Title:

Primary repair of symptomatic neonates with tetralogy of Fallot

with or without pulmonary atresia
Abstract

Recently, surgical outcomes of tetralogy of Fallot (TOF) have been improving. For TOF patients more than 3 months of age, primary repair has been advocated regardless of symptoms. However, a surgical approach of symptomatic TOF neonates or very young infants remains elusive. Traditionally, there have been two surgical options for these patients, primary repair versus first aortopulmonary shunt followed by repair. Early primary repair provides several advantages including avoidance of shunt related complications, early relief of hypoxia, promotion of normal lung development, avoidance of ventricular hypertrophy and fibrosis, and psychological comfort to family. Because of advances in cardiopulmonary bypass techniques and accumulated experience in neonatal cardiac surgery, primary repair in neonates with TOF has been performed with excellent early outcomes (early mortality < 5%), which may be superior to ones of aortopulmonary shunt. Regarding surgical options, a remaining question to answer is whether shunt can preserve the pulmonary valve annulus for TOF.
neonates with pulmonary stenosis. Comparing to older babies, symptomatic neonates have different anatomy of RVOT obstruction, which is nearly always caused by a hypoplastic pulmonary valve annulus instead of infundibular obstruction. Therefore, shunt is less likely to save the pulmonary valve annulus comparing to primary repair. Primary repair of TOF can be performed safely in most symptomatic neonates. The patients who had primary repair should be closely followed up to evaluate the RVOT pathology and right ventricular function.

Keywords: tetralogy of Fallot, neonate, early primary repair, palliation
**Introduction**

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease, and characterized by four distinct anatomic features: (1) pulmonary outflow tract obstruction (stenosis or atresia), (2) ventricular septal defect (VSD), (3) overriding aortic root, and (4) right ventricular hypertrophy\(^1\)\(^-\)\(^3\). Since the Fallot’s description in 1888, so called “blue baby operation” or Blalock-Taussig shunt, the first surgical treatment for TOF was performed by Alfred Blalock in 1945\(^4\), followed by the first successful intracardiac repair using human cross-circulation by Lillehei in 1954\(^5\) and using a pump oxygenator by Kirklin in 1955\(^6\). For at least 2 decades, initial palliation followed by repair later in childhood had been the most prevalent strategy. By the early 1980s, primary repair in early infancy had been advocated by Castaneda\(^7\), Barrat-Boyes\(^8\), and others. This approach gained wide acceptance, and many surgeons adopted a therapeutic strategy based on early primary repair in the absence of specific anatomic contraindications or comorbidities such as major non-cardiac anomalies. The
concept of early primary repair was extended to symptomatic neonates, and low operative mortality was achieved\textsuperscript{9-13). However, the management of symptomatic infants with TOF requiring surgical intervention in the first month of life remains controversial\textsuperscript{14). In this article, I would like to summarize the personal experience and review the current practice of early primary repair in TOF neonates with pulmonary stenosis or atresia.

Considerations of the anatomy and pathophysiology of TOF in small babies requiring early intervention

TOF is defined on the basis of anterocephalad deviation of the outlet septum with associated malformation of the septoparietal trabeculation or results from underdevelopment of the subpulmonary infundibulum\textsuperscript{2,15). This one abnormality or pathologic process during embryogenesis produces RVOT obstruction and also is responsible for the malalignment type VSD and the aortic override. The right ventricle hypertrophy is the hemodynamic consequence of the above anatomical lesions\textsuperscript{16).
TOF has a wide spectrum of disease from mild RVOT obstruction to severe obstruction and TOF with pulmonary atresia is at one extreme. The level of obstruction may occur at one or more of the following structures: (1) infundibulum, (2) pulmonary valve, (3) main pulmonary artery, and/or (4) branch pulmonary arteries.

In TOF patients with pulmonary stenosis, the initial manifestation of symptoms depends on the degree of RVOT obstruction. Most commonly, cyanosis is mild at birth and gradually progresses with age as the stenosis increases due to increasing infundibular hypertrophy. Cyanosis tends to become significant within the first 6 to 12 months of life. In such situations, the obstruction is entirely or predominantly at the infundibular level. The pulmonary valve annulus and the branch pulmonary arteries usually are of good size. However, a smaller percentage of patients have marked cyanosis at or soon after birth. In this group the RVOT obstruction is nearly always caused by a hypoplastic pulmonary valve annulus. Cyanosis is constant in these patients because of the fixed nature of the obstruction of pulmonary blood flow. Castaneda et al described the anatomy of RVOT in young infants with TOF presenting with cyanosis. Although
the infundibulum was stenotic, the area of greatest obstruction to pulmonary blood flow in the majority of infants was at the pulmonary valve annulus, in which the pulmonary valve was bicuspid or dysplastic with fusion of commissures. Pulmonary atresia is present in approximately 7% of patients with TOF\textsuperscript{19}. TOF with pulmonary atresia exhibits considerable morphologic variability, particularly with respect to the source of pulmonary arterial flow\textsuperscript{20}. When patients with pulmonary atresia have no major collateral arteries, a PDA is the only source of pulmonary blood flow. In such cases, there may be varying degrees of hypoplasia of the pulmonary arteries, but it is most often the case that all or nearly all lung segments are supplied by branches arborizing from the right and left pulmonary arteries, that is, pulmonary artery arborization is much more predictable\textsuperscript{21}.

**Surgical options in symptomatic TOF neonates**

Symptomatic TOF is defined as prostaglandin dependent or having either hypoxic episodes or severe hypoxemia with resting systemic oxygen saturation of less than 75%. Neonates born with TOF with pulmonary stenosis are known to
uncommonly develop symptoms but a smaller percentage of patients have marked cyanosis at or soon after birth as previously mentioned. TOF neonates with pulmonary atresia are symptomatic or asymptomatic but have inevitably ductal dependent pulmonary circulation. For such patients, surgical options include early primary repair or palliation with a aortopulmonary shunt.

Recently, Al Habib et al\textsuperscript{22} reported contemporary patterns of management of TOF with pulmonary stenosis using The Society of Thoracic Surgeons (STS) Database (3059 operations in 2002-2007). This study showed that primary repair in the first year of life is the most prevalent strategy. However, for the neonatal age group, primary procedures were about equally divided between primary repair and palliation (154 cases vs. 178 cases among total 332 procedures, respectively). This demonstrates that an optimal strategy for neonates with symptomatic TOF is still an unanswered issue even in current years.

\textbf{Aortopulmonary shunt in neonates with symptomatic TOF}
For neonates and young infants with symptomatic TOF, palliation with an aortopulmonary shunt has been performed by many surgeons. Those who prefer this option are likely to agree with the use of primary repair in TOF at 3 months of age or older. Recently, Kanter et al\(^{14}\) reported a study comparing two surgical options such as primary repair and shunt in symptomatic TOF neonates. They concluded that shunting or primary repair in neonates with symptomatic TOF provided equivalent mortality and results and also shunted patients had fewer transannular patch repairs despite having more emergent initial operations.

At this point, two issues should be answered regarding shunting in neonates with TOF: (1) How safely shunting is performed in these patients and (2) whether shunting additionally saves the pulmonary annulus?

### 1. Safety issue of shunting

For infants with TOF, a palliative shunt has been performed safely and with excellent outcomes\(^{23,24}\). Even in small babies, this option still provides good and similar outcomes to primary repair\(^{14,22}\). Recently, Kanter et al\(^{14}\) reported excellent
early outcomes including shorter intensive care unit and hospital stays for the first operation and early mortality of 5.9%. STS database said that discharge mortality of TOF repair in neonates was 11 of 178 (6.2%) for palliation and 12 of 154 (7.8%) for primary repair\(^2\). However, outcomes of shunt in neonates have been reported inconsistently and with fluctuations. In a multicenter study of the effect of aspirin on shunts, clinical outcomes of palliative shunts in infants were poor even in the current era\(^2\).\(^5\). This study showed that event rates of shunt thrombosis and death were 5% and 15%, respectively for TOF patients and 16% and 22%, respectively for patients with pulmonary atresia. Recently, Guzzetta et al\(^2\)\(^6\) reported outcomes of in-hospital shunt occlusion in 207 small infants undergoing only a modified Blalock-Taussig shunt, in which in-hospital shunt occlusion occurred in 14 patients (6.8%). Patients who had shunt occlusion had a harder postoperative course and a higher rate of in-hospital mortality (6.2% versus 21.4%). They concluded that the risk factors of in-hospital shunt occlusion were cardiac diagnosis (pulmonary atresia) and the size of the pulmonary arteries. With regard to the safety of shunt, interim mortality should be issued in infants undergoing shunting\(^1\)\(^3\),\(^2\)\(^7\),\(^2\)\(^8\). Interim mortality occurs during the palliated state
before repair and may account for an additional attrition, which may or may not
be shunt-related\(^{29}\).

2. Issue of preservation of pulmonary valve annulus in neonatal TOF repair

For TOF neonates with pulmonary stenosis, the influence of shunting on the
growth of the pulmonary annulus should be evaluated. Pulmonary regurgitation
after TOF repair results in various adverse long-term outcomes\(^{30}\). Therefore, every
effort should be made to preserve total pulmonary valve function as well as the
pulmonary annulus in TOF repair. Recently, Kanter et al \(^{14}\) suggested that shunted
patients have a greater likelihood of avoiding a transannular patch at the time of
repair. Sousa Uva et al\(^{31}\) reported that initial palliation promoted the growth of
pulmonary annulus and transannular patching was less prevalent for patients who
underwent initial palliation (13\% versus 56\%, \(p = 0.03\)). One year later, however,
they reported on the same issue, in which the observation of increased size of
the pulmonary annulus after shunt could be due to chance only and initial
palliation did not allow for a reduction in incidence of transannular patching\(^{32}\).
The incidence of transannular patching at the time of primary repair in neonates ranges from 84 to 100%. Symptomatic neonates have received a transannular patch because of the morphology, not because of their age. The need for a transannular patch reflects the severity of the RVOT obstruction at the annular level. Parry et al reported outcomes of elective primary repair of acyanotic TOF in early infancy, in which only 28% patients required transannular patching and follow-up echocardiography suggested a trend towards 'catch-up' growth of the annulus. Although in a disease entity different from TOF, Emani et al showed progressive decrease in the pulmonary valve annular size in case of delayed anatomic repair beyond the neonatal period. They suggested the importance of antegrade blood flow as a stimulus for growth of ventricular outflow tract structures and the negative effect of retrograde blood flow from aortopulmonary shunts.

**Primary repair in symptomatic TOF neonates**
Initial study of Kirklin et al\(^ {35} \) suggested that primary repair of TOF at less than three months of age was associated with a high mortality. Over the past several years, however, increasing success with primary repair of TOF in younger infants has been demonstrated by many centers\(^ {9,18,32,36} \). These days, early primary repair in symptomatic neonates with TOF has been performed with excellent early outcomes (Table 1).

Early primary repair provides multiple advantages including avoidance of shunt related complications, early relief of hypoxia, promotion of normal lung development, avoidance of ventricular hypertrophy and fibrosis, and psychological comfort to the young family\(^ {37,38} \).

In the current era, there are essentially no contraindications to early primary repair\(^ {38,39} \). Past considerations for delayed repair include anomalous coronary artery crossing the right ventricular outflow tract, hypoplastic or discontinuous pulmonary arteries and multiple ventricular septal defects\(^ {39} \).

For symptomatic neonates with TOF, Kanter et al\(^ {14} \) suggested that neonates who were smaller and required emergency operation were shunted and those with favorable anatomy and good-sized branch pulmonary arteries had primary repair.
Shunting in smaller neonates and neonates necessitating emergency operation is not absolutely safe and most likely associated with considerable mortality and morbidity. Recently, the accumulation of the experience of neonatal cardiac surgery and advances in cardiopulmonary bypass techniques may provide more stable outcomes after primary repair in such situations.

Regarding the size of pulmonary arteries, this issue should be simplified to identify the presence of major aortopulmonary collateral arteries. If there are no major collateral arteries present, the pulmonary arteries are adequate for primary repair of TOF\textsuperscript{38}. Jonas\textsuperscript{38} emphasized that the pulmonary arteries are underfilled and underpressurized preoperatively, so whatever imaging technique is used, the potential size of the pulmonary arteries is unknown. Van Arsdell et al\textsuperscript{40} pointed out that problems with true small pulmonary arteries are infrequent (1% to 2%) and can be managed with a fenestrated VSD.

Surgical techniques of primary repair in neonatal TOF have been progressively changed over the last several decades. Since the early years, neonatal TOF repair has been performed using cardiopulmonary bypass with a period of deep hypothermic circulatory arrest\textsuperscript{7,10,11,33}. Recently, however, many surgeons have
tried to avoid deep hypothermic circulatory arrest and perform primary repair under continuous moderate hypothermic cardiopulmonary bypass and cardiac arrest instead\textsuperscript{12-14}. The VSD is closed through a transatrial and/or transventricular approach. RVOT reconstruction is performed using various techniques including transannular or non-transannular patching in pulmonary stenosis and transjunctional patching, interposition of a conduit from the right ventricle to the pulmonary arteries, and other techniques in pulmonary atresia. Farouk et al\textsuperscript{20) described the surgical technique in TOF patients with pulmonary atresia and the feasibility of a transatrial approach for VSD closure in all patients.

**Personal experience of primary repair of TOF with or without pulmonary atresia**

My personal strategy for surgical intervention in neonatal TOF is early primary repair if possible. I have reviewed my clinical experiences of surgical treatment in symptomatic neonates with TOF.
**Patient Population**

Between May 2004 and Dec 2012, 27 consecutive neonates with TOF underwent a surgical intervention. Their cardiac diagnoses were TOF with pulmonary stenosis (n = 6) or atresia (n = 21) and no major aortopulmonary collateral vessels. All patients had symptoms before surgery. Twenty-six patients were receiving an infusion of prostaglandin and remaining patient with pulmonary stenosis suffered from anoxic spell and was treated with propranolol and mechanical ventilator care. Ten patients needed mechanical ventilator care temporarily or until repair.

Intracardiac anatomy and the RVOT were preoperatively assessed using transthoracic echocardiography. The morphology and size of pulmonary arteries and the presence of major collateral arteries were assessed by chest computed tomography (CT) scan. Preoperative chest CT scan images were available to measure the size of the branch pulmonary arteries in 24 patients. McGoon ratio\textsuperscript{41} and Nakata index\textsuperscript{42} were median value of 1.1 (range 0.6 to 1.5) and 121 mm\textsuperscript{2}/m\textsuperscript{2} (range 27 to 189 mm\textsuperscript{2}/m\textsuperscript{2}), respectively (Fig 1). The only one patient who had
undergone shunt for small pulmonary arteries had McGoon ratio of 0.6 and Nakata index of 27 mm$^2$/m$^2$ (Fig. 1, black triangle*).

Twenty-five neonates (93%) underwent primary repair. The age at repair was 16 days (median, range 12-29 days) and body weight was 3.2 kg (median, range 2.2–4.2 kg). Two patients (7%) had aortopulmonary shunts, one patient with seemingly small LV size and another with diffuse hypoplastic branch pulmonary arteries despite no major aortopulmonary collateral vessels (Fig 2).

**Operative techniques**

The early primary repair included VSD closure (a transatrial approach in 20 and a transvenous approach in 5), resection of the hypertrophied right ventricular muscle and RVOT reconstruction with various techniques such as a transannular or transjunctional RVOT widening with an autologous pericardial patch (n = 12), interposition of a conduit made with an autologous pericardial roll between the right ventricle and the pulmonary arteries (n = 8, 7 to 10 mm in diameter), RVOT reconstruction using the left atrial auricle as a flap (n = 3), and REV (reparation a
l'etage ventricularie) type reconstruction (native tissue to tissue anastomosis between the posterior wall of the main PA and right ventricle, n = 2). Any materials for preventing the pulmonary regurgitation such as artificial monocusp or bicusp pulmonary valves were not used in any patients. The fenestration of VSD was not necessary in all patients.

**Cardiopulmonary bypass data**

All primary repairs were performed after standard median sternotomy using full-flow cardiopulmonary bypass with moderate systemic hypothermia. Antegrade crystalloid cardioplegia was used for myocardial protection. Cardiopulmonary bypass and aortic cross clamp time were 153 min (median, range 95-257 min) and 75 min (median, range 50-117 min) respectively. Total circulatory arrest was not necessary in all patients.
Early results and postoperative course

There were no hospital deaths. Delayed sternal closure was necessary in 6 patients and postoperative complications requiring an operation occurred in 5 patients including left-side diaphragm palsy (n = 3), postoperative bleeding (n = 1) and wound infection (n = 1). There was no patient showing the development of junctional ectopic tachycardia or complete atrioventricular heart block.

Late results

Follow-up was performed at a median interval of 56 months (range 2 to 105 months). There were 2 late deaths. Actuarial survival rate at 6-month, 1-year, and 5-year were 96%, 92%, and 92%, respectively. Among 23 late survivors, 15 patients (65%) have not needed any surgical intervention after primary repair.

Eight patients have undergone surgical procedures of RVOT at a median interval after total repair of 14 months (range 6.8 to 51 months) and 3 patients have needed second redo operations for RVOT stenosis. The first catheter
intervention for RVOT obstruction has been performed in 14 patients (61%) at a median interval after primary repair of 7.4 months (range 3 to 19 months) and for left pulmonary artery stenosis in 6 patients, right pulmonary artery stenosis in 2, stenosis of both branch pulmonary arteries in 5, and pulmonary trunk stenosis in 1. Eight patients have needed further catheter interventions such as re-ballooning or placement of a stent. Reoperation free survival rate at 6-month, 1-year, and 5 year were 100%, 81%, and 60%, respectively and catheter plus surgery intervention free survival rate at 6-month, 1-year, and 5 year were 79%, 50%, and 33%, respectively. On most recent follow-up echocardiography right and left ventricular systolic function was normal in all patients.

For 23 late survivors, a post-repair RV/LV pressure ratio were 0.61 ± 0.15 (range 0.37 – 0.89), which was not related with preoperative size of the pulmonary arteries (Fig 3). However, in case of the ratio of 0.6 or more, catheter plus surgical interventions were needed significantly more frequent (10/11, 91% vs. 5/12, 42%; p = 0.027 by Fisher's exact test).
Conclusions

Surgical strategy of symptomatic TOF neonates such as primary repair or shunt followed by repair remains elusive. Shunt operation is no longer a safe option in neonates and is less likely to save the pulmonary valve annulus additionally.

Primary repair of TOF can be performed safely in most symptomatic neonates.

The patients who had primary repair should be closely followed up to evaluate the RVOT pathology and right ventricular function.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References


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Legends

Table 1. Outcomes of early primary repair.

*N.A.; not available, NC; non-confluent, PA; pulmonary atresia, PS; pulmonary stenosis, REV; reparation a l’etage ventricularie, RV-PA; right ventricle - pulmonary arteries, TAP; transannular patch

Fig 1. Preoperative size of the pulmonary arteries. Black triangle*; palliative case due to hypoplastic pulmonary arteries, black triangle**; palliative case due to seemingly LV hypoplasia

Fig 2. Preoperative chest CT scan in a patient with diffuse hypoplastic pulmonary arteries who had a palliative shunt (case of black triangle* in Fig 1).

Fig 3. Scatter plots between post-repair RV/LV pressure ratio and preoperative McGoon ratio (A) and Nakata index (B).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Operation year</th>
<th>No of patient</th>
<th>Type of operation</th>
<th>Age at operation (mean)</th>
<th>Early mortality</th>
<th>Follow-up duration</th>
<th>Late mortality</th>
<th>Reoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Donate et al. (1991)</td>
<td>1973-1988</td>
<td>27 PS 14, PA 13</td>
<td>TAP (25) RV-PA conduit (2)</td>
<td>3d</td>
<td>5 (19%)</td>
<td>5 yr</td>
<td>2 (9%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Hirsch et al. (2000)</td>
<td>1988-1999</td>
<td>61 PS 31, PA 24, NC 6</td>
<td>TAP (29/31) RV-PA conduit (2/31)</td>
<td>16d</td>
<td>1 (1.6%)</td>
<td>62 mo</td>
<td>4 (6.7%)</td>
<td>22 (39%)</td>
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<tr>
<td>Kolcz et al. (2005)</td>
<td>1998-2004</td>
<td>46 PS 41, PA 5</td>
<td>N.A.</td>
<td>8d</td>
<td>2 (4.3%)</td>
<td>35 mo</td>
<td>No</td>
<td>3 (6.8%)</td>
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<tr>
<td>Tamesberger et al. (2008)</td>
<td>1995-2006</td>
<td>25 PS 25</td>
<td>TAP (84%)</td>
<td>15d</td>
<td>No</td>
<td>N.A.</td>
<td>No</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Kanter et al. (2010)</td>
<td>2002-2008</td>
<td>20 PS 20</td>
<td>TAP (100%)</td>
<td>9.7d</td>
<td>No</td>
<td>47 mo</td>
<td>2 (10%)</td>
<td>4 (22%)</td>
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<tr>
<td>Kwak et al. (2011)</td>
<td>1997-2008</td>
<td>18 PA 18</td>
<td>TAP (7) RV-PA conduit (5) REV (3) LA auricle (3)</td>
<td>23d</td>
<td>1 (5.6%)</td>
<td>44mo</td>
<td>1 (5.9%)</td>
<td>6 (38%)</td>
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