SERIES 'HIGHLIGHTS ON PULMONARY HYPERTENSION'
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Pulmonary hypertension in childhood

S.G. Haworth

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ABSTRACT: In the presence of pulmonary hypertension, the pulmonary vasculature
fails to remodel after birth. Secondary changes then develop, and do so more rapid-
ly than in the adult lung because the cells are exposed to the insult whilst still relatively
undifferentiated. The commonest causes of pulmonary hypertension in newborn and
young infants are alveolar hypoxia, and congenital heart disease causing a left-to-
right shunt and increased pulmonary blood flow. The initial response of an increase
in pulmonary arterial muscularity is common to both, but intimal proliferation can
develop rapidly in those with complex congenital heart disease. The structural abnor-
malities are accompanied by abnormalities in the control of pulmonary vascular reac-
tivity, a problem which is the focus of much current research activity.
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Dept of Cardiology, Hospital for Sick
Children, Great Ormond Street, London, UK.

Correspondence: S.G. Haworth
Dept of Cardiology
Hospital for Sick Children
Great Ormond Street
London
UK

In the presence of pulmonary hypertension, the pul-
monary vasculature fails to remodel normally after birth.
Secondary changes then develop, and do so more rapidly
than in the adult lung because the infant cells of the lungs
are still relatively undifferentiated. The commonest caus-
es of pulmonary hypertension in newborn and young
infants are alveolar hypoxia, and congenital heart disease
causing a left-to-right shunt and increased pulmonary blood
flow. The initial response is similar with both causes.
There is muscularization of intra-acinar pulmonary arteries,
which are normally only partially- or non-muscualarized
when viewed under light microscopy. In pulmonary hyper-
tensive congenital heart disease, however, these early
changes can soon be followed by a more generalized
increase in pulmonary arterial muscularity of both pre-
and intra-acinar arteries, together with intimal proliferation.
These structural abnormalities are associated physiologically
with a labile pulmonary vasculature. Swings in vasomotor
tone are more extreme than those seen in pulmonary
hypertensive adults. Thus, present research activities focus
on the influence of pulmonary hypertension on normal
pulmonary vascular development, and on the pharmaco-
logical control of pulmonary vascular reactivity in the
immature lung.

*Adaptation to extra-uterine life and postnatal development
in the normal lung*

Adaptation is effected by changes in endothelial and
smooth muscle cell shape and position [1–4]. The vessel
wall is remodelled, without there being a reduction in the
amount of pulmonary vascular smooth muscle. Within a
few moments of birth, the earliest and most dramatic
changes are seen in the precapillary arteries. These thin-
walled vessels consist of only endothelial cells and either

pericytes or intermediate cells, which are smooth muscle
cell precursors. At birth, the endothelial cells are squat,
have a narrow base on the subendothelium, and a low
surface/volume ratio, with considerable overlap of adjacent
lateral cell borders. Five minutes after birth, the endothe-
lial cells have become thinner, show an increase in sur-
face/volume ratio and less overlap. Lumen diameter
increases. Similar structural changes are evident immedi-
ately after birth in the small muscular arteries of the res-
piratory unit (fig. 1). Many small, "unopened" muscular
arteries become recruited into the pulmonary circulation
during the first days of life (fig. 2). Spreading of the
cells within the vessel wall may be facilitated by the lack
of fixed interstitial connective tissue in the walls of the
peripheral pulmonary arteries at birth, and by the lack of
nerve fibres of the vasoconstrictor type at this times [5].

There are a number of possible mechanisms responsible
for these structural changes. They include mechanical
stretch by lung expansion [6], and a loss of hypoxic vaso-
constrictor tone as breathing begins. In addition, a decrease
in the circulating concentration of vasoconstrictor leuko-
trienes C_4 and D_4 (LTC$_4$ and LTD$_4$) [7, 8], together with the
release of bradykinin [9], which appears to have a direct
effect but may also induce prostacyclin release [10]. There
is also a burst of endothelial prostacyclin release, associated
with the onset of ventilation [11]. The endothelial-derived
relaxing factor, (EDRF) nitric oxide, is at least partly
responsible for vasodilatation in the immature postnatal
ovine lung. This dilatation of the pulmonary vasculature is
attenuated by the inhibitors of EDRF synthesis and by
methylene blue, which inhibits the action of nitric oxide
[12–14]. The responses to pharmacological stimuli of
isolated porcine pulmonary arteries taken from newborn
animals are different from those seen from arteries of
mature animals. Although arteries from newborns dilate in
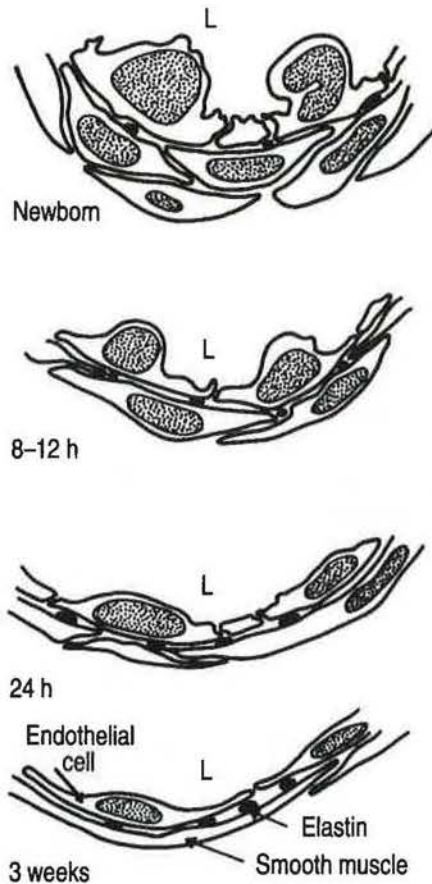response to nitric oxide, a larger dose of nitric oxide was

Fig. 1. – Diagram of transverse sections of terminal bronchiolar arteries to show changes in endothelial and smooth muscle cell shape as the vessel adapts to extrauterine life. L: lumen.
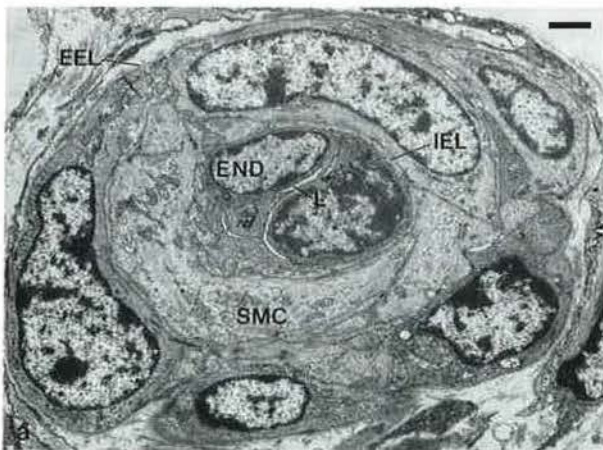

Fig. 2. – Electronmicrograph of transverse section of undilated artery from a newborn, showing endothelial cells (END) surrounded by a single layer of overlapping smooth muscle cells (SMC). The lumen (L) is minute. IEL and EEL: elastin profiles constituting the internal and external elastic laminar, respectively. (Scale bar = 2 µm).

required than in arteries from mature animals, to produce the same effect (personal observations). Also, receptor-mediated relaxation matures with age. Endothelium-dependent acetylcholine-mediated dilatation of pulmonary arteries

is absent at birth, but is present by 3 days, and at 3–10 days it was greater than is seen in mature vessels [15]. Alpha$_2$-adrenoreceptor-mediated relaxation, again endothelium-dependent, is also absent at birth (personal observation).

Once adaptation has occurred, the smooth muscle cells deposit connective tissue around themselves, and so fix the new wall structure. The proportions of the different types of interstitial connective tissue also change with age, which affects the mechanical properties of the vessel wall [16]. Collagens type III and V are abundant at birth, whilst there is relatively little collagen type I in the media and adventitia, suggesting that the newborn pulmonary vasculature is more plastic than that of the adult. Deposition of collagen type I helps to explain the increase in mechanical stiffness of the vessel wall, which occurs during the first month of life [17]. At birth, all the pulmonary vascular smooth muscle cells are immature [1, 2, 4]. Synthetic rather than contractile organelles predominate. The concentration of contractile myofilaments and surface dense bodies increases rapidly during the first six months of life, but the ultrastructural appearance of the smooth muscle cells does not closely resemble that of the adult until about 2 yrs of age.

The major structural remodelling from the foetal pattern takes place during the first two weeks of life. The physiological result is a reduction in pulmonary arterial pressure and vascular resistance. The power output of the right ventricle is halved [18].

During growth, the intrapulmonary arteries increase in size, and wall thickness increases to maintain a constant low relationship to the external diameter. As the respiratory unit arteries grow, smooth muscle cells differentiate from the precursor lying *in situ*, and the arteries appear to become partially or completely muscularized when viewed under light microscopy [19]. Muscle is said to have extended along the arterial pathway with growth. The vessels become innervated as they become muscularized. The nerves contain predominantly tyrosine hydroxylase and neuropeptide tyrosine, vasoconstrictor substances [5]. Fewer of them containing calcitonin gene related peptide (CGRP), and vasoactive intestinal peptide (VIP). Changes also occur in the density and distribution of receptors to endothelin, CGRP and VIP [20].

The number of respiratory unit arteries increases rapidly as new alveoli form during the first year of life. Thus, the cross-sectional area of the precapillary bed increases, which helps to accommodate an increase in cardiac output, without increasing pulmonary vascular resistance, as the child grows.

Failure to adapt normally to extra-uterine life

Babies with idiopathic persistent pulmonary hypertension have an anatomically normal heart, and are the product of an apparently normal pregnancy and delivery. They present soon after birth with cyanosis, due to right-to-left shunting across foetal channels [21, 22]. The pulmonary arteries fail to remodel after birth and the vessels remained thick-walled. Clusters of undilated small, muscular and partially
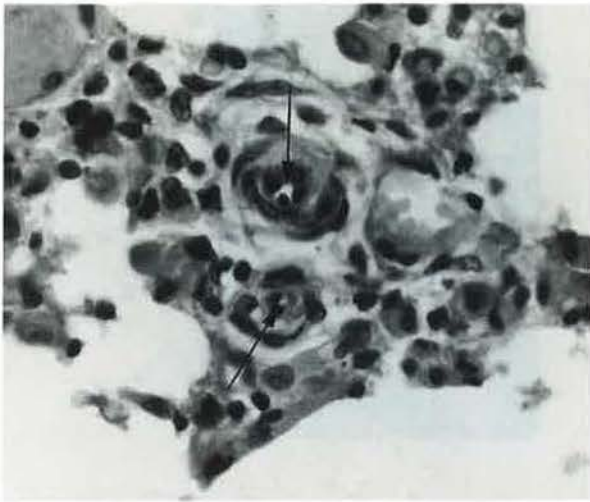
Fig. 3. – Photomicrograph of arteries showing whorled appearance of cells, with minute lumen (arrows). (Magnification ×700)

muscular arteries are characteristic, suggesting that many intra-acinar arteries were never recruited into the pulmonary circulation after birth (fig. 3) [23]. If the baby survives for more than a few days, secondary changes occur, pulmonary arterial muscularity increases and excessive connective tissue is deposited. The structural abnormalities are similar to those seen in the hypoxic newborn lung, but the underlying mechanism is different and unknown. The presence of abnormally thick-walled arteries in babies dying soon after birth has prompted the suggestion that the intrapulmonary arteries may become excessively muscularized during foetal life, becoming unable to adapt normally at birth [22].

Perinatal hypoxia is the commonest cause of persistent pulmonary hypertension. In a group of apparently normal babies, who had a hypoxic delivery, due for example to an accidental haemorrhage, the pulmonary arterial medial thickness remained close to the foetal level, until they died at about 36 h of age. If the damage is less extreme, then secondary changes develop over a longer period of time. These include extension of muscle into respiratory unit arteries, accelerated smooth muscle differentiation, and accelerated and excessive connective tissue deposition. As time passes, vessel wall structure becomes more "fixed" and difficult to treat. Early resolution is crucial.

Animal models of neonatal hypoxia have been helpful in understanding the pathogenesis of these changes. When newborn pigs are placed in a hypoxic environment from the moment of birth, the pulmonary arteries still retain their foetal appearance at three days of age (fig. 4) [24]. By contrast, when animals are allowed to adapt normally to extrauterine life for three days and then exposed to hypoxia for three days, the vessels do not revert to a foetal appearance, and have a thinner wall structure than at birth. However, all animals exposed to hypoxia during the first week of life show an increase in smooth muscle cell myofilament concentration and excessive connective tissue

deposition. These changes are less marked in animals first exposed to hypoxia at 14 days of age, suggesting that a longer period of hypoxic exposure is required in older animals to elicit the same response. On exposure to hypoxia, newborn calves show an increase in smooth muscle cell and fibroblast proliferation, as compared with the normal for age. Such animals show a marked increase in type I collagen gene expression in the media and adventitia [25]. The pattern of matrix protein gene expression within the vessel wall was also abnormal. In situ hybridization studies showed retention of the high foetal tropoelastin messenger ribonucleic acid (mRNA) expression in the outer part of the vessel wall. All of these observations indicate that hypoxia disturbs normal postnatal transition in gene expression of connective tissue components, which will, in turn, affect the mechanical properties of the vessel wall and its pharmacological responsiveness.

The management of babies with persistent pulmonary hypertension is supportive, "buying time" to allow the pulmonary circulation to adapt to extrauterine life. Identifiable precipitating factors are treated. A higher than normal fractional inspired oxygen is given. One interesting new vasodilator treatment is inhaled nitric oxide, which acts selectively on the pulmonary vascular bed in a dose-dependent manner [26].

It is often assumed that early restitution to a normoxic environment leads to reversal of the changes described and subsequent normal development. However, when animals which had been transiently exposed to hypoxia as newborns and appeared to have fully recovered were re-exposed to hypoxia 6 weeks later, they showed a higher pulmonary arterial pressure and greater vascular remodelling than did animals which had been allowed to adapt normally to extrauterine life (HERGET and WACLAV [27], quoted by Stenmark K, personal communication 1992). Premature babies who recover from a neonatal respiratory illness can fail to thrive, and later die. They often have significant pulmonary vascular abnormalities [28]. These abnormalities are present, whether or not they have the clinical and/or pathological features of cor pulmonale. Conversely, those who do develop cor pulmonale do not always have severe pulmonary vascular obstructive disease. Indeed, the changes are usually limited to an increase in pulmonary arterial muscularity (fig. 5).

In a recent study of lung structure in children who had pulmonary hyaline membrane disease, the pulmonary vessels of those who died without recovery from the initial illness at 2–13 weeks of age appeared similar to those of the normal foetus at term [28]. The picture was very similar to that seen in pigs, that had been exposed to hypoxia from the time of birth. In babies who survived longer and appeared to have recovered from the initial illness, the arteries had a more normal postnatal appearance, and pulmonary arterial medial thickness increased with survival time. None showed evidence of classic fibrotic bronchopulmonary dysplasia, but all had an increase in bronchial smooth muscle in small airways and a reduced alveolar number, with concomitant reduction of intra-acinar postnatal arterial development. Intimal disease was uncommon in this series, being present in only 2 of 17 cases, where it was mild, cellular and nonobstructive. STOCKER [29], who
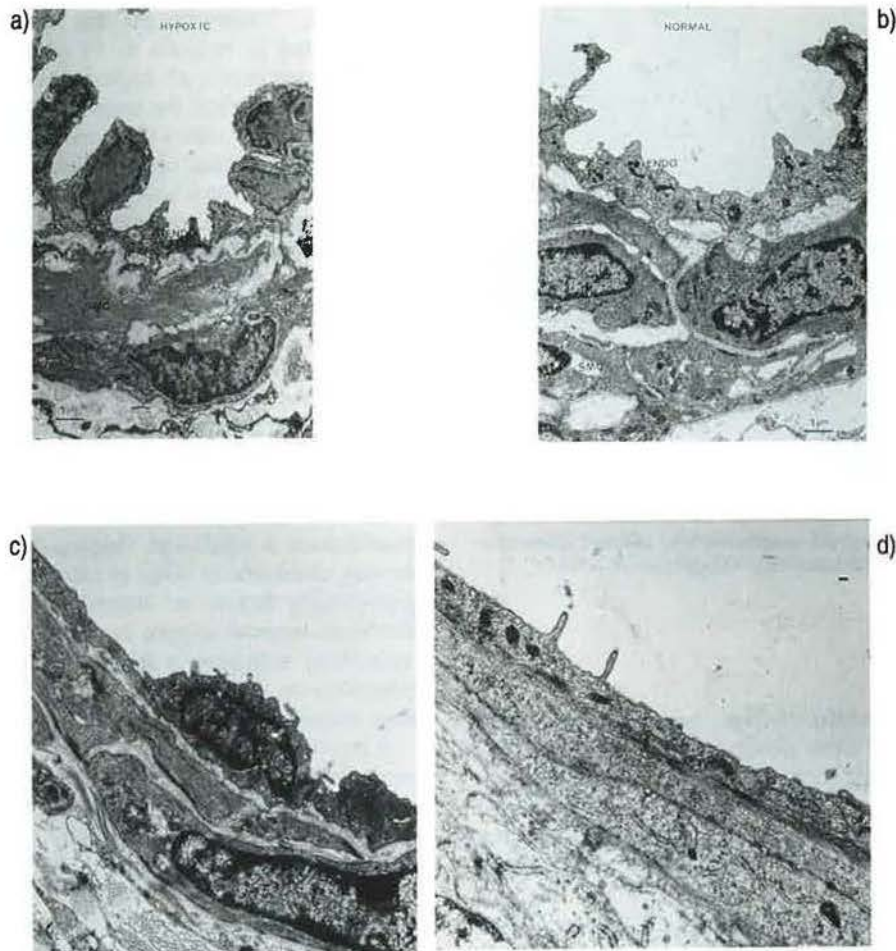
Fig. 4. – Electronmicrographs showing response to hypoxia in newborn piglets: a) normal at birth; b) unadapted wall structure of animal exposed to hypoxia from birth; c) normal at 3 days; and d) following exposure to hypoxia from 3 until 6 days of life. All pictures were taken at the same magnification. Excessive myofilaments are shown in (b) and (d). Note excessive connective tissue in (d). ENDO: endothelium; SMC: smooth muscle cell. (Scale marker = 1 μm).

Fig. 5. – Photomicrograph of the lung of a 7.5 month old child who died with cor pulmonale. The alveoli are of normal shape. Pulmonary arteries have a thick media and collagenous adventitia. (Magnification ×200).

studied 28 cases of bronchopulmonary dysplasia, 50% of whom had right ventricular hypertrophy, found intimal damage in only 11%.

The absence of more advanced pathological lesions suggests that it may be appropriate to adopt a more aggressive therapeutic approach than is customary in these babies, using either long-term oxygen therapy and/or vasodilator drugs after the "recovery" from the initial neonatal illness. The increase in pulmonary vascular smooth muscle seen in hypoxic babies could be the result of disturbed endothelial function. *In vitro*, hypoxia can alter the endothelial metabolism of vasoactive agents, such as 5-hydroxytryptamine and angiotensin-converting enzymes [30, 31]. Endothelial cells can also modulate the phenotype of neighbouring cells, producing mitogens to promote the growth of smooth muscle cells and fibroblasts, and up-regulate the synthesis of connective tissue [32]. Cultured endothelial cells from hypoxic calves show changes in morphology and metabolism, and secrete a substance which increases the elastin synthesis of immature fibroblasts [33, 34]. Also, damage to airway epithelium may have contributed to an increase in pulmonary vascular resistance, since normal epithelium produces a factor which relaxes vascular smooth muscle [35].

Thus, in hypoxic newborn infants the pulmonary vasculature fails to undergo the normal process of remodelling, which constitutes adaptation to extrauterine life. The newborn

lung is certainly more vulnerable than the older lung, and even a short period of normoxia, allowing the lung to adapt to extrauterine life, is protective. Clinical observations suggest that the most severely affected newborns may not recover as well as might be supposed, and are more vulnerable to the effects of subsequent respiratory illness. This observation is compatible with the enhanced response seen on re-exposure to hypoxia in experimental animal studies. In hypoxic lung diseases, both in children and adults, the greatest increase in pulmonary arterial muscle generally occurs in those with right ventricular hypertrophy [36, 37].

Pulmonary hypertension from congenital heart disease

In children who are born with congenital heart disease, a large left-to-right shunt and pulmonary hypertension, the pulmonary circulation fails to remodel and develop normally during the first months of life [38, 39]. Abnormal remodelling leads to pulmonary vascular obstructive disease, if the pulmonary arterial pressure is allowed to remain high [39]. These structural changes are associated with an excessively reactive pulmonary vascular bed.

Structural abnormalities

In children with severe pulmonary hypertension, the rate at which the cellular changes develop in the arterial wall depends upon the type of intracardiac abnormality. For example, both an isolated ventricular septal defect and one associated with transposed great arteries cause a left-to-right shunt and pulmonary hypertension, but the former rarely causes severe pulmonary vascular obstructive disease during the first year, whilst the latter is usually inoperable before patients are one year old. In children with transposition with ventricular septal defect, severe obstructive intimal proliferation is present at 5–6 months of age. Thus, the structural abnormalities present in the lung can usually be predicted from the type of intracardiac abnormality, the age of the child, and the haemodynamic findings at cardiac catheterization. If, however, there is doubt about the likely outcome of intracardiac repair, then an open lung biopsy will clarify the position.

The presence of an increase in pulmonary blood flow with little or no increase in pressure is associated with the differentiation of pericytes and intermediate cells in pre-capillary vessels, giving rise to extension of muscle into more peripheral arteries than normal [40]. In larger vessels, which normally have a muscular coat, the media hypertrophies as the smooth muscle cells increase in size and connective tissue is deposited. As in the hypoxic newborn, the formation of smooth muscle cell contractile myofilaments is accelerated, so that the myofilament concentration normally achieved by six months is seen during the first few weeks of life [39]. These thick-walled arteries are prematurely innervated by nerves which contain predominantly vasoconstrictor substances [5]. If the pulmonary arterial pressure is allowed to remain elevated, the vessel wall remodels, such that the outer subadventitial layers of smooth muscle cells are well-differentiated and contain abundant alpha-actin, whilst the inner subendothelial smooth muscle cells have a more synthetic appearance, contain less of the alpha-actin isotype and show a reduction in cytoskeletal identification [41]. It is from these inner smooth muscle cells that intimal proliferation develops. The cells migrate through gaps in the internal elastic lamina to reach the subendothelium. Intimal proliferation first develops in young children in the small preacinar muscular and terminal bronchiolar arteries. The internal elastic lamina is poorly formed in these arteries at birth, and this may facilitate the early and rapid development of intimal proliferation seen in certain types of congenital heart disease. Poorly organized cellular intimal proliferation develops in arteries accompanying terminal bronchioli throughout the lung, and so increases resistance to flow [38, 42]. Such children die before there has been sufficient time for the deposition of much connective tissue and for the more advanced lesions, characteristic of an elevated resistance and poor prognosis in older patients, to develop, according to the classification of Health and Edwards
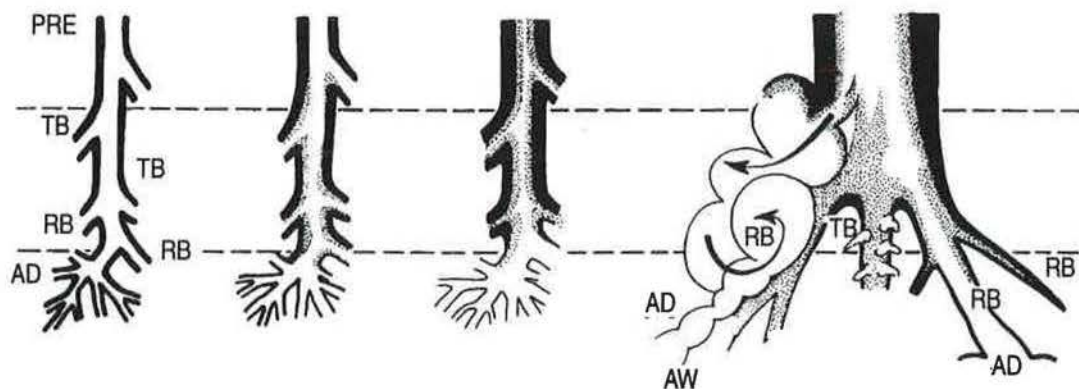

Fig. 6. – Diagram of the end of four arterial pathways, from the pre-acinar (PRE) to the terminal bronchiolar (TB), and the intra-acinar respiratory bronchiolar (RB) and alveolar duct (AD) arteries, showing the gradual development of intimal proliferation (stippling) associated with the progressive increase in wall thickness of pre-acinar, and decrease in wall thickness of intra-acinar, arteries until dilatation lesions develop. The upper interrupted line indicates the plane of section of satisfactory biopsies, and the lower line the plane of section of unsatisfactory biopsies taken too close to the pleura to sample the distal pre-acinar and all the intra-acinar arteries.

[43, 44]. As intimal proliferation increases in severity and narrows the lumen, the medial thickness of more peripheral pulmonary artery decreases (fig. 6). The transitory near-normal appearance of the peripheral intra-acinar arteries can be misleading, because in patients with a high pressure and resistance it reflects the severity of more proximal obstruction, and can be associated with an increased risk of residual pulmonary hypertension, after intracardiac repair. In the presence of severe pulmonary hypertension the number of intra-acinar arteries is reduced [45, 46]. Ultrastructural examination reveals many occluded vessels [46]. This is an early change and can be seen in young infants in the presence of a low resistance. Whether or not there is also a primary failure of postnatal angiogenesis is unknown.

Endothelial cell dysfunction

The pulmonary endothelial cells play a crucial role in determining pulmonary vascular tone and reactivity. In pulmonary hypertension, they are morphologically abnormal from the first weeks of life and endothelial dysfunction precedes morphological change [39]. There is clinical evidence of endothelial dysfunction. In children less than a year of age with potentially reversible pulmonary vascular disease, the circulating levels of prostacyclin and thromboxane A_2 show an imbalance in favour of thromboxane A_2, which favours vasoconstriction and enhanced platelet aggregation [47]. The level of circulating endothelium-derived vasoconstriction peptide, endothelin, is normal [48]. Immediately following open heart surgery, however, the endothelin level rises more in pulmonary hypertensives than in normal patients. In part, this results from reduced pulmonary extraction of endothelin, due to endothelial preoperative damage. Most importantly, pulmonary endothelial dysfunction may contribute to the development of pulmonary hypertensive crises, as a result of imperfect endothelial/smooth muscle cell interaction.

Pathophysiological responses to the pulmonary hypertensive child

In a pulmonary hypertensive crisis, pulmonary arterial pressure rises swiftly, exceeds the systemic arterial pressure, left atrial return falls and the cardiac output plummets [49]. The pulmonary arteries appear to "go into spasm". Pulmonary hypertensive crises characteristically occur immediately after, or during the first few days following intracardiac repair in young children who had a high pulmonary blood flow preoperatively. Such patients usually have potentially reversible pulmonary vascular disease, the peripheral pulmonary arteries showing severe medial hypertrophy, with little if any intimal proliferation. Pulmonary hypertensive crises are precipitated by hypoxia but frequently occur in well oxygenated patients, for as yet unknown reasons. Pulmonary hypertensive crises tend to cluster and become refractory to treatment. Early recognition and treatment is essential. Management consists of hyperoxic hyperventilation, with administration of the

vasodilator substances tolazoline and prostacyclin. For patients with an unstable cardiovascular system following intracardiac repair, inhalation of nitric oxide offers an important alternative selective pulmonary vasodilator therapy. Given by inhalation, it acts as a specific pulmonary vasodilator. The systemic arterial pressure remains stable, and then increases as oxygenation improves.

It is apparent that there is no gold standard for assessing the reversibility of pulmonary vascular disease. Potential reversibility of pathological lesions is not synonymous with operability. Whilst a satisfactory reduction in pulmonary vascular resistance and long-term survival is related to the type of pathological lesions present at the time of repair, the patient must first survive the operation. As we have seen, patients with potentially reversible disease can die with pulmonary hypertensive crises. Age at operation is the most crucial factor in determining long-term outcome, and the age at which it can be expected that the pulmonary vascular resistance will fall to a normal level is dependent upon the type of intracardiac abnormality. Certainly, all children with severe pulmonary hypertension should undergo intracardiac repair during the first year of life, and preferably during the first 8 months in complex types of anomalies.

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