Acute response of the lung mechanics of the rabbit to hypoxia

H. SAKAI, M. FUKUI, Y. NAKANO, K. ENDO, T. HIRAI, Y. OKU, AND M. MISHIMA
Departments of 1Experimental Pathology and 4Medical Systems Control, Institute for Frontier Medical Sciences, and 3Department of Physical Therapeutics, Kyoto University Hospital, Kyoto University, Kyoto 606-8397; 2Shiga Medical Center for Adults, Shiga 524-0022, Japan; and 5Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada H2X 2P2

Acute response of the lung mechanics of the rabbit to hypoxia. J. Appl. Physiol. 86(1): 306–312, 1999.—We measured the change in total lung resistance (R L) and that in total lung elastance (E L) induced by hypoxia (n = 7) and compared the results with those by intravenous injection of histamine bolus (n = 5) at three different positive end-expiratory pressure (PEEP) levels (2, 5, and 8 hPa) in open-chest and vagotomized rabbits. The percent increase ratio of R L (PIRx) and E L (PIEx) was defined as the change in R L and E L induced by hypoxia compared with that in the normoxic condition, expressed as a percentage. PIR values for the change in R L and E L induced by bolus injection of histamine were also calculated. The PIRx and PIER induced by hypoxia and by histamine were positive by a statistically significant amount at every PEEP level, except for the PIRx value at 8-hPa PEEP in the hypoxic challenge. The PIRx-to-PIEx ratio values in the hypoxic challenge at 2-hPa PEEP were significantly larger than those in the histamine challenge (hypoxia: 0.91 ± 0.23%; histamine: 0.37 ± 0.065%, P < 0.05). The increase in E L induced by histamine in the acute phase has been reported to be mainly derived from tissue distortion secondary to bronchial constriction. Thus our results suggest that a part of the increase in E L by hypoxia was originated in different parenchymal responses from histamine and imply that this hypoxic response of lung parenchyma is sensitive to the increase in parenchymal tethering at high PEEP levels.

liver resistance; liver elastance; histamine

PREVIOUS STUDIES on the mechanical change that occurs in the lungs on exposure to hypoxic conditions have focused mainly on the response of the airway in terms of total lung resistance (R L). Dewachter et al. (5) reported that hypoxia causes bronchoconstriction in the rabbit. However, Wetzel et al. (24) reported that hypoxia causes bronchodilation in the pig. Previous studies have also reported contradictory results of the change in R L in response to hypoxia: Goldstein et al. (10) reported that R L increases, Loofbourrow et al. (15) reported that R L decreases, and Saunders et al. (21) reported that R L remains the same. These contradictory results may have been obtained because of the considerable variability among different species and because different experimental preparations were used. Most of the animal studies on hypoxia have been done under closed-chest, nonvagotomized conditions (4, 5, 10, 23, 24). However, Hantos et al. (11) reported that chest wall resistance makes up a substantial component of R L in the rat. Iscoe and Fisher (12) reported that vagal efferent activity contributes to the bronchial smooth muscle tone by 50%.

On the other hand, there have been few reports showing whether hypoxia alters total lung elastance (E L). It is known that hypoxia causes pulmonary parenchymal strips to contract (1, 8). Lung parenchyma contains some contractile cells bearing prominent bundles of actin filaments, such as contractile interstitial cells (CIC), as well as pericytes and myocytes around small vessels and airways. Among them, CIC have been a candidate for the hypoxia-evoked contraction of lung parenchyma (13). Indeed, Fukui et al. (9) showed that CIC isolated from bovine lung contract under hypoxic conditions in vitro. Because the large, elongated CIC in vivo are interposed between the two adjacent alveolar epithelia and their cytoplasmic processes are widely extended into the space between the alveolar epithelium and capillary endothelium (8, 13), the hypoxic contraction of CIC would increase the elastic recoil of the alveolar wall (1, 9).

Our hypothesis is that hypoxia induces the stiffness of the lung tissue through a mechanism involving parenchymal contractile elements, which is different from the secondary tissue distortion caused by airway constriction. To test this hypothesis, we performed experiments on two groups of open-chest, paralyzed, vagotomized rabbits. In the first group of rabbits, we measured the R L and E L values in the normoxic and hypoxic conditions at three different positive end-expiratory pressure (PEEP) levels over time. In the second group of rabbits, we measured the R L and E L before and after an intravenous injection of histamine. The administration of histamine induced a change in E L, which has been reported to be mainly derived from lung tissue distortion secondary to airway constriction (2, 20). In the present study, we compared the changes in R L and E L induced by hypoxia and the respective changes in R L and E L induced by histamine. We also compared the changes in R L and E L between the two groups. With these results, we attempted to assess the contribution of parenchymal contraction to the mechanical change that occurs in the lung under acute hypoxic conditions.

METHODS

Animal preparation. This study was performed in 12 adult Japanese White rabbits that weighed between 2.5 and 3.5 kg
(4 male, 8 female). Seven rabbits were placed in the hypoxia trial group, and five rabbits were placed in the histamine trial group. In each rabbit, a catheter was inserted into a marginal vein of the ear for drug injection. Each rabbit was anesthetized with an initial intravenous injection of 30–50 mg/kg of pentobarbital sodium. Thereafter, a dose of 15–20 mg/kg was administered hourly to maintain anesthesia. The rabbits were tracheostomized, and a cannula (4-mm ID) was inserted. The rabbits were paralyzed with the administration of 1 mg of pancuronium bromide every hour. They were mechanically ventilated with a tidal volume of 5 ml/kg at a frequency of 40 breaths/min. A 5.0-hPa baseline level of PEEP was applied. A catheter was inserted into the left femoral artery to monitor arterial blood gas. Another catheter was inserted into the right jugular vein for the administration of histamine. A midline sternotomy was performed to open the chest wall; a bilateral surgical vagotomy was then performed. The rectal temperature was maintained at 38–39°C with an electric blanket.

Equipment. Tracheal pressure (Ptr) was measured by using a piezoresistive microtransducer (Fujikura FPM-05PG, ServoFlo, Lexington, MA), which was placed in the lateral port of the tracheal cannula. Tracheal flow (V) was measured with a pneumotachograph (TV-241T, Fleisch No. 00; Nihon-Kohden, Kyoto, Japan) and a differential pressure transducer (PX170–14DV, OMEGA). The pneumotachograph was placed between the tracheal cannula and the mechanical ventilator (Harvard Apparatus, South Natick, MA). Before the experiments were performed, normoxic gas (25% O2 in N2) was used to calibrate all of the transducers. The normoxic gas and hypoxic gas (10% O2 in N2) were produced by a gas mixer (DNT 350, MERA, Calgary, Alberta) by using pure O2 and N2. All data were amplified, low-pass filtered (20 Hz), and stored on a 486-based personal computer through a 12-bit analog-to-digital converter (DT2801-A, Data Translation, Marlborough, MA), at a sampling rate of 100 Hz. The LABDAT data-acquisition software package (RHT-Infodat, Montreal, Quebec) was used to control the analog-to-digital conversion.

Measurement protocol. To create a constant volume history, each trial was initiated with inflation of the lungs to a Ptr of 30 hPa three times. The rabbits that were in the hypoxia trial group were mechanically ventilated, first with normoxic gas for 5 min, followed by hypoxic gas for 8 min, and then normoxic gas again for 5 min at PEEP levels of 2, 5, and 8 hPa; the order of the three different PEEP levels was randomly arranged for each rabbit, with an interval of 10 min in between.

In each rabbit, arterial blood-gas analyses were performed three times during the experiment. The first analysis was done 5 min before impedance measurements were begun. From the results of this blood-gas analysis, sodium bicarbonate was administered to the rabbit if necessary, so that the HCO3− level was within the normal range (23–27 mM) in each rabbit. The second arterial blood-gas analysis was performed 2 min after the start of measurement of impedance in the normoxic condition (i.e., at the 2-min measurement point within the total 18-min ventilation period). The third analysis was performed 2 min after the switch to the hypoxic condition. The results from the second arterial blood-gas analysis were used as the values for the normoxic condition; the results from the third analysis were used as the values for the hypoxic condition.

The rabbits in the histamine trial group were ventilated for 5 min with normoxic gas. They were then injected with a bolus of 0.001 mg/kg histamine in 1 ml of saline through the catheter in the right jugular vein. Continuous histamine infusion caused irreversible lung damage, which made repeated measurements at different PEEP levels impossible; therefore, it was administered once as a bolus. The histamine dose to be administered was determined so that it caused a change in Rl equivalent to that caused by hypoxia at 2-hPa PEEP. To prevent tachyphylaxis to histamine, an indomethacin (5 mg/kg iv) mixture was administered 20 min before the experiment was begun; this was followed by supplemental intravenous doses of 2 mg/kg every hour. This mixture contained indomethacin dissolved in saline and 0.05 g/ml of sodium bicarbonate. All measurements in the histamine trial group were made at PEEP levels of 2, 5, and 8 hPa, the order of which was randomly arranged with an interval of 10 min between trials.

Data analysis. Each breathing cycle was defined as the interval between successive peaks of the integrated V. The Rl and El values for each breathing cycle were estimated by multiple linear regression. The following equation was fitted to the measurement of Ptr

$$\text{Ptr}(t) = R_l \cdot V(t) + E_l \cdot V(t) + K$$

where t is time, V is volume, and K is a constant.

The Vi was obtained by numerical integration of the adjusted value of V after offset adjustment to remove any drift in V that might otherwise have occurred. K is a constant that depends on the specific PEEP level; it includes both the applied PEEP and any intrinsic PEEP.

An acrylic tube, which connects the pneumotachograph to the trachea, had an internal diameter of 0.4 cm and a length of 15 cm. The theoretical resistance of the tracheal tube, based on the assumption of a laminar flow, was calculated to be 7.86 hPa·s·l⁻¹, whereas the measured value was 7.96 hPa·s·l⁻¹. Therefore, in the data analysis, each calculated value of Rl was reduced by 7.96 hPa·s·l⁻¹.

Elimination of the trend in the Rl and El values obtained from rabbits in the hypoxia trial group. When the Rl and El values over the 18-min time course of the experiment in the hypoxia trial group were graphed, a small, positive trend in Rl and El was noted (Fig. 1). This small, positive trend is presumably due to microatelectasis. The trend values of Rl and El were calculated by linear regression of the respective Rl and El values during 1 min of normoxia.

Fig. 1. Values of total lung resistance (Rl) and elastance (El) of a representative case in hypoxia trial group. Rabbit was exposed to normoxic gas for first 5 min, then to hypoxic gas for next 8 min, then to normoxic gas again for 5 min.
Assessment of hypoxia- and histamine-evoked change.

To assess the mechanical change in the lung that had occurred because of hypoxia, we developed the following equations, which indicate how much the RL and EL in the lungs of the rabbits changed in response to hypoxia or in response to histamine

\[
\text{PIRR} = \frac{100 \times (\text{MHR} - \text{MNR})}{\text{MNR}}
\]

where PIRR is the percent increase ratio of RL; for the hypoxia trial group, MNR is the average value of RL during 1 min of the normoxic condition (between the 4- and 5-min measurement points) of each rabbit; and MHR is the average value of RL during 1 min of the hypoxic condition (between the 6- and 7-min measurement points).

A PIR for EL (PIRE) was also calculated the same as for RL, by using the following equation

\[
\text{PIRE} = \frac{100 \times (\text{MHE} - \text{MNE})}{\text{MNE}}
\]

where MNE is the average value of EL during 1 min of the normoxic condition (between the 4- and 5-min measurement points) of each rabbit, and MHE is the average value of EL during 1 min of the hypoxic condition.

Figure 3 illustrates the time course of RL and EL in a representative case of the histamine trial group. We also calculated PIRR and PIRe for the rabbits in the histamine trial group to assess the mechanical change of the lung induced by histamine. MNR and MHE were assigned to be the average value of RL and EL, respectively, during the 15-s interval before histamine injection. MHR and MHE were assigned to be the peak value of RL and EL after histamine injection (normoxic). Peak value in EL and RL occurred ~15 s after histamine was injected.

Correction of the difference in viscosity between the normoxic and hypoxic gases. As previously mentioned, all transducers were calibrated with normoxic gas before the experiment. Because the viscosity of the hypoxic gas is less than that of the normoxic gas, the differential pressure at the pneumotachometer would consistently be lower in the hypoxic condition. This situation leads to underestimation of the V̇ in all of the measurements made under the hypoxic condition. A test lung was used to study this effect on the RL and EL values. The test lung was made of an acryl tube with a rubber balloon, and it had RL and EL values that were similar to those in the rabbits. As can be seen in Fig. 4, the measured EL increased in the hypoxic condition; this increase is apparently due to underestimation of the V̇ by the pneumotachometer. The PIRR and PIRe values of the test lung, were 0.031 ± 0.02 (SE) and 2.02 ± 0.02%, respectively (n = 6 trials).
The PIR value in the hypoxic condition with the use of the test lung is near the theoretical PIR value calculated, assuming the flow through the acryl tube is laminar (see APPENDIX for detailed calculation). In contrast, the RL value with the use of the test lung remained constant through both the normoxic and hypoxic conditions. The reason that RL remains constant is that, although the amount of V is underestimated in the hypoxic condition, airway resistance (i.e., the differential pressure) also decreases in the hypoxic condition.

In the hypoxic condition, whether the PIR value and that of PIR were positive or negative was evaluated by comparing MNE with MHE. In the calculation of PIR, the value of MNE was substituted with MNE ·(1 - 0.0202), and the following equation was used to calculate PIR:

\[
\text{PIR} = 100 \times \frac{(M_{\text{NE}} - 0.0202) - M_{\text{NE}}}{M_{\text{NE}}} \quad (4)
\]

Statistical analysis. Friedman's nonparametric two-way ANOVA was used to test whether the difference between the EL and RL values at the three PEEP levels was significant. If a significant difference for a group of EL or RL values was found by ANOVA, then the statistical difference between each pair of values in that group was tested by using Wilcoxon's signed-rank statistic. The Mann-Whitney U statistic was used to test whether the difference between a histamine trial group parameter and the respective parameter in the hypoxia trial group was significant. A P value < 0.05 was considered to be statistically significant. StatView (Abacus Concepts, Berkeley, CA) software was used for all of the statistical analyses. All data are expressed as means ± SE.

RESULTS

RL and EL baseline values in the hypoxia and histamine trial groups in the normoxic condition. In the normoxic condition, the RL and EL values increased as the PEEP was increased in the rabbits of both the hypoxia and histamine trial groups (see Table 1). These results were compatible with previous reports (3, 14). However, there was no statistical difference between the RL or EL baseline value at a particular PEEP level of the hypoxia trial group and the respective baseline value of RL or EL of the histamine trial group at each PEEP level.

Arterial blood-gas parameters. The results of arterial blood-gas analyses and acid-base parameters of arterial blood in the normoxic and hypoxic conditions are given in Table 2. The arterial PO2 in the hypoxic condition was significantly lower than the respective value in the normoxic condition at all PEEP levels. The arterial PCO2 (PaCO2) at 2-hPa PEEP in the hypoxic condition was significantly lower than that in the normoxic condition. In the normoxic condition, the PaCO2 at 2 hPa was higher than that at 5 hPa. The pH values at 2- and 5-hPa PEEP in the hypoxic condition were significantly higher than the respective values in the normoxic condition. However, there were no differences in any of the HCO3 levels among any of the PEEP levels nor between hypoxia and normoxia within a given PEEP level.

Hypoxia trial. No statistical difference existed among the trend values in each of the seven rabbits. A graph of the PIR values at each PEEP level in the hypoxic trial group is shown in Fig. 5. The PIR values at all PEEP levels were statistically positive. However, the differences between pairs of PIR values at the three PEEP levels were not statistically significant. The PIR values were 7.57 ± 1.78, 5.70 ± 1.04, and 7.22 ± 1.78% at 2-, 5-, and 8-hPa PEEP, respectively.

The PIR values were statistically positive at 2- and 5-hPa PEEP. However, there was no significant change in EL at 8-hPa PEEP. The PIR values were 8.07 ± 4.22 (P < 0.05, compared with the PIR value at 8 hPa), 3.14 ± 1.44, and 1.73 ± 0.78% at 2-, 5-, and 8-hPa PEEP, respectively.

Histamine trial. The PIR values at each PEEP level in the histamine trial group are shown in Fig. 6. At 2-, 5-, and 8-hPa PEEP, the values of PIR were statistically positive. However, a statistically significant difference between pairs of PIR values did not exist. The PIR values were 12.95 ± 2.47, 12.97 ± 3.48, and 14.36 ± 1.62% at 2-, 5-, and 8-hPa PEEP, respectively.

In the histamine trial group, the PIR values of all three PEEP levels were statistically positive. However, a statistically significant difference was not found.

Table 1. Baseline values of RL and EL in the hypoxia trial group and in the histamine trial group

<table>
<thead>
<tr>
<th>PEEP, hPa</th>
<th>Hypoxia Trial</th>
<th>Histamine Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>RL, hPa·s·l⁻¹</td>
<td>EL, hPa</td>
<td>RL, hPa·s·l⁻¹</td>
</tr>
<tr>
<td>2</td>
<td>9.14 ± 0.85*</td>
<td>156.46 ± 6.25*</td>
</tr>
<tr>
<td>5</td>
<td>11.81 ± 1.22</td>
<td>239.13 ± 18.26</td>
</tr>
<tr>
<td>8</td>
<td>16.01 ± 1.47*</td>
<td>518.56 ± 45.47*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 rabbits. Hypoxia trial. Histamine trial. * P < 0.05 compared with respective hypoxic value (Wilcoxon's signed-rank test).

Table 2. Arterial blood-gas sampling data in the hypoxic trial group

<table>
<thead>
<tr>
<th>PEEP, hPa</th>
<th>Normoxia</th>
<th>Hypoxia</th>
<th>Normoxia</th>
<th>Hypoxia</th>
<th>Normoxia</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.26 ± 0.024</td>
<td>7.30 ± 0.026*</td>
<td>7.25 ± 0.025</td>
<td>7.30 ± 0.031*</td>
<td>7.29 ± 0.014</td>
<td>7.32 ± 0.013</td>
</tr>
<tr>
<td>PaCO₂, Torr</td>
<td>55.2 ± 4.1†</td>
<td>45.3 ± 3.1*</td>
<td>49.0 ± 3.2</td>
<td>47.0 ± 3.4</td>
<td>48.6 ± 1.7</td>
<td>43.4 ± 2.5</td>
</tr>
<tr>
<td>PaO₂, Torr</td>
<td>102.2 ± 4.9</td>
<td>35.2 ± 1.7*</td>
<td>113.8 ± 8.9</td>
<td>38.7 ± 2.1*</td>
<td>102.9 ± 11.8</td>
<td>38.5 ± 2.5*</td>
</tr>
<tr>
<td>HCO₃-, mM/l</td>
<td>23.6 ± 1.6</td>
<td>21.7 ± 0.6</td>
<td>20.7 ± 0.5</td>
<td>23.0 ± 2.0</td>
<td>22.9 ± 0.65</td>
<td>21.9 ± 0.89</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 rabbits. PaCO₂, arterial PO₂; PaCO₂, arterial PCO₂. * P < 0.05 compared with respective normoxic value (Wilcoxon's signed-rank test); † P < 0.05 compared with respective value at 5-hPa PEEP (Wilcoxon's signed-rank test).
among the PIRE values at the three PEEP levels. The PIRE values were 4.30 ± 0.50, 4.78 ± 0.85, and 3.49 ± 0.85% at 2-, 5-, and 8-hPa PEEP, respectively.

Fig. 5. Percent increase ratio (PIR) of RL (PIRRL) and EL (PIREL) at different positive end-expiratory pressure (PEEP) levels in hypoxia trial group. PIRRL and PIREL values were calculated for each of the 7 rabbits in hypoxia trial group. Graph shows average PIRRL and average PIREL at 2-, 5-, and 8-hPa PEEP. Values are means ± SE. *Hypoxic condition value is significantly different from respective normoxic condition value, P < 0.05 (Wilcoxon’s signed-rank test).

Values of the PIRE-to-PIRR ratio. The ratios of PIRE to PIRR (PIRE/PIRR) for each rabbit in the hypoxia trial group and each rabbit in the histamine trial group were calculated.

As can be seen in Fig. 7, in the hypoxia trial group, as the PEEP was increased, the PIRE/PIRR values decreased. The PIRE/PIRR values in the hypoxia trial group were 0.91 ± 0.23 (P < 0.05, compared with the respective values at 5 and 8 hPa), 0.52 ± 0.23, and 0.23 ± 0.11 at 2-, 5-, and 8-hPa PEEP, respectively.

However, in the histamine trial group, the PIRE/PIRR values at the three PEEP levels did not differ significantly. The PIRE/PIRR values in the histamine trial group were 0.37 ± 0.065, 0.42 ± 0.062, and 0.21 ± 0.052 at 2-, 5-, and 8-hPa PEEP, respectively. The PIRE/PIRR value at 2-hPa PEEP in the hypoxia trial group was significantly larger than the respective value in the histaminetrial group (0.91 ± 0.23 vs. 0.37 ± 0.065; P < 0.05).

**DISCUSSION**

The first finding in the present study is that, at 2-hPa PEEP, the PIRE/PIRR values of the rabbits in the hypoxic trial group were significantly higher than those of the rabbits that received a histamine injection (Fig. 7). The increase in EL induced by histamine injection is assumed to be derived mainly from tissue distortion secondary to bronchial constriction (2, 20). Thus our results suggest that the increase in EL on exposure to hypoxic conditions at low PEEP includes a second tissue response, such as the contraction of CIC, that is independent of the response involving tissue distortion secondary to bronchial constriction. The second finding is that, as the PEEP was increased in the hypoxia trial group rabbits, the PIRE/PIRR value, as well as the PIRE value, decreased (Figs. 5 and 7). This implies that the parenchymal tethering may become increasingly important in the response of the lung tissue to hypoxia at higher PEEP levels.

In previous reports, evaluation of the change in EL because of hypoxia has not been performed properly because the difference in the viscosity of normoxic gas and that of hypoxic gas has not been taken into account. In the present study, the influence from the difference in viscosity between the normoxic and hypoxic gases was corrected after the RL and EL values were measured. The correction values were set to be 0 and 2.02%, respectively, according to the results from the test lung. However, RL of the lung itself also contains lung tissue resistance (RTL), which is closely coupled with EL (7) and airway resistance. If the hysteresivity is assumed to be 0.1 under normoxic conditions, we calculated that
the contribution of \( R_{ti,L} \) to the value of \( R_L \) would be 30% at 2-hPa PEEP (7). At higher PEEP or in hypoxic conditions, the contribution of \( R_{ti,L} \) to \( R_L \) may be greater. Therefore, the practical correction value of \( R_L \) would be between 0 and 2.02, and the actual value of \( P_{IR_R} \) may be smaller. However, the \( P_{IR_E}/P_{IR_R} \) value would be larger, and our results should be the same even if we correct the value of \( R_L \) for \( R_{ti,L} \).

Another option for removing the influence of the difference in viscosity between the normoxic and hypoxic gases from the results of \( R_L \) and \( E_L \) is to use different calibration factors in each condition. This may lead to a direct estimation of \( E_L \). However, the values of \( R_L \) in the hypoxic condition would be smaller, whereas the values of \( R_L \) in the normoxic condition would be as measured, even if the size of the airway caliber is kept constant. In such case, the \( P_{IR_E}/P_{IR_R} \) value would be larger, and our results should again be the same even if different calibration factors are used.

The \( P_{ACO_2} \) at 2-hPa PEEP under hypoxic conditions was significantly smaller than the respective value under normoxic conditions. It has been reported that hypercapnia enhances the response of the lung to hypoxia (5, 12, 18). Therefore, the increase in \( R_L \) and \( E_L \) that we obtained at 2-hPa PEEP in the hypoxic trial group may be underestimated.

Continuous infusion of histamine showed a reversible change in the values of \( R_L \) and \( E_L \), probably due to lung damage. This made repeated measurements at different PEEP levels impossible. For this reason, histamine was administered in a bolus. However, preliminary measurements of continuous infusion of histamine (0.00033 mg·kg\(^{-1}\)·min\(^{-1}\)) at 2-hPa PEEP \((n = 2)\) were made. The \( P_{IR_E} \), \( P_{IR_R} \), and \( P_{IR_E}/P_{IR_R} \) values obtained from the continuous infusion of histamine and the respective values obtained when a bolus of histamine was administered were similar.

The \( P_{IR_E}/P_{IR_R} \) value at 2-hPa PEEP in the histamine study was \( \sim 0.3 \). This value is similar to the previously reported value (2). However, it has also been reported that a negative PEEP dependency exists in both \( P_{IR_R} \) and \( P_{IR_E} \) (2, 17); this differs from our results. The tracheal caliber size and the rabbit lung size are much smaller than those in the canine. The relationship between the response of the canine lung to histamine and the PEEP level may be different from that in the rabbit; there may be species differences that may have an influence on the outcomes of the various studies addressing \( R_L \) and \( E_L \). The very small dose of histamine used in our study may be another explanation. The histamine dose in our study was very small compared with that administered in a previous histamine challenge used in canines (2, 14). The \( P_{IR} \) value in canines from the previous histamine challenge is over ten times larger than that obtained in the present study. Balassy et al. (2) suggested that the negative PEEP dependency of the increased \( R_L \) seen at the histamine injection is due to an increase in the degree of parenchymal tethering, which supports the airway caliber. However, this mechanism may not be applied in the case of the low-dose histamine, especially at the high PEEP level.

In our study, there was actually a lack of PEEP dependency on the \( P_{IR_E} \) values in the histamine challenge, because the response of \( E_L \) to histamine was mainly secondary to changes in \( R_L \), and there was a lack of PEEP dependency on the \( P_{IR_R} \) values. On the other hand, the negative PEEP dependency of \( P_{IR_E} \) was shown in our hypoxic trials despite the fact that there was a lack of PEEP dependency on the \( P_{IR_R} \) values. Therefore, these results suggest the existence of a lung parenchymal response to hypoxia that is much more sensitive to the PEEP level and that is independent of airway constriction.

Kapanci et al. (13) found that alveolar interstitial cells, which occupy 42% of the total interstitial volume of the alveolar wall, possess contractile properties and named them CIC. Fukui et al. (9) purified and cultured CIC from the bovine lung and reported that isolated CIC contract when exposed to hypoxic conditions. Because CIC in the lung are closely associated with the adjacent capillaries, hypoxia-induced contraction of CIC would reduce the patency of the adjacent capillary lumen and increase the vascular resistance at the alveolar capillary level. Additionally, the cell body and the long cytoplasmic processes of CIC are also in close contact with the epithelia of two adjacent alveoli and collagen fibers in the alveolar interstitium (8, 13). Thus the contraction of CIC could induce a change in the elastic recoil of the alveolar wall. Furthermore, it may be expected that the mechanical properties of CIC could be largely influenced by the PEEP level. It remains to be explored whether other contractile cells such as pericytes and myocytes around small pulmonary vessels and airways are also involved in the hypoxia-induced changes in \( E_L \).

The limitation of our study is that we assumed that contraction of CIC under hypoxic conditions would increase \( E_L \) because of their location and mechanical properties. We could speculate that CIC located in the parenchyma are influenced by the degree of parenchymal tethering induced by the PEEP and could make the parenchyma stiff under hypoxic conditions. This assumption is supported by a histological study that demonstrated an increase in the depth of alveolar wall pleats in lung tissue exposed to hypoxia, suggesting hypoxia-induced contraction of the alveolar structure (16). However, further investigation of these phenomena is needed with electron micrographs and histochemical analyses.

The role that contractile elements play in the response of the entire lung to hypoxia was unclear. Our finding that the mechanical change of the lung due to hypoxia includes a contractile mechanism of the lung tissue, which is independent of the tissue distortion caused by airway constriction, has an important physiological implication. In view of the dynamic gas distribution, it has been suggested that the alveolar \( O_2 \) tension on the surface of an acinus varies, because anatomic asymmetry of the acinus gives rise to the variable convective and diffusive gas transport on its surface (6). The response of the lung tissue to hypoxia may enable fine regulation of the ventilation-to-
perfusion ratio under the variable O2 tension on the surface of each alveolus.

APPENDIX

The pressure difference (Pd) during laminar flow is expressed by the following equation: 

$$Pd = 8 \cdot \mu \cdot L \cdot \pi^{-1} \cdot r^{-4} \cdot V^{-1},$$

where \( \mu \) is the viscosity of the gas, \( L \) is the length of the tube, and \( r \) is the radius of the tube. In our experiment, we assigned normoxic gas to be 25% O2 in N2 and hypoxic gas to be 10% O2 in N2. Assuming that the temperature is 37°C and atmospheric pressure is 1,013 hPa, the viscosity of the gas (\( \mu \)) under the normoxic and hypoxic conditions is 1.82 and 1.78 N·s·m⁻², respectively. According to the above-mentioned definition and data, the theoretical value of PIR in the hypoxic condition under laminar flow was calculated to be 2.01 with the use of the following equation

Theoretical PIR

$$= 100 \times \frac{Pd(25\%O_2) - Pd(10\%O_2)}{Pd(10\%O_2)}$$

The authors thank Drs. K. Kuno, M. Ohi, K. Chin, and S. Muro of Kyoto University for continued encouragement and suggestions during this investigation. We are indebted to Dr. Chang-Wen Chen of National Cheng Kung University for suggestions and technical support for our experiments.

Address for reprint requests: H. Sakai, Dept. of Experimental Pathology, Institute for Frontier Medical Sciences, Kyoto Univ., 53 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606–8397, Japan (E-mail: sakai@frontier.kyoto-u.ac.jp).

Received 1 J une 1998; accepted in final form 18 September 1998.

REFERENCES