

Effect of hypoxia on respiratory system impedance in dogs

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Simon, B. A., P. B. Zanaboni, and D. P. Nyhan. Effect of hypoxia on respiratory system impedance in dogs. *J. Appl. Physiol.* 83(2): 451–458, 1997.—The effects of hypoxia on lung and airway mechanics remain controversial, possibly because of the confounding effects of competing reflexes caused by systemic hypoxemia. We compared the effects of systemic hypoxemia with those of unilateral alveolar hypoxia (with systemic normoxemia) on unilateral respiratory system impedance (Z) in intact, anesthetized dogs. Independent lung ventilation was obtained with a Kottmeier endobronchial tube. Individual left and right respiratory system Z was measured during sinusoidal forcing with 45 ml of volume at frequencies of 0.2–2.1 Hz during control [100% inspired O₂ fraction (F_{I,O₂})], systemic hypoxemia (10% F_{I,O₂}), and unilateral alveolar hypoxia (0% F_{I,O₂} to left lung, 100% F_{I,O₂} to right lung). During systemic hypoxemia, there was a mean Z magnitude increase of 18%. This change was entirely attributable to a decrease in the imaginary component of Z; there was no change in the real component of Z. Administration of atropine (0.2 mg/kg) did not block the increase in Z with systemic hypoxemia. In contrast, there was no change in Z in the lung subjected to unilateral alveolar hypoxia. We conclude that alveolar hypoxia has no direct effect on lung mechanical properties in intact dogs. In contrast, systemic hypoxemia does increase lung impedance, apparently through a noncholinergic mechanism.

hypoxic pulmonary vasoconstriction; lung mechanics; resistance; compliance; hypoxemia; atropine

HYPOXIC PULMONARY vasoconstriction (HPV) is a well-known regional mechanism in the lung for regulating the distribution of pulmonary blood flow and optimizing ventilation-perfusion matching. In a complementary fashion, alveolar hypocapnia causes regional pneumoconstriction, which distributes ventilation away from a hypoperfused region (20). The effect of regional hypoxia on lung and airway mechanics, however, remains controversial for several reasons. There appears to be considerable variability among different species and different experimental preparations. For example, there is evidence of airway constriction to hypoxemia in intact dogs (18, 26) but bronchodilation in minipigs (33). In humans, hypoxia has been reported to cause bronchoconstriction (25), to cause bronchodilation (10), and to have no effect (8). Furthermore, there is poor agreement between in vivo and in vitro results. In vitro studies of airway rings or smooth muscle show a consistent relaxation response to hypoxia in tissue from dogs and pigs (5, 6, 24, 28). One possible explanation for these disparities is that systemic hypoxemia may cause variable activation of sympathetic, vagal, and other reflex responses, which could vary among

species or preparations and could cloud the interpretation of direct lung effects.

To investigate whether alveolar hypoxia alters regional lung mechanics, we developed a model in which the left and right lungs can be independently ventilated and their individual mechanical properties measured. We then used this model to compare the effects of systemic hypoxemia with the effects of unilateral alveolar hypoxia [maintaining normal systemic P_{O₂} and normal alveolar P_{CO₂} (P_{A,CO₂})] on unilateral respiratory system impedance in intact, anesthetized dogs. Finally, because vagal reflexes have been implicated in the mechanical response of the lung to hypoxemia in the dog (18), we examined the effect of atropine on the hypoxemic response.

MATERIALS AND METHODS

Animal preparation. All procedures were approved by our institutional review board. Ten adult mongrel male dogs weighing 24–33 kg (mean 27.0 kg) were anesthetized with fentanyl citrate (10 µg/kg) and pentobarbital sodium (20 mg/kg) via an 18-gauge forelimb intravenous catheter. Additional fentanyl (1–2 µg/kg) and pentobarbital (3–5 mg/kg) were given hourly to maintain anesthesia. Pancuronium bromide (3-mg bolus, 1-mg supplement as needed) was administered for muscle relaxation. Approximately 1 liter of Ringer lactate solution was slowly infused over the course of the experiment for maintenance of intravascular volume. A 10-cm 20-gauge catheter was inserted percutaneously into the femoral artery using sterile technique for arterial pressure monitoring and blood-gas sampling. The animals were orally intubated with a modified Kottmeier (Rüsch, Duluth, GA) endobronchial tube (see below) and positioned prone, and independent left and right lung ventilation was provided using a dual-piston ventilator (Harvard Apparatus, S. Natick, MA). Inspired O₂ concentration for each lung was independently controlled and measured with an in-line O₂ analyzer (model OM-10, Beckman). End-tidal P_{CO₂} (P_{ET,CO₂}) was measured at each airway opening with a mainstream infrared CO₂ analyzer (model 78356A, Hewlett-Packard), and the tidal volume (V_T) for each lung was adjusted such that the P_{ET,CO₂} values were within 1–2 Torr of each other under control and hypoxic conditions. Rectal temperature was monitored and maintained at 36 ± 1°C with radiant heat lamps. In two animals [1 during a pilot protocol using 8% inspired O₂ fraction (F_{I,O₂})], a pulmonary artery catheter was inserted using sterile technique via the right external jugular vein for mixed venous blood sampling. At the conclusion of the experiment, the dogs were reintubated with a conventional endotracheal tube, any residual neuromuscular blockade was reversed (3 mg neostigmine + 2 mg atropine), and the animals were allowed to awaken from anesthesia. All animals recovered uneventfully from the procedure.

Lung isolation and independent ventilation were obtained with a Kottmeier endobronchial tube modified for distal pressure measurement at the bronchial openings by the

passage of PE-190 tubing through the lumen to the bronchial opening. Distal airway pressures were measured through side holes in these tubes with solid-state pressure transducers (Argon, Athens, TX), amplified, and recorded on a Gould strip-chart recorder. The frequency response of this air-filled system was flat to >5 Hz. The pressure catheters were flushed before each set of measurements to ensure patency. Adequate lung isolation was determined by ventilating one lung while slowly inflating the Kottmeier cuff to the point where the pressure swings on that side no longer increased, then checking for leaks from the opposite side. This condition could usually be obtained with 18–20 ml of cuff volume, and adequacy of isolation was repeatedly checked throughout the experiment.

Arterial and mixed venous blood gases were obtained in heparinized syringes and stored on ice until analyzed (model ABL-3, Radiometer America). Alveolar gas samples were obtained by stopping the ventilator at end expiration, clamping the endotracheal tube at the airway opening, and withdrawing 60 ml of gas via the distal pressure-monitoring catheters. The first 40 ml of the sample were discarded, and the final 20 ml of gas were measured on the ABL-3 analyzer.

Unilateral respiratory system impedance measurement. The unilateral respiratory system input impedance (Z) was measured using sinusoidal forcing with 45 ml of V_T at 0.2, 0.45, 0.8, 1.4, and 2.1 Hz at functional residual capacity (FRC). Oscillation was provided via a linear-motor piston high-frequency ventilator (21). Flow was measured with a pneumotachograph (model 3719, Hans Rudolph, Kansas City, MO) and solid-state differential pressure transducer (IC Sensors, Milpitas, CA). A computer (Macintosh Centris 650) equipped with data-acquisition hardware and software (SuperScope II, GW Instruments, Somerville, MA) was used to drive the oscillator and simultaneously acquire the pressure and flow data. The impedance of each side was measured separately with the contralateral lung open to atmosphere. The lung was allowed to exhale to FRC, connected to the oscillator system, and then sequentially driven through five cycles at each frequency while the pressure and flow data were acquired at a sampling rate of 100 Hz. The complete five-frequency measurement took 44 s, during which the PET_{CO_2} would rise 2–3 Torr (measured at the resumption of ventilation) and mean airway pressure would fall 0.5–1 cmH₂O. Both lungs were ventilated for 1–2 min between measurements, until the PET_{CO_2} returned to the low-normal range. The pressure and flow waveforms were displayed on the screen in real time, allowing immediate determination and correction of problems with signal quality (as might occur

with secretions or spontaneous breathing), in addition to being stored in a waveform database for later analysis.

Curve fitting and impedance analysis were performed using Igor Pro (Wavemetrics, Lake Oswego, OR) software. Sinusoids were fitted to each single-frequency segment of the pressure and flow waveforms; the initial and final quarter cycle of each segment were discarded to avoid transients due to the frequency changes, and the mean, amplitude, and phase were determined. Fitted waveforms were superimposed on the raw data for visual inspection. The waveforms were highly sinusoidal and were fitted easily by single-frequency sinusoids. The standard deviations of the amplitude and phases, determined from the curve fits, were uniformly $<1\%$ of the parameter values and usually $<0.5\%$. Complex input impedance (Z) was calculated from the amplitudes and phases of the pressure and flow signals ($|P|$, $|F|$, ϕ_P , and ϕ_F) as follows

$$|Z| = |P|/|F|$$

$$\text{Re}\{Z\} = |Z| \cos(\phi_P - \phi_F)$$

$$\text{Im}\{Z\} = |Z| \sin(\phi_P - \phi_F)$$

where $\text{Re}\{Z\}$ and $\text{Im}\{Z\}$ are real and imaginary components of impedance. Impedance data for duplicate runs were averaged at each frequency, and the means were compared using paired *t*-tests (Statview 4, Abacus Concepts, Berkeley, CA) or multivariate analysis of variance (STATA, College Station, TX). Ratio data were log transformed, and $P < 0.05$ was used as the level of significance. Results are presented as means \pm SE.

Experimental protocol. Two experimental protocols were performed to compare the effects of unilateral alveolar hypoxia with systemic hypoxemia on lung mechanics. In all protocols, two sighs of four times the V_T were administered before each change of inspired gas concentration. V_T was adjusted during unilateral hypoxia to maintain PET_{CO_2} in the normal range for each lung. Impedance measurements were made in duplicate 15 min after each change in inspired gas concentration, and arterial blood and alveolar gas samples were drawn just before each set of measurements. In *protocol 1* ($n = 5$), measurements were made under control (C1: 100% $F_{I_{O_2}}$ to both lungs), bilateral hypoxic (H1: 10% $F_{I_{O_2}}$ to both lungs) (Fig. 1), and repeat control (C2) conditions. The entire set of measurements was repeated after administration of atropine (0.2 mg/kg iv; C3, H2, and C4). In *protocol 2* ($n = 5$), measurements were made under control, left lung hypoxia

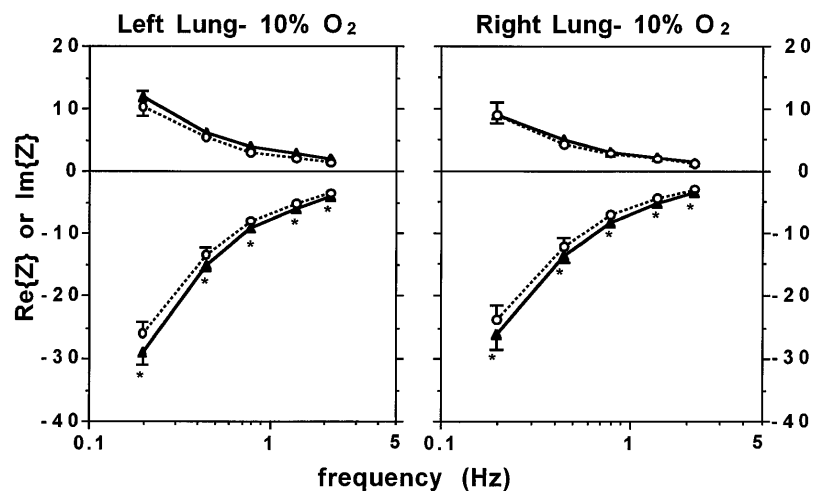


Fig. 1. Real and imaginary components of respiratory system impedance ($\text{Re}\{Z\}$ and $\text{Im}\{Z\}$, respectively) for left and right sides during control [C1: 100% inspired O_2 fraction ($F_{I_{O_2}}$) to both lungs; \circ] and hypoxemia (H1: 10% $F_{I_{O_2}}$ to both lungs; \blacktriangle). Values are means \pm SE. * $P < 0.05$.

(0% $F_{I_{O_2}}$ to left lung, 100% $F_{I_{O_2}}$ to right lung), and repeat control conditions. Because atropine did not alter the response to hypoxemia in *protocol 1*, it was not administered in *protocol 2*.

RESULTS

Blood and alveolar gases. During whole animal hypoxemia, arterial and alveolar P_{O_2} ($P_{a_{O_2}}$ and $P_{A_{O_2}}$) values of 30–35 Torr were obtained (Table 1), along with large increases in arterial blood pressure and heart rate. Unilateral hypoxic ventilation achieved the goal of alveolar hypoxia with left alveolar fraction of O_2 of ~8% ($P_{A_{O_2}} = 58 \pm 4.4$ Torr), without systemic hypoxemia ($P_{a_{O_2}} = 110 \pm 15$ Torr), and with normal $P_{a_{CO_2}}$, arterial P_{CO_2} ($P_{a_{CO_2}}$), and pH (Table 1). The three measurements of mixed venous P_{O_2} ($P_{\bar{v}_{O_2}}$) in two animals during left lung hypoxia suggest that the $P_{A_{O_2}}$ is in equilibrium with the mixed venous blood (Table 2). In addition, although we did not quantify ventilation, it was necessary to significantly decrease the ventilation to the left lung relative to the right lung during unilateral hypoxic ventilation to maintain the $P_{ET_{CO_2}}$ in the desired range. All blood-gas values returned to control levels after unilateral or bilateral hypoxia was terminated.

Hypoxemia. Respiratory system impedance magnitude ($|Z|$) increased ~18% (averaged across all frequencies) on both sides during hypoxemia ($P < 0.01$). Examination of the $Re\{Z\}$ and $Im\{Z\}$ revealed that all the change was due to a decrease in the $Im\{Z\}$ (more negative); there were no significant changes in $Re\{Z\}$ with hypoxemia (Fig. 1). Administration of atropine (0.2 mg/kg iv) caused baseline $|Z|$ to decrease $9 \pm 1\%$ ($P < 0.01$) but did not affect the increase in $|Z|$ with hypoxemia. Again, the effect of hypoxemia after atropine administration was confined to changes in the $Im\{Z\}$ and not the $Re\{Z\}$ (Fig. 2). The fall in impedance with atropine was due to a uniform decrease in $Im\{Z\}$ at all frequencies [$Im\{Z\}$ ratio of control 3 to control 2 ($C3/C2$) = 0.93 ± 0.01 , $P < 0.05$] and a decrease in $Re\{Z\}$ only at the highest three frequencies [$C3/C2$ = 1.03 ± 0.09 ($P = NS$), 0.90 ± 0.05 ($P = NS$), 0.86 ± 0.06 ,* 0.80 ± 0.08 ,* and 0.70 ± 0.10 * at frequencies of 0.2, 0.45, 0.8, 1.4, and 2.1 Hz, respectively; * $P < 0.05$]. There were no differences between the pre- and posthy-

Table 2. Mixed venous and alveolar gas equilibration

Left Lung $F_{I_{O_2}}$, %	Arterial Blood			Mixed Venous Blood			Left Lung Alveolar	
	P_{O_2} , Torr	P_{CO_2} , Torr	pH	P_{O_2} , Torr	P_{CO_2} , Torr	pH	P_{O_2} , Torr	P_{CO_2} , Torr
8	129	33	7.47	62	41	7.44	64.6	40.6
0	300	29	7.56	39	35	7.50	35.3	28.2
0	156	33	7.52	43	36	7.44	45.0	32.2

poxemia controls before or after atropine administration.

Traditional compliance and resistance parameters for the respiratory system are presented in Fig. 3 for the hypoxemia protocol. Compliance, calculated by fitting $C = -(2\pi f Im\{Z\})^{-1}$ (where C is compliance and f is frequency) to the data (assuming negligible inertance at these frequencies), decreased similar amounts during both hypoxemia trials ($H1/C1$ and $H2/C3 = 0.91 \pm 0.03$ and 0.87 ± 0.03 before and after atropine, respectively; $P < 0.05$) and increased with administration of atropine ($C3/C2 = 1.07 \pm 0.03$, $P < 0.05$). Airway resistance, approximated as $Re\{Z\}$ at the highest frequency (2.1 Hz), did not change significantly with hypoxemia but fell 30% after atropine administration.

Unilateral alveolar hypoxia. There were no changes in $|Z|$, $Im\{Z\}$, $Re\{Z\}$, or compliance at any frequency in the hypoxic left or control right lung during unilateral alveolar hypoxic ventilation (Fig. 4).

DISCUSSION

Hypoxia is a life-threatening challenge to an organism and results in a variety of homeostatic neural and endocrine responses. The extent and net effect of these responses may depend on several factors, including the severity and duration of the hypoxemia, use of and type of anesthetic agents, particular experimental conditions, and particular species studied. These responses may have primary or secondary effects on the lung and airways, and the net effects are unpredictable. For example, sympathetic responses and catecholamine release would tend to bronchodilate, whereas vagal responses cause constriction. In addition, changing

Table 1. Arterial blood and alveolar gas analysis

	Arterial Blood Gas			Left Alveolar Gas		Right Alveolar Gas	
	P_{O_2} , Torr	P_{CO_2} , Torr	pH	P_{O_2} , Torr	P_{CO_2} , Torr	P_{O_2} , Torr	P_{CO_2} , Torr
<i>Protocol 1 (10% $F_{I_{O_2}}$ bilateral)</i>							
Control	474 ± 39	33 ± 2	7.41 ± 0.02	637 ± 28	34 ± 5.3	632 ± 15	41 ± 4.2
Hypoxia	35 ± 4	27 ± 2	7.47 ± 0.03	35 ± 8.7	33 ± 4.6	33 ± 0.1	33.5 ± 0.7
+ Atropine							
Control	430 ± 52	36 ± 2	7.39 ± 0.01	591 ± 10	41 ± 3.1	599 ± 17	42 ± 3.2
Hypoxia	31 ± 5	31 ± 1	7.45 ± 0.01	32 ± 3.5	35 ± 0.1	25 ± 5.6	38 ± 0.7
<i>Protocol 2 (0% $F_{I_{O_2}}$ to left lung)</i>							
Control	518 ± 9	28 ± 1	7.49 ± 0.03	638 ± 7	38 ± 1.3	650 ± 5	38 ± 1.6
Hypoxia	110 ± 15	34 ± 1	7.43 ± 0.03	58 ± 4.4	37 ± 2.1	593 ± 22	46 ± 1.9

Values are means ± SE; $n = 10$ animals. $F_{I_{O_2}}$, inspired O_2 fraction.

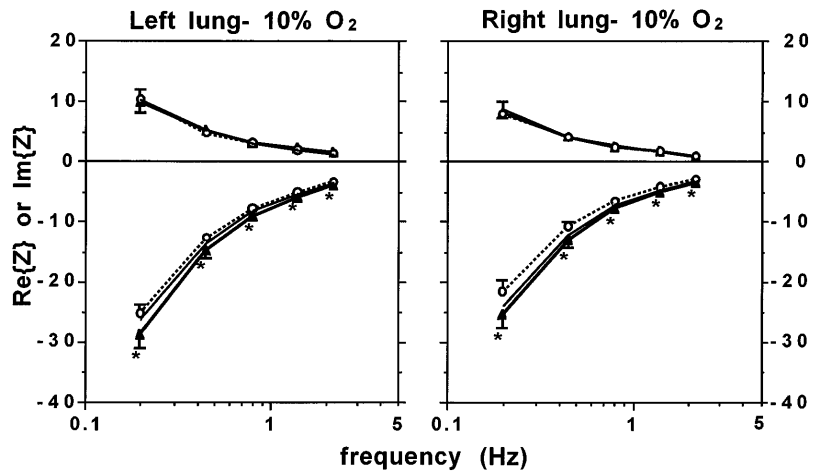


Fig. 2. Re{Z} and Im{Z} for left and right sides under control conditions before atropine administration (C2, solid lines), control after atropine (C3, ○), and hypoxemia after atropine (H2, ▲). Values are means ± SE. * P < 0.05 for hypoxemia effect after atropine.

metabolic conditions (acidosis, hypercarbia) may also have an effect. Thus studies attempting to determine the effects of hypoxia on airway function have yielded results that are inconsistent among species (18, 26, 33), within species with different experimental protocols (8, 10, 25), and between in vivo and in vitro preparations (5, 6, 24, 28). To distinguish the direct effects of alveolar hypoxia on lung and airway mechanical function from the confounding effects of systemic hypoxemia, we have used a model in which the lungs of anesthetized dogs

can be independently ventilated with different gas mixtures and the respiratory system impedance of each side can be determined separately. We then used this model to compare the effects of systemic hypoxemia with the effects of unilateral alveolar hypoxia (maintaining normal systemic P_{O₂} and normal P_{ACO₂}). We found a significant increase in respiratory system impedance during systemic hypoxemia. This increase was primarily in the imaginary component of impedance, which reflects lung elastance. During unilateral hypoxic ventilation, however, there was no change in lung mechanical behavior. The response to hypoxemia was not affected by intravenous atropine. These results suggest that isolated alveolar hypoxia does not affect airway or lung mechanics, and in this model the constriction to hypoxemia is via a nonvagal mechanism.

Methodological considerations. The technique of lung isolation and independent ventilation to separate the effects of systemic from local lung interventions has been used by many investigators for the study of the pulmonary circulation and the airways (9, 12, 20). An important advantage of this approach is that it allows survivable studies in intact, minimally instrumented animals. However, the measurement of input impedance from airway opening pressure and flow only provides information about total respiratory system impedance. To separate lung properties from chest wall properties, a measurement of pleural pressure must be obtained. The most commonly used estimate of pleural pressure changes is esophageal pressure, but this measurement is a poor reflection of regional pleural pressure when lung mechanical properties are nonuniform (9, 14). Methods for measuring regional pleural pressure tend to be invasive (17, 35) and not compatible with survival experiments. Thus these impedance measurements are limited by the presence of the chest wall, which although pharmacologically relaxed and presumably constant throughout the experiments, may cause the measurement to be less sensitive to subtle changes in lung properties than open-chest approaches. Barnas et al. (1), using a similar oscillatory forcing technique on the whole lungs of intact dogs, found that the chest wall contributed ~50% of the respiratory system elastance over this frequency range. Relative contributions

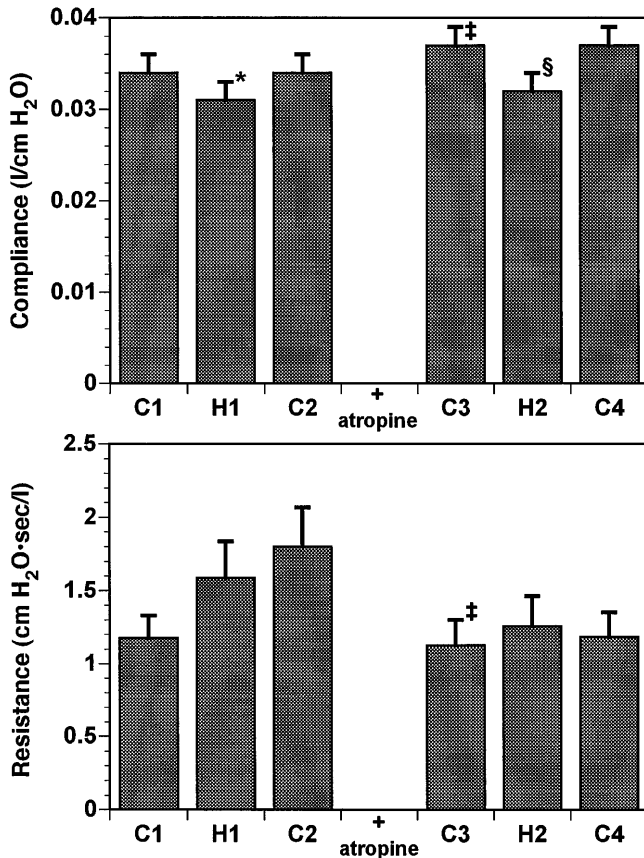


Fig. 3. Respiratory system compliance and resistance changes during hypoxemia protocol. C4, repeat control + 0.2 mg/kg iv atropine. Values are means ± SE. * P < 0.05 vs. C1; † P < 0.05 vs. C2; § P < 0.05 vs. C3.

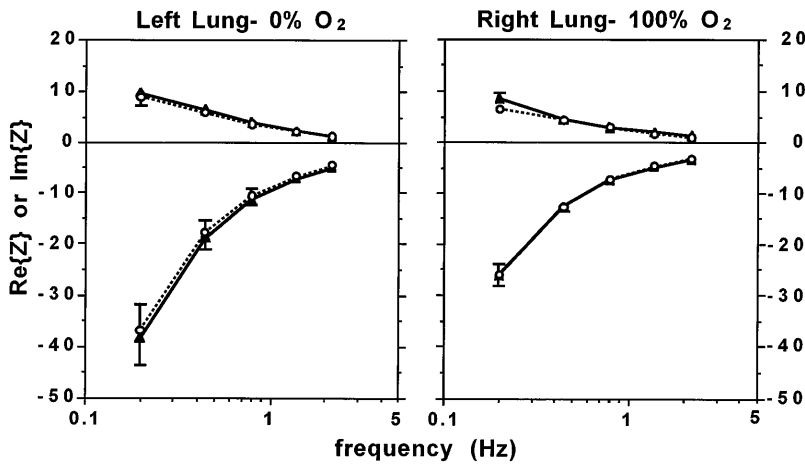


Fig. 4. $\text{Re}\{Z\}$ and $\text{Im}\{Z\}$ for left and right sides during control (100% FIO_2 to both lungs, \circ) and unilateral hypoxic ventilation (100% FIO_2 to right lung, 0% FIO_2 to left lung; \blacktriangle). Values are means \pm SE.

of lung and chest wall to respiratory system resistance (R_{rs}), on the other hand, varied with frequency. The chest wall contributed 60–70% of the resistance at frequencies <1 Hz, contributions of lung and chest wall were about equal at 1 Hz, and the lung contributed 60% of R_{rs} at 2 Hz. Thus the lung contributes 40–60% of the total respiratory system input impedance over the frequency range studied. If it is assumed that there are no changes in the mechanics of the relaxed chest wall, the changes in input impedance reported here are therefore conservative estimates of the mechanical effects on the lung itself. However, it is possible that subtle changes in lung properties, particularly those of the tissue component of resistance, which would be seen at low frequency when chest wall effects are greatest, are masked by this limitation.

A second aspect of this preparation that potentially complicates the interpretation of the data is that the contralateral lung is left open to atmosphere during the ipsilateral impedance measurement. This creates a slightly different configuration than is found in the conventional measurement of “respiratory system” properties, with the lung of interest now in series with the parallel combination of the ipsilateral chest wall and contralateral lung. Furthermore, the chest wall contribution to the measured impedance may be different when only one lung is oscillated and the chest wall expands inhomogeneously. It is not possible to separate the individual contribution of each of these elements without regional pleural pressure measurements. As a result, it is possible that changes in the unilateral impedance measurement could be due in part to changes in the contralateral lung pathway rather than the lung of interest. However, in another study using this method, impedance measurements on the control side did not change when the contralateral lung underwent a 50% increase in $|Z|$ during unilateral hypocapnia from pulmonary artery occlusion (22), suggesting that this effect is small. Thus, again, barring changes in the properties of the relaxed chest wall, changes in impedance measured with this method should still primarily reflect changes in the ipsilateral lung.

We chose to use a relatively small, constant-amplitude volume across the frequency range for our imped-

ance measurement, an approach that can potentially exaggerate the effect of airway resistance at higher frequencies because of the higher peak flows obtained. However, data from Barnas et al. (1), examining impedance changes from 50 to 100 ml of V_T in intact dogs (corresponding to ~ 25 – 50 ml of V_T per single lung) would suggest that one would expect at most a 10–15% fall in chest wall elastance, no change in lung elastance, and minimal changes in chest wall resistance, pulmonary resistance, and R_{rs} . Thus the choice of constant amplitude is not likely to have caused any significant difference from the alternative approach of constant peak flow (i.e., falling amplitude as frequency increases).

Over the course of a measurement run, mean airway pressure typically fell 0.5–1 cmH_2O . This was probably due to O_2 uptake from the closed system and corresponds to a volume loss of ~ 30 ml. This would cause the lung volume to be slightly smaller at the higher-frequency measurements than at the outset, which could cause a small increase in resistance and compliance compared with conditions in which volume remained exactly constant. However, because this effect was similar for all runs, it is not likely a cause of significant error in evaluating changes between conditions.

Effect of atropine. The administration of intravenous atropine caused a 9% decrease in $|Z|$. $\text{Re}\{Z\}$ fell significantly only at the higher frequencies, consistent with an effect on airway resistance. By use of high-resolution computed tomography, this dose of atropine was found to maximally dilate large airways (3), although airways <1 mm could not be measured. In addition, there was a fall in $\text{Im}\{Z\}$ of $\sim 7\%$ across all frequencies or, equivalently, an increase in compliance. These results correspond to the inverse of the increased resistance and decreased compliance in dogs during vagal stimulation (13). In humans, intravenous atropine has been shown to cause a decrease in airway resistance ($\sim 50\%$) and an increase in lung compliance ($\sim 18\%$), along with a 7% increase in FRC (4). We cannot distinguish whether our findings are due to relaxation of vagally mediated smooth muscle/airway tone (with or without an increase in FRC from resulting decreased lung recoil) or

recruitment of additional lung volume, although there is no reason to suspect the latter. In any event, these results confirm the sensitivity of this technique to detect relatively small changes in Z .

Hypoxemia. The primary effect of hypoxemia on lung mechanics was to cause a decrease in compliance, as evidenced by the changes in $\text{Im}[Z]$. There was no change in the $\text{Re}[Z]$. Again, this finding could result from a loss of ventilated lung volume or a fall in FRC. To avoid this, volume history was standardized and large inflations were given to prevent progressive atelectasis over time. Furthermore, the changes in Z occurred rapidly and completely returned to baseline during the repeat control measurement. V_T was maintained in this protocol, as opposed to the unilateral hypoxic ventilation series, in which V_T to the hypoxic lung was decreased to maintain PET_{CO_2} . One would expect to see a greater fall in lung volume and increase in impedance under conditions of reduced V_T due to increased atelectasis, but none was found. Finally, previous experience using this closed-chest model to measure changes in unilateral respiratory system impedance during hypocapnia induced by unilateral pulmonary artery occlusion, in which lung volumes were measured using helium dilution, showed no changes in FRC with considerably stronger hypocapnic constrictions (46% increase in Z) (22). Thus we consider a decrease in FRC due to passive atelectasis to be an unlikely cause of the observed changes.

The lack of effect of atropine on the response to hypoxemia was somewhat surprising, particularly in light of the well-known results of Nadel and Widdicombe (18), in which cooling of the vagi prevented the increase in lung resistance and decrease in tracheal volume seen with hypoxemia. As discussed above, this dose of atropine has been shown to maximally dilate large airways and caused a measurable fall in Z , so it is unlikely that the preserved response was due to inadequate cholinergic blockade. Other investigators have found responses to hypoxemia unaffected by intravenous atropine. Sterling (25) found that atropine had no effect on the decrease in specific airway conductance in awake humans breathing 10–12% O_2 , although the response could be blocked by inhaled β -agonists. This was interpreted to mean that hypoxia acts directly on bronchial smooth muscle. Strieder et al. (26), working in intact dogs, found that hypoxemia caused an increase in lung recoil, which was not blocked by atropine but was decreased by the antihistamine promethazine, and an increase in lung resistance, which was prevented by atropine administration. These authors proposed that hypoxemia causes smooth muscle contraction in the small airways and periphery mediated by local release of histamine. Our results are also consistent with the hypothesis that systemic hypoxemia increases Z via a noncholinergic mechanism that primarily affects small airways and peripheral smooth muscle. In our model there is no significant cholinergic response and no change in the resistance of the large airways. There are changes in compliance and $\text{Im}[Z]$, presumably reflecting changes in lung tissue or periph-

eral smooth muscle properties similar to those seen by Strieder et al. Possibly, a technique in which tissue resistance could be separated from large airway properties would show changes as well.

Unilateral hypoxia. Unilateral hypoxic ventilation had no effect on respiratory system input impedance, despite evidence for a brisk HPV response, as indicated by the decreased CO_2 output of the hypoxic lung. One possible explanation for this finding is that the PA_{O_2} was not low enough to trigger a response. The limited $\text{P}\bar{V}_{\text{O}_2}$ data from two dogs suggest that the PA_{O_2} is in equilibrium with the $\text{P}\bar{V}_{\text{O}_2}$. Our mean PA_{O_2} during hypoxic ventilation was 58 ± 4.4 Torr. Although it is not as low as the PA_{O_2} of 25–35 Torr achieved during hypoxemia, this value is below the FI_{O_2} of 10–12% ($\text{PO}_2 = 70$ –80 Torr) typically used in hypoxemia studies in which an effect was noted (18, 25, 26). Furthermore, because the average systemic PO_2 was only 110 ± 15 Torr, further reduction of the FI_{O_2} to the right lung to reduce the $\text{P}\bar{V}_{\text{O}_2}$ would have resulted in hypoxemia in several of the animals. Although it is difficult to imagine a physiologically relevant situation in which ventilated alveoli have a $\text{PO}_2 < 60$ Torr, it is possible that this delivery of O_2 to the alveoli by mixed venous blood prevented a local hypoxic response.

Another possible explanation for the lack of a response to unilateral hypoxic ventilation involves the bronchial circulation, which may be very important in modulating regional lung mechanical responses. Whereas changes in bronchial blood flow do not appear to directly affect airway caliber or resistance (2), the bronchial blood flow has been shown to modulate airway responses through delivery or clearance of substances that may constrict or relax bronchial smooth muscle (31). Recently, it was demonstrated that up to 90% of the airway response to an intravenous injection of methacholine occurs via the bronchial circulation (32). Decreasing the PO_2 of bronchial blood has been shown to trigger HPV in the absence of alveolar or systemic hypoxia (16), and maintenance of bronchial blood flow has been shown to decrease ischemia-reperfusion lung injury (19). Because the bronchial blood flow increases during hypoxia (30), it is possible that the delivery of this normoxic systemic blood to the airways prevented the constriction response to hypoxic ventilation. Further studies of the effects of changing the O_2 concentration of the bronchial blood flow on the lung mechanical response to hypoxemia and regional alveolar hypoxia are necessary to determine the importance of this interaction.

Another difference between the unilateral hypoxic and hypoxemic conditions relates to the pulmonary circulation. During unilateral hypoxia there is pulmonary vasoconstriction and shunting of pulmonary blood flow to the nonhypoxic lung, but pulmonary arterial pressures do not increase very much because of the reserve capacity of the contralateral pulmonary circulation (11). With hypoxemia, however, the entire pulmonary bed constricts, but because cardiac output is maintained, pulmonary arterial pressure increases dramatically (15). It is possible that this constricted and

high-pressure perfused state of the pulmonary vasculature has a mechanical correlate in increased input impedance. Interdependence between the pulmonary vessels and the airways may affect airway caliber as pulmonary vascular pressures increase by mechanical "crowding" within a fixed volume sheath and/or by causing airway edema and wall thickening (34). Alternatively, changes in lung mechanics may be due to stiffening of the vascular tree or alveolar wall with vascular congestion (7).

Alveolar hypocapnia due to pulmonary artery occlusion has been shown to cause a significant pneumoconstriction, with increased lung resistance and decreased compliance, such that ventilation is redistributed away from the hypoperfused region (20, 23). An interaction between hypoxia, HPV, and hypocapnic constriction may be responsible for some of the effect seen here. Traystman et al. (27) showed that collateral resistance, measured with the wedged bronchoscope method, increased when the distal airways were infused with 5% O₂. This increase was prevented when 5% CO₂ was added to the infused gas mixture. They speculated that the hypoxic gas caused local HPV, decreasing CO₂ delivery to the region with resultant local hypocapnia and constriction. We decreased ventilation to the hypoxic lung to maintain normal P_{ET}CO₂ during unilateral hypoxia and prevent alveolar hypocapnia, which would have prevented this constrictor response. However, this does not explain the lung impedance increases during systemic hypoxemia, during which P_ACO₂ was also normal. Recently, Venegas et al. (Ref. 29 and personal communication) presented data showing a large increase in lung perfusion heterogeneity during hypoxia measured using positron imaging. One could speculate that hypoxemia with continued ventilation resulted in areas of regional hypoperfusion and regional hypocapnic constriction, but net CO₂ elimination was unchanged, since the entire cardiac output must still pass through the lungs and ventilation was maintained. These constricted regions resulted in a measurable increase in lung impedance, and this response would be expected to primarily affect the imaginary component. During unilateral hypoxic ventilation, however, the blood flow could be uniformly shunted to the other lung, and the regional hypocapnia could be avoided. Further studies in which perfusion distribution during unilateral hypoxia vs. hypoxemia is characterized are required to determine whether this hypothesis is valid.

In summary, we have demonstrated that hypoxemia, but not unilateral alveolar hypoxic ventilation, causes an increase in respiratory system input impedance in anesthetized dogs. This finding suggests that alveolar hypoxia, unlike alveolar hypocapnia (20), has no direct effect on lung or airway mechanical properties. The response to hypoxemia is not blocked by prior administration of intravenous atropine and is characterized primarily by a change in lung compliance, consistent with previous findings in anesthetized dogs (26). These results are consistent with the hypothesis that hypoxemia results in an active increase in peripheral or small airway smooth muscle contraction, perhaps due to the

release of histamine (26) or some other noncholinergic reflex or mediator.

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