Abnormal lung growth and the development of pulmonary hypertension in the Fawn-Hooded rat

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1Pediatric Lung Center, Department of Pediatrics, and 2Department of Pathology, University of Colorado School of Medicine and The Children’s Hospital, Denver 80262; 3National Jewish Hospital, Denver, Colorado 80206; and 4Department of Pediatrics, Hallym University, 150-030 Seoul, South Korea

Le Cras, Timothy D., Dug-Ha Kim, Sarah Gebb, Neil E. Markham, John M. Shannon, Rubin M. Tuder, and Steven H. Abman. Abnormal lung growth and the development of pulmonary hypertension in the Fawn-Hooded rat. Am. J. Physiol. 277 (Lung Cell. Mol. Physiol. 21); L709–L718, 1999.—The Fawn-Hooded rat (FHR) strain develops accelerated and severe pulmonary hypertension when exposed to slight decreases in alveolar Po2. We recently observed that adult FHR lungs showed a striking pattern of disrupted alveolarization and hypothesized that abnormalities in lung growth in the perinatal period predisposes the FHR to the subsequent development of pulmonary hypertension. We found a reduction in lung weight in the fetus and 1-day- and 1-wk-old FHR compared with a normal rat strain (Sprague-Dawley). Alveolarization was reduced in infant and adult FHR lungs. In situ hybridization showed similar patterns of expression of two epithelial markers, surfactant protein C and 10-kDa Clara cell secretory protein, suggesting that the FHR lung is not characterized by global delays in epithelial maturation. Barium-gelatin angiograms demonstrated reduced background arterial filling and density in adult FHR lungs. Perinatal treatment of FHR with supplemental oxygen increased alveolarization and reduced the subsequent development of right ventricular hypertrophy in adult FHR. We conclude that the FHR strain is characterized by lung hypoplasia with reduced alveolarization and increased risk for developing pulmonary hypertension. We speculate that altered oxygen sensing may cause impaired lung alveolar and vascular growth in the FHR.

alveolarization; lung development; lung hypoplasia; bronchopulmonary dysplasia

NORMAL LUNG DEVELOPMENT is a highly regulated and coordinated process of cell growth and differentiation that consists of five morphologically distinct stages. In humans, these stages of lung development include the embryonic (up to 6 wk of gestation), pseudoglandular (7–16 wk), canalicular (17–28 wk), saccular (29–35 wk), and alveolar periods (beginning at 36 wk and continuing during postnatal life; see Ref. 10). During the canalicular period, the lung undergoes dramatic remodeling, including marked thinning of the interstitium and increased secondary crest formation, that signals the onset of alveolarization (10). Although similar stages of lung development have been identified in other species, the exact timing of these events varies widely (22). As in the human lung, alveolarization in the rat lung begins in utero, and alveolar number increases markedly after birth (22). The first 3 wk of postnatal life are the critical period of alveolar growth in the rat (7, 26). The exact mechanisms contributing to alveolar development are incompletely understood but are influenced by genetic, mechanical, hormonal, autocrine, and paracrine factors (7–9). Adverse stimuli during this period, such as hypoxia, hyperoxia, or glucocorticoid treatment, can disrupt alveolarization and markedly reduce alveolar number (7–9, 25, 27, 29).

The pulmonary circulation develops concomitantly with distal lung air space growth during late gestation and early postnatal life (15). Early development of the pulmonary vascular bed involves vasculogenesis and angiogenesis during the embryonic period, followed primarily by angiogenesis during lung maturation (16). The precise relationship between alveolar and vascular development during fetal and early postnatal life and the mechanisms that coordinate lung vascular growth with alveolarization are uncertain. However, signals from airway epithelial cells, such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor, and other mediators, play a major role in vascular growth and development during fetal life (6, 30, 40). These findings suggest that mechanisms exist that link lung alveolar growth with vascular development and suggest that disruption of normal alveolarization may also contribute to altered pulmonary vascular growth.

The clinical importance of the relationship between alveolarization and pulmonary vascular development is reflected by the association between neonatal lung hypoplasia and pulmonary hypertension. Lung hypoplasia and pulmonary hypertension contribute to high morbidity and mortality in several neonatal lung diseases including bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH), primary lung hypoplasia, and Down’s syndrome (1, 3, 11, 12, 14, 19, 34, 38).

The Fawn-Hooded rat (FHR) strain is characterized by platelet abnormalities and systemic hypertension, and has been used to study genetic risk factors for the development of “idiopathic” pulmonary hypertension (20, 33). Unlike other rat strains, FHR develop severe pulmonary hypertension when exposed to slight de-
creases in alveolar $P_{O_2}$, such as at Denver’s altitude, even in the absence of hypoxemia (33). In a previous study, treatment of adult FHR with supplemental oxygen to simulate sea-level alveolar $P_{O_2}$ reduced the development of pulmonary hypertension (33).

In preliminary studies, we have observed that, in addition to structural hypertensive vascular disease, histology of the adult FHR lung is also characterized by a striking pattern of alveolar simplification, reflecting decreased alveolarization and lung hypoplasia (21). Based on these findings, we hypothesized that abnormalities in perinatal lung growth and development could predispose the FHR for subsequent development of pulmonary hypertension. Alternatively, abnormalities of pulmonary vascular development may contribute to decreased alveolarization. To test these hypotheses, we characterized maturational changes in lung histology in FHR at fetal and postnatal ages and determined whether perinatal exposure to supplemental oxygen during a critical period of lung development would improve alveolarization and reduce development of pulmonary hypertension. Lung arterial structure and density were studied in adult FHR using barium-gelatin angiograms. We report that lung weight and density were studied in adult FHR using barium-gelatin angiograms. We report that lung weight and density in FHR lungs. In addition, we report that perinatal oxygen treatment reduced arterial filling and density in FHR lungs. In alveolarization. Barium-gelatin angiograms showed reduced arterial filling and density in FHR lungs. In addition, we report that perinatal oxygen treatment during the critical period of distal lung growth reduced the severity of lung hypoplasia and right ventricular hypertrophy in adult FHR.

**METHODS**

**Animals.** All procedures and protocols were approved by the Animal Care and Use Committee at the University of Colorado Health Science Center. FHR were a gift from Dr. T. Steč’ner (Department of Medicine, University of Colorado School of Medicine), and a breeding colony was established. Sprague-Dawley rats (SDR) and Fischer (FSR) rats were used as normal rat strains for these studies (Harlan Laboratories, Indianapolis, IN). Pregnant SDR and FSR were purchased to be terminated at Denver’s altitude at least 1 wk before giving birth. Animals were fed ad libitum and were exposed to 12:12-h day-night cycles. Fetal rat lung tissue was obtained giving birth. Animals were briefly exposed to Denver’s altitude for 12:12-h light-dark cycle was provided by lights in the chamber, controlled by timers. Food and water were supplied ad libitum. Rats were placed in a hyperbaric chamber (chamber) and/or 3 or 10 wk postnatal.

**Oxygen therapy.** Rats were placed in a hyperbaric chamber in which the pressure was increased to 18.5–19 kPa to simulate sea-level alveolar $P_{O_2}$. The chamber air changes 42 times every hour. Carbon dioxide and ammonia buildup were prevented by having absorbent systems present in the chamber. A 12:12-h light-dark cycle was provided by lights in the chamber, controlled by timers. Food and water were supplied ad libitum. Rats were briefly exposed to Denver’s altitude for $<10$ min times a week while the cages were changed and fresh water and food were supplied. FHR were exposed to oxygen therapy for 1 wk prenatal (pregnant female placed in chamber) and/or 3 or 10 wk postnatal.

**Lung histology and radial alveolar counts.** Rat lungs were fixed for histology by tracheal installation of 10% buffered Formalin under constant pressure (10 cmH$_2$O). The trachea was ligated after sustained inflation, and the lungs were excised and immersed in Formalin overnight. Formalin-fixed lung tissue was cut into 4- to 5-mm-thick sections, placed in 10% buffered Formalin, and embedded in paraffin. Paraffin sections (5 µm thick) were serially mounted on Superfrost Plus slides (Fisher Scientific, Fair Lawn, NJ) and were stained with hematoxylin and eosin. At least three lung sections were assessed from each animal for analysis. Alveolarization was assessed by the radial alveolar count (RAC) method of Cooney and Thurlbeck (13) and Emery and Mithal (18). Radial counts were performed by identifying respiratory bronchioles as described by Randell et al. (29). From the center of the bronchiole, a perpendicular line was taken to the edge of the acinus (connective tissue septum or pleura), and the number of alveoli that intersected the line was counted. For each lung section, at least 10 counts were performed.

**Right ventricular hypertrophy measurements.** At death, hearts from adult rats were removed and dissected to isolate the free wall of the right ventricle from the left ventricle and septum. The ratio of right ventricle weight to left ventricle plus septum weight (RV/LV + S) was used as an index of right ventricular hypertrophy (23). Vessel morphometry. Morphometry was performed on small pulmonary arteries (20–80 µm) on hematoxylin and eosin-stained lung sections using a Zeiss Interactive Digital Analysis System. Wall thickness and external diameter were directly measured; percent wall thickness was calculated as $(2 \times \text{wall thickness}/\text{vessel diameter}) \times 100$ to assess medial hypertrophy (2).

**In situ hybridization for surfactant protein C and 10-kDa Clara cell secretory protein (CC10; see Ref. 17).** Hybridized sections were dipped in Kodak NTB-2 emulsion, developed after an appropriate exposure for each probe, and counterstained with hematoxylin.

**Barium-gelatin angiograms and arterial density counts.** Adult FHR and SDR were anesthetized with pentobarbital sodium, and a rapid thoracotomy was performed. Rats were heparinized by injection of heparin (500 units) into the right ventricle. A tracheostomy was performed, and the lungs were inflated with air. Blood was flushed from the lungs with heparinized saline (1 U/ml) through a main pulmonary artery catheter. A barium-gelatin mixture was infused at 73 mmHg pressure in the main pulmonary artery catheter for 3–4 min until surface filling of vessels with barium was seen uniformly over the surface of the lung as described by deMel et al. (16). The main pulmonary artery was tied off under pressure, and the lungs were inflated fixed with Formalin. Left lungs were excised after fixation and imaged to X-ray radiography (16). After radiography, left lungs were embedded in paraffin, and sections were cut and stained with hematoxylin and eosin. Barium-filled pulmonary arteries were counted per high-powered field ($\times100$ magnification). At least five fields were counted per animal. High-powered fields of peripheral lung next to the pleural surface were counted. Fields containing large airways or major vessels were avoided.

**Statistical analysis.** Data are presented as means ± SE. Statistical analysis was performed with the Statview software package (Abacus Concepts, Berkeley, CA). Statistical comparisons were made using ANOVA and Fisher’s protected least significant difference test. $P < 0.05$ was considered significant. All animal groups contained at least four rats.
RESULTS

Lung and body weights, hematocrits, and right ventricular hypertrophy. Lung and body weights were lower in FHR at all ages compared with SDR (P < 0.05; Table 1). Lung-to-body weight ratios were reduced by 32% in fetal, 29% in 1-day-old, and 16% in 1-wk-old FHR compared with SDR (P < 0.05; Fig. 1). At 3 and 10 wk of age, lung-to-body weight ratios were not different between study groups (P > 0.05). Hematocrits were not different for 10-wk-old Denver-raised SDR and FHR (53 ± 1 vs. 52 ± 1, respectively), suggesting that FHR were not chronically hypoxic at Denver’s altitude and that pulmonary hypertension in this strain is not due to polycythemia. To assess right ventricular hypertrophy in adult FHR and SDR, we measured RV and LV+S weights. RV/LV+S was 80% higher in 10-wk-old FHR with to SDR, indicating significant right ventricular hypertrophy in adult FHR (Fig. 2).

Lung histology, morphometry, epithelial marker expression, and barium-gelatin angiograms and arterial density counts. Histology revealed striking differences in lung structure in 3-wk (infant)- and 10-wk (adult)-old FHR compared with SDR (Fig. 3). Lung histology was also examined in FSR and was found to be similar to SDR at all ages (data not shown). Compared with SDR, 3-wk-old FHR lungs showed a pattern of alveolar simplification characterized by larger and fewer air spaces, with a thickened interstitium (Fig. 3). At 10 wk, the adult FHR lungs had persistence of this pattern. Distal air spaces appeared simple and abnormal (Fig. 3). Lung architecture appears less mature in fetal and neonatal FHR lungs as reflected by marked interstitial thickening and cellularity and decreased formation of distal air sacs (Fig. 4). To quantitate changes in alveolar number, we measured RAC in the lungs of FHR and SDR at ages 1, 3, and 10 wk. RAC were reduced by 42% at 1 wk, 48% at 3 wk, and 50% at 10 wk of age compared with SDR (P < 0.05; Fig. 5). These findings further demonstrate decreased alveolarization in addition to the striking histological appearance of lung hypoplasia with alveolar simplification. RAC could not be performed before 1 wk of age in either SDR or FHR, since respiratory bronchioles are generally not clearly identifiable at these early ages.

### Table 1. Body and lung weight

<table>
<thead>
<tr>
<th>Strain</th>
<th>Fetal</th>
<th>1 Day</th>
<th>1 Week</th>
<th>3 Week</th>
<th>10 Week</th>
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<tr>
<td></td>
<td>Lung weight</td>
<td></td>
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<tr>
<td>SDR</td>
<td>0.14 ± 0.02</td>
<td>0.14 ± 0.01</td>
<td>0.28 ± 0.01</td>
<td>0.51 ± 0.02</td>
<td>1.45 ± 0.05</td>
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<tr>
<td>FHR</td>
<td>0.062 ± 0.004*</td>
<td>0.067 ± 0.001*</td>
<td>0.138 ± 0.007*</td>
<td>0.158 ± 0.004*</td>
<td>0.96 ± 0.06*</td>
</tr>
<tr>
<td></td>
<td>Body weight</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SDR</td>
<td>5.54 ± 0.5</td>
<td>6.44 ± 0.3</td>
<td>15.1 ± 0.3</td>
<td>62.1 ± 0.7</td>
<td>347 ± 6</td>
</tr>
<tr>
<td>FHR</td>
<td>3.72 ± 0.15*</td>
<td>4.38 ± 0.12*</td>
<td>8.97 ± 0.19*</td>
<td>20.5 ± 0.8*</td>
<td>233 ± 6*</td>
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Values are means ± SE. Units are grams. SDR, Sprague-Dawley rats; FHR, Fawn-Hooded rats. *P < 0.05 vs. SDR.
To assess lung epithelial maturation, we performed in situ hybridization of lung sections from fetal and 1- and 10-wk-old FHR and SDR lungs for CC10 mRNA in bronchial epithelial cells and SP-C mRNA in type II epithelial cells (Fig. 6). Despite differences in lung architecture between the strains, the patterns of SP-C and CC10 expression appeared similar in FHR and SDR lungs at each of the study ages.

To examine pulmonary arterial structure and to determine arterial density, we infused heated barium-gelatin mixtures into the main pulmonary artery of adult FHR and SDR under high pressure (73 mmHg) as previously described (16). Angiograms of left lungs showed reduced barium filling in adult FHR compared with SDR (Fig. 7). Barium-filled arterial counts were 35% lower in FHR compared with SDR (P < 0.05), indicating a reduction in arterial density (Fig. 8).

Effects of brief and prolonged supplemental oxygen exposure on lung histology, RAC, and right ventricular hypertrophy. To determine if supplemental oxygen exposure during the critical period of lung development could increase alveolarization and reduce pulmonary hypertension in adult FHR, we studied the effects of prenatal (1 wk) and postnatal brief (3 wk) and prolonged (10 wk) periods of mild hyperbaria. Compared with controls, oxygen treatment improved alveolarization and increased RAC in the 10-wk-old FHR lungs (Figs. 9 and 10). Compared with Denver-raised FHR (control), prenatal oxygen treatment alone did not improve alveolarization in 10-wk-old FHR (P > 0.05; Fig. 9). However, 3 wk of postnatal supplemental oxygen increased RAC by 63% (P < 0.05). Combined prenatal and postnatal supplemental oxygen for 3 or 10 wk increased RAC by 105 and 114%, respectively (P < 0.05; Fig. 10).

Prenatal treatment with supplemental oxygen alone did not reduce right ventricular hypertrophy as assessed by RV/LV+S (Fig. 11). However, 3 wk of postnatal supplemental oxygen reduced RV/LV+S 8% and combined prenatal and 3 or 10 wk of postnatal oxygen therapy reduced RV/LV+S by 26 and 29%, respectively, from control values (Fig. 10). Compared with Denver-raised FHR (control), the wall thickness of small pulmonary arteries (with external diameters ranging between 20 and 80 µm) was reduced 30 and 39%, respectively, by combined prenatal and 3 or 10 wk of postnatal supplemental oxygen (P < 0.05) but not by prenatal oxygen therapy alone (P > 0.05; Fig. 12).

DISCUSSION

The FHR is a genetic rat strain that is characterized by the development of severe pulmonary hypertension in adults (20). In contrast with other rat strains, the development of pulmonary hypertension in FHR is enhanced by modest decreases in alveolar PO2 despite the absence of chronic hypoxemia (33). Although the FHR strain has previously been used as a model to study genetic factors that contribute to idiopathic or "primary" pulmonary hypertension (33, 37, 39), we now report that alveolarization is markedly reduced in the FHR. We found abnormal lung development in FHR during the perinatal period, and this resulted in enlarged distal air spaces in adults. In situ hybridization analysis of two markers of lung epithelial differentiation, SP-C and CC10, showed similar patterns of expression in both FHR and SDR, suggesting that the FHR lung is not characterized by global delays in epithelial maturation but rather a more specific failure of alveolar formation. In addition, barium-gelatin angiograms showed reduced filling in adult FHR lungs compared with SDR, and barium-filled arterial counts indicated a reduction in arterial density.

We also report that treatment of FHR with supplemental oxygen (postnatal or combined prenatal and 3 or 10 wk postnatal) to simulate sea-level PO2 improved alveolarization and reduced the development of pulmonary hypertension as reflected by measurements of right ventricular hypertrophy and wall thickness of small pulmonary arteries. Prenatal treatment with supplemental oxygen alone had no effect on alveolarization or markers of pulmonary hypertension, but 3 wk of postnatal treatment increased alveolarization and reduced right ventricular hypertrophy in 10-wk-old adult FHR. Combined prenatal with 3 wk of postnatal oxygen...
treatment increased alveolarization and reduced RV/LV further compared with 3 wk of postnatal treatment alone. However, no further improvement was seen with combined prenatal and 10 wk of postnatal oxygen treatment compared with combined prenatal and 3 wk of postnatal treatment. In SDR, exposure to brief perinatal hypoxia (10% fraction of inspired oxygen; 9 h prenatal and 2 h postnatal) reduces lung alveolarization at 1 wk of age (27). These findings suggest that transient decreases in alveolar Po2 in the perinatal period can have long-lasting effects on alveolarization in normal rats. The FHR at Denver's altitude show similar findings, and reduced alveolarization was partially prevented by low levels of supplemental oxygen in the perinatal period. Based on these observations, we speculate that the FHR exhibits a marked sensitivity to mild decreases in alveolar Po2 during a critical period of lung development that contributes to abnormal lung growth and pulmonary hypertension.

The mechanisms that account for this altered oxygen sensitivity in the FHR are unknown.

Although initially characterized by platelet abnormalities and systemic hypertension (39), it was subsequently recognized that the FHR strain develops progressive pulmonary hypertension (20), especially after slight reductions in alveolar Po2 (33). Lung endothelin (ET)-1 peptide levels are elevated in FHR compared with SDR before the development of pulmonary hypertension (37). Whether increased lung ET-1 levels might also be responsible for the abnormal lung development that we report in the FHR is unknown. At least two studies have suggested that the platelet storage disease is not involved in the pathogenesis of pulmonary hypertension in the FHR (4, 20). The incidence of increased pulmonary artery pressure in FHR was different from the incidence of the platelet storage defect (20), and platelets from both SDR and FHR constricted pulmonary arteries from FHR (4). A preliminary report has localized the high pulmonary artery pressure in this strain to a genetic locus, PH1, on
Fig. 6. Expression of the distal epithelial marker surfactant protein C (SP-C; A) and proximal epithelial marker 10-kDa Clara cell secretory protein (CC10; B) in FHR and SDR lung. In situ hybridization analysis of lung sections shows that the pattern of expression for SP-C and CC10 mRNAs appears similar in FHR compared with SDR. Micrographs are representative and are at the same magnification (×40).
chromosome 1 (36). This locus did not co-segregate with ET-1, ET-2, or the ETA receptor genes, suggesting that these genes may not be involved in the pathogenesis of pulmonary hypertension in the FHR. Whether the genetic basis for the abnormal lung development that we report also co-segregates to the PH1 locus is unknown.

Although past studies have considered the FHR strain as a model of idiopathic pulmonary hypertension, we have observed that the adult FHR lung is characterized by striking reductions in alveolar number and that this pattern is already present in the early postnatal period, well before the earliest age (4 wk) that pulmonary hypertension has been reported in FHR (33). Based on our observations that FHR strain is characterized by abnormal alveolarization and marked susceptibility for the development of progressive pulmonary hypertension, we propose that there is a relationship between abnormal lung alveolar and vascular growth with the development of pulmonary hypertension. Interestingly, in our study, perinatal treatment with supplemental oxygen during the critical period of lung growth improved alveolar number in FHR and prevented the development of pulmonary hypertension in adult FHR.

This is the first report of developmental abnormalities in lung growth in a genetic rat strain that is known to develop pulmonary hypertension. Among several animal models that have been developed to study mechanisms of pulmonary hypertension, the FHR has provided a unique model of genetic factors that may be linked with the development of pulmonary hypertension (33, 37). Pulmonary hypertension contributes significantly to high morbidity and mortality in several human disorders of lung hypoplasia, including CDH, primary lung hypoplasia, and lung hypoplasia associated with oligohydramnios or renal dysfunction (19, 38). In addition, children with chronic lung disease after premature birth (BPD) and with Down's syndrome (with or without congenital heart disease) have abnormal lung growth that is characterized by decreased alveolarization and high risk for pulmonary hypertension (3, 11, 12, 14, 24, 32, 34). The pathogenic mechanisms that link abnormal alveolarization with a high risk for the development of pulmonary hypertension in the setting of lung hypoplasia are unclear, and few animal models are currently available to study this complex relationship.

Because reduction of lung surface area is associated with reduced vascular growth, it is also likely that decreased cross-sectional area of the pulmonary vascular bed is a significant contributing factor to the persistence or late development of pulmonary hypertension in these diseases (3, 11). Although causes of abnormal lung development are uncertain, it is likely that disruption of alveolarization by adverse intrauterine stimuli, premature birth, injury, and other mechanisms contribute to this problem. Past studies have
shown that exposure to hypoxia, hyperoxia, or dexamethasone during the first 3 wk of life in a rat decreases alveolar number (7, 25, 27–29).

Growth and remodeling of the lung occurs by the successive addition of new generations of respiratory bronchioles, alveolar ducts and saccules, and alveoli. Alveoli are the sites of gas exchange in the lung and are formed by septation of large saccules that constitute the gas-exchange region of the structurally immature lung (10, 22, 26). Secondary septa initially form as low ridges that protrude into primitive air spaces to increase their surface area. This growth involves close spatial and temporal coordination between several cell types regarding cell proliferation, differentiation, and matrix production (31, 35). During the stages of alveolarization, the lung is also undergoing marked vascular growth and development (5, 16). Multiple paracrine stimuli, such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), VEGF, and the angiopoietins, contribute to alveolar and vascular growth and development, providing a “cross talk” of signals between epithelium and mesenchyme (31, 35). In addition, the process of septation, which is essential for alveolarization, involves alternate upfolding of one of the two capillary layers on both sides of the primary septa (10). This method of formation of alveolar walls suggests that the failure of capillary network formation and maturation or disruption of the upfolding of the double capillary network could potentially cause failed alveolarization. Thus failure of growth or maturation of the pulmonary microcirculation during the critical period of alveolarization could potentially cause lung hypoplasia by...
decreasing septation. Whether paracrine factors such as VEGF, PDGF, or TGF-β are responsible for abnormal lung development in the FHR is unknown.

We conclude that lung growth is abnormal in the FHR and suggest that decreased alveolarization and altered pulmonary vascular growth contribute to the development of pulmonary hypertension in this strain. We found that postnatal oxygen therapy during the critical period of distal lung growth was sufficient to prevent the development of lung hypoplasia and pulmonary hypertension in adult FHR. We speculate that these findings may have important implications regarding perinatal origins of adult cardiopulmonary disease. Epidemiological studies suggest that factors affecting the fetus and the young may have long-lasting effects as important causes of later diseases such as ischemic heart disease, stroke, hypertension, chronic bronchitis, and emphysema (5). For example, adverse stimuli during critical periods of lung growth may impair lung structure and function and may cause cardiopulmonary abnormalities later in life. We speculate that the FHR strain provides a unique model for further investigation of this hypothesis and mechanisms linking alveolarization, vascular growth, and the development of pulmonary hypertension.
REFERENCES


