Prevalence and optimal management strategy for aortic regurgitation in tetralogy of Fallot

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\begin{abstract}
Objective: Aortic regurgitation (AR) in the tetralogy of Fallot (TOF) is not frequent, but when present it impacts significantly on surgical management. Furthermore, the incidence of late AR development has been increasing, along with surgical interest in current practices.

Methods: Pre- and post-operative studies on 427 patients (TOF, 374; TOF/PA (TOF with pulmonary atresia), 53) who survived corrective operation were reviewed. AR (\(\geq\) mild) was detected in 28.

Results: Nine had AR preoperatively, while 25 (including six with preoperative AR) exhibited AR post-operatively. In the 19 who developed AR post-operatively, the aortic root diameter (AoRoD) and indexed AoRoD (%AoRoD) were 42 \(\pm\) 11 mm and 166 \(\pm\) 36%, increased from the preoperative values of 30 \(\pm\) 10 mm and 149 \(\pm\) 24%. AR-free rate at 20 years was 95.1% of all cases studied, 84.3 vs 96.5% in TOF/PA vs classic TOF (\(P\) ! 0.0001), and 82.2 vs 97.0% in bulboventricular VSD vs infracristal VSD (\(P\) < 0.0001). Older age at repair, and bulboventricular VSD were identified as risk factors for the progression of AR. Aortic valvuloplasty (AVP; \(n = 5\)) or replacement (AVR; \(n = 4\)) was performed nine times in eight patients before (\(n = 1\)), during (\(n = 4\)), or late after TOF repair (\(n = 4\)); all showed improvement of NYHA class. Survival- and reoperation-free survival curves showed no significant difference between patients with or without AR.

Conclusions: After repair of TOF, careful observation for a late progression of AR is needed for the optimal timing of surgical intervention, especially in patients who repaired at higher age with a dilated aortic root or in patients with bulboventricular VSD.

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Keywords: Aortic valve replacement; Aortic valvuloplasty; Aortic regurgitation; Tetralogy of Fallot; Pulmonary atresia
\end{abstract}

1. Introduction

Although, a significant aortic regurgitation (AR) is relatively uncommon among patients with either the tetralogy of Fallot (TOF) or TOF with pulmonary atresia (TOF/PA), it has a significant impact on surgical management whether it is found at the time of initial repair or at the time of a late follow-up. A background involving increased trans-aortic flow with a right-to-left shunt is thought to indicate that in unoperated or palliated patients with TOF, aortic root dilatation and consequent AR is likely to progress in the long-term [1]. An anomaly of the aortic valve, a bulboventricular VSD, infective endocarditis, or surgical manipulation during the repair of a tetralogy can aggravate the AR acutely or chronically [2–5]. In addition, an increasing number of reports, involving a growing cohort of long-term follow-up patients, describe the incidence of late-developing AR in association with aortic root dilatation even after an uncomplicated repair of a tetralogy [6–8].

In this study, we retrospectively reviewed the long-term outcome of our medical and surgical management of AR in patients with either TOF or TOF/PA, before and after their intracardiac repair, in the hope of identifying an optimal management strategy for this combination.

2. Methods

A total of 427 patients (246 male and 181 female) survived surgical correction of TOF at our institution...
between 1968 and June 2003. Their age at operation ranged from 1 month to 60 years (8.0 ± 9.3 years, mean ± standard deviation). Fifty-three patients had pulmonary atresia, 102 had a history of Blalock-Taussig shunt, 68 patients had bulboventricular VSD, and 43 had a right aortic arch. The TOF repair was performed through a right ventriculotomy in 198, with no or a minimal ventriculotomy in 185, and with an external conduit in 44. In patients with bulboventricular type of VSD, the defect was closed through the pulmonary arteriotomy and limited right ventriculotomy (15 mm in length) even after we adopted trans atrial and pulmonary approach in 1978, and a transannular patch was applied, irrespective of the size of the annulus.

The examinations before the TOF repair and those at the latest follow-up were reviewed. The follow-up rate was 92%. The interval between TOF repair and the latest study was 1–36 (15 ± 9) years. The severity of the AR was assessed by echocardiography, by catheterization, or by both, with the quantitative descriptors of AR being none = 0, trivial = 1, mild = 2, moderate = 3, severe = 4 [9]. We recognized 28 patients as having mild AR before or after their TOF repair. In those patients who developed AR after TOF repair, the aortic root size was measured in the examination before TOF repair and again in the latest study or at reoperation. Measurement of aortic root size by echocardiography was obtained from M-mode or 2D echo tracings using a leading-edge to leading-edge measurement of the maximal diameter of the Valsalva sinus at end diastole in the long axis parasternal view [10]. Absolute values for aortic root size (AoRoD) were indexed with reference to the normal predicted value derived from an equation based on body surface area (%AoRoD) [11]. Aortic root size by cineangiography was taken as the average value of measurements obtained from the frontal view and the lateral view. Echocardiographic measurements were preferred to angiographic measurements if both were available.

2.1. Statistical analysis

Data analysis was performed using Statview for Windows (Version 5.0, SAS Institute Inc., Cary, NC). Data are expressed as the mean ± standard deviation, with statistical significance determined at the 95% confidence level. Univariate analysis was performed using either a Student’s t-test or χ²-test, as appropriate. Significant variables were then entered into a multivariate logistic regression analysis. The actuarial freedom-from-AR rate was estimated by the Kaplan–Meier method.

3. Results

3.1. AR before total repair

Mild, moderate, or severe AR was detected in nine patients (TOF, 5; TOF/PA, 4) at examination before intracardiac repair. The one patient with severe AR (due to infective endocarditis) required palliative aortic valve replacement (AVR) prior to the total repair, while four other patients with moderate (n = 4) AR received aortic valvuloplasty (AVP) concomitant with their intracardiac repair. The other four patients with mild AR underwent intracardiac repair without an aortic valve operation.

3.2. AR after total repair

Mild, moderate, or severe AR was detected in 25 patients (TOF, 16; and TOF/PA, 9) at examination after corrective surgery. Thirteen out of the 25 patients (52%) had a bulboventricular VSD. Six of the 25 had mild AR before surgery as were outlined above. In the other 19 patients, who developed AR post-operatively, the average interval between corrective surgery and the detection of AR was 12 ± 9 years. In these 19 patients, the AoRoD and %AoRoD were 42 ± 11 mm and 166 ± 36% at the latest follow-up or at reoperation, values significantly greater than those obtained before corrective surgery (30 ± 10 mm, 149 ± 24%). Table 1 shows those values, and for comparison, data from 20 randomly selected, age-matched patients without progression of AR. In the patients who developed AR, both AoRoD and %AoRoD were significantly larger than in those without AR (preoperatively as well as post-operatively). In the patients without AR, %AoRoD showed no significant increase after surgery. Preoperative %AoRoD exceeded 135 in 18 patients out of 19 who developed AR, while it exceeded 135 in only four out of 20 in control group without AR.

In all patients, the Kaplan–Meier freedom-from-AR rates were 96.3 and 95.1% at 10 and 20 years, respectively.

<table>
<thead>
<tr>
<th></th>
<th>AR(+)</th>
<th>AR(−)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Age at TOF repair (year)</td>
<td>9.1 ± 6.9</td>
<td>6.4 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis TOF: 11, TOF/PA: 8</td>
<td>17 ± 8</td>
<td>20 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Interval between the studies (year)</td>
<td>30 ± 10</td>
<td>23 ± 6</td>
<td>0.03</td>
</tr>
<tr>
<td>AoRoD before TOF repair (mm)</td>
<td>42 ± 11</td>
<td>30 ± 6</td>
<td>0.0008</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0000002</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>%AoRoD before TOF repair</td>
<td>150 ± 25</td>
<td>124 ± 16</td>
<td>0.003</td>
</tr>
<tr>
<td>%AoRoD at last study (mm)</td>
<td>167 ± 37</td>
<td>118 ± 16</td>
<td>0.000006</td>
</tr>
<tr>
<td>P-value</td>
<td>0.006</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Data are shown as mean ± standard deviation. AR, aortic regurgitation; TOF, tetralogy of Fallot; TOF/PA, TOF with pulmonary atresia; AoRoD, aortic root diameter; %AoRoD, indexed value of AoRoD; AR(+), patients who developed AR (≥ mild) post-operatively; AR(−), patients without progression of AR.
By group, the corresponding values were: (a) 87.6 and 84.3% in patients with TOF/PA vs 97.5 and 96.5% for all other patients ($P!0.0001$; log-rank test); (b) 89.0 and 82.2% in those with bulboventricular VSD vs 97.4 and 97.0% in those with perimembranous VSD ($P!0.0001$; log-rank test) (Fig. 1). Four patients who developed moderate-to-severe AR received an aortic valve operation at 20±11 years after their total repair, as described below.

The other 21 patients have been medically followed up for 15±9 years after repair, with mild AR in 19 and moderate AR in two.

3.3. Risk analysis

Potential risk factors for the progression of AR were analyzed using both univariate and multivariate analyses (Table 2). An older age at TOF repair, pulmonary atresia, bulboventricular VSD, and use of conduit at TOF repair were significant risk factors in the univariate analysis, whereas by the multivariate analysis, only older age at TOF repair and bulboventricular VSD remained associated with AR progression.

3.4. Aortic valve operation

Aortic valvuloplasty (AVP, $n=5$) or replacement (AVR, $n=4$) was performed nine times in eight patients (TOF, 4; TOF/PA, 4) for moderate ($n=5$) or severe ($n=4$) AR. These patients’ demographics and parameters are summarized in Table 3. The procedure used for the aortic valve operation was decided on the basis of preoperative echocardiography, intraoperative TEE, and direct inspection of the valve. In four patients who underwent aortic valve replacement, no attempt at valvuloplasty was made because of a dysplastic aortic valve leaflet or a reduced LV function. An aortic valve operation before the corrective surgery was performed in one patient with unoperated TOF/PA/MAPCAs without a central pulmonary artery (case 1). He fell into acute heart failure due to severe AR caused by infective endocarditis, and underwent a semi-emergency palliative AVR with the aid of balloon occlusion of MAPCAs and hypothermic circulatory arrest. This patient subsequently underwent bilateral unifocalization and also an intracardiac repair, including reconstruction of the central pulmonary artery, within one year after the palliative AVR.

Four patients (cases 2–5) underwent an aortic valve operation at the time of the corrective surgery, with AVP being selected for all four patients. Case 2 had a redundant noncoronary cusp with many verrucae on its edge, while case 3 had a prolapsed and thickened right coronary cusp with bulboventricular VSD. In these two patients, cusp plication at the commissure was performed [3]. The patient (case 4) with a marked annular dilatation and prolapse of a noncoronary cusp in TOF/PA/MAPCAs underwent cusp plication at the commissures and subannular aortic plication (Fig. 2). Case 5, who suffered from acute infective endocarditis, developed moderate AR and an occlusion of the right coronary orifice, and he underwent a semi-emergency repair of his tetralogy and coronary artery bypass grafting, together with vegetectomy and closure of the cusp perforation on the noncoronary leaflet. Although the early examination in this patient revealed only mild AR, he had chest pain on exertion in the fourth year and his AR progressed to severe in degree. He therefore underwent AVR. Including this patient, four patients underwent aortic valve operation at a late time after repair of their tetralogy (mean interval, 20±11 years). AVR was performed in three patients (cases 5, 7 and 8) with severe AR. Case 8 had a rare coexistent anomaly, a ruptured sinus of Valsalva from RCC to the pulmonary trunk. Her sinus of Valsalva aneurysm was repaired by patch closure through an aortotomy at the time...
of TOF repair. A mechanical prosthesis was chosen for every patient who underwent AVR. In case 6, an annular dilatation and redundant noncoronary cusp were observed. So, cusp plication and subannular plication were performed in the same manner as in case 4. In cases 5, 6, and 8, a revision of the right ventricular outflow reconstruction was carried out in conjunction with the aortic valve operation.

The diameter of the aortic sinuses was more than 40 mm at the time of the aortic valve operation in seven out of the eight patients. One patient (case 4) with a maximum diameter of 50 mm received a reduction of the aortic dilation by lateral aneurysmorraphy. An additional right lateral thoracotomy was employed for a safe redo sternotomy in case 7 (maximum ascending aortic diameter, 60 mm) whose situation was complicated by severe adhesion underneath the sternum together with an anterior protrusion of the thorax.

The predominant etiology of the AR, besides an aortic root dilatation inferred from preoperative study and operative findings, was considered to be infective endocarditis in four (acute, 2; healed, 2), cuspal prolapse with bulboventricular VSD in two, and repaired Valsalva sinus rupture in one.

### 3.5. Patient outcomes and survivals

Among the 28 patients in whom AR (S mild) was detected before or after TOF repair, there was one late death. This was a witnessed sudden death in a patient with mild AR and moderately reduced LV function (Dd/Ds =

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### Table 3
Summary of data on eight patients who underwent aortic valve operation

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Age at op (year)/sex</th>
<th>Interval between op and TOF repair (year)</th>
<th>Diagnosis</th>
<th>Degree of AR</th>
<th>AoRoD (mm)</th>
<th>Procedure of aortic valve operation</th>
<th>Concomitant procedures</th>
<th>Follow-up (year)</th>
<th>NYHA class preoperative/post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve operation before total repair</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23/M</td>
<td>0.9</td>
<td>TOF/PA/ MAPCAs, acute IE</td>
<td>Severe</td>
<td>46</td>
<td>Palliative AVR (SJM 31)</td>
<td>Balloon occlusion of MAPCAs, circulatory arrest</td>
<td>3</td>
<td>IV/I</td>
</tr>
<tr>
<td>Aortic valve operation concomitant with total repair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16/F</td>
<td>(−)</td>
<td>TOF, healed IE</td>
<td>Moderate</td>
<td>25</td>
<td>AVP (cusp plication)</td>
<td>TOF repair via RVotomy</td>
<td>30</td>
<td>III/I</td>
</tr>
<tr>
<td>3</td>
<td>34/F</td>
<td>(−)</td>
<td>TOF, PDA, subarterial VSD, healed IE</td>
<td>Moderate</td>
<td>43</td>
<td>AVP (cusp plication)</td>
<td>TOF repair via RVotomy</td>
<td>25</td>
<td>III/I</td>
</tr>
<tr>
<td>4</td>
<td>26/F</td>
<td>(−)</td>
<td>TOF/PA/ MAPCAs, s/p bilateral unifocalization</td>
<td>Moderate</td>
<td>46</td>
<td>AVP (cusp plication + annular plication)</td>
<td>TOF/PA repair with PA reconstruction, Asc Ao aneurysmorraphy TOF repair CABG to RCA</td>
<td>5</td>
<td>III/II</td>
</tr>
<tr>
<td>Aortic valve operation after total repair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>36/M</td>
<td>4</td>
<td>TOF, s/p vegetectomy (see above) TOF/PA</td>
<td>Severe</td>
<td>41</td>
<td>AVR (SJM 25)</td>
<td>Infundibulectomy, RVOT patch</td>
<td>9</td>
<td>III/II</td>
</tr>
<tr>
<td>6</td>
<td>29/M</td>
<td>21</td>
<td>TOF/PA</td>
<td>Moderate</td>
<td>47</td>
<td>AVP (cusp plication + annular plication)</td>
<td>ReRVOTR with valved conduit (reRVOTR previously)</td>
<td>3</td>
<td>II/I</td>
</tr>
<tr>
<td>7</td>
<td>44/M</td>
<td>29</td>
<td>TOF/PA, PDA, s/p bilateral BT shunt</td>
<td>Severe</td>
<td>60</td>
<td>AVR (sorin bicarbon 25)</td>
<td>Median sternotomy + right thoracotomy (reRVOTR previously)</td>
<td>1</td>
<td>IV/II</td>
</tr>
<tr>
<td>8</td>
<td>43/F</td>
<td>24</td>
<td>TOF, subarterial VSD, ruptured aneurysm of Valsalva sinus, single coronary artery</td>
<td>Severe</td>
<td>49</td>
<td>AVR (sorin bicarbon 25)</td>
<td>ReRVOTR with valved conduit</td>
<td>1</td>
<td>III/I</td>
</tr>
</tbody>
</table>

IE, infective endocarditis; NYHA, New York Heart Association; RCA, right coronary artery; RVOT, right ventricular outflow tract; RVOTR, RVOT reconstruction.
72/56) at the age of 46 years (some 26 years after his TOF repair). The actuarial survival curves and the reoperation-free survival curves shown in Fig. 3 reveal that there was no significant difference in prognosis between the patients with AR and those without AR. All those who underwent an aortic valve operation are doing well at the mean follow-up period of 10 ± 11 years after their aortic valve operation, and all show improvement in their New York Heart Association (NYHA) functional class after surgery. Their AR status after surgery remains mild except for one who required AVR 4 years after vegetectomy.

3.6. Study limitations

The limitations of this study are primarily related to the retrospective nature of the analysis and to the limited number of patients. In addition, the assessment of AR and the measurement of aortic root size in angiograms and echocardiograms is subjective, and may involve bias and an observational error due to a poor image.

4. Discussion

In 1979, one of the present authors reported five patients who showed an association of AR with TOF or TOF/PA at the time of initial repair [3]. Since then, with the growing number of patients studied after TOF correction, it has increasingly been recognized and reported (and is also our experience) that the progression of an aortic dilatation and development of AR late after correction may be determining factors in the patients’ morbidity and mortality [6–8]. Recently, we experienced a series of patients after TOF repair who required an aortic valve operation, and this stimulated us both to reinvestigate the prevalence of AR in patients with TOF and to try to elucidate the optimal management strategy for this combination.

The etiology of AR before corrective surgery is based on the enlargement of the aortic root due to the increased trans-aortic flow resulting from the presence of a right-to-left shunt. The associated presence of infective endocarditis, a prolapse of the right coronary cusp, the bulboventricular type of VSD, or rarely, inherent abnormalities of the aortic valve cusps can accelerate the progression of AR [1–5]. In this study, the incidence of preoperative mild AR was 2% (9/427), almost the same as in our previous report (5/300) [3]. Recent reports on the initial repair of TOF have seldom addressed the phenomena associated with AR, possibly due to the younger age at operation and to an enlightened, preventive approach to infective endocarditis [12–14]. However, in unoperated adult patients, the incidence of AR is higher, and the AR tends to be progressive and has been ascribed to faulty coaptation of inadequately supported aortic cusps due to root dilatation, which is most pronounced in TOF/PA patients [1]. Marelli et al. reported that the incidence of moderate or severe AR among 26 cyanotic patients with TOF/PA at ages from 18 to 55 years was as high as 77%, which alerted us to the destiny of patients with this condition who have no corrective surgery [15].
With regard to AR late after corrective surgery, an increasing number of reports describe a post-operative, ongoing aortic root dilatation and late progression of AR, along with the increasing number of patients with a repaired TOF. Niwa et al. reported that 32 out of 216 (15%) adult patients with a repaired TOF showed progressive dilation of the aortic root, and four of them (2%) had significant AR [8]. The observation in our study that in patients who developed AR after corrective surgery, the post-operative %AoRoD was significantly larger than the preoperative value, whereas patients without AR did not show a significant increase in %AoRoD, supports the existence of an interaction between aortic root dilatation and the development of AR. Moreover, the larger values for preoperative AoRoD and %AoRoD in patients with AR than in those patients without AR suggests that those with a larger aortic root before TOF repair (%AoRoD > 135) have a propensity to develop AR post-operatively. There have been several reports describing histologic abnormalities of the aortic wall media (such as elastic fiber fragmentation or cystic medial necrosis) in patients with a dilated aortic root after TOF repair [7,16]. However, further investigations will be needed to determine whether such findings represent a preexisting abnormality or the results of prolonged hemodynamic stress [17].

Multivariate risk-factor analysis for the development of AR identified age at repair and bulboventricular VSD. In our study, the patients who developed post-operative AR underwent repair of TOF at the age of 9.1 ± 6.9 years. Contemporary approach of early repair during the first year of life provides chronological reduction of volume overload of the aortic root, thereafter drastic beneficial effect on preventing aortic root dilatation as well as late development of AR may be expected. An association of bulboventricular VSD with TOF is common among Asians [3,18]. Its relationship with the development of AR was first described by Bahnson [19], and was noted in a recent analysis of a similarly sized patient cohort from Japan [20]. The results of our study also warrant classifying those patients as distinct subgroup among TOF patients. Greater attention to technical considerations at the time of the initial repair as well as more careful observation should be mandatory.

Evidence-based criteria to support the surgical indications for AR and/or a dilated aortic root in TOF patients are yet to be established. The recommendation based on data from adult patients with acquired heart disease is that surgery is indicated when the patient shows the presence of overt symptoms, increasing significant LV dilatation with or without dysfunction, or both, in the setting of moderate or worse AR, or when the patient has a dilated aortic root with a diameter of more than 55 mm [21]. Dodds et al. [7], the largest series to date dealing with AR and dilated aortic root in repaired TOF, reported 16 patients who showed moderate or severe AR with an aortic root diameter (AoD) of at least 40 mm. Those patients all underwent prosthetic valve replacement with or without aneurysmorrhaphy of the ascending aorta. Our policy is to employ aortic valvuloplasty unless organic valve deformity is dominant. Application of subcommissural annular plication is likely to be a useful option for patients with a dilated aortic annulus. Although this is as yet a small series, the results are encouraging. At the time of surgery, specific maneuvers for adequate myocardial protection, use of a temporary period of low-flow hypothermic cardiopulmonary bypass, and treatment of associated lesions in the right ventricular outflow tract or tachyarrhythmias are advocated for optimal results.

Our results show no significant difference in the actuarial survival curves and reoperation-free survival curves between patients in whom AR was detected before or after TOF repair and the remaining patients, which is probably because the AR detected in most patients in this study was mild. However, they may be at risk for left ventricular dysfunction or an ascending aortic aneurysm in the future. Serial follow-up studies are important to monitor the development of AR.

In conclusion, we believe that surgical intervention should be considered when significant AR is associated with TOF at the time of primary repair, as well as at late follow-up. AVP may be an important option unless organic valve deformity is dominant. Careful follow-up for a late progression of AR is needed for the optimal timing of surgical intervention, especially in patients with either a dilated aortic root or bulboventricular VSD.

References


