Growth and Development of the Pulmonary Vascular Bed in Patients with Tetralogy of Fallot with or Without Pulmonary Atresia

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SUMMARY In a consecutive autopsy series of 17 patients with tetralogy of Fallot (TOF), including five patients with associated pulmonary atresia (TOF + PA), radiopaque material was injected into the pulmonary and collateral arteries and the lungs were examined using quantitative techniques to assess pulmonary vascular and alveolar structure and growth. Three types of systemic collateral arteries (SCA) were distinguished by their origin, each showing a characteristic type of "anastomosis" with a pulmonary artery: Bronchial artery collaterals arise from bronchial arteries (so judged by origin and distribution) and anastomose with pulmonary arteries inside the lung. Direct aortic collaterals arise from the descending aorta, enter the lung at the hilum and supply a lobe, or at least a segment. Inside the lung, structure and distribution are those of a pulmonary artery; outside the lung, those of a systemic artery. These vessels sometimes anastomose inside the lung with pulmonary arteries from neighboring segments of lobes. Indirect aortic collaterals arise from major branches of the aorta other than bronchial arteries (e.g. internal mammary, subclavian), and usually anastomose with the central pulmonary arteries outside the lung.

All three types of SCAs were found in TOF + PA, but only bronchial artery collaterals were found in TOF. SCAs narrowed at the site of anastomosis with a pulmonary artery; this apparently protected the peripheral intraacinar arteries from high flow and pressure and prevented changes of excessive muscularity and intimal hyperplasia.

In most patients, the intraacinar arteries were smaller than normal; in patients who had large, surgically created shunts of long duration they were fewer in number, of greater muscularity and with severe occlusive changes of intimal hyperplasia. The number of alveoli was reduced in almost all patients, but because alveolar size was increased, only a few patients had a small lung volume.

Early surgical correction of TOF may prevent the impairment in alveolar and vascular growth described here. In TOF + PA patients, selective arteriography of all large aortic collaterals should be performed preoperatively to determine their intrapulmonary distribution and relationship with central pulmonary arteries. This will help in selecting the surgical procedure and identify collaterals that can be safely ligated.

RECENT ADVANCES in cardiac surgery allow correction of tetralogy of Fallot (TOF) in infancy, which may be desirable for normal structural development of the lung. However, no study has been carried out to quantify the extent of impaired lung and vascular growth from infancy to adulthood in patients with TOF, including those with previous palliative procedures. In patients with TOF and associated pulmonary atresia (PA), it is difficult to determine the type and timing of surgical interventions that will optimally increase pulmonary blood flow. This is because of the difficulty in assessing preoperatively the relative importance of the central pulmonary and systemic collateral arteries (SCAs) and the degree of structural abnormality in the peripheral pulmonary vascular bed.

In the present study, we used arteriography and morphometric techniques to quantitatively assess lung growth and vascular development in a consecutive postmortem series of patients with TOF, including some with and some without PA. For each type of SCA distinguished by site of origin, we identified a pattern of anastomosis with pulmonary arteries.
Materials and Methods

Patient Population

We studied autopsy specimens from 17 patients who died during the last 3 years. Twelve patients had TOF without PA and five had TOF and PA (TOF + PA). The latter is often described as a pseudotruncus*1 or ventricular septal defect with PA.*4

Patients with Tetralogy of Fallot (table 1)

The 12 patients with TOF were 36 hours to 31 years old (median 2 years). Four of them had additional abnormalities, two intracardiac and two extracardiac. Eleven of the patients had had one or more surgical procedures. Six had had corrective surgery only, one had a palliative procedure only and four had had both.

TABLE 1. Patient Population, Type of Surgical Procedure and Cause of Death

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Associated abnormalities</th>
<th>Palliative surgery</th>
<th>Corrective surgery</th>
<th>Cause of death</th>
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<tbody>
<tr>
<td>Tetralogy of Fallot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 day</td>
<td>Diaphragmatic hernia</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>2</td>
<td>3 mo</td>
<td>IHSS</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>4 mo</td>
<td>Subglottic stenosis</td>
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<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>4 mo</td>
<td>CAVC</td>
<td>Modified LBT 3 mo 1 mo</td>
<td>4 mo 1 day</td>
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</tr>
<tr>
<td>5</td>
<td>7 mo</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
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<td>6</td>
<td>16 mo</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 yr</td>
</tr>
<tr>
<td>7</td>
<td>2 yr</td>
<td>LBT 3 mo 2 yr</td>
<td>2 yr 1 day</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>2 yr</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2 yr 2 day</td>
</tr>
<tr>
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<td>—</td>
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<td>—</td>
<td>6 yr 1 day</td>
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<tr>
<td>10</td>
<td>17 yr</td>
<td>Acquired pulmonary atresia (age 13–17 years)</td>
<td>(1) LBT 1 yr 11 yr</td>
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<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Waterston 12 yr 4 yr</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>26 yr</td>
<td>Potts</td>
<td>3 yr 12 yr</td>
<td>16 yr 10 yr</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>31 yr</td>
<td>Potts</td>
<td>8 mo 22 yr</td>
<td>22 yr 8 yr</td>
<td>—</td>
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<td>Tetralogy of Fallot with pulmonary atresia</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>2 yr</td>
<td>—</td>
<td>(1) Formalinization PDA 11 days 1 mo</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Waterston 1 mo 2 yr 3 days</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>5 yr</td>
<td>—</td>
<td>(1) RVOT patch and perforated patch closure of VSD 5 days 8 mo</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Patch plasty of pulmonary arteries 5 yr</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>10 yr</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10 yr</td>
</tr>
<tr>
<td>4</td>
<td>18 yr</td>
<td>—</td>
<td>(1) RVOT patch 9 yr 9 yr</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Repair RPA; aortic valve replacement 18 yr</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>20 yr</td>
<td>—</td>
<td>Modified LBT 10 yr 11 yr 20 yr 1 mo</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Patients with myocardial dysfunction who died intraoperatively could not be weaned from cardiopulmonary bypass; those who died in the early postoperative period had persistent low cardiac output.

Abbreviations: IHSS = idiopathic hypertrophic subaortic stenosis; CAVC = common atioventricular canal; LBT = left Blalock-Taussig shunt; VSD = ventricular septal defect; Waterston = Waterston anastomosis; Potts = Potts anastomosis; RVOT = right ventricular outflow tract; RPA = right pulmonary artery; PDA = patent ductus arteriosus.
**Type II:** Direct aortic branches. These are branches arising directly from the descending thoracic aorta.

**Type III:** Indirect aortic branches. These are branches arising from branches of the aorta other than bronchial; e.g., from subclavian, internal mammary and intercostal arteries.

**Hemodynamic Data**

Hemodynamic data obtained at cardiac catheterization are shown in table 2. Pulmonary artery pressure was elevated in four patients; three had surgically created systemic-to-pulmonary artery shunts of greater than 2 years' duration and one had pulmonary venous hypertension secondary to subaortic stenosis. Pulmonary artery pressure may have been elevated in TOF patient 11, who had a surgical shunt at the time of death, although it had been recorded as normal 8 years previously.

**Preparation of the Lungs**

In five of the TOF patients, both lungs were examined, and in seven, only the right lung was examined. Both lungs were examined in four of the TOF + PA patients and only the left lung was examined in the other. The lungs were incubated for 1 hour at 37°C. According to techniques previously described,15, 45, 46 the pulmonary artery was cannulated and a barium gelatin mixture (60°C) was injected at 100 cm H₂O pressure for 7 minutes and the artery was clamped; in the four TOF + PA patients who had direct aortic branch collateral arteries, these vessels were infused first. After each injection, a radiograph was taken to identify the region of lung filled. This procedure was repeated for all vessels. In three of the four patients, the entire lung was filled by injection into a single collateral artery, and in one patient a part of the contralateral lung was filled through a systemic artery branch that crossed the midline.

The lung was then inflated through the trachea or main stem bronchus with 10% formalin at 36 cm H₂O pressure, and when the pleural surface was tense, the bronchus was clamped. The lung volume was then determined by water displacement. The lung was fixed for 1 week in 10% formalin, and the lung volume was measured again.

**Dissection of the Circulation**

After fixation of the lungs, arteriograms were taken at 55 keV with a fixed tube distance of 60 cm. The main axial branch of the pulmonary artery to the lower lobe was then traced on the arteriogram from its origin at the hilum to the point it appeared to end or became difficult to follow accurately (this was usually ½ cm from the pleural surface). The luminal diameter of the artery was then measured at 25% intervals along the traced pathway and at each level its size was assessed by comparison with normal values.45, 46

In patients with TOF + PA, the pulmonary arteries and major SCAs were dissected from hilum to periphery. The relative size of each artery and the presence and size of communications between arteries were observed. Blocks of tissue 1 × 1 × 0.2 cm were taken from the regions of lung tissue with different vascular supply for microscopic analysis. Each large systemic-to-pulmonary artery anastomosis was excised and sectioned for microscopic analysis. One to three such anastomoses were identified in each patient.

The lungs were then cut parallel to the hilum into ½-inch slices. The proportions of the various lung struc-
tures were calculated by microscopic point-counting.47-49 Five random blocks were then taken from each lung, prepared and stained according to standard methods. Hematoxylin-eosin, Gomori’s trichrome and elastic van Gieson stains were used.

Microscopic Analysis

On each tissue section, features were analyzed by techniques previously described and the values were compared with normal values.46-49 The maturity of the peripheral pulmonary arteries was judged by their external diameter at several airway levels (terminal bronchiolus, respiratory bronchiolus, alveolar duct and alveolar wall), as well as by their concentration related to alveolar concentration. The muscularity of the arterioles was judged by the degree of extension of muscle into small peripheral arteries and by the thickness of the muscle coat of the normally muscular arteries calculated as a percentage wall thickness according to the formula

\[ \frac{2 \times \text{wall thickness}}{\text{external diameter}} \times 100. \]

Each section was examined for evidence of arterial thrombosis or the severe structural changes described by Heath and Edwards46 and for evidence of filling of the bronchial arteries. The veins were examined qualitatively for concentration and structure. After microscopic point counting, the number of alveoli per square centimeter and the total number of alveoli were calculated according to the method of Weibel and Gomez.48

Results

Lung Growth

Lung Volume (fig. 2)

Lung volume was small for age in five of 12 patients with TOF and in three of five patients with TOF + PA. The small lung volume did not correlate with the degree of hypoxemia measured at cardiac catheterization, but was associated in a general way with low pulmonary blood flow during the time of active lung growth. This is suggested by the fact that lung volume was normal or nearly normal in six patients with large surgically created systemic-to-pulmonary artery shunts, but was small in TOF + PA patient 1, who outgrew her shunt within 1 year. The volume of the right lung was also reduced in TOF patient 10, who had diminished pulmonary blood flow to that side because of a kinked Waterston shunt. In the same patient, lung volume was increased in a compensatory

<table>
<thead>
<tr>
<th>Pt</th>
<th>Aorta Pressure (mm Hg)</th>
<th>Pulmonary artery Pressure (mm Hg)</th>
<th>Qp/Qs</th>
<th>Hgb (g %)</th>
<th>Hct (%)</th>
<th>Interval cath to death</th>
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<tbody>
<tr>
<td>1</td>
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<td>No catheterization</td>
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<tr>
<td>2</td>
<td>91</td>
<td>120/68 (82)</td>
<td>33/10 (20)†</td>
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<td>35</td>
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<td>3</td>
<td>56</td>
<td>98/49 (69)</td>
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<td>13.3</td>
<td>39</td>
<td>2 mo</td>
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<td>—</td>
<td>80/47</td>
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<td>17.4</td>
<td>58</td>
<td>3 day</td>
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<td>76</td>
<td>104/66 (68)</td>
<td>25/10 (18)</td>
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<td>42</td>
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<tr>
<td>6</td>
<td>90</td>
<td>79/49 (61)</td>
<td>27/13 (19)</td>
<td>1.8</td>
<td>12.0</td>
<td>35</td>
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<td>7</td>
<td>83</td>
<td>87/46 (61)</td>
<td>—</td>
<td>14.1</td>
<td>39</td>
<td>5 day</td>
</tr>
<tr>
<td>8</td>
<td>78</td>
<td>82/53 (67)</td>
<td>—</td>
<td>17.7</td>
<td>59</td>
<td>2 mo</td>
</tr>
<tr>
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<td>83</td>
<td>113/56 (82)</td>
<td>73/48 (54)</td>
<td>1.2</td>
<td>16.5</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>96</td>
<td>106/60 (80)</td>
<td>26/15 (19)*</td>
<td>1.8</td>
<td>16.3</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>95</td>
<td>90/65 (80)</td>
<td>18/9 (15)</td>
<td>2.5</td>
<td>16.3</td>
<td>49</td>
</tr>
</tbody>
</table>

*Pulmonary artery pressure may have been elevated at the time of death in this patient, although it was normal at cardiac catheterization 8 years previously.
†Elevated pressure secondary to pulmonary venous hypertension in a patient with hypertrophic subaortic stenosis.
‡Pressure measured in the left pulmonary artery.

Abbreviations: Hgb = hemoglobin; Hct = hematocrit; ( ) = mean pressure; Qp/Qs = pulmonary-to-systemic flow ratio; cath = cardiac catheterization.
way in the left lung, where there was an adequate Blalock-Taussig shunt.

**Alveolar Number and Size (fig. 2)**

The total number of alveoli was reduced for age in 11 of 12 TOF patients and in two of the four TOF + PA patients in whom this value could be calculated. A reduced number of alveoli accounted for the reduced lung volume in all five TOF patients and in two of three TOF + PA patients. In the other patients with a reduced number of alveoli, lung volume was normal owing to a compensatory increase in alveolar size.

**Postmortem Arteriograms**

**Dissection and Microscopic Analysis of the Large Preacinar Arteries**

From the postmortem arteriograms, the axial pulmonary arteries, their luminal diameter and their rate of tapering could be analyzed in 11 of 12 patients with TOF and in four of five patients with TOF + PA (fig. 3). In two patients, dense background haze or leakage of barium into the parenchyma obscured the outline of the major pulmonary arteries.

**Tetralogy of Fallot**

In six of 11 patients with TOF, the pulmonary arteries at the hilum and proximally within the lung were small, but tapered abnormally slowly so that the luminal diameter tended to be normal or even increased peripherally (fig. 3). In the two patients who had surgically created systemic-to-pulmonary artery shunts for longer than 12 years, the pulmonary arteries were dilated proximally but tapered more abruptly than normal so that the luminal diameter was slightly narrower than normal (figs. 3 and 4). In two patients with TOF, the pulmonary arteries were small from hilum to periphery in one and normal along the whole arterial pathway in the other.

**Tetralogy of Fallot with Pulmonary Atresia**

In all patients with TOF + PA, the main, right and left pulmonary arteries were hypoplastic. Within the lung, however, the size of the pulmonary arteries...
varied greatly, being larger when communications with systemic collateral arteries were large (fig. 3).

**Systemic Collateral Arteries**

SCAs anastomosed with pulmonary arteries in three ways (fig. 1): inside the lung (intrapulmonary) at the hilar margin of the lung (hilar) and outside the lung (extrapulmonary). Each type of SCA anastomosed with a pulmonary artery in a characteristic way.

Bronchial artery branches formed an intrapulmonary anastomosis (fig. 5).

Direct aortic branches formed a hilar anastomosis and within the lung continued as a single vessel, a pulmonary artery, both histologically and in distribution (figs. 6 and 7). Usually, additional intrapulmonary anastomoses were formed between branches of a pulmonary artery from another lobe, the latter originating from a central pulmonary artery (fig. 6).

Indirect aortic branches formed an extrapulmonary anastomosis with a central pulmonary artery (fig. 8). We deduced that there were probably also anastomoses between these collateral and small immediately subpleural intraacinar arteries, although these were difficult to trace.

In all lungs studied, one type of SCA (and anastomosis) was predominant. For example, in TOF + PA patient 2, there were many large bronchial artery branches and some small indirect aortic branches. In TOF + PA patients 3, 4 and 5 we found mainly direct aortic branches (figs. 5-11). TOF + PA patient 1 had a large patent ductus arteriosus but no large systemic collateral arteries. In TOF patients, we found only small bronchial artery branches.

**Histology of the Site of Anastomosis Between a Pulmonary and a Systemic Collateral Artery**

Microscopic study revealed that a direct aortic branch collateral was a muscular systemic artery that anastomosed with, or, more correctly, was replaced by, an elastic pulmonary artery; the junction, in the hilar region of the lung, was marked by an eccentric mound of intimal hyperplasia that partially obstructed the vessel lumen and probably prevented the full transmission of flow and pressure from the systemic to the pulmonary side. Beyond the stenosed segment, which was approximately 1 cm long, the pulmonary artery often showed sinusoidal dilatation (fig. 10). Sometimes, the pulmonary artery within the lung remained dilated and tortuous throughout most of its preacinar arterial pathway (fig. 9). The peripheral intraacinar arteries, however, had only mild structural abnormalities.

The bronchial artery branch collaterals were muscular arteries that formed large intrapulmonary anastomoses with transitional pulmonary arteries (seven to nine elastic laminae). These junctions were marked by eccentric intimal hyperplasia. We believe that this is

**Figure 4.** (A) Postmortem arteriogram of a 2-year-old patient with tetralogy of Fallot (patient 8, table 1) (TOF). The axial arteries taper gradually and the background haze is dense due to filling of the many small peripheral arteries. (B) Postmortem arteriogram of a 26-year-old patient with TOF (patient 11, table 1) who had a Potts anastomosis for 17 years. The pulmonary arteries are dilated proximally but are small peripherally; the background haze is diminished because the number of small peripheral arteries is reduced.
FIGURE 5. (A) Relationship of the normal pulmonary arteries to airways and bronchial arteries. In the left lung, the arteries are shown in front of the bronchi so as not to obscure their structural features. (B) Some of the features dissected in patient 2, who had tetralogy of Fallot and pulmonary atresia. The bronchial arteries to both lungs are enlarged. In the right lung and the left upper lobe, the axial pulmonary arteries are severely hypoplastic, but in the left lower lobe and lingula the diameters of the axial pulmonary arteries are nearly normal. Large anastomoses with bronchial arteries were seen. (C) Dissection of the vessels in the left lower lobe shows large anastomoses (a) between branches of a bronchial artery (b) and a pulmonary artery (p). (D) The postmortem arteriogram shows large anastomosis (a) between a bronchial artery branch and a pulmonary artery in the left lower lobe. On the right, the axial arteries are hypoplastic. The dense background haze results from filling of the enlarged bronchial arteries.

the case for extrapulmonary anastomoses between muscular indirect aortic branch collaterals and elastic central pulmonary arteries or muscular subpleural intra-acinar arteries, but we could not, for technical reasons, study these accurately microscopically.

Structure and Growth of the Peripheral Pulmonary Arteries

The pulmonary vascular changes were similar in all lobes of each patient, with two exceptions. TOF patient 10 had decreased pulmonary blood flow to the right lung because of an obstructed Waterston shunt and increased pulmonary blood flow to the left lung through a Blalock-Taussig anastomosis; abnormalities were more severe in the left lung. In TOF + PA patient 4, almost all of the pulmonary blood flow was directed through the right ventricular outflow patch to the left upper lobe; the most severe abnormalities were in this lobe.

Extension of Muscle (fig. 12)

Increased muscularity, as judged by extension of muscle into arteries more peripheral than is normal, was seen in patients with TOF and TOF + PA who had associated abnormalities that tended to increase pulmonary blood flow or pressure. For example, of 11 patients with increased extension of muscle, seven had chronic alveolar hypoxia (in one patient as a result of a diaphragmatic hernia and in another as a result of subglottic stenosis), one patient had pulmonary venous hypertension (secondary to idiopathic hypertrophic subaortic stenosis) and one
A patient had pulmonary hypertension documented in the left upper lobe after a surgical procedure that directed pulmonary blood flow almost exclusively to that region.

**Wall Thickness (fig. 13)**

Seven of nine TOF and two of five TOF + PA patients who had abnormal peripheral extension of muscle also had an increase in the percentage wall thickness of the normally muscular arteries at intraacinar and preacinar artery levels.

**Arterial Size (fig. 14)**

In 11 of 17 patients with TOF or TOF + PA, arterial external diameter at one or more intraacinar airway levels was smaller than normal. In four of the TOF patients, only the arteries with alveolar ducts were small; in three others (all with systemic-to-pulmonary artery shunts), the arteries with terminal and respiratory bronchioli were also small. In three of five TOF + PA patients, the size of the arteries at each intraacinar airway level was 50–75% of normal. The arterial size was normal in one of the remaining patients and mildly reduced in the other.

**Number of Arteries (fig. 14)**

Only two of 12 TOF patients and two of five TOF + PA patients had a diminished concentration of small peripheral arteries; in the other patients, the number of arteries per 100 alveoli was either normal or slightly high. Considering the reduced number of alveoli, the total number of arteries was normal or somewhat low in most patients. The two TOF patients with a reduced concentration of arteries had surgically created systemic-to-pulmonary artery shunts for more than 12 years; one had elevated pulmonary vascular resistance.

**Figure 6.** (A) Tetralogy of Fallot plus pulmonary atresia in patient 3. Direct aortic branches become pulmonary arteries of the right upper and right lower lobe anteriorly and the left lower lobe and lingula. A smaller direct aortic branch crosses the midline and joins with the larger direct aortic branches. In the left lung, intrapulmonary anastomoses are present between vessels originating from direct aortic branches and pulmonary arteries from neighboring segments of lobes. (B) The postmortem arteriogram shows a direct aortic branch (s) just below the subclavian artery. Another direct aortic branch (t) is from the descending thoracic aorta and supplies the left upper and left lower lobes. Intrapulmonary anastomoses (a) between these vessels and pulmonary arteries of remaining lobes and present.
and the other may have had it as well, although recent hemodynamic data were not available.

The two patients with TOF + PA and a reduced concentration of arteries had pulmonary hypertension. In one, this was associated with a surgically created systemic-to-pulmonary artery shunt. In the other, a surgical procedure had directed pulmonary blood flow almost exclusively to the left upper lobe; the structural abnormality was limited to that region.

**Heath-Edwards Changes**

Two patients with TOF and one patient with TOF

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**Figure 7.** (A) Features of tetralogy of Fallot plus pulmonary atresia in patient 4. Direct aortic branches become pulmonary arteries to right upper lobe, right lower lobe and left lower lobe. There are no intrapulmonary anastomoses between branches of these vessels and branches from pulmonary artery of the right middle or left upper lobe. (B) The postmortem arteriogram of the right lung. c = collateral to right upper lobe; p = pulmonary artery to right middle lobe; s = poststenotic sinusoidal dilatation of collateral branch to right lower lobe. (C) Postmortem arteriogram of left lung. c = collateral branch to left lower lobe; p = pulmonary artery to left upper lobe and lingula.
FIGURE 8. An angiogram from the patient in figure 5. An indirect aortic branch (curved arrow), from the subclavian artery (SA) anastomoses with the pulmonary artery (PA) outside the lung. Poststenotic dilatation occurs just beyond the anastomosis, but distally the axial arteries are hypoplastic (straight arrow).

+ PA had advanced structural changes, grade IV–V of the Heath-Edwards classification. The TOF patients had surgically created systemic-to-pulmonary artery shunts for longer than 12 years. In the patient with an obstructed Waterston anastomosis and a patent left Blalock-Taussig anastomosis, these changes were localized to the left upper lobe; in the patient with a Potts shunt, they were found throughout both lungs. The TOF + PA patient had severe structural changes confined to a postoperatively hyperperfused left upper lobe.

Discussion

The Systemic Collateral Arteries

Embryologic Considerations

The direct aortic branch collaterals seem to have originated from the intersegmental branches of the dorsal aorta, which are normally present during the third and fourth weeks of gestation. This is when looping and conoseptal alignment occur, so it is tempting to speculate that development of PA at this time results in persistence of the connections between the intrapulmonary arteries and the local intersegmental arteries. Several features support this hypothesis: The site of anastomosis is at the hilum; the stenosis at the anastomotic site probably represents an attempt at involution of the intersegmental artery; direct aortic branches may provide the major blood supply to a lobe or a segment of a lobe; and the largest collateral arteries (in effect, the direct aortic branches) are associated with the smallest central pulmonary arteries.

Boyden showed that the bronchial arteries develop in the ninth gestational week, after the paired intersegmental arteries have been resorbed. It follows that the bronchial artery branches will become the dominant collateral blood supply when PA develops later in gestation. This is supported by the observation that large bronchial artery branches are not associated with direct aortic branches.

The origin of the indirect aortic branches seems least certain, but they seem to occur in later gestation. In our studies and in those of others, indirect aortic branches were found with bronchial artery branches but not with direct aortic collaterals.

Anastomotic Site

In studies of patients with TOF + PA, the variability in the type and number of collateral vessels and in the location of anastomoses with pulmonary arteries has been emphasized. Despite this variability, one pattern of collateral blood supply tends to predominate in each patient. Moreover, when a given collateral artery is recognized by its origin, the site at which it anastomoses with a pulmonary artery has, in our experience, been predictable. This is clinically useful because it serves as a guide in the cineangiographic identification of collateral vessels likely to provide nutrient blood supply to a lobe or segment of a lobe (i.e., direct aortic branches) and should therefore not be ligated unless an alternative or dual pathway is certain. It can also be determined whether the central pulmonary arteries have limited intrapulmonary distribution. If so, pulmonary blood flow may not increase appreciably with surgical placement of a conduit or a shunt, and peripheral vascular obstructive changes may develop. By establishing patterns of systemic-to-pulmonary artery anastomoses, we can predict the location of stenotic sites and direct our attention to them on the preoperative cineangiogram. These are important to identify, because if corrective surgery is to be undertaken, a conduit must be extended to an outflow patch placed to relieve any...
pulmonary branch stenosis that may have been caused at an anastomotic junction; if a shunt is to be placed, it should be to the pulmonary artery beyond such a stenotic segment.

An anastomosis without a stenosis may suggest the presence of severe pulmonary vascular changes, described as rare occurrences in the series of Theine et al.42 and Haworth.43 We did not find such changes in our patients. In our experience, direct aortic branches were "replaced" by pulmonary arteries at the hilum. Haworth43 described the occasional case in which the "junction" seems to take place well within the lung. Thus, in each patient, selective arteriography of all collaterals is necessary to obtain accurate diagnostic information.

Growth and Structure of Peripheral Arteries

Factors that Affect Number and Size

Diminished pulmonary blood flow appears to result in poor growth of the peripheral pulmonary arteries. In our series and in that of Hislop and Reid,15 patients who had decreased pulmonary blood flow sec-
ondary to TOF had intraacinar arteries of small external diameter. Patients with TOF + PA may also have small peripheral arteries despite systemic collateral blood supply. This finding suggests that the systemic collateral blood supply is probably inadequate in most patients. In patients with TOF or TOF + PA, arterial concentration is normal, but in patients with a more severe reduction in pulmonary blood flow as a result of PA and intact ventricular septum, Haworth and Reid43 observed that the intraacinar arteries were both small and abnormally few in number.

We have shown that the creation of a systemic-to-pulmonary artery shunt may dilate the axial arteries proximally, but the intraacinar arteries may remain small. Large surgical shunts44 or intracardiac left-to-right shunts45-47 result in a reduced external diameter of peripheral arteries. The internal diameter of the peripheral intraacinar arteries is also reduced because excessive muscularity encroaches on the lumen.

Factors that Affect Muscularity

In most patients with unoperated TOF and even in those with associated PA in the absence of complicat-

![Image](http://circ.ahajournals.org/FIGURE9.jpg)

**Figure 9.** (left) Posterior view of the right lung specimen in tetralogy of Fallot plus pulmonary atresia in patient 3. A direct aortic branch becomes the pulmonary artery of the right upper lobe and the posterior aspect of the right lower lobe. A pulmonary artery branches to the anterior segments of the right lower lobe. Brackets A and B represent areas of lung from which were taken microscopic sections seen to the right. Area A contained vessels that could be traced back to a direct aortic branch; area B contained vessels that could be traced back to a pulmonary artery. In both sections, the alveolar duct (AD) and alveolar wall (AW) vessels are normal in number and muscularity and nearly normal in size. Original magnification × 100; elastic Van Gieson stain.
GROWTH OF THE PULMONARY VASCULAR BED IN TOF/Rabinovitch et al.

**Figure 10.** (A) Anterior view of right lung from tetralogy of Fallot plus pulmonary atresia patient 4. The pulmonary artery (pa) branches to the right middle lobe. A direct aortic branch shows sinusoidal dilatation as it becomes the right lower lobe "pulmonary" artery, branching peripherally (ppa). (B) The left upper lobe has abnormally thick-walled pulmonary arteries (PA) that end in abrupt twigs (T). (C) A microscopic section taken from the region supplied by the ppa. The respiratory bronchiolus (RB) artery is normal in size and structure (thin-walled). (D) A respiratory bronchiolus and its artery from the region supplied by T. There is evidence of thrombosis and recanalization.

In other postmortem studies in which the patients were usually older and had severe, unpalliated TOF, muscular hypoplasia of the pulmonary arteries was described qualitatively. It was suggested that decreased pulmonary blood flow of long duration caused atrophy of pulmonary vascular smooth muscle. In only one patient in our series could we quantitatively show thinning of the media of the pulmonary arteries. She was the oldest patient who had not undergone even a palliative surgical procedure to increase pulmonary blood flow and had been the most severely cyanotic for the longest time.

In our series, the presence of shunts from SCAs in patients with TOF + PA did not result in increased muscularity of the intraacinar arteries, which might be expected if flow to the pulmonary vascular bed is excessive. Surgically created systemic-to-pulmonary artery shunts did cause abnormal extension of muscle into peripheral arteries and increased muscularity of the normally muscular arteries; more severe structural changes occurred if the shunts were of long duration. In some patients with TOF, excessive muscularization of the intraacinar arteries could
be attributed to other causes, such as diaphragmatic hernia, chronic hypoxia or pulmonary venous hypertension. Excessively muscular or small peripheral arteries may put patients with TOF or TOF + PA at higher risk surgically because the high pulmonary vascular resistance associated with these changes may be particularly demanding of a right ventricle after ventriculotomy.

![Figure 11](image1.png)

Figure 11. (A) Posterior view of the left lung in tetralogy of Fallot plus pulmonary atresia patient 4. Beneath the bronchus (Br) a direct aortic branch (DAB) enters the lung and dilates (c). Letters a, b and c denote regions from which the microscopic sections in panel B were taken. a = the aortic branch with a mound of stenotic eccentric intimal hyperplasia; b = distal dilatation of this vessel c = the dilated elastic pulmonary artery. Elastic Van Gieson stain; original magnification X 10.

![Figure 12](image2.png)

Figure 12. The intraacinar branching pattern. The shaded area represents the level at which, for the age listed alongside, half the arteries are muscularized. Each bar represents a patient. All patients with shunts have abnormal extension of muscle into peripheral arteries, as did three additional patients with associated intra- or extracardiac defects mentioned in the text. TOF = tetralogy of Fallot; PA = pulmonary atresia.
Growth and Development of Alveoli

The data from our patients with TOF and TOF + PA and the data of others suggest that diminished pulmonary blood flow results in a reduction in the number of alveoli. In patients with TOF or TOF + PA, lung volumes may be normal despite a reduced number of alveoli, but this means that the alveoli are enlarged and that the lung is somewhat emphysematous. The degree of reduction in the number of alveoli seems to be related to the severity and duration of hypoxemia, as patients with increased pulmonary blood flow due to either large SCAs or large surgical shunts seem to be less severely affected. The impaired growth of the lung in patients with TOF may be an important cause of abnormal pulmonary function.

Because two-thirds of the normal number of alveoli are present by 2 years of age and because the arteries by that age are two-thirds normal size and number, early repair of TOF could result in a normal number of alveoli and normal growth of proximal and peripheral pulmonary arteries. Thus, even during exercise, pulmonary function would be normal and pulmonary vascular resistance low.

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Hemodynamic Determinants of Pulmonary Valve Motion During Systole in Experimental Pulmonary Hypertension

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SUMMARY To clarify the determinants of pulmonary valve (PV) motion in pulmonary hypertension, we examined the correlations among PV echo patterns, the pulmonary artery (PA) flow curve just above the PA orifice and the pulmonary artery–right ventricle (PA–RV) pressure gradient. By constricting the PA, we could produce a variety of PV echo patterns, including mid-systolic semiclosure in open-chest dogs. Throughout the experiments, the PV echo pattern and PA flow curve were similar in pattern and timing. When the PV echo showed mid-systolic semiclosure with reopening, the PA flow curve showed a transient decrease followed by a transient increase during mid-systole. The PA–RV pressure gradient became trans-stenotic positive (PA pressure > RV pressure) and then negative in mid-systole only when the PV echo showed mid-systolic semiclosure with reopening. In conclusion, PV motion during systole may be instantaneously determined by PA flow change and the PA–RV pressure gradient during the cardiac cycle in experimental pulmonary hypertension.

ABNORMAL ECHO PATTERNS of the pulmonary valve (PV), including a small or absent “a” dip, decreased or negative diastolic slope, rapid opening slope, prolonged ejection period and mid-systolic semiclosure, have been reported to be useful in assessing pulmonary hypertension. However, the sensitivity and specificity of these echocardiographic findings are controversial. Acquabella et al. reported a lack of correlation between PV echo patterns and the pulmonary artery (PA) pressure.

The determinants of PV motion must be known to evaluate PV echograms in patients with pulmonary hypertension. This study was undertaken to clarify the hemodynamic determinants of PV motion during systole in experimental pulmonary hypertension.

Materials and Methods

Fourteen mongrel dogs that weighed 19–33 kg were anesthetized with i.v. pentobarbital, 30 mg/kg, and ventilated with room air. The heart was exposed through a mid-sternal thoracotomy. The echocardiographic examination of the PV was performed with a commercially available Sonocardiograph SSL 51U using a 0.5-cm-diameter, 3-MHz transducer. The PA blood flow curve was recorded by an electromagnetic flowmeter (Nihon-Kohden Co., model MF-27) with a probe attached to the PA about 1 cm above the PA orifice. Two catheter-tipped Millar micromanometers were introduced into the PA trunk, one through the right ventricular (RV) apex and the other through a...
Growth and development of the pulmonary vascular bed in patients with tetralogy of Fallot with or without pulmonary atresia.

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