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Progressive Aortic Root Dilatation in Adults Late After Repair of Tetralogy of Fallot

Koichiro Niwa, MD; Samuel C. Siu, MD, SM; Gary D. Webb, MD; Michael A. Gatzoulis, MD, PhD

**Background**—Aortic valve or aortic root (AoRo) replacement is occasionally required because of AoRo dilatation and aortic regurgitation (AR) in repaired tetralogy of Fallot (TOF). We evaluated AoRo size and possible factors associated with its dynamic nature in adults with repaired TOF.

**Methods and Results**—Of 216 patients with TOF repair who underwent echocardiography in 1997, we identified 32 patients (mean age, 36±8.0 years) with AoRo dilatation, defined as ratio of observed to expected AoRo size by standard nomogram >1.5 (group A), and 54 TOF controls, matched for age with AoRo ratio <1.5 (group B), who underwent at least 1 previous echocardiogram in the preceding 10 years. Mean indexed AoRo size (cm²/m²) in 1997 was 2.5±0.5 in group A and 1.7±0.2 in group B (P<0.0001). AoRo rate of change (mm/year) from the first to 1997 study (mean interval, 5.2±3.8 years) was 1.7±3.8 in group A and 0.03±1.6 in group B (P=0.001). Patients from group A had a longer shunt-to-repair interval (P=0.048) with a higher prevalence of pulmonary atresia (P<0.0001), right aortic arch (P=0.03), moderate to severe AR (P=0.002), aortic valve replacement (P=0.02), larger cardiothoracic ratio (P=0.02), and increased left ventricular end-diastolic dimensions (P=0.002).

**Conclusions**—A subset of adult TOF exhibits ongoing dilatation of AoRo late after repair. This dilatation relates to previous long-standing volume overload of AoRo and possibly to intrinsic properties of AoRo and may lead to AR. Meticulous follow-up of AoRo after TOF repair is recommended. (Circulation. 2002;106:1374-1378.)

**Key Words:** tetralogy of Fallot ■ aneurysm ■ aorta ■ follow-up studies ■ heart defects, congenital

Aortic root dilatation is known to be a feature of tetralogy of Fallot (TOF). Increased aortic flow attributable to right to left shunting before repair is thought to be the underlying pathogenic mechanism.1–3 Aortic root dilatation is greater in patients with TOF and pulmonary atresia, particularly in those who have not undergone repair.1,3 Aortic root dilatation may lead to aortic regurgitation (AR), which in turn may necessitate surgery. Aortic valve or aortic root replacement was required in a relatively small number of adult patients with repaired TOF in a recent report from the Mayo Clinic.4 Increased aortic flow and previous trauma to the aortic root during initial TOF repair were thought to be responsible for AR in this surgical series. Furthermore, aortic root dilatation may predispose to aortic dissection and rupture. The aim of our study was to evaluate serially the aortic root in an adult cohort of tetralogy patients late after repair and analyze characteristics and possible predisposing factors for aortic root dilatation.

**Methods**

**Patients**

We reviewed echo data obtained from the 236 consecutive adult patients with TOF (age, 31±11 years) attending the outpatient clinic of the Toronto Congenital Cardiac Center for Adults (TCCCA) who underwent transthoracic echocardiography in 1997. A total of 218 of the 236 patients had previously undergone reparative surgery. Sixteen patients had undergone palliative surgery only or no previous surgery and were excluded from additional detailed analysis. Patients with previous TOF repair and AR secondary to surgical intervention (n=1) or infective endocarditis (n=1) were also excluded.

Of the remaining 216 patients, 32 (14.8%) had marked aortic root dilatation defined as a ratio of observed to expected aortic root size4 >1.5 (group A; dilators). For purpose of comparison, we identified a second subgroup of repaired TOF control patients, matched for age with group A (n=54, ratio of observed to expected aortic root size <1.5, group B; controls). Dilators and controls had undergone at least 1 previous echo study at the TCCCA between 1986 and 1996. None of them had congenital or acquired abnormalities of the left ventricular outflow tract, aortic valve, ascending aorta, or aortic arch. Demographic, morphological, surgical, and clinical details of the patients were obtained from medical records and clinic reviews.

Cardiothoracic ratio was calculated from posteroanterior chest x-rays in the standard manner.

**Definition of Aortic Root Dilatation**

Age, height, body weight, and sex are known to be determinants of aortic root dimensions in the normal heart.5–7 Therefore, we used standard nomograms for aortic root size at the sino-tubular junction from normal adults adapted from Roman et al,5 indexed by body surface area and age. Aortic root dilatation was defined as the ratio of observed to expected aortic root diameter >1.5.5

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Echocardiography

Echo data from the last clinic visit in 1997 and from the first available echo in the preceding 10 years (period 1986 to 1996) were reviewed by a single experienced observer. For the two patients who underwent aortic valve or root surgery during the study period, data from their last available preoperative echocardiography (1991 and 1994) were used for the analysis. Aortic root size was measured from M-mode or 2D echo tracings in accordance with the American Society of Echocardiography guidelines6 using a leading edge–to–leading edge measurement of the maximal diameter of the sino-tubular junction at end diastole in the long-axis parasternal view. Indexed aortic root size (cm/m²) was calculated as absolute aortic root size divided by body surface area. Aortic root rate of change was calculated as the difference on the aortic root size between the last and the first echo data set per individual patient divided by the number of intervening years (mm/year). Indexed aortic rate of change (mm/m² per year) was calculated as aortic rate of change mentioned above indexed for body surface area. Severity of aortic and pulmonary regurgitation was assessed by continuous and pulsed-wave Doppler characteristics and color flow mapping, as previously described,9 and was graded as absent to mild or moderate to severe. Right ventricular inlet size was considered when the right ventricular inlet measured >40 mm. Interobserver and intraobserver variability was determined by repeat measurements of aortic root size on a random sample of 20 TOF patients performed by an independent investigator.

Statistical Analysis

Data analysis was performed using the SPSS for Windows (Version 7.0, SPSS, Chicago, Ill). Descriptive data for continuous variables are presented as mean±SD or median with range when appropriate. In analyses of continuous data between the two groups, pairwise comparisons were performed with the use of the Wilcoxon rank-sum test. Discrete variables were analyzed by χ² tests. In each group, continuous data between the first and the last study were compared with the paired t test. P<0.05 was considered significant.

Interobserver and intraobserver variability in measuring aortic root size was expressed as correlation coefficients. Interobserver and intraobserver differences (mean±SD of the differences between paired measurements) were calculated. The ratio of the SD of the difference between paired measurements and the mean of the two measurements was also calculated as an additional measure of interobserver and intraobserver variability (expressed as percent).

Results

Patients

Patient characteristics, surgical details, and clinical data are shown in Table 1. Aortic valve replacement with aortic root surgery was performed in 2 patients from group A with severe AR; the first had aortic root size of 68 mm (4.3 cm/m²) at the age of 38 years (27 years after repair) and the second had aortic root size of 53 (2.7 cm/m²) at the age of 29 years (17 years after TOF repair), respectively.

There was no significant difference in age at repair, length of follow-up from repair, and time from the first to the last echo study between the two groups. Pulmonary atresia and a right aortic arch were more common in group A. Dilators had a longer time interval from palliation to repair and a greater male predominance.

Echo Data

Echo data on aortic root size from the 2 subgroups are detailed in Table 2. Observed to expected aortic root size for the whole group of 86 patients was 0.9 to 2.4, 1.4±0.3 at the

<table>
<thead>
<tr>
<th>TABLE 1. Patients' Characteristics and Operative Data</th>
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<tr>
<td>Sex, male:female</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Pulmonary atresia</td>
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<td>Right aortic arch</td>
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<tr>
<td>Absent pulmonary</td>
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<tr>
<td>Age at repair, y</td>
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<tr>
<td>Follow-up after repair, y</td>
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<tr>
<td>Shunt-repair interval, y</td>
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<tr>
<td>Aortic valve replacement and root repair</td>
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<tr>
<td>Aortopulmonary shunt</td>
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<td>Blalock-Taussig shunt</td>
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<td>Waterston shunt</td>
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<td>Potts shunt</td>
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<tr>
<td>Transannular patch</td>
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<td>Conduit repair (for pulmonary atresia)</td>
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<tr>
<td>Residual ventricular septal defect</td>
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<td>Blood pressure &gt;140/90</td>
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<td>Cardiothoracic ratio, %</td>
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Values are mean±SD (range) or n (%). Significant correlations are shown in bold.
first echo and 1.5±0.3, 1.0 to 2.7 at the latest (P=0.06). Indexed aortic root size and ratio of observed to expected aortic root size at both the first and the latest echo were significantly greater in group A, as expected. The absolute, indexed, and ratio of observed to expected aortic root size at the last visit had all changed significantly compared with the first echo study in group A (P<0.0001, Figure) but not in group B (P=0.43). In accordance, absolute and indexed aortic root rate of change were significantly greater in group A.

Echo data on parameters other than aortic root size from the 2 subgroups are detailed in Table 3. Moderate to severe AR was found in 4 patients in group A. Measured aortic root size of these 4 patients (range, 44 to 68 mm, 50.8±11.6 mm) was significantly larger compared with the remaining 28 patients from group A (38 to 53 mm, 45.0±3.7 mm, P=0.041). Mean left ventricular end-diastolic dimension in 4 patients with moderate to severe AR was not different from the remaining 28 patients from group A (49 to 61, 54.7±6.0 mm versus 41 to 60, 49.4±6.0 mm, P=0.14). There was no relation between age at repair and aortic root size (r=0.04, P=0.38) within group A. Aortic root size (mm) was 44 to 68, 48±5.8 in male patients and 40 to 48, 44±3.1 in female patients in group A (P=0.11) and 27 to 43, 36±5.1 in male patients and 27 to 38, 32±3.2 in female patients in group B (P=0.01). Interobserver and intraobserver differences on aortic root size were as follows: correlation coefficient, r=0.99 (SEE=1.1) and r=0.99 (SEE=0.9), with variability of 3.7±2.4% and 0.7±0.3%, respectively.

### Discussion

This study shows that a subset of adult patients with TOF exhibits ongoing dilatation of the aortic root late after repair, which may lead to aortic regurgitation necessitating aortic valve and root surgery. This aortic root dilatation relates to previous long-standing volume overload of the aorta and possibly to intrinsic properties of the aortic root itself.

### Aortic Root Size and Dilatation

Approximately 15% of adult patients with repaired TOF from this series had a dilated aortic root. Observed to expected aortic root size was 1.7±0.2 in repaired TOF patients with a dilated aorta and 1.2±0.2 in the remainder. Aortic root size was larger than in healthy controls (reported by Roman et al5), even in the subgroup of repaired TOF controls. Aortic root size markedly increased late after TOF repair in dilators compared with TOF controls. This dramatic change was far beyond any change expected in healthy controls attributed to increased age. Also, it cannot be attributed to intraobserver or interobserver variability, which was small.

This late progressive aortic root dilatation in adults with repaired TOF has not been previously reported.

### Potential Factors Relating to Late Aortic Root Dilatation in TOF

There was a relation between male sex, pulmonary atresia, right aortic arch, longer time interval from palliation to repair, and progressive aortic root dilatation. In contrast, there was no difference in age at repair or length of follow-up from repair between TOF dilators and the remainder. Progressive right ventricular outflow tract obstruction in unrepaired TOF, with the extreme form being pulmonary atresia, increases right to left shunt through the ventricular septal defect and in turn the volume overloaded effect on the aortic root.
In addition, left to right shunting attributable to palliative arterial shunts had a significant volume overload effect on the aortic root and the left ventricle, whereas left ventricular ejection fraction remained unchanged.\textsuperscript{13} Our data substantiate previous suggestions\textsuperscript{2–3} that long-standing volume overload of the aortic root may contribute to aortic root dilatation.

There is no gender predominance among patients with TOF.\textsuperscript{14} In contrast, there was a clear male predominance among patients with dilated aortic root in our study, even after indexing for body surface area and adapting for age from Roman et al.\textsuperscript{2} Aortic root size in healthy men is significantly greater than that of healthy women.\textsuperscript{5–7} This was also the case in our repaired TOF patients. Aortic elasticity and distensibility are known to decline with age; these changes occur earlier and are accelerated among men.\textsuperscript{15} This may also be applicable to TOF patients and may explain in part the male predominance among dilators.

Right aortic arch and absent pulmonary valve were more frequently observed among dilators. Right aortic arch has been reported in 25% of patients with TOF and is more common in patients with TOF and pulmonary atresia.\textsuperscript{14} Furthermore, right aortic arch, pulmonary atresia, or absent pulmonary valve syndrome are common morphological features among TOF patients with 22q11 deletion.\textsuperscript{16,17} This high incidence of right aortic arch (50%) and pulmonary atresia (19%) in our patients with marked aortic root dilatation and the relatively common coexistence of absent pulmonary valve syndrome may suggest a possible link between aortic root dilatation and chromosome 22q11 deletion. However, this is purely speculative and we do not have data on phenotypes or chromosomal analysis for our patients.

Cystic medial necrosis of the aortic root has commonly been found in Marfan syndrome, bicuspid aortic valve, and coarctation of the aorta.\textsuperscript{16,19} Patients with a dilated aortic root in TOF share similar histological changes of the aortic root, suggestive of cystic medial necrosis indistinguishable from the aortic root in patients with Marfan syndrome.\textsuperscript{19} Whether similar histological changes were harbored in our TOF patients with dilated aortic root remains unknown. Furthermore, whether aortic root dilatation is the result of long-standing volume overload of the aortic root or attributable to intrinsic aortic root abnormalities, or more likely both, needs to be additionally investigated.

**Aortic Regurgitation**

Aortic regurgitation (AR) with a dilated aortic root is common in unrepaired or repaired TOF with pulmonary atresia.\textsuperscript{1–3} In TOF with pulmonary stenosis, however, when other causes of AR such as infective endocarditis,\textsuperscript{20} surgical damage of the valve,\textsuperscript{2,4} and bicuspid aortic valve\textsuperscript{19,20} are excluded, significant AR is relatively uncommon.\textsuperscript{4,21} It has been reported that 15% to 18% of patients with repaired TOF had mild AR, and the cause of AR has been suggested to be aortic root dilatation.\textsuperscript{22} Dodds et al\textsuperscript{4} reported 16 patients with repaired TOF, aortic root dilatation, and AR who underwent aortic valve replacement, including 4 patients with aortic root replacement. Eleven of these 16 patients developed progressive AR despite an uncomplicated repair and follow-up. Two of them had TOF with pulmonary stenosis, and the remainder had TOF with pulmonary atresia. The authors speculated that AR might have been attributable to progressive dilatation of the aortic root after repair. In our study, mean aortic root size in the 4 patients with significant AR, all from the dilators group, was significantly larger compared with the remaining 28 patients from the same subgroup. Of note, only 1 of these 4 patients had TOF with pulmonary atresia; the remaining had TOF with pulmonary stenosis. Thus, our data support previous suggestions that progressive aortic root dilatation is the major cause of AR after repair of TOF. Furthermore, AR secondary to aortic root dilatation can occur both in patients with repaired TOF and pulmonary stenosis or repaired TOF and pulmonary atresia.\textsuperscript{4}

**Biventricular Size and Function**

The cardiothoracic ratio in the group of dilators was greater than in the reminder of TOF patients. Enlarged left ventricular size was observed by echocardiography in the group of dilators in keeping with increased cardiomegaly on chest radiography. There was no significant difference in left ventricular ejection fraction between these two groups, however. Furthermore, there was no relationship between left ventricular size and severity of AR in patients with a dilated aortic root. Our data suggest that left ventricular enlargement in our adult cohort of patients with repaired TOF and, in part, dilated aortic root may be attributable to previous long-standing left to right arterial shunts leading to volume overload and not attributable to a direct effect of AR.\textsuperscript{2}

**Prevention of Aortic Root Dilatation in TOF**

\textsuperscript{32} Blockers are the drug of choice for prevention of progressive aortic root dilatation in Marfan syndrome, especially in patients with an aortic root size >40 mm.\textsuperscript{23} Aortic root dissection has not been thus far reported in patients with

### Table 3. Echocardiographic Data: Other Parameters

<table>
<thead>
<tr>
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<th>Group A (n=32)</th>
<th>Group B (n=54)</th>
<th>P</th>
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<tbody>
<tr>
<td>AR: moderate to severe</td>
<td>4 (13)</td>
<td>0</td>
<td>0.0068</td>
</tr>
<tr>
<td>Left ventricular end-diastolic dimension, mm</td>
<td>49±6.6 (34–61)</td>
<td>45±5.0 (34–56)</td>
<td>0.0021</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>54±11 (35–76)</td>
<td>54±12 (23–78)</td>
<td>0.38</td>
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<tr>
<td>Tricuspid regurgitation: moderate to severe</td>
<td>9 (28)</td>
<td>12 (22)</td>
<td>0.52</td>
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<tr>
<td>Pulmonary regurgitation: moderate to severe</td>
<td>11 (34)</td>
<td>25 (46)</td>
<td>0.89</td>
</tr>
<tr>
<td>Right ventricular enlargement: moderate to severe</td>
<td>11 (34)</td>
<td>18 (33)</td>
<td>0.69</td>
</tr>
<tr>
<td>Right ventricular pressure: left ventricular pressure: &gt;0.5</td>
<td>4 (13)</td>
<td>6 (11)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Values are mean±SD (range) or n (%). Significant correlations are shown in bold.
repaired TOF, but, nevertheless, aortic root replacement was performed in 2 patients with dilated aortic root diameters of 47 to 68 mm.4 There is no consensus at present on β-blocker administration for prevention of progressive dilatation of the aortic root in repaired or un repaired TOF. Nor is there information on which patient and at what stage aortic root surgery should be considered. Progressive AR and aortic root dilatation >50 mm are widely accepted as criteria for aortic valve and aortic root surgery for patients with Marfan syndrome.24 Aortic root surgery may also be considered for patients with TOF and aortic root dilatation exceeding 55 mm,25 particularly when the primary indication for surgery is pulmonary valve implantation. However, this is a general recommendation, and available data to date are very limited.

Aortic root dilatation and rate of change were significantly greater in patients with dilated aortic roots in our study. This subset of TOF patients showed a male predominance and shared common morphological features, namely pulmonary atresia and right aortic arch, which may help identify patients at risk of progressive aortic dilatation, AR, and, possibly, with additional follow-up, aortic dissection. In our study and previous studies, patients underwent repair of TOF at a relatively old age (beyond the age of 10 years).2,3 Presently, repair of TOF is routinely performed under the age of 3 years and in many institutions during the first year of life, negating the need for palliative arterial shunts. This approach drastically reduces the period of volume overload of the aortic root and may have a future beneficial effect by limiting or preventing aortic root dilatation in such contemporary cohorts of patients with TOF undergoing early repair.

Limitations of the Study
Data on aortic root size before and early after TOF repair were not available. We have limited our retrospective analysis to a 10-year period to include contemporary echo data obtained by our own laboratory on patients followed-up at the TCCCA. Ascending aortic dilatation was not always available; therefore, we used the diameter of sino-tubular junction as our method of aortic root dilatation. Additional predictors of progressive aortic root dilatation may exist and be identified with a larger patient sample and longer period of observation in future studies. Furthermore, the potential effects of medical or surgical therapy in modifying the course of aortic root dilatation will need prospective assessment.

Conclusions
There is a subgroup of adult patients with TOF with progressive aortic root dilatation occurring late after repair. This dilatation relates to previous long-standing volume overload of the aorta and possibly to intrinsic properties of the aortic root and may cause important aortic regurgitation. Meticulous follow-up of the aortic root after repair of TOF is thus recommended.

Acknowledgments
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References