Pulmonary Vascular Disease with Congenital Heart Lesions: Pathologic Features and Causes

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SUMMARY    Pulmonary vascular disease, a serious complication of many congenital heart lesions, has three major components: increased muscularity of small pulmonary arteries; intimal hyperplasia, scarring and thrombosis; and reduced numbers of intraacinar arteries. The muscularity is due to increased stress on the vessel wall, and is reversible. The intimal changes may be due to endothelial damage, causing an imbalance between prostacyclin and thromboxane A2 production and leading to local platelet aggregation. This, in turn, may stimulate migration and division of myointimal cells, which thicken the intima and lead to scarring and thrombosis. Extensive intimal changes are probably irreversible, but the possibility of preventing them by use of agents that inhibit platelet aggregation needs to be considered. The mechanism of a decrease in numbers of intraacinar arteries is unexplained. The potential for growth of new vessels after corrective surgery of the cardiac defect is an important factor in restoring pulmonary vascular resistance to normal. Available evidence suggests that this growth potential is reduced after 2 years of age and argues for early surgical relief of pulmonary vascular stresses.

PULMONARY VASCULAR DISEASE is one of the most serious complications of many forms of congenital heart disease, particularly cyanotic or acyanotic lesions in which pulmonary blood flow is increased. If the vascular disease is allowed to progress, there will be increase in pulmonary vascular resistance that may interdict satisfactory surgical correction of the cardiac defect.1-18 As a result, fear of the development of pulmonary vascular disease often leads to earlier surgical treatment than might otherwise be desirable.

In 1958, Heath and Edwards4 introduced the first comprehensive classification of the pathologic features of pulmonary vascular disease, and this classification is still in use. Since then, however, new information has been gleaned that modifies or even alters their concepts. Further, some likely mechanisms of the pulmonary vascular changes are being explored, particularly in the fields of prostaglandin and platelet functions. In time, this new understanding may lead to medical therapies for preventing the pulmonary vascular changes. In the following review, we attempt to summarize what is known and suspected about pulmonary vascular disease to bring cardiologists up to date with the subject and stimulate further research into it.

There appear to be three major components of pulmonary vascular disease: increased muscularity of small pulmonary arteries; intimal hyperplasia, scarring and sometimes thrombosis; and a reduced number of intraacinar arteries.

Increased muscularity of small pulmonary arteries is almost certainly a response of smooth muscle in the arterial media to increased isometric or isotonic work. It thus occurs whenever there is pulmonary hypertension; for example, with larger ventricular septal defects, pulmonary venous obstruction or prolonged hypoxic pulmonary vasoconstriction, including intrauterine fetal hypoxia or pulmonary hypertension.6-12 All of these conditions increase pulmonary arterial pressure and increase the pressure work of the arterial walls. Lesions that increase pulmonary blood flow without increasing pulmonary arterial pressure, for example, atrial septal defects, total anomalous pulmonary venous connection and complete transposition of the great arteries without ventricular septal defect or patent ductus arteriosus, may also stimulate growth of pulmonary arterial muscle. Although pulmonary arterial mean pressures may be normal despite these lesions, the increased pulmonary arterial pulse pressures often produce systolic pressures that
are above normal. Further, the wide pulse pressure may imply abnormal distention of small arteries throughout the cardiac cycle. The increased muscularity of small pulmonary arteries in these high-flow, low-pressure lesions may be masked by the dilatation of these vessels, just as increased ventricular muscle mass is less evident in the dilated ventricle with a volume overload than in concentric ventricular hypertrophy due to pressure overload. Special care is needed to identify the increased arterial muscle mass: Some investigators have related the cross-sectional area of medial muscle to the cross-sectional area of adjacent lung parenchyma or to the diameter of the artery after allowing for the amount of contraction by estimating the length of the internal elastic lamina; others have related medial wall thickness at different levels in the bronchial tree to normal values for age.

Not only are the pulmonary arterial walls thicker than normal, but muscle appears more distally than is usual for age. At birth, small pulmonary arteries normally have a complete ring of medial muscle up to but not beyond the terminal bronchiole; only after 2 years of age are small arteries fully muscularized to the end of the respiratory bronchiole. Increased pulmonary blood flow is associated with an earlier-than-normal appearance of muscle in the most distal small pulmonary arteries.

Most of the increase in pulmonary arterial muscle mass is due to hyperplasia rather than hypertrophy. The new cells are probably formed locally from mesenchymal cells rather than from migration of more proximal muscle cells.

We do not know if the excess numbers of muscle cells regress entirely once increased pulmonary pressures and flows are abolished. However, clinical experience and recatheterization data suggest that pulmonary vascular resistance returns to normal with successful treatment if increased muscularity is the sole reason for the increased vascular resistance. Further, lung biopsies after banding of the pulmonary artery have shown regression of medial hypertrophy.

The most striking features of pulmonary vascular disease are the intimal hyperplasia and subsequent structural vascular changes. These features and their probable sequence were first described by Heath and Edwards in 1958, although earlier descriptions exist. The initial sequence is not in doubt. Muscular hypertrophy of small pulmonary arteries, as described above, is grade I. Grade II vascular disease is manifested by medial hypertrophy and intimal hyperplasia varying from minimal thickening to thickening that almost occludes the vessel. In grade III, these intimal cells are replaced by hyalinized, collagenous tissue in what often resembles a concentric “onion-skin” lesion in the artery. Late grade III lesions may be associated with luminal thrombosis and recanalization.

Grades IV, V, and VI indicate the probable sequence defined by Heath and Edwards, but recent work has not confirmed their views. Grade IV is characterized by plexiform lesions, locally dilated segments of an artery with a thin wall showing tissue damage and with the lumen filled with cellular septa, between which are capillary-like channels. These lesions usually occur just after the artery has branched off from its parent vessel. There may also be clusters of thin-walled dilated arteries with patent lumena (angiomatoid lesions); these lesions also occur near the origin of the arterial branch. In grade V, there is extensive fibrosis of the media and intima of the small arteries, which appear as rigid dilated tubes. The various dilatation lesions of grade IV are still present, and the very fragile vessels often rupture. As a result, small foci of hemosiderosis are characteristic of this stage. Finally, grade VI is an acute arteritis with fibrinoid necrosis. Experiments show that fibrinoid necrosis may follow acute pulmonary vasocostriction and hypertension, with a subsequent inflammatory reaction. The plexiform lesions of grade IV appear to develop in areas that have undergone fibrinoid necrosis; they may, therefore, indicate a stage of proliferative repair. The timing and pathogenesis of grade V lesions are unknown. In general, grades IV to VI overlap and represent advanced disease.

The cells that occur in the hyperplastic intima of grade II lesions come from the media, and may be seen crossing the internal elastic lamina and have features of smooth muscle. Whether they come from muscle cells or other mesenchymal cells is unknown.

Although there is some evidence that the thickened intima of grade II lesions can retract and thin after the stimulus is removed, we believe that advanced grade II lesions with marked luminal obstruction or grade III lesions with scarring are irreversible. Operability depends on how many vessels are involved and whether potential for growth of new vessels remains (see below).

The first demonstration of a potential mechanism of these intimal changes was by Fry in 1968. He developed methods for measuring shearing forces made by blood moving past the (stationary) endothelium, and then studied the acute effects of increased shearing forces obtained by constricting the abdominal aorta in the dog. When shearing forces were more than three times the normal value, there was endothelial damage. Endothelial cells were sometimes stripped away from the intima, or remained in place but were necrotic, or else looked normal on light microscopy but were abnormally permeable to lipoproteins.

The gap between these acute studies and the more slowly evolving, hyperplastic intimal changes seen in patients has not been bridged, but there are studies in other fields that suggest logical mechanisms for these changes. It has long been known that intimal injury evokes a proliferative response of smooth muscle cells, and more recently it has been shown that a platelet-derived mitogenic factor plays a major role in this proliferative response. Numerous other factors in the response are summarized in the review by Friedman and Burns. Recently, too, the roles of prostaglandins in platelet aggregation have been explored. Most of these studies have been done in
systemic arteries but the findings almost certainly apply to pulmonary arteries as well. In brief, endothelial injury causes local platelet adherence and platelets are activated. They degranulate and release a variety of substances, including platelet mitogenic factor and substances (ADP for one) that cause further platelet aggregation. Phospholipase A$_2$ in the vessel and platelet walls is activated, and it releases arachidonic acid with the consequent synthesis of prostaglandins and thromboxanes. Among the prostaglandins is prostacyclin (PGI$_2$), which prevents platelet aggregation, whereas thromboxane A$_2$ (mainly released by the platelets) promotes platelet aggregation. The balance between platelet-aggregating thromboxanes and substances that prevent aggregation is influenced by many factors. Aggregation is increased by a family history of hypertension or stroke, smoking, oral contraceptives and high serum concentrations of low-density lipoprotein, whereas it is inhibited by polyunsaturated fatty acids. In support of this hypothesis is the fact that proliferative intimal lesions after endothelial damage are reduced in rabbits made thrombocytopenic$^{35}$ and in baboons infused with homocysteine but also given dipyridamole.$^{36}$ The homocysteine infusion damages the endothelial cells and leads to platelet aggregation on the damaged areas. Preventing platelet aggregation by giving dipyridamole reduces or abolishes the platelet thrombi. On the other hand, it is important to appreciate that the central role of platelet aggregation is challenged by experiments in which neointimal change after arterial injury in rats was not altered by antiplatelet drugs.$^{37}$ There are, of course, innumerable differences between different species and their reactions to drugs and between acute animal experiments and what is found in human disease. However, it is possible to generate potentially useful hypotheses about the causes of proliferative intimal damage and so devise experiments that might abolish or reduce the changes.

The proposed pathophysiologic processes may explain the difference in time of onset of pulmonary vascular disease in atrial and ventricular septal defects. In atrial septal defects, a large left-to-right shunt can develop only after pulmonary vascular resistance and pressure decrease and right ventricular distensibility increases. Therefore, the high flows with atrial septal defects are associated with dilated small pulmonary arteries. By contrast, the maintained high pulmonary arterial pressures when there is a large ventricular septal defect are associated with thick-walled small pulmonary arteries that have a relatively small lumen. For any given volume flow, the velocity of flow will be greater in large ventricular septal defects than in atrial septal defects, so that shearing forces and endothelial damage are likely to be more severe and progressive in the former.

Pulmonary vascular resistance can increase if most of the pulmonary arteries are narrowed and also if there are fewer pulmonary arteries present than normal. The latter possibility was ignored until recently, when Reid and her colleagues began to study normal and abnormal fetal and postnatal pulmonary arterial development.

During normal fetal development, the major airways are formed by 16 weeks of gestation, and the major pulmonary arterial branches accompanying them form at the same time.$^{38}$ Thereafter, there is a continued increase in the numbers of more peripheral acinar units until lung growth is completed by 8–10 years of age.$^{39}$ As new acini form, new intraacinar arteries form with them, and the proportion of intraacinar arteries to alveoli remains constant throughout lung growth.$^{40,41}$

Certain congenital heart lesions modify the numbers (and thickness) of intraacinar pulmonary arteries. In aortic atresia and aortic stenosis, there are more intraacinar pulmonary arteries than normal,$^{42}$ and there are fewer than expected in pulmonary atresia,$^{43}$ some infants exposed to prostaglandin synthetase inhibitors in utero$^{44}$ and fetal lambs with experimental coarctation.$^{45}$ It is possible, therefore, that the early increase in pulmonary vascular resistance in certain lesions, for example, truncus arteriosus and complete transposition of the great arteries with ventricular septal defect, might have its basis in a deficient number of intraacinar pulmonary arteries at term. This remains to be investigated.

More important, patients who have pulmonary vascular disease due to a variety of lesions (ventricular septal defect, atriointerventricular defects or complete transposition of the great arteries) have a decreased arterial-to-alveolar ratio.$^{46,47}$ These decreases in the numbers of intraacinar pulmonary arteries accompanied marked increases in muscularity and distal extension of muscle, and the extent of decrease was closely related to the pulmonary vascular resistance calculated at cardiac catheterization. It is not clear whether arteries already formed disappear or if new arteries do not form when new acini develop, but histologic observations favor the latter.$^{48}$

The capacity for regrowth of lost intraacinar arteries is not known. However, in the normal child, two-thirds of the final number of intraacinar arteries are present at 18 months of age and most of the rest form by 5 years of age. This suggests limited potential for regrowth of arterial numbers beyond infancy.

The pathophysiologic mechanisms outlined above are likely to be responsible for pulmonary vascular disease in those with large left-to-right shunts, with or without pulmonary hypertension, atrial, atriointerventricular or ventricular septal defects, patent ductus arteriosus, truncus arteriosus, transposition of the great arteries with large ventricular septal defect or ductus arteriosus. There are, however, three groups of lesions in which additional mechanisms may be active.

If there is a single pulmonary artery, a hemitruincus, or one hypoplastic lung, or a pneumonectomy in the neonatal period, essentially all the right ventricular output goes into one lung so that resting flows to that lung are about twice normal; with additional left-to-right shunts, the flow is even more increased. In effect, the number of vessels has been halved, so that the tendency for accelerated vascular stress is increased.
The increased flow into a small vascular bed with a high resistance maintains high pulmonary arterial pressures, which in turn delay the postnatal involution of the medial smooth muscle. This may explain why pulmonary hypertension occurs in about 20% of these patients with no added shunts or about 85% of them who have added left-to-right shunts. What is more difficult to explain is the early vascular disease that may occur in children with transposition of the great arteries without a ventricular septal defect or patent ductus arteriosus. Further, it seems that pulmonary vascular disease occurs earlier with a large ventricular septal defect or patent ductus arteriosus if there is a transposition of the great arteries than with normally related great arteries. One explanation is that, if there is an associated large ventricular septal defect or ductus arteriosus, not only will there be high pressure and flow in the pulmonary artery, but also the shear stresses on the endothelium will be augmented by the polycythemia that these children have. Polycythemic blood is more viscous than normal: blood with a hematocrit of 70% has approximately twice the viscosity of blood with a hematocrit of 45%. Whether this is sufficient to explain vascular disease in those with an intact ventricular septum and no ductus arteriosus is uncertain. These children can have normal pulmonary arterial pressures and pulmonary blood flow about twice normal, and may even have thinner than normal pulmonary arteries. However, three other mechanisms have been suggested. Some investigators have speculated that the increased bronchial collateral flow may in some way cause pulmonary vascular disease.

Others have emphasized the frequency with which microthrombi are found in the small pulmonary arteries; microthrombi have even been found in an infant who developed severe pulmonary vascular disease after Mustard's repair of transposition of the great arteries. Therefore, some investigators suggest that an abnormal coagulability may be the basis for initiating the vascular obstruction; however, hypercoagulability has not always been found. A third mechanism that might interact with the others was described by Muster et al. in 1976. They noted that because of the angulation of the main pulmonary artery, there was a tendency for left ventricular blood to be ejected preferentially into the right pulmonary artery. This would then cause increased stress and shearing forces in the vascular bed of the right lung, whereas of the left lung might be subjected to stasis and failure of growth.

Finally, in cyanotic heart disease with low flows, for example, tetralogy of Fallot, there may be more typical focal thrombotic lesions of pulmonary arteries, as described first by Rich in 1948. These lesions could be related to the polycythemia and lowered velocities of flow, although involvement of a variety of coagulation factors cannot be excluded. Now that both transposition of the great arteries and tetralogy of Fallot are being corrected in early infancy, the hope is that these varieties of pulmonary vascular disease will disappear.

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Pulmonary vascular disease with congenital heart lesions: pathologic features and causes.
J I Hoffman, A M Rudolph and M A Heymann

Circulation. 1981;64:873-877
doi: 10.1161/01.CIR.64.5.873
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/64/5/873

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