delivered prematurely and ventilated for 3-4 weeks. The mechanism responsible for the sustained elevation of pulmonary vascular resistance is unclear. Two structural abnormalities that might be responsible are persistent muscularization of the pulmonary arteries and accumulation of elastin in their wall. To test this hypothesis, we determined the amount of smooth muscle and elastin in pulmonary blood vessels of preterm lambs that were delivered by cesarean section at 125±3 d gestation (mean±SD; term=148 d) and were mechanically ventilated for 3-4 weeks postnatally at 20 breaths/min (15±5 mL/kg tidal volume) or 60 breaths/min (5±2 mL/kg tidal volume). All lambs received surfactant at birth and had surgery for ligation of the ductus arteriosus. Control subjects included fetal lambs (126±6 d gestation), term lambs that were <24 h old (postconception matched), and term lambs that were 3-4 weeks old (postnatal matched). Lung histopathology was assessed by fixing the lungs at the prevailing peak inflation pressure. Computer-aided image analysis was used to measure smooth muscle area and elastin area among circular profiles of pulmonary arteries that were landmarked by terminal bronchioles (≥5 vessels per lamb). Summary data are listed in Table 1.

Smooth muscle in the media of small pulmonary arteries did not regress, as it does during normal postnatal development. Elastin accumulated excessively in the media of small pulmonary arteries.

To examine a potential mechanism for the persistence of pulmonary artery smooth muscle, we immunohistochemically localized endothelial nitric oxide synthase (eNOS) because nitric oxide is an inhibitor of smooth muscle growth in vitro. Relative staining intensity was scored from 0 (absent) to 4 (very intense) by three observers. Chronic ventilation resulted in decreased eNOS protein compared to fetal and newborn controls (median rating of 1.22 vs 2.95; 2.69 respectively; p<0.05). This decrease in eNOS protein may contribute to persistent muscularization.

**Reference**


**Hemodynamics Modulate Pulmonary Artery Response to Injury**

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(CHEST 1998; 114:78-88)

Vascular remodeling in primary pulmonary hypertension (PPH) is characterized by medial hypertrophy, adventitial thickening, and neointimal lesions. In contrast, neointimal lesions are not seen in animal models of pulmonary vascular remodeling. One explanation for this difference is that hemodynamic factors modify the pattern of pulmonary vascular remodeling. To test that hypothesis, the pattern of remodeling was studied following monocrotaline-induced injury with or without subsequent changes in hemodynamics.

Male Sprague-Dawley rats (350-380 g) were used for all experiments. Monocrotaline (MCT, 60 mg/kg) was used to initiate remodeling. Left pneumonectomy (P) was used to increase blood flow to the right lung.

Neointimal changes developed by 5 weeks in more than 90% of all acinar vessels with MCT+P. No neointimal lesions were seen in control animals, or animals receiving MCT or P only. The ratio of right ventricular weight to left ventricular+septal weight (RV/LV+S), an index of right ventricular hypertrophy, was 60% greater in animals with neointimal lesions compared with animals with medial hypertrophy alone (Fig 1, top). Neointimal lesions and RVH were similar whether MCT preceded P or vice versa.

P induces compensatory lung growth in the remaining lung. To exclude the possibility that neointimal lesions result from injury plus postpneumonectomy compensatory growth, rather than injury plus altered hemodynamics, a left subclavian-pulmonary artery shunt (S) was used to alter right lung hemodynamics. The right lung receives the entire right ventricular output, similar to the P model, but the left lung remains in place in this anastomotic model. Neointimal lesions and severe right ventricular hypertrophy developed in these animals but were not seen in animals receiving the MCT or S only (Fig 1, bottom).

These studies demonstrate that hemodynamic factors...
modify the pattern of pulmonary vascular remodeling. Studying the pathogenesis of matrix synthesis, smooth muscle replication, and migration in a neointimal animal model of pulmonary vascular remodeling may yield important insights into the pathogenesis of PPH.

**Blood Flow Distribution in the Lung***

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Textbook chapters on the distribution of pulmonary blood flow usually begin with a statement that "The issue of gravity and the topographic distribution of pulmonary blood flow was largely resolved by studies carried out in the 1960s." For the past three decades, the pulmonary circulation has been generally regarded as a largely passive circuit in which blood flow distribution is predominantly determined by hydrostatic gradients. However, recent studies using high-resolution methods and experiments performed in microgravity have revealed an unexpected degree of perfusion heterogeneity. A new perspective emphasizing the geometry of the pulmonary vascular tree postulates that blood flow heterogeneity is a fundamental characteristic of the pulmonary system and can be explained by a fractal branching network. This new perspective has rekindled an interest in the factors determining regional pulmonary blood flow and signifies that the topographic distribution of pulmonary blood flow has not been completely resolved.

The pulmonary vascular tree can be conceptualized as having two components: (1) a fixed structure that is the primary determinant of regional perfusion, and (2) a variable component that acts on top of the fixed structure and is influenced by local factors. The fixed structure can be characterized using fractal geometry, a new mathematical science used to describe "natural objects." The variable component of the vascular tree can be influenced by passive and active regional factors such as recruitment and/or distention due to changing driving or hydrostatic pressures. Active factors such as vasomotion in response to shear stress or hypoxic vasoconstriction will influence regional perfusion. The relative contribution of the fixed and variable components of the pulmonary vascular tree to pulmonary perfusion heterogeneity can be quantitated.

**Perfusion Heterogeneity**

The first observations suggesting that the geometry of the vascular tree is an important determinant of pulmonary blood flow distribution was contributed by Reed and Wood. They demonstrated regional differences in blood flow at equal hydrostatic pressures and concluded that in an intact animal, factors other than pulmonary arterial, venous, and alveolar pressures affect the distribution of blood flow. Greenleaf et al noted a similar discrepancy between the starting resistor model and the variability of blood flow, stating that "effects that are not taken into account by this model contribute significantly to the distribution of pulmonary blood flow." Hakim and coworkers using single photon emission CT to reconstruct planar images of pulmonary blood flow, reported a central to peripheral perfusion gradient of 10-fold within isogravitational planes. Nicolaysen and associates examined the spatial distribution of blood flow in gravity-independent planes using In microaggregates of albumin, planar gamma camera imaging, and well counting. Although they were unable to confirm the findings of Hakim et al, they did observe a coefficient of variation of blood flow of 23.5 to 25% using piece sizes of 0.16 mL that they were unable to explain by chance alone. Beck and Rehdor found large variations of conductances within regions of lung that could not be accounted for by gravity, regional lung expansion, or hypoxic pulmonary vasoconstriction. They concluded that the structure of the vascular system must play a significant role in determining the distribution of pulmonary blood flow.

New technologies providing high-resolution measurements of pulmonary perfusion have confirmed a large degree of spatial heterogeneity. These new observations

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