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Abnormal right atrial and right ventricular diastolic function relate to impaired clinical condition in patients operated for tetralogy of Fallot☆

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ABSTRACT

Background: Atrial enlargement may reflect ventricular diastolic dysfunction. Although patients with tetralogy of Fallot (TOF) have been studied extensively, little is known about atrial size and function. We assessed bi-atrial size and function in patients after TOF repair, and related them to biventricular systolic and diastolic function, and clinical parameters.

Methods: 51 Patients (21 ± 8 years) and 30 healthy controls (31 ± 7 years) were included and underwent magnetic resonance imaging to assess bi-atrial and biventricular size, systolic and diastolic function. Patients also underwent exercise testing, and N-terminal prohormone brain natriuretic peptide (NT-proBNP) assessment.

Results: In patients, right atrial (RA) minimal volume (34 ± 8 ml/m^2 vs. 28 ± 8 ml/m^2, $p = 0.001$) and late emptying fraction were increased; RA early emptying fraction was decreased. Patients had longer right ventricular (RV) deceleration time (0.24 ± 0.10 vs. 0.13 ± 0.04, $p < 0.001$), reflecting impaired RV relaxation, and larger RV volumes. Patients with end-diastolic forward flow (EDFF) had larger RA and RV size, abnormal RA emptying, higher NT-proBNP levels, higher VE/VCO_2 slope (ventilatory response to carbon dioxide production), and the most abnormal LV diastolic function (impaired compliance). Patients with abnormal RA emptying (reservoir function <30% and pump function >24%) had higher NT-proBNP levels and worse exercise capacity. RA minimal volume was associated with RV end-diastolic volume ($r = 0.35$, $p = 0.013$).

Conclusions: In TOF patients with moderate RV dilatation, abnormal bi-atrial function and biventricular diastolic dysfunction are common. Abnormal RA emptying was associated with signs of impaired clinical condition, as was the presence of EDFF. These parameters, together with RA enlargement, could serve as useful markers for clinically relevant RV diastolic dysfunction.

1. Introduction

Chronic pulmonary regurgitation (PR) with subsequent right ventricular (RV) dilatation is an important cause of late morbidity and mortality in patients long after surgical repair of tetralogy of Fallot (TOF) [1–4]. Up to now, it remains difficult to predict the course of RV dilatation and deterioration in TOF patients, and the precise indications and optimal timing to perform a pulmonary valve replacement (PVR) have therefore not been fully clarified.

Biventricular size and systolic functional parameters have been studied extensively in TOF patients, but little information is available on atrial size and function. The atria play a crucial role in the filling of the ventricle during ventricular diastole. It has been reported that left atrial (LA) enlargement reflects the burden of left ventricular (LV) diastolic dysfunction and that LA volumes increase with the severity of diastolic dysfunction [5]. This emphasizes the need for measurement of atrial size and function if diastolic function is assessed.

Diastolic dysfunction may be important as a marker preceding systolic dysfunction [6,7], but isolated diastolic dysfunction with preserved ejection fraction (EF) may also be an independent parameter influencing patient outcome [8]. The relationship between RV

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diastolic function and clinical parameters has been debated in TOF patients [9–13], but relatively little is known on the effects of right sided abnormalities on LV diastolic function.

Magnetic resonance imaging (MRI) is the gold standard technique for the assessment of biventricular size and function [14], and it has also been demonstrated to be an accurate tool for the analysis of atrial size and function [15].

The aim of our study was to assess bi-atrial size and function in patients after repair of tetralogy of Fallot and to evaluate the clinical value of these parameters by relating them to biventricular systolic and diastolic function, exercise capacity, electrocardiographic (ECG) parameters, and N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels.

2. Methods

2.1. Patients

This study is part of a larger, prospective serial follow-up study, for which the inclusion criteria were: 1) surgical repair of tetralogy of Fallot without associated cardiac lesions, 2) the availability of an MRI study at least 3 years before the current study. Patients with more than mild tricuspid regurgitation or evidence of a residual ventricular septal defect were excluded.

Fifty-four patients were included in the current cross-sectional study between September 2007 and February 2010. Patients underwent an MRI study with imaging of the atria, 12-lead ECG, 24-hour Holter monitoring, NT-proBNP assessment, and exercise testing, all on the same day.

Results of MRI parameters were compared to a group of 30 healthy controls (15 male, 31 ± 7 years), within our center. Healthy controls were volunteers without cardiac symptoms.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Our study protocol was approved by the local Ethical Committee; all participants, and if required parents, gave written informed consent.

2.2. Magnetic resonance imaging

Cardiac MRI was performed at a Signa 1.5 Tesla system (General Electric, Milwaukee, WI, USA) and an 8-channel phased-array cardiac surface coil. All patients were monitored by vector cardiogram gating and respiratory monitoring. All images were obtained during breath-hold in end-expiration. A multi-slice, multi-phase data set was acquired using steady-state free precession cine imaging in a short axis direction, covering the whole heart, including the atria. Typical imaging parameters were: repetition time 3.4 ms, echo time 1.4 ms, flip angle 45°, slice thickness 8–10 mm, inter-slice gap 1 mm, field of view 380 × 380 mm, and matrix 160 × 128 mm. Flow measurements of the pulmonary valve were performed perpendicular to flow, using a velocity-encoded MRI sequence. Typical imaging parameters were: repetition time 4.5 ms, echo time 2.4 ms, flip angle 18°, slice thickness 7 mm, field of view 290 × 220 mm, and matrix 256 × 128 mm. Velocity encoding was set at 150 cm/s and was increased whenever phase aliasing occurred.

Analysis was performed on a commercially available Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). Endocardial and epicardial borders of both ventricles were manually traced in end-systole and end-diastole. Endocardial borders of the right atrium (RA), LA, RV, and LV were subsequently defined in all phases and all slices of the short axis set using a previously described semi-automated full cardiac cycle contour detection method [16]. Contours were manually corrected if necessary. The atrial appendages were included in the atrial volumes. The superior and inferior caval veins, coronary sinus and pulmonary veins were excluded at their junction to the atrium. Papillary muscles and trabeculations were included in the ventricular cavity. The interventricular septum was included in the LV mass. When the pulmonary valve was visible in the basal slice, contours were drawn up to the junction with the pulmonary valve. All atrial data-sets were analyzed by 1 observer (RP) and supervised by another observer (SL), who also analyzed all ventricular data-sets and had 4 years of experience in cardiac contour tracing. Fig. 1 shows bi-atrial and biventricular endocardial contour tracing.

2.3. MRI parameters

Time volume curves for the RA, LA, RV, and LV were acquired by summation of the volumes of every slice of each phase. Additionally, time volume change curves were reconstructed (Fig. 2). The terms systole and diastole always refer to ventricular systole and ventricular diastole.

2.4. RA and LA function

The following parameters were assessed for RA and LA function (Fig. 2A, B), as described by Riesenkampff and colleagues [17]: 1) maximal volume (max.vol); 2) minimal volume (min.vol); 3) cyclic volume change, defined as the difference between maximal and minimal atrial volume; 4) cyclic volume change function, which is the cyclic volume change, expressed as percentage of maximal atrial volume; 5) reservoir function, calculated by subtracting the minimal atrial volume at middiastole from the maximal atrial volume, expressed as percentage of ventricular effective stroke volume (SV); 6) pump function, calculated by subtracting the minimal atrial volume from the maximal atrial volume at middiastole, expressed as percentage of ventricular effective SV; 7) conduit function, calculated by subtraction of the sum of reservoir and pump volume from the effective SV of the ventricle, expressed as percentage of ventricular effective SV; 8) early emptying fraction, defined as atrial volume decrease during the first 1/3 of ventricular diastole, expressed as percentage of the cyclic volume change; 9) early peak emptying rate (EPER), defined as the maximal atrial volume change in early ventricular diastole; 10) late emptying fraction, defined as the decrease in atrial volume after the onset of atrial contraction, expressed as percentage of the cyclic volume change; 11) late peak emptying rate (LPER), defined as the maximal atrial volume change in late ventricular diastole; and 12) E/A volume ratio, as the ratio of early emptying volume to late emptying volume. Volumetric parameters were indexed for body surface area (BSA); EPER and LPER were indexed for cyclic volume change.

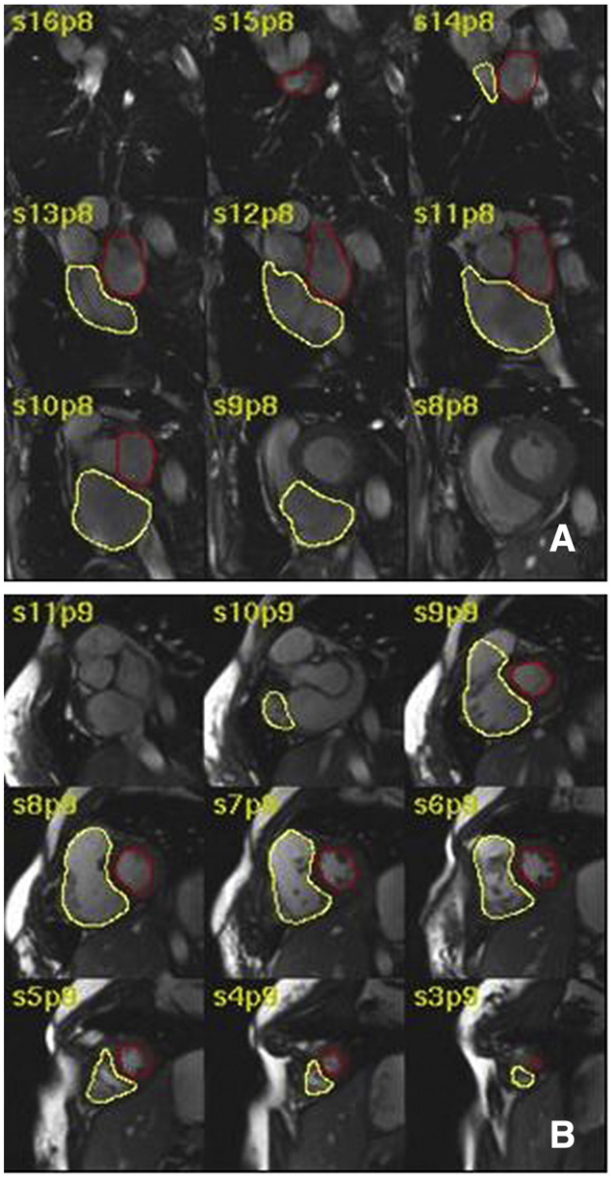

Fig. 1. Contour tracing of atrial and ventricular borders in short axis orientation. A) Right atrial and left atrial contours; B) right ventricular and left ventricular contours.

2.5. RV and LV function

The following parameters were assessed for RV and LV systolic and diastolic function (Fig. 2C, D): 1) biventricular end-diastolic volume (EDV); 2) end-systolic volume (ESV); 3) SV; 4) EF; 5) mass; 6) early filling fraction, defined as ventricular volume

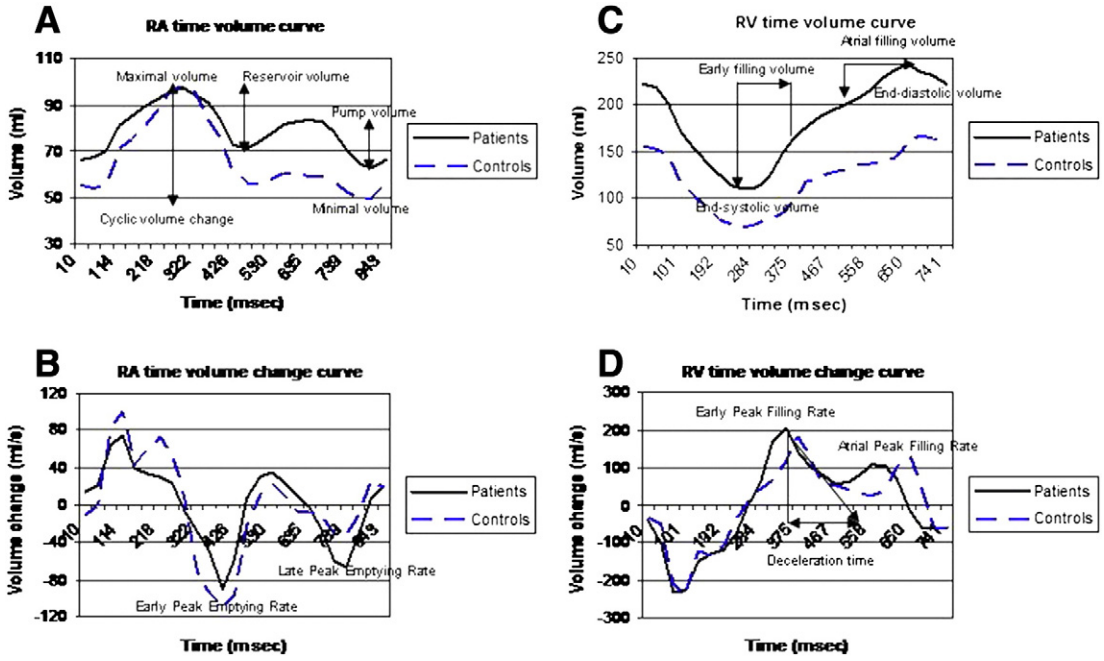

Fig. 2. Time volume curves and time volume changes curves for RA parameters and RV parameters. A) RA time volume curve; B) RA time volume change curve; C) RV time volume curve; D) RV time volume change curve. Abbreviations: RA = right atrium; RV = right ventricle.

increase during the first 1/3 of diastole, expressed as percentage of ventricular SV; 7) early peak filling rate (EPFR), defined as the maximal ventricular volume change in early diastole; 8) deceleration time (Dt), which is the time from EPFR to the extrapolation point of deceleration of flow to the baseline; 9) atrial filling fraction, defined as the increase in ventricular volume after the onset of atrial contraction, expressed as percentage of ventricular SV; 10) atrial peak filling rate (APFR), defined as the maximal ventricular volume change in late diastole; and 11) E/A volume ratio, as the ratio of early filling volume to atrial filling volume. Pulmonary regurgitation was expressed as percentage of systolic SV in the main pulmonary artery. Additionally, RV effective stroke volume (eff.SV) was calculated to correct for PR: RVeff.SV = RVSV − PR volume. End-diastolic forward flow (EDFF) was defined as the presence of late diastolic forward flow in the pulmonary artery.

Volumes and mass were indexed for BSA; Dt for the RR-interval, and EPFR and APFR were indexed for SV.

2.6. Clinical parameters

A standardized 12-lead ECG was obtained to determine QRS duration and QT interval corrected for heart rate (QTc). A 24-hour Holter monitoring was performed on a day with usual activities.

Blood samples were drawn from a peripheral vein after 30 minutes rest in supine position. Plasma and serum were separated immediately after sample collection and stored at −80 °C. NT-proBNP was measured using the following commercially available Elecsys kit: electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany).

Patients performed a maximal bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany). Workload was increased by 20 Watts per minute. Peak workload and peak oxygen uptake (peak VO_2) were recorded and expressed as percentages of predicted values [18,19]. The ventilatory response to carbon dioxide production (VE/VCO_2 slope) was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

2.7. Statistical analysis

Continuous data were tested for normality with the Kolmogorov–Smirnov test. Normally distributed data are expressed as mean (±standard deviation) and non-normally distributed data as median (range). Differences between groups of patients were evaluated using Student *t*-test or nonparametric tests, as appropriate. Categorical data are expressed as counts (percentages) and differences between groups of patients were evaluated with chi-square or Fisher exact test. To test the potential clinical value of parameters of bi-atrial size and function on relevant outcome parameters, correlations were assessed in all patients using linear regression analysis.

Analyses were performed using the SPSS statistical software package version 17.0 (SPSS, Inc., USA). A *p*-value <0.05 was considered to indicate statistical significance.

3. Results

Fifty-four patients were included in our study. Three patients were excluded because of incomplete MRI data. Characteristics of the remaining 51 patients, and results of 12-lead ECG, 24-hour Holter monitoring, NT-proBNP assessment, and exercise testing are displayed in Table 1.

3.1. Patients vs. controls

Results of bi-atrial functional parameters are displayed in Table 2. Compared to healthy controls, patients had a larger RA minimal

Table 1
Characteristics of the study population and results of ECG parameters, NT-proBNP, and exercise capacity.

Parameter	All patients (*N* = 51)
Palliative shunt before corrective surgery	6 (12%)
Age at corrective surgery (years)	0.8 (0.1–9.4)
Transannular patch	41 (80%)
Age at study (years)	21 (±8)
Male (%)	32 (63%)
PVR patients	10 (20%)
BSA (m^2)	1.79 (±0.25)
NYHA class	I: 42 (82%)
	II: 9 (18%)
Heart rate (beats/minute)	75 (±13)
QRS duration (ms)	137 (±26)
QTc interval (ms)	434 (±36)
VT run (number of patients)	1 (2%)
SVT run (number of patients)	2 (4%)
NT-proBNP (pmol/l)	14 (±10)
Peak workload (%)	87 (±12)
Peak VO_2 (%)	89 (±14)
VE/VCO_2 slope	31 (±5)

Results are given as mean (standard deviation), as median (range) or as counts (percentages).
Abbreviations: BSA = body surface area; ECG = electrocardiography; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; PVR = pulmonary valve replacement; QTc = QT interval, corrected for heart rate; SVT = supraventricular tachycardia; VE/VCO_2 = ventilatory response to carbon dioxide production; peak VO_2 = peak oxygen uptake; VT = ventricular tachycardia.

Table 2
Results of bi-atrial functional parameters.

Parameter	RA			LA		
	Controls ($N=30$)	All patients ($N=51$)	p-value ([a])	Controls ($N=30$)	All patients ($N=51$)	p-value ([a])
Maximal volume (ml/m^2)	57 (±11)	55 (±10)	ns	41 (±6)	33 (±6)[a]	<0.001
Minimal volume (ml/m^2)	28 (±8)	34 (±8)[a]	0.001	16 (±3)	15 (±4)	ns
Cyclic volume change (ml/m^2)	30 (±7)	21 (±4)[a]	<0.001	26 (±5)	18 (±4)[a]	<0.001
Cyclic volume change function (%)	52 (±8)	39 (±7)[a]	<0.001	62 (±5)	56 (±6)[a]	<0.001
Reservoir function (%)	41 (±10)	30 (±9)[a]	<0.001	35 (±5)	26 (±6)[a]	<0.001
Pump function (%)	21 (±5)	24 (±9)[a]	0.046	20 (±6)	16 (±6)[a]	0.002
Conduit function (%)	38 (±10)	46 (±12)[a]	0.003	46 (±6)	58 (±9)[a]	<0.001
Early emptying fraction (%)	62 (±15)	52 (±17)[a]	0.008	64 (±12)	56 (±17)[a]	0.017
Late emptying fraction (%)	36 (±9)	51 (±16)[a]	<0.001	40 (±10)	39 (±11)	ns
E/A volume ratio	1.9 (±0.9)	1.1 (±0.5)[a]	<0.001	1.7 (±0.6)	1.6 (±0.8)	ns
EPER/cyclic volume change (/s)	2.0 (±0.5)	1.8 (±0.5)	ns	2.2 (±0.5)	2.3 (±0.6)	ns
LPER/cyclic volume change (/s)	1.3 (±0.5)	1.7 (±0.5)[a]	<0.001	1.5 (±0.6)	1.4 (±0.5)	ns

Results are given as mean (standard deviation).
Abbreviations: E/A volume ratio = ratio of early emptying volume to late emptying volume; EPER = early peak emptying rate; LA = left atrium; LPER = late peak emptying rate; ns = not significant; RA = right atrium.
[a] Significantly different between patients and controls.

volume, a lower RA reservoir function, RA early emptying fraction, and E/A volume ratio; the RA pump function and RA late emptying fraction were higher. Patients had a lower LA maximal volume, LA reservoir function, LA early emptying fraction, and LA pump function than controls. Bi-atrial cyclic volume change function was lower in patients than in controls.

Results of biventricular functional parameters are displayed in Table 3. Patients had larger RV volumes than controls; RVeff.SV and LVSV were smaller, and biventricular EF was lower than in controls. Compared to healthy controls, patients had a lower RV EPFR, LV early filling fraction, LV atrial filling fraction, and LV APFR; the LV E/A volume ratio was higher. Biventricular Dt was longer in patients than in controls.

3.2. Patients with EDFF vs. patients without EDFF

Results for patients with EDFF vs. patients without EDFF are displayed in Table 4: only significant results are shown. RA maximal volume and minimal volume were larger, and RA pump function and RA late emptying fraction were higher in patients with EDFF than in patients without EDFF. Patients with EDFF had more PR and larger RV volumes than patients without EDFF. The LV E/A volume ratio, the NT-proBNP level, and the VE/VCO_2 slope were higher in patients with EDFF than in patients without EDFF.

3.3. Patients with "normal" RA emptying vs. patients with "abnormal" RA emptying

Since results of bi-atrial parameters showed that RA emptying was abnormal in patients (lower RA reservoir function and RA early emptying fraction; higher RA pump function and RA late emptying fraction), we subdivided our 51 patients into 2 groups to evaluate the clinical consequences of abnormal RA emptying: 1) patients with RA reservoir function >30% and RA pump function <24% ("normal" RA emptying) ($N=15$); and 2) patients with RA reservoir function <30% and RA pump function >24% ("abnormal" RA emptying) ($N=36$). These cut-off values for RA reservoir function and RA pump function were based on the mean values of all patients. Results are displayed in Table 5.

EDFF in the pulmonary artery was more present in patients with "abnormal" RA emptying than in patients with "normal" RA emptying. RV mass tended to be larger in patients with "abnormal" RA emptying, but this was not significant. Patients with "abnormal" RA emptying had

Table 3
Results of biventricular functional parameters.

Parameter	RV			LV		
	Controls ($N=30$)	All patients ($N=51$)	p-value ([a])	Controls ($N=30$)	All patients ($N=51$)	p-value ([a])
PR (%)	N/A	28 (±18)[a]	<0.001	N/A	N/A	
EDV (ml/m^2)	94 (±17)	138 (±34)[a]	<0.001	88 (±12)	86 (±13)	ns
ESV (ml/m^2)	42 (±11)	72 (±22)[a]	<0.001	36 (±7)	38 (±9)	ns
SV (ml/m^2)	52 (±8)	66 (±15)[a]	<0.001	51 (±8)	47 (±7)[a]	0.014
Effective SV (ml/m^2)	52 (±8)	46 (±7)[a]	0.003	51 (±8)	47 (±7)[a]	0.014
EF (%)	56 (±6)	48 (±5)[a]	<0.001	58 (±4)	55 (±5)[a]	0.008
Mass (g/m^2)	16 (±4)	25 (±7)[a]	<0.001	51 (±11)	54 (±9)	ns
Mass/EDV ratio	0.17 (±0.02)	0.18 (±0.04)	ns	0.59 (±0.08)	0.63 (±0.09)[a]	0.021
Early filling fraction (%)	38 (±12)	37 (±10)	ns	54 (±17)	46 (±18)[a]	0.046
Atrial filling fraction (%)	31 (±10)	33 (±14)	ns	23 (±8)	17 (±10)[a]	0.006
E/A volume ratio	1.3 (±0.7)	1.6 (±1.3)	ns	2.7 (±1.3)	4.2 (±3.7)[a]	0.008
EPFR/SV (/s)	1.6 (±0.4)	1.3 (±0.3)[a]	0.003	1.9 (±0.3)	1.9 (±0.3)	ns
Dt/RR interval ratio	0.13 (±0.04)	0.24 (±0.10)[a]	<0.001	0.14 (±0.03)	0.16 (±0.04)[a]	0.012
APFR/SV (/s)	1.2 (±0.4)	1.0 (±0.4)	ns	0.9 (±0.4)	0.6 (±0.3)[a]	<0.001

Results are given as mean (standard deviation).
Abbreviations: APFR = atrial peak filling rate; Dt = deceleration time; E/A volume ratio = ratio of early filling volume to atrial filling volume; EDV = end-diastolic volume; EF = ejection fraction; EPFR = early peak filling rate; ESV = end-systolic volume; N/A = not applicable; ns = not significant; LV = left ventricle; PR = pulmonary regurgitation; RV = right ventricle; SV = stroke volume.
[a] Significantly different between patients and controls.

Table 4
Results for patients with and without end-diastolic forward flow.

Characteristic	Patients with EDFF ($N=31$)	Patients without EDFF ($N=20$)	p-value ([a])
PVR patients	2 (6%)[a]	8 (40%)	0.008
RA maximal volume (ml/m^2)	58 (±10)[a]	52 (±9)	0.047
RA minimal volume (ml/m^2)	36 (±9)[a]	31 (±6)	0.047
RA pump function (%)	27 (±8)[a]	20 (±7)	0.003
RA conduit function (%)	43 (±13)[a]	51 (±9)	0.014
RA late emptying fraction (%)	54 (±15)[a]	45 (±15)	0.039
LA cyclic volume change (ml/m^2)	20 (±4)[a]	16 (±4)	0.004
LA cyclic volume change function (%)	58 (±6)[a]	52 (±5)	0.001
LA reservoir function (%)	28 (±6)[a]	24 (±6)	0.023
LA pump function (%)	17 (±6)[a]	13 (±4)	0.013
LA conduit function (%)	55 (±9)[a]	63 (±6)	<0.001
PR (%)	36 (±13)[a]	15 (±17)	<0.001
RVEDV (ml/m^2)	151 (±33)[a]	120 (±27)	0.001
RVESV (ml/m^2)	79 (±22)[a]	63 (±19)	0.010
RVSV (ml/m^2)	72 (±14)[a]	57 (±12)	<0.001
RV mass/EDV ratio	0.17 (±0.04)[a]	0.19 (±0.03)	0.045
LV E/A volume ratio	5.0 (±4.1)[a]	2.9 (±2.5)	0.032
NT-proBNP (pmol/l)	16 (±10)[a]	9 (±9)	0.015
VE/VCO_2 slope	32 (±4)[a]	28 (±6)	0.014

Results are given as mean (standard deviation) or as counts (percentages).
Abbreviations: EDFF = end-diastolic forward flow; other abbreviations as in Tables 1–3.
[a] Significantly different between patients with and without EDFF.

higher NT-proBNP levels, and a lower peak workload than patients with "normal" RA emptying.

3.4. Correlations

Relevant associations between RA parameters and parameters of clinical condition and RV size are displayed in Fig. 3. RA minimal volume was positively associated with RVEDV (Fig. 3A); RA cyclic volume change function was negatively associated with RVEDV (Fig. 3B). A higher RA late emptying fraction was correlated with a higher RVEDV and a higher NT-proBNP level (Fig. 3C, E). A lower RA early emptying fraction was associated with a longer QRS duration (Fig. 3D); a higher RA E/A volume ratio was associated with a higher peak VO_2 (Fig. 3F).

4. Discussion

This cross-sectional study in patients after surgical repair of tetralogy of Fallot demonstrated that in patients with adequate clinical condition, moderately dilated right ventricles and mildly impaired biventricular systolic function, bi-atrial size and function are clearly abnormal. The RA showed a larger minimal volume as well as reduced early emptying and increased late emptying, while the LA showed diminished filling and decreased emptying. The RV showed signs of impaired relaxation, while the LV showed signs of impaired compliance, particularly in patients with EDFF and in patients with "abnormal" RA emptying. "Abnormal" RA emptying was related to signs of impaired clinical condition, as was the presence of EDFF. Furthermore, larger RA size was associated with larger RV size.

In our patients, RA reservoir function and RA early emptying were diminished, which is in agreement with results of a recent study by Riesenkampff et al. [17]. We argue that RA early emptying is in competition with simultaneous inflow in the RV of pulmonary regurgitant backflow. This might also explain the normal filling of the RV in early diastole, despite signs of abnormal RV relaxation. These limitations to early RA emptying explain the observation that RA reservoir function and RA early emptying fraction are decreased and RA pump function and RA late emptying fraction are increased. "Abnormal" RA emptying was related to signs of impaired clinical condition, since patients with "abnormal" RA emptying had a higher NT-proBNP level, a lower exercise

Table 5
Results for patients with "normal" and "abnormal" RA emptying.

Characteristic	"Normal" RA emptying ($N=15$)	"Abnormal" RA emptying ($N=36$)	p-value ([a])
EDFF	6 (40%)	25 (69%)	0.050
RA reservoir function (%)	37 (±5)	27 (±9)[a]	<0.001
RA pump function (%)	17 (±4)	27 (±8)[a]	<0.001
RA late emptying fraction (%)	35 (±11)	58 (±12)[a]	<0.001
RA E/A volume ratio	1.6 (±0.6)	0.9 (±0.4)[a]	0.001
RA EPER/cyclic volume change (/s)	2.3 (±0.4)	1.7 (±0.4)[a]	<0.001
RA LPER/cyclic volume change (/s)	1.3 (±0.3)	1.9 (±0.4)[a]	<0.001
RVEDV (ml/m^2)	132 (±32)	141 (±35)	ns ($p=0.40$)
RV mass (g/m^2)	22 (±4)	26 (±8)	ns ($p=0.074$)
LV E/A volume ratio	3.1 (±2.7)	4.7 (±4.0)	ns ($p=0.19$)
NT-proBNP (pmol/l)	7 (±7)	16 (±10)[a]	0.002
Peak workload (%)	95 (±15)	84 (±9)[a]	0.017
Peak VO_2 (%)	94 (±16)	87 (±12)	ns ($p=0.099$)

Results are given as mean (standard deviation), as median (range) or as counts (percentages).
[a] Significantly different between patients with "normal" and "abnormal" RA emptying. Abbreviations: as in Tables 1–4.

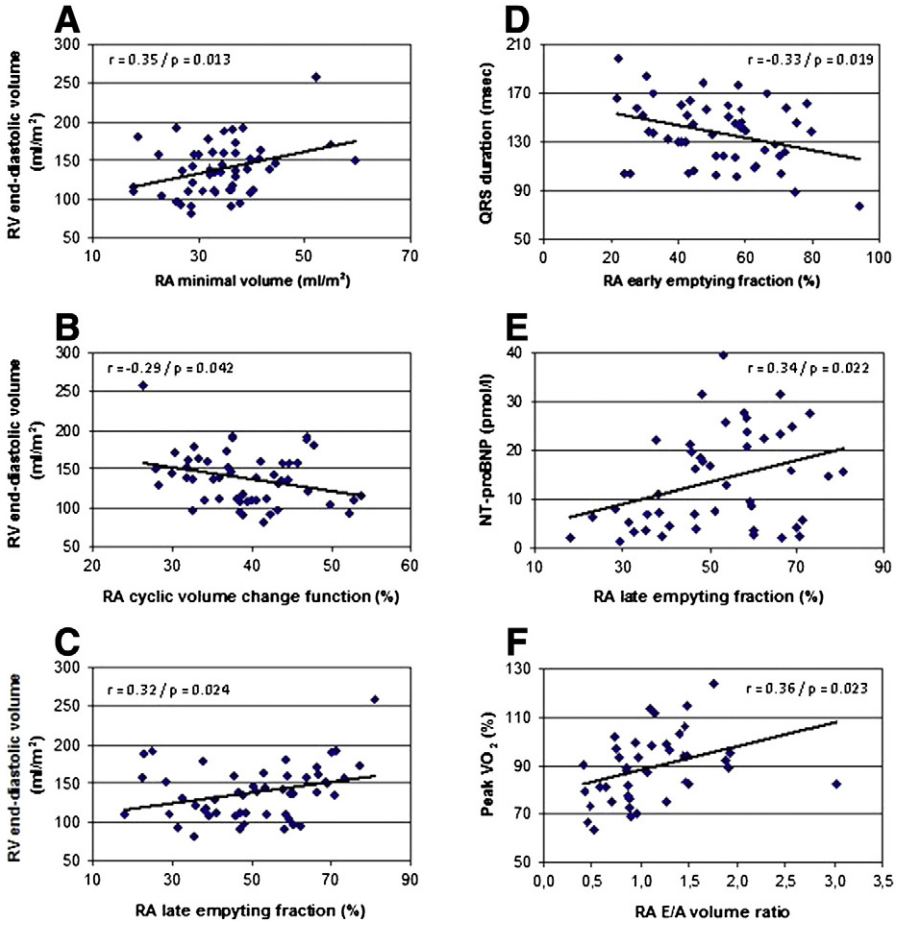

Fig. 3. Correlations between RA parameters and parameters of clinical condition and RV size. Correlation between: A) RA minimal volume and RVEDV; B) RA cyclic volume change function and RVEDV; C) RA late emptying fraction and RVEDV; D) RA early emptying fraction and QRS duration; E) RA late emptying fraction and NT-proBNP level; F) RA E/A volume ratio and peak VO_2. Abbreviations: E/A volume ratio = ratio of early emptying volume to late emptying volume; NT-proBNP = N-terminal prohormone brain natriuretic peptide; RA = right atrium; RVEDV = right ventricular end-diastolic volume; peak VO_2 = peak oxygen uptake.

capacity, and showed a trend towards larger RV volumes than patients with "normal" RA emptying (Table 5, Fig. 3C–F).

In our patients with an important amount of PR, the marked RV dilatation and mildly decreased RV systolic function was not unexpected. Except for the signs of impaired RV relaxation in our patients, i.e. prolonged RV deceleration time and lower RV EPFR, RV diastolic functional parameters were comparable between our patients and healthy controls. Surprisingly, no major differences in RV diastolic functional parameters could be observed between patients with EDFF and patients without EDFF. Whether these observations represent true normal diastolic function or a pseudonormal state [7] cannot be directly determined from our data. Increased RA size has been related to increased RV end-diastolic pressure [20]. We speculate that the higher RA maximal and minimal volume, and the higher RV volumes that we found in our patients with EDFF relate to increased RV end-diastolic pressure. This would point towards abnormal RV diastolic function in these patients, which is compatible to the abnormal finding of EDFF. We have previously demonstrated that with dobutamine stress testing, impaired RV diastolic function is a common finding even in TOF patients with few signs of abnormal RV diastolic function at rest [21]. Assessment of RA size and function may be helpful in clinical practice to identify abnormal RV diastolic function.

End-diastolic forward flow has been recognized as sign of restriction to RV filling, but reports have been equivocal about the effects of EDFF on clinical outcome. Some studies have shown beneficial effects with regard to RV size and clinical condition in patients with EDFF [9,22], but other studies have reported that EDFF should be interpreted as a negative sign [10,11,13]. The latter is in agreement with our results, as we found that patients with EDFF had more PR, more RV dilatation, higher NT-proBNP levels, and a higher VE/VCO_2 slope than patients without EDFF. Lu et al. argued that the differences in effects of EDFF can be explained by the era of treatment of the different patient populations [11]. In the patients who are operated at a younger age, according to current strategies, the presence of EDFF might reflect an overdistended ventricle due to poor compliance from excessive RV dilatation, rather than the traditional definition of RV restriction that represents restricted filling and a decreased RV volume [11].

In our patients, LA maximal volume was lower than in healthy controls. We assume that this reduced LA size is caused by the lower RV effective SV, and subsequently reduced LA filling. Left atrial emptying was also lower than in healthy controls, which presumably relates to the LV diastolic functional abnormalities that we found.

The LV showed signs of impaired relaxation (prolonged deceleration time), and of impaired compliance, as the LV E/A ratio was significantly higher in patients than in healthy controls. Left ventricular diastolic dysfunction is present in up to 25% of adult patients with repaired TOF [23]. The presence of reduced LV compliance might relate to the finding that LV mass/EDV ratio was increased. This might represent chronic underfilling of the LV, but LV volumetric data in our patients do not support this hypothesis. More likely, reduced LV compliance relates to LV fibrosis [24], LV dyssynchrony [25], and abnormal RV–LV diastolic interaction through the interventricular septum [25–28]. The presence of adverse right-to-left interactions is supported by our observation that patients with a large RA and

large RV size showed the most abnormal LV diastolic function. Furthermore, it has been reported that RV pressure overload causes reduced LV compliance through mechanical and molecular effects on the septum and LV myocardium [8]. Our data suggest a relation between RV volume overload and reduced LV compliance as well, since reduced LV compliance was particularly seen in our patients with EDFF, who had a more volume overloaded RV than patients without EDFF. This points towards the clinical relevance of EDFF, a marker that can be easily obtained with different imaging techniques [10].

Supraventricular and ventricular arrhythmias are common after TOF repair [23,29]. The risk of arrhythmias, particularly of intraatrial reentrant tachycardia, increases with larger RA size [23]. Left atrial size, among other factors, has been related to increased risk for atrial fibrillation in an adult TOF population [23,29]. Left ventricular diastolic function and PR are some of the factors increasing the risk for ventricular arrhythmias [2,23]. Despite the presence of several of these factors in our patients, tachyarrhythmias were uncommon. An older age at repair and increasing age have been associated with a higher risk of atrial and ventricular arrhythmias, [2,23,29], which might explain the lower prevalence of arrhythmias in our relatively young patient population operated at young age.

4.1. Limitations

Information about invasive pressure measurements is lacking since our study was noninvasive. Invasive pressure measurements could have given more insight into biventricular diastolic functional parameters and its implications.

Our study has been performed in adolescents and young adults operated on according to current surgical strategies. Our results may therefore be not representative for older TOF patients.

5. Conclusions

In TOF patients with moderately dilated right ventricles and mildly impaired biventricular systolic function, bi-atrial function is clearly impaired and abnormal biventricular diastolic function is common. Right atrial enlargement, impaired RA early emptying and increased RA late emptying were related to signs of impaired clinical condition, as was the presence of EDFF. Assessment of RV diastolic dysfunction in the presence of PR is complex: the presence of EDFF, RA enlargement, and abnormal RA emptying may serve as useful markers for clinically relevant RV diastolic dysfunction in TOF patients, which emphasizes the need for routine assessment of these parameters.

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