Marked disparity in mechanical wall properties between ascending and descending aorta in patients with tetralogy of Fallot

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Received 27 May 2011; received in revised form 11 August 2011; accepted 17 August 2011

Abstract

OBJECTIVES: Recent studies have linked abnormal aortic medial pathology to progressive aortic root dilatation in patients with tetralogy of Fallot (TOF). To explore whether the aortic medial pathology in TOF is linked to aortic mechanical property, the present study tested the hypothesis that the distribution of impaired aortic elasticity corresponds to the known distribution of abnormal medial pathology (confined to the ascending aorta) in TOF.

METHODS: Pulse wave velocity (PWV) of the proximal and distal aortas was measured with a high-fidelity micromanometer in 98 TOF patients (64 with repaired TOF and 34 with unrepaired TOF) and 63 control subjects.

RESULTS: PWV of the proximal aorta was significantly higher in TOF than in the control, but similar in repaired and unrepaired TOF (repaired: 588 ± 205 cm/s, unrepaired: 680 ± 288 cm/s, control: 439 ± 101 cm/s, P < 0.001 for each TOF group vs. control, P = 0.07 for repaired vs. unrepaired TOF). In contrast, PWV of the distal aorta was almost identical among the three groups (repaired: 441 ± 189 cm/s, unrepaired: 430 ± 114 cm/s, control: 461 ± 164 cm/s, P = 0.73, analysis of variance), indicating that abnormal aortic mechanical property is confined to the proximal aorta regardless of the operative status of TOF. This was also confirmed by comparison within the group; PWV of the proximal aorta was significantly higher than that of the distal aorta in both TOF groups (P < 0.001, each), whereas there was no difference in PWV between the proximal and distal aortas in the control subjects (P = 0.61).

CONCLUSIONS: Consistent with the known histopathological disparity between the media of the ascending and descending aortas, aortic stiffness is markedly increased in the proximal but not in the distal aorta of TOF. These results suggest that aortic wall stiffness is a potentially useful clinical marker of aortic dilation in patients with TOF.

Keywords: Aortopathy · Medial pathology · Pulse wave velocity · Tetralogy of Fallot

INTRODUCTION

Patients with tetralogy of Fallot (TOF) exhibit aortic medial pathology characterized by a triad of elastic fibre disruption, loss of smooth muscle cells and increased ground substance [1]. These changes represent abnormal load-bearing characteristics of the aortic wall and thus promote aortic dilation. Indeed, there is general agreement that progressive aortic dilation, which could potentially cause aortic regurgitation or dissection that necessitates surgical intervention, occurs in both repaired and unrepaired TOF, with the severity of pathological abnormality proportional to the degree of aortic dilatation [2-5]. Aortic medial pathology, represented by elastic fibre disruption, could also lead to impairment of aortic wall elasticity. In fact, increased aortic wall stiffness and its association with aortic dilation have been reported in patients with repaired TOF [6-8]. However, to date, there is no evidence for a direct link between medial pathology and abnormal aortic mechanical property in TOF. Because it is difficult to obtain aortic tissue to check for the medial pathology and thereby to evaluate the risk of future aortic dilation, it would be clinically useful if the tissue characterization can be monitored by measuring the mechanical properties of the aortic wall.

Importantly, both aortic medial pathology and aortic dilation in TOF are confined to the proximal (ascending) aorta, whereas medial histology and the size of the distal (descending) aorta are generally normal [2, 4]. Therefore, if the impaired aortic elasticity represents histological changes in the aortic media, then the impaired aortic elasticity should also be confined to the proximal aorta. If so, aortic wall stiffness could be potentially a useful marker for aortic dilation in patients with TOF. The present study was conducted to test our hypothesis that aortic stiffness, measured by pulse wave velocity (PWV), is increased only in the proximal portion of the aorta, the major site of aortic medial degradation, whereas aortic stiffness of the distal portion of the aorta is normally preserved.

METHODS

Patients

The study included 98 consecutive TOF patients who underwent cardiac catheterization. They comprised 64 patients with repaired and 34 patients with unrepaired TOF. Among the latter
group, 24 had Blalock-Taussig shunt and the remaining 10 patients were unoperated. Repaired TOF patients underwent catheterization to check for residual pulmonary stenosis, which had been identified by echocardiography, and to perform catheter interventions if necessary. Sixty-five patients who were considered to have normal two-ventricular circulation were enrolled as the control group. The control group consisted of patients with small ventricular septal defect (VSD, n = 29) or patent ductus arteriosus (PDA, n = 27) and haemodynamically normal heart (n = 7). In control patients with VSD and PDA, the amount of shunt flow was minimal, with a calculated pulmonary-to-systemic flow ratio of less than 1.1. Catheterization had been performed for the VSD until 1999 to check for deformity of the aortic valves and its relation to VSD [9], according to our institutional protocol of those days. The PDA patients underwent catheterization for coil embolization of the ductus to prevent infectious endocarditis. Other patients who were considered to have haemodynamically normal heart included those with paroxysmal ventricular tachycardia (n = 2), chest pain that was eventually considered non-pathological (n = 3), partial anomaly of pulmonary vein return with negligible shunt (n = 1) and small left ventricular diverticulum (n = 1).

Written informed consent was obtained from the parents of all patients, and the procedures strictly followed the Hospital regulations of Saitama Medical University regarding 1) contract business control, 2) prevention of unfair research activities, 3) regulations of Saitama Medical University regarding contract business control, and 4) intellectual property.

Procedures

During cardiac catheterization, aortic pressure was measured by a high-fidelity micromanometer mounted on a 0.014 in guidewire. To obtain PWV, a measure of vascular stiffness, the catheter was withdrawn from the ascending aorta to the thoracic aorta at the level of the diaphragm (proximal aorta) and then from the thoracic aorta to the abdominal aorta just above the iliac bifurcation (distal aorta). The distances between each of the two levels (ascending to thoracic and thoracic to abdominal aortas) were directly measured as the length of the catheter drawn outside the body. The heart rate remained stable during catheter drawback. PWV was then calculated by dividing the distance between the two regions of the aorta by the time delay between the rapid upstroke of the foot of the pulse wave recorded at each site.

Statistical analysis

All values were expressed as mean ± SD. Differences between the values of the three groups (repaired TOF, unrepaird TOF and control) were assessed by analysis of variance (ANOVA), followed by Tukey’s post hoc analysis. The difference in PWV between the proximal aorta and the distal aorta in each group was tested by paired t-test. The difference in PWV between the TOF groups was also tested after controlling for age, sex and the presence of right aortic arch and pulmonary atresia. A probability value of P < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using JMP version 8.0.

RESULTS

Table 1 summarizes the characteristics of the patients of each group. Twenty-six of unrepaired TOF patients were infants under the age of 1 year, and accordingly, patients of the unrepaired TOF group were significantly younger than those of the repaired TOF group, who were of similar age to those of the controls. Significantly more patients of the unrepaired TOF group had pulmonary atresia or right aortic arch than the repaired TOF group. Consistent with previous reports, our TOF had significant dilation of the ascending aorta, with more pronounced dilation in patients with unrepaired TOF than in those with repaired TOF.

Table 1: Patients’ profile

<table>
<thead>
<tr>
<th></th>
<th>Repaired TOF (n = 64)</th>
<th>Unrepaired TOF (n = 34)</th>
<th>Control (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.0 ± 6.6</td>
<td>0.93 ± 0.70*</td>
<td>6.8 ± 4.7</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>21 ± 14</td>
<td>6.8 ± 1.5&lt;1</td>
<td>25 ± 18</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.77 ± 0.37</td>
<td>0.34 ± 0.06&lt;1</td>
<td>0.87 ± 0.41</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>100 ± 14</td>
<td>88 ± 14&lt;1</td>
<td>96 ± 14</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>62 ± 11</td>
<td>49 ± 12&lt;1</td>
<td>64 ± 12</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>38 ± 9*</td>
<td>39 ± 9*</td>
<td>32 ± 7*</td>
</tr>
<tr>
<td>Aortic diameter (%)</td>
<td>156 ± 35*</td>
<td>180 ± 34&lt;1*</td>
<td>111 ± 16*</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>27/37</td>
<td>20/14</td>
<td>35/30</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Right aortic arch</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD or number of patients. BP, blood pressure. Aortic diameter denotes the percentage of normal reference value in Japanese children. *P < 0.01 vs. control. †P < 0.01 vs. repaired TOF.

Aortic stiffness in TOF

As shown in Fig. 1A, aortic stiffness (PWV) of the proximal aorta tended to be lower in repaired TOF (588 ± 205 cm/s) than that in unrepaired TOF (680 ± 288 cm/s), albeit statistically insignificant (P = 0.07). In both repaired and unrepaired TOF, PWV of the proximal aorta (439 ± 101 cm/s) was significantly higher than that in the controls (P < 0.001, each). In contrast, PWV of the distal aorta was almost identical among the three groups (Fig. 1B; repaired TOF: 441 ± 189 cm/s, unrepaired TOF: 430 ± 114 cm/s, control: 461 ± 164 cm/s, P = 0.73 by ANOVA), indicating that abnormal aortic mechanical property is confined to the proximal part of the aorta regardless of the operative status of TOF. This was also confirmed by comparison within the group; PWV of the proximal aorta was significantly higher than that of the distal aorta in both TOF groups (P < 0.001, each), whereas there was no difference in PWV between the proximal and distal aortas in the control subjects (P = 0.61). Because the mean age and the numbers of male patients and patients with pulmonary atresia and right aortic arch were different between the TOF groups, and because PWV may be affected by those factors [10], we further compared the stiffness of the proximal aorta in each TOF group. Multivariate regression analysis that included the above factors as independent variables showed that PWV was marginally higher in the unrepaired TOF group than that in the repaired TOF with borderline significance (P = 0.051).
example, in a study using an animal model of Marfan syndrome such as Marfan syndrome and bicuspid aortic valve [11, 12]. For elastic between aortic medial pathology (particularly fragmentation of aorta. Indeed, several lines of evidence indicate a close link higher risk of aortic dilation. more pronounced histological changes were associated with present since infancy even as early as a few days of age and that [2, 4], which demonstrated that histological abnormalities were dilation in TOF was further substantiated by subsequent studies [16], the aortic volume load generally observed in unrepaired TOF patients. Because increased distention stress on the aortic wall could lead to increased wall stiffness [16], the aortic volume load generally observed in unrepaired TOF patients may act additively/synergistically to increase wall stiffness. This clearly warrants future studies.

**DISCUSSION**

Niwa et al. [1] were the first group to demonstrate a considerable abnormality in the medial histology of the ascending aorta (medial degradation) in a variety of congenital heart diseases, including TOF, and suggested that this histopathology was probably the underlying cause of aortic dilation observed in TOF. The importance of aortic medial pathology as a cause of aortic dilation in TOF was further substantiated by subsequent studies [2, 4], which demonstrated that histological abnormalities were present since infancy even as early as a few days of age and that more pronounced histological changes were associated with higher risk of aortic dilation.

Medial histopathology (loss of architectural integrity of aortic wall) also suggests impairment of the elastic properties of the aorta. Indeed, several lines of evidence indicate a close link between aortic medial pathology (particularly fragmentation of elastic fibres) and increased aortic wall stiffness in diseases that share clinical features of progressive aortic dilation with TOF, such as Marfan syndrome and bicuspid aortic valve [11, 12]. For example, in a study using an animal model of Marfan syndrome that undergoes severe elastic network fragmentation of the aortic wall, Marque et al. [11] demonstrated that fragmentation of elastic fibres was associated with a significant increase in the aortic wall stiffness. In addition, Okamoto et al. [12] 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. In contrast, there are no data directly linking impaired aortic elasticity to aortic medial degradation in patients with TOF, although reduced aortic elasticity and its correlation with aortic dilation have been reported in repaired TOF patients [6, 7]. The lack of information is probably due to the difficulty in studying and comparing aortic medial histology with mechanical property in a given TOF patient. Undoubtedly, there is a clinical need for data that link changes in aortic mechanical properties to changes in medial histology in TOF. Thus, the results of the present study showing confinement of increased aortic stiffness to the proximal aorta, the site of exclusive histological abnormalities within the aorta, are clinically important. In patients with Marfan syndrome or bicuspid aortic valve, aortic stiffening precedes aortic dilation, and thus the former is a potentially useful marker to predict progressive aortic dilation [13, 14]. The present results suggest that measuring aortic stiffness as a surrogate of aortic medial histopathology may also be useful to predict aortic dilation in TOF, similar to Marfan syndrome and bicuspid aortic valve.

Another important finding of the present study was the increased wall stiffness of the proximal aorta even in infants and small children with TOF who had not yet undergone corrective surgery. This finding suggests intrinsic impairment of aortic elasticity in TOF patients and is consistent with the findings of a previous study in an animal model of TOF [15]. That study demonstrated the development of structural abnormalities in cardiac outflow tract, together with impaired development of elastic matrix of the aorta after experimental ablation of cardiac neural crest cells during chick embryogenesis. Extrapolation of the results to human suggests embryological inherency of TOF aortopathy. Based on the previous findings indicating intrinsic aortic medial pathology in TOF [2, 4], our finding of intrinsic impairment of aortic elasticity would further support the close link between aortic medial pathology and aortic mechanical property in this population. In the present study, patients with unrepaired TOF tended to have a higher proximal aortic PWV than those with repaired TOF. Because increased distention stiffness is a suitable alternative for investigating such patients.

**Limitations**

There are several limitations to the present study that need to be discussed. First, although our data suggested a close link between aortic medial pathology and mechanical property, the study provided no direct evidence in support of this since no histopathological examination was conducted. Secondly, the present TOF patients, particularly those with repaired TOF, had residual lesions that necessitated cardiac catheterization. Therefore, the results of the present study cannot be generalized to TOF patients who do not have such lesions or those who do not require catheterization. Non-invasive measurement of aortic stiffness is a suitable alternative for investigating such patients.
Thirdly, because the length of the ascending aorta is short in children, the pulse wave traversing time is very short for the ascending aorta and thus likely to introduce PWV calculation errors. To avoid such errors, the proximal aorta defined in the present study included part of the descending aorta. Therefore, the magnitude of aortic stiffness in the ascending aorta calculated in the present study might be underestimated, although this possibility does not alter but rather strengthen the hypothesis tested in this study. Fourth, our control patients may not necessarily reflect ‘true’ healthy children. However, even if the present control patients have had some abnormality in aortic wall, PWV of the control patients would be overestimated rather than underestimation for that of ‘true’ healthy children, further highlighting the abnormal aortic mechanical property in TOF population. In this regard, VSD patients generally have a relatively low output in the aorta, which may have been the case in our control VSD patients and thus may have affected the results. However, the left-to-right shunt was minimal in our control VSD patients, with a calculated Qp/Qs of less than 1.1. Also, as shown in the table, aortic diameter of the controls was comparable to, or at least no smaller than, that of normal children (111% of normal). In addition, to further confirm that decreased systemic output in the controls did not affect the results, we calculated the systemic output (Qs) directly both in repaired TOF and in VSD patients. The Qs was greater, rather than smaller, in VSD patients (4.42 ± 0.85 l/min/m²) than that in TOF patients (3.72 ± 0.82 l/min/m², P < 0.01). Therefore, we believe that low output in the aorta, which is often observed in VSD patients, was not relevant to our control patients and did not affect the results of the present study. Lastly, assessment of aortic dilation is relatively easy and can be repeatedly documented during follow-up. Although aortic dilation is common in TOF, the number of patients who require surgical correction is much smaller than that of patients with other diseases characterized by progressive aortic dilation, such as those with Marfan syndrome and bicuspid aortic valve. Importantly, some TOF patients show progressive aortic dilation, but others do not, or even show regression of the dilation. To date, there are no long-term data for the identification of TOF patients at risk of development of progressive dilation. Early prediction of the risk of aortic dilation by detecting the aortic medial abnormality would therefore be clinically useful. This could help in selecting patients for follow-up and set up an efficient plan for the follow-up. The usefulness of aortic stiffness as a predictive marker of aortic dilation of TOF needs to be addressed in future studies.

CONCLUSIONS

Consistent with the known histopathological disparity between the media of the ascending and descending aortas, aortic stiffness of the proximal aorta in TOF patients is markedly increased from early life and is strikingly different from that of the distal aorta. These findings would not only suggest that aortic stiffness can serve as a prognostic marker for TOF aortopathy, but also help clarify the anatomic target for the prevention and/or treatment of aortic dilation. Prospective studies are warranted to examine the effects of aortic stiffening and the outcome of therapies designed to reduce such stiffness on the fate of aortic dilation.

Conflict of interest: none declared.

REFERENCES


