Ten Years Follow-up of Dilatation of Aortic Structures in Fallot type Anomalies

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Research Article

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Abstract

Objectives

Dilatation of the aortic root structures or ascending aorta is often observed in patients with Fallot type anomalies. We tried to find how fast the aortic structures dilate and how to manage this phenomenon.

Methods

Among 801 patients who underwent corrective surgery of Fallot type anomalies, [tetralogy of Fallot (TOF) and Fallot type of double outlet right ventricle (DORV)] from 2004 to 2020, 66 patients who had follow-up cardiac computed tomography angiography (CT) images at least over 5-year interval after the initial CT study were enrolled in this retrospective study. We analyzed the diameters and aortic cross-sectional area/height ratio (AH) of aortic annulus, sinus of Valsalva, sinotubular junction and ascending aorta between initial and follow-up CTs. "Dilatation" was defined as a z-score over 2 in each aortic structure.

Results

The median age at initial and follow-up CTs were 5.9 years (Interquartile range (IQR): 0.4~12.4) and 15.9 years (IQR: 9.3~23.4), respectively. The median CT interval (initial ~ latest CT) was 9.5 years (IQR: 6.6~12.0). Sinus of Valsalva was the aortic structure that dilated the most rapidly (0.94 mm/year) and significantly (32.8 mm at follow-up CT) across the study period. The AH ratio increased significantly in the four aortic structures. Patient's age was significantly associated with higher AH in follow-up CT. Aortic dilatation was found in 74.2% at initial CT and 86.4% at follow-up CT.

Conclusions

In Fallot type anomalies, the AH ratio of aortic root structures significantly increased over about 9.5 years. The number of the patients diagnosed within the range of aortic dilatation also increased. Shorter interval for regular follow-up should be considered for these young patients because it could reach a significant dilatation in their mid-20s according to our observation in this study.

Introduction

Tetralogy of Fallot (TOF) is the congenital heart disease which show four main features including pulmonary stenosis, right ventricular hypertrophy, overriding aorta and ventricular septal defect. As the survival of the patients with congenital heart diseases has improved significantly in recent decades, time-related concerns that were not familiar to us in the past become common things to be considered seriously in adult patients with congenital heart disease in these days[1]. One of the concerns is dilatation of the aortic structures, which could cause aortic dissection, rupture, or aortic valve regurgitation[2]. Although aortic structure problems in patients with TOF was mentioned in previous studies[3–5], evidence of progression of aortopathy was unclear, and no specific guidelines for managing pathological changes in the aortic structures in patients with TOF were provided[6, 7]. In this study, we tried to confirm
whether dilatation of the aortic structures does indeed occur in each patient over time using computed tomographic (CT) findings from the patients with TOF and Fallot type of double outlet right ventricle (DORV) using z-score and aortic cross-sectional area/height (AH) ratio. We also tried to find any adequate timing of follow-up intervals in these patients.

Patients And Methods

Ethical statement

This study was approved by our Institutional Review Board (Approval number: 2005-177-1126) in view of the retrospective nature of the study and was conducted in compliance with the Declaration of Helsinki.

Patient characteristics

We reviewed all patients who underwent all kind of surgery for TOF and Fallot type DORV in our center from 2004 to 2020. Among them, we included the patients who follow-up CT images more than five years after the initial CT scans until August 2020. We excluded the patients with other type DORV except Fallot type and the patients who underwent univentricular repair.

Patients’ demographic data, peri-operative clinical information, echocardiographic data, and CT data were collected. The initial and follow-up CT was defined as the first-taken CT and the latest CT in the study duration. The CT interval was defined as duration between the initial CT and the latest CT. Antihypertensive drugs included all types of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers.

Measurement of the aortic structures

The aortic structures were measured by prospective electrocardiogram-gated axial mode CT and reconstructed with three-dimensional rendering. The diameters were measured at four levels: (1) aortic annulus (AA), (2) sinus of Valsalva (SoV), (3) sinotubular junction (STJ), and (4) ascending aorta (AAo). AA was measured as the inter-commissural distance in the aortic valve, SoV was measured at the level of maximal diameter on the axial image, STJ was measured at the level of transitional zone from STJ to AAo, and AAo was measured at the level of the main pulmonary artery bifurcation (Figure 1). Aortic cross-sectional area was calculated by \( \pi \times \left( \text{diameter}/2 \right)^2 \). The AH ratio was calculated as aortic cross-section area divided height.

The largest diameters of each aortic structure as measured based on the chest CT were re-calculated as z-scores according to Colan’s study for aortic root and Gautier’s study for ascending aorta\cite{8, 9}. In our study, “significant dilatation of the aortic structures” was defined as 95% confidential interval (z-score≥2) in diameter of each aortic structures\cite{10}. Echocardiography was performed to check other cardiac deformities, including AR, however, the diameters of echocardiography were not included in the analysis.

Statistical analysis


Categorical variables are presented as numbers with percentages. All continuous variables are presented as median values and interquartile ranges (IQR). The Student’s t-test was used for comparisons of continuous variables. The paired t-test was used for the comparison of the diameters between initial CT and follow-up CT. The normality of all variables was tested by Kolmogorov-Smirnov test. The associations of AH ratio were tested using Pearson's correlation coefficients. Risk factors for aortic dilatation were evaluated using the logistic regression analysis. Demographic, operative and follow-up data were tested. Parameters showing P-value < 0.2 in univariable analyses were included in the multivariable analysis. P-values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, New York, USA).

Results

Patients' characteristics and overall postoperative results during follow-up

Data from 801 patients [TOF (N = 612) and DORV (N = 189)] were reviewed. We excluded the patients who had less than 5-year-interval CT and other types of DORV except Fallot type of DORV in this cohort. Finally, sixty-six patients [TOF(N = 60), Fallot type DORV(N = 6)] were identified in this study. Seventeen (25.7%) patients were female. Median clinical follow-up duration was 18.44 years (IQR: 11.74~26.78). Six (9.1%) patients were diagnosed with the 22q11.2 deletion syndrome. No connective tissue disorders causing aortopathy, such as Marfan syndrome or Loeys-Dietz syndrome were reported. Anatomical and operative data are presented at Table 1. During the follow-up, 1 (1.5%) case of post-operative mortality after discharge were noted. Mortality was post-discharge death after percutaneous pulmonary valve insertion. No death was associated with dilated aortic structures. Endocarditis and mediastinitis occurred in three (4.5%; right ventricle-pulmonary artery conduit in one cases and right ventricle outflow tract in two cases) and one (1.5%) patient, respectively. Antihypertensive drugs were prescribed to 19.6% of patients.

Changes in the aortic structures on CT images

Median interval of CT was 9.47 years (IQR: 6.59~11.99). Median duration between 1st repair and first CT was 4.69 (IQR: 0.00~10.74). Median age, height and body surface area (BSA) of initial CT and follow-up CT were presented at Table 2. Patients’ somatic growth was obtained well.

Table 3 shows that the median diameters and AH ratio of all structures increased as observed in the follow-up period with statistical significance (Figure 2) while the z-score of only two structures (SoV and STJ) increased significantly (Figure 3).

Median increasing rates of aortic structures were 0.62 mm/year for AA, 0.94 mm/year for SoV, 0.85 mm/year for STJ, and 0.66 mm/year for AAo. The aging during follow-up period was correlated with AH ratio on the Pearson’s correlation coefficient test in all aortic structures that we measured (Figure 4).

Significantly dilated aortic structure (> 2 of z-score) in initial CT was found in 39 (59.1%) in AA, 36 (54.5%) in SoV, 19 (28.8%) in STJ and 25 (37.9%) in AAo, respectively. Significantly dilated aortic structure
in follow-up CT was found in 42 (63.6%) in AA, 43 (65.2%) in SoV, 37 (56.1%) in STJ and 34 (51.5%) in AAo, respectively. To sum up, the number of the patients who diagnosed with aortic dilatation (> 2 of z-score in any structure) was 49 (74.2%) and 57 (86.4%) in initial and follow-up CT, respectively. We were not able to reveal any risk factors associated with dilatation of any aortic structures in multivariable analysis although residual stenosis of branch pulmonary arteries during follow-up was nearly significant ($p=0.056$).

**Clinical outcomes**

AR of moderate and severe degrees was confirmed in one (1.5%) patient. The patient had quadricuspid aortic valve, then, we repaired aortic valve cuspid with pulmonary valve replacement due to pulmonary valve insufficiency simultaneously.

**Discussion**

The reasons why aortic structures dilate in the patients with TOF has been suggested in several studies. Niwa et al. suggested that an increase in the flow of aorta from the right to left shunt in pre-corrected TOF status could initially cause aortic dilatation\[4\]. However, their suggestion could not clearly explain the reason why aortic structures continue to dilate even after corrective surgery. Mitsuru et al. proposed multifactorial reasons for aortic dilatation, including aortic stiffness (which includes elastic fiber disruption and matrix expansion) but also aortic volume overload before corrective surgery, chromosomal abnormalities, and even activation of the transforming growth factor-$\beta$ signaling pathway\[11\].

In our study, aortic dilatation was confirmed in 74.2% (49 patients) at initial CT (median 5.95 years old, 4.69 years after initial corrective surgery) according to the z-score >2. Although there was no risk factor associated with the dilatation of aortic structures in our study, the residual pulmonary artery stenosis after corrective surgery was nearly significant with aortic dilatation ($p=0.056$). Sim, et al. suggested old age at total correction, male sex and pulmonary atresia were risk factors for late aortic root dilatation in TOF\[12\]. It seemed that aortic dilatation was developed due to increased blood flow as pulmonary atresia in TOF encouraged right to left shunt. Because right to left shunting lesions were almost completely corrected at the initial operation and there were no sources inducing the aortic blood flow during follow-up after corrective surgery in our cohort, we could not explain our results of marginal relationship between residual branch pulmonary stenosis and dilatation of the aortic structures with above hypothesis. However, we could assume that compression of the pulmonary arteries, which normally run just posterior to the ascending aorta, may result from the dilated aortic structures.

Dilatation of aortic structures may result in aortic valve regurgitation, aortic dissection, and/or eventual rupture\[13\]. Niwa et al. reported that aortic root of patients with TOF dilated at 1.7 mm/year for a 5.2-year observation period, which seems faster than that in our study (0.94 mm/year in SoV)\[4\]. We think the reason for this difference could have resulted from different patient age distributions in these two studies (36 years old in Niwa’s study versus 14.5 years old in our study at the time of the final CT study). Aortic dilatation in TOF has been mentioned in several previous studies\[14\]. Because our study’s patients were
not old enough to apply adult’s standard of aortic dilatation (over 40mm), we defined aortic dilatation by z-score like Nagy’s study[10]. Then, we found aortic dilatation 74.2% at 6 years old and 86.4% at 16 years old. Even if there were a lot of the patients who had aortic dilatation, no one had been diagnosed with severe AR or aortic dissection.

Some authors have insisted the AH ratio as a highly predictive value for a long-term mortality and risk of aortic dissection or rupture in aortic root structures including AAo[15, 16]. And it is suggested as one of predictive of increased risk in recent guideline for aortic disease[17]. The AH ratio is more likely to be helpful and useful especially for small young patients whose aortic structures are relatively small to be exactly evaluated[18]. According to the aforementioned studies, the AH ratio > 10 cm²/m² was risk factor for aortic events. Although we have only one patient who met this condition in our cohort, presumably, because of young age of our cohort (median 14.5 years) of our cohort, we found that the AH ratio tended to increase in the ten years. Therefore, AH ratio could reach the level that we must concern about aortic events at in the future in these young patients even though it could be different from the adult patients. We should observe changes of the aortic structures very carefully even though the current status of patients’ aortic structures is out of the scope of traditional criteria for surgical intervention.

Whereas the authors measured aortic structures by echocardiography in most previous studies, especially for congenital patients, we mainly used cardiac CT rather than echocardiography because CT was exclusively recommended modalities in current thoracic aorta disease guideline[17]. Although CT has some disadvantages such as radiologic hazard in pediatric patients and possible complications associated media contrasts[19], it is more useful tool for detection of aortic aneurysm than other modalities because, (1) it can inspect the whole aorta including deep seated or other vessel variants, (2) it is less expensive cost than magnetic resonance image, (3) it was not different by sonographers in echocardiography, and (4) it is useful for postprocedural aortic conditions such as leaks or pseudoaneurysms. In addition to this, by technical development, we could obtain better images with less examination time and less than 1mSV of radiologic exposure[20]. We don’t want to suggest that routine CT should be scanned all the TOF patient, however, if echocardiography showed the problem of the aortic structures, we should not hesitate the aortic CT scan. In this study, most of the enrolled patients had already showed dilated aortic structures, then, they showed the increase of the AH ratio, we will follow up these patients with the aortic CT.

In our study, SoV was the most vulnerable structures to be dilated (32.80 mm at follow-up CT) by time most rapidly (estimated rate 0.94 mm/year) among the aortic structures. Although the rate of the dilatation was not fast enough to consider surgical intervention, most of our patients’ aortic structures (15.9 years old of the median age at the timing of most recent follow-up CT) are expected to be over 40mm, “significant dilatation” in the established guideline for adulthood, after 10 years when these patients would be expected to reach the age of their mid-twenties[17]. Based on this assumption, we cautiously suggest that aortic structures of patients with Fallot anomalies should be checked more frequently than guideline in which echocardiography should be performed for the adult with congenital heart diseases in every 2 years[6]. We suggest that transthoracic echocardiography should be assessed
with shorter interval than 2 years if once progression of dilatation of the aortic structures was observed in the patients with Fallot type disease, and CT for aortic structure should be seriously considered.

**Limitation**

We have some limitations in this study. This study was retrospectively performed with data of a single center. As this study included broad duration about 18 years, other environmental factors such as improved medical strategy could affect the outcome. Only small portion of the whole cohort was enrolled in our study because many patients did not have sufficient follow-up intervals with reliable CT scans. Consequently, we reviewed only the patients who survived for at least 5 years after their first CT scan and this could make a selection bias be unavoidable in this study. If there had been some patients who died of problems associated with dilatation of the aortic structures without reliable five-year interval CT studies, it could have been possible for us to miss them in our study cohort. The time interval for each patient was inconsistent. We used BSA to index the aortic structure values (z-score of each aortic structures) from a patient because most of our study population consisted of children and adolescents; however, we are not sure that BSA exactly represents patient sizes or relationship between patient body size and aortic structure size. Although we used another reliable parameter, AH ratio, to compensate this problem, using the AH ratio to predict events related with aortic structures of small and young patients seemed not be accepted generally.

**Conclusions**

AH ratio increased in over 10 years of follow-up duration and the number of the patients diagnosed with aortic dilatation also increased in this study. The median age of our patients was just 15.9 years old, and most of them are now expected to have longer lifespans than in the past. After their anomaly was totally corrected, we might have to focus on their aortic roots in addition to their original cardiac anomalies. Furthermore, we suggest that patients with Fallot anomaly should be checked with an aortic CT if they are suspected aortic dilatation in echocardiography.

**Abbreviations**

AA = aortic annulus; AAo = ascending aorta; BSA = body surface areas; AH = aortic cross-sectional area/height; CT = computed tomography; DORV = double outlet right ventricle; IQR = interquartile ranges; SoV = sinus of Valsalva; STJ = sinotubular junction; TOF = tetralogy of Fallot

**Statements And Declarations**

Nothing to declare

**Author contributions**
Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability

Not applicable

References


Tables

Table 1. Demographic, operative and follow-up data
Variables

<table>
<thead>
<tr>
<th>Female</th>
<th>N=66</th>
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</thead>
<tbody>
<tr>
<td>Type of diseases</td>
<td>66 (100%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>60 (90.9%)</td>
</tr>
<tr>
<td>Double outlet of right ventricle</td>
<td>6 (9.1%)</td>
</tr>
<tr>
<td>22q11.2 deletion syndrome</td>
<td>6 (9.1%)</td>
</tr>
</tbody>
</table>

**Anatomical characteristics**

| Pulmonary valve absent | 9 (13.6%) |
| Pulmonary artery stenosis | 26 (39.4%) |
| Right ventricular outlet obstruction | 33 (50.0%) |
| Coarctation of aorta | 2 (3.0%) |
| Right aortic arch | 6 (9.1%) |

**Operative and follow-up data**

| Number of Performed cardiac surgery | 2.7 ±1.3 |
| Palliative surgery | 7 (10.6%) |
| Total correction | 24 (36.4%) |
| Pulmonary valve replacement | 24 (36.4%) |
| Right ventricle-pulmonary artery conduit | 11(16.7%) |
| Other repairs | 7 (10.6%) |
| Including pulmonary artery angioplasty | 48 (72.7%) |
| Endocarditis | 6 (9.1%) |
| Mediastinitis | 1 (1.5%) |
| Antihypertensive medication | 13 (19.7%) |

**Table 2.** Comparison of the aortic diameters and their calculated values in initial and follow-up CT using paired t-test.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Initial CT</th>
<th>Follow-up CT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>5.95 [0.46~13.10]</td>
<td>15.94 [9.28~23.38]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>115.70 [65.90~157.68]</td>
<td>160.25 [133.03~168.63]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>0.80 [0.37~1.41]</td>
<td>1.53 [0.99~1.82]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diameters of the aortic structure (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic annulus</td>
<td>17.10 [12.45~23.88]</td>
<td>23.05 [20.05~27.13]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sinus of Valsalva</td>
<td>24.45 [16.20~31.75]</td>
<td>32.80 [28.45~37.15]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sinotubular junction</td>
<td>19.40 [11.55~23.40]</td>
<td>26.10 [22.43~30.40]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>19.90 [12.55~26.03]</td>
<td>25.40 [21.45~29.23]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Z-score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic annulus</td>
<td>2.59 [1.11~3.27]</td>
<td>2.60 [0.81~3.23]</td>
<td>0.35</td>
</tr>
<tr>
<td>Sinus of Valsalva</td>
<td>2.09 [0.84~3.26]</td>
<td>2.40 [1.54~3.31]</td>
<td>0.041</td>
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<tr>
<td>Sinotubular junction</td>
<td>1.09 [0.00~2.44]</td>
<td>2.31 [0.80~3.35]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>1.67 [0.51~2.77]</td>
<td>2.01 [0.71~2.56]</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Aorta cross sectional area/Height ratio (cm²/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic annulus</td>
<td>2.19 [1.57~3.05]</td>
<td>2.82 [2.27~3.54]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sinus of Valsalva</td>
<td>4.15 [3.06~5.40]</td>
<td>5.44 [4.65~6.71]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sinotubular junction</td>
<td>2.42 [1.61~3.25]</td>
<td>3.49 [2.85~4.54]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>2.47 [1.93~4.08]</td>
<td>3.23 [2.67~4.27]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BSA = body surface area, CT = computed tomography

**Figures**
Figure 1

The aortic structures were measured based on the axial images from computed tomography (CT) scans. 
(A) The aortic annulus was measured inter-commissural distance in the aortic valve. (B) The sinus of Valsalva was measured at the level of maximal diameter on the axial image. (C) The sinotubular junction was measured at the level of transitional zone from the sinus of Valsalva to ascending aorta. (D) The diameter of the ascending aorta was measured at the level of main pulmonary artery bifurcation.
Figure 2

Comparison of aortic cross sectional area/height ratio of each aortic structure.

AH = aortic cross sectional area/height
Figure 3

Comparison of z-scores of each aortic structure.
Figure 4

Pearson's correlation between age and aortic cross sectional area/height ratio.

AH = aortic cross sectional areal/height