Total Correction of Tetralogy of Fallot in the First 60 Days of Life in Symptomatic Infants: Is It The Gold Standard?

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► early age
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Abstract

Background The timing of surgical repair of tetralogy of Fallot (TOF) is a key to alleviate complications and for long-term survival. Total correction was usually performed at the age of 6 months or older under the notion of decreasing the surgical risk. However, avoiding palliation with an aortopulmonary shunt and early correction of systemic hypoxia appear to be of more benefit than the inborn surgical risk in low body weight patients. Our objective was to assess early/midterm survival and operative complications and to analyze patients, surgical techniques, and morphological risk factors to determine their effects on outcomes.

Patients and Methods We retrospectively reviewed 152 patients with TOF who were ≤60 days of age when they underwent total correction of TOF. All patients had either duct-dependent pulmonary blood flow or arterial blood oxygen saturation less than 65% on room air requiring urgent surgical correction. Exclusion criteria included TOF with pulmonary atresia, TOF with nonconfluent pulmonary arteries, TOF with multiple aortopulmonary collateral arteries, and associated complete atrioventricular septal defects.

Results The mean age at repair was 34 ± 19 days, and the mean weight was 3.8 ± 0.9 kg. Before surgery, 96 patients received an infusion of prostaglandin, 45 were mechanically ventilated, and 32 required inotropic support. Right ventricular outflow tract obstruction was managed with a transannular patch in 112 patients, and all the others had a main pulmonary artery patch. Cardiopulmonary bypass (CPB) with moderate hypothermia was the standard, and the CPB time averaged 48 ± 21 minutes. The postoperative intensive care unit stay was 5.7 ± 6 days, with 2.8 ± 4 days of mechanical ventilation. Early mortality was 4.6% (7 of 152), and actuarial survival rates were 95% at 1 year and 92% at 5 years. Univariable and multivariable analyses of the patients' demographics, anatomical characteristics, and operative techniques revealed the presence of small pulmonary arteries and low body weight to be the only independent risk factors for death.

Conclusion Early total correction of TOF during the first 60 days of life can be performed with low mortality and good intermediate-term survival and, from our point of view, “should be the gold standard for TOFs.”
Introduction

Etienne Fallot was the first to publish a full description of the tetralogy of Fallot (TOF) in 1888, whereas the first surgery for TOF was performed by Alfred Blalock in 1945 soon after several systemic-to-pulmonary shunts were being used. In 1954, the first successful intracardiac repair was performed using human cross-circulation at the University of Minnesota by Lillehei and Varco.

Kirklin et al in 1955 reported the use of the first mechanical pump-oxygenator system for the total correction of TOF. Castaneda et al and Barratt-Boyes and Neutze were among the first to perform early primary repair of TOF in symptomatic neonates in the absence of anatomical contraindications or major noncardiac comorbidities. Di Donato et al 1991 first reported their experience with the neonatal repair of TOF at Boston Children’s Hospital.

This approach gained wide acceptance, and thus early primary repair was extended to symptomatic neonates while achieving low operative mortality.

Since then, there were two strategies for management of TOF: shunt followed by total correction or the one-stage total correction. Different surgical centers and surgeons adopt and prefer one strategy more than the other.

Advocates of a two-stage strategy prefer it because it avoids the risks of cardiopulmonary bypass (CPB) in low body weight patients and leads to fewer transannular patch repairs in the second stage. However, early primary repair has the advantage of avoiding potential complications of shunt surgery, such as distortion of the pulmonaryies and occurrence of pulmonary hypertension. In addition to early correction of systemic hypoxia, avoiding progressive right ventricular hypertrophy, early normalization of flow and pressures in all chambers, and earlier return to the normal rate of growth.

Controversy rages over the most preferred surgical option for symptomatic patients with TOF in the first 2 months of life; however, there is evidence that early correction of congenital heart disease is associated with less damage to the heart and other organs.

In the light of advances achieved in anesthesia, preoperative management, and operative techniques, CPB, as well as postoperative intensive care management, we preferred early total correction of TOF in the first 2 months of life. The purpose of this study was to assess early/midterm survival and operative complications and to analyze the data of those patients, surgical techniques, and morphological risk factors to determine their effects on outcomes.

Patients and Methods

Between January 1, 2008, and December 1, 2016, 152 patients (younger than 60 days of age) underwent total correction of TOF. We retrospectively reviewed those patients' data after approval from the ethical committee, and informed consent was waived for its retrospective design. They were all operated upon in a single tertiary center at Cairo University Hospital in Egypt over a period of 9 years. All patients had either duct-dependent pulmonary blood flow or arterial blood oxygen saturation less than 65% on room air requiring urgent surgical correction. As we have advanced surgical armamentarium for neonatal surgeries, we preferred to perform one-stage total repair of Fallot. Exclusion criteria included TOF with pulmonary atresia, TOF with nonconfluent pulmonary arteries, TOF with multiple aortopulmonary collateral arteries, and associated complete atrioventricular septal defects. Preoperative preparation included plain chest X-ray, electrocardiogram (ECG), echocardiography, and multislice computed tomography (CT) in some patients.

There were 83 boys and 69 girls, the average age at operation was 34 ± 19 days (range: 12–59 days), and the mean weight was 3.8 ± 0.9 kg (range: 3.1–4.7 kg). Before surgery, 96 patients received an infusion of prostaglandin E, 45 were mechanically ventilated, and 32 required inotropic support (Table 1).

Surgical Technique

Total repair was performed using CPB through a median sternotomy. After routine aortic and bicaval cannulation, with moderate systemic cooling down to 30°C, aortic cross-clamping was performed and a single dose of cold blood cardioplegia of 25 mL/kg was given. Right atriotomy was performed, and retractors were used to expose the right ventricle (RV) infundibular obstruction, which was relieved by excision of any os infundibulum and division of the parietal and septal extensions of the infundibular septum. The ventricular septal defect was then closed by a 0.4-mm polytetrafluoroethylene (PTFE) patch (Gore-Tex, WL Gore & Associates, Flagstaff, AZ) using a single continuous Prolene 5/0 stitch through the tricuspid valve. Testing of the tricuspid valve was performed, and a commissural stitch was taken if needed to avoid tricuspid regurgitation. The main pulmonary artery (MPA) was then opened longitudinally.
and sizing of the right pulmonary artery (RPA) and left pulmonary artery (LPA) was performed using Hegar dilators. Commissurotomy of the pulmonary valve was performed, and the adequacy of the pulmonary annulus size was compared with the minimal acceptable pulmonary annulus size. If the pulmonary annulus was found to be too small (less than expected Hegar size), then the MPA arteriotomy was extended to the annulus into the RV. And if the RPA and/or LPA was/were found to be smaller than their expected size, an autologous pericardial patch was used and extended to the RPA and/or LPA. Any atrial septal defect or patent foramen oval was then closed. Pressures in the RV and left ventricle (LV) were measured after going off CPB using a direct needle puncture, and the right ventricular outflow tract obstruction (RVOTO) repair was considered to be adequate when RV/LV pressure ratio was <0.75 and weaning from CPB was smooth.

### Statistical Analysis

A multivariable analysis of the following risk factors was performed: age in days at the time of the operation, weight, RPA and LPA z-scores, aortic cross-clamp time, total CPB time, and time to extubation and total hours of intensive care unit (ICU) stay. Values are presented as mean ± standard deviation or as numbers and proportions, as appropriate. The relations between qualitative variables were evaluated using chi-square test or Fisher’s exact test, as indicated. Means were compared using Student’s t-test, and survival after surgery was analyzed using the Kaplan–Meir method. Variables that were statistically significant in univariate analysis were introduced in a forward stepwise Cox regression analysis model to detect independent predictors of survival. All tests were two-sided for two-sided hypothesis, and a p-value of 5% was the limit of statistical significance. Analysis was performed using statistical package software IBM SPSS for MAC, version 24.

### Results

RVOTO was managed with a transannular patch in 112 patients, and all the others (40 patients) had an MPA patch. CPB with moderate hypothermia was the standard, and the CPB time was 48 ± 21 minutes and the ischemic time was 37 ± 14 minutes. The postoperative ICU stay was 5.7 ± 6 days, with 2.8 ± 4 days of mechanical ventilation (Table 2).

Hospital mortality within 30 days of surgery was 4.6% (7 out of 152). Two patients died of right ventricular failure on postoperative days 9 and 13, two had severe chest infection in the form of bronchopneumonia ending in septicemia and died on postoperative days 17 and 21, and two patients died of cardiac dysfunction and multiorgan failure on postoperative days 24 and 27. One patient died of arrhythmia and did not respond to cardiopulmonary resuscitation on postoperative day 11 (Table 3).

### Morbidity

Delayed sternal closure was performed on 13 (8.5%) patients between 2 and 5 days postoperatively. One of those patients developed mediastinitis and was cured and discharged from the hospital on day 25 postoperatively. Junctional ectopic tachycardia (JET) was the commonest arrhythmia occurring in 35 patients (23%), whereas the second commonest was supraventricular tachycardia (SVT) occurring in 19 patients (12.5%). Diaphragmatic plication was performed in 11 patients (7.2%) due to diaphragmatic paralysis (Table 4).

The rate of plication is high as we adopt early intervention for diaphragmatic paralysis.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed sternal closure</td>
<td>13 (8.5%)</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>1 (0.65%)</td>
</tr>
<tr>
<td>JET</td>
<td>35 (23%)</td>
</tr>
<tr>
<td>SVT</td>
<td>19 (12.5%)</td>
</tr>
<tr>
<td>Diaphragmatic paralysis</td>
<td>11 (7.2%)</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>2 (1.3%)</td>
</tr>
</tbody>
</table>

Abbreviations: JET, junctional ectopic tachycardia; SVT, supraventricular tachycardia. Note: Values are presented as mean ± standard deviation or as numbers and proportions, as appropriate.
Late Outcome, Cardiac Catheterization, and Reoperations

The mean follow-up was 3.4 ± 2.3 years (range: 5 months to 9 years). Cases of late mortality after 30 days postoperatively outside the hospital were five (3.4%) during the first year. One patient had sudden death (might be arrhythmia), two had severe pneumonia, and two died of uncertain causes.

Six patients required cardiac catheterization and pulmonary artery dilatation or stenting: four cases of LPA stenosis and two cases of RPA stenosis that needed stents. The average time to catheterization was 378 days, ranging from 72 to 1,371 days.

Actuarial survival rates were 95% at 1 year and 92% at 5 years (Fig. 1, Table 5). Analyses of the patients’ demographics, anatomical characteristics, and operative techniques in the univariable study revealed that both lower body weight and smaller size of the pulmonaries are independent risk factors for death; however, in the multivariate study, smaller size of the pulmonaries was found to be the independent risk factor for death. All other risk factors were found to be insignificant in relation to mortality.

Discussion

The classic approach for treating TOF was the two-stage repair with a systemic to pulmonary shunt followed by complete repair at a later stage. In 1992, Kirklin et al suggested that primary repair of TOF at less than 3 months of age was associated with high mortality. Then several centers advocated one-stage total repair of TOF in young infants with improving results. In several other reports, one-stage repair for young infants has been published with excellent early outcomes. Despite the growing clinical evidence that early total correction of TOF can prevent later complications associated with long-standing RV hypertrophy, concerns regarding the safety of implementation of primary repair in the first 60 days of life remain. A review of Fallot correction from 1973 to 1988 showed 18.5% hospital mortality. A 26-year retrospective study showed a decline in mortality from primary correction in all age groups from 11.1% before 1990 to 2.1% after 1990, followed by two studies reporting 3% mortality for primary repair in neonates and infants. In 2010, the Society of Thoracic Surgeons database showed that the discharge mortality for TOF neonates was 6.2% for palliation with aortopulmonary shunts and 7.8% for total repair. However, excellent results were later reported for total repair in neonates down to 0% hospital mortality.

Late complications such as sudden death have been reported with the two-stage TOF repair and may be related to time-dependent factors that occur prior to repair, leading to myocardial damage. Several researchers highlighted that those pathological changes eventually caused permanent heart damage; meanwhile, there was a lower incidence of ventricular arrhythmias among those repaired at younger ages.

Early relief of RV hypertrophy and fibrosis is of major significance in preventing the occurrence of RV dysfunction and arrhythmias later in life. Seliem et al in their study demonstrated the effect of early relief of RVOTO on RV morphology in relation to time and age of repair. They showed that RV wall thickness and wall thickness to transverse dimension ratio has remarkably decreased in those patients who underwent total repair in the first 6 months of

| Table 5 Actuarial survival rate till 5 years postsurgery |
|-----------------|---------|--------|---------|
| Mortality       | Survival rate (%) | Patients at risk |
| First 30 d      | 95.4    | 145    |
| 1–2 mo          | 94      | 143    |
| 2–9 mo          | 93.4    | 142    |
| 9–12 mo         | 92.7    | 141    |
| 12–48 mo        | 92.1    | 140    |
life in contrary to those who did the repair later as those did not show significant changes in these findings.

Concerns regarding the safety of CPB in the first 2 months of life were argued. Turley et al.\textsuperscript{27} in their study have compared the incidence of occurrence of CPB-related complications in neonates undergoing total repair versus those undergoing palliative procedures in a variety of congenital heart diseases and have found that CPB per se was not an independent determinant of survival; nevertheless, effective repair in conjunction with proper pre- and postoperative management was a critical determinant of survival.

Formerly, the need for a transannular patch was considered a contraindication for total correction in young infants, and its safety in neonates has remained a point of concern. Seliem et al.\textsuperscript{26} Hennein et al.\textsuperscript{28} and Shanley et al.\textsuperscript{29} in their studies have shown that this risk factor has been neutralized.

Our study mortality (4.7%) compares well with that in the study by Kwak et al.\textsuperscript{5} and that of Kolcz and Pizarro (4.3%), which are all in the acceptable range.\textsuperscript{11,21} although Kanter et al.\textsuperscript{22} and Tamesberger et al.\textsuperscript{10} reported 0% hospital mortality. This might be attributed to their number of cases which were 20 and 25 respectively while the number of cases in this series was 152.

The morbidity was significant as well with delayed sternal closure in 12 cases, but this is expected in low body weight infants undergoing any CPB surgery because the myocardium gets edematous and the sternum cannot be closed except after a couple of days. However, this did not cause any significant increase in mediastinitis, which occurred in only one patient.

Arrhythmia is a well-noted complication, but both JET and SVT did not affect the outcome of the patients, and only one patient needed a permanent pacemaker insertion. Those complications are well within the acceptable rate.\textsuperscript{19}

In addition, shunt surgery is less likely to save the pulmonary valve annulus and is generally no longer considered as a safe option, especially that early total repair can be safely performed for symptomatic TOFs in the first 60 days of life.\textsuperscript{30}

The financial environment of medicine encourages maximization of the patient benefit relative to the cost. An analysis performed by Ungerleider et al.\textsuperscript{31} demonstrated that there was a significant reduction in the hospital’s total costs with one-stage TOF repair compared with two-stage repair.

**Conclusion**

In conclusion, we believe that avoiding two surgeries, first for palliation and then for total correction, is an added benefit for symptomatic TOFs in their first 2 months of life. Furthermore, early total correction of TOF during the first 60 days of life can be performed with low mortality and good intermediate-term survival and should be the gold standard for TOFs.

Longer follow-up, especially for the right ventricular function and the degree of pulmonary regurgitation, is required to assess the long-term benefits of early surgical repair.

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None.

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We do not receive any funding from any source.

**Conflict of Interest**

None.

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