Changes in respiratory system resistance and reactance following acute respiratory and metabolic alkalosis in dogs

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Abstract: To differentiate between the effects of respiratory and metabolic alkalosis on respiratory mechanics, respiratory system resistance (Rrs) and reactance (Xrs) were examined in anesthetized, paralyzed, and mechanically hyperventilated dogs. Rrs and Xrs were measured by the forced oscillation method with a random noise input of 0–25 Hz. Restoration to normocapnia by CO_2 inhalation significantly increased Rrs ($+23.4 \pm 4.0\%$), particularly at high-frequency ranges without alterations in Xrs or resonant frequencies, whereas an increase in pH without changes in partial pressure of arterial carbon dioxide ($Paco_2$) by an administration of bicarbonate-carbonate mixture resulted in no significant alteration in Rrs or Xrs. A significant decrease in Rrs ($-16.3 \pm 2.5\%$) following vagotomy or atropine administration was no longer affected by CO_2 inhalation. These results suggest that (1) the vagus nerve appears to play a role in maintaining the resting tension of airway smooth muscle, (2) systemic hypocapnia decreases Rrs presumably due to the central airway dilation, and (3) this response is associated with a change in systemic partial pressure of carbon dioxide (Pco_2) rather than that in pH.

Key words: Alkalosis, Hypocapnia, Respiratory mechanics

Introduction

Although ventilatory response to CO_2 has been extensively studied, the effect of CO_2 on respiratory mechanics is not fully understood. In humans, reported effects of hypercapnia by CO_2 inhalation are conflicting, whereas in anesthetized and intubated dogs hypercapnia has been consistently reported to increase airway resistance [1,2]. Hypocapnia induced by voluntary hyperventilation has been shown to increase respiratory resistance [3–5] and decrease maximum expiratory flow rates [6,7]

in humans; however, no significant change in resistance was also reported [8]. Hypocapnia produced by temporal unilateral pulmonary occlusion invariably increases airflow resistance [9,10]. Conversely, airway dilation with decreased arterial partial pressure of carbon dioxide ($Paco_2$) below the normal range has been demonstrated [10,11]. These incompatible results could be attributable not only to differences in species but also in part to diversities in the methodology. Airway responses to CO_2 appear to be inconsistent in different regions (e.g., upper airway *vs* lower airway or central airway *vs* peripheral airway) and to have dual effects in different circumstances [12]. Furthermore, reflex interactions in response to chemical (CO_2) and mechanical (hyperventilation) stimuli make things more complex [13,14].

Acute changes in $Paco_2$ are usually accompanied by alterations of the acid-base status, which have been reported to affect airway smooth muscle tone in vitro [15,16]. Little attention has been paid to the influence of concomitant changes in the acid-base balance that may also have been responsible for the discrepancies among the previous studies. To my knowledge, few studies have clearly differentiated the effects of $Paco_2$ from that of arterial pH (pHa) on respiratory mechanics in vivo without significant alterations in cardiovascular function.

This study was designed to examine independently the effects of changes in $Paco_2$ and in pHa on resistance (Rrs) and reactance (Xrs) of the respiratory system in dogs without physiologically significant hemodynamic alterations.

Methods

Animal preparation

The study was approved by our institutional animal use and care committee. Seven mongrel dogs, weighing 11.8 ± 1.9 kg (mean $\pm$ SE), were anesthetized with intrave-

nous pentobarbital (20mg·kg^{-1}) and intubated with an endotracheal tube (8.5mm ID). The femoral and pulmonary arteries were cannulated to allow sampling of arterial and mixed venous blood, monitoring of hemodynamic indices (Life Scope 11, Nihon Kohden, Tokyo, Japan), and administration of drugs. Body temperature was maintained between 37° and 39°C with a heating pad (Model K-20, American Hamilton, Cincinnati, OH, USA). The animals were paralyzed with vecuronium (0.2mg·kg^{-1} initially followed by 0.4mg·kg^{-1}·h^{-1}) and artificially ventilated with 100% oxygen by an animal respirator (613D, Harvard Apparatus, South Natick, MA, USA) at a fixed tidal volume of 30ml·kg^{-1}. The purpose of such a large tidal volume was not only to achieve profound hypocapnia but also to minimize the risk of atelectasis, which is inevitable in dogs treated with artificial ventilation in the absence of positive end-expiratory pressure. Monitoring consisted of measurements of blood gases (Model 170, Ciba-Corning Diagnostics, Tokyo, Japan) and of the end-expiratory CO_2 tension (178, Nihon Kohden). Ventilatory frequency was adjusted in an attempt to maintain Paco$_2$ at 20 ± 3mmHg. After a consistent hypocapnic state was obtained, the ventilatory condition remained fixed during the course of the experiments. Anesthesia was maintained by an intravenous infusion of pentobarbital (3.0–4.0mg·kg^{-1}·h^{-1}).

Resistance and reactance determination

Rrs and Xrs were measured using the forced oscillation technique (FOT), similar to the method described by Michaelson et al. [17]. A random-noise signal with a band width of 0–25Hz generated by a noise generator (NJZ-255A, Nihon Musen, Tokyo, Japan) was passed through a power amplifier (POA-7700, Denon, Tokyo, Japan) to excite a loudspeaker (FW-305, Fostex, Tokyo, Japan). The resulting acoustic signal was applied to the respiratory system through a Fleisch-type pneumotachograph (TV-142T, Nihon Kohden). Airway pressure and flow signal were measured by two identical differential pressure transducers (TP-603T, Nihon Kohden), recorded on a magnetic tape by a data recorder (RTP-670A, Kyowa, Tokyo, Japan), and fed into a spectrum analyzer (SD-308A, Scientific Atlanta, San Diego, CA, USA). Fourier analysis allowed the calculation of Rrs and Xrs from the data, which were collected over 10s at functional residual capacity while the animals were apneic. Rrs is determined by the resistive properties of the respiratory system, whereas Xrs reflects the elastic and inertial properties of the system. The validity of the measurements was evaluated at each frequency by a coherence function, and only values with the functions exceeding 0.9 were retained (1.0 means a complete absence of noise or alinearities). The date

were transferred to a computer (Macintosh IIcx, Apple Computer, Cupertino, CA, USA) through the spectrum analyzer and analyzed with standard packages (LabVIEW, National Instruments, Austin, TX, USA and Igor, WaveMetrics, Lake Oswego, OR, USA). To evaluate the overall changes in Rrs and Xrs among these conditions, the area under the curve of Rrs and Xrs as a function of frequency was calculated by the integration and expressed as percent changes from condition I.

Experimental protocol

Rrs and Xrs were measured under four sequential conditions as follows: (I) at Paco$_2$ of 20 ± 3mmHg (hypocapnia); (II) at least 15min after adding CO_2 to the inspired oxygen to maintain a Paco$_2$ of 40 ± 3mmHg (normocapnia); (III) after the pHa was normalized by titrating the bicarbonate-carbonate mixture (0.33M sodium bicarbonate and 0.33M disodium carbonate, BCCmx); and (IV) at least 15min after the discontinuation of CO_2 to allow Paco$_2$ to decrease to as low as 20mmHg. In five dogs, additional measurements were made in three conditions as follows: (V) after atropine injection (0.5mg·kg^{-1}; $n = 2$) or bilateral cervical vagotomy ($n = 3$); (VI) at least 15min after adding CO_2 to the inspired oxygen to maintain a Paco$_2$ of 40 ± 3mmHg; and (VII) 15min after the discontinuation of CO_2 inhalation. Before each measurement, blood gases were measured at least twice 5min apart to confirm achievement of the steady state.

Statistical analysis

All data are expressed as mean ± SEM. Comparisons between the conditions were made by analysis of variance (ANOVA) with repeated measures followed by the Scheffé F-test. The significance level was set at $P < 0.05$.

Results

Table 1 and Fig. 1 summarize the changes in blood gases and acid-base status. Respiratory alkalosis was achieved with mechanical hyperventilation (I). Blood gases were shown to have stabilized within 15–20min after the changes in the condition, confirmed by multiple samplings. CO_2 inhalation by the hyperventilated dogs resulted in decreased pHa (II), which was returned to the baseline level by the administration of BCCmx without a significant change in Paco$_2$ (III). Following the discontinuation of CO_2, Paco$_2$ decreased to the level of condition I, whereas pHa was further increased (IV). Thus, a comparison between (I) and (III) allowed us to

Table 1. Changes in blood gases during the experiment

	I	II	III	IV	V	VI	VII
$Paco_2$ (mmHg)	20.1 ± 0.5	39.4 ± 0.9*	40.1 ± 1.8*	20.4 ± 2.0	20.1 ± 1.6	39.8 ± 1.0*	19.9 ± 1.7
$Pvco_2$ (mmHg)	28.3 ± 1.3	45.2 ± 1.1*	45.7 ± 1.3*	30.2 ± 1.5	29.6 ± 1.8	44.2 ± 1.8	30.0 ± 1.7
pHa	7.49 ± 0.03	7.31 ± 0.03*	7.47 ± 0.02	7.62 ± 0.03*	7.62 ± 0.03*	7.50 ± 0.03	7.63 ± 0.02*
pHv	7.40 ± 0.01	7.28 ± 0.02*	7.39 ± 0.03	7.50 ± 0.03*	7.51 ± 0.03*	7.41 ± 0.03	7.52 ± 0.03*
$Paco_2$ (mmHg)	518.6 ± 83.4	510.4 ± 88.2	512.3 ± 91.7	511.7 ± 86.4	510.6 ± 90.2	510.7 ± 92.6	512.5 ± 89.3

$Paco_2$, partial pressure of arterial carbon dioxide; $Pvco_2$, partial pressure of venous carbon dioxide; pHa, arterial pH; pHv, venous pH; BCCmx, bicarbonate-carbonate mixture.
I, hypocapnia ($Paco_2$ = 20 ± 3 mmHg); II, after CO_2 inhalation ($Paco_2$ = 40 ± 3 mmHg); III, after BCCmx administration to increase pHa; IV, after the discontinuation of CO_2 inhalation; (I–IV: n = 7); V, following cervical vagotomy (n = 3) or atropine administration (n = 2); VI, after CO_2 inhalation; VII, after the discontinuation of CO_2 inhalation (see text for details).
Data are means ± SEM. *P < 0.05 vs I.

Table 2. Changes in hemodynamic indices during the experiment

	I	II	III	IV	V	VI	VII
SAP (mmHg)	116.3 ± 4.9	131.8 ± 5.5*	127.0 ± 5.1*	113.8 ± 5.8	117.2 ± 6.9	120.5 ± 6.6	118.3 ± 7.0
PAP (mmHg)	9.6 ± 0.6	11.1 ± 0.7*	10.8 ± 0.7	9.4 ± 0.6	9.9 ± 0.8	10.1 ± 0.8	10.0 ± 0.9
CVP (mmHg)	7.2 ± 0.4	6.0 ± 0.6*	5.9 ± 0.6*	7.4 ± 0.6	7.4 ± 0.6	7.2 ± 0.6	7.3 ± 0.5
HR (bpm)	126 ± 5	139 ± 8*	139 ± 7*	122 ± 5	132 ± 8	132 ± 7	130 ± 8

SAP, mean systemic arterial pressure; PAP, mean pulmonary arterial pressure; CVP, mean central venous pressure; HR, heart rate; I–VII, same as Table 1 (see text for details).
Data are means ± SEM. *P < 0.05 vs I.
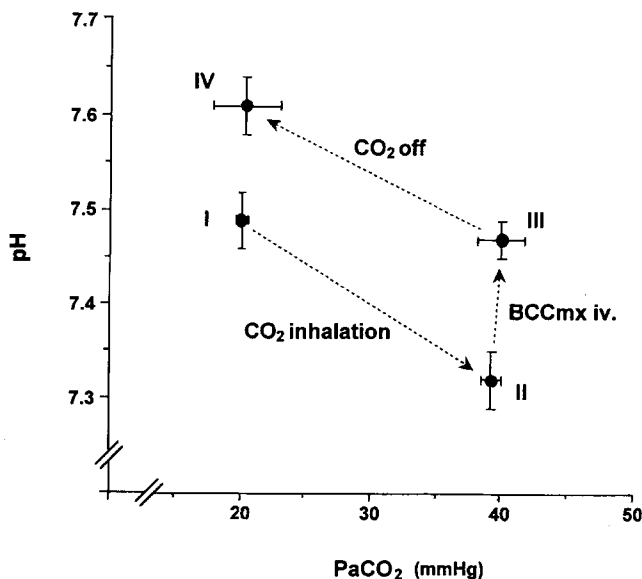
Fig. 1. Relationship between partial pressure of arterial carbon dioxide ($Paco_2$) and arterial pH at each condition. *I*, hypocapnia ($Paco_2$ = 20 ± 3 mmHg); *II*, after CO_2 inhalation ($Paco_2$ = 40 ± 3 mmHg); *III*, after bicarbonate-carbonate mixture (BCCmx) administration to increase pHa without change in $Paco_2$; *IV*, after the discontinuation of CO_2 inhalation (see text). Data are expressed as mean ± SEM

study the effect of a change in $Paco_2$ from hypocapnia to normocapnia, while we could investigate the effect of changes in pHa by comparing (II) and (III) as well as (I) and (IV).

Alterations in hemodynamic indices are shown in Table 2. Following CO_2 inhalation, there were significant increases in systemic and pulmonary arterial pressures and heart rate as well as a decrease in central venous pressure. There was, however, no further change in these indices following BCCmx administration.

Curves representing Rrs and Xrs as a function of frequency are shown in Fig. 2. CO_2 inhalation by the dogs in the hypocapnic state and a resultant increase in $Paco_2$ to normocapnia resulted in a rise in Rrs at all frequencies, particularly the higher ones, which returned to the baseline level after the cessation of CO_2 inhalation. A rise in pHa by BCCmx administration caused essentially no further change in Rrs. Following vagotomy, Rrs no longer responded to an increase in $Paco_2$. Changes is Xrs were similar to those in Rrs, but to a much lesser extent. In this animal, the resonant frequencies deviated somewhat to the left from the mean values (vide infra).

In 5 out of 7 dogs, a coherence value was less than 0.9 at frequencies below 3 Hz, probably due to noise in the measurements, such as cardiogenic oscillation. Consequently, values between 3 and 25 Hz were evaluated (Fig. 3). Rrs increased significantly (+23.4 ± 4.0%) with increasing $Paco_2$ from hypocapnia to normocapnia (condition II), whereas Rrs did not change with an increase in pHa to the level in condition I (+24.2 ± 3.4%, condition III). Following the discontinuation of CO_2 inhalation, Rrs returned to the
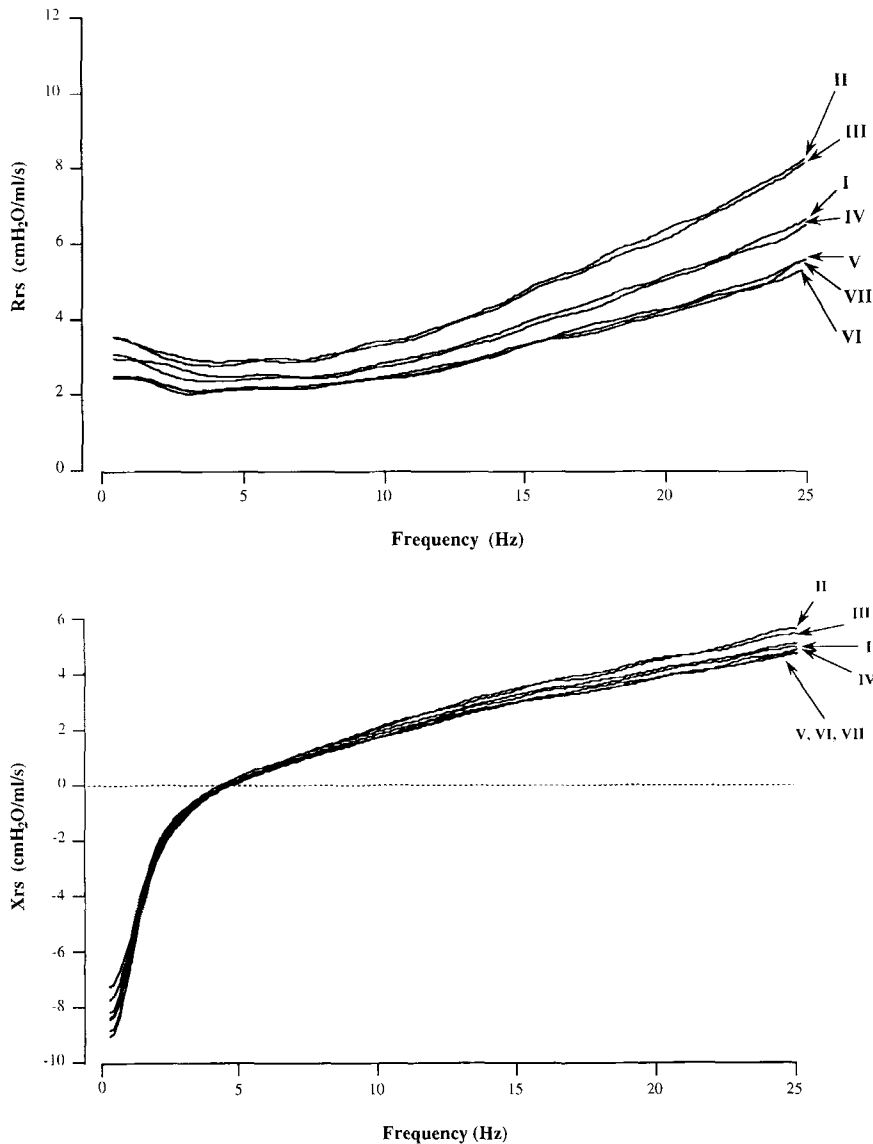
Fig. 2. Typical respiratory system resistance (Rrs, *upper panel*) and reactance (Xrs, *lower panel*) as a function of frequency during the experiment. *I*, hypocapnia ($Paco_2$ = 20 ± 3mmHg); *II*, after CO_2 inhalation ($Paco_2$ = 40 ± 3mmHg); *III*, after BCCmx administration to increase pHa without change in $Paco_2$; *IV*, after the discontinuation of CO_2 inhalation; *V*, following bilateral cervical vagotomy; *VI*, after CO_2 inhalation ($Paco_2$ = 40 ± 3mmHg); *VII*, after the discontinuation of CO_2 inhalation (see text). In this animal, the resonant frequencies deviated somewhat to the left from the mean value

same level as condition I (+1.4 ± 1.9%, condition IV). After vagotomy or atropine administration, there was a significant decrease in Rrs (−16.3 ± 2.5%, condition V), which was unaffected by CO_2 inhalation (−16.5 ± 2.4%, condition VI). Changes in Xrs were not statistically significant.

Since the increased frequency dependence of Rrs and Xrs above 15Hz has been reported to indicate central airway constriction in intubated dogs [18], the slope of Rrs and the Xrs between 15 and 25Hz ($\Delta Rrs/\Delta f$15–25Hz and $\Delta Xrs/\Delta f$15–25Hz, respectively) were plotted (Fig. 4). As for Rrs, the slope increased significantly during normocapnia regardless of pHa, and decreased after vagotomy or atropine injection. A similar trend was observed in the slope of Xrs but was not statistically significant.

The resonance frequency at which Xrs equals 0 was 5.6 ± 0.3Hz at condition I. There was no significant difference in resonance frequencies among the conditions (condition II: 5.1 ± 0.6; condition III: 5.2 ± 0.5; condition IV: 5.4 ± 0.5; condition V: 5.6 ± 0.4; condition VI: 5.5 ± 0.5; condition VII: 5.7 ± 0.6).

Discussion

The present study showed that an increase in $Paco_2$ from the hypocapnic to a normocapnic state without changes in ventilatory condition resulted in a rise in Rrs. By contrast, Rrs was not altered by an increase in pHa without a change in $Paco_2$, whereas a decrease in $Paco_2$ with a further increase in pHa resulted in a decrease in
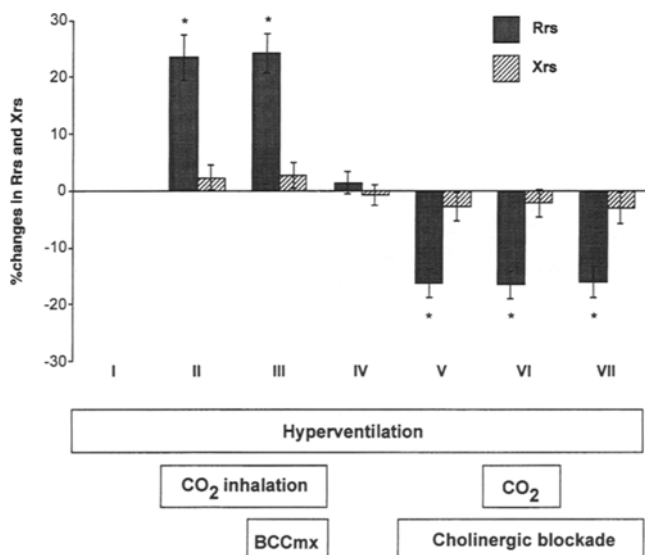
Fig. 3. Percent changes in respiratory system resistance (Rrs) and reactance (Xrs) during the experiments. The area under the curve of Rrs and Xrs between 3 Hz and 25 Hz was calculated and expressed as percent changes from condition I. I–VII, same as in Fig. 2 (see text). Data are expressed as mean $\pm$ SEM. *$P < 0.05$ vs condition I

Rrs. The response to changes in Paco$_2$ was abolished after vagotomy or atropine administration. Thus, the conclusion was reached that systemic hypocapnia results in a decrease in Rrs through cholinergic pathways and that the response is associated with changes in Paco$_2$ rather than those in pHa.

The decrease in Rrs during hypocapnia is consistent with the findings of previous studies in dogs. Hypocapnic blood perfusing the brain has been reported to cause bronchodilatation, probably due to a reduction in vagal tone [11]. Ingram demonstrated that a reduction in Paco$_2$ without a change in alveolar Pco$_2$ (P$_A$co$_2$) was associated with a decrease in airflow resistance, which represented large airway resistance [10].

By contrast, most of the previous studies in humans [3–5], but not all [8], have shown that hypocapnia results in an increase in total respiratory system resistance, which is mainly influenced by large airway function. The diversities in methodology may have played a significant role in this discrepancy. Since the measurement of Rrs in humans was usually made during voluntary hyperventilation to achieve hypocapnia, mechanical factors of increased minute ventilation with intersubject variability may also have affected the results. Indeed, both elevated respiratory frequency and tidal volume increase mechanoreceptor discharge and subsequently diminish the reflex response of airways to chemoreceptor discharge caused by a change in CO$_2$ [13]. In addition, pulmonary resistance has been demonstrated to be

modulated in accordance with the inspiratory activity on the phrenic nerve, reflecting intrathoracic airway smooth muscle contraction with each neural inspiration [14]. In humans [19] as well as in animal preparations [20], passively induced hypocapnia activates vocal cord adductor muscles and decreases the glottic opening, resulting in an increase in laryngeal resistance. Since this resistance represents a significant portion of total airway resistance in the human when measured through a mouthpiece, an increase in the resistance may in part result from increased laryngeal resistance. The animals in the present study were paralyzed, intubated, and apneic during each measurement, while they were mechanically ventilated under the same conditions in the interim, thereby excluding the influence of mechanical factors as well as that of upper airway function.

The FOT with random noise input has been used to characterize Rrs and Xrs over an extended frequency range [5,17]. This technique requires little subject cooperation and only a short period of time for data collection, leading to its high reproducibility. In addition, Kappos et al. [18] observed that, by using the retrograde catheter technique, central airway constriction caused by vagal stimulation increased the frequency dependence of Rrs and Xrs at a higher frequency range (above 15 Hz), indicating the potential usefulness of the FOT for noninvasively differentiating central from peripheral bronchoconstriction. No significant change in Xrs indicates no appreciable alteration in compliance during the experiment. Moreover, the restoration of normocapnia by CO$_2$ inhalation results in an increase in ΔRrs/Δf15–25 Hz without a change in resonant frequen-
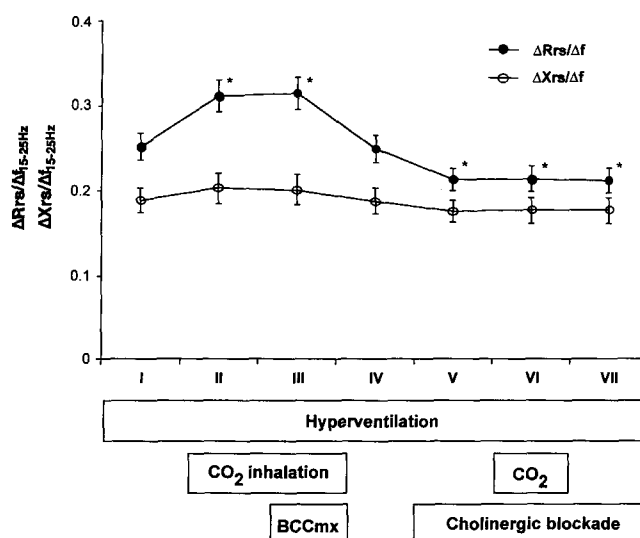
Fig. 4. Slopes of resistance (ΔRrs/Δf15–25 Hz) and reactance (ΔXrs/Δf15–25 Hz) between 15 and 25 Hz at each condition. I–VII, same as in Fig. 2 (see text). Data are expressed as mean $\pm$ SEM. *$P < 0.05$ vs condition I

cies. These features suggest that the predominant sites of bronchodilation secondary to hypocapnia are the central airways [18].

On the other hand, the analysis of flow rates at low lung volumes on maximum expiratory flow volume (MEFV) curves in normal subjects, which are a sensitive index of small airway function, consistently showed a decrease in maximum expiratory flow rates during hypocapnia, indicating peripheral airway constriction [6,7]. Profound alveolar hypocapnia induced by either temporal unilateral pulmonary artery occlusion or extracorporeal circulation, regardless of $Paco_2$, results in an increase in the local airflow resistance and a decrease in compliance [9,10,21]. The major sites of bronchoconstriction in response to alveolar hypocapnia appear to be small airways and the response is not mediated via cholinergic efferents [10,22]. No constrictor response to hypocapnia was observed in the current study, suggesting that the magnitude of bronchoconstriction in the small airways may have been too subtle to lead to the lack of a decrease in Rrs assessed with the FOT. Coon et al. demonstrated that a rise in resistance and a fall in compliance were evident only when P_ACO_2 was below 15mmHg and the pulmonary venous pH was greater than 7.42, although their dogs had a greater metabolic acidosis than ours [23]. Furthermore, gradual attenuation of the constrictor response with prolonged exposure to hypocapnia and tachyphylaxis to repeated exposure have been observed in small airways in dogs [22]. Since the measurements were made at least 15min after the changes in the conditions to assure the stabilization of blood gases, small airway constriction may have been diminished at the time of the measurements. Leaving aside the speculations mentioned above, whether the FOT can be a useful measure to detect small airway function as reliably as the MEFV curve analysis has not yet reached consensus and needs to be studied.

Changes in Pco_2 are often accompanied by alterations in acid-base status, which may also affect respiratory mechanics. The effect of changes in Pco_2 on airway smooth muscle contraction in vitro have been suggested to be pH-dependent [15,16]. In intact dogs in the present study, by contrast, the acute response of Rrs to CO_2 administration is associated with changes in $Paco_2$ but not with those in pHa. Although a few studies have attempted to focus on this issue in vivo, the results are confusing. Changes in pHa by acid [24,25] or bicarbonate infusion [26] do not appear to alter the resistance properties of the respiratory system significantly. On the contrary, tracheal dilation secondary to hypocapnic alkalosis has been shown to be suppressed by a decrease in pHa with hydrochloric acid infusion [27]. However, the changes in pHa were accompanied by an appreciable increase in $Paco_2$ in some of these studies [24,26],

making it difficult to differentiate these two factors. In others, unstable hemodynamics [25,27] and pulmonary edema [25], presumably due to the myocardial depressant effect of metabolic acidosis, were common following the acid infusion. By contrast, the use of BCCmx made it possible to increase pHa without incurring changes in $Paco_2$ or cardiovascular dysfunction. This buffer has been suggested to be more effective for systemic alkalinization than sodium bicarbonate, since it should not generate CO_2 [28]. There were statistically significant changes in hemodynamic indices following CO_2 inhalation which were, however, still within the physiologic range. No significant hemodynamic alterations were observed following BCCmx administration.

Mitchell et al. reported that hypocapnia to produce neural apnea (absence of phrenic nerve activity) caused a decrease in tracheal segment tension to the level achieved by vagotomy or atropine administration [29]. They proposed that cholinergic activity to the airways is driven by the same pattern generators that drive respiration. The intermediate area of the ventral surface of the medulla has been postulated to play a role in the cholinergic responses of the tracheal segment to CO_2 [30]. Moreover, the behavior of intrathoracic airways appears to be similar to that of the trachea [14]. Since CO_2 is a major stimulant to breathing with its ability to pass rapidly through the blood-brain barrier and to decrease pH in the brain, it would be logical to assume that an acute change in systemic $Paco_2$ rather than that in pHa is the more important determinant of central airway smooth muscle tone.

Whereas bronchoconstriction in peripheral airways due to alveolar hypocapnia appears to play a role in regulating regional and collateral ventilation to control ventilation perfusion relationships at the local level [22,31], the functional significance of bronchodilation in central airways responding to systemic hypocapnia remains uncertain.

In summary, a decrease in $Paco_2$ but not an increase in pHa is associated with a fall in Rrs without a significant change in Xrs in intubated and paralyzed dogs. This response is mediated by the vagus nerve. Since the frequency-dependence of Rrs above 15Hz is increased during normocapnia together with unchanged resonant frequencies, the change in respiratory impedance indicates a reflexive dilatory response of central airways to systemic hypocapnia. So far, it is difficult to extrapolate these results immediately to situations in humans. Further investigation is warranted to address this issue in humans.

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