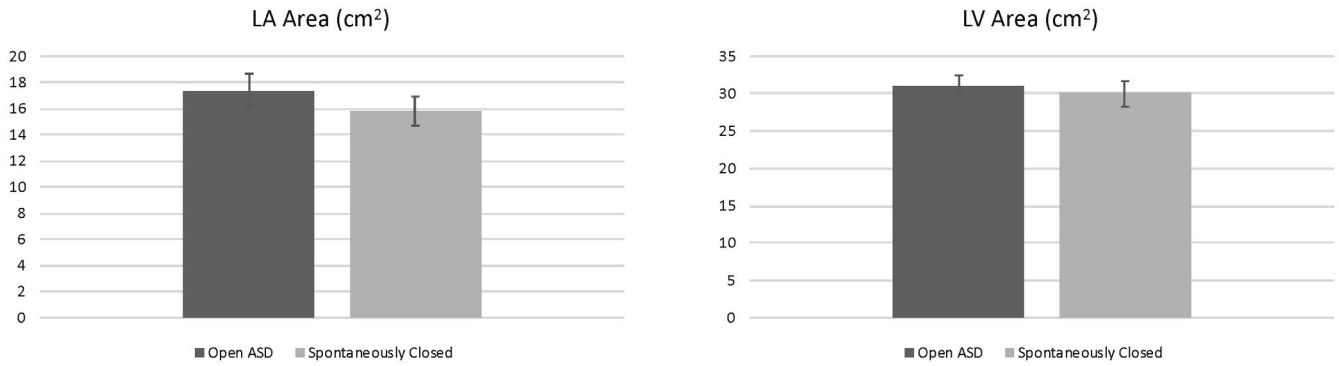

FIGURE 3 Comparison of echocardiographic data. Abbreviations: LA, left atrium; LV, left ventricle

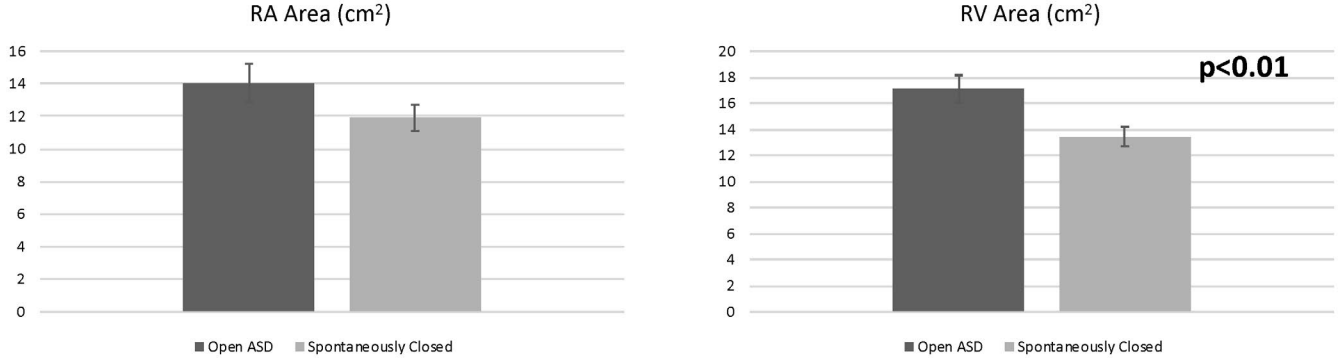

FIGURE 4 Comparison of echocardiographic data. Abbreviations: RA, right atrium; RV, right ventricle

crossfit) and it could be speculated that their oxygen uptake would have been even better with defect closure.

Generally, interpreting register-based data have some limitations. The diagnoses given in the Danish National Patient Registry are of differing validity. Given that ASD is a diagnosis of inclusion (unlikely to be diagnosed when not present) and the diagnosis was validated for the entire cohort, it seems unlikely that they were over-reported. However, some patients with small and insignificant ASDs are possibly not yet diagnosed, and we have no information on these patients. We do not know if these patients are different from those registered with an ASD diagnosis in the Danish National Patient Registry.

6 | CONCLUSION

Adult patients once diagnosed with a small, unrepaired ASD have a significantly impaired exercise capacity. The impairment was present in both patients with an open defect and patients whose defect had spontaneously closed since time of diagnosis, leaving several questions about pathophysiologic mechanisms unanswered. Future studies designed to investigate these mechanisms are needed.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Construction of idea, planning of research, conduct of research, manuscripting writing and revision: Sebastian Udholm, Camilla Nyboe, Vibeke Hjortdal.

Planning and advice on the conduction of cardiopulmonary exercise tests as well as interpretation of the results: Filip Eckerström, Christian Rex.

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