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Halothane Changes the Relationships Between Lung Resistances and Lung Volume

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The authors hypothesized that relaxation of airway smooth muscle by halothane lessens the dependence of airway resistance on lung volume, and that halothane alters the relationship between pulmonary resistance and lung volume by changing both the airway and tissue components of pulmonary resistance. The relationship among airway resistance, tissue resistance, and lung volume was examined in mongrel dogs before and during the administration of halothane, both in airways with reduced smooth muscle tone (after vagotomy) and during moderate increases in smooth muscle tone caused by vagus nerve stimulation (VNS). Resistances were measured at several levels of positive end-expiratory pressure (PEEP, 4–15 cmH_2O) using an alveolar capsule technique. Before halothane administration, airway resistance increased at low PEEP; VNS accentuated this increase. Tissue resistance increased at low PEEP only during VNS. Halothane had no significant effect on any resistance before VNS. During VNS, halothane markedly blunted increases in airway resistance and tissue resistance as PEEP decreased. The authors conclude that during stimulation of airway smooth muscle in dogs, halothane attenuates increases in airway resistance and tissue resistance with reductions in lung volume in dogs. Thus, moderate changes in lung volume have little effect on these resistances during halothane anesthesia under these conditions. (Key words: Anesthetics, volatile: halothane. Lungs: airway resistance; alveolar capsules; pulmonary resistance; tissue resistance. Nerve: vagus; stimulation.)

VOLATILE ANESTHETICS may have at least two potentially confounding effects on airway resistance (R_{aw}). They relax airway smooth muscle by depression of parasympathetic neural pathways innervating airway smooth muscle and by a direct effect on the muscle and its receptor systems.[1–6] This relaxation of airway smooth muscle should decrease R_{aw}. However, anesthesia also reduces the functional residual capacity (FRC) in humans.[7] Because R_{aw} increases as lung volume declines,[8–10] reductions in the FRC should favor increased R_{aw}. Thus, the net effect of the volatile anesthetics on R_{aw} should depend on the interaction between the effects of reductions in lung volume and anesthetic-induced relaxation of airway smooth muscle.

The above considerations have been used to explain unchanged or increased pulmonary resistance (R_L) after induction of anesthesia with volatile anesthetics observed in some studies of human subjects.[11–15] However, the relationship between lung volume and R_{aw} depends on airway smooth muscle tone; relaxation of airway smooth muscle reduces the dependence of R_{aw} on lung volume.[9,16–19] If the volatile anesthetics relax airway smooth muscle, the reduction in FRC may have little effect on R_{aw}.

Prediction of changes in R_L caused by anesthetic-induced changes in lung volume is complicated by another factor. Although most studies of anesthetic effects on smooth muscle tone *in vivo* use R_L as an index of airway diameter and smooth muscle tone, R_L is the sum of R_{aw}, which depends on pressure drops created by gas flow in the airways, and tissue resistance (R_{ti}), which depends on the elastic properties of the lung tissue.[20] Like R_{aw}, R_{ti} also depends on both lung volume[21,22] and the tone of airway smooth muscle[18,23,24] and is reduced by volatile anesthetics.[25,26] However, in contrast to R_{aw}, R_{ti} decreases as lung volume decreases.[21,22,24]

The purpose of the present study was to test two hypotheses: 1) halothane reduces the dependence of R_{aw} on lung volume; and 2) halothane alters the relationship between R_L and lung volume by changing both airway and tissue components of R_L. We examined the relationship between these lung resistances and lung volume in dogs before and during the administration of halothane, both in airways with reduced smooth muscle tone (after vagotomy) and during moderate increases in smooth muscle tone caused by electrical stimulation of the vagus nerve.

Materials and Methods

ANIMAL INSTRUMENTATION

This study was approved by the Institutional Animal Care and Use Committee. Six mongrel dogs (15–20 kg) were anesthetized with chloralose (60 mg · kg^{-1} intravenously [iv]) and urethane (600 mg · kg^{-1} iv), anesthetics that have little effect on increases in R_L during vagus nerve stimulation (VNS) in dogs.[27] This baseline anesthesia was maintained throughout the experiment by administering supplemental doses of chloralose (5 mg · kg^{-1} iv) and ure-

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thane (50 mg · kg^{-1} iv) every 30–60 min. After endotracheal intubation, the dogs were paralyzed with vecuronium (0.5 mg · kg^{-1} iv) followed by supplemental doses sufficient to suppress twitch responses to train-of-four femoral nerve stimulation. Vecuronium was used because it has no effect on the vagal motor pathway.[5] The lungs were mechanically ventilated (Harvard 615) using an open system with an inspired oxygen concentration of 30%, a tidal volume of 15 ml · kg^{-1}, a ratio of inspiratory to expiratory times of 1:1, and a breathing frequency of 15 breaths · min^{-1}. The rectal temperature was maintained between 36 and 38° C. We have previously demonstrated that this anesthetic regimen provides a stable response of R_L to repeated VNS.[5,28]

A median sternotomy was performed to expose the lungs. Positive end-expiratory pressure (PEEP) of 5 cmH_2O was used to maintain an end-expiratory lung volume similar to the FRC of intact dogs.[25,29] Alveolar pressures were measured using a capsule technique previously used by ourselves[25,26,29–31] and others.[24] In this technique, small holes are punched in the underlying pleura, and small capsules are glued on the pleura so that the pressure in a capsule equals the pressure in the alveoli beneath that capsule. The capsules were flanged cylinders with an inner diameter of 1 cm and were glued (Permabond 240) to the visceral lung pleura while the lungs were inflated to a tracheal pressure of 15 cmH_2O. Before capsule attachment, the pleura beneath the capsule was punctured three to six times with a 19-G electrocautery needle to a depth of 1–2 mm. Any bleeding caused by pleural puncture was controlled with electrocautery. Capsule pressures were measured by transducers (Statham PM131) connected to each capsule by an 80-cm length of tubing (PE-200). The capsule-catheter combination has been shown to have adequate frequency response up to 30 Hz.[30] Two or three capsules were used in each dog. Capsules were affixed to the ventral surfaces of the right cardiac, right diaphragmatic, and left diaphragmatic lobes.

The cervical vagus nerves were exposed bilaterally, infiltrated with lidocaine, and divided. Electrodes were applied to the distal nerves for later electrical stimulation to provide moderate tone in the airway smooth muscle.[5,6,25,28] To prevent desiccation, the nerves and electrodes were covered with mineral oil. The animals were pretreated with propranolol (2 mg/kg) to prevent concurrent stimulation of sympathetic fibers in the vagus nerve that would attenuate smooth muscle contraction.[6,18] A femoral arterial catheter was inserted for measurement of blood pressure and arterial blood sampling for gas analysis (Instrumentation Laboratories 1302). The dog was then placed in a volume-displacement body plethysmograph.[28] Alveolar pressure measurements were validated in each capsule by occluding the endotracheal tube while the lung was held at a transpulmonary pressure of 4 cmH_2O and sinusoidally varying the pressure in the plethysmograph.[25] Because there was little or no movement of gas in the lung, tracheal pressure should always equal capsule pressure if the airways are in free communication and if the frequency response of the measurement system is adequate. In properly functioning capsules, there was no difference in magnitude or phase between capsule and tracheal pressures up to 2 Hz. Capsule measurements were validated frequently throughout the experiment and at its conclusion. Flow at the airway opening was measured by a heated pneumotachograph (Fleisch 1) coupled to a differential pressure transducer (Validyne MP 45). Tracheal pressure was sensed (Statham PM131) through a catheter (PE-200) with its tip positioned 3 cm distal to the tracheal end of the endotracheal tube. A mass spectrometer (Perkin-Elmer 1100A) measured end-tidal halothane concentration.

Experimental Protocol

Resistances were measured at four levels of PEEP (15, 10, 6, and 4 cmH_2O, applied in random order) in the absence of halothane (control) and during administration of halothane producing stable end-tidal concentrations of 0.5, 1.0, and 1.5 MAC in random order; actual measured end-tidal halothane concentrations were 0.46 ± 0.01% (mean ± standard error), 0.90 ± 0.01%, and 1.35 ± 0.02%, respectively. Each concentration of halothane was maintained for 20 min before measurements began. Before each measurement of resistances, the lungs were inflated twice to a tracheal pressure of 25 cmH_2O and then were deflated to the desired PEEP. The difference between this lung volume at a tracheal pressure of 25 cmH_2O and the lung volume at a given level of PEEP was noted. After six control breaths, bilateral VNS (25 volts, 3-ms bipolar pulses at 15 Hz) commenced and was maintained for nine breaths. These parameters of VNS were chosen because they produce moderate increases in smooth muscle tone, resulting in an R_{aw} of approximately 2 cm$H_2O \cdot l^{-1} \cdot s$ at 5 cmH_2O PEEP. VNS caused no detectable change in end-expiratory lung volume at any PEEP as measured by the plethysmograph. Arterial blood gases were measured before and after the trials conducted at each dose of halothane. Sodium bicarbonate was given as needed to maintain arterial $pH > 7.35$ (requiring a total of 2.0 ± 0.2 mEq/kg during the experiment). The arterial P_{CO_2} was maintained between 35–40 mmHg by adjusting the tidal volume as necessary.

Data Acquisition and Analysis

All data were written to a chart recorder and digitally sampled at 100 Hz. Mean resistances during each condition were calculated by multiple linear regression of the measured variables applied to a linear lung model; this

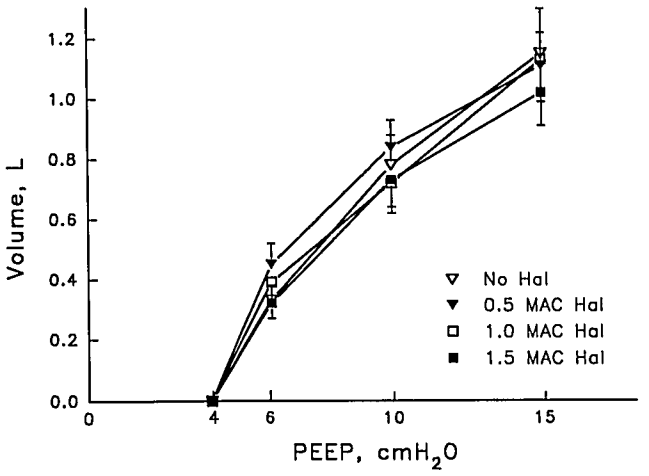

FIG. 1. End-expiratory lung volume as a function of positive end-expiratory pressure (PEEP). Lung volumes are referenced to the lung volume at 4 cmH_2O PEEP. Values are mean ± standard error.

method has been previously described and validated.[25,28,29]§ R_{aw}, which depends on airway diameter, was calculated using the difference between mean capsule pressure and tracheal pressure, flow, and changes in lung volume; R_{ti}, which depends on the elastic properties of the lung tissue, was calculated using the difference between mean alveolar and ambient pressures, flow, and changes in lung volume. R_L is the sum of R_{aw} and R_{ti}. Measurements from a capsule were used to calculate the mean alveolar pressure only if that capsule provided valid measurements throughout the experiment. Reported prestimulation values of resistances were averages of the last three breaths before VNS, while the reported values during VNS were averages of the final six breaths (of a total of nine breaths) during stimulation, a time of maximal, stable response.[5,28]

STATISTICS

Comparisons were made with repeated-measures analysis of variance using one or two factors as appropriate, with $P < 0.05$ considered significant. Values reported are mean ± standard error.

Results

BEFORE HALOTHANE ADMINISTRATION

End-expiratory lung volume decreased as PEEP was reduced (fig. 1). In the absence of halothane and before VNS, both R_L and R_{ti} significantly decreased as PEEP was reduced ($P < 0.0001$ for each variable), *i.e.*, as end-expiratory lung volume decreased (figs. 2B and 2C; table 1). R_{aw} consistently increased at the extremes of lung volume, a small but statistically significant effect ($P = 0.002$; fig. 2A and table 1).

Because VNS caused no change in end-expiratory lung volume as measured by the plethysmograph, the relationship between lung volume and PEEP was unchanged by VNS (data not shown). In the absence of halothane, VNS significantly increased R_{aw}, R_{ti}, and R_L at each level of PEEP ($P < 0.0001$ for each resistance; table 2). These increases were significantly greater at lower levels of PEEP ($P < 0.004$ for each resistance; table 2); however, there was little difference between mean increases at 10 and 15 cmH_2O PEEP. During VNS, R_{aw} significantly increased

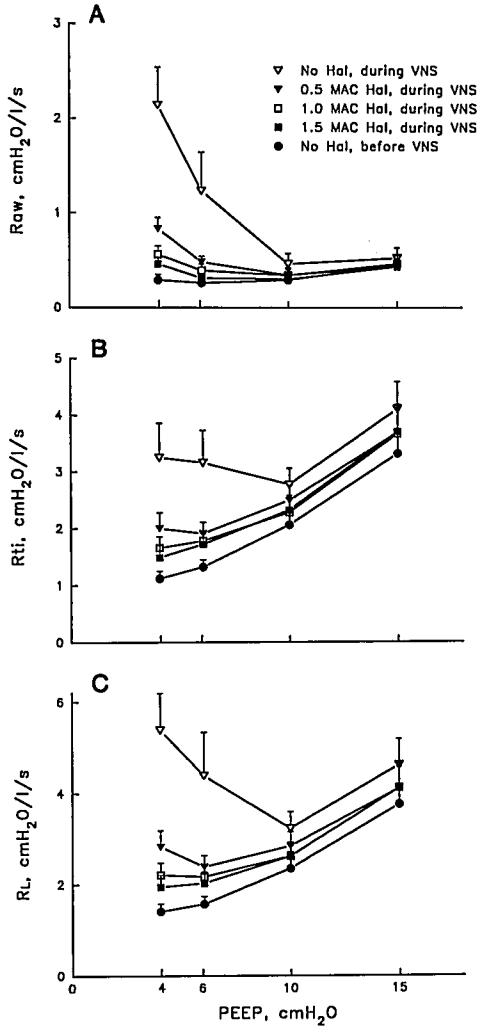

FIG. 2. Airway resistance (R_{aw}, *A*), tissue resistance (R_{ti}, *B*), and pulmonary resistance (R_L, *C*) as a function of positive end-expiratory pressure (PEEP; *i.e.*, lung volume). *Closed circles* are data before vagus nerve stimulation (VNS) obtained in the absence of halothane; all other symbols are data obtained during VNS. Values are mean ± SE.

§ Details of this method, including a discussion of the concept of tissue resistance, have been published previously in this journal (ref. 25).

TABLE 1. Resistances before Vagus Nerve Stimulation

Variable	PEEP	Resistances ($cmH_2O \cdot L^{-1} \cdot s$)			
		0 MAC (Control)	0.5 MAC	1.0 MAC	1.5 MAC
R_{aw}	4	0.29 ± 0.06	0.27 ± 0.04	0.31 ± 0.07	0.27 ± 0.04
	6	0.26 ± 0.05	0.23 ± 0.04	0.24 ± 0.04	0.20 ± 0.03
	10	0.29 ± 0.08	0.24 ± 0.04	0.26 ± 0.07	0.24 ± 0.05
	15	0.45 ± 0.10	0.39 ± 0.07	0.41 ± 0.09	0.39 ± 0.06
R_{ti}	4	1.12 ± 0.13	1.13 ± 0.12	1.17 ± 0.12	1.26 ± 0.15
	6	1.32 ± 0.13	1.35 ± 0.14	1.41 ± 0.14	1.48 ± 0.18
	10	2.06 ± 0.30	2.04 ± 0.20	2.07 ± 0.21	2.17 ± 0.28
	15	3.31 ± 0.37	3.11 ± 0.37	3.35 ± 0.43	3.38 ± 0.44
R_L	4	1.41 ± 0.17	1.40 ± 0.15	1.49 ± 0.17	1.52 ± 0.19
	6	1.57 ± 0.47	1.58 ± 0.17	1.65 ± 0.17	1.68 ± 0.21
	10	2.35 ± 0.37	2.28 ± 0.23	2.33 ± 0.27	2.42 ± 0.32
	15	3.76 ± 0.44	3.50 ± 0.44	3.77 ± 0.51	3.78 ± 0.50

Means ± standard error.

R_{aw} = airway resistance; R_{ti} = tissue resistance; R_L = pulmonary resistance; MAC = minimum alveolar concentration.

as PEEP was reduced ($P = 0.001$; fig. 2A). As PEEP was reduced, R_{ti} first decreased (as PEEP decreased from 15 to 10 cmH_2O) and then increased in each dog (fig. 2B). As a result, R_L (the sum of R_{aw} and R_{ti}) also first decreased, and then increased as PEEP was reduced in each dog (fig. 2C).

During Halothane Administration

Halothane had no significant effect on the relationship between lung volume and PEEP ($P > 0.49$; fig. 1). Halothane also had no significant effect on any resistance before VNS over all levels of PEEP ($P > 0.11$ for each resistance; table 1). Halothane was a significant factor in attenuating the increases in each resistance caused by VNS ($P < 0.0001$ for each resistance; table 2). There was a significant interaction between halothane dose and the level of PEEP ($P < 0.0001$ for each resistance), such that halothane effects were greatest at higher halothane concentrations and at low PEEP.

During VNS, halothane markedly blunted the increases in R_{aw} with decreasing PEEP observed in the absence of halothane (fig. 2A). R_{aw} at a given level of PEEP depended significantly on halothane dose ($P < 0.0002$). During VNS, halothane attenuated the increases in both R_{ti} and R_L observed as PEEP was reduced below 10 cmH_2O in the absence of halothane (figs. 2B and 2C). R_{ti} and R_L at a given level of PEEP depended significantly on halothane dose ($P < 0.001$ for each resistance).

Halothane did not significantly affect any arterial blood gas variable ($P > 0.05$ for each variable; table 3).

Discussion

The principal new finding of this study is that in anesthetized dogs during moderate VNS, halothane in doses

TABLE 2. Increase in Resistances Caused by Vagus Nerve Stimulation

Variable	PEEP	Increase in Resistance ($cmH_2O \cdot L^{-1} \cdot s$)			
		0 MAC (Control)	0.5 MAC	1.0 MAC	1.5 MAC
R_{aw}	4	1.85 ± 0.37	0.56 ± 0.10	0.24 ± 0.03	0.19 ± 0.03
	6	0.97 ± 0.39	0.25 ± 0.03	0.16 ± 0.04	0.11 ± 0.02
	10	0.17 ± 0.04	0.10 ± 0.02	0.07 ± 0.02	0.06 ± 0.01
	15	0.08 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.03 ± 0.01
R_{ti}	4	2.13 ± 0.53	0.87 ± 0.24	0.48 ± 0.11	0.23 ± 0.08
	6	1.85 ± 0.53	0.56 ± 0.10	0.37 ± 0.07	0.24 ± 0.03
	10	0.72 ± 0.19	0.45 ± 0.14	0.22 ± 0.06	0.15 ± 0.03
	15	0.79 ± 0.16	0.57 ± 0.07	0.30 ± 0.08	0.31 ± 0.07
R_L	4	3.98 ± 0.71	1.43 ± 0.31	0.73 ± 0.13	0.42 ± 0.08
	6	2.82 ± 0.90	0.81 ± 0.14	0.52 ± 0.11	0.34 ± 0.04
	10	0.89 ± 0.19	0.56 ± 0.15	0.29 ± 0.08	0.20 ± 0.03
	15	0.86 ± 0.17	0.61 ± 0.07	0.35 ± 0.09	0.35 ± 0.07

Means ± standard error.

R_{aw} = airway resistance; R_{ti} = tissue resistance; R_L = pulmonary resistance; MAC = minimum alveolar concentration.

TABLE 3. Effect of Halothane on Arterial Blood Gas Variables

	0 MAC	0.5 MAC	1.0 MAC	1.5 MAC
Pa_{CO_2} (mmHg)	37 ± 2	37 ± 2	36 ± 2	36 ± 2
Pa_{O_2} (mmHg)	172 ± 5	164 ± 6	166 ± 8	166 ± 5
*p*H	7.38 ± 0.02	7.38 ± 0.02	7.40 ± 0.01	7.39 ± 0.02

Means ± standard error.

as low as 0.5 MAC reduces the dependence of R_{aw} on lung volume. Halothane also alters the relationship between R_{ti} and lung volume. Thus, halothane affects the lung volume dependence of both the airway and tissue components of R_L.

RESULTS BEFORE HALOTHANE ADMINISTRATION

The dependence of R_{aw} on lung volume noted in both humans[8–10] and animals[16–19] has been attributed to the mechanical interaction between airways and the surrounding lung parenchyma.[32] The lung parenchyma is attached to the airways and exerts an outward force that "tethers" the airways, helping maintain airway patency. As lung volume and consequently lung elastic recoil decrease, this force of interdependence also decreases, tending to decrease airway diameter and thus increase R_{aw}.

The data before halothane administration are consistent with previous studies of the effects of changes in lung volume on lung resistances in anesthetized dogs.[17–19] After vagotomy, R_{aw} changed over the range of lung volumes examined, a range that includes the FRC in intact animals (at transpulmonary pressures of approximately 3–5 cmH_2O,[25,29] although the magnitude of this effect was small. Similar results have been seen in animals with intact vagi, because anesthetized dogs have little resting smooth muscle tone.[17–19] Thus, when there was little smooth muscle tone, changes in lung recoil pressure caused by the changes in lung volume studied in these dogs had only a small effect on airway diameter. The tendency toward an increase in R_{aw} with increasing lung volume has been previously observed[10,18] and may be caused by longitudinal stretching of the airways or changes in airway fluid dynamics as airway geometry changes. R_{aw} increases substantially at very low lung volumes as airways collapse[19]; however, these lung volumes were not examined because the alveolar capsules do not reliably function at these lung volumes. For this reason, VNS was applied to produce a moderate increase in smooth muscle tone sufficient to cause a significant dependence of R_{aw} on lung volume within the range of lung volumes that could be studied using the capsule technique. This moderate increase did not change end-expiratory lung volumes as measured by the body plethysmograph.

When airway smooth muscle tone was increased by VNS in the absence of halothane, R_{aw} markedly increased as lung volume decreased.[17,19] Apparently, the smaller forces of interdependence tethering the airways at lower lung volumes allowed greater decreases in airway diameter for a given increase in smooth muscle tone.[31,32] This mechanism would explain the dependence of the relationship between R_{aw} and lung volume on airway smooth muscle tone. This dependence is also present in human subjects, because R_{aw} changes less with changes in lung volume when smooth muscle tone is reduced by atropine.[9,10]

Our values of R_{ti} are similar to those previously reported under comparable conditions in dogs,[24,25,29] confirming that R_{ti} is the major component of R_L under these conditions. As in previous studies, R_{ti} before halothane administration and VNS consistently increased with lung volume[21,22,24,33]; the mechanism responsible for this increase is unknown. During VNS in the absence of halothane, as lung volume decreased, R_{ti} first decreased (as PEEP decreased from 15 to 10 cmH_2O, fig. 2B) and then increased (as PEEP decreased to less than 10 cmH_2O). The initial decrease in R_{ti} parallels the decrease observed in the absence of VNS, whereas the later increase is similar to the increase in R_{aw} during VNS observed at lower lung volumes. The mechanisms responsible for increases in R_{ti} with VNS are not completely understood, but they may involve increases in airway smooth muscle tone that affect the elastic properties of the surrounding attached parenchyma; activation of contractile elements in the parenchyma that change its elastic properties; or changes in surfactant properties and distribution.[23–25,34,35]

RESULTS DURING HALOTHANE ADMINISTRATION

During halothane administration, the relationships between resistances and lung volume during VNS resembled those relationships after vagotomy (fig. 2). Thus, it is likely that halothane, which relaxes airway smooth muscle during VNS by several mechanisms,[1,5,6] reduced the dependence of resistances on lung volume predominantly by reducing airway smooth muscle tone. In addition to this mechanism, halothane could also affect the elastic recoil of the lung parenchyma or the coupling between the parenchyma and the airways, lessening the influence of lung volume on airway diameter. However, the lack of halothane effect on resistances before VNS (table 1) and on the pressure–volume relationship (fig. 1) makes changes in recoil or coupling unlikely. Halothane may also affect R_{ti}, which depends on lung elastic properties, by an effect on surfactant; again, the lack of changes in lung recoil in previous studies,[36] the lack of effect on resistances before VNS (table 1), and the lack of effect on the pressure–volume relationship (fig. 1) make this possibility also unlikely. It may be significant that increases in both R_{aw} and R_{ti} produced by VNS were greater at low PEEP and that halothane was most effective in attenuating increases in

both variables at low PEEP (figs. 2A and 2B), suggesting that both variables are linked to a common factor (*i.e.*, smooth muscle tone).

Application to Human Subjects

These results should be applied to human subjects with caution. The induction of general anesthesia in humans has been reported to increase, to decrease, or not to change R_{aw} and R_L[11–15,37]; the effect of anesthesia on R_{ti} in human subjects is unknown. This variation in anesthetic effect is not surprising given the many factors that may influence lung resistances during anesthesia. Anesthetics and adjuvant drugs may directly alter airway smooth muscle tone[1–6] or release histamine and other autacoids. Reflex effects from tracheal intubation or other stimulation may increase smooth muscle tone.[38] Both R_{aw} and R_{ti} vary with breathing frequency and tidal volume,[21,22,24,26,29] which may change with the induction of anesthesia. Anesthesia increases lung elastic recoil,[7] which may affect R_{aw} independently of lung volume. The effects of anesthesia on airway smooth muscle tone, and consequently the relationship between lung resistances and lung volume, depend on the interaction of these factors.

The interpretation of our findings is also affected by the range of lung volumes examined. Our study examined lung volumes corresponding to those at or above FRC in intact animals, when airways remained patent as assessed by the alveolar capsule technique. Decreases in the FRC in human subjects caused by halothane may cause closure of some airways,[7] which may further affect the relationship between R_{aw} and lung volume. Also, breathing at low lung volumes may cause reflex bronchodilation in human subjects.[39] Thus, our results should be extrapolated to these lower lung volumes with caution. However, our results are consistent with a series of human studies measuring the effects of volatile anesthetics on total respiratory system resistance (the sum of R_L and chest wall resistance)[40–42] over a wide range of lung volumes (including residual volume). In these studies, the component of the total respiratory system resistance that varies with lung volume was calculated as an estimate of R_{aw}. Although the use of this variable to estimate changes in R_{aw} with lung volume is complicated by the dependence of both R_{ti} and chest wall resistance on lung volume,[22,43] volatile anesthetics reduce the dependence of this variable on lung volume when added to a baseline nitrous oxide–opioid anesthetic.[40–42]

Clinical Significance

To the extent that the net effect of anesthesia in human subjects is to relax airway smooth muscle, our results suggest that this relaxation would minimize the effect of lung volume on lung resistances. Thus, it cannot be assumed that a decrease in FRC caused by anesthesia in human subjects is a mechanism that significantly increases R_{aw}. If R_L is considered, explanations involving anesthesia-induced changes in lung volume as a factor influencing R_L must also account for the tissue component of this resistance. Because of these considerations and because of many other factors that may influence lung resistances during anesthesia, changes in lung volume should be invoked only with caution as a primary mechanism explaining the effects of anesthesia on lung resistances.

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