Tetralogy of Fallot With Pulmonary Atresia
Rehabilitation of Diminutive Pulmonary Arteries

Jonathan J. Rome, MD; John E. Mayer, MD, PhD; Aldo R. Castaneda, MD, PhD; James E. Lock, MD

Background. Patients with tetralogy of Fallot, pulmonary atresia, and diminutive pulmonary arteries are a high-risk group for whom there is no consensus on the correct approach to medical management. The purpose of this report is to review a 14-year experience in the treatment of these patients comparing management schemes.

Methods and Results. Between January 1978 and August 1988, 91 patients with tetralogy of Fallot and pulmonary atresia had an adequate evaluation of their pulmonary artery anatomy before any surgical management. Forty-eight of these patients had diminutive pulmonary arteries (38 to 104 mm²/m²) supplied by aortopulmonary collaterals and were managed in four different fashions. Of the 9 patients repaired primarily, 7 died early and the two survivors had poor hemodynamic outcome. Of the 9 patients conservatively managed with no intervention before 5 years of age, 4 died and only 1 had a satisfactory hemodynamic result after repair. Of 10 shunted patients, 3 died and 3 had satisfactory repairs. Since 1984, we have rehabilitated pulmonary arteries with (1) right ventricle to pulmonary artery surgical graft, (2) balloon dilation of residual pulmonary artery stenoses and embolization of collaterals, and (3) surgical closure of ventricular septal defect and repair of remaining obstructions. Of 20 patients so managed, 7 died after various stages, but 10 of 20 had complete repairs. All repaired patients with subpulmonary right ventricular pressures had at least one successful pulmonary artery dilation.

Conclusions. A combined catheter-surgery approach begun at an early age in patients with tetralogy of Fallot and pulmonary atresia with diminutive pulmonary arteries appears to enhance the chances of satisfactory complete repair. (Circulation. 1993;88[part 1]:1691-1698.)

Key Words • heart defects, congenital • balloons • angioplasty • arteries • surgery

Patients with tetralogy of Fallot and pulmonary atresia (TOF-PA) pose a formidable therapeutic challenge, mostly because of the wide range of pulmonary artery sizes and distribution.\(^1,2\) At one end of the spectrum are patients with valvar pulmonary atresia, usually with a duct-dependent pulmonary circulation and essentially normal pulmonary arteries. At the other extreme are patients with TOF-PA and diminutive or absent central pulmonary arteries; pulmonary blood flow in these patients is supplied principally or exclusively by multiple aortopulmonary collaterals. Therefore, no single treatment plan is suitable for this heterogeneous group of patients. Generally, children with adequate-sized pulmonary arteries are successfully managed by complete primary repair. In contrast, patients with TOF-PA and diminutive or absent central pulmonary arteries require a different approach.\(^3\)

Before 1984, in our institution, patients with TOF-PA and diminutive arteries were managed nonsystematically, either medically or surgically, including primary repair, or by creating systemic to pulmonary artery shunts.\(^4,5\) By 1984, we had learned that hypoplastic and stenotic pulmonary arteries could be enlarged by transcatheter balloon dilation.\(^6,7\) Consequently, a new collaborative approach to the management of patients with TOF-PA and diminutive pulmonary arteries evolved, combining early surgical relief of right ventricular outflow tract obstruction without closure of the ventricular septal defect (VSD), followed by interventional catheterization to dilate peripheral pulmonary artery stenosis and also to coil redundant aortopulmonary collaterals.\(^8\) These preliminary procedures were then followed by surgical relief of any residual right ventricular outflow tract obstruction and closure of the VSD.

The purpose of this report is to analyze a 14-year experience in patients who presented during a 10-year span (January 1978 to August 1988) with TOF-PA and diminutive pulmonary arteries, comparing treatment approaches and reviewing in more detail the group undergoing our more recent combined staged treatment plan.

Methods

Study Group

The Children's Hospital cardiology files were searched to identify all patients with TOF-PA born between January 1978 and August 1988. Excluded were patients with acquired pulmonary atresia, VSDs of the atroventricular canal type, abnormalities of ventricular looping, hypoplastic ventricles, or transposition of the great arteries. Clinical information, hemodynamic data, and cineangiograms were examined in all patients meet-
ing these criteria. One hundred three patients were initially identified. Twelve patients were excluded from further study because angiographic data were either unavailable or inadequate to precisely delineate the pulmonary circulation. The remaining 91 patients were classified based on pulmonary artery anatomy and size at the initial angiogram. We determined pulmonary artery size by measuring the diameters of right and left pulmonary arteries immediately proximal to their first branch points. Magnification errors were corrected by using previously determined values from our laboratory or by relating vessel size to the known size of the angiographic catheters. Pulmonary artery size is reported as the sum of the cross-sectional areas of right and left pulmonary arteries indexed to body surface area as described by Nakata and collaborators. The normal Nakata index is $330 \pm 30 \text{ mm}^2 / \text{m}^2$. Pulmonary arteries were defined as diminutive when the pulmonary artery index (PAI) was $< 90 \text{ mm}^2 / \text{m}^2$ and normal sized when the PAI was $\geq 150 \text{ mm}^2 / \text{m}^2$. Patients with PAI between $90 \text{ mm}^2 / \text{m}^2$ and $150 \text{ mm}^2 / \text{m}^2$ (n=14) were assigned to the diminutive or normal groups, based on pulmonary artery anatomy: Patients with continuous pulmonary arteries supplied by a restrictive PDA were classified as normal (n=5) and patients with pulmonary arteries supplied by multiple aortopulmonary collaterals were classified as diminutive (n=9).

**Treatment Approaches**

Patients with TOF-PA and diminutive pulmonary arteries were managed in one of the following ways: (1) conservative treatment (no operation before 5 years of age), (2) primary repair (primary repair, including VSD closure as the first operation), (3) systemic artery to pulmonary artery shunts (either a classic Blalock-Taussig or a modified [Gortex graft] shunt before 5 years of age), (4) right ventricular to pulmonary artery outflow (patch or valved homograft interposition without VSD closure before 5 years of age), and (5) primary unifocalization (attempted in 1 patient).

**Outcome**

Follow-up information was obtained during calendar year 1992 by review of hospital records, catheterization data, and survey of primary physicians and parents. The following outcomes were determined: (1) mortality for each patient who died, with the date and cause of death (if known); (2) hemodynamic result (status) of patients alive at last follow-up (patients were considered successfully repaired if they had no significant shunts, a right ventricular pressure of $< 0.8 \text{ systemic}$, and distal mean pulmonary arterial pressure of $< 25 \text{ mm Hg}$ on both right and left sides at postoperative catheterization; they were deemed unreparable if distal pulmonary hypertension [pulmonary arterial pressure greater than two-thirds systemic] or inadequate arborization [pulmonary artery flow to less than the equivalent of one lung or 10 segments] persisted despite apparently optimal anatomic management), and (3) functional status based on questionnaires of primary physicians and parents, cardiovascular disability and neurodevelopmental status of all surviving patients. Cardiovascular disability was rated via a modified New York Heart Association functional classification. Neurodevelopmental status was assessed by a modification of the Cerebral Performance Category Scale. Preschool children were evaluated with the Vineland Adaptive Behavior Examination. The functional status classification scheme is shown in Table 1.

**Data Analysis**

Treatment groups were compared with respect to outcome in the following manner. Mortality was evaluated by generating Kaplan-Meier survival curves for each treatment group. The significance of differences among the groups was then determined by log-rank test. Hemodynamic outcome was evaluated by comparing the number of patients successfully repaired with those unsuccessfully repaired or unable to be repaired (as described above) for treatment groups. Patients were excluded from this analysis if information was inadequate to classify them because their treatment or hemodynamic data were incomplete. The significance of differences between groups was evaluated with the Fisher's exact test. Finally, differences in functional status at follow-up were evaluated by comparing the number of patients in each group with more than minimal disability (Table 1). The significance of a difference between groups was evaluated by Fisher's exact test. A value of $P \leq 0.05$ was considered significant for all analyses.

**Results**

**Operative Management of Patients with TOF-PA**

Forty-nine patients with TOF-PA met criteria for this analysis (average PAI, $56 \pm 37 \text{ mm}^2 / \text{m}^2$). One 12-day-old patient died at attempted primary unifocalization and will not be discussed further. The remaining 48 patients were managed by one of the four schemes described above; 17 (37%) were repaired, and 21 (44%) died. Patients were a mean of 9.3 years of age at last follow-up. See Table 2.

**Conservative therapy.** Nine patients had no intervention before 5 years of age; 4 of these patients died. The 5 survivors were 11.8 years of age at last follow-up. Two were repaired, 1 underwent placement of a right ventricle to pulmonary artery conduit after 5 years of age, and 2 remained unoperated.

**Primary repair.** Nine patients underwent complete repair as a primary procedure at a mean age of 1.4 years; 7 died in the perioperative period from ventricular failure and low cardiac output. The other 2 patients are alive at 11 and 14 years of age.

**Initial systemic artery to pulmonary artery shunt procedures.** There were no operative deaths among the 10 patients undergoing shunting procedures at an average age of 18 months (range, 1 day to 4 years, 4 months). Two patients died while awaiting further studies. Five patients were subsequently repaired, 1 after a staged right ventricular outflow procedure. Thus, 3 patients in this group died and 7 patients survived, at an average age of 8.8 years.

**Establishment of right ventricular to pulmonary artery continuity (without closure of VSD).** Right ventricular outflow procedures without VSD closure were performed in 20 patients at a mean age of 1.6 years (range, 1 month to 4.9 years); 4 died shortly after staging operations, and 1 died late because of dilation-induced aneurysm. Among the remaining 15 children,
TABLE 1. Functional Status Grading Scheme: Exercise Tolerance and Cerebral Performance Outcome

<table>
<thead>
<tr>
<th>Grade</th>
<th>School-Aged Children</th>
<th>Preschool Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise tolerance*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>No limitations</td>
<td>No limitations</td>
</tr>
<tr>
<td>Mild disability</td>
<td>Doesn't keep up in gym</td>
<td>Takes extra naps, stops to rest</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>Unable to participate in gym, tires walking 1 block</td>
<td>Significant exercise limitation compared with peers</td>
</tr>
<tr>
<td>Severe disability</td>
<td>Unable to perform any activity without fatigue</td>
<td>Same</td>
</tr>
<tr>
<td>Cerebral Performance*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Age-appropriate functioning; in age-appropriate grade, regular classroom</td>
<td>Developmentally age-appropriate†</td>
</tr>
<tr>
<td>Mild disability</td>
<td>Age-appropriate interactions; minor motor deficit does not interfere with daily functioning; attends regular school but is not in age-appropriate grade</td>
<td>Same; developmental age delayed between 1 and 2 years</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>Below age-appropriate functioning; neurological disease severely limits activities; attends special classroom</td>
<td>Same; developmental age delayed 2 to 3 years</td>
</tr>
<tr>
<td>Severe disability</td>
<td>Dependent on others for activities of daily living; abnormal motor movements may include nonpurposeful responses to pain</td>
<td>Same; developmental age more than 3 years delayed</td>
</tr>
</tbody>
</table>

*The worst level of performance for a single criterion is used for categorizing.
†Developmental age plus mean adaptive age for communication, daily living skills, and socialization domains on Vineland Adaptive Behavior Scale.12

12 have since undergone repair, including closure of their VSDs, with 2 perioperative deaths. Nine of the 10 surviving repaired patients (90%) had coil embolization (Fig 1), and all underwent successful pulmonary artery dilation procedures (Fig 2) either before7 or after3 VSD closure. Successful pulmonary artery rehabilitation was achieved even in 3 patients with an initial PAI of <$20 mm²/m². The overall mortality for this group was 35%, and the 10 repaired survivors survived at an average of 3.9 years after surgery. See also Fig 3 through Fig 5.

Outcome of Patients With Tetralogy of Fallot, Pulmonary Atresia, and Diminutive Pulmonary Arteries

Mortality. Survival curves for patients with TOF-PA by treatment scheme are shown in Fig 1. Patients who underwent complete repair as a primary procedure had a cumulative survival of 20% at 5 years of age and were significantly less likely to live compared with all other groups (P<.03). Among the three other groups, the cumulative survival at 10 years of age varies between 60% and 65% and is not significantly different. It is noteworthy

TABLE 2. Operative Intervention in Patients With Tetralogy of Fallot and Diminutive Pulmonary Arteries

<table>
<thead>
<tr>
<th></th>
<th>Conservative Therapy Group</th>
<th>Primary Repair Group</th>
<th>Shunt Group</th>
<th>Staged Outflow Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td>Pulmonary artery Index, mm²/m² (SD)</td>
<td>85 (20)</td>
<td>70 (30)</td>
<td>52 (35)</td>
<td>44 (25)</td>
<td>56 (30)</td>
</tr>
<tr>
<td>Mean age staged procedure</td>
<td>...</td>
<td>...</td>
<td>1.5 y</td>
<td>1.6 y</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1 d-4.3 y</td>
<td>1 mo-4.9 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attempted repair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>3 (33)</td>
<td>9 (100)</td>
<td>5 (40)</td>
<td>12 (60)</td>
<td>29 (60)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>5.8</td>
<td>1.4</td>
<td>6.0</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>4 (44)</td>
<td>7 (78)</td>
<td>3 (30)</td>
<td>7 (35)</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Survivors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Repaired</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Palliated</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Unoperated</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
that all deaths among the patients in the outflow group occurred before 5 years of age; after that, their cumulative survival remained constant at 62% for the duration of follow-up: almost 10 years. In contrast, the risk of dying appears to continue at an undiminished rate in the conservatively managed patients, with a cumulative survival at 5 years of 90% dropping to under 50% by 13 years of age. All deaths in the outflow group were related to surgical or catheter interventions (see below), whereas those in the conservatively treated patients were related to underlying cardiovascular dysfunction (3 had documented distal pulmonary artery hypertension and 1 was severely cyanosed at the time of sudden death).

Hemodynamic result: primary repair and conservative therapy. The hemodynamic result of surviving patients was correlated with management strategy (Tables 3 and 4). Only 1 of the 5 surviving patients managed conservatively was successfully repaired. Among the 4 others, 1 was repaired with distal pulmonary artery hypertension and systemic right ventricular pressure, 1 patient was unreparable because of inadequate arborization, and 2 patients were palliated. Both survivors of attempted primary repair had unacceptable results with systemic right ventricular pressure.

Hemodynamic result: staged management with shunt or outflow. Three of 4 repaired patients in the shunted group had a successful hemodynamic outcome and one had persistent right ventricular hypertension. The 3 palliated patients were unreparable. The successfully repaired patients all underwent successful pulmonary artery dilations: In 1 patient, this was after a staged right ventricular outflow procedure and before VSD closure. The other 2 patients underwent pulmonary artery dilations when right ventricular hypertension persisted after VSD closure: The ratio of right ventricular to systemic pressure fell from 90% and 100% to 50% and 55%, respectively. Ten patients in the staged outflow group had completed repairs: 8 had a successful outcome, 1 did not have postoperative catheterization, and 1 had an unacceptable result caused by right ventricular hypertension. Among the 3 palliated patients in this group, only 1 was known to be unreparable because of inadequate arborization; the other 2 await further study. In summary, 11 patients managed with staged outflow or shunt and subsequent pulmonary artery dilation were successfully repaired, and 2 had an unsuccessful outcome. In comparison, only 1 patient managed conservatively or by primary repair was successfully repaired, and 4 had an unacceptable hemodynamic result. This difference in hemodynamic result is significant (P=.02).

Functional status. Functional outcome of surviving patients was assessed by phone questionnaire of parents (Table 1). Patients managed conservatively or by primary repair were more likely to have significant limitation in exercise tolerance at follow-up (3 of 7 patients) than those managed with shunt or outflow (1 of 20, P=.05). There were no other significant differences in functional status.
among groups. Overall, 15% (4 of 27) of patients had significant neurodevelopmental delays (Table 2).

**Review of Mortality Among Patients Undergoing Rehabilitation**

The 7 patients who died during the rehabilitation process were reviewed in detail. Of the 4 patients who died during the initial outflow procedure, 2 deaths (early in the experience) were due to severe neurological deficits discovered early after surgery. These deficits were thought to have been due to collateral-induced, poor somatic perfusion during cardiopulmonary bypass. The technique for the initial outflow procedure was altered to reduce the potential for central nervous system hypoperfusion. Similarly, 1 of the patients who died at repair from severe central nervous system dysfunction had a moderate-sized (3 mm), unrecognized collateral arising from the base of the vertebral artery; the vessel was not closed before surgery. The patient with the angioplasty-induced aneurysm was dilated very soon (7 weeks) after creation of the homograft to pulmonary artery anastomosis, which, over the course of 3 months, progressively enlarged to encompass the entire front of the heart, including the left anterior descending coronary artery (injured at the time of attempted surgical repair).

**Discussion**

The review of our experience with TOF-PA covering the period of 1978 to 1988 supports several previous observations. Patients with TOF-PA and diminutive pulmonary arteries (PAI < 90 mm²/m²) carry a much higher risk of mortality and morbidity; relatively few of these patients have adequate late results after repair.
Clearly, primary repair in this group of patients proved far too risky and should be abandoned. Although the mortality rates (30% to 44%) did not differ significantly among the other three approaches (conservative treatment, shunts, staged combined therapy), there appeared to be an important difference in overall long-term outcome (Table 4). Only 1 of the 9 patients managed conservatively lived with a satisfactory outcome after repair, and only 1 additional patient in this group was potentially repairable. In contrast, 40% (8 of 20) of patients after staged procedures were successfully repaired.

The poor late outcome of patients conservatively managed for the first 5 years of life is largely attributable to the development of pulmonary vascular obstructive disease (4 of 9, 44%). There is some evidence that infants with pulmonary atresia, and hence decreased intraluterine pulmonary blood flow, develop fewer pulmonary arterioles when compared with patients with normal pulmonary blood flow. Further, in patients with unobstructed collateral flow, proliferative changes appear early in the distal pulmonary arterioles, whereas in areas of lung supplied by stenosed collateral, a decreased number of microvessels may develop. Shunts or outflow tract procedures late in life, i.e., after 5 years of age, may increase the size of the central pulmonary arteries in these patients; however, right ventricular hypertension after VSD closure persists and is usually the result of an obstructed distal microvascular bed.

The systemic to pulmonary artery shunt and right ventricular to pulmonary artery homograft or right ventricular outflow patch provide increased flow to the native pulmonary arteries and may reduce the late incidence of vascular disease, especially if combined with collateral embolizations. The use of aortic or pulmonary valved homografts arising from the right ventricle has several additional advantages. Homografts have allowed successful surgical outcomes in patients with extremely small pulmonary arteries. For example, 5 of 7 patients (age, 9 months or younger) underwent successful placement of valved homograft in pulmonary arteries 3 mm or less in diameter, with long-term preservation of flow to both pulmonary arteries in all
patients. An additional important advantage of creating right ventricular to pulmonary artery continuity early in life is that it allows access to pulmonary arteries for balloon dilation of peripheral stenotic vessels, which appears to be necessary for a successful outcome in the overwhelming majority of these patients. The precise identification of native pulmonary artery segmental distribution can be made most accurately after adequate flow is provided to central pulmonary arteries. The latter can best be assessed by selective injections into the distal pulmonary artery tree (Fig 2). Finally, the staged approach allows selection of patients for final repair based on more complete physiological and anatomic data. Since most aortopulmonary collaterals can be closed by embolization,6 eventually most or all pulmonary blood flow in these patients will be supplied antegradely through the right ventricular outflow tract. Hence, any patient with TOF-PA who develops a net left-to-right shunt must have greater than systemic flow through mediastinal pulmonary arteries and should therefore tolerate VSD closure. This approach obviates the need for relying solely on measurements of pulmonary artery size to determine who might be an appropriate candidate for complete repair.18

This staged approach was originally based on several hypotheses: (1) increased flow through central pulmonary arteries encourages increases in vessel size and also angiogenesis of distal microvessels, whereas decreased pulmonary artery flow has the opposite effect, (2) these phenomena are most important early in life, and (3) aortopulmonary collaterals are unreliable sources of pulmonary blood flow because the stenoses that are often present are not amenable to repair or dilation; when unobstructed, these vessels lead to early distal obstructive changes. The relatively high success rate, in this first study of its kind bringing these patients to a satisfactory repair, appear to support these hypotheses.

Despite these advantages of the staged approach, which appears likely to allow ultimately successful repair in at least half of the patients with TOF-PA and diminutive pulmonary arteries, several important issues remain unsolved: (1) precise preoperative quantification of pulmonary arteries too small to permit primary repair remains uncertain, (2) the optimum timing for outflow tract creation, pulmonary artery dilations, and collateral embolizations is unclear, (3) the role for unifocalization, although necessary in some patients, remains uncertain, and (4) optimal methods for intraoperative protection of the myocardium and also of the central nervous system requires a clearer understanding at the cellular or ultrastructural level. Although the overall mortality rate (35%) was quite high, 4 of the 7

| TABLE 4. Hemodynamic Data Among Repaired Patients |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Conservative Therapy Group | Primary Repair Group | Shunt Group | Staged Outflow Group† |
|                                | 2               | 2               | 4             | 9               |
| Mean right ventricular/aortic pressure | 0.75           | 0.93           | 0.72          | 0.64          |
| Range                           | 0.4-1.1        | 0.85-1.0       | 0.5-0.77      | 0.5-0.95      |
| Mean pulmonary artery pressure, mm Hg* | 39             | 25             | 19            | 16            |
| Range                           | 10-68          | 14-44          | 16-20         | 11-25         |

*Mean of right and left pulmonary artery pressures combined.
†Nine of the 10 repaired patients in this group have undergone catheterization studies.
deaths can be attributed to inexperience with the process and may be avoidable.

It is difficult to draw firm conclusions from this initial procedure description for several reasons. There was a small number of patients in each subgroup, and lesions were heterogeneous. Important variables, including pulmonary artery size and distribution, number and distribution of multiple aortopulmonary collaterals, and age at surgical intervention, will need to be subjected to a more rigorous statistical analysis based on outcome variables. Biases may have been reinforced by dividing patients into anatomic and treatment categories to facilitate this study. Although this analysis has not permitted a definition of the optimal treatment for TOF-PA and diminutive pulmonary arteries, establishment of early right ventricle to pulmonary artery continuity with subsequent pulmonary artery dilations and collateral embolization has permitted eventual successful repair in a large percentage of patients. At the present time, we favor this management protocol. We anticipate that this alternative approach, which relies heavily on collaboration regarding decisions and management steps between cardiac surgeons and interventional cardiologists, will eventually allow successful repair in the major proportion of patients with TOF-PA and diminutive pulmonary arteries. Since the overall results using the other treatment modalities have been for the most part inadequate, we believe that these preliminary results justify further exploration of early staged repair.

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