Postpneumonectomy alveolar growth does not normalize hemodynamic and mechanical function

SHIN-ICHI TAKEDA,1 MURUGAPPAN RAMANATHAN,1 AARON S. ESTRERA,2 AND CONNIE C. W. HSIA1
Departments of 1Medicine and 2Surgery, University of Texas Southwestern Medical Center, Dallas, Texas 75235-9034

Takeda, Shin-Ichi, Murugappan Ramanathan, Aaron S. Estreira, and Connie C. W. Hsia. Postpneumonectomy alveolar growth does not normalize hemodynamic and mechanical function. J. Appl. Physiol. 87(2): 491–497, 1999.—Immature foxhounds underwent 55% lung resection by right pneumonectomy (n = 5) or thoracotomy without pneumonectomy (Sham, n = 6) at 2 mo of age. Cardiopulmonary function was measured during treadmill exercise on reaching maturity 1 yr later. In pneumonectomized animals compared with Sham animals, maximal oxygen uptake, ventilatory response, and cardiac output during exercise were normal. Arterial and mixed venous blood gases and arteriovenous oxygen extraction during exercise were also normal. Mean pulmonary arterial pressure and resistance were elevated at a given cardiac output. Dynamic ventilatory power requirement was also significantly elevated at a given minute ventilation. These long-term hemodynamic and mechanical abnormalities are in direct contrast to the normal pulmonary gas exchange during exercise in these same pneumonectomized animals reported elsewhere (S. Takeda, C. C. W. Hsia, E. Wagner, M. Ramanathan, A. S. Estreira, and E. R. Weibel. J. Appl. Physiol. 86: 1301–1310, 1999). Functional compensation was superior in animals pneumonectomized as puppies than as adults. These data indicate a limited structural response of conducting airways and extra-alveolar pulmonary blood vessels to pneumonectomy and suggest the development of other sources of adaptation such as those involving the heart and respiratory muscles.

Exercise; pulmonary arterial pressure; pulmonary arterial resistance; arteriovenous oxygen extraction; ventilatory power output; work of breathing; lung resection; dog

MATERIALS AND METHODS

Experimental groups. All protocols were approved by the Institutional Review Board for Animal Research. Twelve litter-matched purebred male foxhounds underwent either right pneumonectomy (n = 6) or right thoracotomy without pneumonectomy (Sham, n = 6) at 2 mo of age. Under isoflurane anesthesia, a lateral thoracotomy was performed through the right fifth intercostal space. The right main pulmonary artery and veins were doubly ligated with silk sutures. The right main bronchus was then divided and closed with titanium staples. The thorax was closed in layers after hemostasis was confirmed, and a check was made for air leakage by immersion of the bronchial stump under saline. Residual air in the pleural space was partially evacuated with a catheter connected to an underwater seal. One animal died in the immediate postoperative period because of postpneumonectomy pulmonary edema, leaving five animals in the pneumonectomy group. All other dogs were raised to maturity. Physiological and radiological studies were performed in puppies at rest under anesthesia during maturation and were previously published (24, 25). On reaching maturity 1 yr later, dogs were trained to run freely on a motorized treadmill while wearing a customized leak-free respiratory mask (1) and attachments necessary for ventilatory measurements. Bilateral subcutaneous carotid artery loops were constructed to allow repeated catheterization (18).

Exercise training. The treadmill speed was maintained at 6 or 8 miles/h (mph), depending on the preference of the dog. After a warm-up period at 6 mph and 0% grade, the treadmill grade was raised by 5% every 3 min up to 60 or 80% of the previously achieved maximal workload. Exercise was sustained for 15 min, followed by a rest period for rectal temperature, heart rate, and respiratory rate to return to baseline. This protocol was repeated for a total of 30 min of exercise daily, 5 days/wk. Maximal workload and the corresponding O2 uptake, CO2 output, heart rate, and respiratory rate were measured at intervals, and the training workloads were adjusted accordingly.

Respiratory measurements. The dog breathed through a large one-way respiratory valve (Hans Rudolph 2700, Kansas City, MO). The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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Ventilatory power requirement against the combined viscous resistance of the airway and lung tissue was calculated as the area of the $\Delta P_{\text{tp-Vt}}$ loop of each breath as described previously (12, 15). Total ventilatory power requirement of the lung was the sum of the power requirement against viscous resistance plus that part of the power requirement against lung elastic recoil not recovered during expiration (21). All signals were digitized by computer at 50 Hz, and calculated results were averaged over a predetermined number of breaths.

Catheterization. Percutaneous catheterization of the carotid and pulmonary arteries was performed in the awake dog under local anesthesia on the day of study. A Swan-Ganz catheter was introduced via the jugular vein into the pulmonary artery under pressure monitoring. Arterial pressure was recorded by using a fluid-filled transducer (Statham Instruments, P23 ID) through a Hewlett-Packard carrier amplifier and digitized by computer. Measurements were averaged over a predetermined number of heartbeats. Arterial pressures were referenced to the midthorax by an open fluid-filled catheter attached to the side of the animal at a position midway along the anteroposterior diameter of the chest.

Exercise protocol and measurements. Exercise began with a 5-min warm-up period at 6 mph and 0% grade. Then, the workload was increased to a preselected level and sustained for ~4 min. After each exercise period, the dog cooled down by walking on the treadmill for 5 min. Between exercise periods, the dog rested on the treadmill until heart rate, respiratory rate, and body temperature had returned to baseline. During exercise, ventilation, $O_2$ uptake, $CO_2$ production, heart rate, end-tidal $Pm$ and Pes, and rectal and blood temperatures were measured continuously, and the data were digitized by a computer at 50 Hz. At the end of minute 3, arterial and mixed venous blood (3 ml each) were drawn anaerobically into heparinized syringes and analyzed immediately. Conventional blood gases were measured by an ABL-3 analyzer (Radiometer, Copenhagen, Denmark) and corrected to the actual blood temperature during exercise. Hemoglobin concentration was measured spectrophotometrically (Beckman, BD, Fullerton, CA). Hematocrit was determined with a microcapillary centrifuge (International Equipment, model MB, Needham Heights, MA). $O_2$ content was measured directly (Lex-O2-Con-TL, Lexington Instruments, Waltham, MA). Cardiac output was obtained by the Fick principle. Pulmonary arterial resistance was calculated as mean pulmonary arterial pressure divided by pulmonary blood flow at each workload. Pulmonary capillary wedge pressure could not be consistently measured during exercise. Measurements were repeated while dogs were breathing room air or a hypoxic gas (15% $O_2$-balance of $N_2$).

Maximal $O_2$ uptake was determined on a separate day by a continuous incremental protocol adapted from Seeherman et al. (22). After the warm-up period, the workload was increased by 5% grade every 2 min; arterial blood was drawn during the last 30 s at each workload. Maximal $O_2$ uptake was defined as the point where $O_2$ uptake no longer increased with further increment in workload, associated with a rising blood lactate concentration.

Statistical analysis. Results were expressed as means ± SE. Hemodynamic data were analyzed with respect to cardiac output; the slopes and intercepts of linear relationships were compared between groups by analysis of covariance. At peak exercise intensity, comparisons between groups were made by analysis of variance. Ventilatory power requirements were averaged over successive intervals of ventilation and compared between groups by repeated-measures analysis of variance. Analysis was performed by using Statview (version 4.0, Abacus Concepts, Berkeley, CA). Differences between groups were considered significant if $P < 0.05$.

RESULTS
Table 1 summarizes the ventilatory and hemodynamic data at maximal exercise. Maximal $O_2$ uptake and the increase in minute ventilation during exercise were similar between groups. There were no significant differences in hematocrit, ventilatory variables, blood gases, cardiac output, and stroke volume between groups. There was no significant difference in mean systemic arterial pressure between groups; however, mean pulmonary arterial pressure was higher in pneumonectomized than Sham animals at peak exercise.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham (n = 6)</th>
<th>R-Pnx (n = 6)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>30.9 ± 1.9</td>
<td>30.7 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>53.8 ± 0.9</td>
<td>55.7 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>275 ± 4</td>
<td>278 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>138 ± 2</td>
<td>138 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Minute ventilation, l·min⁻¹·kg⁻¹</td>
<td>6.26 ± 0.28</td>
<td>6.11 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Tidal volume, ml/kg</td>
<td>45.0 ± 0.7</td>
<td>45.2 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>$O_2$ uptake, ml·min⁻¹·kg⁻¹</td>
<td>132.1 ± 3.8</td>
<td>134.0 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>$CO_2$ production, ml·min⁻¹·kg⁻¹</td>
<td>139.6 ± 3.9</td>
<td>144.3 ± 7.4</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.199 ± 0.025</td>
<td>7.170 ± 0.026</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial $P_{O_2}$, Torr</td>
<td>80.3 ± 2.3</td>
<td>75.6 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial $P_{CO_2}$, Torr</td>
<td>52.0 ± 2.1</td>
<td>52.8 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, ml·min⁻¹·kg⁻¹</td>
<td>672.2 ± 28.4</td>
<td>669.0 ± 13.0</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume, ml/kg</td>
<td>2.37 ± 0.10</td>
<td>2.32 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mmHg</td>
<td>179.0 ± 2.1</td>
<td>180.2 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mmHg</td>
<td>45.9 ± 1.8</td>
<td>55.8 ± 1.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are means ± SE. $n$, No. of dogs; Sham, thoracotomy without pneumonectomy; R-Pnx, right pneumonectomy; NS, not significant.
The relationships of cardiac output and stroke volume estimated by the Fick principle to O₂ uptake were also similar between groups, as shown in Fig. 1, A and B, respectively. Mixed venous O₂ tension declined to a similar extent during exercise in both groups (Fig. 2A). Arteriovenous O₂ content difference was not different between groups (Fig. 2B). The slope of the relationship of mean pulmonary arterial pressure to cardiac output while breathing room air was significantly higher in the pneumonectomized animals (P < 0.05 vs. Sham) (Fig. 3A). Total pulmonary arterial resistance was significantly higher in the pneumonectomized animals (P < 0.001 vs. Sham) (Fig. 3B). Mean pulmonary arterial pressure and total pulmonary arterial resistance did not change during exercise in animals breathing the hypoxic gas (data not shown).

In the pneumonectomized animals, dynamic ventilatory power requirement against the lung was significantly elevated at any given ventilation. This increased requirement reflects a greater power needed to overcome elastic resistance of the lung at lower exercise intensities and combined elastic as well as viscous resistance at high exercise intensities (Fig. 4, A and B).

**DISCUSSION**

**SUMMARY OF RESULTS.** In dogs raised to maturity after removal of 55% of lung at 2 mo of age, aerobic capacity and maximal cardiac output returned to normal despite persistent abnormalities in pulmonary hemodynamics and mechanical function. Mean pulmonary arterial pressure and total pulmonary arterial resistance were 20% higher at a given workload in pneumonectomized dogs than in Sham animals. Ventilatory power requirements on the lung were 60% higher at a given minute ventilation than in Sham animals. The increased power...
was required to overcome both elastic and viscous resistances of the lung. In contrast to the higher right ventricular afterload and increased power requirements for ventilation in these dogs after lung resection as puppies, alveolar-capillary gas exchange at rest and during exercise and maximal O₂ uptake were completely normal, as reported for the same dogs in another study (23). These dissociated responses in hemodynamic, mechanical, and gas-exchange function after lung resection indicate disparate compensatory mechanisms in the associated structural components of the lung, as discussed below.

Comparison of alveolar gas-exchange response in immature and adult animals. Our laboratory previously reported that, in adult dogs after left pneumonectomy (45% lung resection), adaptation for gas exchange is achieved through 1) recruitment of existing reserves in diffusing capacity of the remaining lung (4) and 2) remodeling of existing alveolar structure, i.e., enlargement of the alveolar air spaces and thinning of the alveolar tissue barrier (9). Compensatory lung growth did not occur after left pneumonectomy (45% lung resection) but did after resection of the larger right lung (55% resection). Because there is no intrinsic difference between the two lungs, these data suggest a threshold of resection (~50%) below which the existing structure can adapt adequately to maintain an acceptable level of function; above this threshold, the remaining structure can no longer compensate effectively and regenerative growth of new alveolar units is stimulated (10). Regardless of the mechanism of response (physiological recruitment, structural remodeling, or growth), the ultimate functional compensation in adult dogs is limited, i.e., at 1 yr after left or right pneumonectomy, arterial O₂ saturation, CO diffusing capacity, pulmonary hemodynamics, cardiac output, and pulmonary mechanics at peak exercise all remain abnormal (6–8, 11–14).

Fig. 3. A: relationship of mean pulmonary arterial pressure (PAP) to Qc between groups. R-Pnx: PAP = 5.50 + 63.99Qc (r = 0.93); Sham: PAP = 7.63 + 45.81Qc (r = 0.85). Mean PAP was significantly higher in R-Pnx than Sham animals (P < 0.05). B: total pulmonary arterial resistance (PAR) at a given Qc. R-Pnx: PAR = −63 log(Qc) + 182 (r = 0.44). Sham: PAR = −142 log(Qc) + 120 (r = 0.58). Total PAR was significantly higher in R-Pnx than Sham animals (P < 0.001).

Fig. 4. A: total ventilatory power requirement to overcome elastic resistance of the lung. Error bars, SE. Total ventilatory power was significantly higher at a given minute ventilation in R-Pnx animals vs. Sham (P < 0.001). B: ventilatory power requirement at given ventilation to overcome viscous resistance of airway and lung tissue. Ventilatory power requirement at given ventilation was significantly higher in R-Pnx animals vs. Sham (P < 0.001).
Although physiological recruitment of diffusing capacity reserves must also have occurred, the postpneumonectomy adaptive response of immature animals is characterized by active alveolar proliferation. We previously reported the serial measurements of resting lung function during maturation in the present group of immature dogs (from 4 wk to 1 yr after surgery) (24, 25). Results showed the following. 1) Resting CO diffusion capacity, measured by a rebreathing technique, returned to normal by 8 wk after pneumonectomy and remained normal up to maturity. 2) Volume of fine septal tissue, measured physiologically by a rebreathing technique, rapidly returned to normal. Volume of nonseptal lung tissue, measured by combined rebreathing and computerized tomography techniques, remained below normal up to maturity. 3) Static lung volume-Ptp relationship, lung elastic recoil, and total pulmonary resistance remained abnormal up to maturity. 4) Pneumonectomy did not selectively affect the development of the thoracic cage. Findings 1 and 2 suggest active compensatory alveolar-capillary growth, which has been confirmed by morphometric analysis in these same dogs reported in a separate study (23). In addition, findings 3 and 4 indicate a disparity between compensatory growth of respiratory tissue (alveolar-capillary membrane) and nonrespiratory tissue (small blood vessels and airways) after pneumonectomy. Greiville et al. (5) inferred from physiological measurements of maximal expiratory flows in immature dogs after left pneumonectomy that compensatory airway growth lagged behind alveolar growth. McBride (17) reached a similar conclusion on the basis of anatomic measurements of airway number and cross-sectional area in the remaining lung of immature ferrets after right pneumonectomy. This so-called "dysanaptic growth" of conducting airways and blood vessels can explain the higher ventilatory power requirements and pulmonary arterial pressure during exercise in the pneumonectomized dogs. However, despite the evidence supporting dysanaptic growth, the dogs pneumonectomized as puppies were able to reach the same maximal O2 uptake at maturity as Sham animals.

Comparison of hemodynamic response in immature vs. adult dogs. In Fig. 5, mean pulmonary arterial pressure is compared between dogs after right pneumonectomy as adults (14) and as puppies. Even after the slightly higher pressure in the adult Sham group is taken into consideration, mean pulmonary arterial pressure at a given cardiac output was consistently lower in dogs raised to maturity after pneumonectomy as puppies than in adult dogs after pneumonectomy as adults. In dogs pneumonectomized as adults, mean pulmonary arterial pressure at peak exercise was ~60% higher than in corresponding Sham animals at the same cardiac output; maximal cardiac output was lower by ~25%. In dogs pneumonectomized as puppies, mean pulmonary arterial pressure at peak exercise was only ~20% higher than in corresponding Sham animals, and maximal cardiac output was not reduced. Several possible explanations can be advanced. 1) Normally, about one-third of the resistance to pulmonary blood flow resides in the pulmonary microvasculature (3); thus postpneumonectomy compensatory alveolar growth can provide a significant reduction in pulmonary vascular resistance. 2) Remodeling of pulmonary arterioles may be more pronounced in immature animals, resulting in greater postpneumonectomy arteriolar vasodilation than in animals operated on as adults. 3) Some degree of vascular regenerative growth may have occurred in postpneumonectomy puppies involving large and medium-sized blood vessels.

We were not able to measure pulmonary wedge pressure reliably during exercise, so cannot rule out the possibility of an elevated left atrial pressure as the cause of pulmonary arterial hypertension after pneumonectomy. However, our laboratory previously found in adult dogs after pneumonectomy that ventilation-perfusion distributions at rest and during exercise were unaltered from control values despite a similar or greater elevation of pulmonary arterial pressure than in immature dogs after pneumonectomy (8, 14). Thus interstitial pulmonary edema is unlikely to have developed. The fact that maximal stroke volume and cardiac output are normal in these dogs after pneumonectomy also argues against an intrinsic cardiac cause for the elevated pulmonary arterial pressure.

Comparison of mechanical response in immature vs. adult dogs. Barnas et al. (2) showed that, at low respiratory frequencies, hysteresis in the stress-strain relationship of lung tissues predominates over viscous resistance in airways as a source of energy dissipation. As respiratory frequency increases above 1 Hz, tissue viscous resistance becomes negligible and airway viscous resistance becomes predominant. This shift occurs because there is insufficient time for stress relaxation in the tissues; hence energy losses from tissue friction rapidly decline while lung elastance increases correspondingly. In our laboratory's previous studies in dogs, respiratory frequency exceeds 1 Hz above a minute ventilation of ~50 l/min, and, at heavy exercise, dy-
Maximal ventilation at peak exercise in dogs pneumonectomized as puppies compared with Sham animals, pneumonectomized animals could reach the same level of ventilation, cardiac output, and O₂ uptake at maximal exercise as in Sham animals. This must mean either that right ventricular afterload and ventilatory power requirements are not imposing the limit to maximal exercise in dogs or that other mechanisms of compensation have been acquired in the pneumonectomized animals. Other mechanisms of compensation may include hyperplasia of the myocardium as well as of respiratory muscles during the period of maturation after pneumonectomy. These possibilities were not directly examined in the present study, but others have suggested that myocardial hyperplasia (as opposed to simple myocardial hypertrophy) does occur in immature dogs subjected to an increased ventricular afterload. Overy et al. (20) showed that immature lambs demonstrated a greater potential for increasing right ventricular mass in response to a chronically increased systolic blood pressure than did adult sheep. The period of normal postnatal myocyte hyperplasia can apparently be extended by increasing myocardial workload (19). Previous studies in our laboratory have shown that diaphragmatic hyperplasia develops in adult dogs after right pneumonectomy, resulting in a 20% increase in the mass of the right hemidiaphragm (12). In animals from the present study, raised to maturity after pneumonectomy as puppies, postmortem mass of the right hemidiaphragm was slightly but not significantly higher than in Sham animals (by 10% unpublished observations), consistent with their correspondingly lower ventilatory work during moderate exercise compared with dogs pneumonectomized as adults (Fig. 6).

In summary, we conclude that, in immature dogs raised to maturity after 55% lung resection, compensation in pulmonary hemodynamic and mechanical function during exercise is incomplete even though there is complete restoration of gas-exchange capacity (23). This dissociation in compensatory response is consistent with the hypothesis that structural adaptation involving the conducting airways and blood vessels of the remaining lung is limited. Despite these abnormalities, maximal O₂ uptake and maximal cardiac output remain normal in pneumonectomized animals, suggesting there are additional extra-alveolar sources of adaptation, e.g., involving the heart and respiratory muscles.

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Present address of S. Takeda: First Dept. of Surgery, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.

Address for reprint requests and other correspondence: C. W. Hsia, Dept. of Medicine, Univ. of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9034 (E-mail: Connie.Hsia@email.swmed.edu).

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Fig. 6. Comparison of total ventilatory power requirement of lung in immature and mature R-Pnx and Sham dogs. Error bars, SE. Data in adult dogs are taken from Hsia et al. (12).
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REFERENCES


