Comparison of Outcomes in Adults With Ventricular Septal Defect Closed Earlier in Life Versus Those in Whom the Defect Was Never Closed

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Ventricular septal defects (VSDs) have recently demonstrated poorer functional outcome with disrupted ventricular contractility during exercise in young patients. It is not known whether this will change with age. Therefore, echocardiography was performed in older patients with congenital VSDs, either surgically closed or unrepaired and all without Eisenmenger physiology, to compare functional outcomes with healthy peers. Transthoracic echocardiography was performed at rest and during supine bicycle exercise, with tissue velocity Doppler for assessment of primary end points: isovolumetric acceleration and systolic velocities. In total, 30 surgically closed VSDs (51 ± 8 years) with 30 healthy controls (52 ± 9 years) and 30 unrepaired VSDs (55 ± 12 years) with 30 matched controls (55 ± 10 years) were included. Surgical patients displayed lower right ventricular (RV) systolic and early diastolic-filling velocities compared with controls, p <0.01, lower tricuspid annular plane systolic excursion (17.8 ± 5 vs 22.7 ± 3mm, p <0.01) and lower fractional area change (37.8 ± 6 vs 46.4% ± 7%, p <0.01). Unrepaired VSDs also had lower RV fractional area change than matched controls (39.9 ± 7 vs 48.4% ± 7%, p <0.01). Both patient groups had more tricuspid regurgitation and larger RV outflow tract dimensions than controls, p <0.01. During exercise, isovolumetric acceleration and systolic velocities were lower in both patient groups compared with controls, with the difference increasing with workload level. In conclusion, adults in their mid-50s with surgically closed or unrepaired VSDs have abnormal RV function at rest, with even more pronounced differences during exercise. These results suggest that a VSD, whether repaired early or considered hemodynamically insignificant, is not a benign lesion and continuous follow-up of adults is warranted. **(Am J Cardiol 2020;133:139−147)**

Improvements in diagnosis and treatment of congenital heart diseases over the last decades have resulted in remarkably improved outcomes and so, the population of adults exceeds that of children.[1,2] Among the most common defects is ventricular septal defect (VSD), considered to have a benign outcome without serious impact on patients' adult life, when either surgically closed in childhood or being so small as not to require intervention. As a result, most adults are discharged from follow-up at specialized centers. Recently, our research group found lower resting ejection fraction and cardiac output, as well as reduced functional capacity and biventricular contractility as measured by force-frequency relations on exercise, in young adults in their mid-20s with either surgically closed or unrepaired VSDs compared with healthy peers.[3-9] Other studies investigated patients in their 30s to 40s and found decreased exercise capacity and abnormal right ventricle (RV) parameters in surgically corrected VSDs,[10,11] and mild left ventricle (LV) diastolic dysfunction, decreased ejection fraction, and aortic regurgitation in unrepaired VSDs.[12,13] However, reports on older VSDs are scarce and it is unknown whether abnormalities seen in earlier adult life improve, persist or worsen. Therefore, older adults with surgically closed or unrepaired VSDs underwent resting and exercise echocardiography and were compared with healthy peers.

Methods

This study is listed on www.clinicaltrials.gov (identifier: NCT03684161) and the study protocol complies with 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 2013. Following written and oral information all participants gave written consent before study inclusion consistent with Danish law. The study cohort was identified from medical records at Aarhus University Hospital, Denmark, and included adults aged between 40 and 75 years, born with a VSD. Inclusion criteria were either a surgically closed VSD or an unrepaired VSD previously deemed hemodynamically

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insignificant by echocardiography or cardiac catheterization. Exclusion criteria included spontaneous closure of VSDs, nonrestrictive unrepaired VSDs, significant residual VSDs in surgically closed defects, coexistence of serious congenital cardiac lesions, associated syndromes, such as Down's syndrome, or severe pulmonary disease. For comparison, 2 reference groups consisting of healthy age- and gender-matched controls were recruited through announcements on an official webpage (www.forsoegsperson.dk). Patients and controls were studied in random order. For all participants, body composition was determined by bioelectrical impedance analysis (ImpediMed Ltd, model SFB7 analyser, Australia). Participants filled out the *International Physical Activity Questionnaire*,[14] assessing weekly amount of physical activity level. The echocardiographic examination was performed on the same day as the subjects participated in cardiopulmonary exercise testing and extensive lung function study, reported elsewhere.[15]

Transthoracic echocardiographic was performed using Vivid7 (GE Vingmed Ultrasound, Horten, Norway) with a 2.5 MHz probe. Echocardiography was performed in supine position, on the left side and resting measurements were conducted, calculated, and referenced according to international recommendations for adults[16,17] by 2 independent observers. Cardiac cycles were analyzed at end-expiration and end-diastole using Echopac software (GE Vingmed, Horten, Norway) by 1 experienced investigator without knowledge of clinical status. Linear LV measurements included posterior wall and inner chamber diameter. Volumetric 2D measurements and ejection fraction were calculated by the modified biplane Simpson. Septum dimension was measured at end-diastole and -systole. RV longitudinal function, tricuspid annular plane systolic excursion (TAPSE), was measured by M-mode. Maximal transverse diameter at the basal 1/3 of the RV inflow, midlevel transverse diameter by papillary muscles and longitudinal diameter were all measured at end-diastole. Linear dimension of RV outflow tract was measured from the anterior RV wall to the aortic valve at end-diastole. Distal RV outflow tract transverse dimension was measured proximal to the pulmonary valve and transversal dimension of the pulmonary trunk was measured distally from the valve. In the subcostal window, diameter of inferior vena cava was estimated and collapsibility calculated by using the sniff test. Right atrial pressure was estimated according to guidelines, accepting pressure of 3 mm Hg matching with inferior vena cava <21 mm with >50% collapsibility and pressure of 15 mm Hg with >21 mm and <50% collapsibility. In cases where 1 of the 2 factors did not fit, an intermediate value of 8 mm Hg pressure was chosen.[16,17] In the apical 4-chamber view, color tissue Doppler was applied with the following velocities measured at basal lateral corners of mitral and tricuspid annulus and septum: longitudinal color-coded myocardial peak velocities during systolic ejection (s'_{peak}), early diastolic filling, atrial contraction, and isovolumetric contraction. Myocardial acceleration during isovolumetric contraction (isovolumetric acceleration [IVA]) was calculated as the ratio of isovolumetric velocity by the time interval from baseline to peak velocity of isovolumetric contraction.

Following echocardiography at rest, participants were positioned with feet on pedals on an Echo Cardiac Stress Table (Lode, Groningen, The Netherlands) tilted to 45° for optimal apical view. Participants pedaled at a steady speed of 60 to 70 rounds/min and workload was gradually increased throughout the test in response to increase in heart rate, with test-completion when exhaustion was reached. During exercise, longitudinal, color-coded myocardial velocities were measured with frame-rate >165 frames/s. Image loops of 5 consecutive cardiac cycles coinciding with end-expiration were recorded every 5 beat-increase in heart rate while pedaling to ensure sufficient images for off-line analysis without movement artifacts. Curves of force-frequency relation included isovolumetric velocities, s'_{peak} and IVA for the free wall of LV, RV, and septal wall during exercise. For the assessment of interobserver variability, 2 experienced investigators without knowledge of clinical status, independently measured and calculated IVA for LV, RV, and septal focus points of 2 random participants at 7 predefined heart rate levels yielding 84 observations. Intraobserver variability was estimated by 1 investigator where IVA was calculated for LV, RV, and septal wall in 10 randomly selected participants at 3 different heart rate levels,

Table 1
Demographics in patients with either surgically closed or unrepaired ventricular septal defects and in 2 groups of healthy, matched peers

Variable	Closed VSDs (n = 30)	Healthy controls (n = 30)	p value	OpenVSDs (n = 30)	Healthy controls (n = 30)	p value
Age (years	51±8	52±9	0.56	55±12	55±10	0.97
Male	15 (50%)	15 (50%)		13 (43%)	13 (43%)	
BMI (kg/m^2)	28±4	26±4	0.10	27±7	26±4	0.54
Height (cm	173±9	174±9	0.73	171±9	172±8	0.78
Weight (kg)	84±15	80±15	0.26	78±24	76±17	0.67
Lean body mass (%)	72±8	75±6	0.07	72±8	74±5	0.27
BSA (m^2)	2.0±0.2	2.0±0.2	0.34	1.9±0.3	1.9±0.2	0.85
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
HR (beats/min)	75±15	73±16	0.63	72±10	77±21	0.28
Exercise						
High-intensity (min/week)	0 (0−2880)	28 (0−1680)	0.15	0 (0−1800)	10 (0−1680)	0.32
Moderate-intensity (min/week)	90 (0−4800)	60 (0−1050)	0.57	90 (0−1680)	60 (0−1050)	0.43
Low-intensity (min/week)	210 (10−5040)	308 (0−2940)	0.67	300 (0−1680)	315 (0−2940)	0.57

Data presented as mean ± standard deviation, total number with (percentage) or median with (total range). BMI = body mass index; BP = blood pressure; BSA = body surface area; HR = heart rate; VSD = ventricular septal defect.

yielding 60 observations. Degree of variability was calculated by the absolute difference divided by the mean of the repeated observations, expressed as percentage.

Primary end points were peak IVA and s'_{peak} of LV, RV, and septal wall at the end of the exercise test, as these parameters had previously been found to be decreased in younger patients with VSDs.[7,8] Secondary end points included resting parameters: LV ejection fraction, RV TAPSE and fractional area change, and biventricular s'_{peak} and myocardial velocities during early diastolic filling and atrial contraction. Correlation analyses were applied to IVA and s'_{peak} at rest and during peak exercise, TAPSE, tricuspid regurgitation, and RV dimensions and correlated with current peak oxygen uptake (VO_{2peak}), as reported elsewhere. For surgically closed VSDs, correlations were tested between TAPSE and age, year, and type of operation. For unrepaired VSDs, association was examined between peak Doppler gradient across the defect and exercise capacity. Comparative studies were performed on raw data from our recently published study on force-frequency relation on 34 adults with unrepaired VSDs (age 27 ± 6 years) and 28 age- and gender-matched healthy controls (age 27 ± 5 years) with similar demographics, in which they undergo identical echocardiographic exercise testing performed by the same investigators.[8] Force-frequency curves of isovolumetric velocities, s'_{peak} and IVA were compared with that of the currently studied older patients with unrepaired VSDs to assess potential time-related changes in ventricular contractility. Raw data from a previous study on young adults with surgically closed VSDs were not available for comparison.[7] Regarding statistical considerations, normally distributed data were reported as mean with standard deviation and nonparametric data as median with 95% confidence interval. Normally distributed data were tested with unpaired Student's *t* test and correlation analyses with Pearson's correlation *r*. p values <0.01 were considered statistically significant. Power calculations were based on VO_{2peak} from an upright bicycle test performed on younger adults with surgically closed VSDs,[6] as the current echocardiography study is part of a larger setup including cardiopulmonary exercise testing. An 80% difference of the previously found result in surgically closed VSDs was expected with a 90% statistical power and 5% significance level. At least 19 participants were needed in each group, but in order to account for dropout or missing values each group included 30 participants. Statistical analyses and drawing of plots were performed using StataIC 11.2 (StataCorp LP, College Station, TX) and GraphPad Prism 7 (GraphPad Software, La Jolla, CA).

Results

Diagnosis-code search revealed 391 adults with congenital VSDs above age 40, of which 74 were eligible surgically closed and 67 eligible unrepaired VSDs. In total, 30 surgically closed VSDs and 30 controls along with 30 unrepaired VSDs and 30 controls were studied between September 2018 and August 2019 at Aarhus University Hospital, Denmark. For eligible patients who declined or did not respond, age, gender, and age at time of surgical closure were comparable to eligible patients included. Table 1 displays similar demographics between included patients and respectively matched controls. Patients used more cardiac-related prescription medication than controls, with 6 surgical patients on antihypertensive medications, 4 on anticoagulants, and 1 on antiarrhythmic compared with 5 controls on antihypertensive medication. For unrepaired VSDs, 8 patients received antihypertensive medication, 6 anticoagulants, and 2 antiarrhythmic, compared with 6 controls on antihypertensive medication. Of the surgical patients, 7% were in New York Heart Association functional class-III, one-quarter in class-II, and the rest in class-I. Of unrepaired VSDs, 23% were in class-II and the rest in class-I. All matched controls were in class-I, except for 1 who was in class-II. From another study conducted on the same day, examination of functional capacity revealed lower VO_{2peak} in surgical patients, 24 ± 7 ml/kg/m^2, compared with

Table 2
Clinical characteristics of patients with either surgically closed or unrepaired ventricular septal defects

Variable	Closed ventricular septal defects (n = 30)	Unrepaired ventricular septal defects (n = 30)
QpQs	2.1±0.5*	1.3±0.1*
VSD-type; Perimembranous	18*	17
Muscular	1	7
Inlet	1	4
Outlet	4	2
Cardiac catheterization; times 1/≥2	5 / 19	11 / 9
Other congenital abnormality	9**	2**
Banding, yes/no	10 / 11***	0 / 30
Age at banding (months)	3.7 (1.6 − 30)	*N/A*
Age at surgical closure of defect (years)	6.3 (1.4 − 54)	*N/A*
≤10 (n = 20)	5.5 (1.4 − 8.6)	
>10 (n = 10)	31 (17 − 54)	
Sternotomy	21***	*N/A*
Type of operation; atriotomy/ventriculotomy	5 / 16***	*N/A*
Patch/direct suture	20 / 6	*N/A*
Cardiopulmonary bypass-time (min)	88±29	*N/A*
Aortic occlusion-time (min)	59±28	*N/A*
Days until discharge	15±5	*N/A*
Causes of readmission		
Chest pain or dyspnea	4	17
Palpitations	10	8
Syncope	2	3
Aortic insufficiency		1
Infective endocarditis	4	5
RBBB, complete/incomplete	16 / 6	1/1

Data presented as mean ± standard deviation, median with (total range), percentage or total number. QpQs = pulmonary-to-systemic ratio; RBBB = right bundle branch block; VSD = ventricular septal defect.

* Corresponds to preoperative measurements, missing information on QpQs in 15 surgically closed patients. For unrepaired VSDs, QpQs is calculated from old catheterization-reports, some >30 years old. Missing information in 14 unrepaired VSDs.

** 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). In unrepaired VSDs: bicuspid aortic valve (n = 1), subvalvular membrane (n = 1).

*** Missing information on 9 surgically closed patients.

Table 3
Echocardiographic parameters in patients with either surgically closed or unrepaired ventricular septal defects and in 2 groups of healthy, matched peers

Variable	Closed VSDs (n = 30)	Healthy controls (n = 30)	p value	OpenVSDs (n = 30)	Healthy controls (n = 30)	p value
Left ventricle						
LVIDd (mm)	45.5±5	45.1±1	0.78	43.0±7	44.1±6	0.52
LVIDs (mm)	33.3±6	30.9±6	0.16	28.6±6	29.9±6	0.43
LVPWd (mm)	11.8±2	11.1±2	0.26	12.1±3	11.2±3	0.20
LVPWs (mm)	17.7±4	16.8±3	0.36	18.1±3	16.7±3	0.10
LVOT diameter (mm)	23.5±3	20.4±3	<0.01	22.0±3	20.3±3	0.04
Ascending aorta (mm)	28.2±4	25.6±4	0.06	26.1±4	25.7±3	0.74
Mass index (g/m^2)	103±27	95±30	0.33	100±21	94±30	0.39
EDVi (ml/m^2)	40.1±9	41.1±12	0.76	41.7±12	39.2±13	0.48
ESVi (ml/m^2)	14.7±5	14.7±7	0.98	13.1±6	13.8±7	0.68
Ejection fraction (%)	62.6±8	65.2±7	0.23	67.5±8	65.7±8	0.50
Fractional shortening (%)	26.8±10	30.7±9	0.14	33.8±9	31.8±11	0.43
Ventricular septum						
VSd (mm)	12.1±3	11.3±3	0.33	12.1±2	11.0±3	0.09
VSs (mm)	16.4±4	15.9±3	0.54	16.5±3	15.6±2	0.17
Right ventricle						
Basal dimension (mm)	43.9±8	37.8±7	<0.01	39.8±7	38.7±8	0.18
Mid-level dimension (mm)	24.6±6	20.4±4	<0.01	20.3±4	19.8±3	0.69
Longitudinal dimension (mm)	70.5±9	67.8±11	0.07	67.9±12	65.9±10	0.75
Fractional area change (%)	37.8±6	46.4±7	<0.01	39.9±7	48.4±7	<0.01
$RVOT_{proximal}$ (mm)	34.1±4	30.4±4	0.03	36.3±6	30.2±5	<0.01
$RVOT_{distal}$ (mm)	27.0±6	23.4±3	<0.01	25.1±5	23.2±3	0.05
$PA_{proximal}$ (mm)	25.8±5	21.2±4	<0.01	24.9±5	21.0±4	0.01
TAPSE (mm)	17.8±3	22.7±3	<0.01	21.8±4	22.3	0.65
TR (mm Hg)	21 (6; 39)	10 (3;18)	<0.01	21 (8; 38)	11 (4;13)	<0.01
Tricuspid annulus (mm/m^2)	38.0±6	33.4±5	<0.01	36.3±5	32.3±5	<0.01
Right atrium						
Minor dimension (cm/m^2)	2.1±0.3	1.8±0.3	<0.01	2.1±0.3	1.8±0.3	<0.01
Major dimension (cm/m^2)	2.5±0.3	2.3±0.3	<0.01	2.6±0.4	2.4±0.3	<0.01
Volume (ml/m^2)	26.8±8	19.1±5	<0.01	24.5±8	17.7±5	<0.01
IVC (mm)	16.1±7	17.1±6	0.39	16.3±6	16.1±6	0.90
IVC collapse (%)	58±13	61±10	0.53	56±12	62±11	0.09
RAP (mm Hg)	5.5±3	3.7±2	0.03	5.6±3	3.5±2	0.01

Data presented as mean ± standard deviation or as median with (95% confidence interval).

IVC = inferior vena cava; LVIDd and LVIDs = left ventricular inner diameter at end-diastole and end-systole; LVPWd and LVPWs = left ventricular posterior wall diameter at end-diastole and end-systole; PA = diameter of pulmonary artery; RAP = estimated right atrial pressure; RVOT = right ventricular outflow tract; TAPSE = tricuspid annular plane systolic ejection; TR = tricuspid regurgitation; VSD = ventricular septal defect; VSd and VSs = ventricular septum diameter at end-diastole and end-systole.

controls, 34 ± 9 ml/kg/m^2, p <0.01. In unrepaired VSDs VO_{2peak} was 26 ± 6 ml/kg/m^2 compared with controls 33 ± 8 ml/kg/m^2, p <0.01. Blood pressures, respiratory exchange ratios, and heart rates were all comparable. In Table 2, clinical characteristics of patients are displayed. For surgical patients, all procedures were performed through median sternotomy on cardiopulmonary bypass with a cross clamp on the aorta at Aarhus University Hospital between 1967 and 2015, except for 1 patient operated in Canada in 1964. Closure was performed with either Dacron- or pericardial patch, or by direct suture through a right atrial or ventricular approach. One surgically closed VSD revealed insignificant residual shunting visualized by echocardiography. All surgical patients were initially discharged after closure, with 60% eventually referred again for check-up in outpatient clinics 1 or more times. Currently, 2 surgical patients are followed with regular visits due to a mechanical aortic valve and a marginally dilated RV, respectively. For the unrepaired VSDs, 83% had been discharged from follow-up at a median age of 19 years (total 6 to 24 years). Following discharge, 80% were referred back 1 or more times and 7 are currently followed.

Table 3 displays linear and volume measurements of the LV, RV, and septal focus points at rest. For unrepaired VSDs, the mean gradient across the open defect was 97 ± 25 mm Hg (range 54 to 139 mm Hg). All unrepaired patients and all controls had normal LV ejection fraction, whereas 13% of surgical patients displayed mildly abnormal values. Regarding valvular pathology, 12 surgical patients had mild mitral regurgitation compared with 7 controls and 8 unrepaired VSDs compared with 5 controls, none with moderate or severe. For aortic regurgitation, 8 surgical patients and 2 controls demonstrated mild regurgitation, whereas 10 unrepaired VSDs had mild and 1 had moderate regurgitation compared with 4 controls with mild regurgitation. For RV measurements, 30% of surgical and 7% of unrepaired VSDs had TAPSE <17 mm, whereas all controls had normal values. RV fractional area change was <35% in 8 surgical and 4 unrepaired VSDs, whereas it was normal for all controls. Regarding tricuspid regurgitation,

Table 4
Tissue Doppler parameters at rest and peak exercise in patients with either surgically closed or unrepaired ventricular septal defects and in 2 groups of healthy, matched peers

Variable	Closed VSDs (n = 30)	Healthy controls (n = 30)	p value	OpenVSDs (n = 30)	Healthy controls (n = 30)	p value
Left ventricle						
e'$_{peak}$ (cm/s)	8.6±3	9.8±2	0.07	8.3±3	9.6±2	0.03
a'$_{peak}$ (cm/s)	5.6±2	5.8±2	0.77	7.6±2	5.8±2	<0.01
s'$_{peak}$ (cm/s)	5.1±1	7.3±2	<0.01	6.4±2	7.1±2	0.21
IVV (cm/s)	4.9±2	5.6±2	0.16	5.1±2	5.6±2	0.27
IVA (cm/s)^2	77.8±31	148.7±57	<0.01	98.6±49	149.9±56	<0.01
At peak exercise						
s'$_{peak}$ (cm/s)	8.4±3	11.0±3	<0.01	9.0±3	10.4±2	0.05
IVA (cm/s^2)	140±50	331±119	<0.01	192±68	327±110	<0.01
Ventricular septum						
e'$_{peak}$ (cm/s)	7.2±2	9.0±2	<0.01	7.2±2	8.7±2	<0.01
a'$_{peak}$ (cm/s)	6.1±2	6.7±1	0.22	6.7±2	6.6±1	0.92
s'$_{peak}$ (cm/s)	4.9±1	6.8±1	<0.01	6.0±1	6.7±1	0.05
IVV (cm/s)	3.6±1	5.1±2	<0.01	4.4±1	5.1±2	0.08
IVA (cm/s^2)	71.5±43	144.9±79	<0.01	90.0±34	141.0±80	<0.01
At peak exercise						
s'$_{peak}$ (cm/s)	7.4±2	10.8±2	<0.01	8.6±2	10.4±2	<0.01
IVA (cm/s^2)	132±53	294±105	<0.01	165±65	298±97	<0.01
Right ventricle						
e'$_{peak}$ (cm/s)	7.1±2	10.±2	<0.01	8.1±2	10.4±2	<0.01
a'$_{peak}$ (cm/s)	7.2±3	9.4±2	<0.01	10.7±3	9.5±3	0.14
s'$_{peak}$ (cm/s)	7.1±2	10.1±2	<0.01	9.1±2	10.0±1	0.03
IVV (cm/s)	4.6±1	7.8±2	<0.01	6.0±3	7.6±2	0.01
IVA (cm/s^2)	81.9±47	170.3±72	<0.01	112.4±44	169.9±80	<0.01
At peak exercise						
s'$_{peak}$ (cm/s)	9.9±2	15.1±3	<0.01	12.1±3	15.3±3	<0.01
IVA (cm/s^2)	183±60	393±101	<0.01	229±92	391±111	<0.01

Data presented as mean ± standard deviation or as median with (95% confidence interval). a'$_{peak}$ = peak a-wave velocity; e'$_{peak}$ = peak e-wave velocity; IVA = isovolumetric acceleration; IVV = isovolumetric velocity; s'$_{peak}$ = peak s-wave velocity; VSD = ventricular septal defect.

18 surgical VSDs displayed measurable regurgitation compared with 8 controls and 20 unrepaired VSDs compared with 6 controls. Using a tricuspid regurgitation velocity <2.8 m/s to define normal RV pressure,[18] 90% of all surgical and 87% of unrepaired VSDs were normal, with all controls demonstrating normal regurgitation velocity. Tricuspid annulus index was >21 mm/m^2 in 7 surgically closed, 9 unrepaired VSDs and 2 controls. Degrees of pulmonary valve insufficiency were found in 20 surgical VSDs and 6 controls, and 19 unrepaired VSDs and 5 controls.

Table 4 shows tissue Doppler imaging values at rest and peak exercise for all 4 groups. For RV s'$_{peak}$ at rest, 67% of surgical VSDs compared with 23% of healthy peers were below the cut-off value of <9.8 cm/s. In unrepaired VSDs, 60% were below compared with 30% of controls. Peak velocity at early RV filling was <7.8 cm/s in 53% of surgical patients and 37% of unrepaired VSDs, whereas 10% of controls were below that threshold. Comparing patient groups, surgically closed VSDs were lower than unrepaired VSDs for RV and septal s'$_{peak}$, as well as peak velocity at atrial contraction for the 3 focus points, p <0.01. Remaining parameters were comparable. Exercise force-frequency curves of isovolumetric velocities, s'$_{peak}$, and IVA were consistently lower in LV, RV, and septal focus points in patients compared with controls (Figure 1). The difference was most pronounced between surgical VSDs and controls, and increased with workload. Peak heart rate did not differ between surgical VSDs and controls (146 ± 11 vs 147 ± 12 beats/min, p = 0.64) or unrepaired VSDs and controls (141 ± 11 vs 144 ± 12 beats/min, p = 0.23). Comparing peak exercise between patients, surgical VSDs were lower than unrepaired VSDs on RV IVA and s'$_{peak}$ as well as LV IVA, p <0.01. Regarding degree of variability for IVA measurement, the interobserver variability was 12% and the intraobserver variability was 7%. Correlation analyses could not be demonstrated for resting tissue Doppler values and VO_{2peak}, except in unrepaired VSDs for LV IVA and exercise capacity (r = 0.51, p <0.01). Considering s'$_{peak}$, and age, a tendency toward lower s'$_{peak}$ values with increasing age was seen in surgically closed VSDs (r = -0.42, p = 0.02), their controls (r = -0.65, p <0.01), in unrepaired VSDs (r = -0.66, p <0.01) and their controls (r = -0.60, p <0.01). RV peak isovolumetric velocity and IVA in surgical VSDs were positively correlated with VO_{2peak} (r = 0.44, p = 0.01, and r = 0.41, p = 0.01, respectively), but not in controls. For unrepaired VSDs, positive correlations were seen for VO_{2peak} and LV peak isovolumetric velocity (r = 0.49, p <0.01) and s'$_{peak}$ (*r* = 0.48, p <0.01), but not for VO_{2peak} and peak gradient across defect. No relations were found for surgical VSDs between TAPSE <17 mm and age, year or type of operation. No associations were seen for either patients or controls between TAPSE, tricuspid regurgitation, RV dimensions, and VO_{2peak}. Figure 2 illustrates comparative force-frequency curves of young and old patients with unrepaired VSDs with no clear change in difference between patients and controls with age.

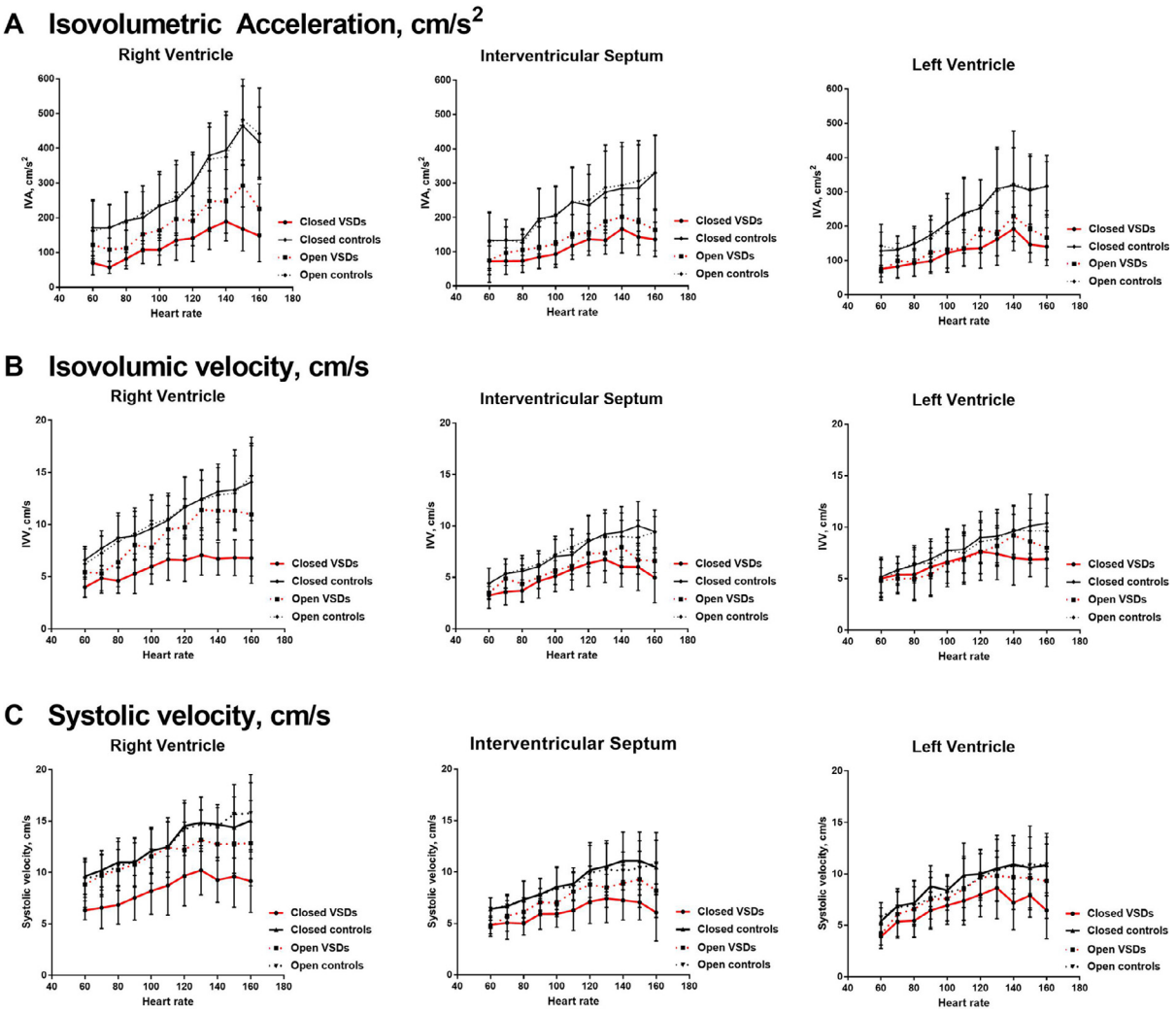

Figure 1. Force-frequency curves in patients with surgically closed or unrepaired VSDs and their healthy peers. (*A*) IVA velocities during exercise in patients and controls for the left ventricle, interventricular septum, and right ventricle. (*B*) IVV during exercise in patients and controls for the left ventricle, interventricular septum, and right ventricle. (*C*) Peak systolic velocities during exercise in patients and controls for the left ventricle, interventricular septum, and right ventricle. IVA = isovolumetric acceleration; IVV = isovolumic velocities; VSDs = ventricular septal defects.

Discussion

This is the first study to assess and compare functional outcomes in patients with a congenital VSD over the age of 40 years with healthy peers. Our data show a number of important novel findings: At rest, surgically closed VSDs reveal markedly lower RV tissue Doppler and TAPSE reflecting disrupted systolic function when compared with healthy peers. This was also observed in unrepaired VSDs, although not as pronounced. Going along with this, both patient groups display increased RV dimensions and lower fractional area change. During exercise, surgical VSDs have lower isovolumetric velocities, s'$_{peak}$, and IVA compared with controls with increasing difference with workload. The most distinct differences are seen in the RV parameters, although LV parameters are also lower in patients than in controls. One of the most overt signs of RV systolic dysfunction was an abnormal systolic velocity, present in 67% of surgical and 60% of unrepaired VSDs. Interestingly, 23% and 30% of the respectively matched controls also demonstrated abnormal RV systolic velocities, which, whereas this was significantly lower incidence than the patients, suggest that better age-related normal values are required. As correlation analyses revealed an inverse relation between increasing age and declining tissue Doppler measurements, the findings may reflect overall age-related decline in these longitudinal myocardial velocities. Regretfully, no large set of normative reference values exist for the age-related change in measured tissue Doppler velocities, emphasizing the need for studies having carefully matched healthy control populations. Fractional area change is a commonly used method of describing global RV systolic function. A little over 1/4 of surgical VSDs and 1 in 7 unrepaired VSDs had fractional area change <35%, whereas all controls had normal values. Furthermore, 30% of surgical VSDs, 7% of unrepaired VSDs, but no controls had abnormal TAPSE, suggesting abnormal long-axis function which is fundamental to global RV systolic function.[16] Interestingly, in a study by Menting et al,[10] 14% of surgically closed VSDs age 40 had abnormal fractional area

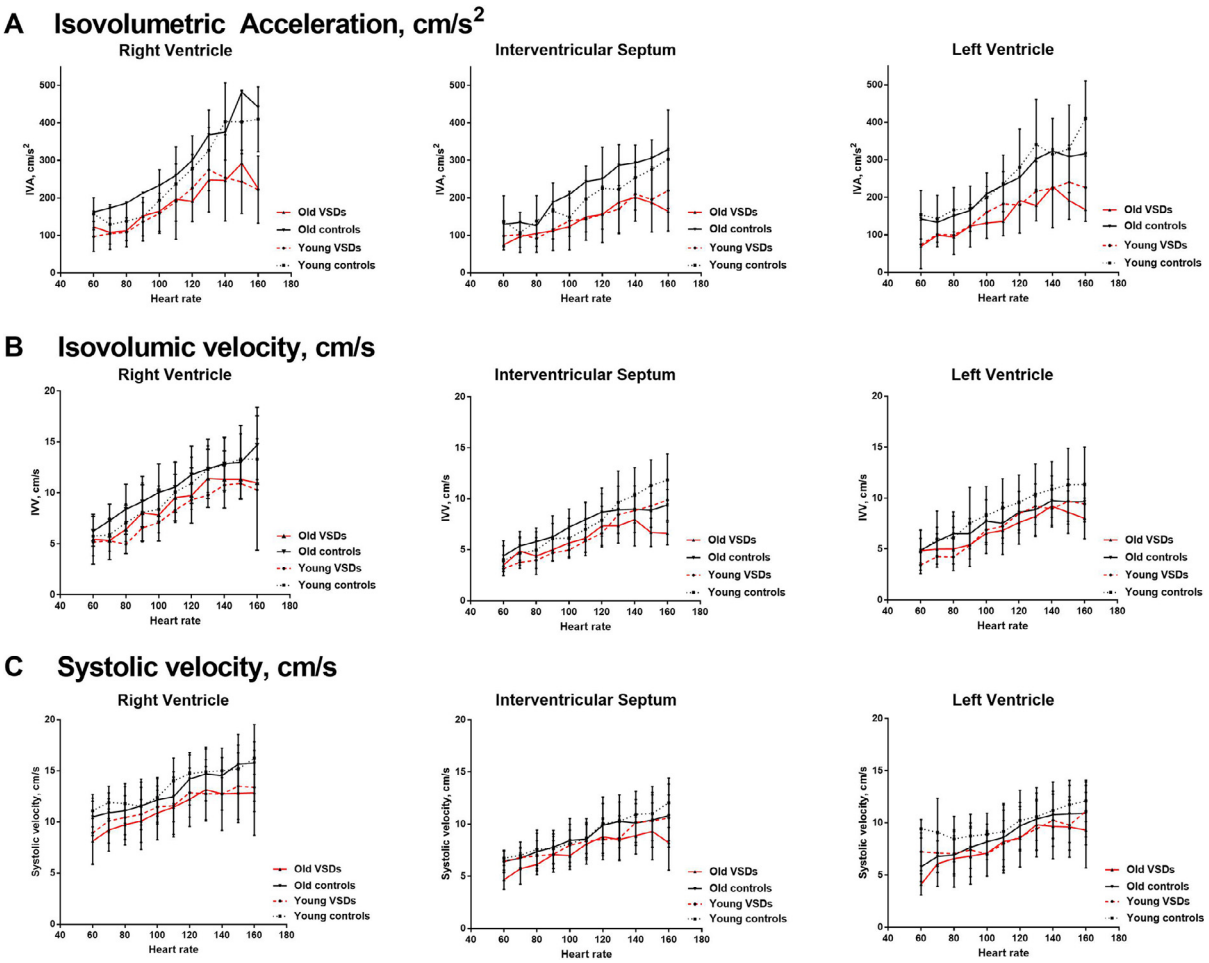

Figure 2. Force-frequency curves in young and old patients with unrepaired VSDs and their healthy peers. (*A*) IVA velocities during exercise in patients and controls for the left ventricle, interventricular septum, and right ventricle. (*B*) IVV during exercise in patients and controls for the left ventricle, interventricular septum, and right ventricle. (*C*) Peak systolic velocities during exercise in patients and controls for the left ventricle, interventricular septum, and right ventricle. IVA = isovolumetric acceleration; IVV = isovolumic velocities; VSDs = ventricular septal defects.

change and only 3% had abnormal TAPSE, perhaps suggesting these abnormalities worsen with increasing age. This is important as newly published material on 1,039 healthy adults, followed for 13 years with echocardiography, shows that decreasing TAPSE is predictive of symptomatic cardiovascular disease.[19]

On average, our patients had a 20% to 30% reduction in VO_{2peak} during maximal exercise, which is compatible with our previous findings of reduced VO_{2peak} and cardiac output during exercise in younger surgical and unrepaired VSDs.[5,6] As demographics or less active daily exercise habits cannot explain lower VO_{2peak}, we proposed that patients with congenital VSDs have mild or occult increases in pulmonary vascular resistance that is worsened with exercise.[4,20] This theory has also previously been emphasized by results in younger adults with VSDs where MRI revealed increased RV volume and trabeculation,[3] increased pulmonary regurgitation during exercise,[4,20] lower maximal cardiac output and decreased RV contractility during exercise.[7,8] In this current echocardiographic study, results further strengthen this hypothesis, as 10% of surgical VSDs and 13% of unrepaired VSDs had tricuspid regurgitation velocity ≥2.8 m/s. It is not suggested that these subgroups of patients suffer from pulmonary hypertension, as high regurgitation velocity does not provide a definite diagnosis. Nevertheless, the probability of pulmonary hypertension being present does increase with rising tricuspid regurgitation velocities.[21] Whether related to abnormal pulmonary vascular hemodynamics or not, younger surgical and unrepaired VSDs have previously been found with disrupted patterns of ventricular contractility during exercise, particularly of the RV.[7,8] Although comparison of force-frequency curves in younger and older unrepaired VSDs did not seem to differ, it is worth emphasizing that older patients displayed abnormal resting parameters, not seen in the younger cohort.[8] With this in mind, the majority of our patients are not currently seen in a regular follow-up regime at a specialized center reflecting the general notion in specialists that a VSD is a benign condition when treated correctly in childhood. Nevertheless, in the most recent guideline from the American Heart Association,[22] it is recommended that adult VSDs, both surgically closed and unrepaired, enter a routine follow-up program. This may be the first step in a changing attitude in physicians toward the congenital VSD in adulthood, and ultimately a better understanding of the truly long-term consequences of their disease.

A limitation of the current study is the cross-sectional study design and therefore, age-related differences could also reflect an era effect, rather than true physiologic deterioration. Although we did see an increased proportion reporting reduced functional class, it is difficult to ascribe noninvasive indices to the reported functional capacity, although some were correlated with objective measurements of exercise capacity. Furthermore, such associations do not address the issue of causation. If, for example, our speculation that the subtle residual differences in pulmonary vascular function account for the abnormalities of RV function, and in turn functional capacity, a more robust measurement of pulmonary hemodynamics, for example Swan-Ganz catheterization during cardiopulmonary exercise testing, would be required and may now be justifiable given our results. In conclusion, persistent abnormalities of right ventricular function and functional capacity have been demonstrated in older patients with congenital VSD, with a signal toward worse outcomes in those following surgical closure, and with older age. Continued follow-up and longitudinal studies to investigate the mechanisms of these abnormalities are warranted.

Authors' Contribution

Maagaard M: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Writing - Original Draft; Visualization; Supervision; Project administration.

Eckerström F: Conceptualization; Methodology; Validation; Investigation; Writing - Review & Editing; Project administration.

Redington A: Methodology; Writing - Review & Editing.

Hjortdal V: Conceptualization; Methodology; Validation; Resources; Writing - Review & Editing; Supervision; Funding acquisition.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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