Lung Biopsy in Congenital Heart Disease: 
A Morphometric Approach to Pulmonary Vascular Disease

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SUMMARY Fifty patients with congenital heart disease, ages 2 days–30 years (median 12 months) at cardiac surgery, underwent lung biopsy to assess pulmonary vascular disease (PVD). Twenty-six had ventricular septal defects (VSD), 17 d-transposition of the great arteries (D-TGA), and seven, defects of the atrioventricular canal (AVC). Quantitative morphologic data was correlated with hemodynamic data. Three new grades of PVD were observed. Abnormal extension of muscle into peripheral arteries (grade A) was found in all patients; all had increased pulmonary blood flow. In addition, 38 of 50 patients had an increase in percentage arterial wall thickness (grade B); this correlated with elevation in pulmonary artery (PA) pressure ($r = 0.59$). Another 10 of 50 patients had, in addition to A and B, a reduction in the number of small arteries (grade C); nine of 10 were patients with elevated PA resistance > 3.5 u/m² ($P < 0.005$). All three patients with Heath-Edwards changes of grade III or worse also had grade C. Reduction in peripheral arterial number probably precedes obliterator PVD and may identify those patients in whom, despite corrective surgery, PVD will progress.

MOST CONGENITAL HEART DEFECTS can now be corrected surgically during infancy or early childhood, but the timing of operative intervention is critical since the presence of pulmonary vascular disease (manifest as severe elevation in the pulmonary vascular resistance (PVR)) is the primary impediment to a successful outcome. Choosing the best time for surgery is difficult because clinical, electrocardiographic, echocardiographic, and hemodynamic findings do not always distinguish reversible from irreversible disease. It is also not possible to predict in which patients pulmonary vascular disease will progress despite successful surgical repair, nor is it possible to identify those who will survive but with an abnormal pulmonary circulation, as judged by inappropriate increase in pulmonary arterial pressure on exercise.

Help with these difficult clinical problems is provided by structural analysis of the pulmonary vascular bed. Heath and Edwards graded pulmonary vascular disease according to structural changes in the pulmonary arteries, but their classification as a method of analysis has several drawbacks. First, the more severe Heath-Edwards changes (grade IV and higher), although seen, are unusual in the first two years of life, even in the presence of severely elevated PVR. Second, those advanced changes, if present, are often "spotty" or irregularly distributed throughout the lung so that they may not be present in a small piece of biopsy tissue.

Recently, by a new quantitative method of analysis, additional features of pulmonary vascular changes associated with congenital heart disease have been analyzed. This new method was first applied to the study of postmortem lungs in which the pulmonary arteries were distended with a barium-gelatin mixture and the bronchial tree subsequently inflated with formalin. Three important characteristics of pulmonary artery development were assessed by histologic examination of the lung tissue: 1) the degree of extension of muscle as judged by the size and position of small arteries in which it was present, 2) the thickness of the arterial medial muscular coat, and 3) the concentration of small peripheral arteries per unit area, judged in relation to the alveolar concentration. These features were compared with the normal for the same age and changes established, quantified and analyzed for statistical significance. Thus, appropriate evaluation of abnormalities in the very young and developing lung was possible. Since the distribution of such abnormalities has been shown to be uniform throughout the lung, their assessment by examination of biopsy material is possible.

In our study this method of analysis was applied to lung tissue obtained at biopsy from patients, mostly under 2 years of age, who were being operated on for one of three congenital heart defects associated with the development of pulmonary vascular disease: 1) ventricular septal defect (VSD); 2) d-transposition of the great arteries (D-TGA); and 3) defects of the atrioventricular canal (AVC). We have analyzed the structural changes and correlated them with hemodynamic data obtained both preoperatively at a recent cardiac catheterization, and immediately postoperatively in the recovery room. We have studied
the reproducibility of our results and have speculated about their prognostic significance.

Materials and Methods

Patient Population

Over a 12-month period, lung biopsy was performed on 50 patients, 26 of whom had a VSD, 17 of whom had D-TGA and seven of whom had defects of AVC, incomplete in two (primum atrial septal defect) and complete in five. Patients ranged in age from 2 days–30 years (median 12 months) and in weight from 3–50 kg (median 7 kg). Additional cardiac defects were often present. Of the patients with VSD, 10 of 26 had other abnormalities, including coarctation of the aorta (two), pulmonary stenosis (two), aortic regurgitation (two), atrial septal defect (two), and patent ductus arteriosus (two). In patients with D-TGA nine of 17 had additional abnormalities, including sub-pulmonic obstruction in five with a gradient of less than 60 mm Hg in three, 10 mm Hg in one case associated with a VSD, and with an unknown gradient in the remaining case. Other abnormalities associated with D-TGA included isolated VSD (one), VSD and pulmonary band (two) and patent ductus arteriosus (one). Of the seven patients with AVC two had pulmonary stenosis secondary to pulmonary artery banding in early infancy, necessitating a right Blalock-Taussig anastomosis in one patient.

Cardiac catheterization preceded surgery by a median period of four weeks (range two days to six years). Although in four of 50 patients the most recent available hemodynamic data was from a preoperative catheterization one to six years before surgery, two were older patients in whom there was evidence that the pulmonary artery pressure (PAP) had been normal for many years. In the other two, a very tight pulmonary artery band had made it impossible to enter the pulmonary artery later for pressure measurement. In 15 patients, hemodynamic calculations of pulmonary vascular resistance were based on measured oxygen consumption, while in 35 assumed oxygen consumption values were used.\textsuperscript{36, 37} In all patients pulmonary blood flow (PBF) (1/min/m\textsuperscript{2}), mean pulmonary artery pressure (PAP) (mm Hg), and mean pulmonary vascular resistance (PVR) in units/m\textsuperscript{2} were measured. \textsuperscript{37}PVR was calculated from the difference between mean pulmonary artery and left atrial pressures divided by the pulmonary oxygen consumption, then divided by the difference in oxygen saturation between pulmonary arteries and veins multiplied by the hemoglobin capacity. Hemodynamic data was available immediately after surgery from studies in the postoperative recovery room in 19 of 26 patients with VSD and in five of seven with AVC. For these studies all calculations were based on assumed oxygen consumption values.\textsuperscript{36, 37}

Biopsy Technique

Biopsy was performed after the intracardiac repair was completed and portamine had been administered. The lungs were fully inflated at a pressure of 22–34 cm of water. Two “c” clamps were placed on the upper medial aspect of the right lung to isolate a piece of tissue 1 × 2 × 0.5 cm. The tissue between the clamps was incised and the distal clamp containing the inflated tissue was submerged for 10 minutes in either glutaraldehyde (2.5%) 1:2 in 4% formalin, or glutaraldehyde (2.5%) (osmolarity = 434 mosm/l). The clamp was then released and the tissue was taken to the pathology department for 2 additional hours of fixation. After routine paraffin embedding, sections were stained with hematoxylin eosin, Gomori’s trichrome and elastic Van Gieson stain. The last was the most useful for measuring the thickness of the arterial muscular coat and assessing the extension of muscle into small peripheral arteries.

Quantitative Assessment of Biopsy Tissue

The state of the lung tissue and degree of inflation was assessed. Figure 1 shows a well-inflated biopsy from a patient with an AVC. Poor inflation, gross hemorrhage, collapse or infection made interpretation of the pulmonary vascular changes difficult.

The Arteries

Microscopically, the total number of arteries present in all fields of section was evaluated (mean 25, range 8–40). The following features of peripheral arterial structure were studied: The external diameter of an artery was measured with a calibrated eyepiece micrometer between the external elastic laminae across the shorter axis of the vessel. Wall thickness was measured from external to internal elastic lamina. Percent wall thickness was then calculated:

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

Arteries were grouped according to size and the percentage wall thickness calculated for each size range. The structure of the arterial wall, whether muscular, partially muscular or nonmuscular, was established. Where a small artery accompanied a small airway, it was also characterized or landmarked by reference to the type of airway it accompanied; the levels recognized were pre-acinar (PA) terminal bronchiolus (TB), respiratory bronchiolus (RB) alveolar duct (AD) and alveolar wall (AW). In this way, the structure of the artery could be related to airway level offering one way of assessing extension of muscle along the arterial pathway. Thus, increased arterial muscularity is apparent from an increased wall thickness as related to the size of an artery or to the presence of muscle in arteries which are either smaller or in a more peripheral position along the arterial pathway than is normal. The number of arteries larger than 10 μm and alveoli were counted in the lung section and the results were expressed as a ratio. This made allowance for any difference in the degree of inflation in the various biopsy specimens. For each biopsy all fields in the section were ex-
LUNG BIOPSY IN CONGENITAL HEART DISEASE/Rabinovitch et al.: A typical, well-inflated biopsy, this one from a patient with a defect of the atrioventricular canal. (Elastic Van Gieson stain; magnification ×10).

FIGURE 1. A typical, well-inflated biopsy, this one from a patient with a defect of the atrioventricular canal. (Elastic Van Gieson stain; magnification ×10).

examined, the mean number at ×20 power being 8 fields (range 5–16).

Normal Values

Age-related measurements of arterial structure in the normal lung have only been established on distended vessels, injected at autopsy. Four of the patients in the present series died within two weeks of surgery, so findings in the injected lung were compared with those in the uninjected biopsy tissue and "correction" factors were determined (table 1). The external diameter of injected arteries was 1.3–2.5 times greater than arteries at a similar level all along

<table>
<thead>
<tr>
<th>Name</th>
<th>Age (mo)</th>
<th>A/a</th>
<th>Mean % WT 50-100%</th>
<th>% Arteries in alveolar walls with muscular wall</th>
<th>External diameter</th>
<th>Externally muscularized arteries</th>
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<td>BX PM</td>
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<td>17 17</td>
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<td>6</td>
<td>6</td>
<td>10 4</td>
<td>30 30</td>
<td>120 300</td>
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</table>

*Normal Values* for lungs where arteries were distended have been obtained from references 28-35. Extrapolated biopsy values represent the upper and lower limits of normal for percent wall thickness and external diameter, respectively.

Abbreviations: A/a = alveolar artery ratio; BX = biopsy; PM = postmortem; RB = respiratory bronchiolar artery; RAC = radial alveolar count; %WT = mean percent wall thickness; %AW = mean percent alveolar wall arteries muscularized; mo = month.
Table 2. Ventricular Septal Defects (26 Patients)

<table>
<thead>
<tr>
<th>Name</th>
<th>Age (years)</th>
<th>Preop/postop cath data</th>
<th>Interval cath-surgery (wks)</th>
<th>RAC</th>
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<td>Mean (mm Hg)</td>
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<td>56/---</td>
<td>16/-</td>
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<tr>
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<td>8/</td>
<td>12.5/-</td>
</tr>
<tr>
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<td>9/5</td>
<td>4.1/2.9</td>
</tr>
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</tr>
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<td>57/-</td>
<td>10/-</td>
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<td>11/-</td>
<td>7/-</td>
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</table>

* Measured oxygen consumption.

Abbreviations: a = coarctation; b = patent ductus arteriosus; c = pulmonary stenosis; ii = Heath-Edwards Grade II; iii = Heath-Edwards Grade III; d = atrial septal defect; e = aortic regurgitation; PBF = pulmonary blood flow; preop = preoperative; postop = postoperative; PAP = mean pulmonary arterial pressure; LAP = mean left atrial pressure; PVR = pulmonary vascular resistance; RAC = radial alveolar counts; A/a = alveolar artery ratio; RB = accompanying respiratory bronchioles; AD = accompanying alveolar duct; AW = accompanying alveolar wall; 0–50 μ, 50–100 μ = artery diameter; M = fully muscularized; P = partially muscularized; N = nonmuscularized (applies to alveolar duct and wall arteries).

the intra-acinar arterial pathway in biopsy tissue. To avoid overestimating the difference, arteries in biopsy tissue were judged abnormally small only if they were less than 40% of the size of distended vessels at a similar level. Arteries in which there was marked constriction, as judged by a very curly appearance of the external and internal elastic laminae, were noted but not measured. On biopsy tissue, nonmuscular vessels less than 10 μm were considered capillaries.

The mean percentage wall thickness of arteries 50–100 μm in diameter in biopsy tissue was as much as 2.5 times greater than of arteries of the same size in the injected lung. In distended vessels of 50–100 μm diameter, a percentage wall thickness of 8% is considered normal in children younger than 4 months of age, and 4% is considered normal in older children. By applying a correction factor of 2.5 we considered increased muscularity to be present if the percentage wall thickness was greater than 20% before the first four months and greater than 10% thereafter. Thus, we probably underestimated the muscularity of some vessels. The majority of muscular arteries most evenly distended seen in the biopsy tissue were 50–100 μm in diameter, so in this group, because of sample size, the
thickness of the medial muscle coat was evaluated most accurately. The extension of muscle along the arterial pathway is considered in relation both to the position (accompanying airways) and size of the vessels. The position of an artery in the lung field is obviously the same in the injected and uninjected lung, but a correction factor must be applied in relating the structure of the vessel to its size. The ratio of arteries to alveoli is the same in the injected and uninjected lung.

Other Studies (Veins and Parenchyma)

In the veins increased muscularity was assessed qualitatively by an increase in wall thickness of the larger vessels and by the presence of muscle in smaller veins than normal. The state of alveolar development was determined by radial alveolar counts.

Briefly, a perpendicular is drawn from the center of a RB to the periphery, be that a connective tissue septa or the pleural surface. The number of alveoli transected is a measure of alveolar development at any age.

Observer Variation

To assess interobserver variation, 10 biopsies were evaluated by two observers. To assess intraobserver variation, five were read twice by the same observer six months apart. No significant difference between or within observers was noted (P < 0.005). For the various landmarked artery groups, mean measurements of external diameter differed by ± 5 μm. Measurements of percentage wall thickness usually varied by no more than ± 2-3% in the various size groups and the assessment of the extension of

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**Table 2. (Continued)**

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<th>Artery size (μ)</th>
<th>External wall thickness</th>
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<td>RB</td>
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<td>65.2 ± 4.8</td>
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<td>31.9 ± 3.4</td>
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TABLE 3.  Transposition of the Great Arteries (17 Patients)

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<th>Name</th>
<th>Age (years)</th>
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<th>Interval cath-surgery</th>
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<td>PBF (l/min/m²)</td>
<td>PAP Mean (mm Hg)</td>
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<td>NE 5</td>
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<tr>
<td>2. NW</td>
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<td>3/12</td>
<td>6.6</td>
<td>16 4</td>
</tr>
<tr>
<td>5. CZ</td>
<td>3/12</td>
<td>5.4*</td>
<td>9 8</td>
</tr>
<tr>
<td>6. JT</td>
<td>5/12</td>
<td>15.2</td>
<td>10 8</td>
</tr>
<tr>
<td>7. BR</td>
<td>6/12</td>
<td>—</td>
<td>15 5</td>
</tr>
<tr>
<td>8. LT</td>
<td>7/12</td>
<td>—</td>
<td>10 6</td>
</tr>
<tr>
<td>9. PC</td>
<td>8/12</td>
<td>18.2</td>
<td>9 3</td>
</tr>
<tr>
<td>10. CD</td>
<td>8/12</td>
<td>—</td>
<td>10 8</td>
</tr>
<tr>
<td>11. JT</td>
<td>9/12</td>
<td>—</td>
<td>NE 9</td>
</tr>
<tr>
<td>12. DB</td>
<td>10/12</td>
<td>—</td>
<td>NE 4</td>
</tr>
<tr>
<td>13. MG</td>
<td>11/12</td>
<td>—</td>
<td>NE 5</td>
</tr>
<tr>
<td>14. RW</td>
<td>1 4/12</td>
<td>10.5</td>
<td>20 5</td>
</tr>
<tr>
<td>15. AS</td>
<td>1 10/12</td>
<td>8.3</td>
<td>23 8</td>
</tr>
<tr>
<td>16. MS</td>
<td>8</td>
<td>1.4</td>
<td>7 4</td>
</tr>
<tr>
<td>17. ES</td>
<td>12</td>
<td>6.3*</td>
<td>78 4</td>
</tr>
</tbody>
</table>

Abbreviations: f = status post pulmonary artery band; g = ventricular septal defect; iv = Heath-Edward Grade IV; v = Heath-Edward Grade V; LVP = left ventricular pressure; NE = not entered. See tables 1 and 2 for other abbreviations.

Results (tables 2, 3, 4 and 5)

Ventricular Septal Defect (26 patients) (table 2)

**Hemodynamic Data**

Of the 26 patients with VSDs, seven had normal PAP and 19 had pulmonary artery hypertension (PAP > 20 mm Hg). Ten of those with pulmonary artery hypertension had elevated PVR > 2.4 u/m², and in six of 10 PVR was > 3.5 u/m². Hemodynamic data was available immediately after surgery in 19 of 26 patients. In 13 of 16 with preoperative pulmonary artery hypertension, PAP had fallen to between 13-35 mm Hg. In three it remained unchanged. Three of 13 with residual elevation in PVR (PVR > 3 u/m²) had elevated PAP > 35 mm Hg preoperatively.

The VSD was closed in all except one child (patient 15) who had elevated PVR of 12 u/m² and a coarctation of the aorta; only the coarctation was resected.

**Arteries**

In all 26 patients muscle had extended into arteries more peripheral than normal for age. This was the only abnormality noted in four patients, all having increased PBF but a normal PAP. When PAP was elevated and other pulmonary arterial changes present, the abnormal extension of muscle into peripheral arteries was more pronounced (fig. 2).

In 22 patients abnormal extension of muscle into peripheral arteries was accompanied by an abnormally thickened medial muscular coat of the muscular intra-acinar arteries. In three, all with normal PAP, this was less than twice normal for age. In 16 of 19 patients with elevated PAP, wall thickness approached or was greater than twice normal (P < 0.008) (fig. 3). Two of three patients with pulmonary artery hypertension but with increased percent wall thickness less than twice normal were both less than 2 months of age. The other patient had only mild increase in PAP.

The arteries were abnormally small in 18 of the 21 patients 5 months of age or older. In 15 of these patients, they were about two-thirds of normal size and in three, approximately half the normal size. Arterial size was normal in four out of five patients 4 months of age or less (P < 0.01).

Six patients had, in addition to abnormal extension of muscle and medial hypertrophy greater than twice normal, a reduction in the number of small peripheral arteries for age (fig. 4). All six had significant elevation in PVR preoperatively, to > 3.5 u/m² (P < 0.005).

Three of the VSD patients had arterial changes,
more severe than those classified by Heath and Edwards as grade I (medial hypertrophy); two patients (3 and 12) had grade II (intimal change) and the other (patient 15) grade III (occlusive changes with intimal hyalinization). One of the patients with grade II and the patient with grade III changes also had a reduced number of small peripheral arteries.

**Veins**

In 16 of 26 cases the veins showed an increase in muscularity which did not correlate with either the level of left atrial pressure, the magnitude of the left-to-right shunt or the duration of congestive heart failure. The greatest increase in venous muscularity occurred in two patients with coarctation of the aorta, although neither had evidence of left ventricular dysfunction.

**Alveoli**

The radial alveolar counts were normal in all patients older than 5 months of age, but in younger patients were more than 2 sds above the normal value.

**D-Transposition of the Great Arteries (17 Patients) (Table 3)**

**Hemodynamic Data**

In 14 of 17 patients with D-TGA the pulmonary artery was entered. In 11 of 14 the PAP was normal and in three it was elevated. In one, who was 1 month of age with a patent ductus arteriosus (patient 2), it was three-fourths systemic; in one, 12 years of age with a VSD (patient 17), it was equal to systemic; and in one, 22 months of age with a VSD and pulmonary artery band (patient 15) it was only mildly elevated. Immediate postoperative hemodynamic data were not available in any of the patients.

**Arteries**

In all 17 patients muscle extended into smaller and more peripheral arteries than is normal and in seven of 17 patients this was the only abnormality observed; all had increased PBF but normal PAP. Three young patients with abnormal extension of muscle which was particularly severe required an early Mustard operation after developing progressive cyanosis despite an adequate septostomy. Also, abnormal extension of muscle along the arterial pathway occurred even in the presence of pulmonary stenosis.

Abnormal extension of muscle was associated with increased thickness of the medial muscular coat in the remaining 10 patients. In three of five patients where the medial hypertrophy was mild with respect to age the PAP was normal for age. One exception was an infant less than 1 month of age in whom the PAP was 41 mm Hg. The other, an older child in whom the PAP was only mildly elevated. Severe medial hypertrophy (% wall thickness = 51%) in one patient was associated with systemic PAP. Another patient also had severe medial hypertrophy but a PAP of only 10

**Table 3. (Continued)**

<table>
<thead>
<tr>
<th>Artery size (μ)</th>
<th>External wall thickness</th>
<th>Extension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-50μ</td>
<td>50-100μ</td>
</tr>
<tr>
<td>RB 55 ± 4.2</td>
<td>24</td>
<td>23.7 ± 1.4</td>
</tr>
<tr>
<td>AD 39 ± 1</td>
<td>31</td>
<td>25 ± 2.7</td>
</tr>
<tr>
<td>48.4 ± 4.3</td>
<td>44 ± 1.4</td>
<td>31.5 ± 3.8</td>
</tr>
<tr>
<td>40 ± 30</td>
<td>72 ± 3</td>
<td>34 ± 1</td>
</tr>
<tr>
<td>99.2</td>
<td>60.8</td>
<td>43.7</td>
</tr>
<tr>
<td>71.6 ± 14.9</td>
<td>54 ± 6.7</td>
<td>26.3 ± 22</td>
</tr>
<tr>
<td>92 ± 1.8</td>
<td>41.6 ± 9.3</td>
<td>29.4 ± 4.5</td>
</tr>
<tr>
<td>69.5 ± 44</td>
<td>40.2 ± 7.6</td>
<td>27.5 ± 3.6</td>
</tr>
<tr>
<td>54.6</td>
<td>58.8 ± 2.7</td>
<td>24.5 ± 2.8</td>
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<tr>
<td>79.6 ± 7.6</td>
<td>38 ± 4</td>
<td>23.6 ± 1.7</td>
</tr>
<tr>
<td>84.5</td>
<td>74.2 ± 7</td>
<td>36.4</td>
</tr>
<tr>
<td>67.5 ± 8</td>
<td>64.5 ± 7</td>
<td>41.4 ± 4.4</td>
</tr>
<tr>
<td>50.1 ± 3.2</td>
<td>20.8 ± 12.5</td>
<td>31.8 ± 1.8</td>
</tr>
<tr>
<td>73.7 ± 7</td>
<td>55 ± 5</td>
<td>36.8 ± 2.9</td>
</tr>
<tr>
<td>79.6 ± 11.2</td>
<td>54 ± 3</td>
<td>34</td>
</tr>
<tr>
<td>82.5 ± 12</td>
<td>—</td>
<td>26</td>
</tr>
<tr>
<td>52.5 ± 7.5</td>
<td>—</td>
<td>30</td>
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TABLE 4. Endocardial Cushion Defects (Seven Patients)

<table>
<thead>
<tr>
<th>Name</th>
<th>Age (years)</th>
<th>PBF (l/min/m²)</th>
<th>PAP Mean (mm Hg)</th>
<th>LAP Mean (mm Hg)</th>
<th>PVR cath-surgery (u/m³)</th>
<th>Interval cath-surgery (wks)</th>
<th>RAC</th>
<th>A/a</th>
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<tbody>
<tr>
<td>JP</td>
<td>5/12</td>
<td>9/3.6</td>
<td>66/52</td>
<td>18/14</td>
<td>6/10.6</td>
<td>1</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>JV</td>
<td>1</td>
<td>8.1/6.4</td>
<td>55/28</td>
<td>6/13</td>
<td>5.9/2.2</td>
<td>20</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>WM</td>
<td>1/2/12</td>
<td>11.5/7.5</td>
<td>65/29</td>
<td>6/12</td>
<td>5.1/2.7</td>
<td>12</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>KD</td>
<td>1/4/12</td>
<td>16.3/—</td>
<td>50/—</td>
<td>18/—</td>
<td>2/—</td>
<td>4</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>EE</td>
<td>7</td>
<td>7/4.9</td>
<td>25/26</td>
<td>6/14</td>
<td>2.8/6.9</td>
<td>2 yrs</td>
<td>8</td>
<td>10</td>
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<tr>
<td>MT</td>
<td>12</td>
<td>2/—</td>
<td>8/—</td>
<td>8/—</td>
<td>1/—</td>
<td>1 yr</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>AH</td>
<td>15</td>
<td>9.3/6.6</td>
<td>28/26</td>
<td>8/6</td>
<td>3/1.1</td>
<td>3</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

*Atrial septal defect primum and mitral regurgitation as opposed to complete atrioventricular canal (no asterisk).

Abbreviation: h = status post-right Blalock-Taussig anastomosis. (See tables 1, 2 and 3 for other abbreviations).

mm Hg. This patient (16) had severe subpulmonic stenosis, an associated defect which, in patients with D-TGA, does not always permit accurate preoperative evaluation of PAP.12

In the two patients over 2 years of age, the arteries were significantly smaller than normal. In those less than 2 years of age they tended to be smaller, but not significantly so.

Two patients had, in addition, a reduction in the number of small arteries. Both had obliteratorive arterial change. One (patient 17) showed plexiform lesions (Heath-Edwards grade IV) and one (patient 16) chronic dilatation lesions (Heath-Edwards grade V). In patient 17 PAP was at systemic level; patient 16 had severe subpulmonic stenosis.

Veins

In 10 patients the veins were muscularized and in seven they were normal. The abnormal musculariza-

![Figure 2](http://circ.ahajournals.org/)

A) Alveolar wall artery in a 2-year-old patient with a ventricular septal defect and normal pulmonary artery pressure; there is no muscular extension present. B) Alveolar wall arteries in a 2-year-old patient with a defect of the atrioventricular canal, a large left to right shunt, and 3/4 systemic pulmonary artery pressure. There is a complete and thick wall of muscle surrounding each artery. (**Elastic Van Gieson stain; magnification ×250**).
tion did not correlate with either PAP or the left arterial pressure, nor did it correlate with pulmonary arterial oxygen saturation.

**Alveoli**

Radial alveolar counts were within the normal range in patients over 6 months of age, but as in VSD, in the younger patients they were 2 standard deviations above the normal value.

**Defects of the AVC (Seven Patients) (Table 4)**

**Hemodynamic Data**

In six patients the PAP was elevated and in one it was normal. In two with elevation, the left atrial pressure was also significantly increased on the basis of severe mitral regurgitation. There was evidence of pulmonary venous desaturation in only one patient. In five the PVR was increased; in two it was > 2.5 u/m² and in three it was greater than 3.5 u/m².

---

**Table 4. (Continued)**

<table>
<thead>
<tr>
<th>Artery size (μ)</th>
<th>External wall thickness</th>
<th>Extension (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>RB  AD  AW</td>
<td>AD  AW  M, P, N</td>
</tr>
<tr>
<td>84 ± 15</td>
<td>45 ± 2.1 30</td>
<td>35.2 ± 2.9 26 ± 4.7 100 100 M</td>
</tr>
<tr>
<td>79.6 ± 5.2</td>
<td>70 ± 15.4 48.1 ± 3.5</td>
<td>18.5 ± 3.7 24 ± 4 100 100 M</td>
</tr>
<tr>
<td>66.2 ± 1.2</td>
<td>22.1 ± 3.5 26.3 ± 2.2</td>
<td>38.3 ± 4.8 25 ± 4.4 100 100 M</td>
</tr>
<tr>
<td>54</td>
<td>48 ± 31.5 ± 1.1</td>
<td>35.8 ± 3.9 44 100 100 M</td>
</tr>
<tr>
<td>56 ± 4.7</td>
<td>56.2 ± 2.6 36.3 ± 3.4</td>
<td>13.2 ± 1.9 9.1 ± 0.7 100 100 M</td>
</tr>
<tr>
<td>63.2 ± 4.5</td>
<td>48.1 ± 4.6 25.2 ± 1.7</td>
<td>17.9 ± 1.5 11.2 ± 0.8 100 55 M</td>
</tr>
<tr>
<td>75 ± 12</td>
<td>51 ± 13 28.5 ± 15.2</td>
<td>14.9 ± 2 14.9 ± 1.7 100 100 M</td>
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</tbody>
</table>

---

**Figure 3.**  
*A*) Respiratory bronchiolus artery in a 2-year-old patient with a small ventricular septal defect. The wall thickness is only slightly increased.  
*B*) The same level artery in a patient with a defect of the atrioventricular canal and pulmonary artery hypertension. The wall thickness is markedly increased.  
(Elastic Van Gieson stain; magnification X100). Arrows denote wall thickness and external diameter.
TABLE 5. Pulmonary Arterial Changes in Patients with Congenital Heart Defects

<table>
<thead>
<tr>
<th>Defects</th>
<th># Pts.</th>
<th>Extension</th>
<th>%WT</th>
<th>Art. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>26</td>
<td>26</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>D-TGA</td>
<td>17</td>
<td>17</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>AVC</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td>38</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: # Pts. = number of patients; Extension = abnormal extension of muscle into peripheral arteries; %WT = increased percent wall thickness of normally muscular arteries; Art. # = reduction in artery number; VSD = ventricular septal defect; D-TGA = d-transposition of the great arteries; AVC = defect of the atrioventricular canal.

Postoperative hemodynamic data was available in five patients. None had a residual left-to-right shunt. PVR was elevated > 3 u/m² in two patients; both had severe postoperative mitral regurgitation.

Arteries

Abnormal extension of muscle into peripheral arteries was seen in all patients; this was the only arterial abnormality noted in one, a patient who had only mild elevation in pulmonary artery pressure.

Six out of seven patients had, in addition, abnormally increased arterial wall thickness. In two patients this change was mild; the PAP was normal in one and only mildly increased in the other. In the remaining four patients with more severe medial hypertrophy (greater than twice normal for age) the PAP was elevated at or almost at systemic level. Artery size was significantly reduced in all patients over 1 year of age.

In two patients with a reduction in artery number, the PVR was > 3.5 u/m². Arterial number was normal despite a high PVR in one 5-month-old patient with severe mitral regurgitation.

One (patient 2, table 4) showed intimal change (Heath-Edwards grade II).

Veins

Increased venous muscularization was present in all, but most marked in two patients with moderately severe mitral regurgitation.

Alveoli

In all seven patients studied, radial alveolar counts were normal.

Summary of Results (table 5, figs. 5 and 6)

Arterial Structure

Abnormal extension of muscle into smaller and more peripheral arteries for age of the patient was observed in all patients studied. Increased PBF was a feature common to all patients. In 12 of 50 patients it was the only arterial abnormality. In 11 of those the PAP was normal, and in one it was mildly elevated.

Increased thickness of the medial muscular coat of the normally muscular intra-acinar arteries was seen.

FIGURE 4. A) A low-power field from a patient with a small ventricular septal defect and normal pulmonary artery pressure and resistance. Note the abundance of small arteries. B) A similar low-power field from a patient with a complete defect of the atrioventricular canal and elevated pulmonary vascular resistance of 4 u/m². A reduction of small arteries is seen. (Elastic Van Gieson stain; magnification X25).
in 38 of 50 patients. When this increase was mild, i.e., less than twice normal for age, the PAP was still found to be normal with only two exceptions. One was very young infants less than 4 months of age. In this age group elevated PAP may be based largely on incomplete regression of medial musculature. The other exception was older children in whom the PAP was mildly elevated. In the remaining patients with more severe medial hypertrophy (percent wall thickness almost or greater than twice normal), there was pulmonary artery hypertension, with a good correlation between its severity and the increase in percent wall thickness; for the whole group $r = 0.59$ (fig. 6). This correlation coefficient was improved to 0.8 ($P < 0.005$) when one age group was considered, e.g., the 11 patients 1–4 years of age with VSD.

Reduction in artery size was evident in most infants over 1 year of age and in all those older than 2 years. In 10 of 50 patients there was also a reduction in the number of small peripheral arteries. Although this was inferred by increased alveolar artery ratio per unit area, alveolar number was estimated as normal by Emery-Mithal radial alveolar counts. In all but one patient, a reduction in artery number was associated with moderate-to-severe elevation in PVR (> 3.5 u/m$^2$ (figs. 6 and 7).

Two of three patients with Heath and Edwards grade II change and all three with grade III or higher

**Figure 5.** A summary of schema showing morphometric changes of extension of muscle into peripheral arteries, percent wall thickness and artery number (alveolar arterial ratio (ALV/Art) ) as they relate to age. Above panel is normal development. Bottom shows abnormalities in all three features in the 2-year-old child with a hypertensive ventricular septal defect (VSD). TB = artery accompanying a terminal bronchioles, RB = artery accompanying a respiratory bronchioles, AD = artery accompanying an alveolar duct, AW = artery accompanying an alveolar wall.

**Figure 6.** (left) Percent wall thickness (%WT) of the intra-acinar arteries 50–100 μ as it related to mean pulmonary artery pressure (PAP), showing a correlation between the severity of the two ($r = 0.59$, %WT = 0.39PAP + 10.8 ± 10.4 SEE, $P < 0.005$ confidence limits (0.4–0.75). Dotted lines separate most of the normal and mildly abnormal from most of the very abnormal patients with respect to both elevation in pulmonary artery pressure and percent wall thickness. (right) Pulmonary artery resistance as it relates to alveolar artery ratio. The dotted lines separate most of the normal or mildly abnormal patients from the clearly abnormal patients. The two exceptions which stand out are the patient with transposition and pulmonary stenosis and the patient with a defect of the atrioventricular canal who had severe mitral regurgitation. In both figures, symbols denote the defects, i.e., ventricular septal defect, d-transposition of the great arteries, defect of the atrioventricular canal.
changes had a reduction in number of small peripheral arteries.

**Development**

Alveolar development was normal in all the patients.

**Veins**

A variable degree of muscularization of the veins was associated with increased PBF and was most marked when there was also disease on the left side of the heart, such as mitral regurgitation or coarctation of the aorta.

**Discussion**

**The Method of Biopsy**

The technique of lung biopsy in which the lung is inflated at a known pressure, clamped and fixed-inflated, provides us with tissue which can be analyzed quantitatively. Under such conditions, measuring the diameter and wall thickness of arteries, evaluating extension of muscle, and counting alveoli to assess alveolar/arterial ratios or to perform radial alveolar counts can all yield satisfactory results. The upper medial aspect of the right lung was the site chosen for taking tissue. Since the right lung in patients with D-TGA has an increased PBF relative to the left lung\(^4\), \(^4\) we would expect this lung to show more pulmonary vascular changes than the other. In VSD or AVC defects preferential flow to the right lung does not occur, but for consistency the right lung was evaluated in all patients. The upper lobe was chosen, as it generally shows less pulmonary edema and congestion than the more dependent parts of the lung, and the medial aspect was chosen since it is most easily accessible to the surgeon.

**Hemodynamic Data**

Values of PBF and resistance were based on measured oxygen consumption in only one-third of the patients. Since many of the children were referred from institutions in which the techniques for measuring oxygen consumption in small infants are not available, this could not be avoided. While we agree that direct measurements are optimal, tables of assumed values are probably useful in children over 3 years of age; under this age, assumed values are far less accurate.\(^4\) When we compared hemodynamic with structural data in those 15 patients where oxygen consumption was measured, the relationship between the severity of the changes was improved (fig. 7). This suggests that the morphologic data was more accurate in assessing the level of PVR than measurements calculated with assumed oxygen consumption values. A second difficulty with hemodynamic data is that when the saturation in the pulmonary artery is very high, calculations of PBF according to the Fick equation are misleadingly high,\(^4\), \(^4\) and as a result they underestimate the level of PVR. This problem was first described experimentally in dogs in whom VSDs were created surgically.\(^4\) Angiographic studies in patients with D-TGA and an intact ventricular septum have also shown that PBF was significantly overestimated.
Abnormal extension of muscle into small arteries has been previously reported in postmortem lungs from patients with congenital heart defects and increased PBF, while this has not been a feature in the arteries of children with low PBF as in pulmonary atresia.

Experimental studies in rats have shown that abnormal extension of muscle at least secondary to hypoxia is a reversible process. The new muscle is produced by differentiation of the precursor cells and this seems at least in part to be reversible.

The second pulmonary arterial abnormality, B, is increased thickness of the medial muscular coat; on biopsy tissue, this can be well assessed quantitatively in the small intra-acinar arteries. It is never seen without accompanying evidence of abnormal extension of muscle into small arteries. We found that if the increase in medial wall thickness is only mild, PBF is increased without corresponding increase in PAP, but when this morphologic change is more severe, i.e., if the wall thickness is twice normal, PAP is also increased.

Our criteria of normal wall thickness correspond to values used by Newfeld et al. They are higher than those of Wagenvoort. While it appears that he used only one wall thickness, our calculations, measuring wall thickness on both sides, accounted for a twofold difference. Applying correction factors, we can compare our abnormal values of medial thickness to those reported by Hislop and Haworth in similar cases, e.g., children with VSDs and pulmonary artery hypertension where the arteries were measured in a distented state. Our values still tended to be somewhat higher than theirs. In undistended arteries (50–100 \( \mu \) in diameter), because of their small size, when the wall thickness is greater than 25%, small measured differences yield large changes in percentage, and the relation of increase in percent wall thickness with level of PAP shows more variation. Since our series of cases was larger and had a wider age range, we would expect a larger variance. Increased thickness of the muscular coat has also been described with a variety of congenital heart defects and in particular those with VSD, D-TGA, defects of the AVC, mitral atresia, tetralogy of Fallot with systemic pulmonary anastomosis and total anomalous pulmonary venous connection. We, as Newfeld et al., found no examples in our series of patients with transposition of the great arteries of "medial atrophy" as described by Wagenvoort. He described this as a feature of children younger than 7 months with hematocrit values greater than 65%. None of our patients fell into this clinical category.

Regression of medial hypertrophy was described by Damman and Ferencz following banding of the main pulmonary artery in patients with VSD. Experimental studies in rats have also shown that medial hypertrophy secondary to hypoxia can regress, but only partially when the animals are returned to room air. We observed an occasional animal where medial hypertrophy alone was responsible for the persistent...
elevation in PAP. It is possible that in those younger patients whose biopsies showed mild medial hypertrophy, complete regression will occur after surgical repair; those who were older and whose biopsies indicated more severe change may have elevated PVR based on this increased muscularity, perhaps only evident by an abnormal rise in PAP with exercise.

The decrease in size of the small intra-acinar arteries was a consistent feature in all patients older than 2 years. In patients with VSD or defects of the AVC this was observed even at 6 months of age. This feature has also been described in arteries from injected postmortem lungs of patients with VSD and defects of the AVC. It seems that abnormal extension of muscle and increased wall thickness probably alter the growth of the small intra-acinar arteries. The reduction in the size of arteries beyond a critical point may not be reversible and may also result in a persistent increase in PVR after surgical correction.

The reduction in the number of small peripheral arteries, change C, the third change both chronologically and in severity, was never seen unless there was extension of muscle into smaller arteries than normal (A) and severe medial hypertrophy (B). With one exception, all patients with this feature had significant elevation in PVR. The one exception was an older patient with D-TGA, VSD and subpulmonic obstruction (PS) who, in addition to a reduction in the number of arteries, had Heath-Edwards grade V changes. It has been previously reported that since in the complex D-TGA VSD and PS the PBF is low, deficit in the pulmonary vascular bed cannot always be assessed by direct pressure measurement. The patient with a defect of the AVC who had high PVR but a normal number of arteries also had severe mitral regurgitation and elevated left atrial pressure. This undoubtedly contributed to the elevation in pulmonary artery resistance. Previous studies have shown a general tendency for artery number to be normal or even slightly increased in patients who have elevated pulmonary artery resistance associated with elevation of left atrial pressure.

A reduction in the number of small arteries was described on injected postmortem lungs in patients with VSD and defects of the AVC, with elevated PVR. Experimentally, studies in rats have shown that when reduction in the number of small arteries was secondary to hypoxia, most frequently only minimal patchy return occurred upon return to room air. This implies that the loss of small arteries is a relatively permanent change and suggests that a reduction in the number of small arteries may also be a serious sign in a child with a congenital heart defect. This feature is new and was not described in the Heath-Edwards classification of pulmonary vascular change. We have seen reduction in artery number in association with Heath-Edwards grade I change but have not seen it in one case where grade II change was present but the elevation in PVR was mild. This feature was always observed if a more severe change (grade III or higher) was present.

In young children with only grade I or II change, reduction in artery number probably means that the growth of new arteries has not kept up with the growth of new alveoli. We base this impression on the fact that it is the "new arteries," i.e., those accompanying the alveolar ducts and walls, that are striking in their absence. Also, the "lost" number of arteries is never more than would be expected if new arteries simply did not develop. Our ideas as to how reduction in artery number occurs are purely speculative. It is probable that secondary to the preceding severe medial hypertrophy and endothelial swelling, the contour of pulsatile blood flow through the peripheral pulmonary vascular bed is altered. Perhaps a particular waveform is necessary for the propagation of new and more peripheral small arteries. It is also possible that secondary to medial hypertrophy and endothelial swelling some of the small peripheral arteries may effectively be blocked off. The small artery no longer capable of accepting blood disappears by absorption, as shown experimentally in the rabbit ear chamber. Since we have not seen any evidence of disappearing arteries we tend to favor the former hypothesis. When more severe changes (Heath-Edwards grade III and higher) are observed, however, some of the reduction in arterial number may arise from disappearance secondary to occlusion.

If after cardiac correction, the pulmonary vascular bed is capable of generating enough new arteries, normal or near-normal hemodynamics may be achieved; if not, elevated PVR may be permanent or progressive and quantitation of reduced artery number will provide us with an index of severity. The growth of new arteries is most rapid within the first 18 months of life, as there is a 20-fold increase over the number present at birth. This represents two-thirds of the final arterial number; the growth of the remaining third is complete by 5 years of age. For this reason, one might expect that the very young child with a reduction in artery number might have a better capacity for generating new arteries than the older child. Also, in the presence of grade III change the degree of reduction in artery number may identify grade III disease which is still operable from that which is inoperable or closer to grade IV.

Although immediate postoperative hemodynamic data obtained in the recovery room indicated that in some patients with a reduction in artery number PAP returned to normal after repair, later cardiac catheterization, including resting and exercise studies, will be necessary to establish whether this improvement is maintained.

Veins

A variable degree of muscularization of the veins was found; the venous response in patients with VSD as well as those with D-TGA was not consistently abnormal. The two patients who had associated coarctation of the aorta had striking venous muscularization; this concurs with previous reports. In all patients
with defects of the AVC, abnormal venous muscularization was always present. These patients all had some degree of mitral regurgitation. Samuelson\textsuperscript{a} and Wagenvoort\textsuperscript{a} also found venous muscularization consistently present in patients with mitral valve disease.

**Alveolar Development**

Our radial alveolar counts from biopsy tissue by the Emery-Mithal method corresponded to those originally published by them, except during the first 6 months of life, when they were higher, suggesting that at this time the periphery may grow faster than the deeper regions.

**Summary**

In lung tissue from patients with either VSD or defects of the AVC, three structural changes can be observed. Two grades, A and B, are refinements of Heath-Edwards grade I. The third, grade C, is a new finding and indicates more severe disease.

**Grade A**

Extension of muscle into smaller and more peripheral arteries than is normal may be found alone. As such, it is associated with increased PBF without evidence of increased PAP.

**Grade B**

In association with abnormal extension of muscle, the medial muscular coat of the small intra-acinar arteries is thicker than normal; this feature is most effectively recognized on biopsy by analyzing arteries 50-100 \( \mu \)m. When mild, it is not associated with pulmonary artery hypertension; when more than twice normal, it invariably is.

**Grade C**

In association with abnormal extension of muscle and increased thickness of the medial muscular coat, the number of small arteries is reduced. This change is associated with moderate-to-severe elevation in PVR.

Since, experimentally, complete regression of medial hypertrophy has not yet been shown to occur and the reduction in the number of small arteries (probably based on a failure of proliferation) seems to be permanent, patients with grade C and perhaps even more severe grade B may have permanent alteration of the pulmonary vascular bed. Only follow-up will indicate whether these are the patients who, after correction of a congenital heart defect, show an unexpected increase in PVR with exercise or go on to develop progressive increases in PVR at rest.

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**References**


31. Haworth SG, Reid L: Structural changes in the pulmonary circulation in the newborn infant with aortic atresia, stenosis or coarctation. Thorax 32: 121, 1977
55. Sandison JC: Observations in the growth of blood vessels as seen in the transparent chamber introduced into the rabbit's ear. Am J Anat 41: 475, 1928
Lung biopsy in congenital heart disease: a morphometric approach to pulmonary vascular disease.
M Rabinovitch, S G Haworth, A R Castaneda, A S Nadas and L M Reid

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