Vascular structure in lung tissue obtained at biopsy correlated with pulmonary hemodynamic findings after repair of congenital heart defects

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ABSTRACT At the time of surgical repair, a lung biopsy was performed on patients with congenital heart defects who either had pulmonary hypertension or in whom it would be likely to develop if the lesion were not corrected. Pulmonary vascular changes, assessed morphometrically and also according to the classification of Heath and Edwards (Circulation 18: 533, 1958), were correlated with the postoperative pulmonary hemodynamic findings: mean pulmonary arterial pressure the day after correction and mean pulmonary arterial pressure and pulmonary vascular resistance measured 1 year later. On the first postoperative day, increased mean pulmonary arterial pressure was uncommon in patients with morphometric grade A or B (mild) biopsy findings and Heath-Edwards grade N (normal), and if it was present it was of a mild degree. Mean pulmonary arterial pressure was commonly elevated in those with grade B (severe) or C (mild or severe) and Heath-Edwards grade I biopsy results and was more frequently elevated in those with grade II findings. Moderate-to-severe elevation of mean pulmonary arterial pressure was invariable in patients with Heath-Edwards grade III changes regardless of the morphometric grade. One year after repair, mean pulmonary arterial pressure and/or pulmonary vascular resistance were normal in all patients whose conditions were corrected surgically before 9 months of age regardless of the severity of the pulmonary vascular changes. Values were normal in patients whose conditions were repaired surgically at 9 months of age or later who had grade A or B (mild) morphometric findings with any Heath-Edwards grade or grade B (severe) morphometric findings with Heath-Edwards grade I but were increased in half of the patients with grade B (severe) morphometric findings and Heath-Edwards grade II or with grade C (mild or severe) and Heath-Edwards grade I or II changes. Pulmonary arterial pressure and pulmonary vascular resistance were increased in all patients whose conditions were repaired after 2 years of age with grade C morphometric findings and to a severe degree if associated with Heath-Edwards grade III. Thus, although the Heath-Edwards grade can usually be used to identify patients at risk for pulmonary hypertension in the early postoperative period, both the morphometric and the Heath-Edwards grades as well as the age of the patient at the time of repair can be used to determine whether pulmonary arterial pressure and resistance eventually return to normal or remain elevated.


WE PREVIOUSLY analyzed lung tissue obtained at biopsy during surgical repair from patients with congenital heart defects and correlated the morphometric findings with the preoperative pulmonary hemodynamic data. We observed abnormalities in muscularization and growth of the pulmonary arteries associated with increased pulmonary blood flow, pressure, and resistance. In the present study, both the morphometric findings and the changes described by Heath and Edwards have been correlated with mean pulmonary arterial pressure and pulmonary vascular resistance after surgical repair. Hemodynamic data were assessed both in the immediate postoperative period and about 1 year after surgery at the time of the routine follow-up cardiac catheterization study. We also considered whether severe pulmonary vascular changes may have influenced mortality at surgery or during the follow-up period.

Materials and methods

Patients undergoing biopsy. At the Children’s Hospital Medical Center, Boston, over a 4½ year period (July 1976 to January 1981 inclusive), patients with congenital heart defects...
of the type frequently complicated by pulmonary hypertension underwent lung biopsy at the time of corrective surgery (table I). No attempt was made to select patients, but biopsies were more regularly performed in those who had elevated pulmonary arterial pressure and less regularly in those who had complications such as a prolonged cardiopulmonary bypass time or excessive bleeding.

Assessment of lung specimens. In each patient, the lung specimen was taken, processed, and analyzed according to a protocol previously reported. Structural findings of increased muscularization and impaired growth of the pulmonary arteries were assessed morphometrically and graded as follows:

Grade A: Extension of muscle into peripheral arteries is normally nonmuscular, either as a solitary finding or associated with a mild increase in the medial wall thickness of the normally muscular arteries (≤1.5 times normal).

Grade B: Extension as in grade A but greater mediastral hypertrophy; subdivided into B (mild) if medial wall thickness is greater than 1.5 but less than 2 times normal and B (severe) if wall thickness is 2 times normal or greater.

Grade C: Features of B (severe), with a decreased number of peripheral arteries relative to alveoli and usually decreased arterial size; subdivided into C (mild) when more than half the normal number of arteries is present and C (severe) when half the normal number of arteries or less is observed.

The morphometric grading system evolved from correlation with preoperative pulmonary hemodynamic findings. Grades A and B (mild) correlated with increased pulmonary blood flow but normal or minimal elevation in mean pulmonary arterial pressure; grade B (severe) correlated with increased pulmonary vascular resistance.

### TABLE 1

<table>
<thead>
<tr>
<th>Major diagnosis</th>
<th>No. of lung biopsy samples analyzed</th>
<th>Ppa and/or Rp measured after</th>
<th>Ppa measured day and time</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD Simple</td>
<td>72</td>
<td>46</td>
<td>21</td>
</tr>
<tr>
<td>Complexa</td>
<td>9</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>d-TGA Simple</td>
<td>49</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>d-TGA Complexb</td>
<td>5</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>CAVC</td>
<td>34</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Left-sided obstruction or regurgitation</td>
<td>21</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>ASD II</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ASD I</td>
<td>15</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>9</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>215</td>
<td>74</td>
<td>67</td>
</tr>
</tbody>
</table>

Ppa = pulmonary arterial pressure; Rp = pulmonary vascular resistance; VSD = ventricular septal defect; d-TGA = d-transposition of the great arteries; DORV = double outlet right ventricle; CAVC = complete arteriovenous canal; ASD II or I = atrial septal defect secundum or primum; PDA = patent ductus arteriosus.

aAssociated abnormality, e.g., coarctation of the aorta, PDA.
bLarge VSD or PDA.

Each biopsy section was also graded according to the Heath-Edwards classification. In Heath-Edwards grade N (normal) there is no striking evidence of medial hypertrophy (i.e., equivalent to morphometric grade A or B [mild]). In Heath-Edwards grade I medial hypertrophy can be appreciated subjectively (i.e., equivalent to morphometric grade B [severe]). Heath-Edwards grade II describes the presence of eccentric or concentric intimal hyperplasia, and in grade III occlusive intimal hyperplasia with hyalinization of the media is observed. The more severe Heath-Edwards grade IV through VI pulmonary vascular changes are not relevant to this analysis. One patient had grade IV changes, but no postoperative pulmonary hemodynamic data are available. The others with grade IV through VI changes had marked elevation in pulmonary vascular resistance and the preoperative cardiac catheterization study. Thus they underwent biopsy first, and when the severity of pulmonary vascular disease was confirmed they were excluded from definitive repair.

Assessment of pulmonary hypertension on the first postoperative day. In the 74 patients who underwent lung biopsy, had catheters placed during the operation, and were stable (i.e., not receiving dopamine or vasodilators), we were able to correlate structural findings with values of mean pulmonary arterial pressure obtained 18 to 24 hr (1 day) after repair. Mean pulmonary arterial pressure was measured during expiration with the patient on the respirator, fraction of inspiratory oxygen (FlO2) of 0.4 or less, an intermittent mandatory ventilation rate of 8/min or lower, and a positive end-expiratory pressure of 4 cm H2O or less. In all patients, mean left atrial pressure was 15 mm Hg or lower, systemic arterial saturation was 95% or greater, and, if present, the step up in saturation between the right atrium and the pulmonary artery was 5% or less.

We also compared values of mean pulmonary arterial pressure obtained the day after surgery with the assessment of mean pulmonary arterial pressure and pulmonary vascular resistance from the preoperative cardiac catheterization study performed a median interval of 1 month before repair (range 1 day to 2 years). In all cases pulmonary vascular resistance was calculated by the Fick principle with a measured O2 consumption.

Assessment of pulmonary hypertension at routine 1 year postoperative cardiac catheterization. In 67 patients we were able to correlate the findings of the lung biopsy with mean pulmonary arterial pressure and in 60 of 67 with pulmonary vascular resistance values obtained at the routine 1 year postoperative cardiac catheterization study. Excluded from this analysis were only a few patients with hemodynamically significant residual intracardiac shunting (ratio of pulmonary to systemic flow greater than 2:1) or mitral regurgitation or stenosis (mean left atrial pressure greater than 12 mm Hg). Nearly all patients underwent catheterization 12 months after surgery but a few patients, because of family convenience, were studied either as early as 9 months or as late as 2½ years after operation.

Each patient was sedated half an hour before the catheterization study with meperidine compound (25 mg meperidine, 12.5 mg promethazine, 12.5 mg/ml chlorpromazine) given at a dose of 1 ml per 10 kg. Hemodynamic measurements were made before the cineangiographic studies. Pulmonary vascular resistance was calculated by the Fick principle with the use of a measured oxygen consumption or by thermodilution technique. In 10 patients, pulmonary arterial pressure and resistance were assessed both in room air and after 10 min of breathing a hypoxic gas mixture (FlO2 0.15). In four patients mean pulmonary blood flow and elevated mean pulmonary arterial pressure (usually at least half systemic level) but normal pulmonary vascular resistance; with grade C (mild) pulmonary vascular resistance was usually 3.5 U/m² or greater but less than 6 U/m² and with grade C (severe) pulmonary vascular resistance was often 6 U/m² or greater.
arterial pressure was measured and pulmonary vascular resistance was assessed 5 min after an intravenous infusion of isoproterenol was started (0.05 \( \mu \)g/kg/min) and in one patient mean pulmonary arterial pressure was measured both at rest and during 5 min exercise on the bicycle.

Values of mean pulmonary arterial pressure and pulmonary vascular resistance from the 1 year postoperative cardiac catheterization study were compared with those obtained before surgery. In 22 patients, pulmonary arterial pressure was measured both on the first postoperative day and 1 year later (table 1); these values were also compared.

**Analysis of data.** Associations between grade of biopsy specimen and mean pulmonary arterial pressure the day after surgery were tested with the chi-square test. Data from all patients were included in one analysis and another was done on data from the subgroup with isolated ventricular septal defects only. Normal mean pulmonary arterial pressure was taken as 18 mm Hg or less and normal pulmonary vascular resistance as less than 3.5 U/m\(^2\). as previously published. Linear regression analysis was used to determine whether there was a correlation between preoperative and postoperative mean pulmonary arterial pressure and pulmonary vascular resistance.

**Results**

**Pulmonary arterial pressure the day after surgical correction** (figure 1). Increased mean pulmonary arterial pressure the day after surgical correction correlated in frequency and severity with the Heath-Edwards grade of pulmonary vascular change, i.e., I, II, or III (chi-square = 17.54, \( p < .001 \); figure 1, A). When the subgroups of patients with isolated ventricular septal defects were analyzed separately in a similar manner by the chi-square test differences were also significant (chi-square = 15.45, \( p < .01 \)).

While 15 of 20 patients with Heath-Edwards II and III changes also had grade C morphometric findings, the morphometric grade did not indicate the propensity for increased mean pulmonary arterial pressure any more accurately than did the Heath-Edwards grade. For example, in two of seven patients with Heath-Edwards III changes and morphometric A and B (mild) changes mean pulmonary arterial pressure was as high the day after repair as in the five with morphometric C changes.

In the individual patients there was not a close correlation between the mean pulmonary arterial pressure or pulmonary vascular resistance measured before surgery and the mean pulmonary arterial pressure the day after repair (figure 1, B and C), although a significant trend was apparent: \( r = .48 \) where postoperative mean pulmonary arterial pressure = 0.24 preoperative mean pulmonary arterial pressure + 12.2 (\( p < .01 \)) and \( r = .25 \) where postoperative mean pulmonary arterial pressure = 0.82 preoperative pulmonary vascular resistance + 20.1 (\( p < .05 \)).

**Pulmonary arterial pressure and resistance 1 year after surgical correction** (figure 2, A and B). Increased mean pulmonary arterial pressure and pulmonary vascular resistance at the 1 year postoperative cardiac catheterization study correlated with the age at repair and with both the morphometric as well as the Heath-Edwards grade of the lung biopsy. For example, of 33 patients whose lesions were surgically corrected before they were 9 months of age, only two had a minimal elevation in mean pulmonary arterial pressure (19 and 21 mm Hg, respectively) and in neither was pulmonary vascular resistance increased — this, despite the presence in lung biopsy specimens taken at surgery of structural changes as severe as morphometric grade C and/or Heath-Edwards grades II and III in seven patients (figures 2, A and B and 3A).

Six of the 24 patients whose lesions were surgically corrected when they were between 9 months and 2 years of the age, however, had increased mean pulmonary arterial pressure, and in four pulmonary vascular resistance was also elevated. One undergoing repair at age 9 months had complete atrioventricular canal and another transposition of the great arteries. One other undergoing repair at 1 year had complete atrioventricular canal and the last patient undergoing correction at 2 years had a ventricular septal defects, but a coarctation had been repaired in earlier infancy. All four had C (mild) and/or Heath-Edwards II changes (figure 3B and table 2). Five of the 10 patients who underwent surgical correction after 2 years of age had increased mean pulmonary arterial pressure and in four pulmonary vascular resistance values were also elevated. All four had grade C (severe) changes, and one had Heath-Edwards grade I and the other three Heath-Edwards grade III (table 2) changes.

It was of interest that changes of Heath-Edwards grade III were not associated with elevated mean pulmonary arterial pressure or pulmonary vascular resistance at the 1 year postoperative assessment in the two patients who were less than 2 years of age at repair and in whom muscularity and growth of the pulmonary vascular bed had been relatively normal (i.e., of morphometric grade A or B [mild]).

**Response of the pulmonary vascular bed to stress.** Arterial \( P_{o_2} \) decreased significantly (mean ± SE, 87 ± 2.7 to 46.1 ± 1.5 mm Hg) in the 10 patients who, at the time of the 1 year postoperative catheterization study, were exposed to short periods of hypoxia (\( F_{o_2} \) 0.15; figure 4, A). Regardless of the severity of changes observed in the previous lung biopsy specimen, if pulmonary vascular resistance was normal in room air (eight of 10 patients) the value during hypoxia was at best mildly elevated (<5 U/m\(^2\)). Both patients with elevated pulmonary vascular resistance values in room...
FIGURE 1. a, Lung biopsy grade is correlated with mean pulmonary arterial pressure recorded the day after surgical repair. The dashed vertical line separates the normal from the abnormally elevated pressure values and the dotted horizontal lines separate the biopsy grades. Note that with the more severe Heath-Edwards changes on lung biopsy tissue there is a trend toward a greater proportion of patients with elevated pulmonary arterial pressure and higher values. A, B, and C are morphometric grades; M = mild, S = severe; N, I, II, & III are Heath-Edwards grades; N = normal; * = no patients in this group. VSD = ventricular septal defect, DTGA = D-transposition of the great arteries, CAVC = complete atrioventricular canal; complex = associated abnormality. b, The correlation between preoperative and postoperative pulmonary arterial pressure values illustrated. c, The correlation between preoperative pulmonary vascular resistance and postoperative pulmonary arterial pressure.
air (5 to 6 U/m²), however, had a marked further rise during hypoxia (7 to 10 U/m²).

All four patients given isoproterenol infusion and the one that exercised on a bicycle increased their cardiac output by 25% to 50% (figure 4, B). There was a decrease in pulmonary vascular resistance value with isoproterenol infusion in three of four patients, including one in whom baseline pulmonary vascular resistance was elevated and who had had grade C (severe) and Heath-Edwards III changes. In the remaining patient and in the one who exercised on the bicycle baseline pulmonary vascular resistance did not change.

Patients in whom mean pulmonary arterial pressure values were available before surgery and the day and the year after repair and with grade B (severe) and Heath-Edwards grade I or II changes showed a decrease in this parameter at each postoperative time and values 1 year after repair were normal or near normal.

**FIGURE 2.** Graph correlating lung biopsy grade with mean pulmonary arterial pressure (a) and with mean pulmonary vascular resistance (b) both of which were recorded at the 1 year postoperative cardiac catheterization study. Vertical lines separate normal from abnormally elevated values and horizontal lines separate the various biopsy grades. Patients who underwent repair within the first 8 months of life, but not those operated upon later, had normal or near normal pulmonary arterial pressure and normal resistance 1 year after surgery regardless of the severity of their structural changes. Abbreviations are as in figure 1.
In the group of patients with C (mild or severe) and Heath-Edwards I and II changes there was no significant difference between the 1 day and 1 year postoperative mean pulmonary arterial pressure values (figure 5).

There was no correlation between the pulmonary arterial pressure or resistance values recorded in the preoperative study and those obtained 1 year after surgery. For example, postoperative elevation in pulmonary vascular resistance was present in three of 21 patients with preoperative elevations and in five of 35 with normal preoperative values.

Mortality. In each patient that died a complete postmortem examination was carried out and the diagnosis made after the lung biopsy was confirmed by morphometric analysis of the injected pulmonary vascular bed. In none of the patients studied who died either at surgery or during the follow-up period was mortality the result of high pulmonary vascular resistance due to any other apparent cause than severe structural changes in the pulmonary vessels (table 3). We can only speculate on the basis of data previously presented in this article that patients with more severe structural abnormalities had higher pulmonary arterial pressure values after surgery and this may have added to the risk from otherwise manageable complications, such as moderate mitral regurgitation or a residual ventricular septal defect.

Discussion

Grading pulmonary vascular changes. We graded the pulmonary vascular changes both according to the morphometric as well as the Heath-Edwards systems with the assumption that morphometric grade B (severe) was approximately equal to Heath-Edwards grade I. By ranking the specimens from lung biopsy according to the severity of abnormality by Heath-Edwards grade we were able to predict whether pulmonary hypertension would be present, and to some extent how severe it might be, in the early postoperative period. This ranking system proved less predictive of the presence and severity of pulmonary hypertension in the late postoperative period. It seems, at least for patients undergoing surgery in the first 2 years of life, that even severe intimal change (Heath-Edwards grade III) is not prognostic of persistent elevation in pulmo-
FIGURE 3B. Photomicrographs taken of lung biopsy tissue obtained at repair of a 9-month-old patient with a complete atrioventricular canal (grades I and C [mild]). Observe the mild intimal hyperplasia (arrows) and severe medial hypertrophy in the respiratory bronchioles arteries in A (left) and the reduced arterial concentration relative to alveolar in the field in B (right). Arrow indicates one artery. This patient had persistent elevation in pulmonary vascular resistance 1 year after surgery.

TABLE 2
Patients with abnormal pulmonary hemodynamics 1 year after repair

<table>
<thead>
<tr>
<th>Diagnosis (associated lesion)</th>
<th>Age at repair</th>
<th>Pprepair $P_{pa}$, $P_{la}$, $R_{p}$</th>
<th>1 year postrepair $P_{pa}$, $P_{la}$, $R_{p}$</th>
<th>Lung biopsy grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(mm Hg)</td>
<td>(U/m²)</td>
<td>(mm Hg)</td>
</tr>
<tr>
<td>Patients with elevated pulmonary vascular resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAVC (9 mo)</td>
<td>1 yr</td>
<td>40</td>
<td>4.0</td>
<td>27</td>
</tr>
<tr>
<td>VSD (s/p CoA)</td>
<td>2 yr</td>
<td>45</td>
<td>1.1</td>
<td>27</td>
</tr>
<tr>
<td>IAA (VSD) (8 yr)</td>
<td>1 yr</td>
<td>43</td>
<td>19</td>
<td>36</td>
</tr>
<tr>
<td>Patients with elevated pulmonary arterial pressure only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD (4 mo)</td>
<td>2 yr</td>
<td>45</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>CAVC (8 mo)</td>
<td>2 yr</td>
<td>45</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>ASD II (VSD and ASD) (15 yr)</td>
<td>2 yr</td>
<td>44</td>
<td>9</td>
<td>40</td>
</tr>
</tbody>
</table>

$P_{la}$ = mean left atrial pressure; $M$ = morphometric grade; H-E = Heath-Edwards grade; $C_1 = C$ mild; $C_2 = C$ severe; $B_2 = B$ severe; IAA = interrupted aortic arch; s/p CoA = stent post repair of coarctation of the aorta; other abbreviations are as in table 1.
Pulmonary hypertension in the early postoperative period. Since in the early postoperative period cardiac output was not measured we were unable to assess the degree of elevation in pulmonary vascular resistance. It is possible that some of the variation in pulmonary arterial pressure may have been associated with differences in cardiac output and hence may have reflected a similar degree of elevation in pulmonary vascular resistance. While some patients with a mild degree of elevation in mean pulmonary arterial pressure may have had normal pulmonary vascular resistance owing
to a high cardiac output, it is unlikely that this was the case in patients with larger increases.

That structural changes grade B (severe)–Heath-Edwards grade I may be associated with moderate elevation in mean pulmonary arterial pressure in the early postoperative period suggests that the abnormally muscular pulmonary vascular bed has a heightened reactivity. In experimental studies Tucker et al. have related the severity of hypoxic pulmonary vasoconstriction in different species of animals to their amount of pulmonary vascular smooth muscle. The postoperative stimuli that might trigger heightened pulmonary vascular reactivity, i.e., severe pulmonary vasoconstriction, have been discussed by Jones et al. and, in addition to hypoxia, these include acidosis, hypoglycemia, and hypocalemia. Also, platelets damaged by cardiopulmonary bypass may release thromboxane A2, a potent vasoconstrictor. Abnormal handling or production of vasoactive substances by the vascular endothelium of the lung may continue in the early postoperative period and this could also conceivably cause pulmonary vasoconstriction. It is in the group of patients with increased pulmonary vascular reactivity that pulmonary vasodilators may be most effective.

Pulmonary hypertension is observed in the early postoperative period with a similar range of severity when the pulmonary vascular bed is either abnormally muscular (grades I and B) or abnormally muscular as well as restricted in terms of number and size of vessels (grades I and C). Increased muscularity may therefore be a more important determinant of heightened pulmonary vascular reactivity than decreased reserve. Regardless of the morphometric grade, in patients with intimal hyperplasia (Heath-Edwards grades II and III) pulmonary hypertension is consistently present in the early postoperative period and is usually quite severe. This is either because the hyperplastic endothelium so occludes the vascular lumen as to cause severe restriction to flow or because it is so metabolically deranged that vasoactive mediators, which heighten the reactivity of the pulmonary circulation, are produced in high concentration. Alternatively platelets may interact with this abnormal endothelium, causing release of thromboxane A2, which results in vasoconstriction.

Analysis of lung tissue from biopsy should be particularly useful in choosing appropriate candidates for Fontan-type surgical procedures. In this group of patients pulmonary hemodynamics may be difficult to assess before surgery and the Fontan principle requires normal pulmonary arterial pressure in the early postoperative period. While pulmonary vasodilators may be effective in lowering pulmonary arterial pressure, they cannot always be depended upon to do so, and their efficacy remains essentially unproven in the patient who has undergone Fontan’s procedure. We have therefore maintained as a guideline for operability our previously published criteria of lung biopsy findings. That is, we are concerned that a patient may not be a suitable Fontan candidate if there are structural changes as severe as morphometric grade B (severe)–Heath-Edwards grade I.

**Residual pulmonary hypertension.** Previous investigators have examined either regression of structural changes in the pulmonary vascular bed after surgical palliation of a congenital heart defect or functional recovery of the pulmonary circulation after correction. This is the first study in which both the morphometric and Heath-Edwards pulmonary vascular changes have been correlated with both the early and late postoperative pulmonary hemodynamics. It was reassuring to observe that patients who underwent surgical correction in infancy (first 8 months of life) had normal pulmonary hemodynamics 1 year after repair despite marked abnormalities at the time of repair with regard to structural remodeling and growth of the pulmonary arteries and/or intimal hyperplasia. The normal response to hypoxia, isoproterenol, or exercise attests to appropriate reactivity and reserve of the pulmonary circulation and suggests that after surgery there is both regression of the structural changes as well as subsequent growth of new vessels and perhaps even some “catch-up” growth. Some of the patients operated on at 9 months of age or later with pulmonary
TABLE 3  
Characteristics of patients who died

<table>
<thead>
<tr>
<th>Major diagnosis (associated diagnoses)</th>
<th>Age at death (mo)</th>
<th>Time after surgery (mo)</th>
<th>Factors contributing to death and other details</th>
<th>Lung biopsy grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD (PDA)</td>
<td>1 3/4</td>
<td>5/30</td>
<td>Sepsis; subglottic stenosis</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>VSD (double-outlet left ventricle)</td>
<td>2</td>
<td>1/30</td>
<td>Left ventricular infarct</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>VSD (multiple midmuscular VSDs)</td>
<td>3</td>
<td>2/30</td>
<td>Right ventricular infarct</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>VSD</td>
<td>3</td>
<td>2</td>
<td>Suddenly at home; aspiration</td>
<td>C&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>VSD (ASD II)</td>
<td>30</td>
<td>7/30</td>
<td>Residual VSD; low cardiac output after reoperation</td>
<td>C&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>D-TGA (VSD and PS)</td>
<td>1</td>
<td>4/30</td>
<td>PA band place after residual VSD; papillary muscle infarction; dic</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>DORV</td>
<td>1 14/30</td>
<td>1/30</td>
<td>Recurrent atrial and ventricular arrhythmias exploratory right ventriculotomy: right ventricular infarct</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>D-TGA (VSD)</td>
<td>1 21/30</td>
<td>At surgery</td>
<td>Right ventricular fibrosis and calcification</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>D-TGA (VSD)</td>
<td>2</td>
<td>At surgery</td>
<td>Severe left ventricular outflow obstruction</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>D-TGA (VSD)</td>
<td>5</td>
<td>5</td>
<td>One day after reoperation for pulmonary venous obstruction; cause of death uncertain</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>D-TGA</td>
<td>7</td>
<td>5/30</td>
<td>Respiratory arrest after aspiration of feeding</td>
<td>A N</td>
</tr>
<tr>
<td>CAVC</td>
<td>2</td>
<td>17/30</td>
<td>At reoperation for mitral valve regurgitation</td>
<td>C&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>CAVC</td>
<td>6</td>
<td>14/30</td>
<td>Severe postoperative mitral regurgitation; died at cardiac catheter study after LV angiogram</td>
<td>C&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>CAVC</td>
<td>7</td>
<td>1 2/12</td>
<td>Low output after mitral valve replacement</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>CAVC</td>
<td>7</td>
<td>At surgery</td>
<td>? right coronary arterial air embolism</td>
<td>C&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>CAVC (coa)</td>
<td>7</td>
<td>1/30</td>
<td>Reoperation for coarctation of aorta then renal shutdown</td>
<td>C&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>CAVC</td>
<td>7</td>
<td>1 18/30</td>
<td>Severe mitral regurgitation; low output after mitral valve replacement</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>CAVC</td>
<td>12</td>
<td>2</td>
<td>Suddenly at home; cause not established</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>CAVC</td>
<td>12</td>
<td>7/30</td>
<td>Dehiscence of prosthetic mitral valve</td>
<td>C&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>CAVC (s/p PA band)</td>
<td>13</td>
<td>3/30</td>
<td>Postoperative mitral stenosis and residual VSD</td>
<td>A 0</td>
</tr>
<tr>
<td>CAVC</td>
<td>14</td>
<td>18/30</td>
<td>One week after reoperation, residual VSD sepsis; dic</td>
<td>C&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
<tr>
<td>ASD primum</td>
<td>9</td>
<td>7/30</td>
<td>Low output; mitral stenosis</td>
<td>B&lt;sub&gt;1&lt;/sub&gt; I</td>
</tr>
</tbody>
</table>

M = morphometric grade; H-E = Health-Edwards grade; PA = pulmonary artery; PS = pulmonary stenosis; M = mild; S = severe; dic = disseminated intravascular coagulation; LV = left ventricular; other abbreviations are as in tables 1 and 2.

vascular changes as severe as in those operated on earlier had persistent elevation in pulmonary vascular resistance. This suggests that regression of extension of muscle, medial hypertrophy, and intimal hyperplasia was less complete, that the potential for growth of new normal vessels was limited, or both.

In studies of patients with a ventricular septal defect, DuShane et al. observed that persistent elevation in pulmonary vascular resistance was common only in those corrected after 2 years of age. In our series, one patient with a ventricular septal defect who had undergone repair of coarctation of the aorta in infancy and who was operated on again at 2 years of age had persistent elevation in pulmonary vascular resistance but it was mild. Two patients with complete atrioventricular canal corrected at 9 and 12 months, respectively, and one patient with D-transposition of the great arteries and an associated ventricular septal defect repaired at 9 months of age had persistent elevation in pulmonary vascular resistance. Thus, there seems to be some influence of the congenital heart lesion itself on the propensity for residual pulmonary hypertension as well as for the early development of severe pulmonary vascular changes.

It was of particular interest that the intimal hyperplasia documented in the arteries of a patient with D-transposition of the great arteries and intact ventricular septum was not prognostic of rapidly progressive elevation in pulmonary vascular resistance after repair as has been suggested in studies of others.
In patients operated on when they were between 9 months and 2 years of age, medial hypertrophy seemed to regress but it appeared that there was limited growth of new vessels, i.e., patients with grades I and C changes may have persistent pulmonary hypertension. There is probably little capacity for regression of intimal hyperplasia (Heath-Edwards grade II or III), and patients with a numerically limited vascular bed, e.g., grade II or III-C, may be at a particular disadvantage since they have little capacity for growth of new normal arteries. These features are even more evident in patients operated on after they are 2 years of age.

Hallidie-Smith et al.22 studied the functional status of patients who had pulmonary hypertension associated with large ventricular septal defects closed when they were between 3 and 12 years of age. They observed striking pulmonary hypertension on effort 6 to 16 years after repair.

Experimental data support the observation made in this clinical study that the age at which an abnormal stimulus is relieved may be critical in allowing for regression and new growth. Rendas and Reid23 have shown catch-up growth in the pulmonary vascular bed of piglets after the takedown of previously constructed aortopulmonary shunts. In our experiments we subjected infant rats to a month of hypobaric hypoxia beginning when they were 8 days old.24 The rat lung, however, is fully developed after the first month of life,25 so that subsequent recovery in room air resulted in incomplete regression of hypoxia-induced extension of muscle and medial hypertrophy, minimal new growth of vessels, and significant residual pulmonary hypertension.

Ultrastructural studies of Meyrick and Reid26 have shown that regression of hypoxia-induced medial hypertrophy in the pulmonary artery of the rat is accompanied by an increase in the production of elastin apparent in the subintima. Thus, the vessel, while less muscular, may be still less compliant. This suggests a mechanism for the effort-induced pulmonary hypertension reported in the study of Hallidie-Smith et al.22

It is difficult to explain why a few patients with grade C and/or grade II changes had near-normal pulmonary arterial pressure in the early postoperative period but elevations in pressure at later follow-up cardiac catheterization. Conceivably, the cardiac output in the early postoperative period was low, and so pulmonary vascular resistance was either the same or higher than that observed later. A high cardiac output explains the normal levels of pulmonary vascular resistance in a few patients studied in the late postoperative period who had mild elevation in pulmonary arterial pressure.

Mortality and pulmonary vascular changes. Natural history,27 catheter, autopsy,28 and lung biopsy29 studies have increased our awareness of the congenital heart defects in which pulmonary vascular disease will occur at an early age and progress rapidly. This, coupled with the success of surgical repair in infancy over the past decade,30,31 has resulted in the referral of patients for corrective procedures at an earlier age. Thus, few children are expected to die as a result of severe structural changes in the pulmonary vascular bed and severely elevated pulmonary vascular resistance alone in the early postoperative period. Patients at high risk for this fatal outcome can be identified by severe and irreversible elevation in pulmonary vascular resistance at the preoperative cardiac catheterization study or, when the findings are equivocal, by severe pulmonary vascular changes in lung biopsy tissue obtained before repair.14,32 The pulmonary vascular bed with less than prohibitive structural changes may, however, be abnormally reactive and severe elevation in pulmonary vascular resistance may ensue with relatively minor postoperative complications.

Pathogenesis of the structural changes in the pulmonary vascular bed. During childhood the intra-acinar pulmonary arteries become muscular as they grow in size.33 This presumably results from differentiation of precursor cells (pericytes and intermediate cells) located within the vascular wall to mature smooth muscle.34 Muscularization is accelerated in patients with congenital heart defects that produce a left-to-right shunt, perhaps because the wide pulmonary pulse pressure stretches the peripheral arteries, which simulates growth.

The increase in the medial wall thickness of the normally muscular arteries seems to result from failure of the fetal muscularity to regress35 and from hypertrophy and hyperplasia of preexisting smooth muscle cells. Since this structural change appears only when extension of muscle into peripheral arteries has become severe, it may represent a work hypertrophy that is a response to the increased resistance in the distal pulmonary vascular bed produced by abnormally muscular and constricted small arteries. Alternatively, the shearing forces produced by increased pulmonary blood flow and pressure may lead to platelet release of a smooth muscle mitogenic factor.36

Reduction in arterial concentration relative to alveolar concentration probably results either from small vessels closing down and being reabsorbed, from their failure to proliferate normally, or from both. In small and abnormally muscular peripheral arteries, the endothelium bulges into the lumen. It is tempting to specu-
late that abnormal interaction of platelets with this "swollen" endothelium may lead to the release of thromboxane A₂ and subsequent vasoconstriction. The vessel may then shut down completely or plug with a fibrin platelet thrombus and, when no longer able to accept blood, may resorb. Alternatively, abnormally muscularized peripheral arteries may in some way be inhibited in their ability to grow in number and size and therefore may not be able to maintain pace with alveolar development.

The pathogenesis of intimal hyperplasia and of the later degenerative changes described by Heath and Edwards is not known. Ultrastructural studies of lung biopsy tissue from patients with congenital heart defects and increased pulmonary blood flow and pressure have demonstrated partial denudation of the endothelium of the more proximal intra-acinar arteries, i.e., those at terminal and respiratory bronchiolus level. Intimal hyperplasia may represent an overwhelming experimental attempt to regenerate these areas as this has been shown experimentally and is believed to be the basis for atherogenesis in systemic arteries. While the endothelium is more likely to become denuded when the shearing forces are strongest, i.e., with high flow and high pressure, high flow alone may be enough. This might explain the appearance of intimal hyperplasia without medial hypertrophy in several patients in our series and in patients with atrial septal defects. Intimal hyperplasia may also occur in the polycythemic patient with either low or high flow stimulated by fibrin deposition and thrombus formation.

Conclusions. It seems that early corrective surgery is the best safeguard against the persistence or progression of structural changes in the pulmonary vascular bed. Future directions in research should be aimed both at determining how to induce regression of structural changes (extension of muscle, medial hypertrophy and mild intimal hyperplasia) and how to stimulate growth of new vessels. Also, achieving a better understanding of the mechanism of abnormal pulmonary vascular reactivity should lead to its ultimate control.

We thank Dr. Alexander S. Nadas, Chief, Department of Cardiology, for his continued interest and support of our work and Dr. Margaret M. Wood, Biostatistician, The Hospital for Sick Children, Toronto, Ontario, for help with the statistical analysis of this study. We also thank Mr. Carl Chipman for helping to gather the postoperative data, Ms. Linda Washington and Ms. Ellen Hornung for secretarial assistance, and Ms. Emily Flynn for preparing the illustrations.

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Erratum

The influence of changes in lipid values induced by cholestyramine and diet on progression of coronary artery disease: results of the NHLBI Type II Coronary Intervention Study. Circulation 69: 325, 1984

The names of two authors were inadvertently excluded from the submitted manuscript. They are Frank T. Lindgren, Ph.D., and David W. Anderson, M.D., Ph.D., both of Donner Laboratory, Lawrence Berkeley Laboratory, University of California, Berkeley.
Vascular structure in lung tissue obtained at biopsy correlated with pulmonary hemodynamic findings after repair of congenital heart defects.
M Rabinovitch, J F Keane, W I Norwood, A R Castaneda and L Reid

Circulation. 1984;69:655-667
doi: 10.1161/01.CIR.69.4.655
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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