Reducing lung strain after pneumonectomy impairs oxygen diffusing capacity but not ventilation-perfusion matching

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WE HAVE PREVIOUSLY SHOWN THAT after right pneumonectomy (Pnx; removal of 55% of lung tissue) in the adult foxhound, compensatory enhancement of O₂ exchange in the remaining lung restores maximal O₂ uptake to 85% of that in the normal foxhound (15, 22). The sources of compensation include 1) recruitment of remaining physiological reserves, 2) remodeling of remaining alveolar capillary network, and 3) regenerative growth of new alveolar septal tissue. Volume of the remaining lung increases to 90% of that for two lungs via expansion across the midline into the empty right hemithorax, whereas diffusing capacity of the remaining lung at heavy exercise increases to ~80% of that in two lungs of a normal foxhound at the same cardiac output (14).

Mechanical lung strain is a potent stimulus of cell proliferation and tissue remodeling (19, 22); sustained mechanical strain on the remaining lung after Pnx is believed to stimulate adaptive responses leading to functional compensation. We have shown that reducing lung strain after right Pnx in adult dogs by an inflated prosthesis significantly impairs compensation in carbon monoxide diffusing capacity (DLCO) (27) and septal tissue growth (17); however, effects on O₂ exchange have not been directly examined. Sustained mechanical strain also induces adaptive changes in the remaining conducting airways and blood vessels. For example, the remaining conducting airways lengthen initially, followed by later dilatation to partially mitigate the expected increase in airways resistance (3). Similarly, chronic traction on the remaining conducting blood vessels after Pnx may induce vascular remodeling (4) to mitigate the expected increase in pulmonary vascular resistance.

Our goal was to determine the extent to which mechanical lung strain contributes to the compensatory functional response after Pnx. In this study, we examined the effects of lateral expansion of the remaining lung after right Pnx on the efficiency of O₂ exchange and pulmonary hemodynamic function at rest and during exercise in adult dogs. We hypothesized that restricting expansion and mechanical strain of the remaining lung would 1) impair ventilation-perfusion (V̇ₐ/Q̇) matching and further exacerbate pulmonary arterial hypertension and 2) reduce diffusing capacity for O₂ (DLco) via impaired recruitment of existing alveolar capillary reserves and/or diminished strain-related signals that initiate regenerative alveolar-capillary growth.

METHODS

Lung prosthesis. All protocols were approved by the University of Texas Southwestern Medical Center Institutional Review Board. 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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Animal Care and Use Committee. The manufacture of prosthesis has been described previously (27). Briefly, a normal adult foxhound (25 kg body wt) was anesthetized, intubated, and ventilated. In the supine position, consecutive transverse magnetic resonance images were obtained at 10-mm intervals from the apex to the costophrenic angle with the breath held at functional residual capacity. The outline of the lung on each image was digitized, and a three-dimensional model of the right lung was reconstructed from stacked images. An inflatable silicone prosthesis (CUI, Carpinteria, CA) was fabricated in the shape and size of the right lung model, with an injection tube attached to the dorsolateral surface via a reinforced patch.

Animal surgery. Each adult male foxhound (1 yr of age) underwent resection of the right lung under general anesthesia by following established procedures (10). After removal of the right lung, the silicone prosthesis was placed in the empty hemithorax. The injection tube was brought out through an intercostal space, tunneled to the back of the neck, connected to the filling port, and buried subcutaneously. In five animals (Inf group), the prosthesis was inflated with an equal mixture of air and SF$_6$ to a volume equal to the animal’s functional residual capacity measured in the supine position. Mixing air with SF$_6$ retards the rate of gas absorption from the prosthesis. In the other five animals (Def group), the prosthesis remained deflated, containing <50 ml of gas to prevent pleating. After ensuring hemostasis, the thorax was closed in five layers. After recovery, volume in the prosthesis was checked by helium dilution via the subcutaneous filling port once a week for the first month and then once a month for the duration of the study. After each volume measurement, the prosthesis was refilled to the desired level with the air-SF$_6$ mixture, and the position of the mediastinum was verified by chest X-ray.

Exercise training and studies. Beginning 3–4 wk after surgery, animals were trained to run freely on a treadmill by protocols described previously (13), which consisted of running for 30 min a day, 5 days a week at workloads between 60 and 100% of previously achieved maximal workload while wearing a customized leak-free respiratory mask (1) and attachments necessary for ventilatory measurements. Exercise training continued throughout the duration of the study. Bilateral carotid artery loops were constructed (21) to allow repeated acute catheterization. The present studies were performed at rest and during exercise between 4 and 7 mo after Pnx. Separate studies, including measurement of $D_{CO}$ at rest and exercise, computerized tomographic (CT) scan of the thorax, and postmortem analysis of lung structure, have been reported separately (17, 27).

Apparatus for ventilatory measurements. The dog breathed through a two-way respiratory valve (no. 2700, Hans Rudolph, Kansas City, MO). The inspiratory port opened through a screen pneumotachometer (Hans Rudolph no. 3813) to either room air or a meteorological balloon containing 14% $O_2$. The expiratory port led to a mixing chamber and another heated screen pneumotachometer. Expired flow was integrated to obtain tidal volume. Expired gas concentrations were sampled continuously distal to the mixing chamber by a mass spectrometer (Perkin-Elmer, MGA 1100). The pneumotachometer-computer system was calibrated on each day of study (28). Electrocardiogram and rectal temperature were continuously monitored. Signals were digitized at 50 Hz. Ventilation, $O_2$ uptake, CO$_2$ production, respiratory rate, tidal volume, and heart rate were calculated and averaged over a predetermined number of breaths. Pulmonary and systemic arterial pressures and reference pressure were recorded with identical fluid-filled transducers (Statham Instraments, P23 ID) through Hewlett-Packard carrier amplifiers, digitized, and averaged over a predetermined number of heartbeats. Pressure transducers were calibrated with a mercury manometer on the day of study.

Peak $O_2$ uptake. Room temperature was kept at 19°C. The jugular vein was cannulated under local anesthesia on the day of study for blood drawing. Ventilatory parameters, rectal temperature, and heart rate were continuously recorded. With the dog standing on the treadmill, a baseline blood sample (3 ml) was drawn to measure lactate concentration (Yellow Springs Instruments, Yellow Springs, OH). After 5 min of warm-up exercise at 6 mph 0% grade, the treadmill speed was increased to 8 mph, and the grade was increased by 5% every 3 min until the animal began to lag on the treadmill or until rectal temperature exceeded 41°C. Blood lactate concentration was measured during the last 30 s of each workload and every 2 min after cessation of exercise until the value returned to baseline.

Hemodynamic studies during steady-state exercise. On a separate day and with the dog standing in a sling, a catheter was inserted under local anesthesia into the exteriorized and corrected for differences between the animal’s arterial blood samples. An introducer was inserted into each external jugular vein. A balloon-tipped triple-lumen thermal dilution catheter was inserted through one jugular introducer into one pulmonary artery for monitoring blood temperature and drawing mixed venous blood; position of the catheter was confirmed by pressure monitoring and by wedging. The other jugular venous catheter was used for infusion of inert gases. Catheters were sutured to the skin and flushed with heparinized saline. A reference catheter was sutured to the skin of the lateral chest at the level of the right atrium midway between the sternum and the spine, and secured with tape. From measurements of $O_2$ uptake and arterial and mixed venous $P_O_2$ and $O_2$ saturation (see below), cardiac output was determined by the direct Fick method.

Steady-state exercise and the multiple inert gas elimination technique. $V_A/Q$ distributions were measured by the multiple inert gas elimination technique (6, 15). Six inert gases (SF$_6$, ethane, cyclopropane, enfuran, acetone, and ether) were dissolved in saline and infused at a constant rate via a jugular venous catheter. The infusion rate was maintained at ~1/4,000th of the dog’s minute ventilation under all conditions to ensure an adequate signal-to-noise ratio. At rest, the infusion began 20 min before sampling. At exercise, equilibrium of inert gas exchange at the blood-gas interface is achieved rapidly, therefore, sampling could be done after 3 min of infusion. Baseline measurements at rest were made with the dog standing on the treadmill. After 5 min of warm-up exercising at 6 mph 0% grade, the workload was increased quickly to a preselected level equivalent to 25, 50, and 80% of the animal’s previously measured maximal $O_2$ uptake and sustained for 4 min. By the end of the third minute at a given workload, duplicate arterial blood samples (7 ml each) and quadruplicate mixed expired gas samples (30 ml each) were collected in glass syringes for analysis of inert gas concentration by a gas chromatograph (Hewlett-Packard, model 5890A). Expired gas samples were collected after blood samples by a time delay equal to the time of gas transit through the mixing chamber. Blood-gas partition coefficients of the inert gases were measured in duplicate for each dog and corrected for differences between the animal’s blood temperature during exercise and the water bath temperature at which samples were equilibrated. Inert gas concentrations of mixed venous blood were calculated from arterial and expired values, ventilation, and cardiac output by mass conservation. After collection of the inert gas samples, additional
arterial and mixed venous blood (3 ml each) was drawn for analysis of conventional blood gases (Radiometer, ABL-500, Copenhagen, Denmark), O₂ content, hemoglobin concentration (Radiometer, model OSM3), and lactate concentration (Yellow Springs Instruments). Values of PO₂, PCO₂, and pH were adjusted to the measured blood temperature. Hematocrit was determined by a microcapillary centrifuge (International, model MB). After each exercise bout, the dog walked on the treadmill for 5–10 min to cool down. The dog rested for at least 1 h between exercise periods, or until heart rate, respiratory rate, and ventilation returned to baseline. Measurements were repeated with the dog inspiring either 21 or 14% O₂ in balanced order.

Data analysis. Data were normalized by body weight and expressed as means ± SE. Ventilatory parameters were related to O₂ uptake or cardiac output by multiple linear regressions; individual slopes and elevations were compared between groups by the method described by Zar (29). Dispersion of the Va/Q distribution about the mean was quantified by the log-scale second moments with respect to ventilation (log SD V) and perfusion (log SD Q). From the inert gas data, cardiac output, ventilation, hemoglobin concentration, blood temperature, base excess, barometric pressure, inspired PO₂ and PCO₂, mixed venous PO₂ and PCO₂, the arterial PO₂, arterial PCO₂, and alveolar-arterial O₂ tension gradient (A-aDO₂) attributable to Va/Q inhomogeneity could be predicted (25). When the measured A-aDO₂ exceeded that predicted, the difference reflects the combined contribution from alveolar-endcapillary diffusion impairment and postpulmonary shunting to overall hypoxemia.

Breathing 21% O₂ accentuates the A-aDO₂ caused by Va/Q mismatch and intrapulmonary shunt while minimizing the A-aDO₂ caused by diffusion impairment and extrapulmonary shunt. Breathing 14% O₂ has just the opposite effect (18). Differences arise because both O₂ and inert gases are perturbed by the log-scale second moments with respect to ventilation and O₂ uptake or cardiac output by multiple linear regressions; individual slopes and elevations were compared between groups but remained lower in the Inf group compared with the Def group (Table 1). Arterial PO₂, saturation, and A-aDO₂ were similar, but arterial lactate concentration was lower in the Inf group.

However, during breathing of 14% O₂, peak O₂ uptake, CO₂ output, arterial PO₂, and arterial O₂ saturation were significantly lower in the Inf group compared with Def group. Peak lactate concentration increased more during hypoxic than normoxic exercise in both groups but remained lower in the Inf group compared with the Def group. Peak A-aDO₂ was significantly higher in the Inf group. Saturation data are shown in Fig. 1.

VA/Q relationships. Dispersion of the ventilation distribution (log SD V) was significantly greater in the Def group (P < 0.0001) than in the Inf group breathing 21 or 14% O₂ (Fig. 2, A and C), associated with a markedly and unexpectedly higher resting respiratory rate (breaths per min) in the Def group (51 ± 9 breathing 21% O₂ and 94 ± 19 breathing 14% O₂) compared with the Inf group (26 ± 2 breathing 21% O₂ and 33 ± 1 breathing 14% O₂, P < 0.05 between groups). At exercise, the differences in log SD V diminished as respiratory rate became similar between groups (Table 1). In the Def group, log SD V declined with respect to O₂ uptake (P < 0.02). In the Inf group, log SD V increased from rest to exercise to levels similar to those in the Def group. The pattern of log SD V response to exercise was therefore significantly different between groups (P < 0.01) because of differences at rest, but there were no differences during exercise.

At rest, dispersion of the perfusion distribution (log SD Q) was slightly lower in the Inf group. At exercise
Table 1. Data at peak workload

<table>
<thead>
<tr>
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<th>Inspired O2 Concentration</th>
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<tr>
<td></td>
<td>21%</td>
<td>14%</td>
<td></td>
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<tr>
<td></td>
<td>Inflated</td>
<td>Deflated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflated</td>
<td>Deflated</td>
<td></td>
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<tr>
<td>Minute ventilation, l·min⁻¹·kg⁻¹</td>
<td>4.05 ± 0.64</td>
<td>4.23 ± 0.32</td>
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<td>Respiratory rate, breaths/min</td>
<td>117 ± 15</td>
<td>119 ± 8</td>
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<tr>
<td>O₂ uptake, ml·min⁻¹·kg⁻¹</td>
<td>83 ± 9</td>
<td>95 ± 8</td>
<td></td>
</tr>
<tr>
<td>CO₂ output, ml·min⁻¹·kg⁻¹</td>
<td>77 ± 9</td>
<td>95 ± 9</td>
<td></td>
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<tr>
<td>Respiratory exchange ratio</td>
<td>0.92 ± 0.04</td>
<td>1.00 ± 0.04</td>
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<td>Heart rate, beats/min</td>
<td>293 ± 9</td>
<td>279 ± 11</td>
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<tr>
<td>Cardiac output, ml·min⁻¹·kg⁻¹</td>
<td>510 ± 55</td>
<td>596 ± 31</td>
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<tr>
<td>Hematocrit, %</td>
<td>50.0 ± 1.2</td>
<td>52.8 ± 2.3</td>
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<tr>
<td>Mean systemic arterial pressure, mmHg</td>
<td>169 ± 7</td>
<td>167 ± 6</td>
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</tr>
<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
<td>57 ± 5</td>
<td>58 ± 4</td>
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<td>Arterial pH</td>
<td>7.25 ± 0.01</td>
<td>7.21 ± 0.03</td>
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<tr>
<td>Arterial PCO₂, Torr</td>
<td>51.0 ± 0.5†</td>
<td>45.5 ± 1.0</td>
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<tr>
<td>Arterial PO₂, Torr</td>
<td>66.2 ± 2.7</td>
<td>70.8 ± 1.8</td>
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<td>Lactate concentration, mM/l</td>
<td>1.5 ± 0.5*</td>
<td>3.9 ± 0.6</td>
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<tr>
<td>A-aDO₂, Torr</td>
<td>16.8 ± 3.3</td>
<td>15.9 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Arterial O₂ saturation, %</td>
<td>81.9 ± 1.7</td>
<td>79.1 ± 2.0</td>
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<tr>
<td>Log SD V</td>
<td>1.15 ± 0.05</td>
<td>0.90 ± 0.04</td>
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<tr>
<td>Log SD Q</td>
<td>0.62 ± 0.03</td>
<td>0.62 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>DLO₂, ml·min⁻¹·mmHg⁻¹·kg⁻¹</td>
<td>1.97 ± 0.24</td>
<td>2.29 ± 0.10</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. A-aDO₂, alveolar-arterial O₂ tension gradient; log SD V, dispersion of ventilation distribution; log SD Q, dispersion of perfusion distribution; DLO₂, diffusing capacity of O₂. Inflated and deflated indicate prosthesis group. Comparison between groups at the same inspired O₂ fraction: *P < 0.05, †P < 0.001, ‡P < 0.0001.

log SD Q rose significantly (P < 0.0001) in both groups (Fig. 2, B and D). There was no significant difference in the values of log SD Q as a function of exercise between groups during breathing of 21% O₂. During breathing of 14% O₂, log SD Q rose more rapidly with respect to O₂ uptake in the Inf group, but the magnitude did not exceed that in the Def group at peak exercise because of a lower peak O₂ uptake.

Diffusion impairment. During breathing of 21% O₂ (Fig. 3A), the A-aDO₂ predicted from V/Q dispersion increased only slightly from rest to exercise in both groups, indicating a minimal change in V/Q mismatch and/or intrapulmonary shunt. The measured A-aDO₂ was lower than predicted at rest and low exercise workload but significantly exceeded that predicted in both groups at heavy exercise. The difference, (measured – predicted) A-aDO₂, was similar between groups at a given O₂ uptake (Fig. 3C, left), indicating a similar degree of diffusion impairment and/or extrapulmonary shunt in the two groups.

During breathing of 14% O₂ (Fig. 3B), the A-aDO₂ predicted from V/Q dispersion either stayed constant or increased slightly from rest to exercise in both groups, indicating a minimal change in V/Q distributions. At exercise, measured A-aDO₂ rose significantly above that predicted in both groups; the increase was greater in the inflated group than in the deflated group. As a result, the difference, (measured – predicted) A-aDO₂, was significantly greater in the inflated group at a given O₂ uptake (Fig. 3C, right), indicating a more severe diffusion impairment and/or extrapulmonary shunt. We did not directly measure extrapulmonary shunt during exercise, but any extrapulmonary shunt would have to be very large (>30% of cardiac output) and open only during hypoxia to explain the (measured – predicted) A-aDO₂.
DLO₂ expressed per kilogram of body weight was calculated from the difference between measured A-aDO₂ and that predicted from V˙A/Q˙ distribution during breathing of 14% O₂ (Fig. 4). The slope of the increase in DLO₂ during exercise with respect to cardiac output was similar in both groups, indicating a similar pattern of microvascular recruitment. However, DLO₂ was significantly lower with respect to workload in dogs with Inf prosthesis analyzed by repeated-measures ANOVA (P < 0.01). The elevation of individual regression lines of DLO₂ with respect to cardiac output normalized by body weight was also significantly lower in the Inf group compared with the Def group (P < 0.05).

Pulmonary hemodynamics. Mean pulmonary arterial pressure was higher at any given cardiac output in the Inf group compared with Def group breathing either O₂ concentration (Fig. 5, A and C). Therefore, total pulmonary vascular resistance was systematically greater in the Inf group. During breathing of 21% O₂, cardiac output was slightly but significantly lower in the Inf group at rest and moderate exercise, but it was similar between groups at heavy exercise. During breathing of 14% O₂, cardiac output at a given workload was similar between groups, but peak cardiac output was reached at a lower O₂ uptake in the Inf group (Fig. 5, B and D).

DISCUSSION

Summary of findings. This is the first study to define the effects of chronic mechanical lung strain on adaptation of O₂ exchange and pulmonary hemodynamics during compensatory lung growth. Preventing lateral expansion of the remaining lung by the Inf prosthesis diminished but did not completely eliminate the post-Pnx increase in lung volume, because the remaining lung was able to change shape and enlarge in other directions by displacing the diaphragm and rib cage (27). After right Pnx, the presence of a deflated prosthesis reduced peak O₂ uptake by ~23% compared with pneumonectomized adult dogs without prosthesis (13). Keeping the prosthesis inflated further impaired peak O₂ uptake by 13% in normoxia (21% O₂) and 28% in hypoxia (14% O₂) but had only minor effects on the uniformity of V˙A/Q˙ matching and no significant effect on maximal cardiac output. However, mean pulmonary arterial pressure was higher at a given cardiac output, indicating greater total pulmonary vascular resistance. Keeping the prosthesis inflated did not impair the increase in DLO₂ with respect to cardiac output, consistent with normal alveolar-capillary recruitment but significantly reduced the magnitude of DLO₂ at any given cardiac output consistent with blunted alveolar structural growth (8). Thus the mechanical strain imposed by lateral expansion of the remaining lung after Pnx provides significant signal(s) for the subsequent compensation in diffusive O₂ exchange.

Effect of mechanical lung strain on V˙A/Q˙ inequality. After Pnx, the negative intrathoracic pressure cause the remaining lung to expand across the midline, increasing its volume to nearly that of two normal lungs within a few days. In early studies of Pnx, summarized by Schilling (23), expansion of the remaining lung was
thought to induce an “emphysema-like” morphology, leading to detrimental consequences on gas exchange. However, recent studies suggest that sustained mechanical strain on the remaining lung is in fact a major signal that initiates beneficial adaptive responses, including more complete utilization of existing microvascular reserves for gas exchange, remodeling of existing septal tissue, accelerated growth of new alveolar septal tissue, as well as lengthening and dilatation of the conducting airways (3, 11, 12). These adaptive responses confer significant long-term functional compensation evidenced by the maintenance of a near-normal exercise capacity in adult dogs 1 yr after removal of 55% of lung by right Pnx (13).

In dogs during Pnx surgery, \( V_{A}/Q \) distributions become acutely bimodal as one pulmonary artery or main bronchus is clamped (5), but they eventually return to normal after Pnx. Long-term uneven distribution of ventilation develops in human subjects after Pnx (26). We previously found in adult dogs that \( V_{A}/Q \) inequality
was not altered by right or left Pnx (10, 15), suggesting proportional adaptation of conducting airways and blood vessels. In growing dogs, the remaining conducting airways became lengthened early after right Pnx followed by later dilatation, assessed by high-resolution CT scan, but similar assessment has not been done in dogs pneumonectomized as adults. Structural adaptation of the conducting blood vessels has not been examined in vivo. We hypothesized that restricting expansion of the remaining lung would blunt adaptation of the conducting structures. In the presence of the inflated prosthesis, ventilation and perfusion must flow through a smaller airway and vascular tree, respectively. This might cause uneven distributions of ventilation to perfusion and increase pulmonary vascular shear forces at a given cardiac output. Accordingly, we expected to find higher values of log SD V˙ and log SD Q˙ and greater pulmonary arterial hypertension in the Inf group. To our surprise, ventilation and perfusion matching at a given O₂ uptake during heavy exercise was not significantly worse in the Inf group breathing normoxic or hypoxic gas. In fact, ventilation heterogeneity at rest and during moderate exercise was more pronounced in the Def group, related to a markedly higher resting respiratory rate, i.e., panting, an effect similar to that observed during high-frequency oscillatory ventilation (20). Under all conditions, values of log SD V˙ and log SD Q˙ during exercise were within the range expected in pneumonectomized dogs.

Fig. 4. O₂ diffusing capacity of the lung (DLO₂) was calculated from the difference between measured and predicted A-aDO₂ during breathing of 14% O₂. DLO₂ was consistently lower at a given workload in dogs with Inf prosthesis than in dogs with Def prosthesis. Values are means ± SE. *P < 0.01 for group interactions by repeated-measures ANOVA. The elevations of individual regression lines of DLO₂ with respect to cardiac output were also significantly lower in the Inf group (P < 0.05), but the slopes were similar between groups.

Fig. 5. Mean pulmonary arterial pressure and cardiac output at rest and during exercise during breathing of 21% O₂ (A and B) and 14% O₂ (C and D). At a given cardiac output, mean pulmonary artery pressure was higher in dogs with Inf prosthesis than in dogs with Def prosthesis breathing either O₂ concentration (A and C). Cardiac output at a submaximal O₂ uptake was slightly lower in the Inf group particularly during breathing of 21% O₂ (P < 0.05); however, peak cardiac output was similar between groups (B and D). Values are means ± SE. *P values indicate group interactions by repeated-measures ANOVA.
dogs without prosthesis or in normal dogs (15). From these data alone we cannot establish how conducting structures might have remodeled in adult dogs after Pnx, but it seems that airways or blood vessels responded equally to the presence or absence of chronic mechanical lung strain so that changes in distribution of ventilation and perfusion remain matched.

**Effect of mechanical lung strain on pulmonary hemodynamics.** The present results are consistent with previous studies in pneumonectomized adult dogs showing pulmonary arterial hypertension during exercise with a mean pulmonary arterial pressure exceeding 60 mmHg (15). In the Inf group, mean pulmonary arterial pressure at a given cardiac output was consistently higher than that in the Def group, indicating a higher total vascular resistance, possibly owing to greater vascular shear forces as the same blood flow is forced through a smaller vascular cross-sectional area when lung expansion is prevented, consistent with morphological findings of microvascular congestion in the remaining lung of the Inf group (17). This is also consistent with the lower O₂ diffusing capacity shown in Fig. 4. An exaggerated pulmonary arterial hypertension with the Inf prosthesis is associated with a lower submaximal cardiac output, but maximal cardiac output was not altered, suggesting that the right ventricle can overcome the further increased afterload, via dilatation and/or hypertrophy, to maintain its output.

**Effect of mechanical lung strain on O₂ exchange.** In adult dogs after left or right Pnx, impaired diffusive gas transport in the lungs is the major source of exercise limitation (9, 15). Reducing post-Pnx lung strain as we show in the Inf group further impairs O₂ diffusing capacity at a given cardiac output. The consequence of exaggerated diffusion limitation is an earlier decline in arterial O₂ saturation during exercise, particularly during breathing of a hypoxic gas mixture (shown in Fig. 1). On the basis of studies in normal and pneumonectomized human subjects and dogs, we have developed a framework for interpreting diffusion limitation from rest to exercise, taking into consideration both structural and nonstructural determinants of diffusing capacity (2, 8). Structural determinants of diffusing capacity include the effective alveolar-capillary surface area and the mean harmonic diffusion distance from the air-tissue interface to the capillary red blood cells. Nonstructural determinants include pulmonary blood flow and its distribution, red cell mass (hematocrit) and its distribution, and lung volume. There is a linear increase in DlCO, or DlCO with respect to pulmonary blood flow that continues from rest to peak exercise without reaching an upper limit in normal subjects (16) or pneumonectomized dogs (14, 24). The slope of this relationship is indicative of functional recruitment of microvascular reserves (15), whereas the magnitude at a given blood flow reflects the structural determinants of diffusion. In adult dogs, both the magnitude of DlCO and the slope of its recruitment with respect to blood flow are impaired early after Pnx without lung prosthesis; DlCO improves with time but never completely returns to normal (15). Results are consistent with postmortem findings in the same animals of a limited compensatory septal tissue growth in the remaining lung (12). In immature dogs undergoing right Pnx and subsequently raised to maturity, diffusing capacity and its recruitment are completely normal, associated with normal gas-exchange indexes as well as exercise capacity (24). These results are consistent with postmortem findings of complete compensatory septal tissue growth that restored septal tissue dimensions to that expected in two normal lungs (24).

In the present study, adult pneumonectomized dogs with Inf prosthesis show a systematically lower DlCO, at a given pulmonary blood flow than dogs with Def prosthesis, whereas the slopes of the DlCO-blood flow relationship from individual or pooled data are similar between groups. Results mirror the changes in DlCO previously reported in these same animals (27) and suggest that reducing lung strain does not alter microvascular recruitment but impairs post-Pnx structural adaptation of gas-exchange tissue. The latter conclusion is also consistent with postmortem findings in these same animals reported separately (17), i.e., smaller increases in septal tissue volume and alveolar-capillary surface areas in animals with Inf prosthesis than in animals with Def prosthesis. Relative to pneumonectomized adult dogs without lung prosthesis, ~70–80% of the compensatory increase in total lung volume and septal tissue volume was prevented when lateral mechanical lung strain was reduced by the Inf prosthesis. The residual 20–30% of the compensatory response must be attributed to other mechanical and/or nonmechanical signals, such as endothelial dysfunction or sepsis, exercise-induced hypoxemia, and hormonal or paracrine growth factors.

In conclusion, reducing post-Pnx mechanical lung strain by an inflated prosthesis impairs gas exchange compensation through a marked reduction of DlCO, at any given cardiac output, consistent with the reduced DlCO observed in the same animals (24), and likely results from a blunted compensatory growth of alveolar septal tissue (17). This is also consistent with greater pulmonary arterial hypertension during exercise. However, in spite of the increased afterload after Pnx, which is further exaggerated by the inflated prosthesis, the right ventricle remains effective in maintaining a normal maximal cardiac output, and alveolar microvascular recruitment remains normal. In contrast, Vₐ/Q inequality during exercise is essentially independent of prosthesis inflation, suggesting that conducting airways and blood vessels adapt proportionally regardless of mechanical lung strain.

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