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Assessment of long-term cardiac adaptation in adult patients with type II atrial septal defect

A cardiovascular magnetic resonance (CMR) study

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Abstract

Objectives In type II atrial septal defect (ASD) patients, the left-to-right (LR) shunt causes adaptation of the heart and circulation. The study objective was to evaluate with cardiovascular magnetic resonance imaging (CMR) the impact of LR shunt on left (LV) and right ventricular (RV) volumes, function, and myocardial strain.

Methods Thirty-five patients (42 ± 17 years, 17 male) were compared to a control group ($n = 40$). Cine imaging was used to calculate ventricular volumes and ejection fraction (EF), global longitudinal (GLS) and circumferential strain (GCS), and longitudinal free wall (FWS) and interventricular septal (IVS) strain. Phase-contrast imaging was used to calculate pulmonary flow to systemic flow ratio (Qp/Qs).

Results The LR shunt (Qp/Qs 2.2 ± 0.6) resulted in larger RV end-diastolic volume (EDVi) (152 ± 42 vs 82 ± 11 ml/m²), lower LV EDVi (72 ± 16 vs 83 ± 9 ml/m²), and higher RV/LV EDVi ratio (2.2 ± 0.5 vs 1.0 ± 0.1) than controls (all $p < 0.001$). Functionally, stroke volumes were larger in RV and lower in LV (both $p < 0.001$) with a strong trend toward lower RV EF in patients ($p = 0.08$). The LR shunt negatively impacted RV GLS ($p = 0.03$) but not RV GCS. Longitudinal IVS but not RV FWS were significantly lower in patients, i.e., $p < 0.001$, of longitudinal IVS. Shunt severity correlated with RV size and stroke volume, right atrial size, and pulmonary trunk diameter (all $p < 0.001$), but not with functional nor strain parameters.

Conclusion Long-term cardiac adaptation in ASD patients, with RV overfilling and LV underfilling, has a negative impact on systolic RV performance, a phenomenon which likely can be attributed to longitudinal dysfunction of the interventricular septum.

Key Points

- An LR shunt in type II ASD patients causes cardiac remodeling characterized by RV overfilling and conversely underfilling of the left ventricle.
- At the long term, there is evidence of systolic dysfunction of the right ventricle in this group of patients.
- Septal dysfunction underlies the observed impairment in RV function.

Keywords Magnetic resonance imaging · Heart defects, congenital · Atrial septal defect · Heart function tests

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Abbreviations

AA	Ascending aorta
ASD	Atrial septal defect
CMR	Cardiovascular magnetic resonance imaging
EDV	End-diastolic volume
EDVi	Indexed end-diastolic volume
EF	Ejection fraction
EF SR	Ejection fraction to global strain rate
ESV	End-systolic volume
ESVi	Indexed end-systolic volume
FWS	Free wall strain

GCS	Global circumferential strain
GLS	Global longitudinal strain
ICC	Intraclass correlation coefficient
IVS	Interventricular septal strain
LA	Left atrium
LR	Left to right
LV	Left ventricle
PA	Pulmonary artery
PT	Pulmonary trunk
RA	Right atrium
RV	Right ventricle
SR	Strain rate
SV	Stroke volume
SVi	Indexed stroke volume
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

Introduction

Atrial septal defect (ASD), the second most common congenital heart defect, is a common cause of right heart dilatation, but as it is often well tolerated, the defect may remain undiagnosed till at a later age [1, 2]. As filling pressures in the left atrium exceed right atrial pressures, the shunt direction is typically left to right (LR), causing a right heart volume overload at the expense of left ventricular filling (LV) [3]. Long-standing left-to-right (LR) shunt, however, may lead to shunt reversal, if right heart pressures increase secondary to pulmonary arterial hypertension, leading to the so-called Eisenmenger syndrome [3]. Cardiac imaging in ASD patients is important to depict, describe, and size the defect, but also to determine the impact on ventricular volumes, function, and strain, to estimate pulmonary arterial hypertension [4]. Moreover, imaging in ASD patients is particularly important to exclude additional defects, i.e., abnormal pulmonary venous return, as it has important therapeutic consequences. Transthoracic (TTE) and transesophageal (TEE) echocardiography are first-line imaging modalities in the diagnostic work-up of ASD [3–7]. Besides, cardiovascular magnetic resonance imaging (CMR) and cardiac computed tomography (CCT) are increasingly used in the diagnosis of this congenital defect [3, 4, 8]. Although CCT provides excellent anatomic detail, for assessment of ventricular volumes and estimation of intracardiac shunt severity, substantially higher radiation doses are needed [8]. CMR, in contrast, provides accurate and reproducible data on ventricular volumes and function. It allows measuring flow velocities and volumes, and thus calculating shunt volume either directly through the defect or indirectly by means of the difference between the pulmonary trunk and ascending aorta forward volume (Q_p/Q_s) [3, 4, 9–14]. CMR is highly valuable to depict abnormal pulmonary venous return [15, 16]. Finally, LV and RV myocardial strains can be

calculated on cine images with feature tracking and/or elastic registration algorithms, or by using specific tagging sequences [17–19]. In this monocentric retrospective study, we aimed to evaluate the impact of LR shunt in ASD secundum type (type II) patients on LV and right ventricular (RV) volumes, function, and strain by means of CMR, comparing patient findings to the healthy control group.

Materials and methods

Study population

For this monocentric, retrospective study, we searched for all patients with confirmed ASD type II referred to CMR over the last 10 years. Of the 40 patients, 5 patients were not included because of the presence of the Eisenmenger syndrome ($n = 3$), a concomitant patent ductus arteriosus ($n = 1$), and severe biventricular heart failure ($n = 1$). Findings in the ASD group were compared to those of an age- and gender-matched normal control group. The study protocol conformed to the Declaration of Helsinki and was approved by the ethical committee of our hospital. Because of the retrospective nature of this study, patient informed consent was waived. From the medical files, we used data with regard to patient demographics and clinical presentation, as well as data obtained by echocardiography and cardiac catheterization.

Cardiovascular magnetic resonance protocol

All CMR studies were performed on 1.5-T scanners (i.e., Achieva (2009–2014), Ingenia (2015–2019) (Philips Medical Systems)) with commercially available CMR imaging software, electrocardiographic triggering, and a cardiac-dedicated phase-array coil. For assessment of ventricular dimensions, function and strain steady-state free-precession breath-hold cine images were acquired in the following orientations: vertical and horizontal long axis, short axis, transverse, and LV and RV outflow tract view. Typical imaging parameters were repetition time/echo time, 3.6/1.8 ms; sense factor, 2; flip angle, 60°; section thickness, 8 mm; matrix, 160 × 256; field of view, 300 mm; pixel size, 1.6 × 1.6 mm; and number of phases, 30, phase percentage, 67%. In cardiac short axis and transverse direction, the ventricles were encompassed completely using a slice gap of 2 mm. As the focus of the CMR was on evaluation of ventricular volumes, and function, and calculation of shunt volumes, no postgadolinium imaging was performed. For calculation of the shunt volume, a phase contrast (PC) cine MR sequence at breath hold was positioned perpendicular through the sinuses of Valsalva, and through the pulmonary trunk. Optionally, a PC cine MR sequence was performed en face through the ASD as well. Typical sequence parameters for the fast-field-

echo (FFE) PC cine sequence were repetition time/echo time, 4.0/2.3 ms; sense factor, 2; flip angle, 12°; section thickness, 8 mm; matrix, 140 × 117; field of view, 350 × 300 mm; pixel size, 2.50 × 2.58 mm; and number of phases, 40, phase percentage, 50%.

CMR analysis

All images were analyzed on an off-line workstation using a commercially available software package (ViewForum or IntelliSpace Portal (ISP) Philips Medical Systems) and analyzed by CMR experts (minimal 5 years of experience). Ventricular volumes and function were measured by manual planimetry of the endocardial borders from the short-axis and/or transverse images at end diastole and end systole. The papillary muscles were considered part of the LV cavity. Subsequently, LV and RV end-diastolic, end-systolic, and stroke volumes, as well as ejection fraction, were calculated by summation of these contours. Flows from the PC cine images were calculated by contouring the vessel or region of interest and propagating the contour over all phases of the cardiac cycles, yielding information about the forward and backward flow through the vessel or region of interest. The effective (or net) forward flow, used to calculate the shunt

volume and ratio, was determined between deducting the backward flow from the forward flow. The cardiac shunt ratio was calculated as the net forward flow through the pulmonary trunk (Qp) over the net forward through the aortic root (Qs) (i.e., Qp/Qs). If performed, the flow through the ASD was calculated by contouring the area of the ASD.

Myocardial strain analysis

For myocardial strain analysis, we calculated the global myocardial strain in both longitudinal as well as circumferential direction. This was performed manually on IntelliSpace Portal (ISP) (Philips Medical Systems) by an expert reader with more than 10 years of CMR experience. For circumferential strain, a midventricular short axis was selected, and the endocardial LV and RV borders were contoured at end diastole and end systole. In longitudinal direction, we calculated global longitudinal LV and RV strain, free wall LV and RV strain (FWS), and interventricular septal strain (IVS) (Fig. 1). Strain was calculated as the difference in contour length between end diastole and end systole (defined on a midventricular short-axis cine slice as the smallest ventricular cavity at the end of systole) and expressed as an absolute value (i.e., mm of shortening), as well as a percentage. Systolic shortening is typically

Fig. 1 Calculation of circumferential and longitudinal ventricular strains. Composed image showing end-diastolic (upper row) and end-systolic (lower row) time frames in a 28-year-old woman with ASD. For global circumferential strain (GCS), on a midventricular short axis, the LV (blue) and RV (red) endocardial borders are drawn at end diastole (a) and end systole (d). For global longitudinal strain (GLS), on the four-chamber view, the LV (blue) and RV (red) are contoured at end diastole (b) and end systole (e). The contour starts at the insertion of the lateral leaflet and runs to the septal leaflet insertion of the tricuspid valve and mitral valve for the right and left ventricles, respectively. In the

interventricular septum, the contour is drawn in the midwall. For calculation of the free wall (FW) of RV (red) and LV (blue), the free wall is contoured at end diastole (c) and end systole (f). The contour starts at the insertion of the lateral leaflet and runs to the LV apex for the LV, and to the insertion of the RV FW with the left ventricle for the RV. For the strain calculation of the interventricular septum (IVS), a line following the midwall is drawn from the insertion of the septal leaflet of the mitral valve to the LV apex (green) at end diastole (c), and end systole (f). tv and mv indicate the tricuspid and mitral valve plane, respectively

Table 1 Clinical and CMR characteristics of the ASD and normal group

	ASD patients (<i>n</i> = 35)	Controls (<i>n</i> = 40)	<i>p</i> value
Age (years)	42 ± 17	35 ± 13	0.09
Male sex (%)	17 (49)	20 (50.0)	0.99
Weight (kg)	70 ± 13	72 ± 15	0.41
Length (m)	1.69 ± 0.08	1.74 ± 0.09	0.02
BSA (kg/m ²)	1.81 ± 0.19	1.86 ± 0.24	0.36
Heart rate (bpm)	71 ± 14	69 ± 17	0.45
Cardiac symptoms			
Chest pain	6 (17)		
Dyspnea	17 (49)		
Palpitations	15 (43)		
Syncope	3 (9)		
Arrhythmia	9 (26)		
CMR findings			
Morphology and function			
Left heart			
LVEDVi (ml/m ²)	72 ± 16	83 ± 9	0.001
LVESVi (ml/m ²)	30 ± 9	33 ± 6	0.1
LVSVi (ml/m ²)	41 ± 9	50 ± 7	<0.001
LVEF (%)	58 ± 7	60 ± 5	0.34
LA area indexed (cm ² /m ²)	13 ± 4	11 ± 2	0.002
Right heart			
RVEDVi (ml/m ²)	152 ± 42	82 ± 11	<0.001
RVESVi (ml/m ²)	65 ± 24	33 ± 7	<0.001
RVSVi (ml/m ²)	87 ± 21	49 ± 6	<0.001
RVEF (%)	58 ± 6	60 ± 4	0.08
RA area indexed (cm ² /m ²)	16 ± 5	11 ± 2	<0.001
RVEDVi/LVEDVi ratio	2.1 ± 0.5	1.0 ± 0.1	<0.001
Leftward cardiac rotation (°)	49 ± 15	30 ± 5	<0.001
L-R shunt assessment			
ASD area (cm ²)	3.0 (1.2–4.9)		
ASD shunt volume (ml)	74 ± 34		
Qp (ml)	155 ± 42		
Qs (ml)	75 ± 16		
Qp-Qs (ml)	80 ± 44		
Qp/Qs (ml)	2.2 ± 0.6		
Ascending aorta (AA) (cm)	2.8 ± 0.4	3.1 ± 0.3	0.003
Pulmonary trunk (PT) (cm)	3.4 ± 0.6	2.8 ± 0.2	<0.001
PT/AA ratio	1.24 ± 0.23	0.92 ± 0.06	<0.001

expressed as negative values, lengthening as positive values. Myocardial velocity (*v*) was calculated as the degree of systolic shortening divided by the length of systole and expressed as meters per second. Strain rate was expressed as the myocardial strain (%) divided by the length of systole and expressed as percent per second. Moreover, the GLS/GCS ratio was determined, providing information with regard to

the respective contribution of the longitudinal versus the circumferential strain to the ejection of blood. We also determined the EFSR ratio defined as the ejection fraction to global longitudinal strain ratio. For the current study, we opted to use manual contouring rather than feature-tracking-based analysis of cine images as it was recently shown that feature-tracking software may not track reliably fast-moving myocardium as for example in the RV free wall [18]. If feature-tracking-based algorithms fail, manual correction is either not possible or difficult to apply. Moreover, in a direct comparison between manual and feature-tracking-based myocardial strains in a clinically representative cohort of patients, manually derived strains showed an excellent intra- and inter-reader agreement, not inferior to the commercially available feature-tracking algorithms [20].

To appreciate atrial size, left atrial and right atrial area were measured in the horizontal long-axis image at end systole. Mitral and tricuspid regurgitation were visually graded using a score from 1 (minimal regurgitation) to 4 (severe regurgitation). An aortic to pulmonary diameter ratio was calculated by measuring the transverse diameter of the aortic root and pulmonary trunk. The size of the ASD was measured on the en face PC contrast cine image and expressed as an area (cm²). If there was more than one defect, the number of defects was mentioned. The leftward transverse rotation of the heart was expressed by measuring on a transverse or four-chamber view image the angle between a virtual line drawn between the mid-sternum and the mid-spine and a virtual line drawn connecting the LV apex with the middle of the mitral valve. Finally, hypertrophy of the RV free wall and trabeculations was visually assessed on the short- and long-axis cine images. Moreover, the configuration of the interventricular septum was assessed during diastole, and scored as normal right-sided convexity, flattened, or inverted.

Statistical analysis

All statistical analyses were performed using R Statistical Software (Foundation for Statistical Computing, v.3.5.2). The Shapiro-Wilk test was used to test the normality of the data distributions. Continuous variables were expressed as means ± standard deviation (SD) or medians with interquartile ranges (IQR) as appropriate. Categorical variables were expressed as frequency with percentage. Differences between the patients and control subjects were tested using a two-tailed unpaired Student *t* test. The Pearson correlation coefficient was used to assess the association between the shunt severity, i.e., Qp/Qs ratio, and CMR parameters. All tests were 2 tailed, and a *p* value < 0.05 was considered as statistically significant.

Results

The ASD group consisted of 35 subjects (17 male) ranging from 20 to 85 years. Thirty-three patients (94%) were in NYHA class I–II, 17 patients experienced dyspnea at rest ($n=5$) or during exercise ($n=12$), 15 patients presented with palpitations (43%), three patients had (pre)-syncope, and a history of chest pain was noted in 6 patients (Table 1). Arrhythmic events were present in 9 patients (26%), i.e., supraventricular tachycardia ($n=4$), ventricular extrasystoles ($n=2$), atrial flutter/fibrillation ($n=2$), Wolf-Parkinson-White syndrome ($n=1$), and out-of-hospital cardiac arrest ($n=1$).

All patients presented a LR shunt with a shunt volume through the ASD of 74 ± 34 ml, resulting in a Qp/Qs of 2.2 ± 0.6 (range 1.3–3.6) at CMR, compared to 2.4 ± 0.6 (range 1.4–3.6) measured invasively (Table 1). The mean ASD diameter was 17 ± 7 mm, resulting in a median defect area of 3.0 cm^2 (Q1, 1.2 cm^2 /Q3, 4.9 cm^2). One patient had a multi-fenestrated ASD. An abnormal pulmonary venous return was excluded in all patients. Systolic pulmonary artery pressures were 35 ± 12 mmHg at transthoracic echocardiography and 31 ± 11 mmHg invasively. Invasive mean pulmonary artery pressure was 20 ± 7 mmHg. Nineteen patients (54%) had a systolic PA pressure <35 mmHg, 14 (40%) between 35 and 50 mmHg, and 2 patients (6%) between 50 and 70 mmHg. The diameter of the ascending aorta was smaller in the patient group, i.e., 2.8 ± 0.4 vs 3.1 ± 0.3 cm ($p=0.03$), while the pulmonary trunk was larger, i.e., 3.4 ± 0.3 vs 2.8 ± 0.2 cm, resulting in an increase of the pulmonary trunk/aortic root ratio, i.e., 1.24 ± 0.23 vs 0.92 ± 0.06 ($p<0.001$). In 31 patients

(88%), closure of the ASD was performed (interventional $n=20$ /surgical $n=8$) or planned ($n=3$). In one patient with a small Qp/Qs, i.e., 1.3, no intervention was performed. The device diameter was 27 ± 5 mm (range, 18–33 mm). Indications for surgery were presence of an insufficiently broad rim to implant an ASD occluder ($n=7$) and the presence of a multi-fenestrated ASD ($n=1$).

ASD patients presented smaller LV cavities (EDVi 72 ± 16 vs $83 \pm 9 \text{ ml/m}^2$, $p=0.001$) and smaller stroke volume (SVi 41 ± 9 vs $50 \pm 7 \text{ ml/m}^2$, $p<0.001$) but similar LV EF (58 ± 7 vs $60 \pm 5\%$, $p=0.34$) than control subjects (Fig. 2). In contrast, the opposite was found for the right ventricle with larger cavities (EDVi 152 ± 42 vs $82 \pm 11 \text{ ml/m}^2$, $p<0.001$) and higher stroke volume (SVi 87 ± 21 vs $49 \pm 6 \text{ ml/m}^2$, $p<0.001$), with a trend toward lower EF (58 ± 6 vs $60 \pm 4\%$, $p=0.08$) in the patient group. This resulted in a significantly increased RVEDVi/LVEDVi ratio in the patient group, i.e., 2.1 ± 0.5 vs 1.0 ± 0.1 ($p<0.001$). Twenty-five patients (71%) had evidence of mild to moderate RV hypertrophy. Diastolic septal flattening or inversion was found in 20 (57%) and 5 (14%) patients, respectively. Patients had increased leftward transverse rotation of the heart, i.e., $49 \pm 15^\circ$ vs $30 \pm 5^\circ$ in normal, $p<0.001$. Moreover, ASD patients had significantly larger indexed LA (13 ± 4 vs $11 \pm 2 \text{ cm}^2/\text{m}^2$, $p=0.002$) and RA (16 ± 5 vs $11 \pm 2 \text{ cm}^2/\text{m}^2$, $p<0.001$) areas.

The impact of a LR shunt on LV and RV myocardial strain showed a mixed pattern (Table 2, Fig. 3). For the RV, absolute circumferential and free wall (FW) shortening, as well as RV FW velocities, was increased in ASD patients. However, RV GCS, FW longitudinal strain, and strain rate were not different

Fig. 2 Ventricular volumes, function, and RV/LV volume ratio in ASD patients and control group

Table 2 Left ventricular, right ventricular, and septal strain in the ASD and control groups

	ASD	Control	<i>p</i> value
Left ventricle			
LV FWS (mm)	24.7 ± 8.3	27.8 ± 6.5	0.09
LV FWS (%)	−23.7 ± 6.3	−24.5 ± 4.6	0.54
LV FWS vel (m/s)	0.078 ± 0.028	0.089 ± 0.029	0.17
LV FWS SR (%/s)	0.075 ± 0.023	0.078 ± 0.022	0.72
LV GLS (mm)	44.5 ± 11.1	46.9 ± 7.3	0.27
LV GLS (%)	−21.9 ± 5.0	−21.6 ± 3.1	0.74
LV GCS (mm)	40.1 ± 10.0	43.8 ± 7.1	0.23
LV GCS (%)	−19.4 ± 4.6	−20.3 ± 2.8	0.35
LV GLS/GCS ratio	0.88 ± 0.31	0.81 ± 0.15	0.23
LV EFSR	2.81 ± 0.70	2.83 ± 0.44	0.88
Longitudinal strain interventricular septum			
IVS (mm)	13.5 ± 3.6	20.0 ± 3.4	<0.001
IVS (%)	−15.6 ± 3.7	−22.3 ± 3.1	<0.001
IVS vel (m/s)	0.043 ± 0.013	0.063 ± 0.013	<0.001
IVS SR (%/s)	0.050 ± 0.014	0.070 ± 0.013	<0.001
Right ventricle			
RV FWS (mm)	46.5 ± 9.5	41.3 ± 7.9	0.01
RV FWS (%)	−35.3 ± 6.4	−36.8 ± 5.2	0.26
RV FWS vel (m/s)	0.150 ± 0.037	0.131 ± 0.30	0.02
RV FWS SR (%/s)	0.114 ± 0.063	0.117 ± 0.023	0.6
RV GLS (mm)	59.3 ± 13.3	59.2 ± 11.9	0.95
RV GLS (%)	−27.2 ± 5.7	−29.9 ± 4.5	0.03
RV GCS (mm)	38.5 ± 12.2	27.1 ± 8.7	<0.001
RV GCS (%)	−17.7 ± 3.7	−16.2 ± 5.2	0.16
RV GLS/GCS ratio	1.82 ± 0.63	2.37 ± 0.77	0.002
RV EFSR	2.24 ± 0.59	2.05 ± 0.36	0.12

Abbreviations: *EFSR* ejection fraction to global longitudinal strain ratio, *FWS* free wall strain, *GCS* global circumferential strain, *GLS* global longitudinal strain, *IVS* interventricular septal strain, *LV* left ventricle, *RV* right ventricle, *vel* velocity

from those of the controls. Remarkably, RV GLS was decreased in the patient group, i.e., $-27.2 \pm 5.7\%$ vs $-29.9 \pm 4.5\%$, $p = 0.03$, which could be attributed to significantly impaired longitudinal strain and strain rate in the interventricular septum (both $p < 0.001$). For the LV, except for a trend toward a lower absolute FW strain in ASD patients, strain and strain rate values were similar between groups.

Shunt severity, expressed by Q_p/Q_s , was positively related to RV size, indexed stroke volume, $RVEDVi/LVEDVi$ ratio, RA area indexed, size of the pulmonary trunk, and pulmonary trunk to aortic root ratio (all $p < 0.001$) (Table 3) (Fig. 4). In contrast, none of the strain-related parameters were related to shunt severity. Age was weakly correlated to RV FW longitudinal strain ($p = 0.007$) and RA area indexed ($p = 0.02$) but not to the other volumetric, functional, or flow parameters (Fig. 5).

Discussion

The onset of a LR shunt in ASD patients—immediately after birth—alters the normal ventricular loading causing overfilling of the right heart and pulmonary circulation, and conversely underfilling of the left heart and systemic circulation [3]. Although this conditioning of the heart is usually well tolerated, symptoms occur if atrial arrhythmias arise, if patients start to get complaints of pulmonary arterial hypertension, or more rarely if patients experience stroke or a transient ischemic attack secondary to paradoxical embolism. The goal of this monocentric, retrospective study was to achieve a better view on the relationship between shunt severity and morphological and functional remodeling, i.e., “adaptation,” of the heart and great vessels, using CMR as prime cardiac imaging modality.

The results of our study, obtained in an adult patient population, show that shunt severity well correlates with volumetric measures of right heart and pulmonary arterial volume overload. The LR shunt causes a right atrial and RV dilatation, with increased leftward rotation of the heart, and dilation of the pulmonary trunk. Also, RV stroke volume correlates with shunt severity. The opposite is found for the left heart with significantly lower LV end-diastolic and LV stroke volumes and a smaller ascending aorta, when compared to an age- and gender-matched control group. The combined RV/LV remodeling—expressed as RV/LV EDVi ratio—correlates best with shunt severity. Our study results indicate that at the long term, LR shunt causes RV systolic dysfunction. Strain analysis comparing global ventricular strains as well as regional strains, i.e., free versus septal wall, indicates

Fig. 3 Global longitudinal strain of LV and RV, free wall strain, and longitudinal strain in the interventricular septum in ASD patients and control group. Abbreviations: FWS, free wall strain; GCS, global circumferential strain; GLS, global circumferential strain; IVS, interventricular septum

Table 3 Correlation between Qp/Qs and CMR parameters

	R	p value
Global morphology and function		
Left heart		
LVEDVi (ml/m ²)	−0.032	0.85
LVESVi (ml/m ²)	0.156	0.37
LVSVi (ml/m ²)	−0.161	0.35
LVEF (%)	−0.180	0.30
LA area indexed (cm ² /m ²)	0.170	0.34
Right heart		
RVEDVi (ml/m ²)	0.713	<0.001
RVESVi (ml/m ²)	0.603	<0.001
RVSVi (ml/m ²)	0.719	<0.001
RVEF (%)	−0.133	0.44
RA area indexed (cm ² /m ²)	0.583	<0.001
RVEDVi/LVEDVi ratio	0.825	<0.001
Aorta—pulmonary trunk		
AA (cm)	0.072	0.68
PT (cm)	0.647	<0.001
PT/AA	0.652	<0.001
Myocardial strain		
Left ventricle		
LV FWS (mm)	−0.140	0.42
LV FWS (%)	−0.130	0.46
LV FWS vel (m/s)	−0.011	0.95
LV FWS SR (%/s)	−0.108	0.54
LV GLS (%)	−0.042	0.81
LV GCS (%)	−0.325	0.07
LV GLS/GCS ratio	0.138	0.46
LV EFSR	0.003	0.98
Interventricular septum		
IVS (mm)	0.042	0.81
IVS (%)	−0.071	0.69
IVS vel (m/s)	−0.046	0.79
IVS SR (%/s)	−0.154	0.38
Right ventricle		
RV FWS (mm)	0.186	0.28
RV FWS (%)	−0.206	0.24
RV FWS vel (m/s)	0.002	0.99
RV FWS SR (%/s)	−0.330	0.05
RV GLS (%)	−0.185	0.29
RV GCS (%)	−0.277	0.13
RV GLS/GCS ratio	−0.166	0.38
RV EFSR	−0.016	0.93

Abbreviations: *EFSR* ejection fraction to global longitudinal strain ratio, *FWS* free wall strain, *GCS* global circumferential strain, *GLS* global longitudinal strain, *IVS* interventricular septal strain, *LV* left ventricle, *RV* right ventricle

septal dysfunction, in particular impaired longitudinal strain and strain rates.

While the Frank-Starling mechanism is responsible for the beat-to-beat adaption of cardiac contraction to changes in preload, in the chronically volume ($\pm$ pressure)-overloaded ventricle, myocyte and ventricular remodeling are the responsible mechanisms, causing progressive remodeling of the cardiac chambers. Although initially the LR shunt causes exclusively a volume-overload remodeling the right ventricle, it is believed that pulmonary arterial pressure may increase and thus impose an additional pressure load on the right heart. Even though most patients were in NYHA I–II, nearly half of them had evidence of mild and some moderate pulmonary hypertension. Moreover, a majority of patients had evidence of diastolic septal flattening/inversion, and at least some degree of RV hypertrophy at CMR, phenotypic markers pointing toward a RV pressure overload.

Most studies, so far, have used echocardiography to study the effects of LR-shunt-related cardiac remodeling on ventricular function and myocardial strain, as well as the reversed remodeling after ASD closure [3–7, 21]. However, as CMR combines accurate volumetric assessment with accurate flow quantification and is moreover appealing for myocardial strain imaging, it is increasingly used to study the pathologic RV. Literature shows variable, often contradictory, results with regard to global RV systolic performance in ASD patients [22–26]. Our findings—indicative of impaired function—are in line with the work of Stephensen et al [27]. The discrepancy between studies can, most likely, be explained by differences in the age of the study population, the concomitant presence of pulmonary arterial hypertension causing RV hypertrophy and/or RV dysfunction, and the complex geometric structure of the RV with 3 distinct parts (i.e., inlet part, apical trabecular, outlet part (infundibulum)) challenging accurate quantification of RV volumes and function with standard imaging modalities such as echocardiography. Moreover, the fiber orientation in the thin free wall is quite complex, with the outer layers having a circumferential course whereas the deeper fibers are longitudinally oriented [28]. Longitudinal shortening is the major contributor to RV contraction, accounting for approximately 80% of the RV stroke volume, compared to approximately 60% for the LV stroke volume [29, 30]. Eyskens et al reported higher RV peak systolic velocities but normal RV deformation indices in the RV free wall in young ASD patients [7]. They concluded that peak systolic velocities, but not systolic strain rates, are load dependent. Van De Bruaene et al found in an adult ASD group higher apical peak systolic strain values but similar basal values between an open ASD and normal control group [28]. After ASD closure, reversed RV remodeling occurs with near-normalization to normalization of RV volumes [27, 31]. However, functionally, there is substantial evidence that after ASD closure persistent impairment in RV function and strain occurs [7, 27, 28, 32]. This suggests that long-standing RV volume ($\pm$ pressure) overload is detrimental, and function does not completely normalize after

Fig. 4 Correlation between shunt severity (Q_p/Q_s) and RV and RA size. **a** RV EDVi; **b** RV ESVi; **c** RA area indexed; **d** RV/LV EDVi ratio

closure of the defect. Moreover, it is believed that the placement of an ASD occluder may negatively affect ventricular septal function [7].

Longitudinal septal dysfunction underlying global RV dysfunction in ASD patients has not been reported to our knowledge. Although at first sight our findings are in contrast to the work by Eyskens et al, they are more likely complementary [7]. As our patient group was more than 3 decades older, i.e., 41.7 versus 7.9 years, it is reasonable to believe ongoing ventricular remodeling and superimposed pressure overload may affect RV performance, causing RV dysfunction. Evidence for this hypothesis is provided by the weak negative correlation between age and RV free wall longitudinal strain (Fig. 5). It should be noted that interpretation between age and volumetric, functional, and strain parameters should be interpreted with caution as only adult patients were included in the current study. Work by Hsiao comparing volume- with pressure-overloaded RV supports the above hypothesis [25]. Moreover, it is likely that decreased LV filling directly contributes to the impaired septal strain. A lower LV preload leads to a lower

diastolic septal stretch, and consequently to a lower systolic septal strain. Thus, it is likely that the observed RV dysfunction can be in part explained by an altered interventricular dependence. Finally, Akula et al reported diastolic dysfunction in older ASD patients (i.e., >40 years), preceding systolic dysfunction [33]. It is, therefore, questionable whether concomitant or underlying diastolic dysfunction affects longitudinal septal strain, thus impairing global systolic RV performance.

Limitations

Firstly, we included only ASD type II patients. Other defects, such as sinus venosus defects $\pm$ abnormal pulmonary venous return, were not included, but it is known from literature that the latter group typically presents with higher shunt ratios, and a higher tendency toward more severe pulmonary arterial hypertension [4]. Also, as mentioned above, patients with a bi-directional shunt or with Eisenmenger syndrome were excluded. These patients, typically, have severe RV deterioration. Secondly, our patient group might be biased as we studied

Fig. 5 Correlation between age and RV EDVi (a), RV/LV EDVi ratio (b), RA area indexed (c), RV GLS (d), RV FWS (e), and IVS (f)

only ASD patients referred for CMR, usually pre-intervention. Thirdly, we used a manual approach for myocardial strain analysis. However, this approach was advantageous to study the pathologic right ventricle, and is not inferior with regard to reproducibility compared to feature-tracking algorithms. Finally, differences in reported strain values may differ between imaging modalities [34]. It should be noted that a typical temporal resolution of cine imaging is approximately 30 ms, which may not be sufficient to obtain strain curves, but likely should suffice to calculate end-systolic strain and to estimate strain rate.

In conclusion, ASD patients with long-standing LR shunt have evidence of systolic RV dysfunction, which likely is due to longitudinal septal dysfunction. Further investigation is needed to assess whether this marker is important in clinical decision-making and affects RV functional recovery post ASD closure.

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Ethical approval Institutional Review Board approval was obtained.

Methodology

- retrospective
- observational
- performed at one institution

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