

ORIGINAL RESEARCH

Elevated Left and Right Atrial Pressures Long-Term After Atrial Septal Defect Correction: An Invasive Exercise Hemodynamic Study

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BACKGROUND: Despite correction of the atrial septal defect (ASD), patients experience atrial fibrillation frequently and have increased morbidity and mortality. We examined physical capacity, cardiac performance, and invasive hemodynamics in patients with corrected ASD.

METHODS AND RESULTS: Thirty-eight corrected patients with isolated secundum ASD and 19 age-matched healthy controls underwent right heart catheterization at rest and during exercise with simultaneous expired gas assessment and echocardiography. Maximum oxygen uptake was comparable between groups (ASD 32.7 ± 7.7 mL O₂/kg per minute, controls 35.2 ± 7.5 mL O₂/kg per minute, $P=0.3$), as was cardiac index at both rest and peak exercise. In contrast, pulmonary artery wedge v wave pressures were increased at rest and peak exercise (rest: ASD 14 ± 4 mm Hg, controls 10 ± 5 mm Hg, $P=0.01$; peak: ASD 25 ± 9 mm Hg, controls 14 ± 9 mm Hg, $P=0.0001$). The right atrial v wave pressures were increased at rest but not at peak exercise. The transmural filling pressure gradient (TMFP) was higher at peak exercise among patients with ASD (10 ± 6 mm Hg, controls 7 ± 3 mm Hg, $P=0.03$). One third of patients with ASD demonstrated an abnormal hemodynamic exercise response defined as mean pulmonary artery wedge pressure ≥ 25 mm Hg and/or mean pulmonary artery pressure ≥ 35 mm Hg at peak exercise. These patients had significantly elevated peak right and left atrial a wave pressures, right atrial v wave pressures, pulmonary artery wedge v wave pressures, and transmural filling pressure compared with both controls and patients with ASD with a normal exercise response.

CONCLUSIONS: Patients with corrected ASD present with elevated right and in particular left atrial pressures at rest and during exercise despite preserved peak exercise capacity. Abnormal atrial compliance and systolic atrial function could predispose to the increased long-term risk of atrial fibrillation.

REGISTRATION INFORMATION: clinicaltrials.gov. Identifier: NCT03565471.

Key Words: atrial septal defect ■ cardiopulmonary exercise test ■ echocardiography ■ hemodynamic ■ right heart catheterization

The clinical and hemodynamic severity of an atrial septal defect (ASD) is determined by factors such as size, atrial pressures, ventricular compliance, and diastolic filling.^{1,2} Despite correction of the ASD, whether it be percutaneously or surgically, long-term

mortality is increased compared with the background population.³ Additionally, the risk of atrial fibrillation (AF) is increased with a progressive incidence with age, and so is the hospitalization risk because of pneumonia and antibiotics use.⁴⁻⁶

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For Sources of Funding and Disclosures, see page 11.

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CLINICAL PERSPECTIVE

What Is New?

- Patients with a corrected atrial septal defect demonstrate elevated right and left atrial pressures at rest and at peak exercise, and elevated transmural filling pressure at peak exercise, while preserving exercise capacity.

What Are the Clinical Implications?

- These subclinical findings are indicative of impaired atrial performance and/or altered ventricular properties, which may predispose to long-term complications such as atrial fibrillation.

Nonstandard Abbreviations and Acronyms

CO	cardiac output
CPX	cardiopulmonary exercise test
mPAP	mean pulmonary artery pressure
mPAWP	mean pulmonary artery wedge pressure
mRAP	mean right atrial pressure
PAWP	pulmonary artery wedge pressure
RA	right atrium
RHC	right heart catheterization
sPAP	systolic pulmonary artery pressure
TMFP	transpulmonary filling pressure gradient
VO₂	oxygen uptake
vPAWP	pulmonary artery wedge v wave pressure
WU	wood units

ASD correction improves survival if treated before the age of 25 years, but may not fully alleviate abnormalities in the cardiac function.⁷ Correction immediately reduces right atrial (RA) and right ventricular (RV) volume overload, and the right-sided chamber dimensions and function tend to near-normalize along with increasing left ventricular (LV) dimensions.⁸⁻¹⁰ Percutaneous correction has been shown to reduce left atrial (LA) volume index, increase LV size, and improve biventricular myocardial performance Doppler index while the LV ejection fraction is unchanged.¹¹

The aim of an ASD correction is to reduce RV volume overload and pulmonary arterial pressures, preventing the development of persistent pulmonary arterial hypertension, which has a prevalence of 5% to 8% in a mixed cohort of patients with corrected and uncorrected secundum ASD.^{3,12} Pulmonary and cardiac filling pressures are conventionally evaluated at

rest, whereas evaluation of the cardiopulmonary function during exercise may provide additional information on abnormalities in the cardiac and pulmonary arterial system.

The objective of this study is to examine the physical capacity, cardiac performance and hemodynamics by exercise right heart catheterization in patients with corrected ASD secundum compared with age-matched healthy participants. The hypothesis is that a previous presence of an atrial shunt has altered the hemodynamics of the heart, resulting in impaired cardiopulmonary performance. The hypothesized hemodynamic changes are thought to be lasting and may explain the long-term health complications seen in patients with ASD and point towards areas of importance for clinical follow-up.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request and according to applicable legal and ethical requirements.

In this clinical observational study, adults with a corrected isolated secundum ASD were identified through the hospital system at Aarhus University Hospital, Denmark. Age-matched healthy controls were found through public announcements. Thirty-eight patients with an ASD, 19 with percutaneous device closure and 19 with surgical closure, and 19 controls were included. Of the patients with surgically corrected ASD, 10 were closed with patches (5 Dacron and 5 pericardium) and 9 without. Eight of the controls have previously participated in another invasive hemodynamic exercise study.¹³

Patients were eligible if the ASD was diagnosed at a minimum age of 2 years and >3 years had passed since the corrective procedure. Indication for ASD correction was right ventricular enlargement, which all patients with ASD had; however, precorrective hemodynamic measurements were not consistently available. All participants were at least 18 years of age at the time of the present investigation.

The study was conducted at Aarhus University Hospital, Denmark, from August 2018 to October 2019.

The Danish Data Protection Agency (j.no. 1-16-02-154-18) and The Regional Committee on Health Research Ethics of the Central Denmark Region (j.no. 1-10-72-50-18) approved this study, which is registered on ClinicalTrials.gov (ID NCT03565471). We complied with the Declaration of Helsinki, and participants submitted written informed consents.

Echocardiography

With patients at rest, transthoracic echocardiography was conducted using the Vivid E95 system (GE

Healthcare, Horten, Norway) with the M5S and 4V-D transducers to obtain 2-dimensional and 3-dimensional images as per current guidelines.¹⁴ During cardiopulmonary exercise testing, apical views of the left ventricle, and a modified 4-chamber view of the right ventricle were obtained at each load increment using the M5S (2-dimensional) transducer. The images were blinded and analyzed using EchoPAC PC SW-Only version 202 (GE Healthcare, Horten, Norway).

Right Heart Catheterization

Participants were studied in the fasted state. Right heart catheterization (RHC) was performed using a 7.5-Fr Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA) through an 8-Fr sheath via the right internal jugular vein. Transducers were zeroed at the phlebostatic axis using a self-levelling laser caliper.

Pressure tracings from the RA, RV, pulmonary artery (PA), and pulmonary artery wedge (PAWP) were recorded continuously, digitized (240 Hz), and stored for offline analysis using Mac-Lab Hemodynamic Recording System (GE Healthcare, Chicago, IL). Data were analyzed blinded to clinical and exercise data by manually reviewing the recorded pressure curves obtained during rest and exercise on the Mac-Lab system and averaging the values for 3 consecutive complexes at end expiration.

We measured noninvasive systolic and diastolic blood pressure, heart rate, RA mean pressure, peak a wave, and v wave (mRAP, right atrial peak a wave pressure (aRAP), right atrial v wave pressure (vRAP) systolic right ventricular pressure (sRVP), diastolic right ventricular pressure (dRVP), right ventricular end-diastolic pressure (RV EDP)), RV maximal pressure change over time, mean, systolic, and diastolic PA pressure (mPAP, systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP)), and PA wedge mean pressure, peak a wave, and v wave (mPAWP, pulmonary artery peak a wave pressure (aPAWP), pulmonary artery v wave pressure (vPAWP)).

Cardiac output (CO) was measured using thermodilution. In a few cases where peak exercise CO exceeded Mac-Lab's thermodilution measuring range of 20 L/min, peak exercise CO was calculated using direct Fick's principle: $CO = \text{oxygen uptake (VO}_2\text{)}/\text{arteriovenous saturation difference} * [\text{Hb}](\text{g/dL}) * 1.36 \text{ mL O}_2\text{/g Hb}$. Cardiac index was CO indexed to body surface area. Stroke volume was CO divided by heart rate.

Blood samples were obtained from the PA and superior cava vein at rest (to exclude patients with residual shunts) and from the PA at peak exercise to measure hemoglobin, oxygen saturation, and serum lactate level.

From the measured parameters, we calculated: mean arterial pressure (MAP)= $1/3 * \text{systolic blood pressure} +$

$2/3 * \text{diastolic blood pressure}$, arterial pulse pressure= $\text{systolic blood pressure} - \text{diastolic blood pressure}$, pulmonary pulse pressure= $\text{systolic pulmonary artery pressure} - \text{diastolic pulmonary artery pressure}$, transpulmonary pressure gradient (TPG)= $\text{mPAP} - \text{mPAWP}$, transmural filling pressure gradient (TMFP)= $\text{mPAWP} - \text{mRAP}$, systemic vascular resistance= $(\text{MAP} - \text{mRAP})/\text{CO}$, total arterial compliance= $\text{stroke volume}/\text{arterial pulse pressure}$, pulmonary vascular resistance= $\text{transpulmonary pressure gradient}/\text{CO}$, and pulmonary arterial compliance (PAC)= $\text{stroke volume}/\text{pulmonary pulse pressure}$. The changes in PAWP/CO ($\Delta\text{PAWP}/\Delta\text{CO}$) is calculated as the difference in mPAWP from rest to peak divided by the difference in CO from rest to peak.

Cardiopulmonary Exercise Test

With the catheter in situ, participants performed a cardiopulmonary exercise test (CPX) on a semisupine ergometer (GE eBike L Ergometer, Freiburg, Germany) with simultaneous expired gas analysis (Jaeger MasterScreen CPX, CareFusion, 234 GmbH, Hoechberg, Germany). The exercise protocol began at 0 W with load increments every 3 minutes. The first increase was 50 W followed by either 25 W or 50 W stepwise increases based upon the participants' self-reported fitness level.

Hemodynamic pressures were measured in the time interval of 1.5 to 3.0 minutes at each load increment. Participants exercised until maximal exhaustion defined as a respiratory exchange ratio (RER) ≥ 1.1 .

CPX values were manually reviewed by averaging the values for the last 1 minute 30 seconds at each load increment to obtain an averaged steady-state value at each workload.

We measured ventilation, VO_2 , carbon dioxide production, respiratory exchange ratio, heart rate, systolic blood pressure, and diastolic blood pressure. We calculated: metabolic equivalent of task= $(\text{VO}_2/\text{weight})/3.5 \text{ mL O}_2\text{/kg per minute}$, and $\Delta\text{CO}/\Delta\text{VO}_2 = (\text{CO}_{\text{peak}} \text{ L/min} - \text{CO}_{\text{rest}} \text{ L/min})/((\text{VO}_{2\text{peak}} \text{ mL/min} - \text{VO}_{2\text{rest}} \text{ mL/min})/1000)$. Expected workload and expected VO_2 at peak exercise were calculated by the CPX software using the Wasserman equation.¹⁵

Subgroup Analysis

Participants with an abnormal exercise response (ASD-abnormal) were compared with participants with a normal exercise response (ASD-normal and controls). An abnormal exercise response was defined as mPAWP ≥ 25 mm Hg and/or mPAP ≥ 35 mm Hg at peak exercise.

Statistical Analysis

The power calculation was based upon VO_2 max values (the primary end point). A normal exercise test

result is 48 mL O₂/kg per minute with a SD of 7 mL O₂/kg per minute.¹⁶ With an expected difference between groups and healthy controls of 15% and a power of 85%, the number of patients needed in each subgroup (controls, surgically corrected ASDs, and percutaneously corrected ASDs) is 18.

Results are reported as mean± SD or number (%) for Gaussian distributed and categorical variables, or median (interquartile range) for nonnormally distributed variables unless otherwise indicated. If nonnormally distributed variables achieved a Gaussian distribution through log-transformation, this was done before any statistical analyses. The calculated log(mean) and log(SD) were transformed back using the exponential function.

Normally distributed continuous data were analyzed using ANOVA and unpaired Student *t* test. Nonparametric continuous data were tested with the Kruskal–Wallis test and Wilcoxon rank-sum test. Binomial data were analyzed using Fisher exact test. Linear regression was used to calculate the slope between parameters. Pearson correlation coefficient was calculated for the correlation analyses. The significance level is set at 5%. Data were collected and managed using REDCap electronic data capture tools hosted at Aarhus University, Denmark.^{17,18} Stata/SE 16.1 (StataCorp LLC, TX) was used for data analyses.

RESULTS

Baseline Demographics and Echocardiography Data

Of the 57 participants, we have complete RHC and CPX data on 37 patients with ASD and 17 controls. Two controls were excluded from the RHC analyses because 1 did not undergo RHC examinations and 1 developed a brief self-limiting period of AF during the RHC. One patient with ASD did not complete the CPX because of a prolonged vasovagal episode and was excluded from both the RHC and CPX analyses.

The ASD and control cohorts were comparable on all demographic parameters besides sex (Table 1). Median age at ASD diagnosis was 7 years (range 2–14 years), mean ASD size was 17±7 mm, and mean age at correction was 10±2 years. Patients with ASD were on average examined 18±7 years since their ASD correction. Echocardiographic data on LV and RV systolic and diastolic function are displayed in Table 1. No differences were noted regarding biventricular volumes or ejection fractions; however, RVEF is borderline reduced in patients with ASD. LV mass index was comparable between groups. Mitral E-deceleration time was borderline prolonged for patients with ASD compared with controls. Tricuspid annular place systolic excursion and RV global longitudinal strain were significantly

Table 1. Demographics and Echocardiographic Data

	Controls n=19	ASD n=38	P Value
Age at examination, y	33 (24–43)	27 (24–39)	0.5
Females, n (%)	7 (37)	26 (68)	0.04
BSA, m ²	1.9±1.1	1.9±1.1	0.5
Diabetes mellitus, n	0	1	...
Hypertension, n	0	1	...
Current smokers, n/ Previous smokers, n	0/2	9/4	...
Echocardiography			
LV EDV, mL	111±22	105±24	0.3
LV ESV, mL	42±1	40±1	0.5
LVEF, %	57±5	58±7	0.7
LV mass index, g/m ² (Devereux formula)	76±18	82±21	0.3
LAVi, mL/m ²	19.8±1.4	18.5±1.4	0.5
E/A	1.9±0.6	2.2±0.7	0.1
E-DT, ms	195±50	223±59	0.08
E/é	6.7±1.7	7.4±2.4	0.3
RV EDV (3D), mL	109±32	93±22	0.04
RV ESV (3D), mL	55±9	54±14	0.8
RVEF (3D), %	47±12	42±7	0.2
TAPSE, cm	2.3±0.5	2.0±0.4	0.05
RV GLS, %	-24.3±4.3	-18.1±4.7	<0.0001
RAVi, mL/m ²	18.1±4.9	21.3±6.4	0.06

Data are presented as mean±SD, median (interquartile range), or number (frequency). BSA indicates body surface area; E/A, early (E) to late (A) diastolic mitral inflow velocity ratio; E-DT, mitral E-wave deceleration time; E/é, early diastolic mitral inflow velocity (E) to early diastolic mitral annular velocity (é) ratio; LAVi, left atrial end-systolic volume index; LV EDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LV ESV, left ventricular end-systolic volume; LV mass index, left ventricular mass index; RAVi, right atrial end-systolic volume index; RV EDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RV ESV, right ventricular end-systolic volume; RV GLS, right ventricular global longitudinal strain; and TAPSE, tricuspid annular place systolic excursion. The reported RV volumes are obtained from 3-dimensional (3D) images.

reduced compared with controls but within the normal range. RA volume index was borderline enlarged in patients with ASD compared with controls (*P*=0.06).

Habitual activity level assessed using the International Physical Activity Questionnaire showed that both patients with ASD and controls conducted moderate- to high-intensity exercise for 4 to 5 hours/wk (*P*=0.4).

Cardiopulmonary Exercise in Patients With ASD and Controls

The cardiopulmonary exercise values are shown in Table 2. At rest, heart rate was higher in the ASD group compared with controls. Systolic and diastolic blood pressures were comparable between groups. The maximal workload was comparable between groups (ASD 166±46 W, controls 188±50 W, *P*=0.1). Peak VO₂

Table 2. Cardiopulmonary Function

	Controls n=18	ASD n=37	P Value
Resting cardiopulmonary function			
METS, mL O ₂ /kg per min	1.3±0.2	1.4±0.3	0.2
HR	64±8	74±16	0.006
sBP	121±14	126±14	0.2
dBp	74±9	72±9	0.4
VO ₂ , mL/kg per min	4.6±0.8	4.9±1.1	0.2
RER	0.8±0.05	0.8±0.07	0.1
Lactate, mmol/L	1.7±1.4	2.1±1.5	0.1
Peak exercise cardiopulmonary function			
Workload, W	188±50	166±46	0.1
METS, mL O ₂ /kg per min	10.1±2.2	9.4±2.2	0.3
HR	170±19	174±14	0.3
sBP	212±49	209±46	0.9
dBp	80±1	86±1	0.6
VO ₂ , mL/kg per min	35.2±7.5	32.7±7.7	0.3
RER	1.2±0.06	1.2±0.09	0.8
Lactate, mmol/L	10.5±2.9	10.9±3.7	0.7

Data are presented as mean±SD. ASD indicates patients with atrial septal defect; dBp, diastolic blood pressure; HR, heart rate; METS, metabolic equivalent of task; RER, respiratory exchange ratio; sBP, systolic blood pressure; and VO₂, oxygen uptake.

was 32.7±7.7 mL/min per kg for ASDs and 35.2±7.5 mL/min per kg for controls (*P*=0.3). Of all the participants, 89% of patients with ASD and 67% of controls reached at least 80% of the expected workload, and 92% of patients with ASD and 94% of controls reached at least 80% of the expected VO₂ max. Both groups had comparable peak RERs (>1.1) and reached a peak serum lactate >10 mmol/L indicating maximal physical effort.

Hemodynamic Performance at Rest and at Peak Exercise in Patients With ASD and Controls

The hemodynamic results are displayed in Table 3. Resting mRAP, mPAP, and mPAWP were not different between groups, but notably, resting vRAP and vPAWP were significantly higher in the group with ASD (Figure 1). Systolic right ventricular pressure was 27±4 mm Hg in patients with ASD and 25±4 mm Hg in controls (*P*=0.3), and right ventricular end-diastolic pressure was 8±3 mm Hg in patients with ASD and 9±3 mm Hg in controls (*P*=0.08).

Transpulmonary pressure gradient increased from rest to peak exercise for both groups (rest: ASD 5±2 mm Hg, controls 6±2 mm Hg, *P*=0.03; peak: ASD 11±4 mm Hg, controls 13±3 mm Hg, *P*=0.2), while systemic vascular resistance decreased (rest: ASD

Table 3. Hemodynamics

	Controls n=17	ASD n=37	P Value
Resting hemodynamics			
mPAP, mm Hg	15±2	14±3	0.2
sPAP, mm Hg	22±4	22±4	0.9
dPAP, mm Hg	10±2	9±4	0.03
CO, L/min	5.2±1.3	5.3±1.0	0.7
CI, L/min per m ²	2.7±0.7	2.9±0.5	0.4
SV, mL	82±19	74±17	0.2
TMFP, mm Hg	4±3	4±2	0.5
PVR, WU	1.2±0.5	0.9±0.4	0.03
Peak exercise hemodynamics			
mPAP, mm Hg	27±7	31±7	0.04
sPAP, mm Hg	39±9	45±9	0.03
dPAP, mm Hg	17±6	22±10	0.04
CO, L/min	18.5±4.1	17.7±4.4	0.5
CI, L/min per m ²	9.9±2.1	9.6±2.2	0.6
SV, mL	107±1	99±1	0.2
TMFP, mm Hg	7±3	10±6	0.03
PVR, WU	0.7±0.2	0.7±0.3	0.7

Data are presented as mean±SD. ASD indicates patients with atrial septal defect; CI, cardiac index; CO, cardiac output; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; sPAP, systolic pulmonary artery pressure; SV, stroke volume; TMFP, transmural filling pressure; and WU, wood units.

16.5±3.6 WU, controls 17.0±4.6 WU, *P*=0.7; peak: ASD 7.4±2.6 WU, controls 6.8±2.0 WU, *P*=0.5).

At peak exercise, significantly higher PA pressures (mPAP, systolic pulmonary artery pressure, and diastolic pulmonary artery pressure) and PAWP (mPAWP, pulmonary artery peak a wave pressure, and vPAWP) were demonstrated in patients with ASD compared with controls (Table 3 and Figure 1). Pulmonary vascular resistance was not different between groups at peak exercise. ΔPAWP/ΔCO was significantly higher for the ASDs (1.0±0.7 mm Hg /L per minute) when compared with controls (0.4±0.4 mm Hg /L per minute) (*P*=0.003). ΔCO/ΔVO₂ was comparable between ASDs (6.3±1.5) and controls (6.1±1.2) (*P*=0.7). The time interval from ASD correction to study time was not correlated with the main findings, nor did the type of surgical correction affect the findings.

Thirteen patients with ASD demonstrated an abnormal exercise response, while all controls had a response within normal limits (Table 4). VO₂ at rest was 4.5±0.7 mL/min per kg for controls, 4.9±1.2 mL/min per kg for ASD-normals, and 5.0±1.0 mL/min per kg for ASD-abnormals, showing no difference between groups (*P*=0.3). Resting vPAWP was higher for the ASD-abnormal group compared with controls (Figure 2). Systemic vascular resistance at rest was within normal limits and without difference between groups (controls 17.0±4.6 WU, ASD-normal 15.9±3.1

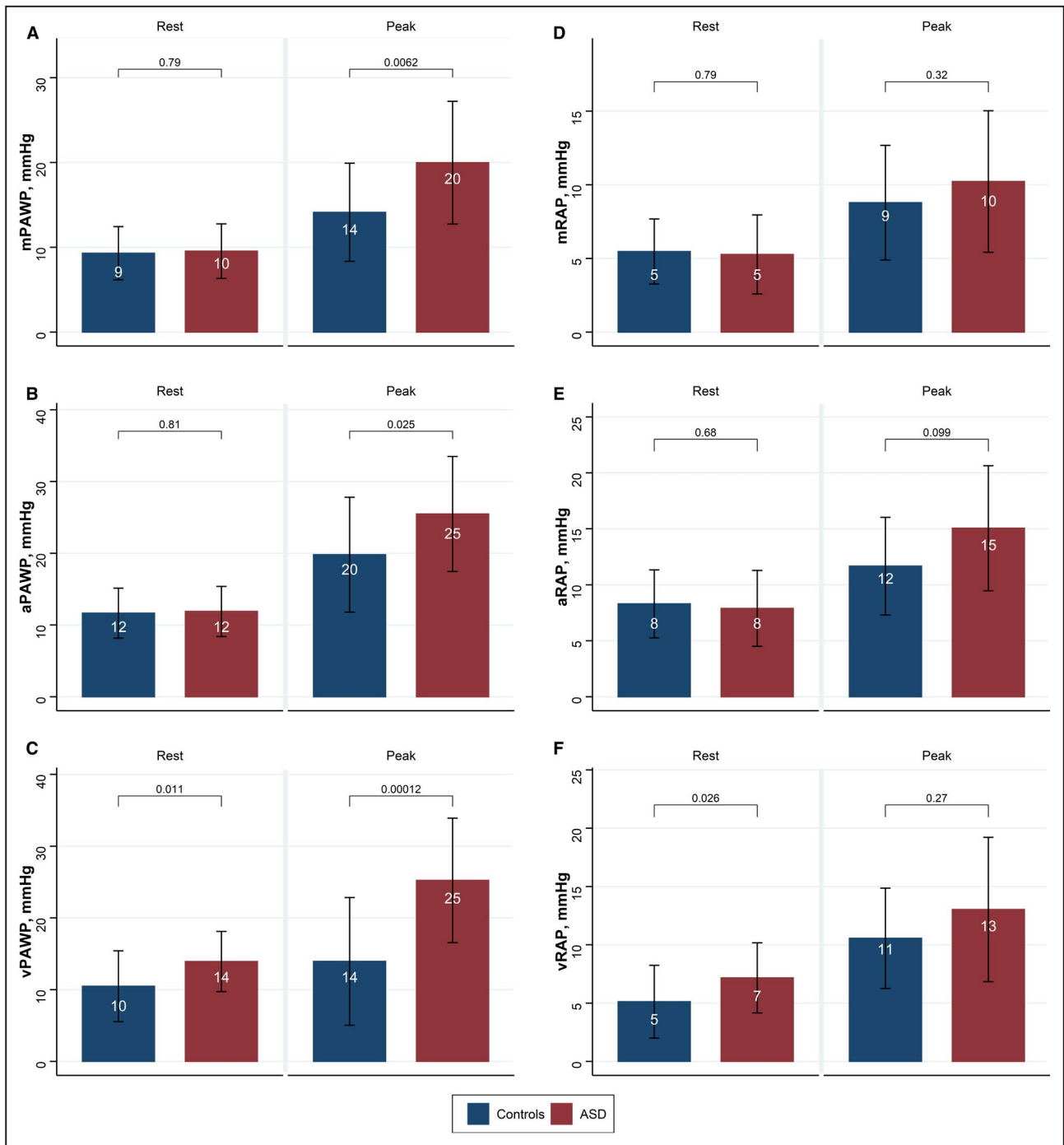


Figure 1. Atrial pressures during rest and exercise

Mean pulmonary artery wedge pressure (A), pulmonary artery wedge a wave pressure (B), pulmonary artery wedge v wave pressure (C), mean right atrial pressure (D), right atrial a wave pressure (E), and right atrial v wave pressure (F) at rest and peak exercise for controls and patients with ASD. Data visualized as mean values and SD bars. Unpaired Student *t* test was used for comparative analysis between controls and patients with ASD. ASD indicates patients with atrial septal defect; aPAWP, pulmonary artery wedge a wave pressure; aRAP, right atrial a wave pressure; mPAWP, pulmonary artery wedge mean pressure; mRAP, right atrial mean pressure; vPAWP, pulmonary artery wedge v wave pressure; and vRAP, right atrial v wave pressure.

WU, ASD-normal 17.7±4.1 WU, *P*=0.4). Peak cardiopulmonary exercise capacity was comparable between all groups as VO₂ max was 35.2±7.5 ml/kg per minute for controls, 32.6±8.9 mL/kg per minute

for ASD-normals, and 32.9±5.3 mL/kg per minute for ASD-abnormals (*P*=0.5). Peak systemic vascular resistance showed no difference between groups (controls 6.8±2.0 WU, ASD-normal 7.8±3.0 WU, ASD-abnormal

Table 4. Cardiopulmonary Exercise Test and Hemodynamic Values When ASDs Are Subdivided Based on Peak Pressures

	Control n=17	ASD-Normal n=24	ASD-Abnormal n=13	P Value
Rest				
mPAP, mm Hg	15±2	14±3	15±2	0.2
CO, L/min	5.2±1.3	5.4±1.2	5.1±0.7	0.6
CI, L/min per m ²	2.7±0.7	2.9±0.6	2.9±0.3	0.7
SV, mL	82±19	78±17	68±14	0.1
PVR, WU	1.2±0.5	0.9±0.4	1.0±0.4	0.08
Peak				
mPAP, mm Hg	27±7	28±4	38±4	...
CO, L/min	18.5±4.1	18.1±5.2	16.9±2.4	0.6
CI, L/min per m ²	9.9±2.1	9.6±2.5	9.6±1.4	0.9
SV, mL	107±1	102±1	93±1	0.3
PVR, WU	0.7±0.2	0.7±0.3	0.6±0.3	0.7

Data are expressed as mean±SD. ASD-abnormal defined as mean pulmonary artery wedge pressure ≥25 mm Hg and/or mean pulmonary artery pressure ≥35 mm Hg at peak exercise. ASD indicates patients with atrial septal defect; CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; SV, stroke volume, and WU, wood units. ANOVA was used for comparative analysis among all 3 groups. No P values are reported for mPAP at peak exercise because this is the variable used to divide patients into subgroups.

6.6±1.6 WU, $P=0.3$). Δ PAWP/ Δ CO was higher for ASD-abnormal when compared with both controls and ASD-normals (Figure 3B). TMFP was 2.2 times higher for ASD-abnormal when compared with controls and ASD-normal, respectively (Figure 3A). The correlation between the increase in mRAP, mPAWP, and TMFP and the increase in CO from rest to peak is visualized in Figure 4 for controls and ASD-abnormals.

DISCUSSION

The main study findings in patients with ASD secundum 20 years after correction are as follows: (1) RA and LA compliance seem abnormal expressed by elevated vPAWP at rest as well as during peak exercise compared with healthy controls; (2) abnormal LV filling might also be involved as indicated by the increased TMFP at peak exercise in patients with ASD compared with controls; (3) atrial systolic function at peak exercise seems impaired as right atrial v wave pressure and pulmonary artery peak a wave pressure were significantly higher compared with controls; (4) the abnormal LV filling properties did not reduce the maximal exercise capacity or maximal oxygen consumption in patients with ASD compared with controls; and (5) a subgroup of patients with ASD with an abnormal hemodynamic exercise response demonstrated a pronounced increase of a and v wave pressure measurements of LA and RA at peak exercise, and finally TMFP was significantly increased at rest and peak exercise, indicative of potential abnormal LV diastolic properties.

All patients with ASD in this study had RV enlargement and overload before closure, which was relieved after correction. The volume overload in the uncorrected ASD affects the structure and function of the

RA and RV, which reverse to normal or near-normal conditions immediately after correction.⁸ Similarly, the dilated LA volume diminishes significantly after ASD closure.¹¹ LV dimensions increase and LV myocardial performance by Doppler index improves after correction, which is indicative of preclosure LV underfilling and abnormal LV performance. These changes are typically not detected by measures such as LVEF, which is often unchanged and normal in the uncorrected ASD condition.^{8,9,11} This correlates well with the study by Booth et al.¹⁹ demonstrating an abnormal LV diastolic pressure–volume relationship, and hence LV compliance impairment, in a subset of patients with uncorrected ASD.

By echocardiography, we demonstrated normal LV systolic function expressed as LVEF and LV mass within the normal range. Cardiac index was also normal, indicating preserved LV systolic performance. The E/A ratio tended to be higher and the E-deceleration time tended to be prolonged among patients with ASD compared with controls, yet was statistically insignificant. However, the invasive assessment revealed significantly higher PAWP and TMFP at peak exercise, which implies that abnormal exercise-induced LV diastolic properties might be present in some of the patients with corrected ASD. Another explanation could be the occurrence of an intrinsic abnormal atrial function because of increased volume flow through both atria during the period in which the ASD was uncorrected. In the present study, we demonstrated increased v wave pressures for both the left and right atria at rest, which is indicative of impaired atrial compliance among patients with ASD. At peak exercise, the vPAWP increased even further in addition to a significant elevation of the a wave pressure of

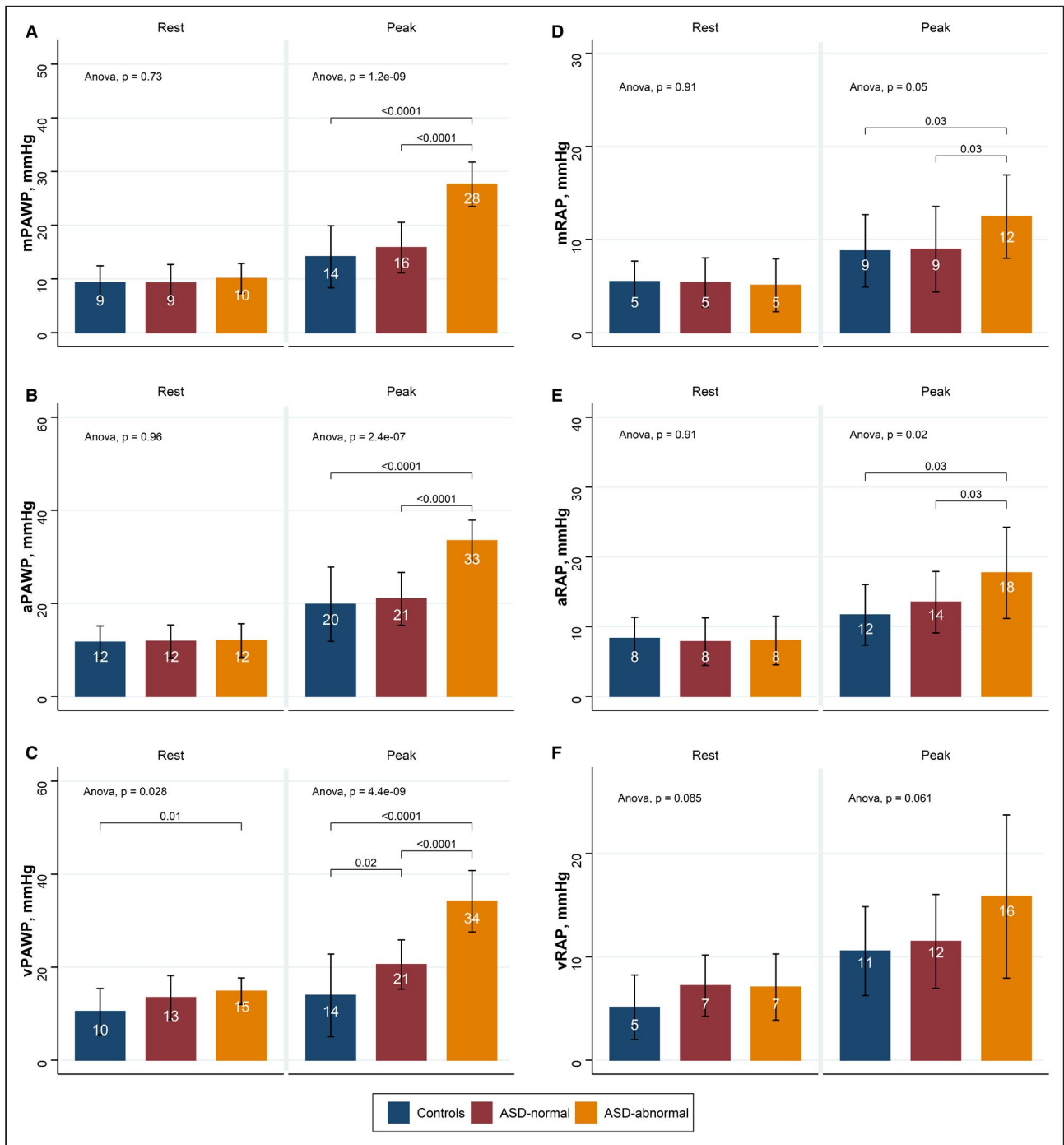


Figure 2. Atrial pressures during rest and exercise for ASD subgroups

Mean pulmonary artery wedge pressure, pulmonary artery wedge a wave pressure, mean right atrial pressure, right atrial a wave pressure, and right atrial v wave pressure at rest and peak exercise for controls, ASD-normals, and ASD-abnormals. ASD-abnormal defined as mean pulmonary artery wedge pressure > 25 mm Hg and/or mean pulmonary artery pressure >35 mm Hg at peak exercise. Data visualized as mean values and SD bars. Comparative analysis between controls, ASD-normals, and ASD-abnormals was performed using the unpaired Student *t* test if the ANOVA was significant. ASD indicates patients with atrial septal defect; aPAWP, pulmonary artery wedge a wave pressure; aRAP, right atrial a wave pressure; mPAWP, pulmonary artery wedge mean pressure; mRAP, right atrial mean pressure; vPAWP, pulmonary artery wedge v wave pressure; vRAP, right atrial v wave pressure.

LA as well as RA, suggestive of abnormal atrial function in terms of atrial systolic performance. In accordance with previous observations, we noted that one

third of patients with ASD had an abnormal hemodynamic exercise response with respect to the mPAP and mPAWP levels at peak exercise. In this subgroup

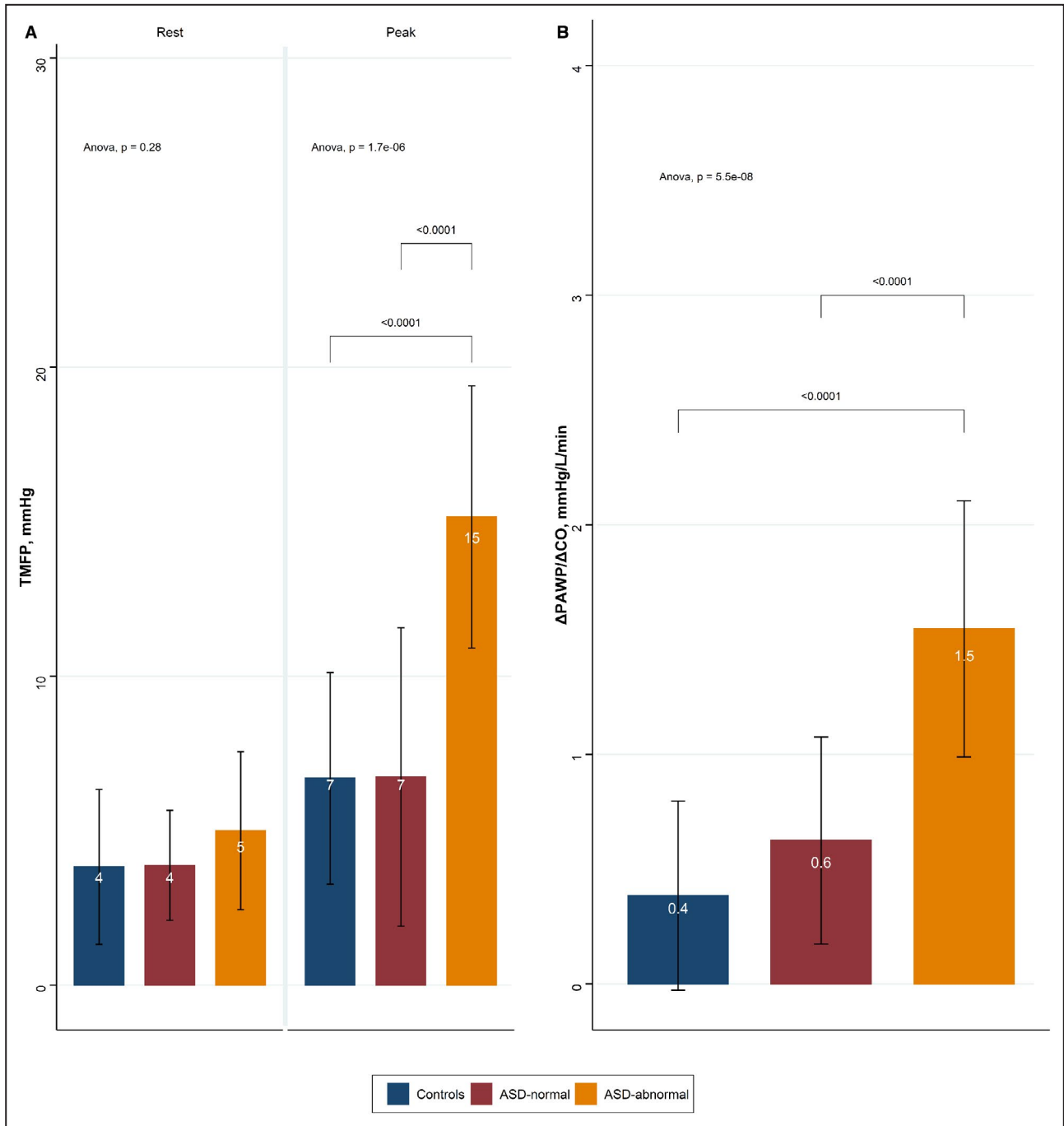


Figure 3. Transmural filling pressure and Δ PAWP/ Δ CO for ASD subgroups

Transmural filling pressure at rest and peak exercise for controls, ASD-normals, and ASD-abnormals. The ratio between delta mean pulmonary wedge pressure and delta cardiac output for controls, ASD-normals and ASD-abnormals. ASD-abnormal defined as mean pulmonary artery wedge pressure >25 mm Hg and/or mean pulmonary artery pressure >35 mm Hg at peak exercise. ASD indicates patients with atrial septal defect; CO, cardiac output; PAWP, mean pulmonary artery wedge pressure; Δ PAWP/ Δ CO is calculated as the difference in mPAWP from rest to peak divided by the difference in CO from rest to peak; and TMFP, transmural filling pressure. Data visualized as mean values and SD bars. Comparative analysis between controls, ASD-normals and ASD-abnormals was performed using the unpaired Student t test if the ANOVA was significant.

there were significant increases in LA a and v wave pressures at peak exercise, indicative of both abnormal systolic and diastolic atrial function. In addition,

a significant increase of the RA a wave pressure was noted. Again, the elevation of TMFP at both rest and peak exercise implies that an underlying LV diastolic

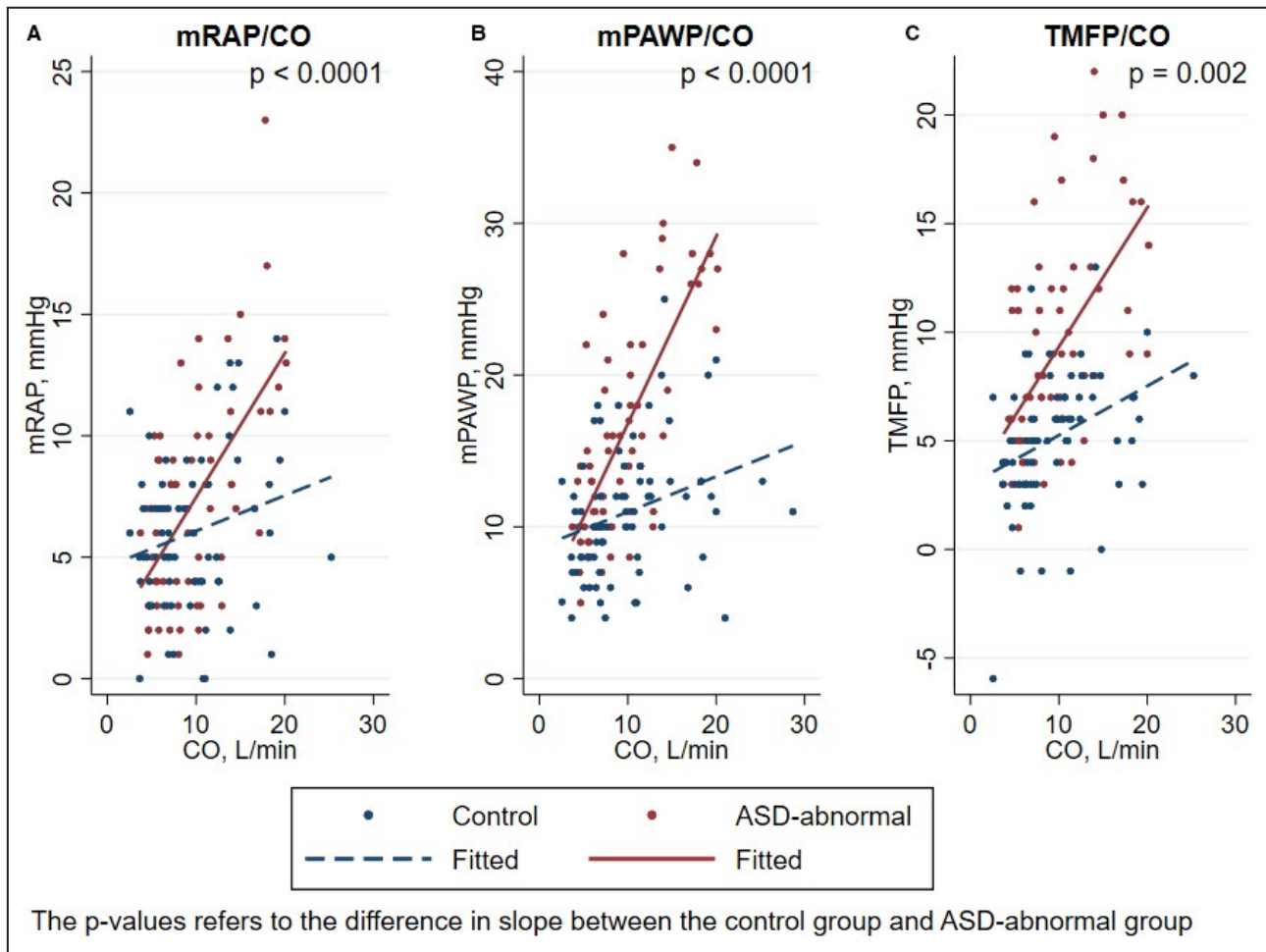


Figure 4. Correlation between pressure and CO from rest to peak exercise
 The relation between the increase in mRAP (A), mPAWP (B), and TMFP (C) to the increase in cardiac output from rest to peak. Linear regression is performed to visualize the slopes for pressure as a function of cardiac output. The P values refer to the difference in slopes between the ASD-abnormal patients and controls. ASD indicates patients with atrial septal defect; CO, cardiac output; mPAWP, mean pulmonary artery wedge pressure; mRAP, mean right atrial pressure; and TMFP, transmural filling pressure.

abnormality (impaired compliance) might be present. Because we did not directly measure LV pressures during diastole, we cannot determine whether the LA pressure abnormalities are a consequence of intrinsic LA abnormalities, impaired LV diastolic properties, or a combination of the two. The LV distending pressure is reflected by the left ventricular TMFP when RV pressure and pericardial pressures are normal as in the case of the patients with ASD. Therefore, TMFP seems to be a clinically interesting invasive hemodynamic parameter that may reveal early signs of abnormal LV diastolic filling, particularly during exercise. Of note, this subgroup of patients with ASD was without cardiopulmonary symptoms and had a peak exercise capacity comparable to that in controls and as such, our findings can at present be considered subclinical finds. However, abnormal LV compliance capacity may be of long-term clinical significance because patients with ASD have an increased risk of developing AF.^{4,5}

It is well documented that the presence of LV systolic or diastolic dysfunction increases the risk of AF. Even though the present abnormal findings might be considered subtle, the exercise-induced increase in LV filling pressures may affect the LA structure and function over time, causing stretching of atrial myocytes and formation of atrial fibrosis demonstrated in AF.^{20,21}

We noted a borderline enlarged RAVI in patients with ASD, which might imply abnormal RV diastolic function, but RVEDP was within normal limits. RV systolic parameters assessed by echocardiography seemed within the normal or borderline normal range; however, both RV global longitudinal strain and tricuspid annular plane systolic excursion were significantly lower compared with the matched controls. RVEF in patients with ASD, while still comparable to that of controls, is reduced because the 3-dimensional echocardiographic-derived RV EF cutoff level is at 45%.²² These findings regarding RV systolic function are in accordance with

previous studies reporting that RV systolic function after ASD correction is either normal or, at most, mildly impaired.^{23,24} This suggests that the RV is borderline impacted with resistance to ventricular filling.

Patients with ASD have been reported to have an unexplained increased risk of hospitalized pneumonia with increased use of antibiotics.⁶ Whether the demonstrated high exercise-induced PAWP in a subset of patients with ASD could be linked to the observed increase of pneumonia is speculative. However, theoretically, abnormally high LA pressures have the potential to induce episodes of transient subclinical pulmonary alveolar stasis and thereby form a local milieu disposing to infection.

Evaluation of pulmonary pressures is relevant, because increased pulmonary arterial pressures are seen in patients with uncorrected ASD and long-term survival is partly predicted by systolic pulmonary arterial pressures.⁷ In the present study, we did find the resting RV pressure and pulmonary arterial pressures within normal ranges, and our patients with ASD did not have persistent pulmonary arterial hypertension postcorrection in contrast to what has been documented by Zwijnenburg et al.²⁵ Nor do our patients with ASD fulfill the suggested criteria for exercise-induced pulmonary hypertension of mPAP >30 mm Hg at a CO <10 L/min and pulmonary vascular resistance >3 WU at peak exercise established by Naeije et al.²⁶ Yet, our subgroup analysis shows a tendency towards pulmonary hypertension (PH) during exercise (primarily venous PH because of elevated LA pressure and affected LV diastolic function rather than arterial PH).

There are few invasive hemodynamic studies on patients with ASD, which were mainly performed at rest in uncorrected patients or corrected patients with suspected PH.^{19,27–29} To our knowledge, our study is the first to combine invasive hemodynamic measurements and cardiopulmonary exercise testing with simultaneous expired gas analysis in a cohort with ASD years after correction, enabling us to study the long-term physiological changes.

Limitations

This study may have resulted in recruitment bias, because not all invited patients with ASD wished to participate. We may therefore report the results from patients with ASD who generally do well. We do not have preoperative measures on our patients and cannot determine hemodynamic changes over time. Our results are based on a relatively small study cohort; however, the study population was intensively examined with hemodynamic assessment as rest and during exercise in addition to cardiopulmonary exercise testing and echocardiography.

We report comparable peak VO₂ values that are still lower than published reference values for 30-year-olds,

which may be because of the exercise setup, because exercise testing on a supine bicycle yields a 16% to 21% lower VO₂ max compared with the upright bicycle or treadmill testing from which reference values are determined.^{30,31}

Matching for sex was not possible because of the available controls.

CONCLUSIONS

In patients with corrected ASD, elevated RA and LA pressures at rest and in particular at peak exercise were demonstrated as indicative of either impaired intrinsic atrial performance and/or alteration of ventricular diastolic properties. Even though the noted hemodynamic changes may be considered as subclinical findings given that peak exercise capacity was preserved, the elevation of atrial pressures could predispose to the increased long-term risk of AF and pneumonia documented in patients with ASD.

ARTICLE INFORMATION

Received December 24, 2020; accepted May 25, 2021.

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Acknowledgments

This project was conducted with help from the staff at the Department of Cardiology, Aarhus University Hospital, and research secretary Jette Breiner. The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Sources of Funding

The Children's Heart Foundation Denmark (18-R110-A5174-26044), Aarhus University, and Helga and Peter Korning's Fund has funded this project. Vibeke E. Hjortdal is funded on a grant from Novo Nordic Foundation (NNFSA170030576) since May 2019.

Disclosures

None.

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