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Follow-up aortic dilatation in patients with repaired tetralogy of Fallot using cardiovascular magnetic resonance

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HIGHLIGHTS

- Most repaired adolescents with TOF have significant aortic dilatation.
- Mild increase aortic size with regression of aortic growth index are common.
- Aortic growth among adolescents is a part of physiologic growth.
- Aortic growth does not produce adverse effect on aortic regurgitation.
- Severity of initial aortic size is not a predictor for the rate of aortic growth.

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ABSTRACT

Purpose: The study sought to determine the rate of aortic expansion and correlation with somatic growth in patients with repaired tetralogy of Fallot (rTOF), and predictors for determining the annual growth rate of the aorta (Ao-AGR).

Methods: Ninety-four rTOF patients (mean age 14.5 ± 4.4 years) with two cardiac magnetic resonance tests (CMR) (median duration 52 months, interquartile range, IQR 24–71) were analyzed for aortic diameter (AoD) at the annulus, the sinus of Valsalva (SoV), the sinotubular junction, and the ascending aorta (AAo), and compared with the normal limit AoD (NL-AoD) values. The median age-at-repair was 60 months (IQR 36−84). Ao-AGR and its index (Ao-AGRI) were derived from changes of the AoD and AoD-index, respectively, divided by the duration between the two studies. Three potential predictors (baseline AoD, sex, and age-at-repair) for the progression of Ao-AGR were analyzed.

Results: There was a significant larger AoD than NL-AoD ($p < 0.001$). Slow aortic growth was encountered in 78–85 % of patients. The Ao-AGR was slow, the median AGR ranged from 0.37 mm (IQR 0.13−0.72) at annulus to 0.56 mm (IQR 0.22−0.91) at AAo. There was a regression in Ao-AGRI, ranged from -1.41 mm (IQR -1.94, -0.87) at annulus to -2.36 mm (IQR -3.09, -1.63) at SoV. The three predictors were not correlated with severity of Ao-AGR.

Abbreviations: AGR, annual growth rate; Ao-AGR, annual growth rate of the aorta; AoD, aortic diameter; AoR, aortic root; AAo, ascending aorta; CMR, cardiac magnetic resonance; rTOF, repaired tetralogy of Fallot; cine bSSFP, cine balanced steady-state free precession; STJ, sinotubular junction; SoV, sinus of Valsalva; TOF, tetralogy of Fallot.

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Conclusion: Most adolescents with rTOF show significant aortic dilatation. There is a slow Ao-AGR with regression of Ao-AGRI, which may suggest that the rate of aortic growth is slower than the somatic growth. There are no significant predictors of the progression of Ao-AGR.

1. Introduction

Patients with definitive surgical repaired tetralogy of Fallot (rTOF) require long-term follow-up to monitor right- and left-sided hemodynamic changes, including pulmonary regurgitation, right ventricular dysfunction, aortic dilatation, and left ventricular volume overload [1,2]. Aortic dilatation is a well-known sequela in patients with rTOF, where the dilatation process began before surgical correction as the aorta was exposed to long-term volume overload from left-to-right shunt [3–5]. The incidence of aortic dilatation ranged between 15 % and 88 %, depends on the criteria used to define [6]. Moreover, aortic root (AoR) growth can be out of proportion to somatic growth [4]. Changes of AoR diameter over time have been reported with a diversity of results [4,7,8]. A large study of 768 children with rTOF, using echocardiographic assessment, demonstrated a decrease in AoR Z-score over the median follow-up period of 3.7 years. Nevertheless, the sizes did not regress to within the normal range [6]. With the use of cardiovascular magnetic resonance (CMR) to follow 110 adults with rTOF, there was a high prevalence (47 %) of progressive AoR diameter during the median follow-up period of 6.3 years, at a progression rate of between of 0.2−0.4 mm/year [7]. Knowledge of the expected aortic growth may aid in determining an appropriate follow-up imaging strategy to detect patients at risks for aortic complications.

2. Purpose

To date, there are a few studies of rTOF conducted in adolescents, which is a period of maximum growth and were the expected change in aortic size over time has not been fully established. Our study sought to evaluate the annual growth rate (AGR) of the aorta at four levels: annulus, sinus of Valsalva (SoV), sinotubular junction (STJ), and proximal ascending aorta (AAo) and compared with the somatic growth. We also sought to identify possible predictors influencing rate of aortic growth in adolescents with rTOF by using CMR.

3. Materials and methods

3.1. Study population

This was a single-center, retrospective study, which included patients with definitive surgical repair for a preoperative diagnosis of tetralogy of Fallot (TOF) or double outlet right ventricle of TOF type, who had at least 2 CMR studies between 2009 and 2019. The study excluded patients with rTOF associated with pulmonary atresia, congenital aortic valvular disease (aortic stenosis and bicuspid aortic valve), syndromic aortopathy (Marfan syndrome and Turner syndrome), and patients with percutaneous pulmonary valve implantation. A total of 113 patients were initially identified. Nineteen patients were excluded for the following reasons: incomplete CMR data ($n = 17$) and non-diagnostic CMR from metallic artifacts ($n = 2$). Thus a total of 94 patients were included in the analysis. Demographic and age at surgery were obtained from medical records. Age and aortic regurgitation (%) at initial and follow-up CMR scans was collected from CMR reports. The study was approved by the institutional research ethics committee.

3.2. Cardiac magnetic resonance protocol

CMR images were acquired from a 3.0-tesla scanner, with the use of one of two models (Intera Achieva or Ingenia, Philips, Best, the Netherlands): between 2009 and 2013- the Intera Achieva model and from 2014 to 2019-the Ingenia model. Images of AoR in the oblique sagittal left ventricular outflow tract (LVOT) view were obtained with the use of breath-hold, retrospective electrocardiography-gated segmented k-space, cine balanced steady-state free precession (cine bSSFP) in a 6−8 mm slice thickness, with a spatial resolution of 1.5 × 1.5 mm to 1.6 × 1.8 mm, and 30 cardiac phases of the cardiac cycle. A through-plane phase contrast CMR images of the AAo at the level approximately 2.0–3.5 cm above the aortic valve annular plane was used to measure AAo dimensions and areas. The prescribed location was evaluated for the absence of turbulent flow or interference of valve leaflets prior to data acquisition. The imaging parameters of the phase contrast pulse sequence were as follows: a slice thickness of 6−8 mm, a spatial resolution of 1.5 × 1.5 mm to 2.0 × 2.0 mm, a temporal resolution of 60 milliseconds, velocity encoding at 180−200 cm/sec, and 30–40 cardiac phases throughout the cardiac cycle. Images were acquired during breath-hold at expiration. The breath-hold period was approximately 15 s.

For children under 11 years of age, CMR images were obtained under general anesthesia by an anesthesiologist.

3.3. Image analysis

CMR images were transferred to the Picture Archiving and Communications System (PACS), using a DICOM Conformance (Synapse version 3.2.0, FUJIFILM Medical Systems USA's Synapse® PACS System, USA). Maximum aortic diameter at the levels of annulus, SoV and STJ were measured from the cine bSSFP images in the oblique sagittal LVOT plane during ventricular systole, and perpendicular to the long-axis of the AoR [6] (Fig. 1). Maximum AAo diameter, and maximum and minimum AAo areas were measured from the magnitude images of the phase contrast pulse sequence (Fig. 2). Aortic diameters (AoD) were indexed to body surface area (BSA) and expressed as aortic diameter index (mm/m^2) with BSA derived from the Dubois and Dubois formula (BSA $[m^2] = 0.007184$ x height $[cm]^{0.725}$ x weight $[kg]^{0.425}$) [9,10]. AGR and annual growth rate index of the aorta were derived from the

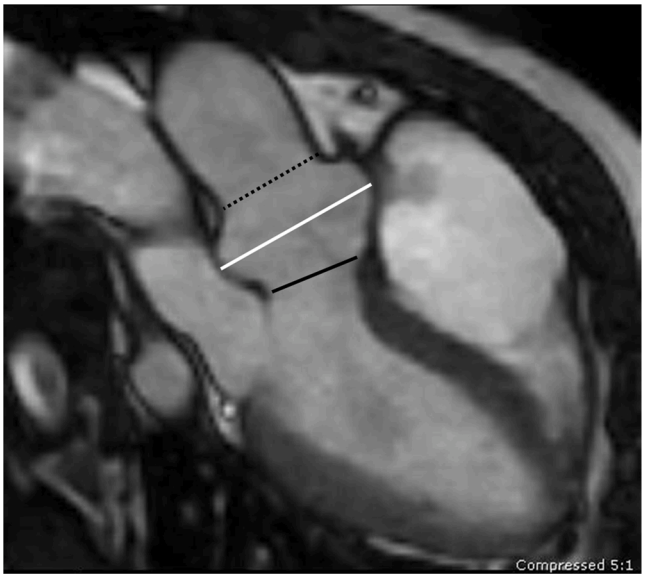

Fig. 1. Cine bSSFP in an oblique sagittal LVOT plane view during systole showing the measurements at the annulus, sinus, and sinotubular junction.

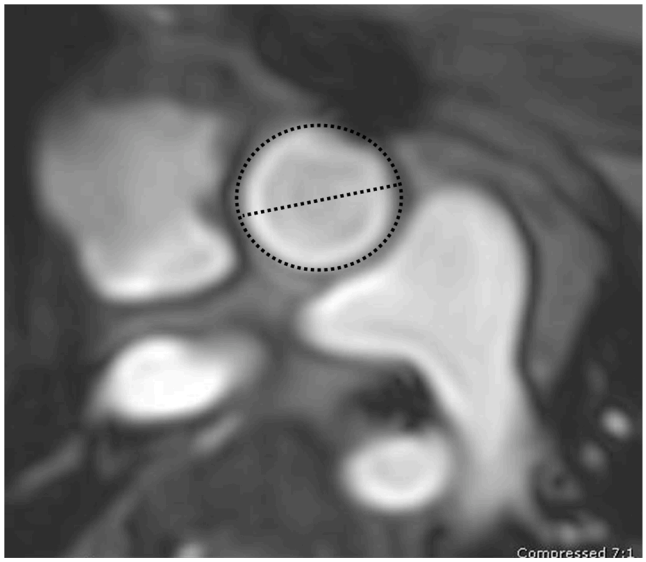

Fig. 2. Phase contrast magnitude image of proximal ascending aorta showing the measurements of ascending dimension and maximal ascending aortic luminal area.

changes of aortic diameter (mm) and diameter index (mm/m^2) between the initial and follow-up CMR studies, divided by the length of the interval between the 2 CMR examinations, and expressed as mm/year and mm/m^2/year, respectively.

The expected normal age range- and sex-matched AoD were calculated and expressed as upper limit of normal aortic diameter (NL-AoD). In children (≤ 17 years old), the NL-AoD data were derived from these formulas: at annulus = 19.57 x (BSA)$^{0.47}$ (male) and 19.11 x (BSA)$^{0.44}$ (female); at SoV = 26.95 x (BSA)$^{0.49}$ (male) and 26.36 x (BSA)$^{0.44}$ (female); at STJ = 22.29 x (BSA)$^{0.47}$ (male) and 21.76 x (BSA)$^{0.42}$ (female); and at AAo = 22.74 x (BSA)$^{0.46}$ (male) and 22.20 x (BSA)$^{0.46}$ (female), where BSA was derived from the Dubois and Dubois formula [11]. For patients over 17 years of age, the NL-AoD was recorded, using the mean value of the normal aortic dimeter in the 16–29 year-old population reported by Vriz O, et al., as follows: at annulus = 10.8 mm (male) and 11.1 mm (female); at SoV = 15.2 mm (male) and 15.7 mm (female); at STJ = 12.6 mm (male) and 13.3 mm (female); and at AAo = 13.3 mm (male) and 14.5 mm (female) [12]. The difference between patients' AoD and the calculated NL-AoD were also analyzed.

Ascending aortic distensibility was defined by the formula: ([AAo maximum area- AAo minimum area]/ AAo minimum area x pulse pressure in 10^{-3} mmHg^{-1}), where pulse pressure was derived from systolic blood pressure minus diastolic blood pressure [13].

Predictors (baseline AoD, sex and age at repair) which may influence the rate of progression of aortic size at SoV and AAo levels were analyzed. Baseline AoD was divided into 4 grades based on aortic root Z-scores proposed by Gautier et al. [11] as follows: normal (Z-score <2), mild dilatation (Z-score ≥2 to <4), moderate dilatation (Z-score ≥4 to <6), and severe dilatation (Z-score ≥6). Eighteen patients who were older than 18 years were excluded because of the ages were outside the upper limit. A total of 76 out of 94 patients with the mean age of 12.9 ± 3.1 year were included in the analysis.

Age at repair was divided into 3 groups as followed: repair at age ≤3 years, 4−6 years, and >6 years.

3.4. Statistical analysis

Statistical analyses were performed using STATA software version 16.0 (Stata Corp, College Drive, Texas, USA). Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR], 25th, 75th percentile) and categorical variables were summarized as percentages. Wilcoxon signed-rank test was used to assess change in aortic regurgitation from the initial exam to follow-up. Statistically significant changes in AGR of aorta and aortic distensibility based on baseline aortic size at SoV and AAo were analyzed using median regression analysis and linear regression analysis, respectively. A univariate logistic regression model was use to analyze whether sex and age at repair were significantly associated with AGR of the aorta. A p-value of <0.05 was considered as statistically significant. Intra-observer agreement was displayed as mean ± SD and 95 % confidence interval (CI), using a Bland-Altman analysis.

4. Results

4.1. Patients data

Patient clinical characteristics and hemodynamic data for the 94 patients with definitive surgical repair by closure of the ventricular septal defect and transannular patch are summarized in Table 1. The median operative age was 60 months (interquartile range [IQR] 36, 84). Median duration between the initial and the follow-up CMR examinations was 52 months (IQR 24, 71). Most patients at the initial and follow-up CMR studies belonged to the pediatric (74 %) and adult (64 %) age groups, respectively. For the initial CMR study, all patients had trace to mild aortic regurgitation (regurgitation fraction <30 %). In the follow-up CMR, ninety-one patients had trace to mild aortic regurgitation, and three patients had moderate aortic regurgitation (regurgitation fraction 30–49 %). There was no statistically significant difference in aortic distensibility (p = 0.56) and aortic regurgitation (p = 0.78) between the two CMR studies.

4.2. Aortic size and annual growth rate of the aorta

CMR measurement data of the aorta presented as AoD index, AoD,

Table 1
Patients clinical characteristics and hemodynamic data (N = 94).

Characteristics	Values	
Male (N, %)	63 (67.0 %)	
Diagnosis TOF	90 (95.7 %)	
DORV (TOF type)	4 (4.3 %)	
Age at repair (months) *	60 (36, 84)	
Interval from definitive repair to initial CMR (months)	108 (72, 144)	
Time between the two CMR studies (months)	52 (24, 71)	
	Initial CMR	Follow-up CMR
Pediatric ≤17 years	70 (74.5 %)	33 (35.1 %)
Adult >17 years	24 (25.5 %)	61 (64.9 %)
Age at CMR examination (years)	14.5 ± 4.4	18.7 ± 4.9
Male	14.19 ± 3.7	18.36 ± 4.5
Female	15.12 ± 5.5	19.53 ± 5.5
Height (cm)	149.7 ± 17.8	159.6 ± 13.9
Weight (kg)	43.4 ± 17.8	54.6 ± 19.0
BSA (mm^2)	1.33 ± 0.33	1.54 ± 0.30
Male	1.35 ± 0.35	1.58 ± 0.34
Female	1.28 ± 0.33	1.44 ± 0.28
SBP (mmHg)	112.1 ± 12.9	111.6 ± 13.1
DBP (mmHg)	69.3 ± 10.4	70.2 ± 1.8
Pulse pressure (mmHg)	42.8 ± 9.3	41.5 ± 2.3
Maximum aortic area (cm^2)	6.99 ± 2.46	7.92 ± 2.58
Minimum aortic area (cm^2)	5.79 ± 2.10	6.68 ± 2.38
Aortic distensibility (10^{-3} mmHg^{-1})	5.00 ± 1.76	4.87 ± 2.11
Aortic regurgitation (%)	3.2 (2.0, 6.2)	3.4 (2.1, 5.5) **

Continuous variables presented as mean ± SD or median and interquartile range (25th, 75th percentile) as appropriate, and categorical variables presented as N (%).

BSA = body surface area, SBP = systolic blood pressure, DBP = diastolic blood pressure.

* N = 82.

** Statistically significant change in aortic regurgitation derived from Wilcoxon signed-rank test.

and calculated NL-AoD are shown in Table 2. For the initial CMR study, there was a statistically significant difference in AoD at all levels when compared with the NL-AoD ($p < 0.001$). The mean difference in aortic size was predominately at SoV and AAo. Table 3 demonstrates the changes of aortic size during the median follow-up of 52 months (IQR 24, 71). An increase in aortic size was noted in 78 %–85 % of patients depended on different aortic level. Moreover, an increase in aortic size at all four levels was encountered in 64 patients (68.1 %). There was a concomitant significant decline in AoD index during the follow-up period ($p < 0.001$). A growth rate per year of the aorta was analyzed and presented in Table 4. AAo was the region with the greatest AGR, followed by STJ, SoV and annulus, respectively. Nevertheless, there was a decline in AGR index at all levels of the aorta.

Except for at STJ, the aortic growth per year in three patients who had moderate aortic regurgitation was within the range of the study population as follows: at annulus, SoV, STJ, and AAo were 0.21 (-0.03, 1.12), 0.32 (0.22, 2.90), 0.60 (0.05, 4.80), and 0.45 (0.21, 1.17), respectively.

4.3. Predictors for increasing rate of aortic growth

Annual growth rates of the aorta at the level of SoV and AAo based on grading severity of aortic dilatation expressed as aortic root Z-scores are summarized in Table 5. Compared with patients with normal baseline aortic size, there was a tendency toward an increased growth rate at both SoV and AAo as the aorta changed from normal to mild dilatation. However, in patients with a baseline moderate aortic dilatation, there was relatively lower AGR than in the mild aortic dilatation group. There was a tendency for progression in aortic stiffness when the SoV was progressively dilated. Nevertheless, the degree of baseline aortic dilatation was not a significant predictor for annual aortic progression, using median regression analysis. When comparing a group of normal aortic size with the mild dilated and moderate dilated aorta, the *p*-values were as follows; at sinus: $p =$ 0.77 and 0.36, respectively and at AAo: $p =$ 0.27 and 0.69, respectively.

Although male had slightly faster aortic growth per year than female, sex was not a significant factor influencing aortic growth, except at the STJ region ($p =$ 0.04) (Table 6). There was no patient underwent definitive surgical repair at age less than 1 year in our study and only 3 out of 82 patients had definitive repair at 1 year of age. There were no statistically significant difference in AGR of SoV and AAo between the three groups of age at repair (Table 7).

4.4. Intraobserver agreement

We randomly selected 31 patients (every 3rd patient) from the initial CMR study for determination of intra-observer agreement using Bland-Altman analysis. There was no significant differences between the two measurements [mean difference (95 % CI)] with details as followed: at annulus = -0.18 mm (-5.12, 4.77), at SoV = 0.04 mm (-2.15, 2.22], at STJ = 0.06 mm (-2.37, 2.43), and at AAo = 0.14 mm (-2.87, 3.15), AAo-maximum area= -0.96 mm^2 (-64.70, 58.77), AAo-minimum area = -7.08 mm^2 (-64.27, 80.42) (Fig. 3A–F).

Table 3
Changes of aortic size at the four different levels during the median follow-up of 52 months ($N = 94$).

Site	Progression of aortic size		Aortic diameter index changes (mm/m^2)
	N (%)	Diameter (mm)	
Annulus	84 (89.4 %)	1.79 [1.23, 2.34]	−1.41 [-1.94, -0.87] *
SoV	78 (82.9 %)	1.96 [1.39, 2.54]	−2.36 [-3.09, -1.63] *
STJ	85 (90.4 %)	2.11 [1.66, 2.57]	−1.63 [-2.29, -0.96] *
AAo	85 (90.4 %)	2.17 [1.77, 2.57]	−1.84 [-2.46, -1.22] *

Data derived from paired t-Test, and expressed as mean difference (95 % confidence interval).
SoV = sinus of Valsalva, STJ = sinotubular junction, AAo = ascending aorta.
* = $p < 0.001$.

Table 4
Annual growth rate of aorta and aortic index ($N = 94$).

Site	Annual growth rate (mm/year)	Annual growth rate index (mm/m^2/year)
Annulus	0.37 [0.13, 0.72]	−0.32 [-0.72, 0.02]
SoV	0.41 [0.18, 0.97]	−0.40 [-1.05, -0.00]
STJ	0.45 [0.18, 0.93]	−0.26 [-0.88, 0.11]
AAo	0.56 [0.22, 0.91]	−0.29 [-0.75, -0.01]

Data presented as median difference and interquartile range (25th, 75th percentile).
SoV = sinus of Valsalva, STJ = sinotubular junction, AAo = ascending aorta.

5. Discussion

The present retrospective study evaluates the changes of aortic size in 94 patients with rTOF with the median follow-up period of 52 months (IQR 24, 71) and reveals three findings:

1 Most adolescents with rTOF show significant aortic dilatation compared with the calculated normal age range- and sex-matched aortic size. The greatest difference is at the AAo.
2 There is a slow progression of aortic diameter per year with a concomitant regression of the AGR index of the aorta, which could imply that the somatic growth progresses faster than the aortic growth in this study population.
3 Baseline aortic size, sex, and age at repair are not significant predictors of increased rate of aortic progression.

Table 2
CMR data of aortic diameters at the four different levels ($N = 94$).

Site	Initial CMR				Follow-up CMR	
	Aortic diameter index (mm/m^2)	Aortic diameter (mm)			Aortic diameter index (mm/m^2)	Aortic diameter (mm)
	Patient data	Patient data	NL-AoD data	Mean difference (95 % CI)	Patient data	Patient data
Annulus	17.37 ± 3.97	22.32 ± 4.34	18.65 ± 5.00	3.67 (2.27, 5.01) *	15.97 ± 3.20	24.11 ± 4.86
SoV	25.25 ± 5.00	32.50 ± 5.36	25.86 ± 6.83	6.64 (4.79, 8.48) *	22.90 ± 4.11	34.47 ± 5.35
STJ	20.44 ± 4.56	26.23 ± 4.57	21.34 ± 5.50	4.89 (3.38, 6.41) *	18.81 ± 3.47	28.34 ± 4.82
AAo	22.57 ± 4.61	29.07 ± 5.09	21.94 ± 5.37	7.13 (5.60, 8.67) *	20.73 ± 3.87	31.25 ± 5.27

Data presented as mean ± SD.
SoV = sinus of Valsalva, STJ = sinotubular junction, AAo = ascending aorta, NL-AoD = normal limit of aortic diameter.
* = $p < 0.001$.

Table 5
Annual growth rate at sinus of Valsalva and ascending aorta: Categorized into four grades of aortic dilatation based on aortic Z-score ($N = 76$).

Four grading severity of aortic dilatation				
Normal (Z-score <2)	Mild dilatation (Z-score ≥2 to <4)	Moderate dilatation (Z-score ≥4 to <6)	Severe dilatation (Z-score ≥6)	
Sinus of Valsalva				
N (%)	23 (30.3 %)	44 (57.9 %)	9 (11.8 %)	–
Age (years)	12.5 ± 2.8	13.1 ± 3.4	12.8 ± 2.7	–
Diameter (mm)	27.77 ± 4.17	32.42 ± 3.90	37.62 ± 3.91	–
Annual growth rate (mm/year)	0.55 (0.22, 0.97)	0.56 (0.23, 1.37)	0.22 (0.15, 0.97)	–
Aortic regurgitation (%)	2.3 (1.1, 4.3)	3.5 (2.0, 5.6)	5.2 (3.2, 7.4)	–
Aortic distensibility (10^{-3} $mmHg^{-1}$)	5.43 ± 1.67	5.01 ± 1.74	4.92 ± 1.96	–
Ascending aorta				
N (%)	9 (11.8 %)	53 (69.7 %)	13 (17.1 %)	1 (1.3 %)
Age (years)	13.3 ± 3.4	12.7 ± 3.3	13.6 ± 1.8	9
Diameter (mm)	23.02 ± 3.98	27.79 ± 3.98	33.58 ± 3.99	35.69
Annual growth rate (mm/year)	0.42 (0.22, 0.68)	0.69 (0.28, 1.04)	0.54 (0.21, 0.72)	1.18
Aortic regurgitation (%)	2.0 (1.2, 4.5)	3.1 (1.9, 4.9)	4.9 (3.1, 11.5)	5.2
Aortic distensibility (10^{-3} $mmHg^{-1}$)	5.40 ± 1.37	5.02 ± 1.84	5.32 ± 1.65	5.75

Continuous variables presented as mean ± SD or median and interquartile range (25th, 75th percentile) as appropriate, and categorical variables presented as *N* (%).
Annual growth rate presented as median difference and interquartile range (25th, 75th percentile).

Table 6
Sex differences in annual growth rate of aorta.

	Annual growth rate (mm/year)		
Site	Male ($N = 63$)	Female ($N = 31$)	*P* value
Annulus	0.38 [0.11, 0.74]	0.30 [0.13, 0.67]	0.58
SoV	0.47 [0.15, 1.19]	0.35 [0.18, 0.62]	0.50
STJ	0.60 [0.23, 1.05]	0.29 [0.06, 0.52]	0.04
AAo	0.58 [0.29, 1.07]	0.54 [0.09, 0.70]	0.81

Annual growth rate presented as median difference and interquartile range (25th, 75th percentile).
Data (*p* value) derived from median regression analysis.
SoV = sinus of Valsalva, STJ = sinotubular junction, AAo = ascending aorta.

Table 7
Differences in annual growth rate at sinus of Valsalva and ascending aorta: Categorized into three groups based on age at repair ($N = 82$).

Group 1−3: age at repair	*N* (%)	Diameter (mm) Mean ± SD	Annual growth rate (mm/year)	Comparison among groups
Sinus of Valsalva				
1: ≤3 years	24 (29.3 %)	32.67 ± 6.78	1.46 (0.33, 4.05)	
2: 4−6 years	35 (42.7 %)	30.92 ± 4.30	2.33 (0.29, 3.42)	Gr1: 2, $p = 0.53$
3: >6 years	23 (28.1 %)	34.87 ± 5.02	1.44 (0.20, 2.86)	Gr2: 3, $p = 0.28$
Ascending aorta				
1: ≤3 years	24 (29.3 %)	28.62 ± 6.28	1.56 (0.79, 2.70)	
2: 4−6 years	35 (42.7 %)	28.19 ± 4.28	1.98 (0.72, 4.07)	Gr1: 2, $p = 0.73$
3: >6 years	23 (28.1 %)	31.15 ± 4.61	1.98 (0.75, 4.00)	Gr2: 3, $p = 1.00$

Continuous variables presented as mean ± SD or median and interquartile range (25th, 75th percentile) as appropriate, and categorical variables presented as *N* (%).
Annual growth rate presented as median difference and interquartile range (25th, 75th percentile).
Data (*p* value) were derived from median regression analysis.

5.1. Aortic diameter and expansion rate

Our study found that the baseline aortic size in adolescents with rTOF was significant larger than the calculated NL-AoD. The greatest size difference was found at the AAo region. The significant greater in aortic size in our study could be slightly underestimated owing to the difference measurement methods comparing with the studies that we used as references. Both Gautier M, et al. and Vriz O, et al. measured aorta using leading-edge to leading-edge at end-diastole [11,12], while our study used inner-edge to inner-edge at systole at the moment of maximum aortic dimension. The study in adult population (42 ± 15 years, 18–80 years) showed that aorta measurements in leading-edge to leading-edge method resulted in about 2 mm larger than the measurements performed in inner-edge to inner-edge method which owing to the aortic wall thickness. However, average differences between aortic diameters at end-diastole were around 1 mm smaller than at end-systole [14]. The information in this issue and aortic wall thickness in children or adolescent was limited. Therefore, with the difference measurement method, our results should had a total smaller aortic dimension comparing with normal references data, at approximately ≤ 1 mm as children and adolescent had a lesser aortic wall thickness comparing with adults.

There was a higher incidence of aortic expansion and growth rate per year compared with a previous study using CMR as a follow-up tool [7]. With a median follow-up duration period of 52 months (IQR 24, 71), AoD increased in 78–85 % of the population and most commonly occurred at the AAo and STJ levels. The previous study reported that the incidence of aortic growth in adults with rTOF was 25–35 % of the population, and the most common encounter at the AAo which was similar to our study. A slow progressive rate of aortic diameter in adults with rTOF has been reported [7,15]. A mean growth of SoV was reported as 0.29 ± 1 mm/year in one study [15], while another study revealed an aortic growth rate ranged from 0.23 mm/year at SoV to 0.37 mm/year at AAo [7]. Our current study reveals a slightly faster AGR of the aorta, ranging from 0.41 mm/year at SoV and 0.45 mm/year at STJ to 0.56 mm/year at AAo.

The slight differences in results could be explained by the different study populations and the normal physiologic growth of the aorta for each age. Growth of the heart and great arteries after birth is at a predictable rate, reaching 50 % of the adult aorta size at birth, 75 % at 5 years, and 90 % at 12 years [16]. The growth of thoracic aorta in healthy children and young adults (age 2–27 years) has a linear relationship with the BSA [17]. In addition, the aortic root size gradually increases in mid-to-late adulthood by 0.9 mm in men and 0.7 mm in women for each decade of life, assuming a normal BMI and adjusting for blood pressure [18]. Therefore, increasing aortic dimensions are normal physiologic

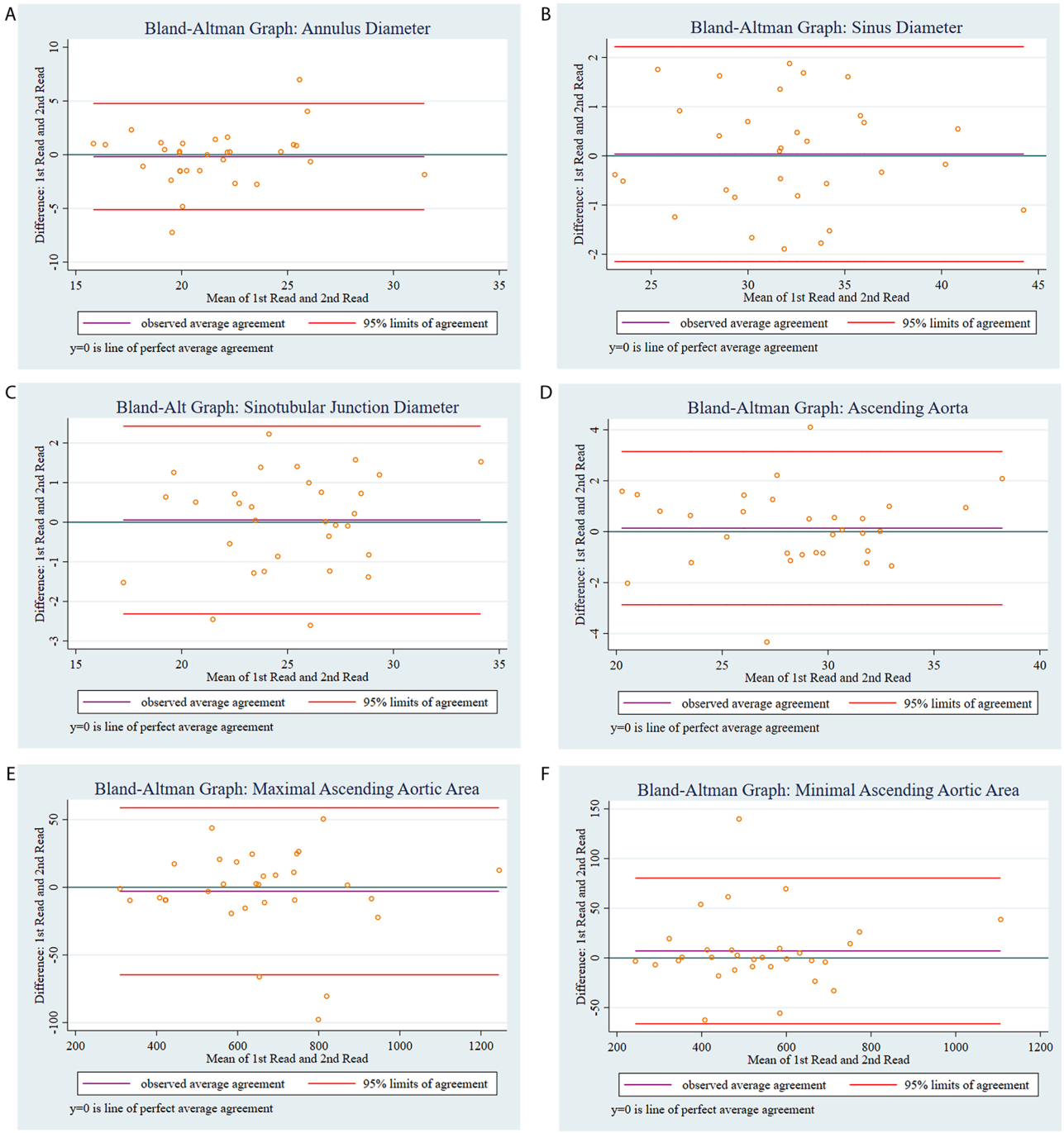

Fig. 3. Bland-Altman plots of the intraobserver agreement in the measurements for annulus diameter (**A**), sinus diameter (**B**), sinotubular junction diameter (**C**), ascending aorta diameter (**D**), maximum ascending aortic area (*E*), and minimum ascending aortic area (**F**). The lower and upper red lines indicate the lower and the upper margins of 95 % limits of agreement, respectively. The central violet line indicates the mean difference between the first and the second reads.

changes from newborn to late adulthood. In addition, the major growth spurt (expressed as BSA) in life occurs maximally at adolescent period [19]. Our study population belonged to early to middle adolescents (mean age 14.5 ± 4.4 years) while the population from the previous study was in early adulthood (median age 30.9 years), hence, the faster aortic growth per year in this study may reflect age-related increase aortic size.

Our data suggest that aortic dilatation and aortic growth are common in patients with rTOF, however, the growth rate may be dynamic over different stages of development. Comparisons of aortic growth should take this into consideration. This study increases our knowledge of aortic growth in the adolescent population.

5.2. *Aortic expansion and somatic growth*

Although, few studies have been conducted on the aortic growth indexed to BSA, Grotenhuis HB, et al. reported that aortic root dimension remained stable in the majority of children population. The mean marginal increase of AAo was 0.04 Z-score unit per year during the median follow-up period of 3.7 years (IQR 0.5, 6.9). Our study found that despite an increment in aortic diameter (ranging from 0.3 to 0.5 mm/year), there was a small negative growth rate index of the aorta (ranging from -0.3 to -0.4 mm/m^2/year) in the adolescents with rTOF. This is probably explained by the rate of body growth in the adolescents being faster than in children. In addition, the growth spurt in the

adolescent age group progresses faster than the rate of aortic growth. Our study also found that there was no statistically significant increase in aortic regurgitation during the median follow-up of 52 months (IQR 24, 71). Aortic regurgitation in the initial and follow-up CMR was 3.2 % (IQR 2.0–6.2 %) and 3.4 % (IQR 2.1–5.5 %). Therefore, aortic growth in adolescent population may be a part of physiologic growth and does not produce a significant change in aortic regurgitation. In addition, a few cases who had moderate aortic regurgitation in our study showed no difference in aortic growth compared with patients with mild aortic regurgitation.

5.3. Predictors for increasing rate of aortic growth

Baseline aortic size was not a significant predictor for an increased rate of aortic expansion, even though there was a propensity for increasing rate of aortic growth per year and aortic stiffness with the baseline aortic size up to mild dilatation. Conversely, a decreasing rate of aortic growth was observed when the baseline aorta had moderate dilatation. However, the results in the moderate dilatation could be affected by the relatively small numbers of patients. Such findings could be explained by the histologic changes of aorta in rTOF. The decrease aortic distensibility is an important factor in progressive aortic dilatation rather than the enlarged aorta itself, therefore, baseline AoD does not always lead to subsequent progressive dilatation [2,20]. In addition, a progressive rate of aortic dilatation could be a multifactorial cause.

Sex was not correlated with the rate of aortic growth, except at STJ region where sex was a marginally significant factor. While age at repair was not a significant predictor for aortic expansion rate in patients who had definite repair after 1 year of age.

5.4. Study limitations

There are several limitations in this study. First, this was a single-center, retrospective study and the data may have been influenced by selection bias, with only survivors referred to our tertiary imaging center. Second, although we used the same imaging plane to measurement aortic size in both initial and follow-up CMR studies, the measurement of aortic root from a single sagittal oblique LVOT view may cause an inadequate view of all aortic root regions in some cases. Third, since the data of ascending aortic dimension was derived from phase contrast studies where the prescribed image may not be acquired at the exact location in all patients and as in the follow-up CMR, this may degrade the accuracy in estimation of ascending aortic growth rate and aortic regurgitation grade. Fourth, the reference age and sex-matched aortic size was estimated instead of compared directly in a population-based case-control study. Another limitation is that our data was derived from CMR while the normal reference aortic data is derived from echocardiography. Difference imaging modalities may influence the aortic dimension. In addition, different methods of measurement in our study (inner-edge to inner-edge at systole) and the reference normal limit aortic size (leading-edge to leading-edge in end-diastole) underestimates aortic size up to 1 mm. Finally, the follow-up duration between the 2 CMR examinations was not of uniform duration and limited to a median duration of 52 months. This may have influenced the estimate of the aortic growth rate per year.

6. Conclusions

Our results demonstrates that most adolescents with repaired TOF have significant aortic dilatation, and that a slow increment in aortic size is commonly encountered. Nevertheless, we observe that a regression of aortic growth indexed to body growth suggests that aortic growth among adolescents may be a part of normal physiologic growth, and does not necessarily produce an adverse effect on aortic regurgitation. The severity of initial aortic size, sex, and age-at-repair are not significant predictors of the rate of aortic growth. Data from this study bridge the gap between previously conducted studies in children and adults. Despite the new observation of regression of aortic growth index in the adolescent age group, long term follow-up aortic dilatation among patients with rTOF is still required due to aortic dilatation and aortic growth are of multifactorial effects.

CRediT authorship contribution statement

Suvipaporn Siripornpitak: Conceptualization. **Suvipaporn Siripornpitak:** Methodology. **Suvipaporn Siripornpitak, Apichaya Sriprachyakul, Saruntorn Wongmetta:** Data collection. **Suvipaporn Siripornpitak:** Formal analysis and investigation. Suvipaporn Siripornpitak: Writing- original draft preparation. **Suvipaporn Siripornpitak, Apichaya Sriprachyakul, Saruntorn Wongmetta, Piya Samankatiwat, Pirapat Mokarapong, Suthep Wanitkun:** Writing-review and editing, **Suvipaporn Siripornpitak:** Supervision.

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Ethical statement

The study was approved by the institutional Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

All procedures performed in this studies were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Declaration of Competing Interest

The authors report no declarations of interest.

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