Elective Primary Repair of Acyanotic Tetralogy of Fallot in Early Infancy: Overall Outcome and Impact on the Pulmonary Valve

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OBJECTIVES
We sought to determine if early primary repair of acyanotic tetralogy of Fallot (ToF) can be performed safely with low requirement for transannular patching (TAP) and thereafter allow normal right ventricular outflow tract (RVOT) growth.

BACKGROUND
Early primary repair of ToF normalizes intracardiac flow patterns, which may allow subsequent normal RVOT growth. Traditionally repair is deferred until symptoms occur or children are deemed of adequate size for operative risk to be acceptable because of a perceived increased requirement for TAP in small infants.

METHODS
Between July 1992 and March 1999, 42 acyanotic infants aged 4 to 87 days (median 62) and weight 2.6 to 6.6 kg (median 4.55) underwent complete repair of ToF. Pulmonary annulus measured 4 to 10.5 mm (median 6.5) with “z-value” of −5.6 to +3.0 (median −1.9). RVOT reconstruction was tailored to each patient; pulmonary valvotomy was performed in 26, main pulmonary arterioplasty in 22, and infundibular patching in 2. Only 10 (24%) required TAP.

RESULTS
Postoperative RVOT gradient was 0 to 30 mm Hg (median 10) and pRV/pLV ratio 0.3 to 0.6 (median 0.44). Pulmonary insufficiency was trivial/mild. There were no deaths. Junctional ectopic tachycardia developed in seven; only one required treatment. ICU stay was 2 to 14 days (median 4) and hospital stay 4 to 22 days (median 7). At follow-up 12 to 64 months later (median 38) there were no deaths. One child required reoperation for recurrent RVOT obstruction and two required balloon pulmonary arterioplasty. Follow-up RVOT gradient was 0 to 36 mm Hg (median 12), unchanged from early postoperative condition, and median z-value was −1.2 (−2.8 to +2.5); pulmonary insufficiency remained trivial/mild.

CONCLUSIONS
Complete repair of acyanotic ToF can be performed in early infancy with low morbidity and mortality and low requirement for TAP. Though results are not statistically significant, early repair may allow normal RVOT growth thereafter. (J Am Coll Cardiol 2000;36:2279–83) © 2000 by the American College of Cardiology

Tetralogy of Fallot (ToF) is a spectrum of disease. Essential to the diagnosis is anterior malalignment of the conoventricular septum, which secondarily gives rise to the four features classically described by Fallot in 1888 (1): malalignment ventricular septal defect (VSD), overriding of the aorta, right ventricular outflow tract (RVOT) obstruction, and right ventricular hypertrophy. The severity of the RVOT obstruction determines the degree of cyanosis demonstrated by the child. Although some children are severely cyanotic from birth, there is a subgroup of patients with typical morphology and hemodynamics who remain clinically asymptomatic for a period of time, the so-called pink variant.

There has been much controversy recently regarding the ideal age for complete correction of children with cyanotic ToF (2–6). The argument hinges on the morbidity and mortality of the operation at various ages and whether early operation allows more normal development of the heart and lungs after correction. Similar arguments apply to children with the acyanotic variant, though the secondary changes are less severe due to the milder primary anatomic abnormality. However, in these infants even more than in their cyanotic counterparts, the traditional approach has been to wait until symptoms develop or the infants are older for two reasons. First, it is generally considered that the morbidity and mortality of the operation fall with increasing size of patient (2,3). Second, there is a perceived increased requirement for transannular patching if a complete repair is undertaken at a young age (7,8). This latter fear, however, does not appear logical because the RVOT is unlikely to grow if there is reduced flow through it. Prolonging the period of reduced flow is therefore only likely to increase the discrepancy in size of RVOT structures. In addition, extrapolating data regarding the necessity for transannular patching from previous studies of neonatal primary repair is inappropriate, as these studies have of necessity selected out severely cyanotic patients with disadvantageous anatomy. Building on our experience of children with cyanotic ToF, we hypothesized that early total correction of children with acyanotic ToF could be achieved with low morbidity and mortality, with low requirement for transannular patching, and after repair allowed normal growth of RVOT structures.

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PATIENTS AND METHODS

Patients

Between July 1992 and March 1999, 42 patients with acyanotic ToF underwent elective primary repair at 90 days of age or less. During the same time period 39 infants with cyanotic ToF also underwent surgery in our unit. All these patients underwent complete repair; none underwent first-stage palliation.

Median age at repair was 62 days (4 to 87 days) and median weight was 4.55 kg (2.6 to 6.6 kg). All patients had baseline arterial oxygen saturations >90% (most around 95%) and none had demonstrated any clinical episodes of cyanosis. One patient had trisomy 21. Deletions of chromosome 22q11 were not routinely assessed. All patients underwent preoperative echocardiographic examination, but only two had cardiac catheterization performed.

Operative Procedures

All patients underwent repair with cardiopulmonary bypass and cardiopulmonary arrest. Deep hypothermic circulatory arrest was employed in only one patient, the second patient in this series. After initiation of bypass, a right atriotomy was performed and the atrial septum was inspected. In patients with a patent foramen ovale or atrial septal defect, we generally allowed the foramen to remain patent or created a functional foramen by suturing the free edge of the septum primum to the left side of the rim of the limbus, using a single polypropylene suture, in effect creating a one-way flap valve. Working through the tricuspid valve, the VSD and RVOT were inspected. The VSD was closed first using a patch of autologous pericardium, generally with interrupted horizontal mattress sutures reinforced with felt pledgets. Continuing to work through the tricuspid valve, we resected muscle from the infundibular free wall and/or the septal and parietal bands as necessary, though minimal myectomy was necessary in most of these neonates and young infants due to the infrequency of advanced secondary infundibular hypertrophy.

Through a longitudinal incision in the pulmonary trunk, the branch pulmonary arteries, pulmonary valve, and subvalvar region were inspected. The diameters of the pulmonary annulus and branch pulmonary arteries were measured using graduated Hegar dilators. In many cases, the pulmonary valve was bicommissural, with partial commissural fusion at the mural attachment of the leaflets. Even in trileaflet valves there was often valvar stenosis from commissural fusion. In patients with partial commissural fusion, a scalpel was used to incise the affected commissures to the wall of the pulmonary artery. Additional subvalvar infundibular muscle was resected through the pulmonary valve if necessary.

In most patients, transannular patching was not required, and the pulmonary trunk was augmented with a pericardial patch. If the annulus was moderately to severely hypoplastic, however, the outflow tract was enlarged with a transannular patch. In order to relieve the obstruction at the annular level while simultaneously preserving as much valvar function as possible, we utilized a technique of limited transannular patching. The longitudinal pulmonary arteriotomy was extended across the pulmonary annulus only as far as necessary, often only a few millimeters onto the infundibulum. In addition, the transannular incision was performed through a commissure (usually the anterior), exactly splitting it, and a very narrow pericardial patch was used to augment the annulus. Regardless of whether transannular patching was performed, the outflow tract patch was generally extended distally onto the proximal left pulmonary artery, beyond the insertion of the ductus arteriosus.

In patients with significant pulmonary outflow obstruction at the infundibular level that could not be relieved by myectomy alone, infundibular patching was employed. In patients who underwent transannular patching, the infundibulum was augmented with an extension of the transannular patch. In patients who did not require annular enlargement, a separate infundibular patch was used to enlarge the subvalvar region. In such circumstances, a vertical right ventriculotomy was performed from just proximal to the annulus extending 25% to 30% of the distance to the apex. The infundibulum was enlarged by closing the incision with an elliptical patch of pericardium or expanded polytetrafluoroethylene membrane.

Data Collection and Statistical Analysis

Patient records were reviewed retrospectively and cross-sectional follow-up was carried out by physician contact or direct review of patient records. The maximal instantaneous gradient across the RVOT was calculated from the peak spectral Doppler velocity using the modified Bernoulli equation (4,5). Cardiac dimensions and valve function were assessed by two-dimensional echocardiography and “z-values” for the pulmonary valve were determined from published data. Patients were followed until their most recent physician contact prior to the time follow-up was conducted. Data are presented as mean ± standard deviation or median (range). Independent samples t tests and Fisher exact tests were used to compare between group means and dichotomous variables, respectively. Statistical calculations were performed using SPSS for Windows 7.0 (SPSS Inc., Chicago, Illinois) or Statview version 5 (SAS Institute Inc., Cary, North Carolina).
RESULTS

Operative Results

The median duration of cardiopulmonary bypass was 126 min (76 to 203 min), and the median duration of cardioplegic arrest was 72 min (31 to 122 min). In the patient who underwent surgery with deep hypothermic circulatory arrest, the duration of circulatory arrest was 45 min.

The pulmonary valve was noted on intraoperative inspection to be bicuspid in 27 patients (60%) and tricuspid in the other 15. The median diameter of the pulmonary annulus measured at the time of surgery was 6.5 mm (4 to 10.5 mm), corresponding to a median z-value of −1.9 (range −5.6 to +3.0). The median diameter of both the left and right branches of the pulmonary artery was 5 mm (left 3 to 8 mm, right 2 to 8 mm). Two patients had abnormal coronary arterial anatomy, one with a large conal branch, the other with the left anterior descending arising from the right coronary artery and passing across the subvalvar infundibulum.

All patients underwent repair through a combined transatrial-transpulmonary approach. This was augmented by a transventricular approach in only six patients, who thereafter underwent transannular or infundibular patching. All patients underwent infundibular myectomy. Limited transannular patching was employed in 10 patients (24%), and infundibular patching in a further 2 (4.8%). The pulmonary annulus was significantly smaller in patients who underwent transannular patching than in those who did not (5 mm [4 to 7.5 mm] vs. 6.5 mm [4 to 10.5 mm], p = 0.011; z-values −3.9 [−5.4 to −1.6] v −1.5 [−4.1 to +3], p = 0.0007), but age and branch pulmonary artery size did not differ. Among the 32 patients who did not undergo transannular patching, 22 had the pulmonary trunk and proximal left pulmonary artery augmented with a patch and 26 underwent pulmonary valvotomy/commissurotomy. No patients required placement of a right ventricle to pulmonary artery conduit.

Early Results

There were no perioperative deaths. The only major complication was focal seizures in the patient who underwent surgery with circulatory arrest. Postoperative rhythm abnormalities included transient junctional ectopic tachycardia in 9 patients (21%). Of these patients only two showed signs of cardiovascular compromise and both of these patients were loaded with digoxin. The others were either managed expectantly or conservatively by minimization of inotropic support and moderate surface cooling to a core temperature of between 35.0°C and 35.5°C. By the time of discharge all patients had reverted to a normal sinus rhythm. Three patients who left the operating room with an open sternotomy underwent delayed closure on postoperative day 2 or 3. The median duration of postoperative mechanical ventilatory support was 2 days (1 to 4 days). The median duration of stay in the intensive care unit was 4 days (2 to 14 days) and the median duration of hospital stay was 7 days (4 to 22 days). Factors leading to delayed discharge included postoperative seizures in one patient, repair of an inguinal hernia in one, and bronchiolitis due to respiratory syncytial virus in one. On the last postoperative echocardiogram prior to discharge, the median peak gradient across the RVOT was 10 mm Hg (0 to 30 mm Hg). This did not differ significantly according to age or the type of repair.

Late Results

Patients were followed for a median of 38 months after surgery (12 to 64 months). There were no late deaths. One patient required reoperation for recurrent RVOT obstruction. Two patients underwent balloon dilation of the branch pulmonary arteries (gradients >50 mm Hg) with good results. On most recent follow-up echocardiography right and left ventricular systolic function was normal in all patients and the median peak gradient across the RVOT was 12 mm Hg (0 to 36 mm Hg). Since the discharge echocardiogram the peak gradient had increased by 10 mm Hg or more in 7 patients and decreased by 10 mm Hg or more in 9. The size of the pulmonary valve annulus at follow-up for those patients who did not receive a transannular patch was 9.6 mm (range 7.7 to 17.0 mm), which was significantly different from the preoperative value of 6.5 mm (range 4.5 to 10.5 mm) (p = 0.0007). This corresponds to a median z-value at follow-up of −1.2 (−2.8 to +2.5), not significantly different from the preoperative value of −1.9 (−5.6 to +3.0) but suggesting a trend towards “catch-up” growth of the annulus. Pulmonary regurgitation was mild or less in 36 patients (83%) and moderate in 6 (17%), 5 of whom underwent repair with a transannular patch. The other five patients who received transannular patches had only mild pulmonary valvar regurgitation at the time of follow-up. Seven patients had mild tricuspid regurgitation and one patient with atroventricular septal defect also had mild mitral regurgitation. Three patients had very small, hemodynamically insignificant residual interventricular communications.

DISCUSSION

The spectrum of disease. The underlying single cardiac developmental abnormality that gives rise to ToF (anterior malalignment of the conoventricular septum) produces a spectrum of disease that ranges from severely cyanotic, duct-dependent neonates with pulmonary atresia to children who are essentially asymptomatic. When cyanosis is severe the child unquestionably requires operative intervention. The nature of this intervention, however, remains the cause of significant discussion; many argue for early primary repair (6–8) whereas others advocate palliation (2,3) until the child has grown sufficiently for a definitive procedure to be performed with a perceived lower morbidity and mortality. However, at the other end of the spectrum is the
anacynotic child who essentially has a large VSD that will not close spontaneously but who also has some element of protection of their pulmonary vascular bed rendered by the RVOT obstruction. Evidently these children do not require surgery as a neonate, but when is the appropriate time to operate on these clinically asymptomatic children? The most common approach is to wait until symptoms develop, or at least until the child is out of infancy. However, the detrimental effects of the abnormal circulation would be well established by this time.

**Long-term sequelae of delayed repair.** The advantages of early repair have been presented by our group and others many times previously to justify an early approach to the surgical treatment of patients with cyanotic ToF. Most of these benefits also pertain to early intervention in patients with the acyanotic variant; the fundamental lesion remains the same, only the severity differs between the two groups. Some element of RVOT obstruction always occurs in ToF. At birth the obstruction is primarily valvar or supravalvar with little proximal (infundibular) obstruction in the RVOT (6). With time this (supra)valvar narrowing causes right ventricular muscular hypertrophy, which produces chronic myocardial ischemia, then fibrotic replacement of the myofibrils (9,10). It has been documented previously that this hypertrophy is a progressive, postnatal development (6) and it is therefore rational to conclude that early repair could prevent this sequence. The fibrosis, as well as contributing to biventricular dysfunction, may be the focus for arrhythmias that lead to further long-term morbidity (11,12). In addition, normalizing pulmonary arterial flow has been shown to optimize pulmonary angiogenesis and alveogenesis (13). Lung volumes and vascular bed development are both significantly depressed in patients in whom definitive repair was delayed, especially in those older than 2 years at the time of repair (14), as lung growth and remodeling are most rapid before this age.

These secondary changes have all been demonstrated to occur in children with cyanotic ToF, and it has been demonstrated that early complete repair of the complex significantly reduces the incidence of long-term complications. Though anatomically they are part of the same spectrum, it is clear that children with the acyanotic form of ToF have differing hemodynamics to other children with cyanotic ToF. Consequently, it has not been proved that similar secondary changes develop in children with the acyanotic form of the disease; indeed, it is unlikely that pulmonary angiogenesis and alveogenesis will be compromised in those with bluntly little diminution in pulmonary blood flow. However, the natural history of those with the acyanotic variant of the complex is to develop cyanosis later. Evidently there will be some element of right ventricular hypertension with the attendant complications of muscular hypertrophy and ventricular fibrosis. If this is true, it follows that early complete repair will reduce the risk of these long-term complications, accepting that the rate of deterioration and severity of damage will probably be proportionately less in these patients because of the lesser severity of the malformation.

As well as preventing detrimental sequelae, early complete repair may also have some positive effects. According to the “flow theory” of cardiac development (15), it could be argued that pulmonary annular growth can only occur if there is normal flow across the valve. Perpetuating the state of reduced pulmonary flow will therefore cause the valve to become relatively smaller with time (as is known to be the natural history of the lesion), increasing the likelihood that a transannular patch will be required at the time of the delayed definitive repair. In addition, in the subgroup of patients with acyanotic ToF in whom the RVOT obstruction is insufficient to prevent pulmonary overcirculation, complete repair will reverse the accompanying failure to thrive.

**The argument for early repair.** If we accept the above arguments, early intervention could therefore be advocated so long as the operation is not associated with significant morbidity or mortality, most particularly without compromising pulmonary valve function. As surgical experience with neonates and small infants has grown, the operative mortality has fallen dramatically, as again demonstrated in this current study where the short- and long-term mortality rate is 0%. So, the operation can be performed safely at a young age, but is it detrimental to do so? General acceptance of an early approach to full correction of cyanotic ToF has been slow in coming because of a perceived increase in need for a transannular patch resulting in damage to the pulmonary valve. This fear is even more acute in patients with the acyanotic variant; if the patient is not even cyanotic why impose an early repair with a (perceived) higher incidence of transannular patching? This argument, however, is an inappropriate application of the data from previous studies in which severely cyanosed neonates have undergone primary repair. In all previous reports repair was performed in severely symptomatic infants; infants with the worst anatomy were selected out to undergo surgery. This inevitably comprised the children with very small pulmonary annuli. Therefore, the high incidence of transannular patches is reflective of the selection process for surgery rather than being intrinsic to early repair.

Our results demonstrate that complete repair of acyanotic ToF can be achieved in early infancy with a very low incidence of transannular patching (23%). Functionally, this translates into a very minor degree of pulmonary regurgitation even at midterm follow-up, being mild or less in 83% of patients including 5 of the 10 patients who required a transannular patch. This reflects our approach of inserting a very limited transannular patch that allows adequate enlargement of the RVOT while preserving function of the pulmonary valve. Further, as predicted by the flow-related theory of cardiac development (as outlined above), we found that the gradient across the pulmonary valve did not increase between the two follow-up times, suggesting that there was appropriate growth of the pulmonary valve relative to body
size after flow patterns through the heart had been normalized. This was confirmed by the finding at late follow-up that the valves had grown normally, and that in fact the z-value had actually increased slightly compared with its preoperative value.

Conclusions. From the current study we conclude that early total correction of acyanotic ToF can be performed in early infancy with a very low mortality and morbidity. Early definitive repair is not associated with an increased requirement for transannular patching, and after repair the growth of the pulmonary annulus is appropriate to that of the rest of the body; therefore the gradient across the valve does not increase with time over an intermediate period of follow-up. There is a trend towards actual catch-up growth of the pulmonary valve annulus as demonstrated by the increase in z-value. Importantly, this has occurred without any evidence of increasing pulmonary valvar regurgitation, suggesting that the growth is true growth and not simply abnormal dilation as may occur with large transannular patches.

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