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Pulmonary Hypertension in Congenital Heart Disease

Ricardo Drut

Pulmonary hypertension is a feared complication of congenital heart disease (CHD); however, early surgical correction of the malformation may prevent what initially is a functional vascular disorder from becoming an anatomically fixed lesion. Table 21-1 estimates the incidence of pulmonary vascular disease in untreated cases of CHD.[1]

Pulmonary hypertension and its accompanying arterial lesions progress at different rates depending on the type of the cardiovascular malformation,[2–5] and the latter may be classified in one of three categories: shunts at the atrial level (*i.e.*, pretricuspid shunts); shunts at the ventricular or aortopulmonary arterial level (*i.e.*, post-tricuspid shunts); and obstructed pulmonary venous flow.[6] Display 21-1 shows the most common types of CHD in each of these categories.

Pretricuspid shunts are associated with high pulmonary flow. Pulmonary hypertension develops from young adulthood to later in life, if at all, and the vascular lesions are usually mild. In post-tricuspid shunts, the pulmonary arterial lesions are more florid and severe because pulmonary hypertension has been present since birth. This is the high-flow–high-pressure group because the pressure of the arterial side of the circulation is transmitted directly to the pulmonary arterial tree. The third group, with obstruction to pulmonary venous flow, represents a peculiar range of lesions involving the whole vascular tree of the lungs from arteries to large veins; the vascular pathology is different from that in the other two groups.

Pulmonary blood pressure is the result of pulmonary blood flow and peripheral resistance. Significant increments in either may result in pulmonary hypertension; if both are elevated, pulmonary pressure may be extremely high. In the normal lung, the small preacinar muscular arteries and terminal parabronchiolar arterioles have a slightly higher relative wall thickness than the more proximal arteries and are considered to be the resistance vessels of the lung. It is at this level that the most remarkable changes take place.[5]

The sequence of pulmonary arterial changes associated with pulmonary hypertension, especially in arterioles (<100 μm in diameter) and muscular arteries (70–500 μm in diameter), follows the same pattern as in systemic arterial hypertension, and the consequences are comparable.

PATHOLOGIC FINDINGS

Elastic Pulmonary Arterial Changes

Variable degrees of medial hypertrophy due to proliferation of smooth muscle cells and an increase in elastic fibers are present. Changes in the elastic configuration of the pulmonary trunk are discussed in Chapter 24. The intimal changes range from mild fibrosis to atheroma formation with thrombosis and calcification.

Plexogenic Arteriopathy

This term, established by a committee of experts,[7] designates several sequential morphologic patterns in the small pulmonary arteries (SPA) and arterioles induced by pulmonary hypertension. The hallmark of the process is the plexiform lesion, although it is not necessarily present in all stages of the process. The lesions are identical to those found in primary pulmonary hypertension and are listed in Display 21-2 (see Chap. 23).

Medial Hypertrophy and Muscularization of Arterioles

Mild increments in medial thickness of pulmonary muscular arteries are difficult to appreciate and require careful comparison with normal controls. Collected data indicate that the average medial thickness in normal adults ranges from 3% to 7% of the diameter of the vessel as delineated by the external elastic lamina. From

TABLE 21-1
Incidence of Pulmonary Vascular Disease in Congenital Heart Malformations*

Lesion	Percent	Total Number	Number at Risk
Ventricular septal defect	30	9000	3000
Patent ductus arteriosus	9	2700	900
Atrial septal defect	7	2100	700
Atrioventricular septal defect	3	900	800
Aortic stenosis	5	1500	0
Pulmonic stenosis	7	2100	0
Coarctation of aorta	6	1800	0
Tetralogy of Fallot	5	1500	200
Transposition of the great arteries	5	1500	500
Hypoplastic right heart	2	600	50
Hypoplastic left heart	1	300	0
Double outlet ventricle	0.2	60	60
Total anomalous pulmonary venous connection	1	300	300
Univentricular heart	0.3	90	100
Miscellaneous	18.5	5550	2625
Total	100	30,000	9235 (31%)

**Assuming there are 3 million live births per year and a 1% incidence of congenital heart disease.*

From Friedman WF, ed. Proceedings of the National Heart, Lung, and Blood Institute Pediatric Cardiology Workshop: pulmonary hypertension. Pediatr Res 1986;20:811.

7% to 10%, the hypertrophy is considered mild; from 10% to 15%, moderate; and it is considered severe when it exceeds 15%.[8]

Under normal circumstances, the muscular coat of pulmonary arterioles 60 to 100 μm in diameter dramatically disappears after birth.[9] In plexogenic arteriopathy, medial hypertrophy of arterioles reappears and usually parallels the increase in medial thickness of muscular arteries; arterioles 20 to 30 μm in diameter or even smaller may show a complete layer of smooth muscle (Figs. 21-1 through 21-3).

Cellular Intimal Proliferation

This lesion consists of layers of cells between the endothelium and the internal elastic lamina (Fig. 21-4). Early intimal proliferation shows the cells to be arranged perpendicularly to the lamina. Intimal proliferation and concentric intimal fibrosis, to be de-

DISPLAY 21-1. CONGENITAL HEART MALFORMATIONS THAT MAY BE ASSOCIATED WITH PULMONARY HYPERTENSION

Pretricuspid Shunts
- Atrial septal defect
- Communication between coronary sinus and left atrium
- Anomalous pulmonary venous drainage to the right atrium or superior vena cava

Post-tricuspid Shunts
- Ventricular septal defect
- Atrioventricular septal defect
- Transposition of the great arteries with ventricular septal defect
- Truncus arteriosus
- Patent ductus arteriosus
- Aortopulmonary window
- Transposition of the great arteries with intact ventricular septum
- Surgically induced systemic pulmonary shunt

Obstruction to Pulmonary Venous Flow
- Congenital mitral stenosis
- Cor triatriatum
- Hypoplastic left heart syndrome

DISPLAY 21-2. ARTERIAL LESIONS IN PLEXOGENIC ARTERIOPATHY

Main Lesions
- Medial hypertrophy and muscularization of arterioles
- Cellular proliferation of intima
- Concentric intimal fibrosis and fibroelastosis
- Plexiform lesions
- Dilatation lesions
- Fibrinoid necrosis and arteritis

Additional Lesions and Alterations
- Tortuosity
- Intimal longitudinal smooth muscle
- Endothelial changes
- Generalized and uniform dilatation
- Bronchopulmonary anastomoses

From Wagenvoort CA, Mooi WJ. Biopsy pathology of the pulmonary vasculature. Biopsy pathology series 13. London: Chapman and Hall, 1989:56.

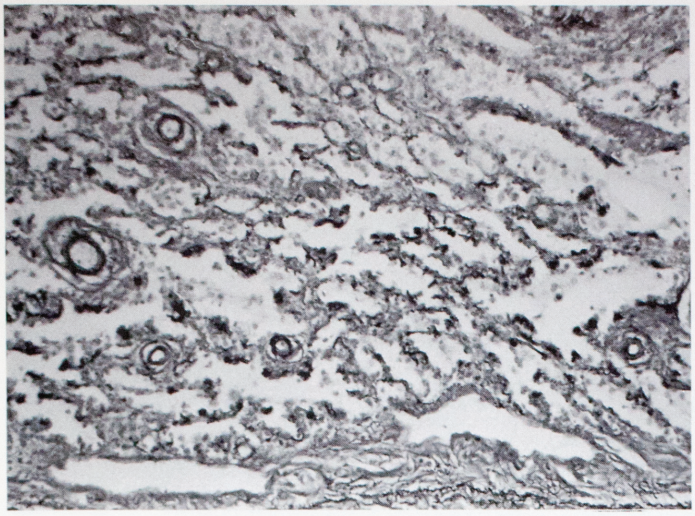

FIGURE 21-1. Muscularization of small intralobular arteries and arterioles. The lower margin of the picture shows pleural tissue with dilated lymph vessels. (Elastic tissue stain; low magnification.)

scribed next, commonly extend to the area of origin from the parent vessel. Because the cells seem to be myofibroblasts, an origin from the media has been proposed.

Concentric Intimal Fibrosis

As the previously described lesion advances, its peripheral layers become collagenized, producing an onion-skin appearance of the intima (Fig. 21-5). In long-standing cases, elastic fibers may also become part of the process; advanced stages may produce a substantial reduction of the vascular lumen. This thick and stiff concentric intimal fibroelastosis may lead to medial atrophy as a result of poor nutrition, poor oxygenation, and inactivity (Fig. 21-6). A further stage consists of virtual obliteration of the lumen, medial atrophy, and collapse of the elastic laminae.

Fibrinoid Necrosis and Arteritis

In this particular stage of plexogenic arteriopathy, always associated with severe hypertension, the small muscular arteries show

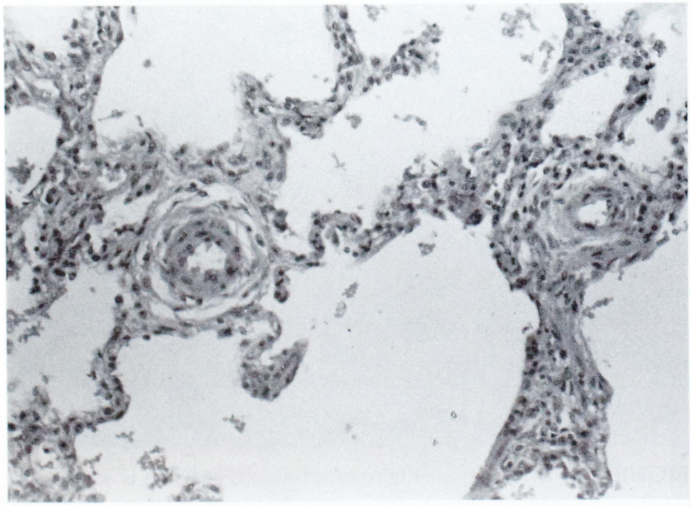

FIGURE 21-2. Complete muscularization of pulmonary arterioles. (H & E stain; low magnification.)

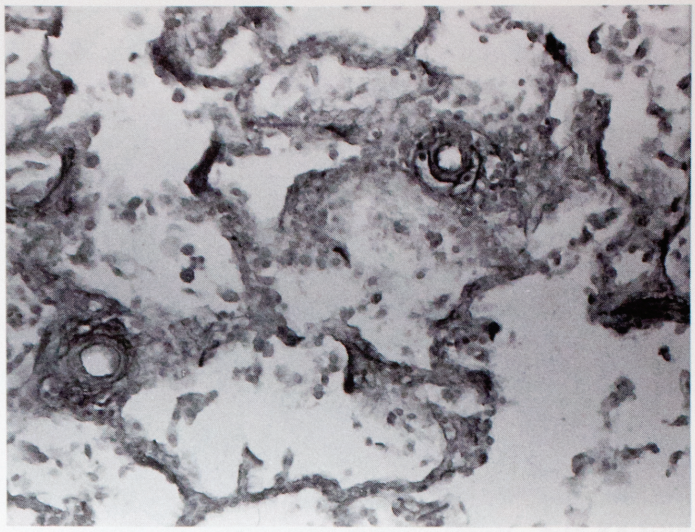

FIGURE 21-3. The muscularization of small arterioles is highlighted by elastic tissue stain. (Low magnification.)

necrosis and fibrin imbibition of the media and intima. Frequently there is concentric fibrosis of the intima with fragmentation of elastic fibers. A thrombus composed of fibrin and platelets is also usually present (Fig. 21-7).

Fibrinoid necrosis or necrotizing arteritis may involve the whole vessel or part of its circumference. The inflammatory infiltrate consists mainly of polymorphonuclear leukocytes and lymphocytes involving the artery and extending to the adjacent lung tissue. Necrotizing arteritis is rare in infants and children.

Plexiform Lesions

This peculiar lesion consists of a muscular artery with atrophy or partial destruction of its wall and an associated plexus of tortuous, endothelium-lined, narrow channels. Different stages of development may be apparent. The first recognizable stage consists of a clot in a poststenotic dilated arterial segment (see Fig. 21-7). The

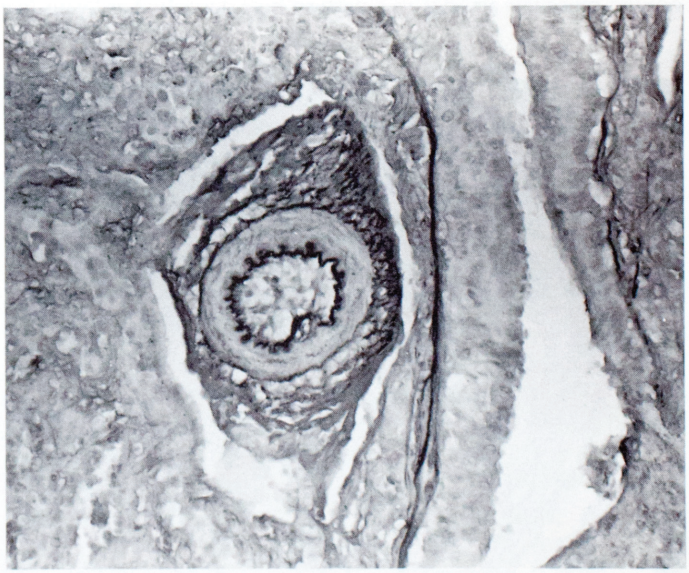

FIGURE 21-4. Marked medial hypertrophy and cellular intimal proliferation of a pulmonary artery. (Elastic tissue stain; intermediate magnification.)

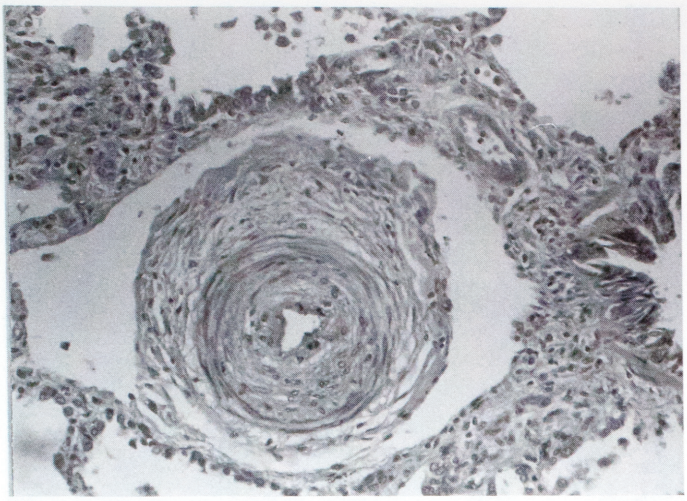

FIGURE 21-5. Marked concentric intimal fibrosis with extreme reduction of the arterial lumen. (H & E stain; intermediate magnification.)

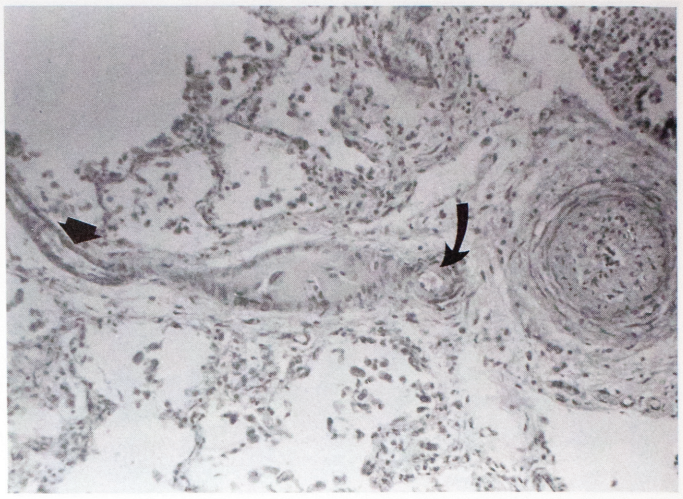

FIGURE 21-7. A small pulmonary artery that arises perpendicularly from a parent vessel (*long arrow*) shows organizing fibrinous thrombus. Note the severe concentric intimal fibrosis of the present vessel. Distal to the thrombosed segment, the artery is free of lesions (*short arrow*). (H & E stain; low magnification.)

clot becomes progressively organized by a papillary proliferation of endothelial and mesenchymal cells until a plexus is formed, sometimes referred to as an angiomatoid, glomoid, or glomeruloid structure. Later stages may show fibrous septa and a widened vascular lumina. The parent artery regularly shows severe intimal cellular proliferation or concentric fibrosis (Figs. 21-8 through 21-10). Fibrinoid necrosis and necrotizing arteritis probably precede these changes. The size of the lesion ranges from 200 to 400 μm. Serial, computer-aided reconstructions have shown that plexiform lesions are more common in supernumerary arteries arising laterally from a large parent vessel than in dichotomous branches, a finding that may reflect a difference in hemodynamic conditions at these sites, such as pressure load or shear stress.

Dilatation Lesions

A well-developed plexiform structure is frequently associated with dilatation lesions, which consist of a plexus of thin-walled, engorged muscular arteries in a pattern best described as "vein-like branches of arteries."[9] They surround a narrowed arterial segment and the plexiform lesion proper, providing an alternate route to blood flow.

The dilatation lesion implies severe and fixed pulmonary hypertension.[10,11] It is more often observed in adults, but there are several reported examples in infants.[12] Although not definitively settled, its pathogenesis appears related to the development of local circulatory disturbances resulting from the narrowing of small muscular arteries. A jet effect at places of branching probably triggers focal necrosis of the vascular wall and thrombosis. Subsequent proliferation of vasoformative cells at the poststenotic and necrotic segment leads to the angiomatoid structure and later to a fully developed plexiform structure. Similar vascular alterations have been described in extrapulmonary sites in cases of malignant hypertension.[13,14]

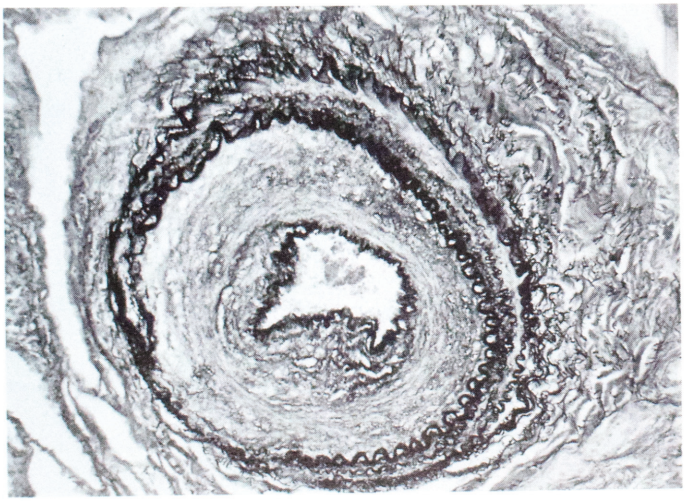

FIGURE 21-6. Concentric intimal fibroelastosis in an artery that also shows segmental medial atrophy and fragmentation of the internal elastica. (Elastic tissue stain; intermediate magnification.)

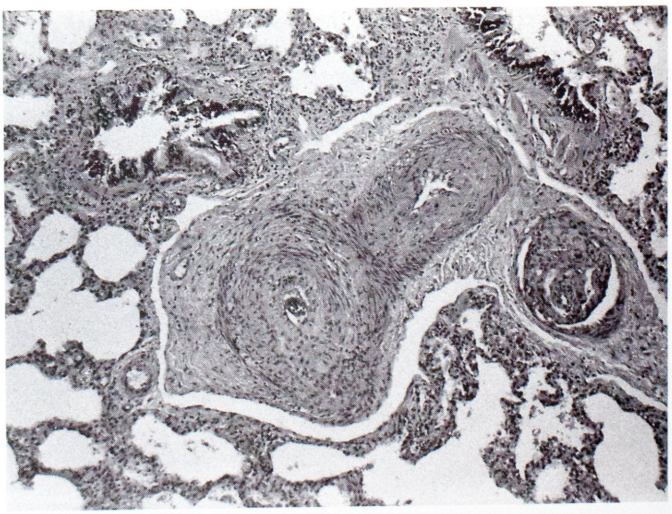

FIGURE 21-8. A typical angiomatoid plexiform lesion is seen in the artery on the right, the lumen of which is dilated and contains a meshwork of capillaries. The parent artery is tortuous at the site of severe concentric intimal fibrosis. (H & E stain; low magnification.)

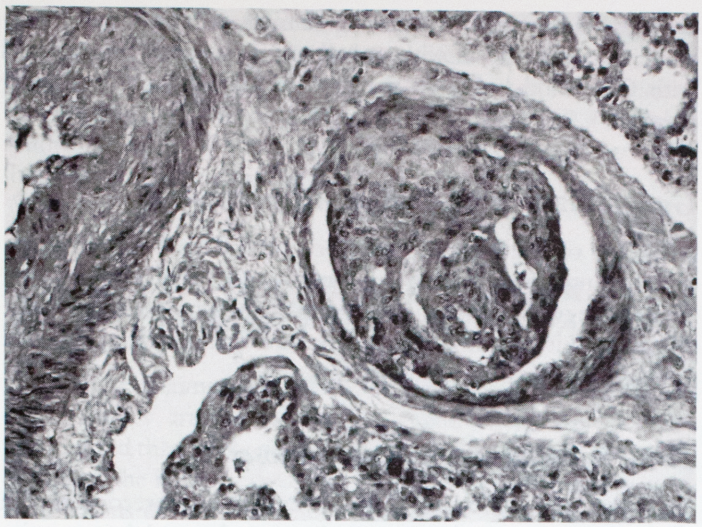

FIGURE 21-9. The artery with the angiomatoid plexiform lesion has atrophic media, microaneurysmal dilatation, and an intraluminal mass with multiple, small, endothelial-lined spaces. (H & E stain; intermediate magnification.)

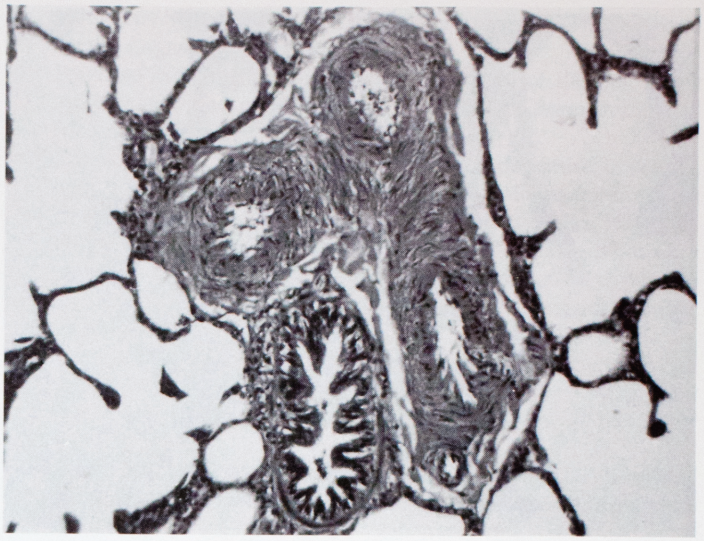

FIGURE 21-11. Tortuosity of pulmonary arteries occurs in pulmonary hypertension associated with congenital heart disease. This area has an arterial/bronchial index of 3. (H & E stain; low magnification.)

Tortuosity

Although often mentioned and recognized by pulmonary researchers, this peculiar alteration of pulmonary arteries has not been appropriately evaluated. Its presence is constant in cases of CHD associated with pulmonary hypertension. Multiple cross sections of arteries in rows or clusters appear to be the hallmark of this alteration. A more objective way to demonstrate tortuosity is by establishing the arterial-bronchial index. Normally, after counting the number of arteries and bronchi in five low-power fields, the relation is 1, whereas in cases of pulmonary hypertension the value of this index is from 2 to 3.22. Increased values for this index have been detected even in 2- to 3-day-old neonates, with transposition of great arteries (Fig. 21-11).

Intimal Longitudinal Smooth Muscle

Sometimes, groups of longitudinal smooth muscle cells are present in the intima in between reduplicated internal elastic laminae. These are commonly associated with medial hypertrophy and are most often recognized in children and infants.[15] The cells stand out as round to oval nuclei surrounded by a clear halo (Figs. 21-12 and 21-13).

Endothelial Changes

Scanning electron microscopy of the normal endothelial surface of pulmonary arteries shows that cells arrange in narrow, even ridges with a corduroylike appearance. Thick-walled arteries of pulmo-

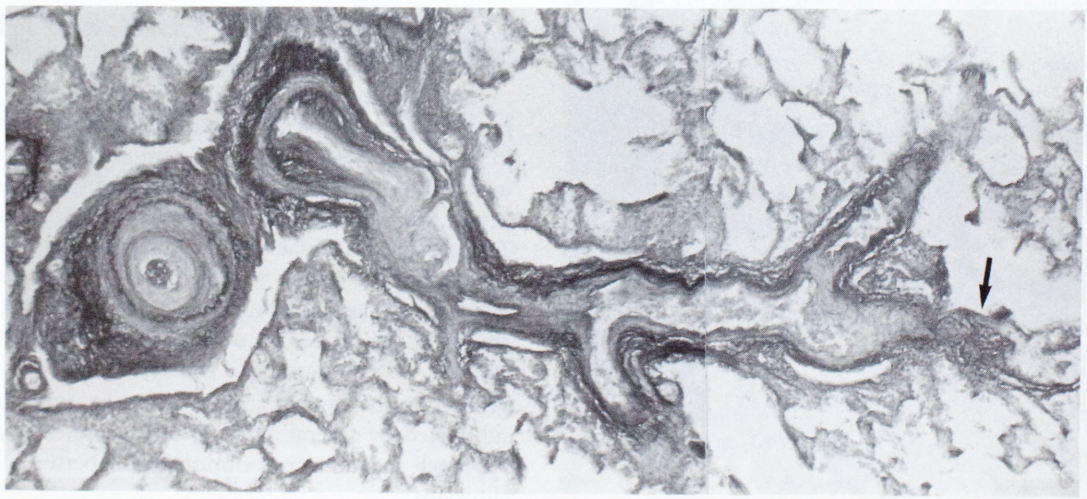

FIGURE 21-10. Arterial changes occur in severe fixed pulmonary hypertension associated with congenital heart disease. The main artery on the left follows a tortuous course and exhibits severe and advanced concentric intimal fibrosis and fibroelastosis. There is a plexiform lesion (*arrow*), and very distal branches show medial atrophy. Dilatation lesions are present along the course of the involved artery. (Elastic tissue stain; low magnification.)

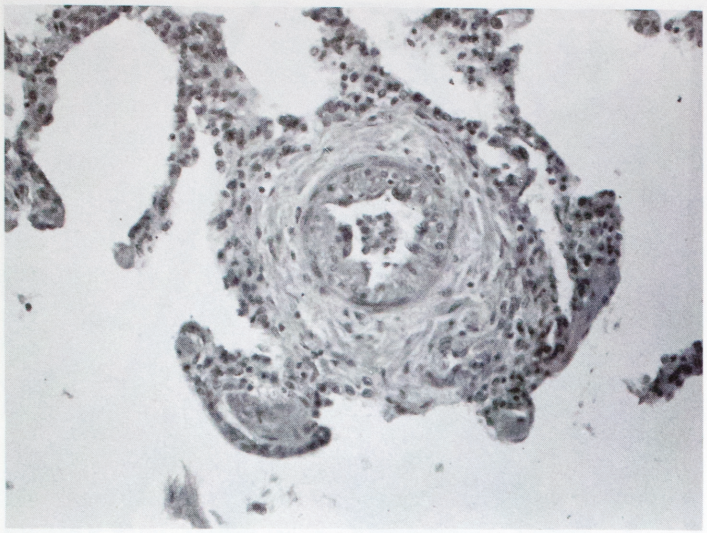

FIGURE 21-12. Intimal longitudinal smooth muscle bundles are present in this small, muscular pulmonary artery. (H & E stain; low magnification.)

nary hypertension reveal a pattern of twisted cablelike ridges, whereas advanced stages of arterial disease exhibit a chenillelike pattern in which high ridges alternate with narrow, misshapen ones.

Transmission electron microscopy has revealed an increase in rough endoplasmic reticulum and microfilament bundles in endothelial cells of pulmonary hypertension.[16] Immunohistochemical stains have shown increased staining for factor VIII–related antigen.[17] These findings may be interpreted as hyperfunction secondary to increased workload and remodeling of inner arterial surface. These alterations have been linked to the possibility of an increased or abnormal interaction with circulating platelets and leukocytes as well as the production of mitogens, which are like growth factors and may account for the proliferation of vascular cells.[18] Endothelin, an endothelium-derived peptide that has vasoconstricting activity and is capable of inducing smooth muscle proliferation, has been demonstrated to be increased in the pulmonary circulation of patients with pulmonary hypertension associated with CHD and linked to the pathophysiology of the vascular lesions.[19]

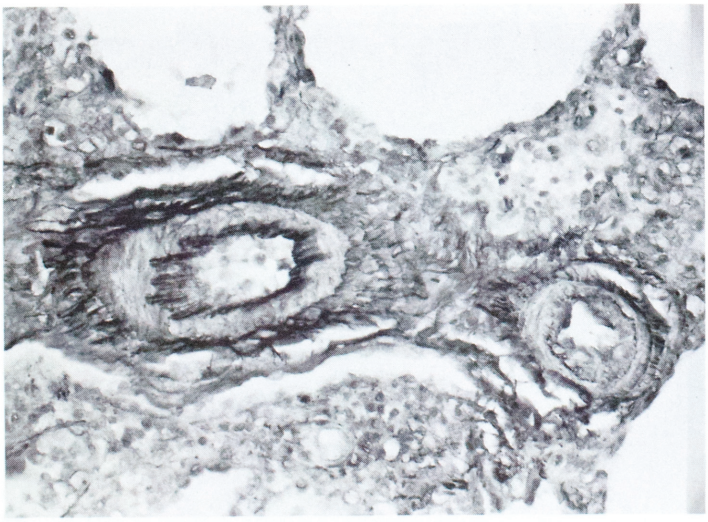

FIGURE 21-13. A severe degree of medial hypertrophy is present in this pulmonary artery. The branch on the right shows intimal longitudinal smooth muscle fibers with reduplication of the internal elastica. (Elastic tissue stain; low magnification.)

Generalized and Uniform Dilatation

Dilatation of pulmonary arteries beyond the diameter of the accompanying airway branch is present in cases of high pulmonary flow. A degree of medial hypertrophy may be masked by the dilatation, but morphometric studies have demonstrated a normal arterial wall thickness-diameter ratio.[8]

Bronchopulmonary Anastomoses

Yaginuma and colleagues, in a computer-aided reconstruction study, have presented evidence that in advanced hypertensive vascular disease, blood reaches alveolar capillaries by way of small remaining channels in the obstructive lesions or through bypass-type collateral vessels by way of bronchial arteries.[11] The bypass-type collateral vessels originate proximal to stenotic sites and anastomose with dilatation lesions, allowing blood to flow to alveolar capillaries.

REVERSIBILITY UPON CORRECTION OF CONGENITAL HEART DEFECTS

Wagenvoort and colleagues have presented their experience with the arterial status before and after banding of the pulmonary artery in children with cardiovascular anomalies.[20] They have established that medial hypertrophy is reversible, and that the same appears to be true for cellular intimal proliferation. However, concentric intimal fibroelastosis, dilatation lesions, fibrinoid necrosis, and plexiform lesions are irreversible. They have proposed that the point of no return is somewhere between mild and severe intimal thickening, when there is an average reduction of 33% to 50% of the vascular lumen by concentric intimal fibroelastosis.

LUNG BIOPSY IN CONGENITAL HEART DISEASE

Histologic evaluation of pulmonary arteries represents a key step in deciding operability. Biopsy specimens must be properly fixed in the distended position by formaldehyde injection with a fine needle and syringe, and cut serially. Elastic stains are mandatory. The different arterial segments can be easily identified by the segment of the airway to which they are associated. Careful clinicopathologic and hemodynamic studies suggest that lung biopsy should be performed to determine operability in cases with pulmonary vascular resistance greater than 8 U $\times$ m^2.[21] Although grading[10] and morphometry,[21] at the time of reporting, are supported by several authors, others prefer a careful descriptive approach to enhance communication between pathologists and clinicians.[8]

Yamaki and colleagues have developed an index of pulmonary vascular disease (IVPD) based on the mean rating obtained after grading all the SPAs in each histologic section.[21] The grading was

done according to the following histologic findings: no hypertrophy of the intima of SPA, cellular proliferation of the intima of SPA, fibrous thickening of the intima of SPA, and destruction of the media of SPA. They regarded an IVPD rating of 2.2 in Down syndrome and 2.1 without the syndrome as the upper permissible limits for surgical intervention.[21]

LESIONS IN OBSTRUCTED VENOUS FLOW: CONGESTIVE VASCULOPATHY

Under these circumstances, medial hypertrophy and intimal fibrosis of pulmonary arteries are said to appear earlier and be more pronounced than in the other conditions. However, cellular proliferation of the intima, concentric intimal fibroelastosis, and plexiform lesions do not occur. The pulmonary veins that suffer the pressure burden undergo arterialization with the appearance of internal and external elastic laminae and intimal fibrosis. The term "congestive vasculopathy" has been suggested to encompass the scope of pulmonary vessel alterations under these circumstances (see Chap. 20).[22]

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