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Article

Aortic Root Dilatation Measured by Cardiac Magnetic Resonance in Patients with Repaired Tetralogy of Fallot

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Abstract

Background: Aortic root dilatation (AoD) frequently occurs following repaired tetralogy of Fallot (rTOF). The objective of this study was to assess aortic dimensions, investigate the prevalence of AoD, and identify predictors of AoD in rTOF patients. **Methods**: A cross-sectional retrospective study was conducted in repaired TOF patients from 2009 to 2020. Aortic root diameters were measured by cardiac magnetic resonance (CMR). Severe AoD of the aortic sinus (AoS) was defined as a Z-score (z) of >4, reflecting a mean percentile ≥99.99%. **Results**: Two hundred forty-eight patients, with a median age of 28.2 years (10.2–65.3 years), were included in the study. The median age at the time of repair was 6.6 years (0.8–40.5 years) and the median interval between the repair and CMR study was 18.9 years (2.0–54.8 years). The prevalence of severe AoD was found to be 35.2% when defined by an AoS z greater than 4 and 27.6% when defined by a AoS diameter ≥40 mm, respectively. A total of 101 patients (40.7%) had aortic regurgitation (AR), with 7 patients (2.8%) having moderate AR. Multivariate analysis revealed that severe AoD was only associated with the left ventricular end diastolic volume index (LVEDVi) and a longer duration after repair. The age at the time of repair for TOF was found not to be correlated with the development of AoD. **Conclusions**: After repair of TOF, severe AoD was found to be prevalent, but no fatal complications were observed in our study. Mild AR was also commonly observed. Larger LVEDVi and a longer duration after repair were identified as factors associated with the development of severe AoD. Therefore, routine monitoring of AoD is recommended.

Keywords

aortic dilatation; tetralogy of Fallot; cardiac magnetic resonance

Introduction

Tetralogy of Fallot (TOF) is a prevalent cyanotic congenital heart disease that demonstrates remarkable surgical outcomes and allows for survival into adulthood. Numerous studies have extensively examined pulmonary regurgitation and the impact of tetralogy of Fallot (TOF) repair on the right ventricle [1,2]. However, our understanding of the aortic root and its associated complications remains limited. Recent studies have primarily focused on the progressive dilatation of the aorta following TOF repair [3–5]. Despite favorable clinical outcomes, a significant proportion of patients experience continuous aortic dilatation, leading to aortic regurgitation (AR) that may require aortic valve replacement. The precise mechanisms underlying aortic dilatation remain unclear, but it is believed that both hemodynamic factors and intrinsic wall abnormalities contribute to its development [4,6,7].

The reported risk factors for the development of aortic dilatation (AoD) in patients with TOF include right-sided aortic arch, male gender, previous pregnancy, history of an aortopulmonary shunt, older age at the time of TOF repair, and genetic factors such as 22q11 deletion and FBN1 mutations [4,6–10].

European studies have provided insights into the severity and progression of AoD and AR in both pediatric and adult patients following repair of TOF [8,9]. Grotenhuis *et al.* [10] observed that AoD can occur both prior to and after TOF repair during childhood, with most patients demonstrating stability and a low incidence of aortic root-related complications. Studies involving adults have reported varying prevalence rates of aortic dilatation and identified different factors associated with aortic complications, depending on the imaging modality used (echocardiography, cardiac magnetic resonance imaging) and the specific sizing criteria [8,11].

Although echocardiography is readily available for monitoring aortic root dimensions, it may present limitations in evaluating the aortic root. Cardiac magnetic resonance imaging (CMR), on the other hand, offers precise

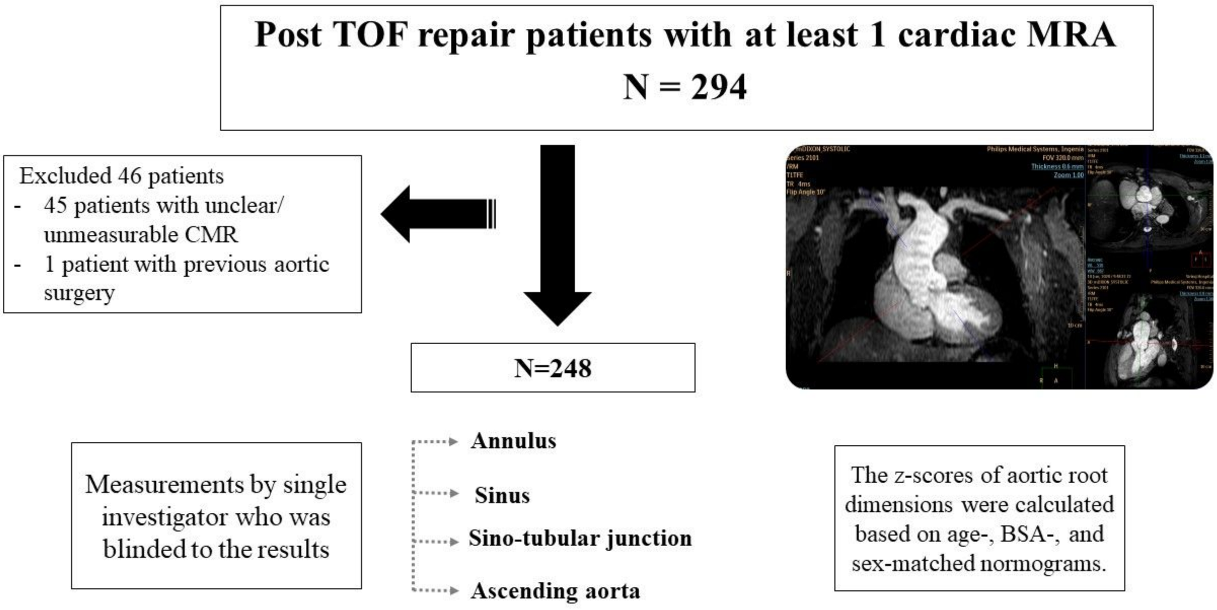

Fig. 1. Summary of study methodology. Abbreviations: TOF, tetralogy of Fallot; MRA, magnetic resonance angiography; CMR, Cardiac magnetic resonance; BSA, body-surface area.

measurements of aortic dimensions and is commonly utilized for follow-up assessments in repaired tetralogy of Fallot (rTOF) patients.

We aimed to assess aortic dimensions and investigate the prevalence and predictors of AoD among Asian adolescents and adults who underwent late TOF repair. Additionally, we aimed to identify aortic-related complications associated with AoD after late TOF repair, including AR.

Methods

A retrospective, cross-sectional study was performed at Siriraj Hospital, Mahidol University, Thailand. The study included repaired TOF patients who underwent cardiac CMR at Siriraj Hospital between 2009 and 2020. We excluded one patient who underwent aortic root repair prior to the CMR study, along with 45 patients who had unclear or immeasurable CMR results (Fig. 1). Electronic medical records were reviewed and baseline characteristics, including biographical information and medical history were obtained. Surgical details, age at TOF repair, previous palliative shunts such as modified Blalock-Taussig shunts (MBTs), and systemic aorto-pulmonary shunt, aortic arch sidedness, duration between repair and CMR study, and CMR parameters were recorded for comparative analysis. The study was approved by the Siriraj Institutional Review Board (SIRB) (no. 363/2563(IRB1)).

Due to the extended waiting list, CMR scans were scheduled for patients when they reached adolescence and did not require anesthesia. The selection criteria for patients undergoing CMR included not only those with clinical symptoms of heart failure, significant pulmonary regurgitation, and right ventricular (RV) dilatation, and echocardiographic evidence of wide QRS duration (>180 msec), but also asymptomatic patients.

Indexed diameter to body surface area (mm/m^2) and Z-scores have been used to account for variations in body size [12]. The use of Z-scores allows for differentiation between physiological and pathological dilation in growing adolescents [13]. While generic cutoff aortic dimensions based on adult heights have commonly been employed due to height stability over time [14], several studies in adults have highlighted age-related changes, gender effects, body size factors (height, weight, body surface area), and blood pressure on the aortic diameters [15–19], which may be significant confounding factors when interpreting aortic root values. The use of Z-scores enables a more systemic comparison of measurements rather than relying solely on generic cutoff values [13,20]. In fact, the Z-score has demonstrated its utility in guiding decision-making regarding treatment of the ascending aorta treatment in bicuspid aortic valve surgery in adults [21]. Therefore, in our population, we utilized Z-scores to compare aortic dimensions across a wide range of ages, body sizes, and genders.

Aortic Root Dilatation and Severity

CMR studies were conducted using standardized protocols on 1.5-T and 3-T whole-body scanners (Ingenia and Intera Achieva; Philips, Best, the Netherlands). Cine short-axis, long-axis, and 4-chamber images were acquired during end-expiratory breath holds to facilitate ventricular and functional analyses. Consistent with the 2010 ACC/AHA guidelines for CMR imaging of the thoracic aorta [22], aortic diameters were measured at specific locations, including the annulus, sinus, sinotubular junction, and ascending aorta at the level of the right pulmonary artery. Each aortic segment was measured at standard anatomic landmarks perpendicular to the axis of blood flow using 3D multiplanar reconstruction CMR images, either from static magnetic resonance angiography (MRA) or respiratory navigated and electrocardiogram (ECG) gated modified Dixon MRA in systole. All measurements were performed by a single reader (PWC) who was blinded to clinical outcomes.

Z-scores for aortic root dimensions were calculated using age, body-surface area (BSA), and sex-matched normograms. For patients under 20, normograms from a MRA study of normal children and adolescents by Kaiser *et al.* [23] were used. For patients aged 20 and above, Z-scores were based on measurements from MRA studies of adults without cardiovascular risk factors as published by Davis *et al.* [15] A Z-score of >4 corresponds to a mean percentile ≥99.99% [24]. According to a recent scientific statement from the American Heart Association and American College of Cardiology, AoD is defined as mild, moderate, and severe based on aortic sinus Z-score values (AoSz) falling between 2 to 3, 3.01 to 4.0, and >4.0, respectively [25]. Therefore, we defined severe AoD as AoSz >4. The CMR results were used to determine the volume and severity of aortic regurgitation (AR).

Statistical Analysis

Categorical data were expressed as numbers and percentages, while continuous data were presented as median and interquartile range (25th, 75th percentile) or mean ± SD as appropriate. The Chi-square test or Fisher's exact test was used to compare categorical data. Independent sample *t*-tests were used to compare continuous data. Pearson or Spearman rank correlation analysis were conducted to examine the relationship between continuous variables. Factors associated with the aortic sinus Z-score were determined using multiple linear regression analysis. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Software (version 20, IBM Corp., Chicago, IL, USA).

Results

The study included 248 patients who had undergone TOF repair and had a cardiac CMR and MRA. The study population consisted of adolescents and adults with a median age of 28.2 years (range: 10.2–65.3 years), the median age at the time of repair was 6.6 years (range: 0.8–40.5 years) and the median duration between total repair and CMR study was 18.9 years (range: 2.0–54.8 years). Baseline characteristics for each age group are summarized in Table 1.

Prevalence of Aortic Root Dilatation (AoD) and Aortic Regurgitation (AR)

The mean absolute aortic sinus (AoS) diameter was 37.2 ± 5.2 mm and the mean AoSz was 3.2 ± 1.8 (Table 1). The corresponding Z-scores for the sinus, sinotubular junction, and ascending aorta were calculated and are presented in Table 1. Overall, the prevalence of severe aortic root dilatation (Z-score >4) was 35.2%. The prevalence of sinus diameter of ≥50 mm and ≥40 mm was 2.8% and 27.6%, respectively.

Among the patients, 101 patients (40.7%) had AR (Table 1). The majority of patients had mild AR, while only seven patients (2.8%) had moderate AR. Univariate analyses showed that the presence of AR was associated with larger Z-scores at the sinus (p = 0.04). Patients with moderate AR had a significantly larger left ventricular end-diastolic volume index (LVEDVi) ($p < 0.001$), but there was no significant difference in LVEDVi between patients with no AR and mild AR (p = 0.15) (Fig. 2). Two patients required aortic root surgery due to aortic complications. One patient, who underwent total repair at age 15.7 years, had an aortic sinus diameter of 36.5 mm (Z-score 4.0) with moderate AR. The other patient, who underwent total repair at age of 31.3 years, had an AoS diameter of 55.3 mm (Z-score 7.7) and moderate AR.

Factors Associated with Severe AoD (Z-score ≥4)

The factors associated with severe AoD (Z-score of aortic sinus >4) were analyzed using univariate and multivariate analyses. Age at CMR, duration after total repair, history of previous palliative shunt, LVEDVi and right ventricular end-diastolic volume index (RVEDVi) showed associations in the univariate analyses (Table 2). The multivariate analyses revealed that a longer duration after repair and larger LVEDVi were associated with severe AoD (Table 2).

Table 1. Baseline characteristics, aortic root diameters and Z-scores.

Baseline characteristics	All
	N = 248
Age at CMR, y	30.8 ± 13.3
Gender: male, n (%)	125 (50.4%)
Height, cm	160.1 ± 10.4
Weight, kg	56.8 ± 15.2
BSA, m^2	1.6 ± 0.2
Age at repair, y	8.9 ± 7.4
Time since repair, y	22.0 ± 11.0
Age at MBTs, y	3.8 ± 4.6
Systemic shunt, n (%)	53 (21.4%)
- RMBTs, n (%)	36 (14.5%)
Interval of shunt to repair, y	5.8 ± 5.7
Right aortic arch, n (%)	53 (21.4%)
Hypertension, n (%)	16 (6.4%)
Aortic root	
Annulus	
- diameter (mm)	29.4 ± 4.1
Sinus	
- diameter (mm)	37.2 ± 5.2
- Z-score	3.2 ± 1.8
Sinotubular junction	
- diameter (mm)	32.8 ± 4.8
- Z-score	4.2 ± 1.9
Ascending aorta	
- diameter (mm)	34.9 ± 5.6
- Z-score	3.6 ± 2.0
CMR parameters	
- LVEDVi (mL/m^2)	80.2 ± 19.6
- LVESVi (mL/m^2)	33.7 ± 17.1
- LVEF (%)	59.8 ± 8.9
- RVEDVi (mL/m^2)	161.2 ± 53.2
- RVESVi (mL/m^2)	86.9 ± 41.3
- RVEF (%)	47.9 ± 8.9
Presence of AR	
- mild	94 (37.9 %)
- moderate	7 (2.8 %)

Abbreviations: y, year; RMBTs, right modified Blalock-Taussig shunt; CMR, cardiac magnetic resonance; BSA, body surface area; MBTs, modified Blalock-Taussig shunt; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; RVEDVi, right ventricular end-diastolic volume index; RVESVi, right ventricular end- systolic volume index; RVEF, right ventricular ejection fraction; AR, aortic regurgitation.

Discussion

Presently, no specific recommendations define the severity of dilated aortic root in repaired TOF patients.

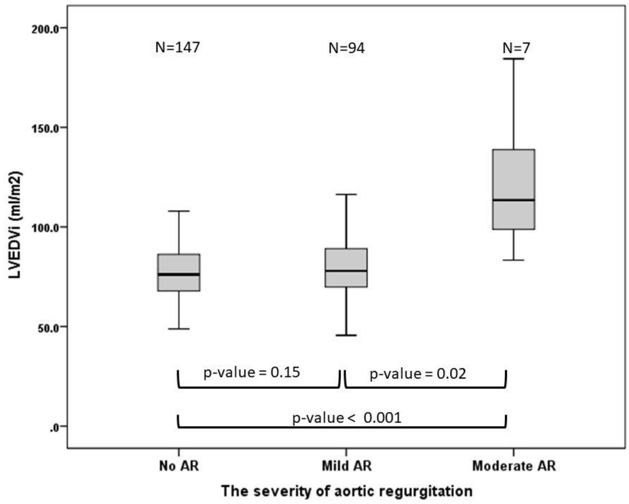

Fig. 2. Comparison of left ventricular end diastolic volume index and severity of aortic regurgitation.

Studies have examined the average normal size of aortic root in postoperative TOF patients, both in children and adults [26,27]. Various parameters, including absolute diameter, aortic size indexed body surface area, and Z-score have been used to define AoD. The indications for surgical repair for AoD differ among different diseases. Absolute aortic sinus diameter and Z-score have commonly been used in adult and pediatric patients with Marfan syndrome [28–30], while, the Z-score has been primarily used in children and adolescents [31]. Adjusting the aortic size for age, gender, and body size effect is important in the adult population [15,19]. In patients with bicuspid aortic valve, Z-score-based decision thresholds have been used for ascending aorta intervention, particularly in younger patients, compared to simple aortic size guidelines [21]. Echocardiography has also been used in several studies to measure the aorta in repaired TOF patients [5,10,11]. The prevalence of aortic dilatation varies widely (15% to 87%), depending on the chosen cut-off values and imaging modality [5,11,27,32]. In a large multicenter cross-sectional study, aortic root diameter of ≥40 mm was observed in 28.9% of adults with repaired TOF [5], which aligns with our findings using the absolute diameter definition of AoD and is also consistent with previous studies [5]. The optimal definition and severity of AoD, as well as the cut-off aortic diameter for early intervention in repaired TOF patients, have not been established. The International Registry of Acute Aortic Dissection showed that 60% of cases with an aortic diameter <55 mm and 40% with an aortic diameter <50 mm presented with acute ascending aorta dissection [33]. All case reports of repaired TOF and aortic dissection reported an aortic root size equal to or greater than 55 mm [34]. Given this prevalence, a small percentage of post-repaired TOF patients in our study were at risk of aortic dissection, highlighting the importance of routine monitoring for the progression of AoD.

Table 2. Risk factors associated with severe aortic root dilatation.

Risk Factors of severe AoD (aortic sinus Z-score >4)	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Age at CMR, y	0.96	0.94–0.96	0.001			
Gender: female	1.01	0.60–1.70	0.96			
Age at repair, y	0.97	0.94–1.01	0.14	0.96	0.91–1.00	0.06
Time since repair, y	1.08	1.00–1.19	0.09	0.96	0.93–0.99	0.01
Age at palliative shunt, y	0.91	0.78–1.07	0.25			
Previous palliative shunt	1.96	1.05–3.66	0.04	0.99	0.34–2.94	0.99
Interval of shunt to repair, y	1.08	0.99–1.19	0.09	1.08	0.94–1.25	0.29
Right aortic arch	0.94	0.90–1.77	0.84			
CMR parameters						
- LVEDVi	1.02	1.01–1.04	0.006	1.03	1.00–1.04	0.005
- RVEDVi	1.01	1.00–1.01	0.07	1.00	1.00–1.01	0.15
Presence of AR	1.15	0.68–1.95	0.60			

Abbreviations: CI, confidence interval; OR, odds ratio; CMR, cardiac magnetic resonance; Y, year; AoD, aortic root dilatation; LVEDVi, left ventricular end-diastolic volume index; RVEDVi, right ventricular end-diastolic volume index; AR, aortic regurgitation.

We observed a high prevalence of AR (40.7%), which is higher compared to previous studies [5,11,32]. However, only 2.8% of our patients had moderate AR, consistent with a previous study [5]. Among our patients, only two individuals with moderate AR required aortic valve replacement or aortic rood repair due to aortic root aneurysm. No cases of aortic dissection or rupture were reported. Interestingly, we found that LVEDVi was associated with the presence and severity of AoD. Although AR can contribute to a larger LVEDVi, our study did not find a correlation between mild AR and larger LVEDVi, similar to previous publications [8]. Since most of our patients had only mild AR, the association between a larger LVEDVi and presence of AoD cannot be solely explained by the presence of AR. A previous study reported abnormal histological findings in the aortic root of TOF patients as early as infancy, occurring prior to the development of AR [35]. Abnormal flow dynamics and altered wall properties may be present in TOF patients, even if they underwent early repair and have a normal aortic size [36]. This suggests that intrinsic abnormalities in the aortic root of TOF patients may contribute to subsequent AoD, independent of AR. To further understand the hemodynamic changes in AoD, a 4D CMR study was used to demonstrate abnormal flow patterns and energy loss associated with aortic dilatation [37]. Schäfer *et al.* [38] also demonstrated abnormal aortic flow associated with higher viscous energy loss in post-repair TOF patients, which was associated with lower left ventricular ejection fraction (LVEF) and larger LVEDVi. We did not find an association between LVEF and AoD, suggesting that LVEF may be less sensitive to early or minor changes. Two studies have reported that aortic root Z-scores in children and young adolescents with repaired TOF are larger than controls [26,39]. Sim *et al.* [32] and Benbrik *et al.* [40] also reported that repair after the first two years of life may lead in AoD. These findings support the hypothesis that prolonged increased aortic flow before total repair leads to AoD. To support this hypothesis, Niwa *et al.* [11] showed that progressive dilation of the aortic root in adults with a longer shunt-to-repair interval. However, we did not find a correlation between age at TOF repair, previous palliative shunt, and shunt-to-repair interval with severe AoD. It is important to note that the majority of our patients underwent repair during late childhood or adolescence. This suggests that high aortic flow alone may not be the sole factor influencing AoD. Interestingly, we found that a longer duration after repair was also associated with severe AoD in our study, indicating ongoing progression of aortic root dilatation even after repair. Unfortunately, we were unable to confirm this hypothesis due to the lack of follow-up CMR data in our patients. Based on our hypothesis, AoD may be influenced by intrinsic factors of the aorta in TOF patients, and the presence of AoD leads to flow dynamic changes associated with enlarged LV.

Limitations

This study had certain limitations and potential biases due to its retrospective, cross-sectional design. Although the study included a relatively large sample size, it did not include all post-repair TOF patients. For example, not all repaired TOF patients underwent CMR imaging, and patients who had undergone aortic root repair before CMR were not included, potentially introducing selection bias and limiting the generalizability of our findings. Additionally, the study lacked long-term outcome data for repaired TOF patients with AoD. However, one strength of this study is that it utilized CMR, which is considered the most accurate measurement method for assessing aortic root dimensions. Another strength is the inclusion of postoperative

TOF patients spanning a wide range of ages at the time of operation and durations after repair, which contributed to a more comprehensive understanding of the associated factors.

Conclusions

Severe AoD was found to be prevalent among post-repair TOF patients, but no fatal aorta-related complications were observed in our study. While the presence of AR was common, only two patients with moderate AR required aortic root surgery. We observed a correlation between LVEDVi and longer duration after repair was correlated with severe AoSz. Therefore, it is important to monitor the progression of AoD regularly.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors designed and gave the main idea of research study as well as performed the research. PaC, CK and SN collected the data. PaC, CK and CV analyzed the data. All authors contributed to interpret the data and editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take responsibility for appropriate portions of the content.

Ethics Approval and Consent to Participate

The study was approved by the Siriraj Institutional Review Board (SIRB) (no. 363/2563(IRB1)).

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Conflict of Interest

The authors declare no conflict of interest.

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