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The Effects of CO_2 on Respiratory Mechanics in Anesthetized Paralyzed Humans

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Background: **There is little information concerning the carbon dioxide–related effects on respiratory mechanics in anesthetized, paralyzed subjects; however, hypocapnia or hypercapnia is often permitted in patients with severe brain injury or acute respiratory distress syndrome. Therefore, the carbon dioxide dependence of respiratory mechanics in healthy anesthetized, paralyzed subjects was investigated.**

Methods: **Interrupter resistance (Rint), additional tissue viscoelastic resistance (ΔR), and quasi-static elastance (Est) of lung (L) and chest wall were assessed by means of the rapid end-inspiratory occlusion method in two groups of seven healthy paralyzed subjects anesthetized with diazepam or isoflurane. They underwent ventilation with a fixed pattern and hyperoxic gas mixtures with different fractions of inspired carbon dioxide (F_{ICO_2}) to produce a partial pressures of arterial carbon dioxide (Pa_{CO_2}) of 24.4 ± 3.4, 39.6 ± 3.2, and 62 ± 4.1 (SD) mmHg.**

Results: **Chest wall mechanics and Est,L were unaffected by Pa_{CO_2} changes. With diazepam anesthesia, Rint,L decreased linearly, with increasing Pa_{CO_2}, from 2.3 to 1.4 cm $H_2O \cdot s \cdot l^{-1}$, whereas ΔR,L decreased from 2 to 1.7 cm $H_2O \cdot s \cdot l^{-1}$, though not significantly. With isoflurane anesthesia, the decrease of Rint,L (0.2 ± 0.5 cm $H_2O \cdot s \cdot l^{-1}$) was not significant, and ΔRL remained unchanged. With diazepam, Rint,L was 45 (hypercapnia) to 110% (hypocapnia) greater than with isoflurane.**

Conclusions: **Changes of Pa_{CO_2} from 20–65 mmHg cause increasing bronchodilation in anesthetized, paralyzed subjects, this effect being attenuated or abolished by drugs (*e.g.,* halogenated anesthetics) that depress smooth muscle tone substantially. The carbon dioxide bronchodilating effects are probably direct for peripheral structures and are paralleled by a tendency of lung tissue resistance to decrease. Because local Pa_{CO_2}-related changes in bronchomotor tone promote $\dot{V}_A/\dot{Q}$ matching, this mechanism should be impaired by anesthetics that cause bronchodilation.**

ALTHOUGH patients with severe brain injury are routinely made to hyperventilate[1] and permissive hypercapnia is advocated for patients with acute respiratory distress syndrome,[2] there are no reports on the effects of changes in partial pressure of arterial carbon dioxide (P_{CO_2}) on respiratory mechanics in patients undergoing mechanical ventiliation and healthy subjects, except for the report by Don and Robson.[3] Using the rapid end-inspiratory occlusion technique, they measured the interrupter resistance (Rint,rs) of the respiratory system in healthy subjects anesthetized with nitrous oxide (N_2O) and found that, during hypocapnia, Rint,rs was significantly higher than during normocapnia. The high mean value of Rint,rs obtained during normocapnic conditions suggests that the anesthetic regimen used by these authors increases bronchomotor tone. Conversely, during inhalation of halogenated agents (halothane, enflurane, methoxyflurane), which markedly reduce bronchomotor tone, a progressive decrease of hypocapnic bronchoconstriction has been found with increasing concentration of the anesthetic agents in isolated dog lobes.[4] To our knowledge, there are no reports on the effects of either hypocapnia or hypercapnia on Rint and the additional resistance (ΔR), which reflects pressure dissipation caused by viscoelastic behavior and time constant inequality, in humans anesthetized with halogenated agents.

Accordingly, in the current study, we assessed the effects of hypocapnia and hypercapnia on Rint and ΔR of the lung (L) and chest wall (w) on a group of healthy subjects anesthetized with isoflurane. In addition, we repeated the measurements on another group of healthy subjects anesthetized with diazepam. In contrast to isoflurane, diazepam, at least at subanesthetic doses, has been shown to enhance bronchomotor tone in healthy volunteers.[5]

Methods

Fourteen patients (10 men) undergoing general anesthesia for minor surgery were observed before undergoing intervention. None was obese or had a history or showed clinical evidence of cardiopulmonary disease. The institutional ethics committees (Azienda Ospedaliera di Lecco, Lecco and Istituti Clinici di Perfezionamento, Milan, Italy) approved the investigation, and informed consent was obtained from the patients. Depending on the type of anesthesia, they were classified into two groups (seven subjects, each; mean age (± SD), weight, and height were 27 ± 10 yr, 64 ± 10 kg, and 173 ± 6 cm, and 28 ± 5 yr, 69 ± 11 kg, and 171 ± 13 cm.

In the first group of patients, premedication and induction of anesthesia were obtained using diazepam (0.15 mg/kg intramuscular and 0.3–0.4 mg/kg intravenous, respectively); anesthesia was maintained with additional aliquots of diazepam (0.15 mg/kg intravenous) according to clinical requirements. The second group was premedicated with diazepam (0.2 mg/kg

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intramuscular) and anesthesia was induced using intravenous thiopental sodium (5–7 mg/kg); however, anesthesia was maintained with isoflurane (0.8–1%). In all cases, muscle relaxation was induced using pancuronium bromide (0.1 mg/kg) and maintained with additional aliquots (0.03 mg/kg), as needed. Placed in the supine position, the subjects were transorally intubated using a cuffed endotracheal (ET) tube (Mallinkrodt Medical, Athlow, Ireland; 7.5–8.5 mm ID; length, 30–36 cm) and underwent mechanical ventilation (Siemens Servo Ventilator 900C, Berlin, Germany). To reduce the resistance and compliance of the circuit, a single length of standard low-compliance tubing (2 cm ID; length, 110 cm) was used, and the humidifier was removed during the experiments.

Flow ($\dot{V}$) was measured using a heated pneumotachograph (Fleisch No. 2; Lausanne, Switzerland) connected to the breathing circuit *via* a cone and to a differential pressure transducer (Statham 270; Hewlett-Packard, Andover, MA). The response of the pneumotachograph was linear over the experimental range of flows. Tracheal pressure (Ptr) was measured by means of a pressure transducer (1290A; Hewlett-Packard) connected to a polyethylene catheter (1.5 mm ID; length, 50 cm), the tip of which, protected by a 2-mm thick ring to avoid the entrance of mucus, jutted 3 to 4 cm from the ET tube into the trachea. Esophageal pressure (Pes) was measured with a similar transducer connected to a thin-walled latex balloon (8 cm) filled with 0.5–1 ml of air through a polyethylene catheter (2 mm ID; length, 120 cm) with multiple holes in the last 5 cm near the closed tip. The validity of Pes measurements was verified before the induction of paralysis by use of the occlusion test.[6] Transpulmonary pressure was obtained as Ptr − Pes. With this recording system, phase shift or alteration in amplitude up to 20 Hz did not affect pressure measurements. The signals from the transducers were amplified (Carrier 20-3615-45; Gould, Valley View, OH) and recorded on a personal computer *via* a 16-bit analog-to-digital converter at a sample rate of 200 Hz.

Arterial blood partial pressure of oxygen (P_{O_2}), P_{CO_2} and pH were measured by means of a blood gas analyzer (IL 1620; Instrumentation Laboratory, Lexington, MA) on samples drawn at the beginning and at the end of each test. In the group of subjects during diazepam anesthesia, plasma obtained from these blood samples was also processed for assessment of catecholamine concentration.[7] The heart rate (range: 80–105 min^{-1}), mean systemic arterial pressure (range: 90–105 mmHg), oxygen saturation (always $\geq$ 98%), and end-tidal concentration of carbon dioxide were continuously monitored in addition to the electrocardiogram (Siemens Monitor 7000).

Procedure and Data Analysis

The ventilator settings consisted of a fixed tidal volume (V_T; range: 0.77–1.02 l), inspiratory duration (T_I; range: 0.71–0.97 s) and flow ($\dot{V}$) range: 0.97–1.12 l/s). Respiratory frequency (range: 13–17 min^{-1}) was chosen to decrease the end-tidal carbon dioxide concentration while ventilating with a mixture of 60% N_2 in O_2. Two other mixtures, 5% CO_2–55% N_2 in O_2 and 9% CO_2–51% N_2 in O_2, were used sequentially to perform ventilation of the patients, before returning to the initial mixture. Each mixture was breathed for 9–10 min to ensure a steady end-tidal carbon dioxide concentration; thereafter a series of 25–30 breaths was obtained, in which an end-inspiratory pause, lasting 0.4–0.5 s, depending on the duration of inspiration, was automatically introduced by the ventilator, thus providing end-inspiratory occlusions on a breath-by-breath basis. Moreover, during 5 to 6 breaths, an end-inspiratory occlusion lasting 5 s was introduced by pressing the end-inspiratory hold button of the ventilator. A normally open, solenoid valve, with a closing time of 10 ms, placed between the Y piece of the breathing circuit and the pneumotachograph, was triggered by the inspiratory transistor–transistor logic signal of the ventilator. All measurements were performed at zero end-expiratory pressure applied by the ventilator.

Data analysis was performed as previously described in detail.[8,9] Briefly, for each subject and gas mixture, 25 breaths with the short-lasting end-inspiratory pause and 5 to 6 breaths with the long-lasting end-inspiratory pause were ensemble averaged, and the signals of the individual breaths were superimposed at the onset of airway occlusion as detected on the flow trace. End-inspiratory airway occlusion was followed by a rapid initial decrease in transpulmonary pressure and Pes from the end-inspiratory (Pmax) to a certain value (P1), and by a slow decay that in breaths, with long-lasting occlusions eventually reached in approximately 4 s an apparent plateau value (P2). The rapid pressure decreases (Pmax − P1) divided by the flow preceding the occlusion yield Rint,L and Rint,w, respectively. The slow pressure decreases (P1 − P2) divided by the flow preceding the occlusion yield ΔR,L and ΔR,w, respectively. Finally Est,L and Est,w were computed by dividing the corresponding P2 value by V_T, obtained by numerical integration of the flow signal. In all instances, there was a pause (zero flow) at end-expiration, indicating absence of intrinsic positive end-expiratory pressure.

While Rint,L represents the flow resistance of the airways, ΔR,L reflects the additional pressure dissipation caused by viscoelastic behavior and time constant inequality.[8,10] Similarly, Rint,w and ΔR,w represent, respectively, the ohmic resistance and the viscoelastic behavior of the chest wall tissues.[8,9]

Statistical Analysis

Results are presented as the mean ± SD. Paired Student *t* test was used to compare values of two samples from the same group of subjects. When a significant

Table 1. Arterial Blood Gases, pH, and Catecholamine Concentration at Different Inspired Carbon Dioxide Concentrations in Seven Normal Subjects Anesthetized with Diazepam (A) or Isoflurane (B)

F_{ICO_2}	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pHa	E (pg/ml)	NE (pg/ml)
0					
A	233 ± 22	23.7 ± 2.8	7.53 ± 0.03	150 ± 26 (10–100)	191 ± 72 (150–300)
B	230 ± 32	25.1 ± 4.0	7.50 ± 0.06		
0.05					
A	249 ± 44	40.6 ± 3.7	7.39 ± 0.03	143 ± 27	183 ± 68
B	246 ± 42	38.6 ± 2.5	7.37 ± 0.04		
0.09					
A	222 ± 38	60.9 ± 4.8	7.27 ± 0.02	168 ± 58	203 ± 72
B	208 ± 26	63.1 ± 4.5	7.22 ± 0.05		
0					
A	244 ± 52	25.0 ± 3.0	7.50 ± 0.03		
B	235 ± 34	28.3 ± 6.0	7.45 ± 0.09		

Values are mean ± SD. Normal values for plasma epinephrine (E) and norepinephrine (NE) concentration[6,10] are shown in parentheses.
F_{ICO_2} = fraction of inspired carbon dioxide; Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension; pHa = arterial pH.

difference was found, the Bonferroni *t* test was performed to determine significant difference between different experimental conditions. Linear regression was computed using the least-squares method and statistical assessment was made by covariance analysis (ANCOVA). The criterion of statistical significance was $P < 0.05$.

Results

The average values of arterial P_{O_2}, P_{CO_2}, and pH obtained in the two groups of subjects breathing mixtures of various carbon dioxide concentrations (F_{ICO_2}) are shown in table 1. For any given F_{ICO_2}, none of these values differed significantly between subjects anesthetized with diazepam or isoflurane. In diazepam-anesthetized patients, catecholamine concentration did not change systematically with changes in F_{ICO_2} or time. Norepinephrine concentration remained below the upper limits of healthy, awake resting subjects; however, that of epinephrine exceeded those limits.[7,11]

In all subjects, the rapid decrease in transpulmonary pressure after airway occlusion was easily recognizable on the individual breath records, whereas no such decrease could be seen in the tracings of Pes. Conversely, the rapid decrease in Pes became evident only after ensemble averaging, whereas the decrease in transpulmonary pressure after airway occlusion became clearer (fig. 1). Thus, ensemble averaging proved effective in markedly reducing the cardiac artefact, allowed the measure of Rint,w, and provided a better definition of Rint,L.

The average values of Rint,w and Rint,L obtained in the two groups of subjects at various F_{ICO_2} are shown in table 2. In all subjects, Rint,w did not change with F_{ICO_2}, and its mean value was independent of the type of anesthesia. However, in the subjects anesthetized with diazepam, Rint,L decreased significantly when F_{ICO_2} was increased to 0.05 (ΔRint,L = −0.51 ± 0.2 cm $H_2O \cdot s \cdot l^{-1}$; $P < 0.001$), and from 0.05 to 0.09 (ΔRint, L = −0.46 ± 0.16 cm $H_2O \cdot s \cdot l^{-1}$; $P < 0.001$). In all these subjects, Rint,L increased when breathing at F_{ICO_2} = 0 was resumed; the average values of Rint,L of the first and last test were similar. A tendency for Rint,L to decrease with increasing F_{ICO_2} was observed also in the group of subjects during isoflurane anesthesia, but even the difference in Rint,L for the largest F_{ICO_2} changes (ΔRint,L = −0.2 ± 0.5 cm $H_2O \cdot s \cdot 1^{-1}$) was not significant. Conversely, the values of Rint,L were significantly

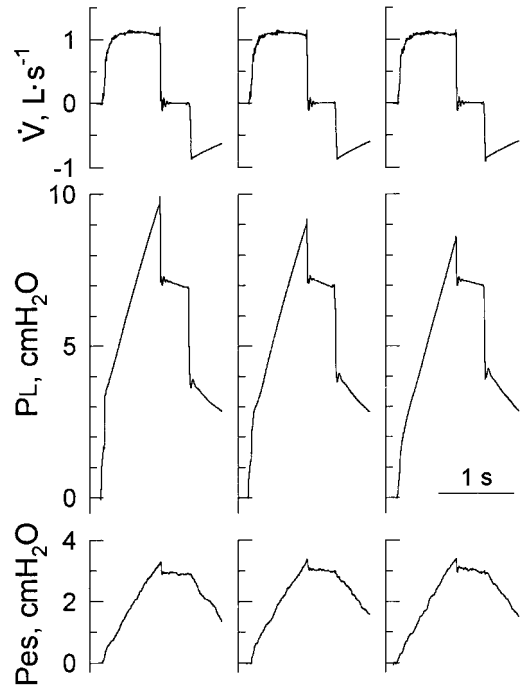

Fig. 1. Ensemble average of records of flow (V̇) and changes in transpulmonary pressure (PL) and esophageal (Pes) pressure from 25 consecutive breaths in a representative subject during hypo- (Pa_{CO_2} = 21 mmHg; *left*), normo- (Pa_{CO_2} = 39 mmHg; *middle*) and hypercapnic conditions (Pa_{CO_2} = 66 mmHg; *right*).

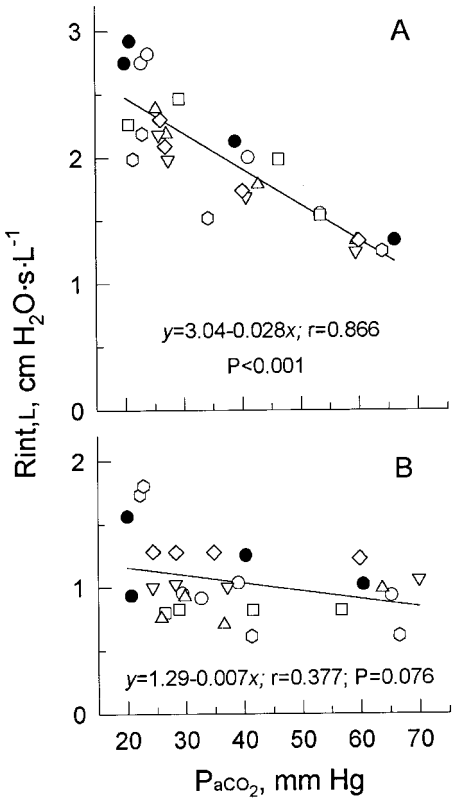

Fig. 2. Relation between arterial P_{CO_2} and lung interrupter resistance (Rint,L) obtained in subjects anesthetized with (*A*) diazepam (*B*) or isoflurane. Different symbols refer to different subjects.

greater in the group of subjects during diazepam anesthesia at all levels of F_{ICO_2} (table 2). Differences in the effects of carbon dioxide on Rint,L between the two groups were not related to larger intersubject variability within the two groups; the sample standard deviation from the regression between individual values of Rint,L and P_{aCO_2} (fig. 2) were similar in the group of subjects undergoing diazepam and isoflurane anesthesia (0.26 and 0.28 cm $H_2O \cdot s \cdot l^{-1}$, respectively).

The average values of ΔR,w and ΔR,L obtained in the two groups of subjects at various F_{ICO_2} are shown in table 2: neither ΔR,w nor ΔR,L changed with increasing F_{ICO_2}; nor did the corresponding mean values differ significantly between the groups receiving diazepam or isoflurane anesthesia. When individual values of ΔR,L were plotted against those of P_{aCO_2} (fig. 3), a tendency for ΔR,L to decrease with increasing P_{aCO_2} was observed only in the subjects anesthetized with diazepam. Also shown in table 2 are the average values of Est,w and Est,L obtained in the two groups of subjects at the various F_{ICO_2}: none of these variables changed significantly with changes in F_{ICO_2}, nor did the corresponding mean values differ significantly between the two groups of subjects.

Discussion

Reported effects of P_{aCO_2} changes in respiratory mechanics of spontaneously breathing, unanesthetized subjects are controversial; with inhalation of carbon dioxide mixtures pulmonary resistance has been shown to increase,[12] decrease,[13] or remain unchanged,[14] whereas hypocapnia was found to cause bronchoconstriction[15–17] and bronchodilation.[18] Part of this variability probably reflects the multiple mechanisms and sites of action of carbon dioxide, especially the balance between contrasting systemic effects[15,19–21] and that between antagonistic local and systemic effects,[19,22] but part could be a result of the various methods used to measure resistance,[23] the changes in the breathing pattern that occur with changing P_{aCO_2}, because hyperventilation is itself bronchoconstricting, or individual differences in bronchial or parenchymal reactivity. Moreover, it has been suggested that in spontaneously breathing unanesthethized subjects the carbon dioxide-related changes of respiratory mechanics are entirely caused by upper airway resistance.[14] On the basis of these results, it is not possible to predict the effects of carbon dioxide on airway resistance in anesthetized subjects undergoing artifical ventilation.

The current study is the first report in which the effects of hypocapnia and hypercapnia on respiratory mechanics have been assessed in healthy, anesthetized, paralyzed subjects. Although with diazepam and isoflurane there was no carbon dioxide-related effect on chest wall mechanics, the effect of carbon dioxide on lung mechanics differed between the two anesthetic agents.

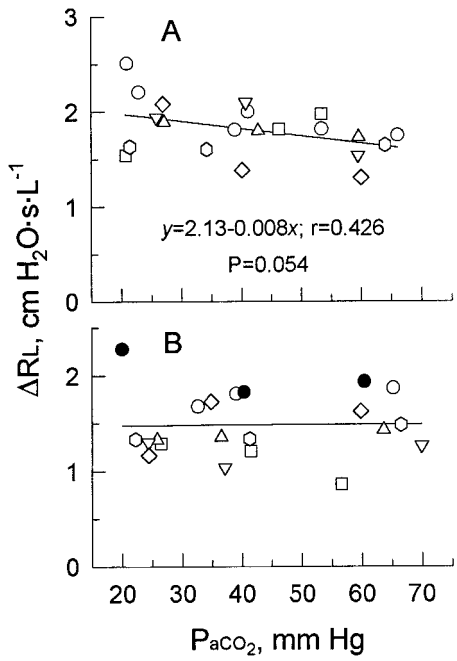

Fig. 3. Relation between arterial P_{CO_2} and lung additional resistance (ΔR,L) obtained in subjects anesthetized with (*A*) diazepam or (*B*) isoflurane. Different symbols refer to different subjects.

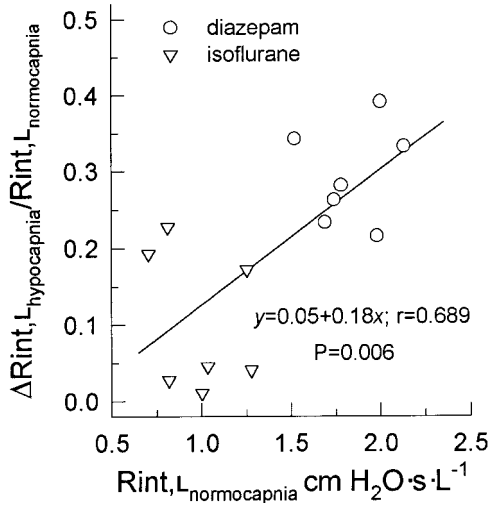

Fig. 4. Relation between changes in lung interrupter resistance (ΔRint,L) during hypocapnia, expressed as a fraction of Rint,L during normocapnia, to normocapnic Rint,L during different types of anesthesia.

With isoflurane, the changes in $Paco_2$ had no significant effects on Rint,L, whereas with diazepam Rint,L increased with hypocapnia and decreased with hypercapnia, the changes being inversely related to $Paco_2$ in the range of 20–70 mmHg. This different response probably occurred because isoflurane can cause marked bronchodilation,[4,24] whereas with diazepam some bronchomotor tone was still present, as indicated by the significantly higher normocapnic values of Rint,L with diazepam as compared with isoflurane (table 2). The baseline bronchomotor tone during normocapnia seems to play an important role in determining the magnitude of the carbon dioxide-related changes in Rint,L, as shown in figure 4, which depicts the relation between the changes in Rint,L caused by hypocapnia (ΔRint,L) and the corresponding normocapnic values. Indeed, ΔRint,L correlates significantly with the normocapnic values of Rint,L. The relevance of the baseline bronchomotor tone is further supported by the results obtained by Don and Robson[3]: their mean value of Rint,L during normocapnia (3 ± 0.5 cm $H_2O \cdot s \cdot l^{-1}$) was markedly greater than that of the subjects anesthetized with diazepam (table 2), and the relative increase of Rint,L with hypocapnia was also greater (~40 *vs.* ~30%). It should be noted that Don and Robson[3] measured the interrupter resistance of the total respiratory system (Rint,rs = Rint,L+Rint,w). Because Rint,w is relatively small and independent of both the level of carbon dioxide and the anesthetic used (table 2), Rint,L was computed by subtracting 0.47 cm $H_2O \cdot s \cdot l^{-1}$ (the mean value of Rint,w in table 2) from Rint,rs given by Don and Robson.[3]

Associated to the changes of Rint,L with changing $Paco_2$ in diazepam-anesthethized subjects, there were parallel, though smaller, changes in ΔR,L (fig. 3A), likely reflecting changes in tissue viscoelastic properties. In fact, the greater decrease in Rint,L with carbon dioxide administration observed in hypocapnic subjects by Don and Robson[3] was paralleled by significant decrease in the difference between dynamic and static elastance of the respiratory system, *i.e.,* a significant decrease in ΔR,L because, as in the current study, inflation volume and flow were the same during hypo- and normocapnia, and Est,w was found to be independent of $Paco_2$ (table 2). Conversely, ΔR,L with isoflurane anesthesia and Est,L with diazepam and isoflurane anesthesia did not change with changes in $Paco_2$ (table 2). Furthermore, although Est,L was similar with diazepam and isoflurane at all levels of $Paco_2$ studied, ΔR,L with hypocapnia was significantly larger with diazepam anesthesia (table 2).

Bronchoconstriction with hypocapnia and bronchodilation with hypercapnia can be ascribed to the direct action of carbon dioxide because these effects are observed in isolated preparations of airway smooth muscles.[25,26] The decrease in Rint,L with increasing Pco_2 in hypocapnic subjects during diazepam anesthesia, which was probably attenuated by the increased plasma levels of catecholamines (table 1), can be therefore explained

Table 2. Lung and Chest Wall Mechanics at Different Inspired Carbon Dioxide Concentrations ($Fico_2$) in Seven Normal Subjects Anesthetized with Diazepam (A) or Isoflurane (B)

$Fico_2$	Rint,L (cm $H_2O \cdot s \cdot l^{-1}$)	Rint,w (cm $H_2O \cdot s \cdot l^{-1}$)	ΔRL (cm $H_2O \cdot s \cdot l^{-1}$)	ΔRw (cm $H_2O \cdot s \cdot l^{-1}$)	Est,L (cm H_2O/l)	Est,w (cm H_2O/l)
0						
A	2.34 ± 0.26	0.45 ± 0.05	1.97 ± 0.26	0.82 ± 0.33	8.4 ± 4.8	5.3 ± 0.7
B	1.15 ± 0.38*	0.51 ± 0.11	1.48 ± 0.38†	0.85 ± 0.08	7.7 ± 2.4	5.6 ± 1.0
0.05						
A	1.83 ± 0.21‡	0.44 ± 0.15	1.79 ± 0.24	0.85 ± 0.36	8.2 ± 4.9	5.4 ± 0.7
B	0.94 ± 0.28*	0.50 ± 0.12	1.47 ± 0.31	0.82 ± 0.33	7.6 ± 2.5	5.5 ± 1.1
0.09						
A	1.37 ± 0.12§	0.44 ± 0.16	1.68 ± 0.21	0.80 ± 0.39	8.6 ± 4.5	5.4 ± 0.6
B	0.95 ± 0.19*	0.48 ± 0.12	1.50 ± 0.37	0.90 ± 0.21	7.9 ± 2.5	5.2 ± 0.9
0						
A	2.41 ± 0.30	0.46 ± 0.15				
B	1.11 ± 0.34*	0.47 ± 0.12				

Values are mean ± SD for interrupter (Rint) and additional resistance (ΔR) and quasi-static elastance (Est) of lung (L) and chest wall (w). Values are significantly different from A under iso-$Fico_2$ conditions (*$P < 0.001$; †$P < 0.05$), at $Fico_2 = 0$ (‡$P < 0.01$), and at $Fico_2 = 0.05$ (§$P < 0.01$).

on the basis of the local effects of carbon dioxide. The latter can also explain the tendency of ΔR,L to decrease with increasing Pa_{CO_2} (fig. 3A) and the finding that the greater decrease in Rint,L observed by Don and Robson[3] with carbon dioxide administration in hypocapnic subjects was paralleled by a significant decrease in ΔR,L. It is conceivable that a decrease in smooth muscle tone occurring in the most peripheral airways and lung parenchyma eventually affects the viscoelastic properties of lung tissue, manifested in ΔR,L changes. Involvement of systemic effects in the observed response to carbon dioxide cannot be ruled out because atropine was not administered in the current study. Systemic effects of carbon dioxide are mediated *via* vagal parasympathetic pathways and are therefore prevented by atropine administration.[15,19–21] They could substantially affect Rint,L because the larger bronchi are the main site of vagally mediated reflexes.[19] However, the impact of the reflex effects of carbon dioxide on bronchomotor tone was probably very small during the current experimental conditions, partly because of the opposite effects caused by central[21] and peripheral chemoreceptor stimulation[22] and partly because of the depression exerted by general anesthetics on ganglionic and central nervous system synapses of the parasympathetic bronchomotor pathway.[27] The vagolytic effect of pancuronium bromide,[28] though modest, should have further contributed to minimize the role of parasympathetic reflexes. Finally, it should be noted that sympathetic responses were not involved in the carbon dioxide-related effects observed in diazepam-anesthetized subjects because plasma catecholamine concentrations were not affected by changes in Pa_{CO_2} (table 1).

From a clinical standpoint, there are two aspects of interest that stem from the current study. (1) In anesthetized, paralyzed, healthy subjects, the carbon dioxide-related changes in resistance offered by intrathoracic airways (Rint,L) are either abolished, as with isoflurane, or relatively small, as with diazepam. Whether this is also the case in patients with acute respiratory distress syndrome undergoing mechanical ventilation or patients with severe brain injury undergoing hyperventilation must be determined. Our results, however, suggest that the high values of pulmonary resistance found in patients with brain injury[1] are not caused by hypocapnia *per se*. (2) Local changes in bronchomotor tone mediated by changes in P_{CO_2} are believed to play an important role in promoting $\dot{V}_A/\dot{Q}$ matching.[29–32] Accordingly, the changes in bronchomotor tone reflected by those in Rint,L with changing P_{CO_2} in subjects anesthetized with diazepam or as anesthetized in the Don and Robson[3] study indicate that during these conditions this mechanism is preserved. In contrast, the regulation of $\dot{V}_A/\dot{Q}$ *via* local changes in P_{CO_2} should be impaired in subjects anesthetized with isoflurane, in whom the carbon dioxide–related changes in Rint,L are abolished.

In conclusion, this study has shown that, in healthy subjects anesthetized with isoflurane, changes in Pa_{CO_2} have no effect on respiratory mechanics, whereas with diazepam pulmonary resistance decreases during hypercapnia and increases during hypocapnia, probably because of the local effects exerted on peripheral airways.

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