Pulmonary arterial structure in pulmonary atresia after prostaglandin E₂ administration

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SUMMARY Administration of long-term, oral prostaglandin E₂ in two babies with pulmonary atresia did not appear to influence pulmonary arterial smooth muscle development, nor was there evidence of damage to the vessel walls, as has previously been reported after treatment of the same condition with prostaglandin E₁.

Experimental studies have shown that the prostaglandins E₁ (PGE₁) and E₂ (PGE₂) are potent relaxants of ductus arteriosus smooth muscle.^{1,2} They are now widely used to maintain perfusion of the ductus dependent pulmonary circulation.³⁻⁵ PGE₁ relaxes isolated strips of pulmonary vascular smooth muscle and, in the intact animal, lowers pulmonary vascular resistance.⁶⁻⁸ By contrast, PGE₂ is not a pulmonary vasodilator, and its effect on pulmonary arterial smooth muscle is uncertain.

Infusion of PGE₁ for between 30 hours and 12 days in neonates with pulmonary atresia has been associated with a reduction in pulmonary arterial smooth muscle.⁹ We now report the effect of PGE₂ on the intrapulmonary arteries of two babies with pulmonary atresia who died after long-term oral treatment. The techniques of arterial injection and quantitative morphometry were the same as those used to study the lungs of infants with pulmonary atresia given PGE₁, untreated cases of pulmonary atresia, and normal infants.⁹⁻¹²

Clinical summaries

CASE 1

A 2.9 kg baby became cyanosed soon after birth and cardiac catheterisation at 5 days of age showed pulmonary atresia, an intact ventricular septum, a hypoplastic right ventricle, and a persistent ductus arteriosus. She was treated with oral PGE₂, 125 µgm hourly for 26 days, then every two hours for 50 days. She then underwent surgical correction, consisting of pulmonary valvotomy and enlargement of the right ventricular outflow tract, using a peri-

cardial patch. She died 11 days after an initially successful operation. Necropsy confirmed the diagnosis and showed satisfactory enlargement of the right ventricular outflow tract, the circumference of the pulmonary valve ring including the patch measuring 2.6 cm. A persistent ductus arteriosus had an internal diameter of 2 mm.

CASE 2

A 3.0 kg baby was cyanosed from birth. Cardiac catheterisation on the second day of life showed pulmonary atresia with an intact ventricular septum, a hypoplastic right ventricle, a persistent ductus arteriosus, and stenosis at the origin of the right pulmonary artery. She was treated with oral PGE₂, 125 µgm hourly for six days, then every two hours for 109 days, and then the frequency of administration was gradually reduced until in the last four days of life it was every eight hours. The total duration of PGE₂ treatment was 126 days. An aortogram at 15 weeks of age showed a large ductus arteriosus with considerable dilatation of the left pulmonary artery and an abnormally small right pulmonary artery stenosed at its origin. The diagnosis was confirmed at necropsy.

Pathological techniques

The right lung of case 1 and both lungs of case 2 were available for study. The pulmonary arteries were injected with a "Micropaque"-gelatin suspension at 60°C and at a pressure of 100 cm water. This injection technique fills and distends all vessels larger than 15 µm in diameter. The lungs were then inflated with a buffered formol saline solution at a pressure of 45 cm of water and allowed

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to fix. Lung volume was determined by water displacement, and each lung radiographed and sliced,^{13 14} blocks of tissue being selected for microscopical examination by a random sampling technique.¹⁵

QUANTITATIVE ANALYSIS OF STRUCTURAL FEATURES OF LUNG

From the arteriogram the intrapulmonary arterial branching pattern and arterial size were assessed. Microscopically, the following features of peripheral arterial structure were studied: (1) the external diameter and medial thickness were measured in approximately 100 vessels in each lung; the arteries were then divided into size ranges and the mean percentage medial thickness calculated for each size range. (2) Where a small artery accompanies a small airway it can be characterised by reference to the type of this airway. The structure of the arterial wall, whether muscular, partially muscular, or non-muscular was described at each airway level and in this way the degree of extension of muscle along the arterial pathway was established. In addition, the external diameter of all arteries at each airway level was measured and the mean was calculated. (3) The number of arteries and alveoli were counted in the same area of lung section and the result was expressed as a ratio: this made allowance for any difference in the degree of inflation in various lungs. (4) The proportion of lung volume occupied by various structures was established by both macroscopical and microscopical point counting techniques.¹⁵ From these determinations, the total number of alveoli in each lung was calculated.

Results

The results are summarised in the Table.

Table Summary of structural features

Case no.	1		2	
	Right lung		Left lung	
Lung volume	N	N	↓	
Arterial branching pattern	N	N	N	
Intrapulmonary arterial size on arteriography	N/↓	↑	↓	↓
Bronchial and pleural arteries	↑	↑	↑	↑
Arterial muscularity	N	↑	N	
Extension of muscle by position	N	↑	↓	↓
Intra-acinar arterial size	↓	↓	↓	↓
Intra-acinar arterial number	N	↑	N	
Total alveolar number	N	N	N	

N, normal, ↓, decreased; ↑, increased.

CASE 1

The right lung had a normal volume of 151.5 ml. Injection of the right pulmonary artery also filled the bronchial arteries. Both hilar and intrapulmonary bronchial arteries were abnormally large and an abnormal number of small, tortuous, pleural vessels filled from both bronchial and intrapulmonary arteries. Microscopically, large bronchial arteries accompanying both cartilaginous and non-cartilaginous airways were filled with injection material and anastomosed with small pulmonary arteries lying with the alveolar walls. Pulmonary arterial muscularity was normal, as judged by percentage arterial medial thickness (Fig. 1) and by extension of muscle along the arterial pathway. The

Fig. 1 Percentage arterial medial thickness related to external diameter (μm). Muscularity was normal in case 1 and in the right lung of case 2, but significantly increased in the left lung of case 2 in arteries smaller than 200 μm in diameter ($p < 0.01$).

● — ● Normal
● - - - Case 1
● — ● Case 2, left lung
● - - - Case 2, right lung.

Fig. 2 Case 2, showing an abnormally small right lung (volume=85 ml), large left lung (volume=116 ml), enlarged bronchial and pleural arteries, particularly in the right lung, and vessels connecting the two arterial circulations across the mediastinum.

mean external diameter of pulmonary arteries accompanying each type of peripheral airway was below the normal for age. For example, arteries accompanying the respiratory bronchioli had a mean external diameter of $94.8 \mu\text{m}$, as compared with a normal value of $122 \mu\text{m}$ at this age.¹¹ Vein wall structure appeared normal. A normal alveolar/pulmonary arterial ratio of 8.9 indicated a normal number of intra-acinar arteries in the presence of a normal alveolar number per unit area (an acinus is all lung

tissue distal to a terminal bronchiolus). The total number of alevoli in the lung was normal.

CASE 2

The volume of the hypoperfused right lung, 85 ml, was less than that of the left lung, 116 ml, and the total lung volume of 201 ml was slightly below normal for age (220 ml)¹² (Fig. 2). The bronchial and pleural arteries were enlarged in both lungs,

Fig. 3 Case 2, arteriogram, showing small intrapulmonary arteries in the right and dilated arteries in the left lung. Arrow indicates an enlarged bronchial artery (original magnification $\times 0.7$).

considerably so in the right lung (Fig. 3). Arteriography and dissection (Fig. 2 and 3) showed that the "Micropaque"-gelatin mixture injected into the left pulmonary artery pursued the following course: left pulmonary artery → left pulmonary arteries within the lung and bronchial and pleural arteries of that lung → mediastinal arteries → bronchial and pleural arteries of the right lung → apical, medial, anterior basal, and lateral basal pulmonary segmental arteries of the right lower lobe.

In the hyperperfused *left* lung, arteriography showed dilatation of lobar and segmental pulmonary arteries (Fig. 3). Microscopically, percentage arterial medial thickness was increased in arteries less than 250 μm in diameter, the difference being statistically significant in arteries 100 to 200 μm in diameter ($p < 0.01$) (Fig. 1). Muscle was also present in smaller arteries than those in which it is normally found (Fig. 1). In addition, arteries accompanying the peripheral airways showed an increase in proportion of muscularised vessels. Normally muscle extends further along the arterial pathway with increase in age. In this specimen, however, 47 per cent of the arteries accompanying respiratory bronchioli had an entirely muscular coat, compared with only 17 per cent in the normal child at an older age of 10 months. The mean external diameter of arteries accompanying peripheral airways was, at each airway level, abnormally small, being 104.9 μm at respiratory bronchiolar level, as compared with a normal value of about 122 μm at this age.¹¹ The veins were abnormally thick walled, but the change was compatible with the increase in arterial muscularity. An increase in number of small arteries was suggested by an increase in density of the background haze on the arteriogram¹⁶ and confirmed by finding a reduced alveolar/arterial ratio of 7.15 (normal = 8–10), the number of alveoli per unit area of lung being normal. The total number of alveoli was within normal limits for age.

In the hypoperfused *right* lung, the alveoli had a mature appearance but were abnormally small. Areas of the middle lobe showed collapse with an increase in elastic tissue within the alveolar wall. Arteriography showed extremely small intrapulmonary arteries (Fig. 3). Microscopically, percentage arterial medial thickness was normal in those arteries which normally contain muscle (Fig. 1). Muscle was therefore less in the right lung than in the left. As in the left lung, muscle was present in smaller arteries than normal, but in the right lung this was the result not of abnormal extension of muscle along the pathway, but of a greater reduction in vessel size. The mean external diameter of arteries accompanying the peripheral airways was 77.1 μm below the normal mean level (122 μm)

and was also less than that found in the left lung ($p < 0.001$).

Examination of the structure of arteries accompanying the peripheral airways showed a reduction in muscularity. The distribution of non and partially muscularised and muscular arteries at each airway level was similar to that seen in the normal at 3 days of age, indicating a reduction in the normal process of muscularisation of the arterial pathways after birth. Vein wall structure appeared normal. The alveolar/arterial ratio was within normal limits for age, 8.88, indicating a normal number of intra-acinar arteries. The number of alveoli per unit area was greater in the right lung than in the left, and, despite the abnormally small lung volume, the total number of alveoli in the right lung was similar to that in the left.

Discussion

PGE₁ maintains patency of the ductus arteriosus and also relaxes pulmonary arterial smooth muscle and lowers pulmonary vascular resistance in vivo.^{1 7 8} PGE₂ also maintains ductal patency but, by contrast, its action on the pulmonary vasculature is less certain. In the present study, it did not appear to have influenced pulmonary arterial smooth muscle development. In case 1, muscularity was normal. In case 2, the hypoperfused right lung showed a reduction in proportion of muscularised arteries within the acinus, a change compatible with a low pulmonary blood flow. In the hyperperfused left lung, muscularity was increased, a change compatible with an increase in pulmonary blood flow and possibly an increase in pulmonary arterial pressure. Case 2 thus provided a vicarious experiment in which the effect of PGE₂ on lungs subject to different haemodynamic conditions could be observed, and in each lung the changes in muscularity could be attributed to the haemodynamic abnormality alone.

These findings are compatible with in vivo and in vitro studies of PGE₂ on the pulmonary circulation. PGE₂ has been shown to increase pulmonary vascular resistance in the intact calf¹⁷ and to cause contraction of isolated strips of bovine and canine intrapulmonary vein but to have no effect on mature intrapulmonary arteries of either species in vitro.¹⁸ In the present study, the structural findings did not suggest that PGE₂ had maintained the pulmonary arteries in a contracted state, since muscularity was not increased above normal, save in the hyperperfused left lung of case 2. In addition, vein wall structure appeared normal except in the left lung of case 2, where the change was compatible with the increase in arterial muscularity.

Patency of the ductus arteriosus allowed sufficient pulmonary blood flow for almost normal development of the lung in case 1 and of the left lung in case 2. Furthermore, the presence of a normal amount of pulmonary arterial muscle in case 1 suggests a reasonable pulmonary blood flow because in untreated cases of pulmonary atresia dying during the first month of life muscularity is reduced.¹⁰

The structural findings in the right lung of case 2 did, however, suggest that the pulmonary arterial stenosis had caused a pronounced reduction in flow and compromised lung development. The lung itself was abnormally small and the flow of blood through the pulmonary artery was supplemented by systemic arterial blood from enlarged bronchial and mediastinal vessels which anastomosed with intrapulmonary arteries. All these features have been observed in animals in which the left pulmonary artery had been ligated or severely stenosed from birth (personal observation).

The reduction in intra-acinar arterial size present in all lungs in these two cases suggests, however, that flow was below the normal level. A reduction in intra-acinar arterial size appears to be a feature of pulmonary atresia in young infants. It has been described in babies dying at birth and during the first month of life, both untreated and having received PGE₁.^{9, 10}

Thus in two babies with pulmonary atresia, long-term oral PGE₂ treatment maintained patency of the ductus arteriosus for three to four months¹⁹ and ensured a pulmonary blood flow sufficient to allow the lungs to grow almost normally when the extrapulmonary arteries were not stenosed. In addition, administration of PGE₂ did not appear to influence pulmonary arterial smooth muscle development, nor was there evidence of damage to the vessel walls, as seen after infusion with PGE₁.⁹ These are¹⁰ important considerations because infants with pulmonary atresia are being treated with prostaglandins at a time when the pulmonary circulation is adapting to postnatal life and is probably at its most vulnerable.

PGE₂ is a natural constituent of the ductus arteriosus, is considered the main active prostaglandin in the tissue, and probably maintains patency of the ductus in fetal life.¹⁹ Thus there appear to be both theoretical and practical advantages in giving PGE₂ rather than PGE₁ to neonates with a ductus dependent pulmonary blood flow.

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