Long-term results of correction of tetralogy of Fallot in adulthood


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Abstract

Objective: The natural history of tetralogy of Fallot (TOF) allows that a minority of patients reach adulthood without any treatment, representing mild forms of the disease. The aim of this study is the long-term evaluation of patients with TOF surgically treated in adulthood, in order to define its real benefit.

Methods: Between November 1982 and January 2001, 39 patients older than 18 years of age with tetralogy of Fallot underwent total correction. Mean age was 26.6 years (range 18–67) and 21 patients (53.8%) were females. A previous modified Blalock–Taussig shunt was performed in four patients (10.3%). Fifteen patients (38.5%) were in NYHA functional class III or IV. Mean hematocrit was 53.6 ± 10% and the mean gradient across the right-ventricular outflow tract was 93.9 ± 24.8 mmHg. The operation was performed via transtrial/transpulmonary approach in 16 patients (41%) and six patients (15.4%) required transannular patch. Pulmonary valvotomy was necessary in 13 patients (33.3%) and pulmonary valve replacement with bioprosthesis in 3 patients (7.7%).

Results: Hospital and late mortality were 5.1 and 7.7%, respectively. The mean follow-up was 45.1 months (range 1–194 months). Actuarial survival was 91.2 ± 4.9%, 85.5 ± 7.2% and 68.4 ± 16.3% at 3, 7 and 15 years, respectively. In the latest follow-up, 27 (79.4%) of the survivals are presently in NYHA functional class I (P < 0.001). Echocardiography has shown moderate/severe pulmonary insufficiency in 9 patients (26.5%), moderate pulmonary stenosis in 3 patients (8.8%) and residual ventricular septal defect in 4 patients (11.8%). Arrhythmias were identified in 38.9% of patients with symptoms suspicious of rhythm disturbances. There was impairment of right-ventricular function in 13 patients (38.2%). Three patients were reoperated on to close residual ventricular septal defects in two patients and for pulmonary valve replacement in one patient.

Conclusions: The overall survival of surgically treated adult patients with TOF is acceptable. The great benefit of the complete repair at this age is the functional improvement. On the other hand, late complications closely related to chronic hypoxia, such as arrhythmia and ventricular dysfunction might direct for a more careful follow-up after the surgical correction.

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Keywords: Tetralogy of Fallot; Cyanosis; Congenital heart disease

1. Introduction

Epidemiological studies and autopsy records demonstrated that approximately 2% of all patients with tetralogy of Fallot (TOF) reach the fourth decade of life [1]. Adult patients often represent unrecognized diagnosis related to problems in the health system, or due to mild forms of the disease with no exuberant clinical suspicion.

Nevertheless, the natural history of the chronic hypoxia that characterizes TOF is responsible for cerebral complications, myocardial dysfunction, and propensity to ventricular arrhythmias. Previous studies [2–6] have addressed this issue, especially in regard to the treatment approach. Indication for corrective surgery in this specific population remains controversial, due to doubtfully beneficial effects. The aim of this study is the long-term evaluation of patients with TOF surgically treated in adulthood, in order to define its real benefit in terms of morbidity and survival.

2. Materials and methods

From November 1982 to January 2001, 39 patients older than 18 years of age were submitted to total correction of tetralogy of Fallot at Heart Institute, University of São Paulo Medical School, São Paulo, Brazil. All available data on hospital charts for preoperative, surgery and postoperative periods were retrospectively analyzed. The follow-up was
obtained through periodic consultations with echocardiographic assessment in our service, as well as through family contacts. Patients already submitted to total correction at younger ages were excluded.

Table 1 describes the demographics of all patients. There were 22 females (56.4%) and 17 males (43.6%), with a mean age of 26.6 ± 11.1 years (median 24; range 18–67 years). Twenty-four patients (61.5%) were in NYHA class II, 12 patients (30.8%) in class III and 3 patients (7.7%) in class IV. The clinical presentation was predominantly through syncope in nine patients (23.1%) and arrhythmias in 5 patients (12.8%). Four patients (10.3%) had had major stroke, 3 patients (5.1%) hemoptisis and 1 patient (2.6%) endocarditis. Types of arrhythmia identified were atrial fibrillation in three and non-sustained ventricular tachycardia in two. At initial presentation, the mean arterial saturation was 84.8 ± 9.9% (median 88%; range 56–95%), and the mean hematocrit was 53.6 ± 10% (median 54%; range 35–75%).

The diagnosis was confirmed by bidimensional echocardiography in all patients. The mean gradient across the right-ventricular outflow tract was 93.9 ± 24.8 mmHg (median 95; range 40–134 mmHg). Cardiac catheterization was performed in 31 patients (79.5%). It offered valuable hemodynamic information, as well as excluded coronary artery disease in patients older than 35 years of age. Almost everyone had equalized right- and left-ventricular pressures.

Associated anomalies were identified in 14 patients (35.9%): severe tricuspid regurgitation (n = 2), pulmonary valve agenesis syndrome (n = 2), hypoplastic branch pulmonary arteries (n = 1), atrial septal defect (n = 3), partial anomalous pulmonary venous connection (n = 1), mitral regurgitation (n = 1), aortic regurgitation (n = 1), patent ductus arteriosus (n = 1) and right coronary–right ventricle fistulae (n = 2). One of the patients with pulmonary valve agenesis syndrome had extrinsic compression of the left-main coronary artery with documented left-ventricular ischemia. Four patients (10.3%) have been submitted to modified Blalock–Taussig shunts previously, in a mean of 25 years before the complete repair, ranging from 16 to 45 years.

Other co-morbidities were present in three patients: coronary artery disease in one, non-insulin dependent diabetes mellitus in one and hypothyroidism associated with hepatic cirrhosis in the last.

3. Surgical techniques

All patients were submitted to standardized techniques of anesthesia and cardiopulmonary bypass. The routine use of epsilon aminocaproic acid or aprotinin and cell saver were important in order to minimize the postoperative bleeding. Median sternotomy with aortic and bicaval cannulation were performed. All the Blalock–Taussig shunts were dissected out before administration of heparin, and then they were divided just after cardiopulmonary bypass has been commenced. The procedure was carried out under moderate systemic hypothermia and intermittent antegrade cold crystalloid cardioplegia was the method of myocardial protection. The left side of the heart was vented by direct suction through the foramen ovale. In patients with extensive bronchial collaterals, even lower temperatures were employed (around 20 °C). Limited periods of low-flow cardiopulmonary bypass allowed better surgical exposure, especially in patients that required branch pulmonary artery reconstruction.

3.1. The intracardiac portion of the repair

The preferred surgical approach was transatrial/transpulmonary. Unfortunately, the latter was performed in only 16 patients (41%). In 23 patients (59%), the right ventriculotomy was necessary to ensure complete resection of muscle bundles and to complete the ventricular septal defect closure in extremely difficult and particular cases. Obstructing parietal muscle bundles were dissected off of the ventricular infundibular fold and transected away from the ventricular septal defect and aortic annulus, toward the right-ventricular free wall. A large wedge of muscle was usually resected from this location, particularly because of severe hypertrophy of these obstructive muscle bands. Obstructing muscle bundle extensions from the infundibular septum along the septal aspect of the right-ventricular outflow tract usually were also resected. A great amount of endocardial fibrosis was usually identified, sometimes making the infundibular resection hazardous. The ventricular septal defect was closed in all patients with a bovine pericardium patch trimmed appropriately to shape. Interrupted pledgged polypropylene sutures were rigorously used to sew in the patch.

3.2. The pulmonary artery portion of the repair

After resection of obstructing muscle bundles in the right-ventricular outflow tract, the pulmonary valve was probed using graded dilators. If the pulmonary valve

Table 1
Preoperative characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>26.6</td>
</tr>
<tr>
<td>NYHA class III or IV N%</td>
<td>15 (38.5)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>53.6 ± 10</td>
</tr>
<tr>
<td>RV-PA mean gradient (mmHg)</td>
<td>93.9 ± 24.8</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>84.8 ± 9.9</td>
</tr>
<tr>
<td>Syncope N%</td>
<td>9 (23.1)</td>
</tr>
<tr>
<td>Arrhythmias N%</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Stroke N%</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Hemoptisis N%</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Endocarditis N%</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Previous Blalock–Taussig shunt N%</td>
<td>4 (10.3)</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association classification for heart failure, RV-PA—right-ventricular to pulmonary artery.
was too small, a longitudinal incision was made in the main pulmonary artery in order to inspect the pulmonary valve. Full commissurotomies were performed in 13 patients (33.3%) and then the pulmonary valve was probed again. A bovine pericardium transannular patch with a porcine monocusp was required in six cases (15.4%) when the predicted valve annulus size was still under 20 mm of diameter. The reconstructive procedures of the pulmonary artery and right-ventricular outflow tract are demonstrated in Table 2. Excluding those patients with transannular patch, the reconstruction of the right ventriculotomy was performed with a diamond shaped bovine pericardium patch in 17 patients (43.6%). Pulmonary valve replacement with bioprosthesis was done in three patients (7.7%) with decent annulus size, although dysplastic pulmonary valves. Two patients had specific features that deserve mention. One had absent pulmonary valve syndrome, and was submitted to pulmonary valve replacement associated with plication of aneurysmal dilatation of the main and right-pulmonary arteries. The other patient had discontinuous pulmonary arteries, with the left-pulmonary artery arising directly from the aortic arch. Besides the complete repair of TOF, this patient was submitted to left-pulmonary artery reimplantation into the main pulmonary artery, followed by extensive pericardial patch reconstruction.

Associated procedures were performed in 8 patients (20.5%), consisting of tricuspid valve repair \( \left( n = 2 \right) \), mitral valve replacement associated with myocardial revascularization \( \left( n = 1 \right) \), repair of partial anomalous pulmonary venous connection \( \left( n = 1 \right) \), coronary artery fistulae ligation \( \left( n = 1 \right) \), aortic valve repair \( \left( n = 1 \right) \), patent ductus arteriosus ligation \( \left( n = 1 \right) \) and atrial septal defect closure \( \left( n = 1 \right) \).

Median cardiopulmonary bypass and cross-clamp times were 109 min (range 68–225) and 80 min (range 40–128), respectively.

After weaning off from cardiopulmonary bypass, a routine direct measurement of the right- and left-ventricular systolic pressure ratio was helpful to rule out significant right-ventricular outflow tract residual obstruction.

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>( N(%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infundibular resection</td>
<td>34 (87.2)</td>
</tr>
<tr>
<td>RVOT patch</td>
<td>17 (43.6)</td>
</tr>
<tr>
<td>Pulmonary valvotomy</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Transannular patch</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Pulmonary valve replacement</td>
<td>3 (7.7)</td>
</tr>
</tbody>
</table>

RVOT, right-ventricular outflow tract.

4. Statistical analysis

Statistical analysis was performed with software Statview, Berkeley, CA. Numeric variables were expressed in median, mean and standard deviation. The \( \chi^2 \) test was performed to compare categorical variables. The level considered to be statistically significant was less than 5%. Probability of survival after operation was calculated by Kaplan–Meier method, with 95% confidence limits.

5. Results

Early and late mortality were 5.1% (2 patients) and 7.7% (3 patients), respectively. Causes of early death were multiple organ failure in one patient and anoxic encephalopathy in the other. The former was in NYHA functional class IV with right-ventricular failure and history of chronic atrial fibrillation. He has been submitted to complete repair through right ventriculotomy and he developed cardiogenic shock, pulmonary edema and acute renal failure unresponsive to appropriate treatment. The latter has been submitted to surgical repair with pericardial transannular patch. In the first postoperative day, he had massive hemorrhage due to dehiscence of the patch. This patient was resuscitated and explored for bleeding. After a prolonged period of hypotension, irreversible brain damage was diagnosed and he died on the fourth postoperative day.

Median ICU and hospital stay were 2 and 8 days, respectively. Reoperation for bleeding was performed in 4 patients (10.3%) and 3 patients (7.7%) required prolonged mechanical ventilation. The majority of patients had relatively uncomplicated postoperative courses. Inotropic support was usually provided with low doses of dopamine or dobutamine and extubation was usually possible in the first 12–48 h after surgery.

The mean follow-up was 45.1 ± 54.7 months (median 28.9 months; range 1–194 months). Actuarial survival was 91.2 ± 4.9%, 85.5 ± 7.2% and 68.4 ± 16.3% at 3, 7 and 15 years, respectively (Fig. 1). Three patients died during late follow-up, and all deaths were cardiac-related. The first patient has been submitted to implant of a transannular patch and developed free pulmonary insufficiency, chronic atrial fibrillation, right-ventricular failure, with impairment of the left-ventricular function also. Nine years after the initial procedure, he presented with end-stage heart failure, and multiple organ failure. The second patient had moderate pulmonary insufficiency due to the presence of a transannular patch implanted 43 months before. Ventricular arrhythmia was the cause of death. At autopsy, signs of severe right-ventricular dilatation were identified. The third patient was in the status-post classic Blalock–Taussig shunt 45 years before the complete repair, and had history of ventricular arrhythmias preoperatively. The TOF repair included a pulmonary valve replacement, associated with coronary artery bypass grafting and mitral valve replacement associated with myocardial dysplastic pulmonary valves. Two patients had
replacement. This patient had a turbulent postoperative course related to biventricular dysfunction, prolonged ventilatory support, acute renal failure and sepsis, leading to multiple organ failure and death after 4 months.

In the latest follow-up, 27 (79.4%) of the 34 survivals are presently in NYHA functional class I (Fig. 2). Improvement in functional class compared to the preoperative period was considered statistically significant ($P < 0.001$). Late echocardiographic assessment revealed residual defects in 10 patients (29.4%). They consisted of moderate/severe pulmonary insufficiency in 9 patients (26.5%), moderate pulmonary stenosis in 3 patients (8.8%) and residual ventricular septal defect in 4 patients (11.8%). In 13 patients (38.2%) with documented impairment of right-ventricular function by echo, and clinically compensated heart failure, gated ventriculography was done. That showed a mean RV ejection fraction of 44.6 ± 11.7% (median 45%; range 25–60%). The left ventricle was also examined, with a mean ejection fraction of 51.3 ± 12.1% (median 48%; range 32–69%).

Fig. 1. Actuarial survival (Kaplan–Meyer) in 39 adult patients with tetralogy of Fallot submitted to complete repair.

Eighteen patients (52.9%) presented arrhythmia-related symptoms and they were submitted to further evaluation with Holter electrocardiography. It showed normal results in 11 patients, supraventricular arrhythmia in two patients and ventricular ectopic beats or nonsustained ventricular tachycardia in five patients. Electrophysiologic studies with radiofrequency ablation were performed in four patients.

Three patients underwent reoperation at 1, 3 and 7 years after total correction. Two patients were submitted to patch closure of residual ventricular septal defects; one had severe tricuspid regurgitation, repaired at the same time. One patient underwent pulmonary valve replacement with bioprosthesis, due to severe pulmonary insufficiency and early signs of right-ventricular failure.

6. Discussion

The operative correction of tetralogy of Fallot has been performed for more than 40 years [7], and the long-term outcome and quality of life have been considered excellent [8]. The predominant trend in the timing of surgical procedure has been toward earlier intervention with elective repair within the first 4–6 months of life [9], although others have advocated earlier repair in symptomatic neonates [10]. Nevertheless, all treated patients continue to be at risk for long-term morbidity [11]. An increasing number of adults with repaired TOF are having late complications such as arrhythmias, heart failure and sudden death [12].

A small subset of patients with TOF present later in life with unsuspected or untreated disease. Tetralogy of Fallot in adults represents a special group with peculiar problems related to the effects of prolonged cyanosis over the heart and other organs. Therefore, there are continuous stimuli for right-ventricular hypertrophy, polycythemia, coagulation defects, and the development of extensive bronchial collaterals. The incidence of hemorrhage and neurological complications in adults is definitely higher when compared to children. Long-standing pressure overload and abnormalities of myocardial mechanical and electrical functions due to chronic hypoxia are the substrate for ventricular arrhythmias and heart failure. Moreover, some of those patients underwent previous palliative shunts that often cause morphological and physiological consequences namely shunt thrombosis, congestive heart failure, pulmonary artery distortion, or pulmonary vascular disease. The natural history illustrates the importance of a complete preoperative assessment. Cardiac catheterization is an important tool in the management of tetralogy of Fallot in adulthood, not only to characterize anatomically the pulmonary arteries but also to demonstrate unexpected abnormalities of clinical relevance or even to perform therapeutic interventions. Indeed, it may simplify surgical management, as demonstrated by Rammohan et al. [6], who performed coil occlusion of major aortopulmonary collateral arteries in 15% of patients.
Older age has been considered as incremented risk factor for surgical mortality and long-term survival in patients with TOF [13,14]. Based on this assumption, indication for surgery after long-standing cyanosis has caused controversy [15]. Inevitably, the undesired preoperative conditions favor for a more complicated postoperative course. The surgical mortality in the literature [4–6] is not irrelevant, ranging between 2.5 and 16%. Dittrich et al. [4] defined as predictors for higher surgical risk in this patient population the presence of severe cyanosis, right- and left-ventricular dilatation, elevated end-diastolic pressures and significant tricuspid regurgitation.

Besides the aforementioned opposite arguments, the few reports [2,5,6] that studied this issue have proved some benefit in repairing adults with TOF. Nollert and coworkers [2] found excellent long-term survival up to 35 years after the surgical repair, being comparable to the life expectancy of the general population. This comes in accordance with our results, since the actuarial survival at 15 years was almost 70%. Most importantly, a significant functional improvement after total repair was observed in this paper, and that was the most beneficial effect of this procedure. Presbitero and coworkers [16] had the same experience, with a marked improvement in functional class, and the long-term survival was superior to the group with medical treatment only.

The surgical correction has many particularities in this population. The marked right-ventricular hypertrophy requires an adequate myocardial protection. Ventricular septal defect should be closed rigorously with interrupted reinforced sutures. The use of anti-fibrinolysis drugs is justified due to a higher bleeding tendency. Temporary periods of low-flow hypothermic cardiopulmonary bypass might help in extensive pulmonary artery reconstructive procedures, as required.

The type of reconstruction of the right-ventricular outflow tract is a matter of controversy in the literature and whether the procedure may affect survival, long-term complications and reoperation rates. Obviously, the preferred approach to relieve the right-ventricular outflow tract obstruction is infundibular resection with or without pulmonary valvotomy. In the adult population, usually the diameter of the pulmonary annulus is of adequate size, since those patients have been able to survive for decades without any intervention. Interestingly, our data supported this concept in only 41% of patients, when the ventriculotomy was avoided. Frequently, TOF in adults is associated with extensive right-ventricular hypertrophy and large amount of endocardial fibrosis. In this instance, a satisfactory infundibular resection may be sometimes demanding, and difficult to accomplish without a small ventriculotomy. That was the case in 59% of our patients. Transannular patch is required more often in children than in adults, in view of a more favorable anatomy encountered in adulthood. Our surgical approach was in accordance with previous studies [4–6,15,16], which demonstrated the need for transannular patch in approximately 40% of adult patients. Postoperative pulmonary valve insufficiency is common sequelae of this approach.

Some surgical groups [17] with high experience in dealing with congenital heart disease in the adult are postulating the routine pulmonary valve replacement with bioprosthesis in this age group, since the pulmonary insufficiency is less tolerated than in children. This fact was documented in our series since two of the late deaths had severe right-ventricular dilatation and dysfunction, which were the substrate to the development of ventricular arrhythmia. In the beginning of our experience, the indication for pulmonary valve replacement was very conservative. May be, those deaths could have been avoided if earlier pulmonary valve replacement had been performed. Bioprosthesis has offered high freedom from reoperation [11,18] and it is considered superior to mechanical prosthesis [19] or homografts [20]. Our preference in more recent patients has been bioprosthesis or cryopreserved homografts in younger patients. The rationale for this approach is based on the establishment of a competent right-ventricular outflow tract, potentially alleviating right-ventricular hypertrophy.

Furthermore, the long-term survival can be jeopardized by impairment of left-ventricular function [21]. Possible mechanisms include myocardial fibrosis following longstanding cyanosis and altered contraction of the interventricular septum due to the presence of a prosthetic patch. In addition, the collateral circulation from the systemic to pulmonary arteries, particularly present in the adult population, causes chronic ventricular overload. In our data, all three late deaths had signs of end-stage heart failure, with biventricular involvement. This is probably the subgroup of patients that the surgical correction has doubtful benefit in improving survival [4].

As pointed out earlier, adult patients with untreated TOF had a higher propensity to arrhythmias, and the most prevalent ones are the ventricular ectopic beats and ventricular tachycardia. More recently, the association between chronic ventricular volume overload identified by QRS prolongation and ventricular arrhythmias and the risk of sudden death has been reported [22]. Atrial fibrillation and flutter, as well as supraventricular tachycardia can be present especially in large right-atrium chambers.

There is controversy in the literature whether the repair can reduce this risk, since the operation itself could be a detrimental risk factor for the development of newer ventricular foci or atrial fibrillation. Most of the evidence in the literature pointed out the benefits of timely repair of any significant pulmonary or tricuspid valve dysfunction. On the other hand, the risk of arrhythmia is not completely avoided since either ventriculotomy scars or the margins of closed ventricular septal defects may play a role in the genesis of this problem. Intraoperative cryoablation or the use implantable cardioverter defibrillators in high-risk patients, as possible, should be helpful.
6.1. Limitations of the study

This is a retrospective study in design. Echocardiography has limitations in the assessment of right-ventricular function due to inaccuracies in inferring its geometry and unpredictability of its dilatation and by the possibility of regional dysfunction. Every right ventriculotomy with or without a patch may alter the echocardiographic evaluation. A more sensitive approach with MRI has been documented [23]. The functional improvement observed did not take into account the exercise tolerance test, which is more sensitive than the NYHA classification. In the follow-up, only patients with palpitations or arrhythmia-related symptoms had further investigation through Holter electrocardiography or electrophysiologic studies, leading to selective bias.

6.2. Conclusions

The overall survival of surgically treated adult patients with TOF is acceptable. The greatest benefit of complete repair at this age is the functional improvement. On the other hand, late complications closely related to chronic hypoxia, such as arrhythmia and ventricular dysfunction might direct for a more careful follow-up after the surgical correction.

Acknowledgements

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