Aortic stiffness and aortic dilation in infants and children with tetralogy of Fallot before corrective surgery: evidence for intrinsically abnormal aortic mechanical property

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Abstract

OBJECTIVE: The present study tested the hypothesis that there is an intrinsic abnormality of aortic elasticity in infants/children with tetralogy of Fallot (TOF) before corrective surgery. The study also determined the independent and quantitative effects of aortic volume load on aortic dilation in this group of TOF patients.

METHODS: Aortic stiffness (pulse wave velocity; PWV) and aortic volume load (aortic volume flow) were measured during catheterization in 37 infants and children with TOF before corrective surgery and in 55 control subjects.

RESULTS: PWV was significantly higher in TOF patients than in controls, irrespective of age, sex, hemodynamic burden on the aortic wall, and existence of aorto-pulmonary shunt. Aortic diameter was also significantly greater in TOF patients than in controls. Multivariate regression analysis identified aortic volume load as an independent determinant of aortic dilation (aortic diameter = 0.72 × aortic flow + 26.1 × body surface area + 2.79, r² = 0.58, p < 0.001). Increased aortic-wall stiffness correlated with the increase in aortic diameter in patients with dominant left-to-right shunt (without aortic volume load); aortic diameter = 0.007 × PWV + 13.5 × body surface area (BSA) + 6.3 (r² = 0.73, p < 0.05).

CONCLUSIONS: The present study highlighted the intrinsic abnormality of the mechanical property of the aortic wall as a feature of aortopathy in TOF. The study also indicated that aortic volume overload and, to a lesser extent, intrinsically high aortic stiffness correlated significantly with aortic dilation in TOF.

Keywords: Aorta • Congenital heart defects • Tetralogy of Fallot

INTRODUCTION

Aortic root dilation and its progressive nature have increasingly been recognized in patients with both repaired and un repaired tetralogy of Fallot (TOF) [1]. This is largely because severely dilated aorta can lead to aortic regurgitation [1–3], dissection or rupture [4,5], which could be fatal and necessitate surgical intervention [1,3–5]. Notably, a histological study of the aortic wall in adult TOF patients has highlighted degeneration of the tunica media of the aorta, including fragmentation of elastic fibers, loss of smooth muscle cells, and increase in grand substance, as an important cause of aortic root dilation [6]. These structural changes in the aortic wall should equate with impaired elasticity of aortic wall because loss of the medial elastic network and structural integrity leads to alteration in the mechanical property characterized by increased wall stiffness [7,8]. Our group and other investigators have indeed demonstrated increased aortic stiffness and its association with aortic dilation in patients with repaired TOF [9,10]. Importantly, the histological abnormalities of the aorta appear to be present since infancy and may be closely associated with a higher risk of aortic dilation [11,12], suggesting that aortic stiffness is also intrinsically increased in infant TOF patients before corrective surgery and contributes to aortic dilation.

In addition to the abnormal medial histopathology that possibly weakens the aortic wall and leads to aortic dilation, aortic volume load, which is often found in infant TOF before corrective surgery due to right-to-left shunt and/or left-to-right shunt through aorto-pulmonary shunt, has also been suggested as another important factor that could potentially enhance aortic dilation in TOF [1,13,14]. However, there is no evidence in the literature for the direct and independent effect of aortic volume overload on aortic dilation or quantitative association between aortic volume load and dilation.

Therefore, the present study was conducted to test our hypotheses that (1) there is an intrinsic increase in aortic stiffness in infant/children with un repaired TOF and that (2) both increased stiffness and aortic volume load are important determinants of aortic dilation in this group of TOF patients. To test these hypotheses, we measured aortic pulse wave velocity (PWV), a marker of aortic stiffness [15,16], and aortic flow volume as a direct measure of aortic volume load, and examined their relationship with aortic dilation in infants and children with TOF before surgical repair.
METHODS

Patients

The study subjects were 37 consecutive infants/children with TOF, who underwent cardiac catheterization before corrective surgery between 2005 and 2008 at our institution. A total of 21 of these were unoperated (four had pulmonary atresia with major aortopulmonary collateral arteries (MAPCAs) and the remaining 17 had pulmonary stenosis). The remaining 16 patients had a Blalock-Taussig (BT) shunt. As many as 55 patients with minimal shunt flow of either ventricular septal defect (VSD, \(n = 22\)) or patent ductus arteriosus (PDA, \(n = 33\)) were enrolled as the control group (the calculated pulmonary-to-systemic flow ratio was <1.1). Until 1999, the VSD had been catheterized to check for deformity of aortic valves and its relation to VSD [17], according to our institutional protocol of those days. The PDA patients underwent catheterization for coil embolization of the ductus to prevent infectious endocarditis. Some of the data of the control group were used and presented in our previous study [10]. A written informed consent was obtained from the parents of each patient and the procedures strictly followed the Hospital regulations of Saitama Medical University regarding (1) contract business control, (2) prevention of unfair research activities, (3) conflict of interest control, and (4) intellectual property.

Measurements

During routine cardiac catheterization, ascending aortic pressure was measured using a high-fidelity pressure transducer mounted on a 0.014-in. guidewire (RADI Medical System AB, St. Paul, MN, USA), placed within a 4-Fr pigtail catheter. The ascending aortic diameter of the sino-tubular junction was measured at end-diastole from two-dimensional transthoracic echocardiograms at the time of the catheterization. The aortic diameter was indexed to the normal reference value for Japanese children [18], and expressed as percentage of the normal value when necessary. The volume load on the ascending aorta was assessed by ascending aortic volume flow, which was calculated by multiplying aortic Doppler flow velocities recorded from the apical long-axis view and aortic annulus diameter [15,16]. The aortic flow was indexed to the body surface area (BSA) of the patient. To estimate PWVs a measure of vascular stiffness, the catheter was withdrawn from the ascending aorta to the thoracic aorta at the level of the diaphragm. The distance between the two levels was directly measured as the length of the catheter drawn outside the body. The stability of the heart rate was confirmed during catheter withdrawal. PWV was calculated dividing the distance between the ascending and descending aorta by the time delay between the rapid upstroke of the feet of recorded pulse waves at each site. The recorded signals were digitized at 500 Hz and PWV was analyzed automatically using custom-made software.

Statistical analysis

All values were expressed as mean ± SD. The significance of differences in mean values between groups was assessed using an unpaired t-test for two-group comparison and analysis of variance (ANOVA) for three-group comparison followed by Tukey post hoc analysis. Differences in PWV among three groups were further tested after controlling for age, sex, aortic pressure, and aortic flow by multivariate regression model. Determinants of aortic diameter in TOF patients were assessed using multivariate regression analysis with BSA, aortic flow, aortic pressure, and PWV included as independent variables for possible determinants. Differences in the relation of aortic diameter to aortic flow between unoperated and operated (BT shunt) TOF patients were evaluated with group and interactive (group × aortic flow) factors additionally included as independent variables. A probability value of \(p < 0.05\) was considered to indicate statistical significance. All statistical analyses were performed using Systat version 6.0.

RESULTS

Table 1 summarizes the patient characteristics of each group. The mean age and BSA of the TOF group were lower than those of the controls. This was due to the fact that infant patients with small shunt VSD/PDA rarely underwent catheterization. Aortic flow was significantly higher in the TOF group than in the control group (\(p < 0.001\)) and TOF patients with BT shunt had a higher aortic flow than the unoperated patients (\(p < 0.01\)). The mean and diastolic aortic pressures were slightly but significantly lower in the TOF patients than in the controls (\(p < 0.05\)). Five unoperated TOF patients were being treated with \(\beta\)-blockers to prevent cyanotic spells and two TOF patients with BT shunt were being treated with diuretics due to increased pulmonary flow.

Aortic stiffness

PWV was significantly higher in TOF patients than in the controls (TOF: 711 ± 298 cm s\(^{-1}\), control: 417 ± 92 cm s\(^{-1}\), \(p < 0.001\) for the TOF group versus the control group, Fig. 1). The mean PWV of each TOF group was also significantly higher than that of the control group, but TOF patients with BT shunt had significantly

### Table 1: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Tetralogy of Fallot group</th>
<th>Control group ((n = 55))</th>
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<tbody>
<tr>
<td></td>
<td>Un-operated ((n = 21))</td>
<td>BT shunt ((n = 16))</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.92 ± 0.63</td>
<td>1.18 ± 0.63</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/6</td>
<td>10/6</td>
</tr>
<tr>
<td>Body surface area (m(^2))</td>
<td>0.34 ± 0.06*</td>
<td>0.36 ± 0.07*</td>
</tr>
<tr>
<td>Aortic flow (l min(^{-1}) m(^{-2}))</td>
<td>5.42 ± 2.56*</td>
<td>9.48 ± 2.49*</td>
</tr>
<tr>
<td>Aortic pressure</td>
<td>85.5 ± 16.3*</td>
<td>91.3 ± 13.8</td>
</tr>
<tr>
<td>Diastolic</td>
<td>50.9 ± 11.8*</td>
<td>47.5 ± 10.2*</td>
</tr>
<tr>
<td>Mean</td>
<td>67.1 ± 13.2*</td>
<td>69.0 ± 11.7*</td>
</tr>
<tr>
<td>Medications</td>
<td>Diuretics (n)</td>
<td>β-Blocker (n)</td>
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<td></td>
<td>5</td>
<td>2</td>
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</table>

Data are mean ± SD.

\*\(p < 0.05\) versus control.

\†\(p < 0.05\) versus Blalock-Taussig (BT) shunt.
higher PWV than the unoperated TOF patients (TOF with BT shunt: 807 ± 327, unoperated TOF: 621 ± 245 cm s⁻¹, p < 0.05). To test whether the high PWV in TOF patients was independent of factors that could affect aortic stiffness, multivariate analysis was performed with age, sex, aortic pressure, and aortic flow as independent variables. There was again a significantly higher PWV in TOF patients than in the controls (p < 0.001 for each TOF group versus the control group and p < 0.05 for age). By contrast, the difference in PWV between the two TOF groups was not significant (p = 0.326) after controlling for age, sex, aortic pressure, and aortic flow. Thus, there was an intrinsic increase in aortic stiffness in infants and children with TOF before corrective surgery, irrespective of age, sex, aortic hemodynamics, and the existence of BT shunt.

Aortic dilation and its determinants

The aortic diameter was significantly larger in TOF patients than the controls (unoperated TOF: 160 ± 21.4, TOF with BT: 200 ± 34.0, control: 105 ± 11.6% of normal, p < 0.001 for each TOF group versus controls, Fig. 2). The diameter was larger in patients with BT shunt than in the unoperated patients (p < 0.01). As shown in Fig. 3(A), aortic diameter in TOF patients correlated significantly with aortic volume load represented by ascending aortic flow (percentage of normal aortic diameter = 7.0 × aortic flow + 127, r = 0.67, p < 0.001). Although a higher PWV tended to be associated with a larger aortic diameter (Fig. 3(B)), some patients with aortic volume overload (highlighted by circles in Fig. 3(B), representing the same patients indicated by arrows in Fig. 3(A)) had dilated aortas without markedly high PWV. Multivariate regression analysis demonstrated a significant correlation between aortic diameter and aortic flow as well as BSA (aortic diameter = 0.72 × aortic flow + 26.1 × BSA + 2.79, r² = 0.58, p < 0.001), but not with aortic stiffness (Table 2). The relationship between aortic diameter and aortic flow was not different between TOF patients with and without BT shunt (p = 0.95 for group and p = 0.61 for interactive effect).

Because PWV has been reported to correlate significantly with aortic dilation in TOF patients after elimination of aortic volume load with corrective surgery [9,10], to further determine the pathophysiological significance of increased aortic stiffness (PWV) in aortic dilation of TOF patients before corrective surgery, we examined PWV and aortic diameter in a subgroup of patients with mild pulmonary stenosis and dominant left-to-right shunt, so called pinkTOF, in which aortic volume overload is minimal (n = 10). The mean Qp/Qs in these patients was 1.5 ± 0.3 (range, 1.1–2.0), and the aortic volume flow was significantly lower (3.46 ± 1.37 l min⁻¹ m⁻²) than the rest of the cyanotic TOF patients (8.74 ± 2.59 l min⁻¹ m⁻², p < 0.001). Furthermore, the aortic diameter was significantly smaller in the pink TOF patients (152 ± 15% of normal) than in the rest of (cyanotic) TOF patients (189 ± 34% of normal, p < 0.01), again indicating the importance of aortic volume overload in aortic dilation before corrective surgery.

Figure 1: Pulse wave velocity in Fallot patients and controls. Data are mean ± SD.

Figure 2: Aortic diameter in the three study groups. Data are mean ± SD.

Figure 3: Relationship between aortic diameter and aortic flow (A) and between aortic diameter and pulse wave velocity (B) in patients with tetralogy of Fallot (TOF). Data of patients with relatively high levels of aortic flow and relatively low levels of pulse wave velocity indicated by arrows in panel A are encircled in panel B. BT: Blalock–Taussig shunt.
surgery. Importantly, aortic diameter was still larger than normal in pink TOF patients (p < 0.001). Interestingly, PWV was significantly higher in both TOF groups (p < 0.001 vs controls) compared to the controls, but was not different between the TOF groups (pink TOF: 619 ± 244, cyanotic TOF: 746 ± 314 cm s⁻¹, p = 0.28). This was still the case even after adjustment for age, sex, aortic pressures, and flow by multivariate regression (p = 0.55 for pink TOF patients vs the rest of TOF patients), suggesting that the increased aortic stiffness in TOF patients is independent of volume overload on the aorta. In the pink TOF patients, aortic diameter correlated significantly with PWV (percentage of normal aortic diameter = 0.031 × PWV + 113.1, r = 0.70, p < 0.05). Multivariate regression analysis identified PWV as well as BSA as significant determinants of aortic diameter in pink TOF patients (Table 2, aortic diameter = 0.007 × PWV +13.5 × BSA + 6.3, r² = 0.73, p < 0.05).

**DISCUSSION**

To our knowledge, this is the first study to examine the aortic elastic property in infants/children with TOF before corrective surgery and to evaluate the effects of aortic elastic property and aortic volume load on aortic dilation in this group of TOF patients. The results showed that aortic stiffness, represented by PWV, is increased already in infants and children with TOF. This held true, even after adjustment for age, sex, and hemodynamic burden on the aortic wall, suggesting the impaired aortic elasticity and, thus, abnormal load-bearing characteristics inherent in TOF. We also found that aortic volume overload, assessed quantitatively by aortic flow, is an independent and significant determinant of aortic dilation before corrective surgery, though the intrinsically high aortic stiffness, which possibly reflects abnormal medial structure, also contributes, to some extent, to the aortic dilation in this population.

**Aortic stiffness in infants with TOF**

Histological examination of the ascending aorta of adult patients with TOF clearly demonstrates abnormal aortic wall structure characterized by elastic fiber disruption in the media together with a loss of smooth muscle cells and increased ground substance [6]. Subsequent studies added further important information: these abnormalities exist since infancy, even as early as a few days of age [11,12]. Because the integrity of the aortic wall architecture, particularly of dense elastic network, is a prerequisite for preserving the elasticity of aortic wall, the reported abnormalities of aortic wall structure should be translated into abnormal mechanical properties of decreased aortic elasticity. Our data indeed demonstrated decreased elasticity of the aortic wall in infants and children with TOF before corrective surgery. The change was observed independent of the hemodynamic burden on the aortic wall and even in patients with dominant left-to-right shunt, suggesting intrinsic abnormality of the aortic wall that could be linked to structural abnormalities. Several lines of evidence support a close link between aortic medial pathology (particularly fragmentation of elastic fibers) and increased aortic wall stiffness. In a study using transgenic mice that undergo severe elastic network fragmentation of the aortic wall, Marque et al. [8] demonstrated that fragmentation of elastic fibers was associated with a significant increase in aortic wall stiffness. In addition, Okamoto et al. [19] used aortic tissues harvested from patients undergoing ascending aortic replacement for Marfan syndrome and bicuspid aortic valve, and demonstrated that reduced distensibility of the aortic wall correlated significantly with the severity of elastic fragmentation assessed by light-microscopic examination.

The present observation of reduced elasticity of the aortic wall in infant/child TOF before corrective surgery extended our previous finding in anatomically repaired TOF patients [10], highlighting the abnormal aortic mechanical property as one of the underlying pathophysiology inherent in this congenital heart disease. This notion would be important because a stiff aorta can potentially lead to diverse cardiovascular—cerebral complications, including coronary artery disease, hypertension, or stroke [20–22] as well as aortic dilation/rupture (discussed below). Long-term follow-up studies of TOF patients are needed to determine the relation between stiff aorta and cardiovascular—cerebral complications.

**Aortic dilation and its determinants**

It is well recognized that the incidence and extent of aortic root dilation are greater in unoperated TOF patients with pulmonary atresia than in those with pulmonary stenosis [13,14]. In addition, Niwa et al. [1] reported that the time interval from shunt palliation to repair was longer, the left-ventricular dimensions were larger, and the incidence of pulmonary atresia was higher in patients with repaired TOF and dilated aorta (defined as aortic diameter >150% of normal reference value) compared with TOF patients with non-dilated aorta. Based on these clinical observations, it has been postulated that volume overload of the aortic root attributable to right-to-left shunt and/or left-to-right shunt from aorto-pulmonary shunt is an important predisposing factor to aortic dilation in TOF [2]. Although such presumption appears valid, no study has described the direct relationship between quantitative aortic volume load and the degree of aortic dilation in TOF. The present study clearly demonstrated that aortic volume load assessed by ascending aortic volume flow is a significant determinant of aortic dilation, even after adjustment for possible confounding factors that could affect aortic diameter.

On the other hand, aortic stiffness that should reflect aortic medial degeneration was not a significant determinant of aortic dilation for the whole group of TOF. This was mainly because

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**Table 2: Determinants of aortic diameter**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Standardized coefficient</th>
<th>p value</th>
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<tbody>
<tr>
<td>Patients with tetralogy of Fallot (n=37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic flow (l min⁻¹ m⁻²)</td>
<td>0.656</td>
<td>0.0002</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.455</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>0.552</td>
<td></td>
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<tr>
<td>Pulse wave velocity (cm/s)</td>
<td>0.217</td>
<td></td>
</tr>
<tr>
<td>Pink Fallot patients (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic flow (l min⁻¹)</td>
<td>0.528</td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.427</td>
<td>0.047</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>0.416</td>
<td></td>
</tr>
<tr>
<td>Pulse wave velocity (cm s⁻¹)</td>
<td>0.616</td>
<td>0.020</td>
</tr>
</tbody>
</table>

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some patients with marked aortic volume load had dilated aorta without marked increases in aortic stiffness. However, in a subgroup of patients with dominant left-to-right shunt (without volume load on the aortic wall), increased aortic stiffness was significantly associated with aortic dilation. Thus, it appears that, in patients with unrepaired TOF, the hemodynamic burden on the aortic wall is a primary etiological factor of aortic dilation, but that intrinsic alteration of aortic wall mechanical property could also contribute to the aortic dilation in this population. The latter notion is supported by the aforementioned animal study demonstrating that fragmentation of elastic fibers in transgenic mice does not only lead to a significant increase in aortic wall stiffness, but also causes aortic dilation [8]. In addition, in patients with Marfan syndrome and bicuspid aortic valve, which share clinical (progressive aortic dilation) and histological (medial degeneration) features with TOF, aortic stiffening precedes aortic dilation and predicts progressive aortic dilation [23,24], indicating that aortic stiffness plays a causative role in aortic dilation. Interestingly, in our previous study of TOF patients after elimination of aortic volume load by corrective surgery [10], recalculation of the normalized aortic diameter showed a much smaller value (138 ± 28%) than in the present patients, consistent with the important contribution of volume load to aortic dilation. Importantly, in the situation where the effect of aortic volume load was eliminated, increased aortic stiffness persisted and significantly correlated with aortic dilation [10], further supporting the fundamental abnormality of aortic mechanical property and its importance in aortic dilation both before and after surgical correction of TOF, though the effect may be masked before corrective surgery by the increased aortic volume load. Future prospective studies of the effects of aortic wall stiffening on aortic dilation could help confirm the importance of abnormal aortic mechanics as the causative mechanism for aortic root dilation. Such studies may also provide evidence that PWV is a useful marker of wall degradation and the risk of aortic root dilation in TOF.

LIMITATIONS

Several limitations must be considered in the present study. First, the age of the control group was not matched to the TOF patients for a practical reason; this is important because PWV is known to show a clear age-dependent change, as advancing age is associated with higher PWV [25]. However, PWV in TOF patients was significantly higher than in the controls despite the younger age and the difference in PWV between TOF and controls was further substantiated after adjustment for age. Thus, the age of the control group does not appear to influence the present results. Second, there is no evidence that histological abnormalities existed in the present TOF patients, and therefore direct evidence linking aortic medial pathology and mechanical property must await future studies in this particular disease (although there is such evidence in Marfan syndrome and bicuspid aortic valve) [19]. Third, the study is limited by the heterogeneity of the TOF patients regarding the distribution of blood in the aorta and in the pulmonary artery. The severity of right-ventricular outflow tract (RVOT) obstruction is associated with changes in the distribution, and generally links with the severity of aortic dilation and cyanosis. However, some patients with extremely severe RVOTO obstruction with almost no flow in the RVOT may be less cyanotic because of MAPCAs. They generally have very large aortas, probably with elastic property anomalies and/or aortic volume overload. In fact, we had four such patients, but, due to the limited number of patients, MAPCAs were not specifically investigated in this study even though they should directly influence the size of the aorta and probably its elastic properties as well. Therefore, this issue must be clarified by further investigation. Lastly, it should be acknowledged that aortic volume load (aortic volume flow) is a highly derived variable, but was measured once in the study. Therefore, the single-point assessment in the present study could have affected the results. In addition, although our data indicated a significant association between measured indices (PWV and aortic volume flow) and aortic diameters, their cause–effect relationship should be determined by studying serial changes in these variables in a long-term study.

CONCLUSIONS

Volume load on the aortic wall is associated with aortic root dilation in proportion to the degree of the load in infant/child TOF patients before corrective surgery. In addition, consistent with the intrinsic histopathological abnormalities of the aortic wall, the elastic property and, thus, the load-bearing characteristic of the aortic wall are impaired in this group of TOF. This relates to aortic dilation particularly in patients without aortic volume load. Because aortic stiffness is reported to remain high even after elimination of aortic volume load by corrective surgery and because progressive aortic dilation can occur in this situation, increased aortic stiffness may also be a possible underlying pathophysiology of aortic dilation in TOF patients. Further studies that include serial assessment of aortic volume load, aortic stiffness, and aortic dilation are needed to confirm our results.

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REFERENCES


