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ORIGINAL PAPER

Dilatation of the ascending aorta is associated with presence of aortic regurgitation in patients after repair of tetralogy of Fallot

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Abstract To evaluate the association between aortic morphology and elasticity with aortic regurgitation in surgically corrected of tetralogy of Fallot (TOF) patients. We retrospectively identified 72 consecutive patients with surgically corrected TOF and 27 healthy controls who underwent cardiac MRI evaluation. Velocity-encoded cine MRI was used to quantify degree of aortic regurgitation (AR) in TOF patients. Ascending aorta diameters were measured at standard levels on MRA images. Aortic pulse-wave velocity (PWV) was quantified with MRI. Morphological and functional MRI variables were compared between groups of TOF patients with and without clinically relevant AR and controls. The association between aortic morphology and elasticity with the presence of AR was evaluated using univariate and multivariate logistic regression. The majority of TOF patients had only trace AR. Nine TOF patients (12 %) had an AR fraction higher than 15 %. Indexed aorta diameter at the sinotubular junction ($p=0.007$), at the RPA level ($p=0.006$), and low left ventricular ejection fraction (LVEF) ($p=0.015$) showed the strongest associations with the presence of at least mild AR, which persisted after controlling for age and gender. Increased ascending aorta dimension is associated with AR in patients after repair of TOF. LVEF was also low in the group of patients with relevant AR compared to those without, suggesting even mild to moderate AR may contribute to LV dysfunction in these patients. Enlarged ascending aorta may be an indication for precise quantification of regurgitant fraction with MRI, since symptomatic patients may need aortic valve repair when moderate regurgitation is present.

Keywords Tetralogy of Fallot · Aortic insufficiency · Aortic dilatation · MRI

Introduction

Tetralogy of Fallot (TOF) is a disease characterized by right ventricular hypertrophy, subpulmonary stenosis, overriding aorta and perimembranous ventricular septal defect [1]. Although right ventricular dysfunction due to chronic pulmonary regurgitation is common following repair of TOF [1–3], there is substantial evidence demonstrating left ventricular and aortic abnormalities occur in TOF patients status post repair [4–6]. Aortic complications may occur many years after the initial surgical repair and include progressive aortic dilation [7], aortic regurgitation (AR), aortic dissection, and aortic rupture [8, 9].

Arotic regurgitation has been reported as more common in TOF patients than in the general population [10, 11]. Though minorities of TOF patients are affected, AR may have important implications in surgical planning, particularly for pulmonary valve replacement late after initial surgical repair [12]. The mechanism underlying AR after TOF repair is incompletely understood, and may include ascending aorta dilation, abnormal aortic elasticity, or type of surgical repair.

MRI is a very accurate non-invasive technique for assessment of thoracic aortic dimensions, ventricular volumes and function, and quantification of AR [13]. It is currently commonly used for follow up of patients after repair of TOF [14]. MRI may be a useful tool for precise quantification of AR, which may indicate the need for closer follow up

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imaging or surgical repair, particularly in symptomatic patients [15].

The goal of this study is to evaluate the association between aortic morphology and elasticity, as measured by MRI, with AR in surgically corrected TOF patients.

Materials and methods

Patients

This was a single-institution retrospective cross-sectional study, which was approved by our institutional Committee on Human Research with waiver of the requirement for written consent. The study was compliant with the Health Insurance Portability and Accountability Act (HIPAA).

All patients with history of corrected TOF who underwent cardiac MR evaluation with MR angiography at our institution between April 2006 and January 2011 were identified. Those patients for whom a body-surface area (BSA) was not recorded and those with a history of aortic valve replacement were excluded from the analysis. In patients with multiple MR studies, only the first MR examination was used for analysis.

Control subjects were selected by identifying patients who were referred to our institution for cardiac MRI studies mainly due to family history of cardiac abnormalities or a questionable echocardiographic abnormality, but who had normal cardiac MRI examinations, during the same time period as the TOF population. Exclusion criteria for control subjects comprised history of corrected congenital heart disease, imaging evidence of pulmonary hypertension, left ventricular ejection fraction (LVEF) <50 %, right ventricular ejection fraction (RVEF) <40 %, greater than trace aortic, pulmonic, mitral, or tricuspid regurgitation, and one or more enlarged cardiac chambers.

Medical records were reviewed for data collection, which included, age, gender, BSA, type of TOF repair, and date of the procedure.

Cardiac MRI technique

All patients underwent cardiac MR evaluation with a 1.5 T unit (Achieva, Philips Medical Systems, Best, The Netherlands, SW release 2.6.3) with a five-channel cardiac coil and using parallel imaging technique (SENSE). The MR protocol included assessment of aortic dimension with gadolinium enhanced MR angiography and measurement of AR.

3D-Fast field echo MR Angiography of the aorta was obtained in the sagittal plane during the administration of 0.1 mmol/kg of gadolinium chelate, with a slice thickness of 2 mm (TR = 5.1 ms; TE = 1.4 ms; flip angle = 40°; FOV = 400 mm).

Velocity-encoded cine MR images were obtained with a navigator based free-breathing sequence, in a plane perpendicular to the direction of blood flow in the ascending aorta, just superior to the origin of the coronary arteries. Forty frames were acquired per average cardiac cycle. The imaging parameters were: slice thickness = 10 mm; TR = 15–30 ms; TE = 5.3–7.5 ms; flip angle = 150°; FOV = 140–300 mm and encoding velocity = 200 cm/s. If aliasing was present, the encoding velocity was increased until the aliasing disappeared (VENC >200–300 cm/s).

Cine MR images were obtained for assessment of right and left ventricular volumes and function. Steady-state free precession (SSFP) images were acquired in the short-axis plane through the entire heart, encompassing 16 phases of the cardiac cycle. The imaging parameters were: repetition time = 1.4–3.0 ms, echo time = 1.4–3.2 ms, flip angle = 70°, field of view = 340 mm, number of excitations = 1, slice thickness = 8 mm with no gap and acquisition matrix = 144 × 256.

Imaging analysis

Ascending aortic dimensions were assessed on a sagittal oblique reconstruction from the MR angiography sequence at three pre-defined levels: the sinus of Valsalva, the sinotubular junction, and at the level of the right pulmonary artery. Maximum aortic dimensions were measured on a PACS workstation (Philips iSite, Philips Healthcare, Andover, MA).

Biventricular volumes and function were measured on the short-axis cine sequences by manually tracing the endocardial surface on all phases of the cardiac cycle, and indexed to BSA. Parameters included LVEF, left ventricular end-diastolic volume index (LVEDVi), left ventricular end-systolic volume index (LVESVi), RVEF, right ventricular end-diastolic volume index (RVEDVi), and right ventricular end-systolic volume index (RVESVi).

AR was measured on the velocity-encoded sequences by calculating the ratio of the backward to the forward flow at the ascending aorta. Forward flow, backward flow and regurgitant fraction were obtained by manually tracing a region of interest around the ascending aorta in the magnitude and phase images. Severity of AR was defined as none [aortic regurgitant fraction (RF) <5 %], trace (RF = 5–14 %), mild (RF = 15–29 %) moderate (RF = 30–49 %) and severe (RF ≥50 %), following American Heart Association guidelines. For statistical analysis, patients were categorized in two groups: those with absent or trace AR were considered to have no clinically relevant AR, and those with mild, moderate or severe AR were considered to have clinically relevant AR. Measurement of left ventricular function and ascending aorta flow was performed using the freely available software, Segment version 1.8 (http://segment.heiberg.se) [16].

Aortic pulse wave velocity (PWV) was derived from information contained on a single axial velocity encoded cine sequence through the proximal ascending aorta and mid descending thoracic aorta. PWV was calculated by the following formula: x/t, where x = the distance between sites of measurement in the ascending aorta and descending aorta, and t = time required for pulse wave to travel from the sites of measurement in the ascending aorta and descending aorta [17, 18]. The distance between measurement sites was measured on a sagittal oblique reconstruction from the MRA sequence (Philips iSite, Philips Healthcare, Andover, MA). Multiple points were drawn on adjacent images such that the path connecting the points was in the center of the aortic lumen. The time difference was calculated by tracing a region of interest around the proximal ascending and descending thoracic aorta (Segment version 1.8; http://segment.heiberg.se) [16], and plotting the velocity of flow through this region versus time. The steepest part of the upstroke was extrapolated to the baseline flow of that curve to determine pulse wave arrival time; the arrival time in the ascending aorta was subtracted from the arrival time in the descending aorta (Fig. 1) [17].

Statistical analysis

Statistical analyses were performed using STATA 11.0 version software (STATA Corporation, Houston, TX, USA). Descriptive statistical analyses were made using the Students *t* test and were reported as mean and standard deviation. ANOVA was used to compare demographic characteristics among controls and TOF patients with and without clinically relevant AR. Chi-squared test was used to compare proportions of RV to PA conduit repair between groups of TOF with and without clinically relevant AR. Direct comparison of anatomic and functional measurements in controls and TOF patients with and without clinically relevant AR were also performed using Students *t* test. Univariate and multivariate logistic regression models were used to identify factors independently associated with the presence of clinically relevant AR. A p value of less than 0.05 was considered indicative of a statistically significant result.

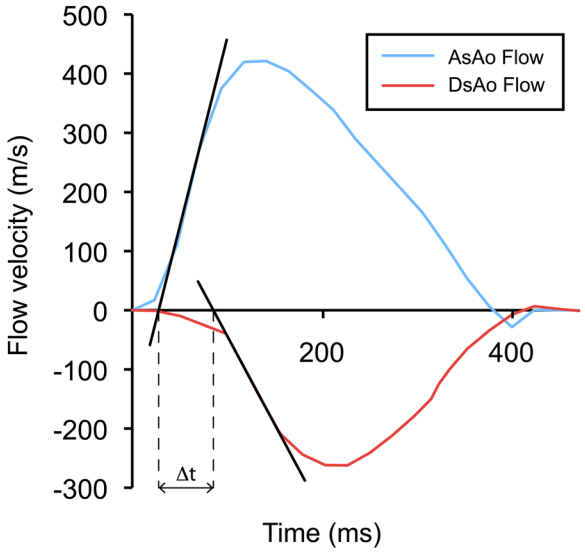

Fig. 1 Δt measurement for pulse wave velocity calculation. The Δt was defined as the difference in arrival time of the pulse wave in the ascending aorta and descending aorta. The steepest part of the flow curve was extrapolated and the intersection of this line with the baseline flow was defined as the pulse wave arrival time. Superiorly directed flow was defined as positive flow (forward flow in the ascending aorta) and inferiorly directed flow was defined as negative flow (forward flow in the descending aorta). *AsAo* ascending aorta, *DsAo* descending aorta

Results

Patients

Seventy-two consecutive TOF patients and 27 controls were identified who met inclusion and exclusion criteria. The sample of TOF patients included pediatric and adult patients, with ages varying from 10 to 79 years. The majority of patients had complete surgical repair within the first 6 months of life. Three patients had total repair at 3 years of age, none of them with more than trace AR. Five patients had total repair of TOF between 10 and 20 years of age, including two patients with AR. The majority of the TOF patients had absent (66.7 %) or trace (20.8 %) AR. The frequency of patients with mild, moderate and severe AR was 8.6, 1.4 and 2.8 %, respectively, with a total of 12.5 % of patients with what was considered clinically relevant AR. Table 1 shows demographic characteristics of the three study groups: controls, no clinically relevant AR, and clinically relevant AR.

Morphologic and functional MRI parameters were significantly different among the three comparison groups, as shown in Table 2. Figure 2 shows summary statistics of the main MRI parameters that differ on *t* test comparison of controls versus TOF patients without clinically relevant AR, TOF patients with versus without clinically relevant AR, and controls versus TOF patients with clinically relevant AR. When direct comparison between groups was performed, the main abnormalities encountered were a larger indexed sinotubular junction diameter, larger indexed aorta at RPA level diameter, larger LVEDVi and LVESVi, and a lower LVEF in TOF patients with relevant AR compared to those without. The ascending aorta diameters were all larger in TOF patients without relevant AR compared to controls; whereas PWV, LV volumes, and LVEF were not significantly different between these groups. Aortic dimensions,

Table 1 Patients characteristics

Parameter	Control N=27	TOF without AR <15% N=63	TOF with AR >15% N=9	p value
Age (years)				
Mean; range (SD)	33; 10–79 (18.9)	25.8; 10–60 (11.2)	42.7; 23–57 (13.2)	0.0103*
Time from surgery (years)				
Mean (SD)	NA	25.1 (10.6)	39.5 (11.4)	0.0004**
Male gender				
n (%)	16 (59.3)	30 (47.6)	4 (44.4)	0.5770*
BSA (m^2)				
Mean (SD)	1.89 (0.27)	1.67 (0.25)	1.88 (0.24)	0.0015*
Type of repair [n(%)]				
RV to PA Conduit	NA	14 (22)	2 (22.5)	0.5837***
Transannular patch	NA	34 (54)	5 (55)	
Infundibulectomy	NA	15 (24)	2 (22.5)	

TOF tetralogy of Fallot, *BSA* body surface area, *RV* right ventricle, *PA* pulmonary artery, *SD* standard deviation

* ANOVA, ** *t* test, *** Chi square

Table 2 MRI parameters

Parameter Mean (SD)	Control N=27	TOF without AR <15% N=63	TOF with AR >15% N=9	*p* value ANOVA
Indexed sinus of Valsalva diameter (cm/m^2)	1.57 (0.21)	2.09 (0.39)	2.29 (0.42)	<0.0001
Indexed sinotubular junction diameter (cm/m^2)	1.34 (0.20)	1.73 (0.29)	2.06 (0.52)	<0.0001
Indexed rorta diameter at RPA level (cm/m^2)	1.42 (0.25)	1.67 (0.27)	2.03 (0.49)	<0.0001
PWV (m/s)	3.89 (0.5)	4.55 (1.18)	5.11 (1.72)	0.1063
RVEF (%)	51.2 (7.4)	56.9 (7.6)	43.4 (8.6)	0.0127
RVEDVi (ml/m^2)	80.9 (22.8)	126.3 (44.9)	139.1 (31.7)	<0.0001
RVESVi (ml/m^2)	42.0 (11.9)	68.5 (27.8)	79.2 (24.6)	<0.0001
LVEF (%)	61.5 (7.7)	56.9 (7.6)	50.2 (8.3)	<0.0001
LVEDVi (ml/m^2)	78.6 (18.9)	79.4 (18.9)	98.4 (34.0)	0.0321
LVESVi (ml/m^2)	32.1 (11.3)	34.6 (11.8)	50.5 (21.5)	0.0012

TOF tetralogy of Fallot, *SD* standard deviation, *RPA* right pulmonary artery, *PWV* pulse wave velocity, *RVEF* right ventricular ejection fraction, *RVEDVi* right ventricular end-diastolic volume index, *RVESVi* right ventricular end-systolic volume index, *LVEF* left ventricular ejection fraction, *LVEDVi* left ventricular end-diastolic volume index, *LVESVi* left ventricular end-systolic volume index

PWV, LV volumes and function were all significantly different between controls and TOF patients with relevant AR.

As expected, patients with TOF had larger RV volumes and lower RVEF compared to controls. However, TOF patients with and without relevant AR did not differ in RVEDVi (139.1±31.7 vs 126.3±44.9 ml/m^2; p=0.413), RVESVi (68.5±27.8 vs 79.2±24.6 ml/m^2; p=0.277) and RVEF (46.4±7.5 vs 43.4±8.6%; p=0.286).

In univariate regression analysis, indexed aorta diameter at the sinotubular junction, indexed aorta diameter at the RPA level, and LVEF showed the strongest association with the presence of clinically relevant AR with p values of 0.017, 0.008 and 0.025 respectively (Table 3). The significant association persisted in multivariable logistic regressions after controlling for age and gender (Table 3).

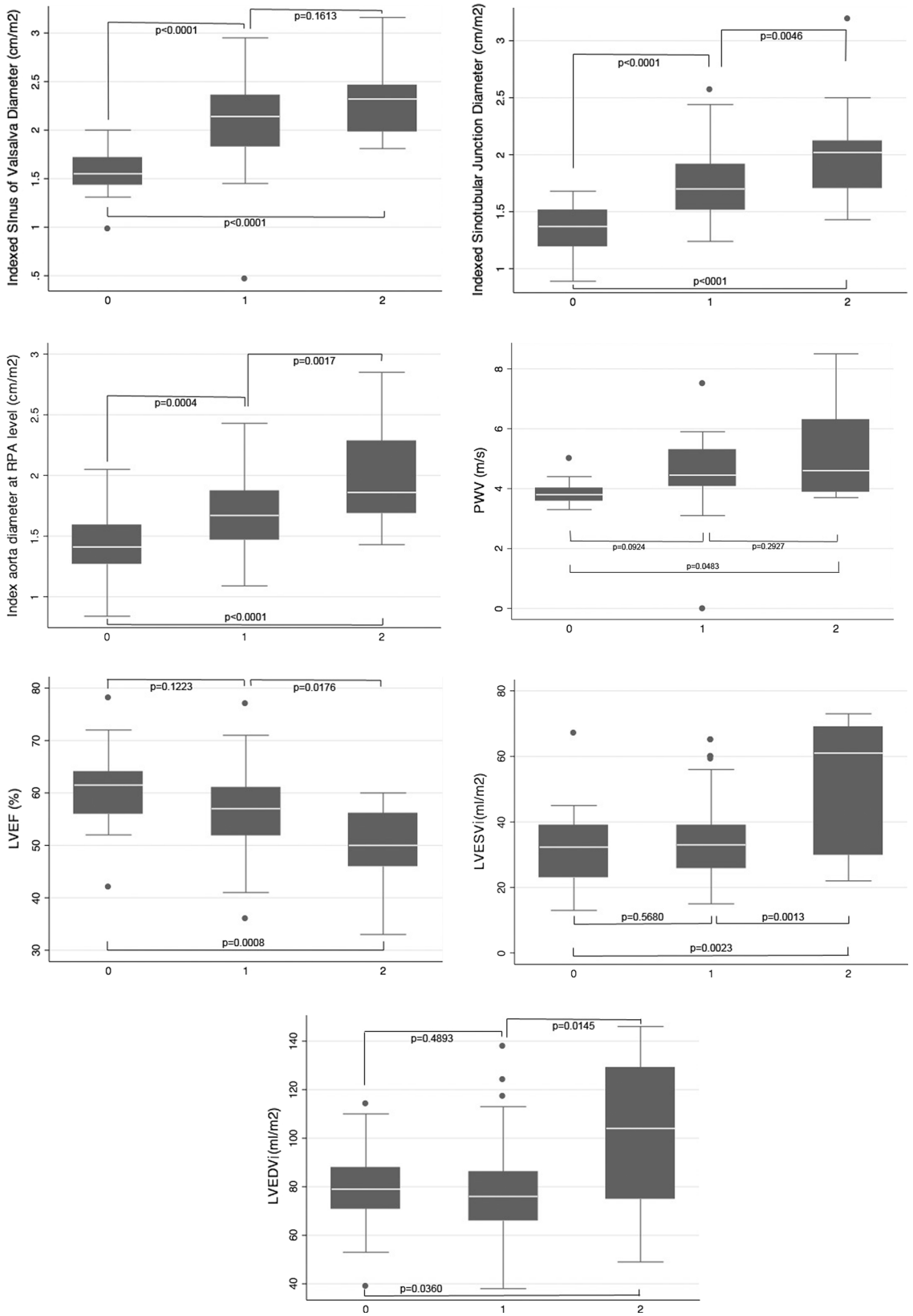

Fig. 2 Direct comparison between study groups: controls (0) and patients without (1) and with (2) clinically relevant aortic regurgitation. *RPA* right pulmonary artery, *PWV* pulse wave velocity, *LVEF* left ventricular ejection fraction, *LVESVi* left ventricular end-systolic volume index, *LVEDVi* left ventricular end-diastolic volume index

Table 3 Logistic regression analysis

	Coefficient	95% confidence interval	p value
Unadjusted models			
Indexed sinotubular junction diameter (cm/m^2)	2.51	0.45–4.57	0.017
Indexed aorta diameter at RPA Level (cm/m^2)	3.01	0.80–5.21	0.008
LVEF (%)	–0.11	–0.21 to –0.01	0.025
Adjusted model 1			
Indexed sinotubular junction diameter (cm/m^2)	4.46	1.24–7.68	0.007
Age (years)	0.16	0.06–0.26	0.002
Gender	2.61	0.03–5.19	0.047
Adjusted model 2			
Indexed aorta diameter at RPA level (cm/m^2)	4.22	1.20–7.25	0.006
Age (years)	0.13	0.05–0.22	0.003
Gender	2.31	–0.034 to 4.66	0.054
Adjusted model 3			
LVEF (%)	–0.17	–0.31 to –0.03	0.015
Age (years)	0.16	0.05–0.26	0.003
Gender	0.06	–1.93 to 2.05	0.952

RPA right pulmonary artery, *LVEF* left ventricular ejection fraction

Discussion

Our study showed that repaired TOF patients with AR fraction higher than 15% have larger ascending aorta dimensions when compared to those with regurgitant fraction less than 15%. More specifically, dilatation of the sinotubular junction and the aorta at the RPA level, but not at the sinus of Valsalva, were associated with clinically relevant AR (Fig. 3). When compared to normal controls, the ascending aorta at all three measured levels was significantly larger in TOF patients irrespective of the presence of AR.

Prior studies have documented the presence of an enlarged ascending aorta in postop TOF patients [19]. However, our study is the first to report an association between aortic dimensions and aortic valve insufficiency, which is independent from age and gender. Based on our data, an enlarged ascending aorta at the sinotubular junction and RPA level could prompt the need for more precise quantification of AR with MRI. Since patients after repair of TOF usually present cardiac symptoms, they could meet AHA criteria for AVR when only moderate AR is diagnosed [15]. Precise quantification of AR and LVEF could be used to document moderate AR, which could be addressed in combination with pulmonary valve replacement when clinically indicated [12].

In our study, dilatation of the sinotubular junction showed stronger association with aortic insufficiency that sinus of Valsalva dilatation. The abnormal morphology of the ascending aorta with an effaced appearance of the sinotubular junction has been previously described in TOF and other conotruncal anomalies [5, 20], and is a known feature of aortopathies such as is Marfan's disease [21]. Prior histological studies have documented aortic wall abnormalities including fibrosis and cystic medial necrosis in deceased TOF patients, supporting the hypothesis that primary aortopathy is an important determinant of aortic dilatation in TOF [4, 5]. Association between an effaced sinotubular junction and aortic insufficiency suggests that an abnormal aortic wall could influence the aortic leaflet and annulus function in patients late after repair of TOF.

Our data also showed that low LVEF was independently associated with the presence of AR greater than 15% in postop TOF patients. Decreased LVEF is a known predictor of poor prognosis in TOF patients [11], and the most accepted LV dysfunction mechanism is related to poor ventricular–ventricular interaction [22]. Our study suggests that even mild AR was associated to LV dysfunction in patients after repair of TOF. This association suggests that the presence of aortic insufficiency may contribute to LV dysfunction in these patients, and could have added effect to the ventricular–ventricular interaction. The presence of a regurgitant jet could potentially introduce increased deformation of the septum in late diastole, which could alter the contractile performance of the ventricle. Our group has previously reported an association between increased ventricular septal excursion during the cardiac cycle and impaired septal myocardial strain in patients with postoperative TOF, supporting this hypothesis [22]. Although TOF patients usually present with mild to moderate AR, which is not an indication for aortic valve replacement in otherwise healthy patients, these

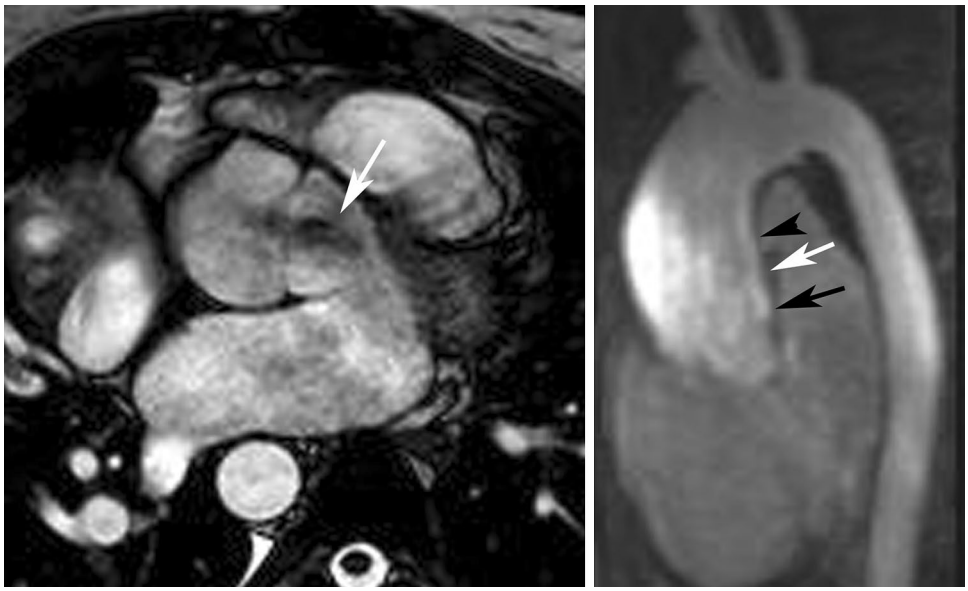

Fig. 3 Enlarged ascending aorta in a patient with tetralogy of Fallot and aortic regurgitation. Axial steady-state free precession image at the level f the aortic valve during diastole (**a**) shows flow jet (*arrow*) consistent with aortic regurgitation. Maximum intensity projection reformation of the gadolinium-enhancement MRA in an oblique sagittal plane (**b**) shows dilatation of the aorta at the sinotubular junction (*white arrow*) and level of the right pulmonary artery (*arrowhead*), relatively sparing the sinus of Valsalva (*black arrow*)

patients may need correction of the aortic valve lesion in order to prevent further degeneration of the LV.

Aortic elasticity, as measured by PWV, was significantly decreased in TOF patients with AR compared to normal controls. Although there was a trend towards increased PWV as one sequentially evaluates normal controls, TOF patients without relevant AR, and TOF patients with relevant AR, the differences did not reach statistical significance, likely due to small sample size. Prior studies have demonstrated an abnormal PWV in TOF patients compared to controls. A study of aortic stiffness in surgically corrected TOF patients using measurements obtained at cardiac catheterization showed an increased PWV of 5.61 m/s in TOF subjects compared to 4.17 m/s in control subjects ($p < 0.01$) [23]. Grotenhuis et al. also showed abnormal aortic elasticity in a small sample of TOF patients compared to age-matched controls [24]. Similarly to our data, a very week association was seen in this study between PWV and the presence of trace AR, which was indeed not higher than 6 %. Our study suggests that although aortic elasticity is abnormal in patients with clinically relevant AR compared to controls, the morphology of the ascending aorta seems to be a better indicator of the presence of aortic insufficiency in patients after TOF repair.

Our study has limitations inherent to the observational and retrospective design, and small number of patients with clinically significant AR. First, this study included TOF patients with varying types of surgical repair, with the minority of patients undergoing RV-to-PA conduit repair, and a few patients undergoing repair in adulthood. The inhomogeneity of the surgical repair could have influenced the severity of AR However, the aorta or aortic valve were not involved in any of the surgical procedures, therefore, the aortic pathology observed in our study is unlikely to be directly related to the type of surgical correction. Second, our population included a small number of subjects with clinically relevant AR (nine patients), which may limit the ability to detect statistical associations between multiple predictors and aortic valvular insufficiency. Therefore, multivariate logistic regression models were limited to two covariates, and three separate statistical models were built to interrogate independent associations with AR. That being said, the small number of positive AR cases does not limit the robustness of positive associations in models with limited number of covariates. Finally, the control population selected was small and had different clinical indications for the MRI study when compared to the TOF patients.

In conclusion, increased ascending aorta dimension is associated with the presence of mild to moderate AR in this cohort of patients after repair of TOF. LVEF was also decreased in the group of patients with clinically relevant AR compared to those without, suggesting that even mild to moderate AR may contribute to LV dysfunction in these patients. Enlarged ascending aorta may be an indication for precise quantification of regurgitant fraction with MRI, since symptomatic patients may need aortic valve repair when moderate regurgitation is present.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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