Significance of the Pulmonary Vascular Bed in Congenital Heart Disease

V. Lesions of the Left Side of the Heart Causing Obstruction of the Pulmonary Venous Return

By Charlotte Ferencz, M.D., and J. Francis Dammann, Jr., M.D.

A microscopic study was made of the lungs of 18 patients with congenital malformations of the heart in which there was obstruction of pulmonary venous drainage. Alterations in various components of the pulmonary vascular bed and of the lung parenchyma were described and correlated with the clinical course and the type of malformation present. A quantitative evaluation of the pulmonary arterial thickening was made by determining the lumen:wall ratio of small vessels. The anatomic alterations found in these children were compared to those of adults with acquired mitral stenosis.

Lesions of the left side of the heart that impede pulmonary venous drainage lead to extensive anatomic and physiologic alterations in the lungs. Studies of the pulmonary changes in acquired mitral stenosis indicate that the altered structure of the alveoli and of the pulmonary vascular bed serves at first as a protective mechanism, but eventually results in irreversible and detrimental changes. Such a progression has been observed in the adaptive pulmonary vascular changes in conjunction with congenital malformations of the heart in which a common systolic force ejects blood into the 2 circulations.

The present report is concerned with the effect of “back pressure” on the lungs observed in 18 patients with congenital lesions that involved the left atrium, mitral valve, or pulmonary veins and caused obstruction of the pulmonary venous return. Although the malformations differed, in all instances the course of the fetal circulation was affected in such a way that the “back pressure” was present before birth. Its continued presence after birth interfered with the normal evolution of the pulmonary vascular bed from the fetal structure to the adult state.

The effect of an elevated pulmonary venous pressure that results from left heart failure in cases of aortic stenosis, coarctation of the aorta, endocardial fibroelastosis, etc., will be considered in a subsequent report. In such instances, pulmonary vascular evolution proceeds normally for a varying length of time and may even be completed before elevation of left ventricular filling pressure affects the lungs. Alterations produced in this group are, therefore, “acquired” and vary with the age of the patient and the severity and duration of the left ventricular failure. The present report is concerned with abnormalities of the heart in which impairment of pulmonary venous drainage influenced the pulmonary circulation before birth.

Methods

A microscopic study was made of the lungs of patients with malformations that affected the left side of the heart proximal to the mitral valve. Sections stained with hematoxylin and eosin and with elastic tissue stain were examined. Evidences of congestive failure and specific changes that involved the entire pulmonary vascular bed and lung parenchyma were evaluated and correlated with the clinical course and the type of malformation present. In order to allow an objective quantitation of the severity of the vascular changes, we have again used the method previously described in which a numerical expression, denoted as the lumen:wall ratio, designates the characteristics of the small pulmonary vessels. This ratio was obtained by direct measurement of the thickness of the media and intima of the small pulmonary arteries. The sum of the intimal and medial thickness was multiplied by 2 and divided into the measurement of the luminal diameter, thus giving the ratio of lumen size to wall thickness. The average reading of 10 small pulmonary vessels was...
The malformations of the heart causing obstruction of the pulmonary venous return in 18 patients are listed in table 1.

In 14 of the 18 patients the lesion that impeded pulmonary venous drainage was associated with other malformations of the heart. In most instances the usual clinical findings of the additional anomaly were modified adversely by this combination of lesions. Brief synopses of the clinical and anatomic findings are given in the appendix.

**Microscopic examination of the lungs** of these patients revealed extensive changes in all components of the pulmonary vascular bed and lung parenchyma. The alterations were similar in all instances. One patient with unilateral congenital pulmonary venous obstruction (case 18) showed, in addition, evidence of serious vascular injury that will be considered separately.

*The muscular pulmonary arteries* showed medial thickening; this was the most uniform and probably the earliest change (fig. 1). Hypertrophy of the smooth muscle and an increase in the elastic tissue accounted for the thickening. This was primarily responsible for the reduction of the lumen:wall ratio. Intimal thickening, usually eccentric, was noted in the large muscular arteries of approximately one third of the patients. It was moderately severe in 2 of the oldest children, but was not uniformly present in all vessels. In 3 instances, including the 2 patients just mentioned, intimal changes were also found in some of the smaller muscular pulmonary arteries.

*The arterioles* were thickened in every case (fig. 2). In the 2 newborn infants the narrow lumens were in accordance with the normal fetal pattern. Thickening of the arteriolar walls by concentric cellular proliferation was frequently seen in the older children, giving an "onion ring" appearance.1 When the media was not clearly defined by the elastic laminae, it was often difficult to distinguish arterioles from small muscular arteries, but the thickening of the wall was uniformly present even in the smallest vessels.

*The veins* were thick-walled in every case except one. It is worthy of note that the thickening of the veins even in the youngest patient was sufficiently definite to be noted at the time of the first microscopic study, which was made before the diagnosis was known to the examiner. In 9 patients intimal thickening of the veins was noted, but in only 1 patient were these changes marked. A subintimal increase in smooth muscle and elastic fibrils accounted for the major portion of the thickening.

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Case number</th>
</tr>
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<tbody>
<tr>
<td>Cor triatriatum (double left atrium)</td>
<td>1</td>
</tr>
<tr>
<td>Congenital mitral stenosis</td>
<td>2</td>
</tr>
<tr>
<td>Pure mitral stenosis</td>
<td>3</td>
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<tr>
<td>Mitral stenosis associated with ventricular septal defect</td>
<td>3</td>
</tr>
<tr>
<td>Single ventricle</td>
<td>4</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>5-7</td>
</tr>
<tr>
<td>Patent ductus arteriosus and coarctation of aorta</td>
<td>8</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>9</td>
</tr>
<tr>
<td>Aortic stenosis and coarctation of aorta</td>
<td>10-11</td>
</tr>
<tr>
<td>Congenital mitral insufficiency &quot;Ebstein's malformation&quot; of the mitral valve</td>
<td>12</td>
</tr>
<tr>
<td>Cleft septal leaflet of mitral valve associated with a left ventricular-right atrial communication and aortic obstruction</td>
<td>13</td>
</tr>
<tr>
<td>Fibroelastosis of mitral valve associated with patenty of the ductus arteriosus</td>
<td>14</td>
</tr>
<tr>
<td>Atresia of the mitral valve with small foramen ovale</td>
<td>15-17</td>
</tr>
<tr>
<td>Unilateral congenital pulmonary venous obstruction</td>
<td>18</td>
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</table>

1. *The alteration of the structure of the alveolar wall* represents the key differential finding that distinguishes the lungs of patients with pulmonary venous obstruction from those of patients with other malformations of the heart. The capillaries and their supporting structure were both affected, but the extent of involvement was variable. A progression of changes was apparent.
In patients with a recent history of pulmonary edema, the capillaries were dilated, tortuous, congested with blood, and were sometimes seen projecting into the alveolar spaces. The capillary basement membrane was prominent (fig. 3). Areas of capillary rupture and hemorrhage were present. The alveolar walls were thickened. In the early stages this thickening was the result of interstitial edema and deposition of a hyaline material.
A more advanced pattern was seen in patients with chronic heart failure. Interstitial collagen deposition or a proliferation of alveolar epithelial cells accounted for marked thickening of the alveolar walls. In some areas several rows of closely packed cuboidal cells interspaced with collagen material formed the alveolar walls (fig. 4). The capillaries often appeared compressed and reduced in number. The cellular appearance of the lung parenchyma was present in some of the youngest infants and was most pronounced in 2 patients with mitral regurgitation, 6 and 26 months of age, respectively. The changes were usually uniform throughout the lung parenchyma but occasionally scattered patches in different stages of progression occurred in the same lung. In a few patients advanced changes were found in the more dependent portions of the lungs, whereas early congestive changes were present in the upper lobes. Congestive cardiac failure with edema, hemorrhage and iron-laden macrophages (heart failure cells) in the alveoli occurred to a variable degree in all patients.

Additional alterations were noted in the lungs of case 18 that differed significantly from those of the other 17 patients. In this patient the pulmonary vein that drained the left upper lobe was markedly constricted and that of the left lower lobe was completely atretic. The right pulmonary veins were normal. Despite this difference the microscopic appearance of the 2 lungs was so similar that one could not distinguish the "obstructed" left lung from the "unobstructed" right lung. Marked medial hypertrophy and increase in elastic tissue, as seen in the other 17 patients, was also present in this instance, but in many vessels the media was destroyed and replaced by extensive intimal proliferation (fig. 5). In some areas this fibrous thickening resulted in complete, or nearly complete obliteration of the arterial lumen. These intimal changes occurred extensively, but not uniformly, in all areas and affected the larger as well as the small branches of the pulmonary arterial tree. The veins were thickened owing to subintimal fibrosis (fig. 6), and extreme intimal proliferation was often but not uniformly present. The changes in the lung parenchyma were similar to those of the other cases but both lungs showed areas in various stages of progression. More extensive areas of capillary dilatation and congestion with intra-alveolar hemorrhage were present in the right lung than in the left. In some portions of the lungs there was marked proliferation of alveolar epithelium with compression of the capillaries. Compensatory emphysema with thin alveolar walls was present in scattered
patches in both lungs. The great variation of the alveolar changes in this patient probably depended upon the degree of obstruction of the vessel supplying or draining the affected area, but there was no clear-cut correlation.

The arterial lumen:wall ratios obtained in these patients as well as the ratios for 15 adults with acquired mitral stenosis, whose lungs were studied for comparison, are plotted in figure 7. The 18 children varied in age from birth to 3 years. The deviation from the normal in the lumen:wall ratio was more pronounced than that observed in any other group with congenital heart disease. Only the 3 youngest infants, who were under 1 month of age, showed a lumen:wall ratio within the normal range. At this age the small pulmonary arteries normally show a thick media. All other patients showed reduced ratios. The deviation from the normal in the lumen:wall ratio varied directly with the age of the patient, indicating a rapid rate of progression of the pulmonary lesions. Death occurred early. The extremely low ratios found in these children under 3 years of age were approximated only by a few of the adult patients who had had mitral stenosis for many years.

The data in figure 7 suggest that "back pressure" on the lungs during fetal life interferes seriously with the normal evolution of the pulmonary vascular bed. Narrowing of the vessels progresses rapidly and is more pronounced than that produced either by a common systolic ejective force present from birth or by long-standing acquired venous obstruction of a previously normal pulmonary vascular bed.

Pulmonary venous obstruction is present in fetal life in instances where the pulmonary veins join into a common trunk that descends into the abdomen and drains into the inferior vena cava through one of its tributaries. This malformation is characterized by difficulty in emptying the pulmonary veins, a high pulmonary vascular resistance, and right-sided cardiac failure. Death usually occurs within the first month of life. A microscopic study of the lungs of 3 such patients was made for comparison. As in the other infants under 1 month of age, the lumen:wall ratios of these patients were not outside the normal range. All 3 children, however, were found to have thickened cellular alveoli and marked capillary dilatation (fig. 8) similar to the parenchymal changes noted in the other 18 patients under discussion.

Many similarities and some significant differences are revealed by a comparison of the
microscopic findings in the lungs of the patients in this series with those of adults with a long-standing mitral stenosis. Despite the youth of the patients with congenital malformations, the lung changes were extensive and severe. Not a single child escaped some alteration either in the pulmonary parenchyma or in the vascular tree. In contrast, only mild abnormalities were noted in several patients in the adult group. Intimal fibrosis or the deposition of a hyaline material on the endothelium was frequently found in the smaller muscular arteries in the oldest patients. Such changes may be present normally after the third decade of life.\textsuperscript{13-14} In every patient with acquired mitral stenosis endothelial thickening and medial hypertrophy led to a significant reduction in lumen:wall ratio. The outstanding difference between the vascular changes noted in patients with congenital obstruction of the pulmonary venous return and those with acquired mitral stenosis was the relative thickening of the media as compared to the degree of intimal change. Medial thickening was predominant in the congenital group, whereas intimal sclerosis was predominant in the acquired group. Thickening of the alveoli with dilatation and increased tortuosity of the capillaries and proliferation of the alveolar epithelial cells occurred to a varying extent in the adult patients (fig. 9), but was never so severe as in the cases with congenital heart disease. None of the adults showed the extensive cellular proliferation of the alveolar walls or the severe capillary congestion that occurred in some of the small children. In making this comparison it must be remembered that sections of the adult lungs were biopsies taken at the time of mitral commissurotomy, whereas the lung material of the pediatric age group was obtained at autopsy.

**DISCUSSION**

The clinical and pathologic findings in patients with congenital lesions of the left side of the heart associated with obstruction of the pulmonary venous return reveal evidence of severe and rapidly progressive pulmonary vascular and parenchymal changes. The nature of the cardiac abnormality is such that the lungs are affected prior to birth. Obstruction or insufficiency of the mitral valve leads to a rise in left atrial pressure, a consequent decrease in right-to-left shunt through the foramen ovale,\textsuperscript{15} and an increase in right ventricular output and in the shunt from right-to-left through the patent ductus arteriosus. This increase is re-
sponsible for the large right side and the small left side of the heart at birth as well as for the thickened cellular alveolar walls that were noted in the 2 newborn infants in this series. Following birth, the increased pulmonary blood flow accentuates the alterations. The stress placed on the lungs during fetal life constitutes the major difference between these lesions and other congenital abnormalities of the heart. As a consequence, it is in this group that the most severe alterations of the lungs are noted. The shift from intra-to-extraterne life is made more difficult by the dependence of the newborn infant upon an already embarrassed respiratory system. The 1 patient in this series whose abnormality did not place stress on the lungs during fetal life was the child with unilateral pulmonary venous obstruction (case 18). In this patient the pulmonary vascular changes were those of injury, that is, extensive intimal proliferation. This occurrence may be explained in part by the fact that the right lung with its unimpaired pulmonary venous drainage sufficed to carry the normal fetal pulmonary blood flow. Stress was placed upon the lungs after birth. The increased pulmonary blood flow exceeded the capacity of the "unobstructed" right lung and a high pulmonary pressure resulted. The left lung was exposed to the same high pulmonary arterial pressure in face of added pulmonary venous obstruction. The arterial changes in this patient suggest a state of "malignant hypertension" in the pulmonary circulation. The close similarity of the changes in the 2 lungs has not been completely explained.

The changes in the lungs resulting from "back pressure" follow a characteristic sequence, which varies in rapidity and severity. The initial changes consist of dilatation, tortuosity, and engorgement of the pulmonary veins and capillaries. Reserve vascular channels are opened. Congestion and elevated intracapillary pressure lead initially to interstitial edema, which later progresses to frank pulmonary edema. Death may occur. If congestive changes are less acute, the interstitial edema is replaced by a hyaline material and then by collagen. Alveolar cells proliferate and become cuboidal and closely spaced. The extracapillary pressure is thereby elevated and may account for the compressed capillaries noted in the most cellular areas. Such an increase in extracapillary pressure means that a higher intra-arterial pressure is required to maintain an effective flow. A vicious cycle is thereby established.

A further result of the increased pulmonary venous pressure is injury to the wall of pulmonary veins, manifested by intimal proliferation and the appearance of the elastic fibrils in the subintimal layer. Venous intimal thickening was a prominent feature in this series. Injury to the veins was more apparent than injury to the arteries. This dissimilarity was not noted in patients with acquired mitral stenosis, and may be explained by the difference between the fetal arterial bed and that of the adult. In the former, the small arteries are composed of a thick medial layer of smooth muscle and elastic fibers and a thick fibrous adventitia that offers an effective barrier to excessive stretch. In contrast, the thin-walled small pulmonary arteries of adults cannot withstand the high intravascular pressure, and injury results.

A reduction in the lumen:wall ratio was noted both in the patients with congenital heart disease and those with acquired mitral stenosis. The cause of the reduction differed. In the former group, excessive medial hypertrophy was predominantly responsible, whereas intimal change accounted for most of the thickening in the older patients.

The pathologic alterations bring about a significant reduction in the ventilatory efficiency of the lungs.2,16,17 Adequate oxygenation is in part dependent upon the intimate contact of red blood cells with the pulmonary capillary wall and the proximity of the capillary wall to the alveolar space. Dilatation of capillaries, the presence of edema fluid, hyaline material, or collagen in the alveolar walls, and also edema fluid within the alveoli, all effectively slow the gaseous exchange. Alveolar thickening decreases the elasticity of the lung and thereby reduces the vital capacity. All of these combined changes bring about a pulmonary vascular resistance of great magnitude that may lead to right ventricular failure. If a large defect between the ventricles or great vessels is present, a right-to-left shunt appears and the effective pulmonary blood flow is reduced. Under these circumstances cyanosis may be present at a very early age, even from
birth. Thus the natural course of malformations of the heart in which a common ejective force is present is accelerated by the presence of an excessive pulmonary vascular resistance caused by pulmonary venous obstruction. 18

In the patients with congenital obstruction of the pulmonary venous return the anatomic and physiologic alterations originate in fetal life. A vicious cycle is probably initiated at birth by the sudden increase in pulmonary blood flow. The life span, however, was variable and the mode of death was not always the same. Some children died in the course of an episode of acute pulmonary edema. In these, pulmonary capillary congestion and vascular dilatation was marked. Others suffered from prolonged congestive failure. In these, cellular proliferation of the alveolar walls was a prominent feature. In 1 instance death was due to an attack of paroxysmal dyspnea that was precipitated by the severe reduction of the pulmonary blood flow. All 18 patients died before 3 years of age.

Summary

Analysis of the pathologic findings in the lungs of 18 patients with congenital lesions of the heart that caused obstruction of the pulmonary venous drainage permits the following conclusions.

When malformations of the heart are associated with pulmonary venous obstruction, severe and rapidly progressive anatomic and physiologic changes occur in the pulmonary vascular bed and in the lung parenchyma. In such instances stress upon the lungs is present prior to birth and major anatomic alterations may be found immediately after birth.

The abrupt increase in the pulmonary circulation at birth accentuates the pulmonary venous obstruction. A rapidly progressive sequence of pulmonary vascular and parenchymal changes is thereby initiated.

Arterial changes are similar to, but usually more severe than, those observed in patients who had a common systolic ejective force. Medial hypertrophy and increase in elastic tissue are the predominant features.

Capillary, venous, and parenchymal changes are present that are not associated with other malformations except in the presence of left heart failure. Capillaries and veins show dilatation, tortuosity, and engorgement, and there is intimal proliferation of the veins. Parenchymal changes consist of interstitial edema, which is followed by collagen deposition and cellular proliferation with consequent increase in the thickness of the alveolar walls. The combination of vascular and parenchymal changes reduces the efficiency of gaseous exchange within the lungs.

The reduction in the lumen:wall ratios of the small muscular pulmonary arteries was greater than in any other group of congenital malformations of the heart. This finding suggests that pulmonary venous obstruction is an important factor in the pathogenesis of pulmonary arterial narrowing.

A comparison of these findings in young individuals and in adults with acquired mitral stenosis shows that changes are more extreme and more rapidly progressive in the congenital than in the acquired forms of pulmonary venous obstruction.

Summario in Interlingua

Le analyse del constatationes pathologic in le pulmones de 18 patientes con congenite lesiones del corde que causava obstruction del drainage pulmo-venose permitte le sequente conclusiones:

Quando malformationes del corde es asso- ciate con obstruction pulmo-venose, sever e rapidemente progressive alterationes anatomic e physiologic occurre in le vasculatura pulmonar e in le parenchyma del pulmon. In tal casos, stress affice le pulmones ante nato, e major alterationes anatomic pote esser trovate immediatamente post le nascentia.

Le abrupte augmento del circulation pulmo- nanor al tempore del nascentia accentua le obstruction pulmo-venose. Un rapidemente progressive sequentia de vascular e parenchymal alterationes pulmonar es assi initiate.

Le alterationes arterial es simile a illos observate in patientes con un commun fortia ejecitio systolico. Usualmente illos es plus sever. Hypertrophi media e augmento de tessuto elastic es le characteristicas predominante.

Alterationes capillar, venose, e parenchymal es presente que non es associate con altere
malformations except in le presentia de disfallimento sinistro-cardiac. Capillares e venas exhibi dilatation, tortuositate, e retention, e il ha proliferation intimal del venas. Le alterationes parenchymal consiste de edema interstitial, sequite per deposition de collageno e proliferation cellular e consequente augmen- tos del spissitate del parietes alveolar. Le combination del alterationes vascular e parenchymal reduce le efficacia del excambio gasose in le pulmones.

Le reduction del proportion passage: parietes in le parve arterias pulmonar muscular esseva plus grande que in non importa qual altere gruppo de malformations congenite del corde. Iste constatatone suggere que obstruction pulmone-venose es un factor importante in le pathogenese del restriction pulmone-arterial.

Un comparation de iste constantationes in juvene individuos e in adultos con acquireite stenosis mitral revela che le alterationes es plus extreme e plus rapidamente progressive in le forma congenite que in le forma acquireite de obstruction pulmone-venose.

**ACKNOWLEDGMENT**

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**APPENDIX**

*Synopses of clinical and anatomic findings* *


**Case 7.** R. C. (C.M.H. Autopsy # 54-93) 4½ months. Occasional cyanosis of left hand and feet. Sudden onset of pulmonary edema at 3 months. Loud systolic murmur, diastolic murmur in fourth left intercostal space. Angiocardiogram: large left atrium and left ventricle. Died following mitral...
valvotomy. Anatomic diagnosis: Mitral stenosis and patent ductus arteriosus. Lumen:wall ratio 0.47.


Case 12. R. J. (S.J.H. Autopsy #A10-54) 6 months. Minimal cyanosis since birth. Cardiac failure at 10 weeks. Loud mitral first sound and split second sound. Short systolic murmur and diastolic rumble at apex. Electrocardiogram: right ventricular hypertrophy. Anatomic diagnosis: right ventricular hypertrophy. Died following catheterization. Anatomic diagnosis: Downward displacement of the mitral valve, posterior leaflet originated from left ventricular endocardium with a large portion of left ventricle incorporated into the left atrium (“Ebstein’s malformation” of the mitral valve.) Functional stenosis and insufficiency of mitral valve. Lumen:wall ratio 0.80.


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