The fate of the aortic root after early repair of tetralogy of Fallot

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Abstract

Objective: Late aortic root dilatation is a growing concern in patients operated for tetralogy of Fallot (ToF). This longitudinal follow-up study sought to evaluate the changes in the aortic root dimensions in relation to body growth, assuming that early repair of tetralogy of Fallot might prevent late aortic dilatation. Methods: A retrospective analysis of the aortic root dimensions was performed in 88 patients repaired early for tetralogy of Fallot by echocardiographic measurement of aortic annulus, sinus of Valsalva and sinotubular junction, adjusted for body surface area and expressed as z-scores. Mean age at repair was 9.7 ± 7.4 months. Median age was 7.3 months (range 45 days—29 months). Results: At the time of repair, all root dimensions were enlarged: z-score of the annulus 3.32 ± 1.66; sinus 3.54 ± 1.49; sinotubular junction 2.74 ± 1.19. Within a mean follow-up of 6.9 ± 4.4 years, the mean z-scores of both annulus and sinotubular junction significantly decreased to normal size at 7 years postoperatively: z-score of annulus 0.95 ± 0.7 (p = 0.006), z-score of sinotubular junction 0.99 ± 1.47 (p = 0.006). The z-score of the aortic sinuses appeared to regress slower to 2.78 ± 1.26 (p = 0.262). The indexed sinus diameter however regressed significantly from a mean of 51.4 ± 13.4 mm m⁻² at correction to 28.9 ± 7.2 mm m⁻² (p = 0.0001) at latest follow-up. Evolution of aortic root size after repair was independent of aortic arch side, sex, age at repair or previous shunt palliation. Conclusions: The initially dilated aortic root in tetralogy of Fallot normalises in size at the level of the annulus and sinotubular junction within 7 years after early repair. This process seems delayed at the level of the aortic sinuses, although the indexed root diameter shows significant regression over time. These results suggest that early repair of ToF abrogates the enlargement of the aortic root, validating one aspect of the need for tetralogy correction at a young age.

Keywords: Congenital cyanotic; Tetralogy of Fallot; Great vessels

1. Introduction

The aortic root has been forgotten for a long time in the follow-up after repair of tetralogy of Fallot (ToF), as focus was mainly directed to the right heart and the fate of the right ventricular outflow tract. As early as in 1982, Somerville mentioned persistence of a large aortic root, but considered it an acquired feature due to long-standing volume overload by years of aortopulmonary shunts before complete repair, and suggested that earlier repair in the first decade of life might prevent this complication [1]. In 1997, the first series on progressive aortic root dilatation in repaired ToF was published by the Mayo Clinic group [2]. The report mentioned that, despite excellent results after ToF repair, a substantial cohort of patients developed progressive aortic dilatation and subsequent aortic valve incompetence, needing re-repair on the aortic root. They first revealed the theory of intrinsic aortic wall abnormalities, perhaps induced by a long period of volume overload, as most patients were over 10 years old at the time of primary repair. In other studies, progressive aortic root dilatation has been reported in relation to patient factors such as right aortic arch, male sex or palliative shunt before repair [3].

The aim of our study was to find out if early repair of ToF could prevent progressive dilatation of the aortic root, or might even promote regression of the aortic root diameter towards normal size during the growth of the child. Therefore, we sought to describe, in a population of children with ToF consistently undergoing early repair, the evolution of the aortic root dimensions from the first treatment for ToF to the latest follow-up, based on echocardiographic measurements related to body size.

2. Materials and methods

2.1. Patient population

A retrospective design was used for the study. Over a 15-year period, from January 1993 to January 2008, 197 patients...
consecutive patients with ToF with or without concomitant atrioventricular septal defect underwent repair at the Cardiac Centre of the University Hospital Gent, Belgium. The operative technique included a standard transatrial—transpulmonary approach, with closure of the ventricular septal defect with a Gore-Tex (W.L. Gore & Associates, Inc., Newark, DE, USA) patch and infundibular resection through a right atriotomy, supplemented with a transannular autologous pericardial patch if necessary. Patients with pulmonary atresia and ventricular septal defect (PA/VSD) were excluded. All patients with a follow-up of at least 12 months were eligible for the study, including data on length and weight at each outpatient visit, and having at least three sequential good-quality echocardiograms of the aortic root available during clinical follow-up. Of the total cohort, 88 patients fulfilled these criteria. In the remaining 109 patients, the echocardiographic data were either not useful for complete measurement of the root, or did not contain a recording of the aortic root.

The institutional Ethical Committee approved the study and waived the need for patient consent, as only routine postoperative echocardiograms during outpatient clinic visits were used to perform the serial measurements of the aortic root.

### 2.2. Methods

The files of all eligible ToF patients were reviewed for anthropometric data at each outpatient visit, and for each patient contact associated with a suitable echocardiogram, the body surface area was calculated according to the Mosteller formula for children. The echocardiography tapes recorded at the outpatient visits were all reviewed by a single experienced observer (M.Z.), unrelated to the patients or the expected result. From the long-axis, two-dimensional parasternal view at mid-systole, measurements of the aortic root were made perpendicular to the long axis of the aorta and focused on the internal diameter of the aortic annulus, the sinus of Valsalva and the sinotubular junction (STJ). A total number of 934 useful measurements were obtained. The absolute values were recorded in millimetres and expressed as z-values with the use of standard algorithms [4]. The z-score represented the standard deviation from the mean aortic diameter normalised for the patient’s body surface area and age. All obtained z-scores were grouped per year of follow-up after correction, and compared per patient at each level (annulus, sinus and STJ) between the time of repair and each year of follow-up. In addition, the difference in absolute root diameters indexed to body surface area (in mm m⁻²) was calculated for each patient between the time of correction and the last measurement, to indicate regression or progression of root dilatation during follow-up.

### 2.3. Statistical analysis

Data were analysed with the SPSS 16.0 program (SPSS Inc., Chicago, IL, USA). Descriptive data are presented as median (range) or mean ± standard deviation. To compare the z-values of the aortic annulus, the aortic sinus and the STJ at yearly intervals following complete repair, the Wilcoxon signed-rank test was used. To determine the influence of categorical variables (previous shunt, side of the aortic arch and sex) on aortic root size, parametric and non-parametric tests were used. The influence of age as a continuous variable was tested with bivariate regression analysis. To compare the diameters at correction and at the last measurement in the same patient, a sign test was used.

Statistical significance was inferred as a two-sided p-value of less than 0.05.

### 3. Results

The patient characteristics are presented in Table 1. The mean age at correction was 9.7 ± 7.4 months, the median age was 7.3 months. Male-to-female ratio was 1.6. Of the 88 study patients, 12 had a right aortic arch (14%). A small transannular patch was used in 68% of patients. In 19 patients (22%), a previous Blalock—Taussig shunt was inserted at a mean age of 2.3 ± 3.4 months, for a median of 1 month (range 2 days—15.2 months). Patients receiving a prior shunt were significantly older at correction: 13.9 ± 7.3 months (p < 0.001), for a median age of 11 months (range 6.6—29 months). The mean interval between shunt and correction in this group was 12.5 ± 6.1 months, for a median of 10.3 months (range 7.2—28.6 months).

After a post-repair follow-up of 6.9 ± 4.4 years, all patients were in the New York Heart Association (NYHA) stage I or II. Re-operations were necessary for right ventricular outflow tract problems: seven patients demonstrated right ventricular outflow tract obstruction after a mean interval of 1.1 ± 0.9 years, and 11 patients needed a pulmonary valve replacement for pulmonary incompetence and right ventricular dilatation after a mean interval of 7 ± 3.9 years after repair. None of the patients needed surgery for aorta-related problems. In five patients, a trace of aortic valve incompetence was noted at latest follow-up. A total number of 934 aortic root echo measurements were considered trustworthy and analysed.

#### 3.1. Aortic annulus size change

The annulus diameter decreased significantly from a mean z-score of 3.32 ± 1.66 at the time of repair to 0.95 ± 0.7 at 7 years (p = 0.006). At each yearly interval since correction, the z-value decreased significantly compared with the starting value (Fig. 1(a)). The size reduction was most

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics.</th>
<th>Number of patients</th>
<th>%</th>
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<tbody>
<tr>
<td>Male gender</td>
<td>54</td>
<td>61</td>
</tr>
<tr>
<td>Right aortic arch</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Transannular patch</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>Previous BT-shunt</td>
<td>19</td>
<td>22</td>
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<tr>
<td>Mean age at correction:</td>
<td></td>
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<tr>
<td>- One stage</td>
<td>9.7 ± 7.4 months</td>
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<tr>
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<td>Median age at correction:</td>
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pronounced during the first 3 years after repair, when the rate of annulus regression was according to an average $z$-score of 0.56 per year. Beyond the 7th year, the $z$-value tended to stabilise, but data were too scarce for statistical contribution. When we compared the indexed annulus diameter at correction and at the last measurement in each individual patient, however, we found a significant regression over time, from a mean of $28.9 \pm 6.9 \text{ mm m}^{-2}$ to $20.4 \pm 5.7 \text{ mm m}^{-2}$ ($p < 0.001$) (Fig. 2), corresponding to a size reduction rate of $-1.4 \pm 2.9 \text{ mm m}^{-2}\text{ year}^{-1}$. In 16 patients with a follow-up longer than 10 years, the mean annulus diameter was $15.8 \pm 2.6 \text{ mm m}^{-2}$ at $12 \pm 1.2$ years. A previous shunt, male sex or side of the aortic arch were not associated with a larger annulus diameter at any time point. Older age at repair was associated with a larger annulus only at the time of correction ($p = 0.043$), but not during follow-up.

### 3.2. Size change of the sinus of Valsalva

The sinus diameter at the time of ToF correction was clearly enlarged with a mean $z$-score of $3.54 \pm 1.49$. During follow-up, the sinus diameter $z$-value decreased not significantly to a mean $z$-score of $2.78 \pm 1.26$ ($p = 0.262$) after 7 years (Fig. 1(b)). The numbers of observed data after 7 years were not powered to draw further conclusions. Using the indexed sinus diameter at correction and at the last measurement for comparison in each individual patient, a significant regression was found, from a mean of $51.4 \pm 13.4 \text{ mm m}^{-2}$ to $28.9 \pm 7.2 \text{ mm m}^{-2}$ ($p = 0.0001$) (Fig. 2). In 16 patients having a follow-up longer than 10 years, the mean sinus diameter even decreased to $21.5 \pm 3.5 \text{ mm m}^{-2}$ overall; this corresponded to a size reduction rate of $-4.8 \pm 5.4 \text{ mm m}^{-2}\text{ year}^{-1}$. Neither patient sex, age at repair, a prior shunt nor side of the aortic arch had any significant association with larger sinus diameters.
3.3. STJ size change

In ToF, the largest aortic root diameters are clearly situated at the annulus and sinus level, with the ascending aorta tapering towards a normal-sized aortic arch. In the study group, the STJ at repair had a mean z-score of 2.74 ± 1.19. The evolution over time showed an analogous pattern as for the aortic annulus: at 7 years, the mean z-value had normalised to 0.99 ± 1.47 (p = 0.006). Again, the fastest reduction was noted during the first years, with an average z-score decrease of 0.35 per year up to 3 years after repair (Fig. 2). Comparing the indexed STJ diameter at correction and at the last measurement in each individual patient showed a significant regression over time, from a mean of 40.8 ± 11 mm m\(^{-2}\) to 22.1 ± 5.9 mm m\(^{-2}\) (p < 0.001) (Fig. 2), corresponding to a size reduction rate of −4.3 ± 4 mm m\(^{-2}\) year\(^{-1}\). In patients with over 10 years of follow-up, the mean STJ diameter was 17.3 ± 2.1 mm m\(^{-2}\) at 12 ± 1.2 years. Shunt, sex, age at repair or aortic arch side did not significantly influence STJ size.

4. Discussion

Dilatation of the proximal aorta is a common feature in patients with ToF and has been attributed to left-sided volume overload in the context of right-outflow obstruction and right-to-left shunt. A right-sided aortic arch, male sex or aortopulmonary shunts have been identified to be promoting factors for dilatation by some reports [3]. Nonetheless, in a series of patients operated at a mean age of 3.2 years, a previous shunt was not associated with larger aortic dimensions [5]. A dilated aortic root at the time of correction was a prominent characteristic in our study, corresponding with z-scores >3 at the annulus and aortic sinus, and >2.5 at the STJ level. We could not find a significant relationship of arch side, sex or previous shunts with persistent aortic dilatation. We have always tried to keep the duration of shunt insertion as short as possible to perform the repair before the age of 1 year, and this may explain why we could not determine an important influence of a shunt or the age at repair on aortic diameters, in contrast to other studies with repair well beyond 1 year of age [6].

The literature on remodelling and size evolution of the aortic root after early ToF repair is limited, and reports demonstrating size regression are scarce. In a long-term follow-up study of children who underwent repair before the age of 2 years in the 1970s, no aortic re-operations occurred during 17 years of follow-up, but the study focused merely on infants and small children with ToF have shown fibrosis, fragmentation of elastin, cystic medianecrosis both on biopsies and post-mortem specimens and wall changes similar to those seen in Marfan patients with aortic dilatation [9,10]. Increased peripheral and central vascular stiffness was found in a young patient group repaired before the age of 1 year, associated with increased aortic diameter, highlighting the importance of regular monitoring of aortic size during long-term follow-up of ToF [11].

4.1. Limitations of the study

As this was a retrospective study, based on echo tapes from routine outpatient clinic visits, it is possible that the maximal diameter of the root was not always recorded. Some of the size measurements may therefore be slightly underestimated. When aortic root imaging at the time of correction was lacking, we used the diameters extracted from a more complete echocardiographic recording at the outpatient clinic visit preceding repair. As this happened only in a minority of study patients, we do not believe this has influenced the data considerably. The small number of patients with a right aortic arch and with operations beyond 1 year of age might explain why statistical analysis did not discover a significant relationship between these factors and root size.

4.2. Conclusions

The originally dilated aortic root in ToF normalises in size at the level of the annulus and sinotubular junction within 7 years after early repair. Although this process seems delayed at the level of the aortic sinuses, significant regression of indexed root diameter over time was observed in the large majority of patients. These findings suggest that consistent early repair of ToF abrogates the enlargement of the aortic root and leads to regression of the aortic root dilatation. However, lifelong follow-up remains mandatory in all patients with repaired ToF in view of the possible intrinsic aortic wall changes.

References

presented on aortic valve replacement surgically corrected in tetralogy of Fallot. You report about? Well, I do not believe this. Hug aortas, but where do they come from? Do they come from these patients however, the absolute diameter of the aorta was not disturbingly large in any 4 cm, it is a 20% risk of death in a given year . But there is a cutoff point in the index of 2.75 cm/m² body surface area which doubles the risk of death from 4 to 8%. Baseline was 4%. And once it’s more than 4 cm, it is a 20% risk of death in a given year. These numbers were clearly exceeded in your infant group as an index; once we look at the index diameters in large aortas and the risk of death, rupture, dissection or any or all of these in noncongenitally diseased patients — and there is a study by the Yale group published in 2006, you didn’t cite that. But there is a cutoff point in the index of 2.75 cm/m² body surface area which doubles the risk of death from 4 to 8%. Baseline was 4%. And once it’s more than 4 cm, it is a 20% risk of death in a given year. These numbers were clearly exceeded in your infant group as an index; however, the absolute diameter of the aorta was not disturbingly large in any patient. But what makes us worrisome now are those reports of adult patients with huge aortas, but where do they come from? Do they come from these patients you report about? Well, I do not believe this. For instance, the report which made us most worrisome was the first series presented on aortic valve replacement surgically corrected in tetralogy patients. But these were only 16 patients in 1996 from the Mayo Clinic. They were patients who had undergone tetralogy correction at a mean age of 17 years, and they were operated for aortic valve disease at 30 years of age. And there is another series in Toronto from the Adult Congenital Cardiac Center. When they looked at their large group of tetralogy patients, they found 15% with an aortic enlargement with an index of 2.5 cm/m², but the mean age of these patients was 36 years.

So my question finally is two parts. As there have been only two patients in the Toronto group who have been re-operated at the age of 38 years, in one case 27 years after tetralogy repair: do we have to be very worried? Do we really have to be worried a lot for our currently operated infant patients? I think not! You have shown that we can be pretty sure that the dilatation we are worried about now in old post-repair tetralogy patients will not be the dilatation we will see in the patients who are timely operated as in your series. Dr Francois: Indeed I agree with you that we are talking probably about two different groups. The publications you mentioned from the Mayo Clinic and from Toronto indeed show a series of patients that have been operated very late and that showed already histological abnormalities in the aortic wall. Patients that we treated here are at most 2 years of age. There are some who are about 2 years of age who had quite long shunts for different reasons. But it seems quite convincing that the aorta is able to come down in size when you operate early enough and take away the volume load.

On the other hand, there have been some reports, not much, but I think two reports about intrinsic wall abnormalities already in infants or babies of about 6 months of age. So I think we have to be very careful in all these patients. That’s why we have to follow them up anyway. But if they don’t show histological abnormalities to start with, and you can take away the volume overload, you might prevent later aortic dilatation.

Dr Ziemer: Do you expect a second wave of redilatation once they are normal now? Dr Francois: Well, the size of the sinus does not give so much confidence. It remains bigger than normal. However, as I said, the patients we followed up a really long time, more than 10 years, 12 years old, continue to come down in size. But it remained a bit more elevated than normal.

So I think we have to be still careful about these patients, but it gives maybe some idea that we do something good starting to repair these patients early on.

Dr G. Ziemer (Tuebingen, Germany): In our current clinical practice, we see two sets of tetralogy patients, either those we operate early on primarily, as in your series, and we see those patients as GUCH patients either with symptoms or not. And they come either for right-sided valve insertion or for consultation regarding a more or less dilated aorta. The GUCH patients you only addressed indirectly while the infants you operated on at 3 months who already had a size. But it remained a bit more elevated than normal. However, as I said, the patients we followed up a really long time, more than 10 years, 12 years old, continue to come down in size. But it remained a bit more elevated than normal.

So I think we have to be still careful about these patients, but it gives maybe some idea that we do something good starting to repair these patients early on. Dr Francois: No, it is really interesting. But what could we find out. But what we could show is that patients that started off with a really big z-score, like 6 or so, came down quite quickly during the first 2 years.

But that was not especially a group that was operated on later on. So we had patients we operated on at 3 months who already had a z-score of 6 but then tended to come down very quickly after 2 years.