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Predictors of right atrial dilatation and long-term function after right ventricular outflow tract surgical repair: Quantification of restrictive physiology matters

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ABSTRACT

Right ventricular (RV) diastolic dysfunction in patients with a surgically-repaired RV outflow tract (RVOT) obstruction merits further studies. Right atrial (RA) dilation and function may be related to (RV) diastolic dysfunction in this setting. The end-diastolic forward flow (EDFF) in the pulmonary artery (PA) has been suggested as a non-invasive marker of poor RV compliance, however, there is controversy regarding its true significance; EDFF quantification may help elucidate this controversy.

Objective: to study predictors of RA enlargement and dysfunction in patients with a surgically-repaired RVOT obstruction and its relationship with quantitative EDFF.

Methods: In 81 consecutive patients (mean age: 37.5 (±7) years), transthoracic echocardiography (Echo) and cardiac magnetic resonance (CMR) were performed. Echo parameters: RA size (indexed RA area (iRAA)), RA function (RA global strain (RAGS)) and maximum EDFF velocity-time integral (VTI-EDFF) obtained during a whole respiratory cycle. CMR-indexed RA area (imRAA) was also obtained. Patients were divided into three groups according to iRAA, imRAA and RAGS; bivariate analysis was performed. A multivariate model was then applied using variables that were found to be statistically significant in the bivariate analysis.

Results: Upon multivariate analysis, higher VTI-EDFF values and the presence of significant tricuspid regurgitation proved to be independent factors associated with increased iRAA and imRAA and lower RAGS, whereas RV volumes, function and pulmonary regurgitant fraction were not.

Conclusion: VTI-EDFF linearly correlated with the degree of RA dilation and deformation; EDFF quantification as against qualitative assessment may be considered a non-invasive tool for diastolic RV dysfunction.

1. Introduction

While left atrial quantification has become one of the key factors for non-invasive diagnosis of left ventricular diastolic dysfunction [1], mechanisms of right atrial (RA) enlargement and its relationship with right ventricular (RV) diastolic dysfunction are poorly understood [2].

The subgroup of adult patients with congenital heart disease (CHD) that underwent surgical repair of RV outflow tract (RVOT) obstruction is prevalent amongst CHD patients, with Tetralogy of Fallot (ToF) and pulmonary stenosis (PS) being the most representative population [3]. RA dilatation has been signaled out as a risk factor for atrial arrhythmias

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Abbreviations

CHD	congenital heart disease
CMR	cardiac magnetic resonance
Echo	transthoracic echocardiography
EDFF	end-diastolic forward flow HC: healthy controls
iRAA	indexed RA area
imRAA	Indexed RA area obtained by CMR
PA	pulmonary artery
PR	pulmonary regurgitation
PS	pulmonary stenosis
RA	right atrial
RAGS	longitudinal right atrial systolic strain with Speckle tracking
RP	restrictive physiology
RV	right ventricle
RVOT	right ventricular outflow tract
RVEDP	right ventricular end-diastolic pressure
RVEDV	right ventricular end-diastolic volume
RVEF	right ventricular ejection fraction
RVESV	right ventricular end-systolic volume
ToF	Tetralogy of Fallot
TR	tricuspid regurgitation
VTI-EDFF	maximum velocity-time integral (VTI) of A wave obtained during a whole respiratory cycle on main PA

in ToF patients [4], which also related to an adverse clinical outcome in post-pulmonary valve replacement status [5]. The study of factors related to RA dilatation and function could help us understand the physiopathology of long-term complications in patients with RVOT surgical repair, mainly atrial arrhythmias.

Non-invasive tools for quantifying diastolic RV dysfunction in CHD within the surgically repaired RVOT population include restrictive physiology (RP), that is characterized by the presence of end-diastolic forward flow (EDFF) on main pulmonary artery (PA). There have been contradictory results regarding their significance, especially in the presence of severe pulmonary regurgitation (PR), since the initial description [6] and even more so since Mori et al., published their data [7]. They demonstrated that EDFF, measured as an all-or-none phenomenon, was present if the RV end-diastolic pressure (RVEDP) value was greater than diastolic pulmonary artery (PA) pressure, irrespective of whether RVEDP was abnormally high or diastolic PA pressure abnormally low due to PR. Therefore, the presence of EDFF would not always correspond with increased RVEDP. We recently demonstrated that EDFF quantification allows defining abnormal EDFF in patients with surgically-repaired RVOT vs. the physiological phenomenon observed in healthy controls (HC) [8]. This study aimed to further analyze the relationship between RA dilatation and quantitative EDFF measurement.

Myocardial deformation imaging derived from speckle tracking represents a new tool for evaluating atrial performance and function in left and, also, right atria [9]. The present study aimed to evaluate RA size and function in adult patients with surgically-repaired obstructive RVOT lesions. All possible risk factors that could produce right atrial enlargement in adult patients with surgically-repaired RVOT lesions were analyzed, including a quantitative EDFF assessment. We hypothesized that quantitative EDFF assessment is key to study the relationship between RA dilatation and function.

2. Methods

2.1. Target population

Patients with CHD and HC) were included. From January 2014 to October 2015, all consecutive patients with repaired RVOT obstructive lesions scheduled for CMR for clinical reasons were invited to enter the study.

2.2. Echocardiography (echo)

Echo was performed using a Vivid 7 ultrasound machine (General Electric, Vingmed, Horten, Norway). A comprehensive Echo study was conducted following current recommendations [10], including annular excursion of mitral annulus (MAPSE) and annular excursion of tricuspid annulus (TAPSE). The pulsed Doppler sample volume was placed distal to the pulmonary valve. Spectral recordings were made with minimal filtering. Integral velocity-time EDFF (VTI-EDFF) was defined as maximum velocity-time integral (VTI) of A wave obtained during a whole respiratory cycle on main PA. RAA was indexed for body surface area (iRAA). Visual PR quantification was performed and PR degree was classified into five groups: absence of PR (PR = 0), mild PR (PR = 1), moderate PR (PR = 2), moderate-to-severe (PR = 3) and severe PR (PR

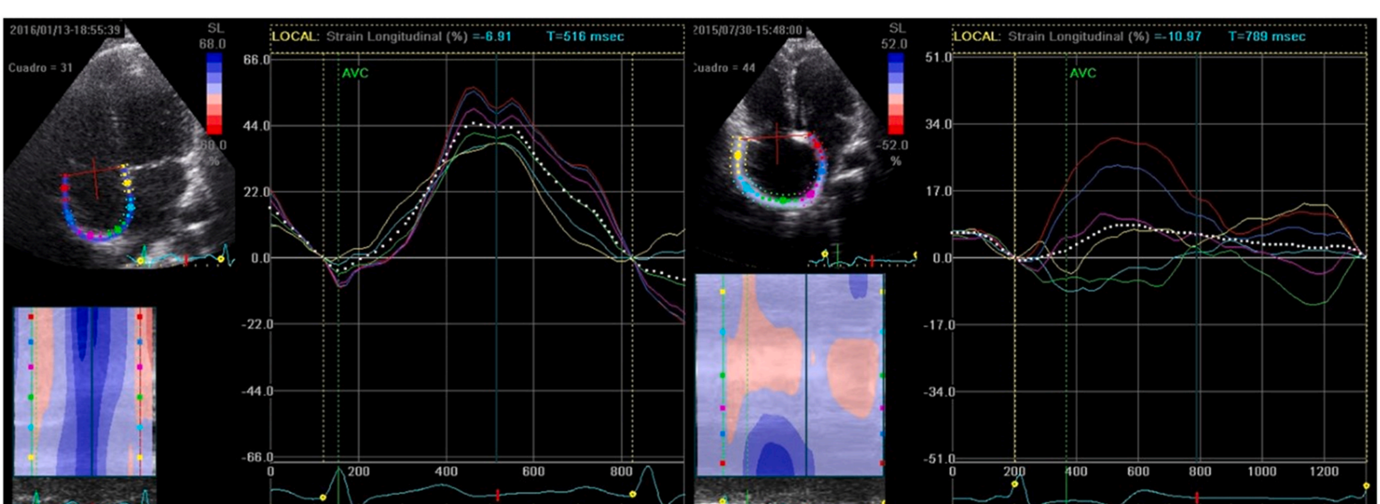

Fig. 1. 1 A - RAGS in a healthy control. 1B - RAGS in a patient with severe RP.

= 4). Visual assessment of tricuspid regurgitation (TR) was performed and TR was also classified into five groups, similar to the PR classification.

2.3. RA atrial deformation study

All patients were in sinus rhythm during the studies. The frame rate of two-dimensional (2D) image acquisition was set at between 60 and 80 frames/sec. Offline analyses of the echocardiographic recordings were made using EchoPAC software (General Electric). Size measurements were taken from three cardiac cycles and the average used for statistical analyses. From the apical four-chamber view, the maximum right atrial areas were measured just before the opening of the atrioventricular valve in end-systole by planimetry. In order to determine RA myocardial deformation, the entire endocardial RA contour was traced and tracked by the software. QRS onset was used as the reference point for determining the peak of total global longitudinal strain (RAGS).

RA longitudinal global strain (RAGS) measurements obtained in HCs are shown in Fig. 1A.

RA longitudinal global strain (RAGS) measurements obtained in patients are shown in Fig. 1B.

2.4. CMR

Studies were conducted with a 1.5 T MR imaging unit (Avanto, Siemens, Germany). The study protocol included 2D balanced steady-state free precession (b-SSFP) cine images in 2-, 3- and 4-chamber long-axis planes, as well as a short-axis stack from the mitral valve to the apex and a stack of axial images covering the whole heart (retrospective ECG gating, temporal resolution 20–45 msec, 25 phases per cardiac cycle and 7–12 s of breath-hold time per image and spatial resolution 1.4 × 1.4 × 8.0 mm), and a 2D phase-contrast through-plane imaging sequence acquired at the main pulmonary artery, 3 mm above the pulmonary valve plane (retrospective cardiac gating, 10–15 s breath-hold, 25 phases with 20–45 msec of temporal resolution, 100–300 cm/s of velocity encoding ensuring absence of aliasing). From these images, 10 to 12 contiguous short-axis slices perpendicular to the long axis of the left ventricle (LV) and 10 to 14 contiguous axial slices of the right ventricle were obtained (slice thickness: 8 mm; interslice gap: 2 mm). Biventricular volumetric analysis was made using Argus software (Siemens Medical Systems). The contour of the RA was manually traced in the four-chamber view excluding the RA appendage and the vena cava at their junction with the RA. The maximum contoured area, just prior to atrioventricular valve opening, was chosen to quantify the RA maximal area indexed to body surface area (imRAA). All data were stored in DICOM format and analyses were performed off-line using the commercially available “Argus” software (Siemens Medical Systems) according to standard recommendations [11]. As Regards pulmonary flow volume, a region of interest was drawn over the contour of the pulmonary artery and adjusted throughout the cardiac cycle. Antegrade and retrograde flow were automatically obtained by integration of the area under the time-flow curve. All volumetric and area parameters were indexed to body surface.

2.5. Statistical analysis

Descriptive statistics for discrete data are expressed in absolute numbers and percentages. Mean values and standard deviation are presented for normally-distributed continuous variables. Student’s t-test for paired samples was used to compare mean values of the right atrial measurements and right atrial strain echocardiographic parameters between patients and matched HC.

Inter-observer reproducibility for the assessment of RA strain using transthoracic echocardiography (Echo) was determined by Bland-Altman analysis. Intra-observer reproducibility was determined by one experienced reader (S.M.) repeating the strain and strain rate measurements at two different time points in 15 randomly selected patients. A second experienced reader (A.P.D.) performed the strain analysis in the same 15 patients, thereby providing inter-observer reproducibility data. The inter-observer variability of echocardiographic measurements was assessed via the intraclass correlation coefficient.

To establish potential predictors of right atrial dilation and dysfunction, bivariate analysis of clinical, CMR and Echo characteristics was initially performed. Patients were divided into three groups according to either a) indexed RAA (iRAA), b) imRAA or c) RAGS values. iRAA groups were <10.4 cm/m^2, 10.4–14.6 cm/m^2, and >14.6 cm/m^2 imRAA groups were 10.4 cm/m^2, 10.4–14.9 cm/m^2, >14.9 cm/m^2. RAGS groups were <13, 13–26, >26.

Mean differences were calculated with 95% confidence intervals as an estimate of the risk associated with each variable. A multivariate model was then applied using variables found to be statistically significant in the bivariate analysis.

Statistical analyses were performed using SPSS software (version 15.0, SPSS, Inc., Chicago, Illinois). All statistical tests were 2-sided and a p-value <0.05 was considered significant.

Table 1
Demographical, surgical and clinical variables of the patient population.

	Value	Number of patients
Age (years)	37.5 (SD ±7)	81
Age at surgical repair (years)	4.3 (SD ±3.7)	81
BSA	1.75 (SD ±0.2)	81
Male (%)	53%	81
Previous palliative shunt (%)	25%	81
Type of sugical repair		81
Transanular patch		
Yes	39.5%	32
No	43.2%	35
Unknonwn	17.3%	14
Redo surgery (%)	21%	81
Residual lesions		
Pulmonary stenosis	8.6%	7
Residual VSD	3.7%	3
Pulmonary valve replacement	8.6%	7

Table 2
Echo and CMR variables of the patient population.

RVEDV ml/m^2	140.2 (SD ±40.5)	81
RVESV ml/m^2	71 (SD ±27)	81
RVEF (%)	50 (SD ±7.8)	81
PRRF	37.8 (SD ±17.7)	81
LVEDV ml/m^2	76 (SD ±25)	81
LVESV ml/m^2	33.5 (SD ± 20)	81
LVEF (%)	58% (SD ±5.9)	81
TAPSE (mm)	18 (SD ±3.2)	81
MAPSE (mm)	17 (SD ±2.8)	81
VTI-EDFF (cm)	6.2 (SD ±3.5)	81
Residual VSD	4 (4.9%)	81
Residual PS (mild)	18 (22.2%)	81
Residual PS (moderate)	10 (12.3%)	81
Residual PS (severe)	0 (0%)	81
		Total number of patients = 81
PR		
	PR = 0	7.4% n = 6
	PR = 1	3.7% (n = 3)
	PR = 2	2.5% (n = 2)
	PR = 3	8.6% (n = 7)
	PR = 4	78% (n = 63)
		Total number of patients = 81
TR		
	TR = 0	n = 4 (4.9%)
	TR = 1	n = 43 (53%)
	TR = 2	n = 20 (24.6%)
	TR = 3	n = 14 (17.3%)
	TR = 4	–

Table 3
Mean values obtained on (RA) dimensions Echo and CMR, including indexed values by BSA. RAGS obtained using Echo is also shown. Left side values correspond to patients and right side values correspond to HC.

	Patients		Healthy controls		P value
RAA	N = 81	22.7 cm^2 (SD ±6.8)	N = 43	14.2 cm^2 (SD ±2.4)	$p < 0.0001$
iRAA	N = 81	13 cm^2/m^2 (SD ±3.5)	N = 43	8.1 cm^2/m^2 (SD ±1.5)	$p < 0.0001$
MRRAA	N = 81	25.5 cm^2 (SD+/−)		–	
imRAA	N = 81	14.7 cm^2/m^2 (SD+/−)		–	
RAGS	N = 80	19.9 (SD ±8)	N = 36	33 (SD ±9)	$p < 0.001$
EDFF-VTI	N = 81	6.2 cm (SD ±3.5)	N = 43	2.3 cm (SD ±0.6)	$p < 0.001$

RAA: right atrial area; **iRAA**: indexed RA area; **iMRRAA**: Indexed RA area obtained by CMR; **RAGS**: right atrial global strain; **VTI-EDFF**: maximum velocity-time integral (VTI) of A wave obtained during a whole respiratory cycle on main pulmonary artery.

3. Results

The patients' main demographic data, type of CHD and repair are shown in Table 1. Patient data regarding Echo and CMR are shown in Table 2. Eighteen percent of patients had mild LV systolic dysfunction and RV systolic function was reduced in 42%.

The results of RA function and dimensions in both populations are given in Table 3. All measurements of right atrium dimensions had significantly higher values in patients compared with HC, $p < 0.0001$. RAGS was significantly lower in patients compared with HC ($p < 0.001$).

In the bivariate analysis, the following parameters were significantly associated with iRAA: age, indexed RV end-diastolic volume (iRVEDV), indexed RV end-systolic volume (iRVESV), VTI-EDFF, and TR = 3. Results of the bivariate logistic regression analysis for iRAA are shown in Table 4.

Similarly, bivariate analysis of imRAA revealed the following significantly associated parameters: age, iRVESV, VTI-EDFF, and TR = 3. The results of this imRAA bivariate logistic regression analysis are shown in Table 5.

As regards RAGS, the bivariate analysis found significant association with the following parameters: LVEF, VTI-EDFF, and TR = 3. The results of the bivariate logistic regression analysis for RAGS are shown in Table 6.

In the multivariate model including all variables found to be significant in the bivariate model, only VTI-EDFF and TR = 3 remained significant when RA dimensions were measured using Echo (iRAA).

Similarly, in the multivariate model using imRAA as the measurement of RA dimensions, only VTI-EDFF and TR = 3 remained significant. The 1 cm increase in VTI-EDFF accounted for a 0.6 cm/m^2 increase in iMRRAA.

Regarding the multivariate analysis of RAGS, both VTI-EDFF and TR = 3 were associated with overall RA function (see Fig. 2).

The plot illustrates the association between VTI-EDFF and iRAA according to the degree of TR (Fig. 3).

The intraclass correlation coefficient to assess the inter-observer variability of RAGS assessment parameters was 0.95 (95%CI 0.90: 0.97; $p < 0.001$).

4. Discussion

The present study established the positive linear correlation between quantitative EDFF assessment and RA size and function in adult patients with surgically-repaired RVOT obstructive lesions.

Some reports that included patients with ToF demonstrated that RA enlargement was related to the presence of EDFF defined as a binary item [12,13]. However, other studies, including a series with almost 400 young adults with repaired TOF, failed to correlate the presence of EDFF, defined as an all-or-none phenomenon, with increased RA dilatation; EDFF was only associated with greater PR regurgitant fraction and larger RV size [14,15]. The studies of Kutty [14] and Merce-Rosa [15] concluded that EDFF could not be used as a marker of RV restrictive physiology and suggested that other mechanisms beyond RV non-compliance may contribute to the presence of EDFF. Even so,

Table 4
Bivariate analysis of risk factors for iRAA measured on Echo.

iRAA cm^2/m^2	<10.4	10.4–14.6	>14.6	Total	Correlation	P value
Age (mean± SD)	36.1 (SD ±6.7)	35.8 (SD ±5)	40.1 (SD ±10)	37.1 (SD ±7.2)	0.23 (p = 0.043)	0.255
Gender M:F	47.4%	47.5%	61.9%	52%	−0.135 (p = 0.234)	0.349
Age at surgical repair (mean± SD)	3.3 (SD ±2)	4 (SD ±3.9)	5.7 (SD ±4.6)	4.3 (SD ±3.8)	0.139 (p = 0.219)	0.202
QRS duration (mean± SD) ms	155 (SD ±30)	142.5 (SD ±38)	150.5 (SD ±45)	147.6 (SD ±38)	−0.085 (p = 0.453)	0.454
RVEF (mean± SD)	52.8 (SD ±7.5)%	49.8 (SD ±7.3)%	48.3 (SD ±8.7)%	50.1% (SD ±7.8)%	−0.156 (p = 0.168)	0.15
PRRF	36.2 (±21.1)	37.4 (±17.3)	40.3 (±16.4)	37.8 (17.7%)		0.229
LVEF (mean± SD)	57.7 (SD ±5.4)%	58.7 (SD ±5.2)%	56.9 (SD ±7.4)%	58 (SD ±5.9)%	−0.147 (p = 0.099)	0.392
iRVEDV (mean± SD)ml/m^2	126.9 (SD ±39.6)	142.3 (SD ±36.7)	148.2 (SD ±46.8)	140.2 (SD ±40.5)	0.221 (p = 0.049)	0.304
iRVESV (mean± SD)ml/m^2	60.5 (SD ±24)	71.7 (SD ±24)	78.7 (SD ±31.5)	70.9 (SD ±27)	0.256 (p = 0.022)	0.092
VTI-EDFF (mean± SD) *Cm*	4.1 (SD ±2.2)	5.7 (SD ±2.7)	9.4 (SD ±3.9)	6.2 (SD ±3.5)	0.604 (p < 0.0001)	<0.0001
TR						
Grade 0	0; 0%)	3 (7.7%)	0 (0%)	3 (3.8%)	0.489 (p < 0.0001)	<0.0001
Grade 1	16 (80%)	21 (53.8%)	6 (28.6%)	43 (54%)		
Grade 2	4 (20%)	9 (23.1%)	7 (33.3%)	20 (25%)		
Grade 3	0 (0%)	6 (15.4%)	8 (38.1%)	14 (17.5%)		

RVEF: right ventricular ejection fraction; **LVEF**: left ventricular ejection fraction; **iRVEDV**: indexed right ventricular end-diastolic volume; **iRVESV**: indexed right ventricular end-systolic volume; **VTI-EDFF**: maximum velocity-time integral (VTI) of A wave obtained during a whole respiratory cycle on main pulmonary artery; TR: tricuspid regurgitation.

Table 5
Bivariate analysis of risk factors for (imRAA).

imRAAcm^2/m^2	<10.4	10.4–14.9	>14.9	Total	Correlation	P value
Age (mean± SD)	36.4 (SD ±6.8)	35.8 (SD ±5)	40.5 (SD ±10)	37.1 (SD ±7.2)	0.229 (p = 0.043)	0.250
Gender M:F	57.9%	50%	35%	48.8%	−0.149 (p = 0.191)	0.154
Age at surgical repair (mean± SD)	3.7 (SD ±2)	4.1 (SD ±3.9)	5.3 (SD ±4.7)	4.3 (SD ±3.8)	0.116 (p = 0.308)	0.623
QRS duration (mean± SD)ms	148 (SD ±32)	145.5 (SD ±38)	150 (SD ±46)	148 (SD ±38)	−0.071 (p = 0.532)	0.780
RVEF (mean± SD)	54.1 (SD ±7.2)%	49.2 (SD ±7.1)%	48.6 (SD ±8.8)%	50.2% (SD ±7.8)%	−0.164 (p = 0.148)	0.024
PRRF	36.2 (±21.1)	37.4 (±17.3)	40.3 (±16.4)	37.8 (17.7%)	0.19 (p = 0.064)	0.854
LVEF (mean± SD)	59.1 (SD ±5.3)%	58.4 (SD ±5.4)%	56.1 (SD ±7.1)%	58 (SD ±5.9)%	−0.188 (p = 0.099)	0.135
iRVEDV (mean± SD)ml/m^2	124.5 (SD ±39)	141.8 (SD ±36.9)	149.5 (SD ±46.1)	140 (SD ±40.5)	0.214 (p = 0.058)	0.162
iRVESV (mean± SD)ml/m^2	58.2 (SD ±24)	71.8 (SD ±23)	79.2 (SD ±31.8)	70.9 (SD ±27)	0.257 (p = 0.022)	0.031
VTI-EDFF (mean± SD) *Cm*	3.9 (SD ±2.2)	5.8 (SD ±2.7)	9.5 (SD ±3.9)	6.3 (SD ±3.5)	0.615 (p < 0.0001)	<0.0001
TR						
Grade 0	1 (5%)	2 (5.1%)	0 (0%)	3 (3.8%)		
Grade 1	16 (80%)	21 (5.8%)	6 (30%)	43 (54.4%)		
Grade 2	3 (15%)	10 (25.6%)	6 (30%)	19 (24%)	0.509 (p < 0.0001)	<0.0001
Grade 3	0 (0%)	6 (15.4%)	8 (40%)	14 (17.7%)		

RVEF: right ventricular ejection fraction; LVEF: left ventricular ejection fraction; iRVEDV: indexed right ventricular end-diastolic volume; iRVESV: indexed right ventricular end-systolic volume; VTI-EDFF: maximum velocity-time integral (VTI) of A wave obtained during a whole respiratory cycle on main pulmonary artery; TR: tricuspid regurgitation.

Table 6
Bivariate analysis of risk factors for RAGS.

RAGS	<13	13.28–26	>26	Total	Correlation	P value
Age (mean± SD)	38.1 (SD ±10)	37.5 (SD ±6)	34.9 (SD ±6)	37 (SD ±7)	−0.227 (p = 0.034)	0.348
Gender F:M	30%	52.5%	55%	47.5%	0.182 (p = 0.106)	0.116
Age at surgical repair (mean± SD)	4 (SD ±4.6)	4.4 (SD ±3.8)	4.4 (SD ±2.8)	4.3 (SD ±3.8)	0.011 (p = 0.922)	0.458
QRS duration (mean± SD)ms	139 (SD ±46)	150 (SD ±36.7)	150 (SD ±32)	147 (SD ±38)	0.042 (p = 0.711)	0.897
RVEF (mean± SD)	48 (SD ±9.6)%	49.5 (SD ±6)%	52.3 (SD ±7.8)%	49.8% (SD ±7.6)	0.176 (p = 0.119)	0.186
LVEF (mean± SD)	56.7 (SD ±7.3)%	57.8 (SD ±5.3)%	59.6 (SD ±5.1)%	57.9 (SD ±5.9)	−0.187 (p = 0.0096)	0.114
iRVEDV (mean± SD)ml/m^2	131.5 (SD ±45)	152.5 (SD ±36)	123 (SD ±36)	141 (SD ±40.1)	−0.122 (p = 0.283)	0.028
iRVESV (mean± SD)ml/m^2	70.1 (SD ±33)	77.1 (SD ±23)	61.4 (SD ±24)	71.5 (SD ±26)	−0.184 (p = 0.104)	0.075
VTI-EDFF (mean± SD) *Cm*	8.46 (SD ±4.7)	5.7 (SD ±2.8)	5.4 (SD ±2.5)	6.3 (SD ±3.5)	−0.386 (p < 0.0001)	0.026
TR						
Grade 0	1 (5%)	2 (5.1%)	1 (4.8%)	4 (4.9%)		
Grade 1	9 (45%)	23 (59%)	11 (52%)	43 (53.8%)		
Grade 2	5 (25%)	7 (18%)	8 (38%)	20 (25%)	−0.236 (p < 0.0035)	0.105
Grade 3	6 (30%)	7 (18%)	1 (4.8%)	14 (17.7%)		

RVEF: right ventricular ejection fraction; LVEF: left ventricular ejection fraction; iRVEDV: indexed right ventricular end-diastolic volume; iRVESV: indexed right ventricular end-systolic volume; VTI-EDFF: maximum velocity-time integral (VTI) of A wave obtained during a whole respiratory cycle on main pulmonary artery; TR: tricuspid regurgitation.

patients presenting EDFF persistence after pulmonary valve replacement were recently demonstrated to have a worse prognosis in terms of atrial arrhythmias [16].

Mori et al. [7], signaled out that future studies should include the quantitative measurement of EDFF to distinguish true restriction from pseudo-restriction They hypothesized that the higher the EDFF value, the greater the difference between RVEDP and PA diastolic pressure would be. Our data suggested that VTI-EDFF could be a non-invasive tool for RVEDP measurement. EDFF presence is a dynamic phenomenon probably reflecting pressure differences; it is plausible that patients with persistent EDFF after pulmonary valve replacement are those with true restriction, thus having an increased risk of atrial arrhythmias [16].

RAGS values were significantly lower compared with HC, as already described in studies including patients with repaired ToF [17] and other

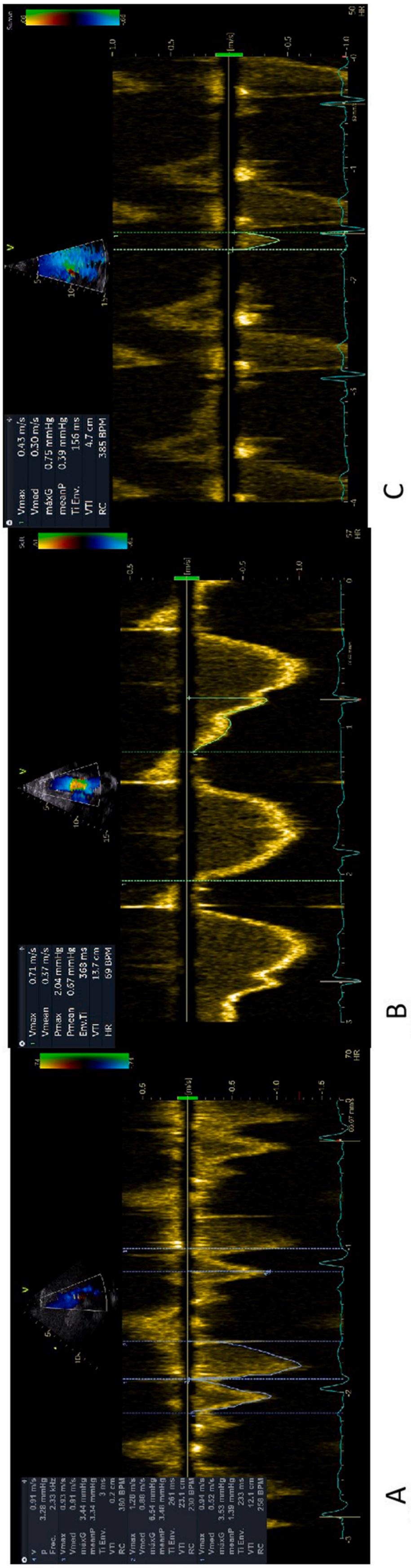

Fig. 2. 2 A: VTI-EDFF corresponding to an A wave of significant value. 2B:VTI-EDFF where antegrade flow starts well before atrial contraction. 2C: VTI-EDFF corresponding to an A wave with a very low value.

types of adult CHD [18]. The analysis of factors related to RAGS in the present study was similar to the findings regarding RA dilatation. In other settings, RAGS was inversely related to increased RA pressures [19] and could provide prognostic information in patients with idiopathic pulmonary arterial hypertension [20]. Its value in surgically-repaired RVOT patients in terms of prognostic implications remains to be established.

RA dimensions were not related to RV systolic function in our study. RV systolic dysfunction was prevalent; however, severe RV systolic dysfunction was not highly represented in our population. Further studies including patients with severe RV systolic dysfunction should be conducted to confirm our results. Severe LV systolic dysfunction was not represented in our population. Similarly, no correlation between LV systolic dysfunction and RA dimensions or function were observed in the multivariable analysis; neither were RA dimensions significantly related to RV volumes in the multivariant analysis. RA dilatation may be more related to increased RVEDP than increased RVEDV.

Age at repair was not predictive of right atrial dilation or deformation in the multivariable model. All our patients were surgically repaired during infancy; presumably, RA dilation appeared progressively in the long term after repair, but the cross-sectional nature of the present study does not allow us to confirm this.

In summary, our results found that RA dimensions and function mainly depend both on the degree of TR and the quantitative EDFF value, with RV dilation not being decisive. Our data supported VTI-EDFF as a highly valuable non-invasive marker of RV diastolic dysfunction and opens the way to future research regarding the functionality of the right atrial chamber and its relationship with RV diastolic function.

5. Limitations

The main limitation of this study was the lack of invasive hemodynamic data. Our healthy controls were sex-and-age matched to the patients; therefore, our findings in the healthy population may not apply to other age groups, particularly extremes (children and the elderly). Right atrial strain could not be obtained in 5% of the population (including HC and patients) owing to technical difficulties. The population was a mixed cohort of patients including ToF, PS, and supravalvar PS, not just Tetralogy of Fallot patients.

6. Conclusions

The quantification of end-diastolic forward flow as against the qualitative assessment of EDFF presence/absence merits more attention since it is proportionally related to the degree of RA dilation and function. It could represent a new non-invasive tool for estimating elevated RA pressures, which in turn have prognostic implications. Further studies including invasive RVEDP measurements and concomitant VTI-EDFF should be performed.

Ethical statement

The Institutional Ethics Committee (EC) of the Vall D'Hebron Hospital, Barcelona, Spain approved the study (PR (AMI)311/2013) on the 29th of January 2014. Written informed consent was obtained from all patients.

Data availability statement

The data supporting the findings of this study are available from the corresponding author, [APD], upon reasonable request.

Data regarding EDFF quantification in the same patient population and differentiation in HC have already been described elsewhere [8]. Eighty-one out of 82 eligible patients accepted and provided their written informed consent approved by the Ethics Committee (PR (AMI) 311/2013). Excluded from this cohort were patients with pulmonary

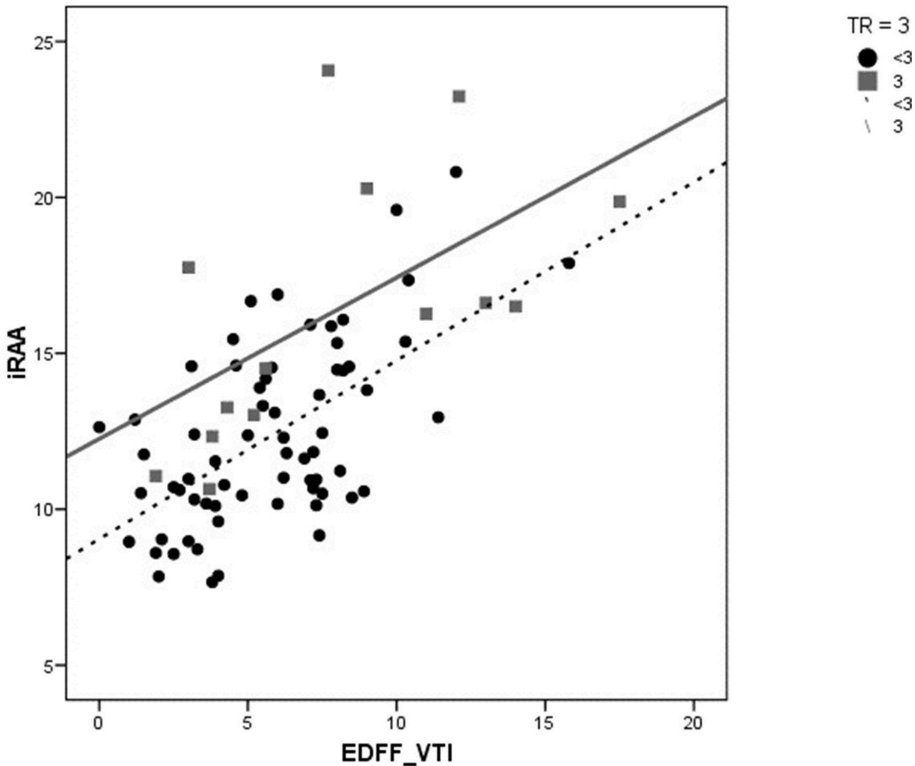

Fig. 3. Graphs showing the relationship between VTI-EDFF and iRAA. There is a positive linear correlation between them. Continuous line indicates TR = 3 value of iRAA is higher than when TR < 3 (dashed line).

atresia or complex conotruncal abnormalities and those not in sinus rhythm at the time of assessment. Inclusion criteria were all consecutive patients with surgically-repaired RVOT obstructive lesions during infancy and scheduled for CMR for clinical reasons. Types of CHD included were ToF, pulmonary stenosis (PS) and supravalvular PS. Data were prospectively collected following institutional review board approval. Data collection included age, functional class, time of heart surgery repair and type of repair, including transannular patch.

HC inclusion criteria: age and sex matched to patient. Exclusion criteria: any acquired or congenital heart disease. Forty-three Echos were obtained from healthy age-and-sex-matched volunteers invited to participate in the study and RAGS was measured.

Declaration of competing interest

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

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