Repair of Tetralogy of Fallot in Neonates and Young Infants

Frank A. Pigula, MD; Philipe N. Khalil, MD; John E. Mayer, MD; Pedro J. del Nido, MD; Richard A. Jonas, MD

Background—The timing of repair of tetralogy of Fallot (TOF) remains controversial. Advantages to early complete repair include removal of right ventricular outflow tract obstruction, alleviation of systemic hypoxia, and avoidance of palliation with an arteriopulmonary shunt.

Methods and Results—This is a retrospective review of 99 children with TOF pulmonary stenosis (TOF/PS) or TOF pulmonary atresia (TOF/PA) who were <90 days of age undergoing early complete repair. Fifty-nine were prostaglandin E dependent, and 91% of neonates were symptomatic at the time of repair. Univariate and multivariate analyses of patient characteristics, anatomic features, and operative management showed the diagnosis of TOF/PA and smaller body surface area to be the only independent risk factors for death. Early mortality was 3% (3 of 99), and actuarial survival rates were 94% at 1 year and 91.6% at 5 years. Freedom from catheterization was 86% at 1 year and 73% at 5 years. Patients repaired for TOF/PA had a significantly lower freedom from reoperation than did those repaired for TOF/PS.

Conclusions—Early complete TOF repair can be accomplished with a low mortality. Children with TOF/PA repaired had a lower freedom from reoperation than those with TOF/PS. Longer follow-up, with emphasis on arrhythmias and right ventricular function, is required to define the long-term benefits of early repair. (Circulation. 1999;100[suppl II]:II-157–II-161.)

Key Words: tetralogy of Fallot ■ surgery ■ pediatrics

The optimal surgical management of neonates and infants with tetralogy of Fallot (TOF) remains controversial. Evidence suggests that early repair of congenital heart disease minimizes the secondary damage to the heart and other organ systems.1-5 This realization, along with significant advances in anesthetic, operative, and postoperative management, has been the stimulus for early primary repair of TOF. However, although early surgical repair has been adopted in many centers, a 2-staged repair (arteriopulmonary shunt with subsequent repair) remains favored by some.

Advantages of early anatomic correction include removal of the stimulus for right ventricular hypertrophy, alleviation of cyanosis, and preservation of myocardial mechanical and electrical function. In addition, this approach avoids the risks of pulmonary artery shunting with its inherent risks, namely shunt thrombosis, congestive heart failure, pulmonary artery distortion, or pulmonary vascular disease. Since DiDonato et al 6 first reported the Boston Children’s Hospital experience with neonatal repair of TOF, early repair has been the institutional standard for these patients. The purpose of this retrospective review is to describe our subsequent experience with early (<90 days of age) complete repair of tetralogy of Fallot.

Methods
Between January 1, 1988, and December 31, 1996, 99 neonates and young infants (age <90 days) underwent complete repair of TOF with pulmonary stenosis (TOF/PS, n=73) and pulmonary atresia (TOF/PA, n=26). Data were obtained from the cardiac database and review of medical records. Preoperative diagnosis and evaluation routinely included echocardiographic examination. When preoperative evaluation suggested confluent pulmonary arteries of adequate size and lack of hemodynamically significant aortopulmonary collaterals, early repair constituted usual management. Some children underwent repair at >3 months of age when diagnosis or referral was delayed or for other logistical reasons. Cardiac catheterization was applied occasionally to clarify coronary anatomy, to better define pulmonary artery anatomy, or to identify aortopulmonary collaterals. Patients identified with nonconfluent pulmonary arteries, absent pulmonary artery syndrome, associated AV canal defect, or significant aortopulmonary collaterals are not included in this review.

There were 55 boys and 44 girls, with an average age at operation of 32.9±26.7 days (median, 27 days; range, 2 to 87 days; Table). Fifty-nine were prostaglandin E dependent. Fifty-seven of these children underwent repair in the neonatal period, and 91% were considered symptomatic on the basis of cyanosis with or without hypercyanotic “spells.” Of the 42 patients repaired between 31 to 87 days of age, 76% were symptomatic.

The surgical technique has been reported previously.7 Operative management used deep hypothermia (18°C to 25°C) with either low-flow cardiopulmonary bypass or circulatory arrest. The use of circulatory arrest was reduced in later years as the advantages of low-flow cardiopulmonary bypass became apparent.8 Repair included transannular patch (61 TOF/PS, 9 TOF/PA), homograft reconstruction (5 TOF/PS, 17 TOF/PA), or infundibular patch (7 TOF/PS). The ventricular septal defect was closed through a right ventriculotomy in 96% of the patients (96 of 99). Median length of follow-up was 4 years (range, 1 to 8.8 years).

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Circulation is available at http://www.circulationaha.org

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Statistical Analysis
A multivariate analysis of the following risk factors for death was undertaken: age at operation, birth and operative weights, body surface area, pulmonary artery Z scores, duration of circulatory arrest, myocardial ischemic time, postoperative arrhythmias, and time to extubation. Time in the intensive care unit and hospital, reoperation, and the need for subsequent cardiac catheterization with pulmonary artery or conduit dilatation or stenting were reviewed. Inotropic requirements at 24 hours were converted to inotropic equivalents for purposes of comparison. Data are expressed as mean ± SD or median (range). The Kaplan-Meier method was used to estimate probabilities of survival, catheterization, and reoperation. Univariate and multivariate analyses were performed by use of the Cox proportional-hazards model for survival and catheterization. A value of P<0.05 was considered statistically significant.

Results

Hospital Mortality
There were 3 hospital deaths (3%, 3 of 99), all within 30 days of operation. One patient (TOF/PA) died of an apparent arrhythmia after a pulmonary artery line was removed, 1 (TOF/PS) died of right heart failure on postoperative day 6, and 1 (TOF/PS) died on postoperative day 24 of progressive cardiac dysfunction and multisystem organ failure.

Late Mortality
Late mortality (out of hospital and ≥31 days after operation) consisted of 5 late deaths. One patient (TOF/PA) died suddenly 3 months after operation, 1 (TOF/PA) died at 3 months with findings of pneumonia at autopsy, 1 (TOF/PA) died at 1 year from a seizure disorder, 1 (TOF/PA) died at 1 year from uncertain causes 3 months after right ventricle to pulmonary artery conduit change, and 1 (TOF/PS) died at 1 year from chronic lung disease.

Actuarial survival rates were 94% at 1 year and 91.6% at 5 years (Figure 1). Multivariate analysis showed diagnosis of TOF/PA and smaller body surface area to be independent risk factors for death. Not found to be significant risk factors for mortality were age at surgery (≤ 1 or ≥1 month of age), sex, weight, pulmonary artery or pulmonary valve size, circulatory arrest time, cross-clamp time, cardiopulmonary bypass time, and inotropic requirements.

Surgical Morbidity
Eight children had delayed sternal closure 4 to 16 days after correction. There were no cases of mediastinitis. There were 3 diaphragmatic plications for paralyzed diaphragms and respiratory impairment 30 to 64 days after operation.

Postoperative arrhythmias occurred in 29 patients (29%), with junctional ectopic tachycardia (JET, 48.3%) and supraventricular tachycardia (17.2%) being the most common diagnoses. There were no deaths directly attributable to these arrhythmias.

Catheterization
Twenty-two patients (13 of 73 TOF/PS, 9 of 26 TOF/PA) required subsequent intervention with cardiac catheterization and pulmonary artery or homograft conduit dilatation or stenting. The time to catheter intervention averaged 434 days (median, 288 days; range, 57 to 1570 days), and there were on average 1.9±1.4 (range, 1 to 5) interventions per child. Although univariate analysis showed diagnosis of TOF/PA, smaller pulmonary artery Z scores, and age ≥1 month were risk factors for catheter intervention, these became statistically insignificant in multivariate analysis. Freedom from catheter intervention was 86% at 1 year and 73% at 5 years (Figure 2).

Reoperations
Excluding chest closures, there were 25 reoperations in 22 children between 1 month and 5 years 10 months. Fifteen children undergoing repair in the neonatal period required reoperation, as did 7 children repaired in early infancy (P=NS). Among all patients (TOF/PS and TOF/PA), freedom from reoperation for any cause was 90% at 1 year, 83% at 2 years, and 72% at 5 years (Figure 3). However, repair of TOF/PA usually requires homograft placement to reconstitute right ventricle to pulmonary artery continuity. These homografts are expected to require reoperation because the child inevitably outgrows them. Although freedom from reoperation is analyzed as a function of diagnosis, ie, TOF/PS versus TOF/PA, the 1-, 2-, and 5-year freedom from reoperation was 94%, 88%, and 81% for TOF/PS but only 79%, 69%, and 50% for TOF/PA (P=0.01, Figure 4).

Morbidity directly ascribed to the TOF repair included 3 presumed phrenic nerve injuries necessitating diaphragmatic plication between 30 to 60 days after operation and a single pacemaker at 2 months for heart block. Nine TOF/PA

Figure 1. Actuarial survival for TOF patients.

Figure 2. Freedom from catheter intervention for TOF patients.

Figure 3. Freedom from reoperation for any reason among all TOF patients.
children required 11 reoperations for replacement of right ventricular to pulmonary artery homografts (9 and 10 months and 1, 1.5, 2, 2.5, 3, 4, 4.25, 4.5, and 5 years).

Four patients (2 TOF/PS, 2 TOF/PA) required extension of the right ventricular outflow tract (RVOT) patch, 2 required some form of pulmonary enlargement (1 TOF/PS, 1 TOF/PA), 2 (TOF/PS) required reoperation for progressive muscular RVOT obstruction, and 2 (TOF/PS) had late atrial septal defect closures.

Discussion

Although the first successful TOF repair was accomplished >40 years ago, surgical controversies remain. Foremost among these is the timing of repair. Traditional practice has incorporated a 2-stage repair, consisting of early arteriopulmonary shunting, followed by later repair.10–12 As a result of advances in neonatology, anesthesia, and surgery, this “later” repair has come progressively earlier in life. The successful repair early in life by Barratt-Boyes et al13 and Castaneda et al14 in the 1970s has led to the adoption of primary complete TOF repair as a neonate or infant at some centers.

Late complications (including sudden death) have been recognized after 2-stage TOF repair and may be related to time-dependent events occurring before repair that permanently damage the myocardium. Several investigators have suggested that these pathological changes lead to permanent heart damage and have found a lower incidence of ventricular arrhythmias among children repaired at younger ages.4–17 Furthermore, Sullivan et al18 and Hegerty et al19 have shown a relationship between age at repair and an abnormal accumulation of fibrous tissue thought to contribute to right ventricular dysfunction.

It is important to emphasize that these changes appear to be time dependent, resulting from the anatomic substrate that defines TOF. Castaneda et al20 have suggested that 1 of these defining features, right ventricular hypertrophy, results from RVOT obstruction that increases with time. This hypertrophy then often requires surgical resection, establishing a potential substrate for the genesis of ventricular arrhythmias. Supporting these authors’ contentions, Murphy et al21 has found mortality to be related to older age at operation.

In addition to direct myocardial effects, others have suggested that early repair minimizes secondary damage to other organs, primarily the brain, resulting from chronic hypoxia.1,2,5 Thus, the impetus for earlier repair is a natural extension of these concerns, as well as the recognition that neonatal surgery can be performed with acceptable mortality and morbidity.

Since 1988, 99 children have undergone early TOF repair (<3 months of age) at Boston Children’s Hospital with a hospital mortality of 3%. This mortality is consistent with other corrective neonatal cardiac procedures (ie, arterial switch operation and interrupted aortic arch) and is comparable to mortality documented in older children undergoing 2-stage TOF repair.17,22,23 Because the in-hospital mortality was a low 3% (3 of 99), no statistical inferences could be drawn. Among late deaths, 2 resulted from lung disease and 1 from a seizure, demonstrating that these children can be burdened with noncardiac comorbidities.

Despite low hospital mortality, postoperative arrhythmias did occur in 29% of our patients. The development of arrhythmias (predominately JET and supraventricular tachycardia) was unrelated to age at operation but was associated with the level of inotropic support required at 24 hours (the Table). Although our incidence of JET (14 of 99) is higher than that reported elsewhere, awareness of JET in the postoperative period has increased, and retrospective reports may underestimate the incidence.24,25 Nevertheless, our data suggest that arrhythmias in the postoperative period should be anticipated. This is particularly important because early recognition and prompt, aggressive treatment are necessary to minimize morbidity and mortality.

Patient Data

<table>
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<tr>
<th></th>
<th>Age &lt;30 d (n=76)</th>
<th>Age 31–87 d (n=23)</th>
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<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
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<tr>
<td>At birth</td>
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<td>At operation</td>
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<td>Z scores</td>
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<td>Circulatory arrest time, min</td>
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<td>Cross-clamp time, min</td>
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<td>Total pump time, min</td>
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<td>96.4±24.8</td>
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<td>Inotropic equivalents, 24 h</td>
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<tr>
<td>Hospital stay</td>
<td>16±15.3</td>
<td>11.2±7.7</td>
<td>0.07</td>
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</table>

BSA indicates body surface area; RPA, right pulmonary artery; LPA, left pulmonary artery; MPA, main pulmonary artery; PV, pulmonary valve; and ICU, intensive care unit.
Our approach represents a significant departure from the standard 2-stage repair consisting of arteriopulmonary shunting followed by later repair, and our results must be evaluated in relation to those obtained with the 2-stage repair. Vobecky et al described their experience with 141 children undergoing palliative modified Blalock-Taussig shunt before repair. In their series, initial palliation failed in 26% (36 of 141), with 2 deaths at palliation and 7 after palliation but before repair (including 1 after subsequent palliation). Twenty-six required subsequent operation for palliation for inadequate palliation, with 2 deaths. Of the remaining 24, 20 underwent repair, with 10 requiring pulmonary arterioplasty. The 5-year actuarial survival rate was \(\approx 90\%\) for these children. These results demonstrate the exacting nature of early palliative shunting and that distortion of the right pulmonary artery can be a significant complication. Beyond the anatomic complications of shunt placement, the undesirable effects of the shunt-imposed volume load on the myocardium need to be considered. These results show that there is a price to pay, with significant mortality, for shunting before repair. These combined considerations support an inherent attraction and rationale for avoiding palliative shunting by proceeding directly to repair early in life. Likewise, data presented with respect to mortality and reoperation in early repair must be viewed from this perspective.

In an attempt to minimize late complications of TOF repair, some groups have attempted to limit or avoid the right ventriculotomy. Karl et al reported an experience with 366 patients undergoing transatrial, transpulmonary TOF repair between 1980 and 1991. Although the number of symptomatic children included is unclear, only 135 (37%) had undergone some form of previous palliation. Karl et al concluded from their results that the transatrial, transpulmonary TOF repair resulted in a similar operative risk compared with transventricular TOF repair, with a 97.5% actuarial survival rate at 42 months. Although closure of the ventricular septal defect was accomplished through the atrium in all cases, the pulmonary annulus was breached with a transannular patch in roughly half of these patients. The transannular incision, when necessary, was extended onto the infundibulum between 5 and 10 mm. The impact of a right ventriculotomy on late outcome is unclear, but our early results suggest that the intracardiac repair can be safely accomplished via this approach.

Our results are comparable to the few published series of early TOF repair, with the advantage of longer follow-up (median follow-up, 4 years). Hennin et al reported a 5-year survival rate of 93% among 30 neonates undergoing repair (median follow-up, 24 months). Groh et al reported their experience with 58 slightly older children (median age, 6 months; mean weight, 6 kg) undergoing repair. They reported a 4-year survival rate of 94% and an 88% freedom from reoperation at 4 years.

Whereas all these studies demonstrate that early repair can be accomplished with acceptable mortality, the need for reoperation among some of these patients must be acknowledged. However, the need for reoperation appears to be largely dictated by the anatomic substrate, ie, PS versus PA, and is inevitable in those patients requiring a homograft to restore right ventricle to pulmonary artery continuity. This recognition explains the significantly lower freedom from reoperation for children undergoing repair of TOF/PA. This should be appreciated, as interpretation of the data of Groh et al may lead one to conclude that freedom from reoperation decreases with age at repair. Although they reported an 88% freedom from reoperation at 4 years, only 5 of 58 patients underwent repair of TOF/PA.

Subset analysis of our data supports the contention that diagnosis rather than age at repair exerts a greater influence on the need for reoperation. Of the 22 children requiring reoperation, 15 underwent repair as neonates (1557 [26%] neonates versus 7 of 42 [17%] infants 31 to 90 days of age; \(P=NS\)). Of the 26 patients undergoing repair of TOF/PA, 10 (38%) have required reoperation, whereas only 12 of 73 requiring TOF/PS repair (16%) have required reoperation. Thus, these reports and our experience would suggest that it is not earlier repair but rather the diagnosis of TOF/PA and the need for homograft insertion that are likely to result in reoperation.

We have demonstrated that early TOF repair can be accomplished with a low mortality, and it is fair to say that the hope expressed by DiDonato et al that “safe elective repair in early infancy” of TOF has been realized. Although repair can be performed with acceptable mortality, further efforts need to be directed at defining and minimizing the need for reoperation. Longer follow-up of morbidity and mortality, with particular emphasis on arrhythmias and right ventricular function, is required to define the long-term benefits of early repair.

Acknowledgment

We wish to acknowledge Gary Piercey for his assistance with the statistical analysis.

References


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Circulation. 1999;100:II-157-II-161
doi: 10.1161/01.CIR.100.suppl_2.II-157
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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