Alveolar diffusion-perfusion interactions during high-altitude residence in guinea pigs

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Yilmaz C, Dane DM, Hsia CC. Alveolar diffusion-perfusion interactions during high-altitude residence in guinea pigs. J Appl Physiol 102: 2179–2185, 2007—We previously reported in weanling guinea pigs raised at high altitude (HA; 3,800 m) an elevated lung diffusing capacity estimated by morphometry from alveolar-capillary surface area, harmonic mean blood-gas barrier thickness, and pulmonary capillary blood volume (Vc) compared with litter-matched control animals raised at an intermediate altitude (IA; 1,200 m) (Hsia CCW, Polo Carbayo JJ, Yan X, Bellotto DJ. Respir Physiol Neurobiol 147: 105–115, 2005). To determine if HA-induced alveolar ultrastructural changes are associated with improved alveolar function, we measured lung diffusing capacity for carbon monoxide (DLCO), membrane diffusing capacity for carbon monoxide (DMCO), Vc, pulmonary blood flow, and lung volume by a rebreathing technique in litter-matched male weanling Hartley guinea pigs raised at HA or IA for 4 or 12 mo. Separate control animals were also raised and studied at sea level (SL). Resting measurements were obtained in the conscious nonsedated state. In HA animals compared with corresponding IA or SL controls, lung volume and hematocrit were significantly higher while pulmonary blood flow was lower. At a corresponding IA or SL controls, lung volume and hematocrit were the conscious nonsedated state. In HA animals compared with corresponding IA or SL controls, lung volume and hematocrit were significantly higher while pulmonary blood flow was lower. To determine if HA-induced alveolar ultrastructural changes are associated with improved alveolar function, we measured lung diffusing capacity for carbon monoxide (DLCO), membrane diffusing capacity for carbon monoxide (DMCO), Vc, pulmonary blood flow, and lung volume by a rebreathing technique in litter-matched male weanling Hartley guinea pigs raised at HA or IA for 4 or 12 mo. Separate control animals were also raised and studied at sea level (SL). Resting measurements were obtained in the conscious nonsedated state. In HA animals compared with corresponding IA or SL controls, lung volume and hematocrit were significantly higher while pulmonary blood flow was lower. At a given pulmonary blood flow, DLCO and DMCO were higher in HA significantly higher while pulmonary blood flow was lower. At a corresponding IA or SL controls, lung volume and hematocrit were significantly higher while pulmonary blood flow was lower. In weanling guinea pigs raised at 3,800 m HA for 3 to 6 mo compared with their littermates raised simultaneously at an intermediate altitude (IA; 1,250 m) (9), we found an elevated lung volume, alveolar-capillary surface area, and alveolar septal tissue volume, as well as a reduced mean harmonic thickness of the diffusion barrier and a smaller alveolar duct volume; these structural changes led to significant increases in DLCO and membrane diffusing capacity (DMCO) estimated by a morphometric technique. Our hypothesis was that alveolar structural adaptation induced by HA residence in guinea pigs is associated with improved lung diffusing capacity. Testing this hypothesis is necessary because structure-function relationships in HA-induced adaptation have not been established in small animals, owing to the lack of suitable methodology for the assessment of lung function. We applied a novel noninvasive rebreathing technique recently developed in our laboratory (22) to measure cardiopulmonary function in conscious unanesthetized guinea pigs raised for 4 or 12 mo at HA compared with littermates raised at IA and with a separate age- and gender-matched control group raised at SL. These studies also provide data for interspecies comparison of HA-induced responses.

METHODS

Animals. The Institutional Animal Care and Use Committees of the University of Texas Southwestern Medical Center and the University of California White Mountain Research Station (WMRS) both approved the protocols. Weanling litter-matched male Hartley guinea pigs born at SL (Harlan Industries, Indianapolis, IN) were raised for either 4 or 12 mo at HA (n = 11 or 9, respectively) at the Barcroft laboratory (3,800 m) or at an intermediate altitude (IA, n = 11 or 10, respectively) at the Owens Valley laboratory (1,250 m) of WMRS. The animals were given food and water ad libitum. The ambient temperature and care schedule were standardized. Body weight and crown-to-rump length were measured each week. All physiological studies were performed at the Owens Valley laboratory (1,250 m); the animals residing at HA were brought down to the 1,250-m location 1 day before measurement. As further controls, a separate group of male weanling Hartley guinea pigs was raised and studied at SL in Dallas, TX, at 4 or 12 mo of age (n = 12 or 10, respectively) (Table 1). The SL animals were used in separate exercise experiments and were trained to run regularly on a treadmill beginning at ~5 mo of age. The animals residing at HA and IA were not trained to exercise. No sedation or medication was given to any animal.

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of 38°C. Volume of the expired gas was eliminated by attaching a moisture trap (model MT120-2, Agilent Technologies, Palo Alto, CA) to the insertion port of the gas chromatograph signal was amplified (Hans Rudolph Amplifier 1, series 2384A, Hans Rudolph, Kansas City, MO), a stopcock, and a small latex balloon. The inspiratory port connected to a reservoir bag. The expiratory port connected via a metallic cooling tube to a pneumotachometer (Hans Rudolph, series 8311) and an anesthetic bag for timed collections of expired gas. The pneumotachometer signal was amplified (Hans Rudolph Amplifier 1, series 1100) and acquired by a data-acquisition card (PCM-DAS08, Computer Boards, Middleboro, MA) on a PC laptop (Pentium III, Dell Inspiron 8000) running Labview 5.0 (National Instruments, Austin, TX) and Universal Library (Computer Boards) acquisition software for real-time measurement of respiratory rate and minute ventilation. All volumes were expressed at BTPS conditions at a body temperature of 38°C.

Expired gas collected in the anesthetic bag was sampled, and the concentrations of O₂, CO₂, N₂, CO, C₂H₂, and SF₆ were measured by a gas chromatograph (CP-4900 Micro GC, Varian, Palo Alto, CA). Linearity of the gas chromatograph was checked by generating a calibration curve using gases of known concentrations. Calibration curves were generated for dry as well as humidified gas. Water vapor was eliminated by attaching a moisture trap (model MT120-2, Agilent Technologies, Palo Alto, CA) to the insertion port of the gas chromatograph.

The pneumotachometer was calibrated before each study by delivering 60 strokes of humidified air at different flow rates using a 20-ml syringe. Since expired gas passed through the metallic cooler tube before reaching the pneumotachometer, we assumed the expired temperature was equal to ambient temperature. Volume of the expired gas collection was measured using a calibrated syringe to verify the ventilation measurement obtained by the software.

Protocol. The protocol has been described in detail previously (22). Each animal had been placed in the chamber-mask assembly with the neck cuff inflated for 20 min on at least one occasion before making any measurement. On the day of study, the animal was fasted for 4 h, weighed, and placed in the chamber breathing room air. Minute ventilation was followed in real time; O₂ uptake and CO₂ output were measured each minute for ~5 min or until a stable baseline was established. Then the animal was exposed to a preselected inspired O₂ concentration (21% or 100% O₂) in random order. Respiratory rate and tidal volume were recorded continuously for 3 min, and the expired air was collected to measure mean expired gas concentrations, as well as expired volume. Following this period, the rebreathing maneuver was performed. The small latex rebreathing bag was prefilled with a known volume (1 ml above average tidal volume, range 5–10 ml) and concentrations of a rebreathing gas mixture (0.3% CO, 0.3% CH₄, 0.6% SF₆, 0.8% C₂H₂, and either 40% O₂ in balance of N₂ or balance of O₂). Although CH₄ was present in the mixture, its concentration was not measured in this study. At a selected end expiration, approximated from continuous recordings of mouth pressure, the stopcock between the rebreathing bag and the mouth was manually switched so that the animal breathed in and out of the rebreathing bag for a measured interval (3, 6, 9, or 12 s in random order). At the end of each rebreathing period, the stopcock was switched again to allow the animal to breathe ambient air or from the inspiratory reservoir bag, and gas concentrations remaining in the rebreathing bag were measured immediately by gas chromatography.

The duration of rebreathing was detected from changes in mouth pressure at the time of stopcock switching. The dead space of the rebreathing apparatus was 0.2 ml. The interval between successive measurements was 5 min. Each study required 1.0–1.5 h, and the entire protocol was repeated the following day with a different order of gas exposure; duplicate measurements under each condition were averaged. At the end of the study, we clipped the animal’s toenail to obtain blood for measuring hematocrit.

Data analysis. System volume was calculated from SF₆ dilution; the apparatus dead space was subtracted to obtain mean lung volume. End-expiratory lung volume is calculated by subtracting rebreathing bag volume from mean lung volume. Pulmonary blood flow and DLCO were calculated from the simultaneous logarithmic disappearance of C₂H₂ and CO, respectively, with respect to SF₆ obtained at the four rebreathing time points. From DLCO measured at two levels of alveolar O₂ tension (PₐO₂), we calculated DmCO and pulmonary capillary blood volume (Vc) using the Roughton-Forster relationship (15):

\[
\frac{1}{D_{LCO}} = \frac{1}{D_{MCO}} + \frac{1}{\theta_{CO} \cdot Vc}
\]

where \(\theta_{CO}\) is the empirical rate of CO uptake by whole blood at 37°C (in ml CO·min⁻¹·mmHg⁻¹·ml blood⁻¹) estimated from mean PₐO₂ (in Torr) during rebreathing. Since the relationship between \(\theta_{CO}\) and O₂ tension is not known for guinea pig blood, we used the values obtained by Holland (8) for dog blood:

\[
\frac{1}{\theta_{CO}} = (0.929 + 0.00517 \cdot PₐO₂) \cdot 0.45 \cdot \text{hematocrit}
\]

Estimates of DmCO and Vc were used to calculate a standardized DLCO at a constant PₐO₂ of 120 Torr and hematocrit of 0.45 (DLCO-std). The time \(\theta\) point from the CO disappearance curve was applied to the C₂H₂ curve to extrapolate the intercept of C₂H₂ disappearance and to estimate acetylene lung tissue volume. Data were normalized by body weight, expressed as means ± SD, and compared with respect to the animal’s baseline (estimation of PAO₂ by factorial ANOVA and Fisher’s multiple comparison (Statview v.5.0, SAS, Cary NC)). DLCO-std, DmCO, and Vc were plotted with respect to pulmonary blood flow; the slope and intercept of linear regression lines were compared as described by Zar (23). A P value of <0.05 was considered significant.

RESULTS

Body weight was similar among groups initially and after 4 mo of exposure. The temporary delay in weight gain in the SL animals at 5 mo coincided with the onset of exercise training in this group (Fig. 1), whereas the HA and IA animals were untrained. By 12 mo, the HA-raised animals exhibited a higher average body weight compared with control littermates raised

<table>
<thead>
<tr>
<th>Group</th>
<th>Location</th>
<th>Altitude, m</th>
<th>Barometric Pressure, mmHg</th>
<th>4 mo Exposure</th>
<th>Weight, g</th>
<th>12 mo Exposure</th>
<th>Weight, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA</td>
<td>Barcroft Laboratory</td>
<td>3,800</td>
<td>485</td>
<td>11</td>
<td>895±67</td>
<td>9</td>
<td>1,294±80*</td>
</tr>
<tr>
<td>IA</td>
<td>Owens Valley Laboratory</td>
<td>1,250</td>
<td>660</td>
<td>11</td>
<td>948±71</td>
<td>10</td>
<td>1,164±160</td>
</tr>
<tr>
<td>SL</td>
<td>Dallas, TX</td>
<td>150</td>
<td>750</td>
<td>12</td>
<td>926±88</td>
<td>10</td>
<td>1,228±33</td>
</tr>
</tbody>
</table>

Values are means ± SD. Guinea pig groups were raised at high altitude (HA), intermediate altitude (IA), or sea level (SL). *P < 0.05, HA vs. IA by 1-way ANOVA.
at IA but not with the animals raised at SL (Fig. 1). Compared with animals raised at IA, HA-raised guinea pigs showed a higher resting hematocrit and higher lung volumes at both time points as well as a higher tidal volume at 4 mo, but they showed a lower respiratory rate, O$_2$ uptake, and pulmonary blood flow (Table 2). Hematocrit was not done at 4 mo in the animals raised separately at SL. Minute ventilation at a given O$_2$ uptake was not significantly different among groups at both time points (Fig. 2).

Table 2 states the average values of DLCO and DMCO without taking into account the concurrent reduction in pulmonary blood flow. However, DLCO expressed at a given pulmonary blood flow was significantly higher in animals raised at HA than in those raised at IA or SL at each PAO$_2$ (Fig. 3); these differences remained significant after standardization of DLCO for PAO$_2$ and hematocrit (Fig. 4). The elevated DLCO is attributed to a higher DMCO at a given pulmonary blood flow while Vc at a given pulmonary blood flow was not different among groups (Fig. 4).

### DISCUSSION

The significance of this study is fourfold. First, we demonstrate that, contrary to common belief, laboratory guinea pigs are not preadapted to HA. These animals actively respond to postnatal HA exposure via ventilatory acclimatization (21), structural growth and remodeling (9), and functional enhancement of lung and membrane diffusing capacities (present data). Second, these are the first data to demonstrate structure-function correspondence during HA adaptation in a small animal model, thereby supporting both the physiological and morphometric methods of estimating diffusing capacity (Table 3). Third, this study establishes the utility of a novel rebreathing technique (22) for monitoring cardiopulmonary function during physiological adaptation in conscious, unanedated resting small animals. This noninvasive technique can also be applied to examine longitudinal responses to lung disease, injury, or therapeutic intervention. Fourth, reporting simple averages of DLCO and its components without considering variable pulmonary blood flow or O$_2$ uptake obscures intergroup differences, especially since such variability is expected to be larger in conscious unanedated animals than in anesthetized animals. These data emphasize the need to consider diffusion-perfusion interactions by interpreting measurements of DLCO and its components with respect to the simultaneously measured pulmonary blood flow.

**Critique of methods.** In a previous publication describing the rebreathing method for assessing lung function in guinea pigs (22), we validated the lung volume measured by sulfur hexafluoride dilution against that by helium washout. Systemic hematocrit in our HA-raised guinea pigs was about 20% higher than that in SL controls, a magnitude consistent with that seen in HA natives compared with lowlanders. From estimates of DMCO and Vc, we expressed DLCO at a constant alveolar O$_2$ tension and hematocrit level; therefore, the elevation of DLCO

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**Table 2. Ventilatory and rebreathing measurements**

<table>
<thead>
<tr>
<th></th>
<th>4-mo Exposure</th>
<th>12-mo Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HA</td>
<td>IA</td>
</tr>
<tr>
<td><strong>Hematocrit, %</strong></td>
<td>53.8 ± 3.1*</td>
<td>51.9 ± 2.2</td>
</tr>
<tr>
<td><strong>Ventilation, ml·min$^{-1}$·kg$^{-1}$</strong></td>
<td>637 ± 167</td>
<td>577 ± 102</td>
</tr>
<tr>
<td><strong>Tidal volume, ml/kg</strong></td>
<td>7.1 ± 0.9†</td>
<td>6.3 ± 1.1</td>
</tr>
<tr>
<td><strong>O$_2$ uptake, ml·min$^{-1}$·kg$^{-1}$</strong></td>
<td>10.9 ± 4.3</td>
<td>10.3 ± 1.9</td>
</tr>
<tr>
<td><strong>CO$_2$ output, ml·min$^{-1}$·kg$^{-1}$</strong></td>
<td>12.0 ± 2.8</td>
<td>12.0 ± 2.0</td>
</tr>
<tr>
<td><strong>End-expiratory lung volume, ml/kg</strong></td>
<td>18.0 ± 5.6†</td>
<td>16.4 ± 4.5</td>
</tr>
<tr>
<td><strong>End-inspiratory lung volume, ml/kg</strong></td>
<td>27.6 ± 6.2†</td>
<td>24.8 ± 3.3†</td>
</tr>
<tr>
<td><strong>Mean PAO$_2$, rebreathing (40% O$_2$, Torr)</strong></td>
<td>98 ± 1.0†</td>
<td>87 ± 9†</td>
</tr>
<tr>
<td><strong>Mean PAO$_2$, rebreathing (98% O$_2$, Torr)</strong></td>
<td>484 ± 16†</td>
<td>471 ± 16†</td>
</tr>
<tr>
<td><strong>DLCO measured using 40% O$_2$, ml·min$^{-1}$·mmHg$^{-1}$·kg$^{-1}$</strong></td>
<td>0.59 ± 0.11†</td>
<td>0.51 ± 0.09†</td>
</tr>
<tr>
<td><strong>DLCO measured using 98% O$_2$, ml·min$^{-1}$·mmHg$^{-1}$·kg$^{-1}$</strong></td>
<td>0.30 ± 0.10†</td>
<td>0.26 ± 0.03</td>
</tr>
<tr>
<td><strong>DLCO-standardized, ml·min$^{-1}$·mmHg$^{-1}$·kg$^{-1}$</strong></td>
<td>0.48 ± 0.14†</td>
<td>0.44 ± 0.12</td>
</tr>
<tr>
<td><strong>DMCO-standardized, ml·min$^{-1}$·mmHg$^{-1}$·kg$^{-1}$</strong></td>
<td>0.98 ± 0.58†</td>
<td>0.95 ± 0.45</td>
</tr>
<tr>
<td><strong>Vc, ml/kg</strong></td>
<td>1.2 ± 0.5</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td><strong>Pulmonary blood flow, ml·min$^{-1}$·kg$^{-1}$</strong></td>
<td>178 ± 29*</td>
<td>203 ± 28†</td>
</tr>
<tr>
<td><strong>Acetylne lung tissue volume, ml/kg</strong></td>
<td>7.2 ± 2.8</td>
<td>7.9 ± 2.6</td>
</tr>
</tbody>
</table>

Values are means ± SD. At 4-mo and 12-mo exposure, data from HA and IA groups were measured at 1,250-m altitude, and data from SL group were measured at 150-m altitude. DLCO, lung diffusing capacity for carbon monoxide; DLCO-standardized, DLCO standardized to alveolar O$_2$ tension (PAO$_2$) of 120 Torr and hematocrit of 0.45; DMCO-standardized, membrane diffusing capacity for carbon monoxide; Vc, pulmonary capillary blood volume. *P < 0.05 vs. IA, and †P < 0.05 vs. SL by factorial ANOVA.
observed in HA-raised guinea pigs was not explained by their higher hematocrit.

Intra- and interanimal variability in resting O₂ uptake, ventilation, and pulmonary blood flow is expected to be greater in conscious unsedated animals than in anesthetized animals. Blake and Banchero (1), using a metabolic chamber to measure O₂ uptake and minute ventilation in unsedated guinea pigs at 1,610-m altitude, reported an O₂ uptake of $13 \text{ ml min}^{-1} \text{ kg}^{-1}$ (range 8–16 ml min$^{-1}$ kg$^{-1}$) and average ventilation $\sim 450 \text{ ml min}^{-1} \text{ kg}^{-1}$ in animals weighing $\sim 1 \text{ kg}$; these values agree with our results in animals raised at IA (1,250 m). In anesthetized animals, O₂ uptake decreased 25–63% and ventilation decreased 45% (1). The range of pulmonary blood flows in the present guinea pigs (133–203 ml min$^{-1}$ kg$^{-1}$) agree with that previously reported by us (135–202 ml min$^{-1}$ kg$^{-1}$) in conscious unsedated guinea pigs but are lower than that reported in unanesthetized chronically catheterized guinea pigs: 273 ml min$^{-1}$ kg$^{-1}$ (18) and 250–350 ml min$^{-1}$ kg$^{-1}$ (17), and also lower than that measured in catheterized awake rats at rest (304 ml min$^{-1}$ kg$^{-1}$) (7). The noninvasive nature of the rebreathing method and the lack of indwelling catheters may account for the lower pulmonary blood flow in the present study. Regardless of body size difference or variability in the resting state, clear and consistent relationships emerged when diffusing capacity and its components were interpreted with respect to the simultaneously measured pulmonary blood flow.

The animals residing at HA were brought to IA, 1 day before making all measurements at the same location. This approach facilitated intergroup comparison of the results by 1) obviating the need to adjust for different barometric pressures, 2) avoiding any question about the effect of hypobaria per se on lung volume and diffusing capacity, and 3) avoiding the problems associated with transporting sensitive equipment up and down the mountain. During the transient period in which the HA animals stayed at IA, compartmental fluid volumes, pulmonary

Fig. 2. Relationships between minute ventilation and O₂ uptake were not different among HA, IA, or SL exposure groups at 4 mo (left) or 12 mo (right).

Fig. 3. Diffusing capacity for carbon monoxide (DLCO) measured at 2 alveolar O₂ tensions while rebreathing a gas mixture containing 40% or 98% O₂ is plotted with respect to pulmonary blood flow after 4 and 12 mo of exposure. *$P < 0.05$ vs. SL, §$P < 0.05$ vs. IA by comparison of regression lines using the method of Zar (23).
blood flow, and hematocrit may have changed, but these parameters were measured simultaneously and taken into account in data interpretation. Therefore, the intergroup differences reported in here represent a conservative estimate of altitude-related adaptation. Differences in diffusing capacity caused by structural adaptation would not be altered by transient exposure to IA.

The present studies confirm our observation in a previous cohort (9) that after ~6 mo of exposure, body weight of the guinea pigs raised at 3,800-m HA were ~11% larger than that in their IA counterparts. Since there was no significant difference in the weight or dimension of long bones after 6 mo of HA residence (9), we attributed the larger body weight to a higher fat content perhaps due to relative inactivity of HA-raised animals. There remains a possibility that HA residence prolonged the duration of somatic maturation by delaying the time course of epiphyseal union. In a subsequent separate study where the activity level in HA and IA groups was standardized by regular treadmill exercise, the difference in body weight was eliminated (unpublished observations). Our conclusions in the present study are unchanged regardless of whether the data were normalized for body weight.

Structure-function correlation. Table 3 shows the relative changes in lung function indices assessed by the rebreathing technique in guinea pigs after 4 and 12 mo of exposure to 3,800 m compared with that assessed postmortem by morphometric techniques in a separate cohort of weanling Hartley guinea pigs raised at 3,800 m for 6 mo, expressed relative to their respective IA controls raised at 1,250 m (9). Both techniques demonstrate significant HA-enhanced lung volume as well as diffusing capacity of the lung and membrane while pulmonary capillary blood volume was unchanged. The major structural adaptation we observed in HA-raised guinea pigs includes a ~10% increase in alveolar-capillary surface areas and a ~28% reduction in mean harmonic thickness of the blood-gas barrier; these changes reduced the barrier resistance to oxygen uptake estimated using a morphometric model (9). The increase in gas exchange surface area likely reflects a combination of alveolar-capillary recruitment and generation of new surfaces. The reduction in mean harmonic thickness of the blood-gas barrier
likely reflects redistribution of alveolar septal constituents; the mechanisms of redistribution remain to be defined. These morphometric and physiological data in guinea pigs demonstrate the structure-function correspondence of alveolar gas exchange similar to the correspondence previously reported in young beagles raised to maturity at 3,100 m (11). The physiological-morphometric correspondence supports the use of morphometric indexes to estimate diffusing capacity and to infer functional adaptation in guinea pigs.

There was an altitude-dependent decrease in body mass-specific acetylene lung tissue volume measured at 12 mo but not 4 mo. This parameter measures the volume of gas exchange sepal tissue and capillary blood that instantaneously comes into contact with the inspired bolus and is therefore sensitive to changes in pulmonary blood flow. Its reduction parallels an altitude-dependent decrease in pulmonary blood flow, as well as an unchanged Vc at rest in HA animals relative to IA control animals. Compared with previously published morphometric data, alveolar septal tissue and capillary blood volumes showed an initial increase in guinea pigs raised for 3 mo at HA compared with IA controls, but differences diminished by 6 mo of exposure (9). Therefore, physiological and morphometric results in guinea pigs were consistent in showing no long-term elevation of alveolar capillary blood volumes after residing at HA for 6 mo or longer.

Interspecies comparison. Table 3 also shows a comparison of the relative changes in lung function in response to HA residence in different species. In young beagle dogs raised to maturity at 3,100 m, lung volume measured by helium dilution during rebreathing or by thoracic CT scan was ~16% higher than in control animals raised at SL (11). In young foxhounds raised at 3,800 m for only 5 mo and then returned to SL, lung volume was 5–12% higher measured at rest and ~23% higher measured during exercise compared with control animals raised at SL (13). In human natives of moderate HA, lung volume was ~14% higher than in lowlanders (3). The increase in lung volume observed in guinea pigs, 10 to 21% depending on the duration of HA residence, is comparable to that in other species. The increases in DLCO and DMCO at a given pulmonary blood flow in our HA-raised guinea pigs ranged from 15 to 35%, at 4 and 12 mo of exposure, comparable to the increases observed in native highlanders and in beagles and foxhounds born at SL and raised at HA during somatic maturation. Vc either did not increase or increased variably in HA-raised guinea pigs and HA natives, respectively, but is 34–47% higher in HA-raised dogs compared with SL controls. Resting acetylene tissue volume was unchanged or decreased in guinea pigs raised at HA but increased in dogs raised at HA (10, 11, 13). Thus, while different species demonstrate largely consistent patterns of enhanced lung function following chronic residence at moderate HA, there are distinct interspecies differences as well. We suspect that the differences in resting Vc and acetylene tissue volume reflect dynamic factors, e.g., sensitivity of Vc and tissue volume to pulmonary blood flow, and regulatory differences in alveolar microvascular tone between species. The HA-raised guinea pigs were only transiently exposed to IA and their resting pulmonary blood flow was below control levels. The dog studies were conducted after HA-raised animals had returned to SL for several weeks and resting pulmonary blood flow was either normal or above control levels (10, 11, 13). Recent morphometric results from our laboratory in dogs raised for 5 mo at HA also showed no long-term increase in Vc or septal tissue volume above that in SL control animals (unpublished data), in agreement with morphometric data from guinea pigs.

The decline in resting pulmonary blood flow in our guinea pigs raised at HA is likely caused by elevated pulmonary vascular resistance, consistent with observations in human subjects acclimatized to HA (5, 20). Right heart preload may also have been reduced because of compartmental fluid shifts. A higher arterial oxygen content due to a higher hemoglobin concentration helps maintain oxygen delivery at any given workload at HA. Because of the reduction in pulmonary blood flow and because diffusing capacity varies directly with blood flow, HA-induced changes in DLCO and DMCO were not apparent (as shown in Table 2) unless they were compared with respect to the simultaneously measured pulmonary blood flow (as shown in Figs. 3 and 4). These data highlight the importance of considering diffusion-perfusion interactions when interpreting alveolar gas exchange parameters.

In summary, we employed a rebreathing technique in conscious unsedated guinea pigs and showed that chronic residence at 3,800-m HA during somatic maturation significantly enhanced resting lung function, evidenced by higher lung volumes as well as higher DLCO and DMCO at a given pulmonary blood flow; enhancement was evident after 4 mo of exposure and persisted with longer exposure up to 12 mo. Because resting pulmonary blood flow declined simulta-
neously during HA residence, the increased $Dl_{CO}$ and $DM_{CO}$ was obscured unless interpreted with respect to blood flow. The pattern of HA-induced adaptation in guinea pigs is largely similar to that in large animals with the exception of $Vc$ and acetylene septal tissue volume; species-specific responses in these parameters may also be explained by differences in pulmonary perfusion. These results emphasize the need to consider perfusion factors when interpreting physiological measurements of diffusing capacity and its components. In addition, these results demonstrate the correspondence between physiological and structural adaptation in the determinants of alveolar $O_2$ transport during chronic HA residence.

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