Chest Wall Responses to Rebreathing in Halothane-anesthetized Dogs

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Background: The pattern of respiratory muscle use during halothane-induced anesthesia differs markedly among species breathing quietly. In humans, halothane accentuates phasic activity in rib cage and abdominal expiratory muscles, whereas activity in the parasternal intercostal muscles is abolished. In contrast, halothane abolishes phasic expiratory muscle activity during quiet breathing in dogs, but parasternal muscle activity is maintained. Respiratory muscle responses to CO_2 rebreathing were measured in halothane-anesthetized dogs to determine if species differences present during quiet breathing persist over a wide range of central respiratory drive.

Methods: Chronic electromyogram electrodes were implanted in three expiratory agonists (the triangularis sterni, transversus abdominis, and external oblique muscles) and three inspiratory agonists (the parasternal intercostal muscle, costal and crural diaphragm) of six mongrel dogs. After a 1-month recovery period, the dogs were anesthetized in the supine position with halothane. The rebreathing response was determined by Read's method during anesthesia with stable 1 and 2 minimum alveolar end-tidal concentrations of halothane. CO_2 concentrations were measured in the rebreathing bag using an infrared analyzer. Chest wall motion was measured by fast three-dimensional computed tomographic scanning.

Results: Halothane concentration did not significantly affect the slope of the relationship between minute ventilation ($\dot{V}_E$) and P_{CO_2} ($0.34 \pm 0;04$ [M ± SE] and $0.28 \pm 0.05\,1\cdot min^{-1}\cdot mmHg^{-1}$ during 1 and 2 minimum alveolar concentration anesthesia, respectively). However, 2 minimum alveolar concentration anesthesia did significantly decrease the calculated $\dot{V}_E$ at a P_{CO_2} of 60 mmHg (from 7.4 ± 1.2 to $4.0 \pm 0.6\,1\cdot min^{-1}$), indicating a rightward shift in the response relationship. No electro-

myographic activity was observed in any expiratory muscle before rebreathing. Rebreathing produced electromyographic activity in at least one expiratory muscle in only two dogs. Rebreathing significantly increased electromyographic activity in all inspiratory agonists. Rebreathing significantly increased inspiratory thoracic volume change (ΔV_{th}), with percentage of δV_{th} attributed to outward rib cage displacement increasing over the course of rebreathing during 1 minimum alveolar concentration anesthesia (from $33 \pm 6\%$ to $48 \pm 2\%$ of ΔV_{th}).

Conclusions: Rebreathing did not produce expiratory muscle activation in most dogs, demonstrating that the suppression of expiratory muscle activity observed at rest persists at high levels of ventilatory drive. Other features of the rebreathing response also differed significantly from previous reports in halothane-anesthetized humans, including (1) an increase in the rib cage contribution to tidal volume during the course of rebreathing, (2) recruitment of parasternal intercostal activity by rebreathing, (3) differences in the response of ventilatory timing, and (4) the lack of effect of anesthetic depth on the slope of the ventilatory response. These marked species differences are further evidence that the dog is not a suitable model to study anesthetic effects on the activation of human respiratory muscles. (Key words: Anesthetics, volatile: halothane. Lung: breathing pattern; blood volume; diaphragm; functional residual capacity; intrathoracic rib cage. Measurement technique: computed tomography; electromyography. Muscle: diaphragm; external oblique; parasternal intercostal; respiratory; transversus abdominis.)

THE pattern of respiratory muscle activity during quiet breathing differs markedly among species anesthetized with halothane.[1,2] In humans, halothane accentuates phasic activity in rib cage and abdominal muscles with expiratory actions,[2,3] whereas activity in the parasternal intercostal muscles, which act to expand the rib cage during inspiration, is abolished.[2,4] In contrast, we found in a previous study that in dogs, halothane abolishes phasic activity in muscles with expiratory actions during quiet breathing, whereas parasternal muscle activity is maintained.[1] These species differences may limit the utility of the intact dog as a model to study mechanisms of anesthetic actions on the control of respiratory muscles, at least during quiet breathing.

Conditions characterized by increased ventilatory demand, such as hyperpnea induced by the rebreathing

of expired gas, are powerful stimuli for respiratory muscle recruitment as well as useful tools to study the control of breathing in intact animals and humans.[5] In halothane-anesthetized humans, rebreathing increases activity in respiratory muscles with expiratory actions, such as the internal intercostal and transversus abdominis muscles.[6] However, the profound depression of parasternal intercostal muscle activity observed during quiet breathing persists, even at high minute ventilation produced by rebreathing. If the response of the respiratory muscles to rebreathing in halothane-anesthetized dogs is similar, with recruitment of expiratory muscle activity and little response of the parasternal intercostal muscles, then the dog and other quadrupeds may still be useful models of human respiratory muscle responses to anesthesia. The availability of such models is important because many invasive neurophysiologic studies, important in exploring mechanisms of respiratory responses to anesthesia, are not possible in human subjects.

The overall objective of this study was to further evaluate the suitability of anesthetized dogs as a model of human chest wall function during anesthesia. We measured respiratory muscle responses to CO_2 rebreathing in halothane-anesthetized dogs and compared these responses to those measured in our previous study of human subjects[6] to determine if species differences noted during quiet breathing persisted over a wide range of central respiratory drives.

Materials and Methods

This study was approved by the Institutional Animal Care and Use Committee. These studies were performed on six male mongrel dogs (weighing 9–16 kg). Results during quiet breathing in this series of dogs have been previously reported[1]; the current report focuses on results obtained during CO_2 rebreathing and comparisons with our previous similar study of human subjects.[6]

Electrode Implantation

Anesthesia was induced in the dogs with thiopental and halothane. Bipolar electrodes fashioned from multistranded 31-G polytetrafluoroethylene-coated stainless steel wire (California Fine Wire AS637, Grover City, CA) were implanted with an intraelectrode distance of approximately 3 mm so that the axis between the electrodes was oriented parallel to the direction of the muscle fibers. Electrodes were implanted into the

parasternal intercostal muscle in the third right interspace, the triangularis sterni muscle in the fifth or sixth right interspace, the transversus abdominis muscle in the ventral axillary line midway between the costal margin and iliac crest, the external abdominal oblique muscle close to the transversus abdominis electrode, and the crural and costal portions of the left hemidiaphragm. The diaphragmatic electrodes were implanted *via* a mid-line laparotomy, which was closed in layers. A tracheostomy was performed using a technique that did not require an indwelling tracheal tube. The dogs were given antibiotics and analgesics, and were allowed to recover for at least 1 month to permit full recovery of diaphragmatic function.[7]

Experimental Procedure

After this recovery period, the rebreathing response was determined during halothane anesthesia. Electromyographic (EMG) signals were amplified (Grass P511, Quincy, MA), bandpass filtered between 30 and 3000 Hz, and recorded on digital audio tape (Teac RT100, Montebello, CA) for later processing. The tracheostomy was intubated with a 7.5 mm inner diameter endotracheal tube, and anesthesia was induced using halothane 2% in O_2. After induction, the inspired anesthetic concentration was adjusted to maintain an end-tidal concentration of approximately 0.87% (Beckman LB-2 gas analyzer, Schiller Park, IL), corresponding to 1 minimum alveolar concentration (MAC).[8]

The dog was placed in the supine position and allowed to breathe 30% O_2, 70% N_2. The femoral artery was cannulated to provide samples for arterial blood analysis (IL 1302 blood gas analyzer, Lexington, MA). Gas flow through the endotracheal tube was measured using a pneumotachograph (Fleisch 1, Richmond, VA) connected to a differential pressure transducer (Validyne MP-45, Northridge, CA). Gas flows were integrated to obtain changes in lung volume, which were corrected to body temperature pressure saturated conditions.

The dogs were placed in the dynamic spatial reconstructor, a high-speed x-ray scanner that uses the computed tomography principle to provide three-dimensional images of the thorax at end inspiration and end expiration.[1,9] Ten minutes before each set of measurements, the lungs were inflated twice to 30 cmH_2O airway opening pressure to provide a consistent volume history.

Dynamic spatial reconstructor scans were first performed during quiet breathing. These measurements

were taken as representative of the pattern of breathing at the onset of rebreathing, and are denoted as "initial" measurements in subsequent text. To determine the response to CO_2 rebreathing, the dogs rebreathed into a 4-L bag initially filled with 7% CO_2, 93% O_2 until the CO_2 concentration in the bag, measured with an infrared analyzer, reached approximately 10%. At this time, dynamic spatial reconstructor scans were obtained. These measurements are denoted as "final" in subsequent text. The inspired concentration of halothane was then increased to produce end-tidal concentrations corresponding to 2 MAC. After stable end-tidal concentrations of halothane were achieved (requiring at least 30 min), measurements were repeated during quiet breathing and CO_2 rebreathing. Because increasing anesthetic depth increases the resting P_{CO_2}, rebreathing during 2 MAC anesthesia was performed with the bag initially filled with 8% CO_2, 92% O_2, and continued until the CO_2 concentration in the bag reached approximately 11%.

Data Analysis

Electromyographic signals recorded on tape were processed with a custom-built third-order Paynter filter to provide a 100 ms moving time average (MTA).[10] Every 30 s, five successive breaths during rebreathing were analyzed. The MTA tracings were digitized. To quantify the EMG activity of the parasternal intercostal muscles and the diaphragm (referred to hereafter as inspiratory muscles), the mean rate of MTA increase during the period of activity was calculated.[6] The duration of electrical activity was measured directly from the raw EMG signals. The presence or absence of phasic activity in the transversus abdominis, external oblique, and triangularis sterni muscles (referred to hereafter as "expiratory muscles") was noted.

To summarize previous descriptions of image processing of images obtained with the dynamic spatial reconstructor,[1,9,11] each scan produced a three-dimensional volume image of the thorax composed of cubic volume elements (voxels) with edge lengths of 1.3 mm. Thoracic volume (V_{th}) was determined by counting the number of voxels in the thoracic cavity. Changes in V_{th} from the beginning to the end of inspiration (ΔV_{th}) were partitioned into volumes displaced by the diaphragmatic and rib cage surfaces. Changes in thoracic liquid volume during inspiration (ΔV_{liq}), presumably representing changes in thoracic blood volume,[1,11] were calculated as the difference between ΔV_{th}

and tidal volume (V_T) measured by the integration of gas flow ($\Delta V_{liq} = \Delta V_{th} - V_T$).

The rate of increase of MTA activity for each muscle was expressed as a fraction of its value during quiet breathing during 1 MAC anesthesia (before rebreathing). By referring activities to those present during 1 MAC anesthesia, effects of anesthetic depth could be examined. Linear regressions of the rate of increase of MTA activity of the parasternal intercostal muscle, costal diaphragm, crural diaphragm, and expiratory minute ventilation ($\dot{V}_E$), against CO_2 partial pressure in the rebreathing bag were performed.[6] Mean correlation coefficients for all conditions studied were 0.91 ± 0.02, 0.95 ± 0.01, 0.95 ± 0.01, and 0.97 ± 0.01 for the parasternal intercostal muscle, costal diaphragm, crural diaphragm, and $\dot{V}_E$, respectively. Regression coefficients (slope and intercepts) were compared among 1 and 2 MAC anesthesia using paired t tests.

Other variables were compared using two-way repeated-measures analysis of variance, with factors being (1) depth of anesthesia, and (2) initial *versus* final measurements during CO_2 rebreathing. The significance of the interaction term between these two factors determined whether changes in a variable produced by rebreathing depended on the depth of anesthesia. The Student-Neuman-Keuls statistic was used for *post hoc* testing. A P value of less than 0.05 was considered significant.

Results

Rebreathing increased Pa_{CO_2} by 20 ± 4 and 23 ± 3 mmHg during 1 and 2 MAC halothane anesthesia, respectively, increases that did not significantly differ (table 1). Halothane concentration did not significantly affect the slope of the relationship between $\dot{V}_E$ and P_{CO_2} (0.34 ± 0.04 and $0.28 \pm 0.05 \, l \cdot min^{-1} \cdot mmHg^{-1}$ during 1 and 2 MAC anesthesia, respectively; fig. 1). However, 2 MAC anesthesia did significantly decrease the calculated $\dot{V}_E$ at a P_{CO_2} of 60 mmHg (from 7.4 ± 1.2 to $4.0 \pm 0.6 \, l \cdot min^{-1}$), indicating a rightward shift in the stimulation-response relationship. Both breathing frequency and tidal volume significantly increased during the course of rebreathing at both depths of anesthesia (table 1). The increase in tidal volume, but not breathing frequency, was significantly greater during 1 MAC anesthesia. These changes were accompanied by a significant decrease in inspiratory time, whereas the ratio of the duration of inspiration to the total period of breathing remained unchanged (table 1). The magni-

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Table 1. Changes in Ventilatory Parameters Produced by Rebreathing

	1 MAC Halothane		2 MAC Halothane	
	Initial	Final	Initial	Final
f (min^{-1})	24 ± 5	33 ± 7*	26 ± 4	36 ± 5*
V_T (ml)	143 ± 8	343 ± 35*	122 ± 4	242 ± 29*
$\dot{V}_E$	3.3 ± 0.5	9.1 ± 1.1*	3.1 ± 0.4	8.7 ± 1.6*
T_I (S)	0.95 ± 0.09	0.79 ± 0.11*	0.87 ± 0.08	0.60 ± 0.06*
T_I/T_{TOT}	0.36 ± 0.04	0.38 ∓ 0.04	0.36 ± 0.04	0.35 ± 0.04
Pa_{CO_2} (mmHg)	45 ± 1	66 ± 4*	53 ± 3†	76 ± 4*

Values are mean ± SE.

MAC = minimal alveolar concentration; f = breathing frequency; V_T = tidal volume; $\dot{V}_E$ = minute ventilation; T_I = inspiratory time; T_{TOT} = total period of breathing; Initial = values measured during quiet breathing; Final = values measured at the conclusion of rebreathing.

*Significant difference from initial value.

† Significant difference in initial value *versus* 1 MAC.

tude of these changes did not depend on anesthetic depth.

The response of the inspiratory muscles to rebreathing was quantified as the relationship between the rate of increase of MTA activity and the Pco_2. Rebreathing consistently increased activity in the parasternal intercostal muscle and both costal and crural portions of the diaphragm (fig. 2). Increasing the end-tidal concentration of halothane to 2 MAC significantly shifted
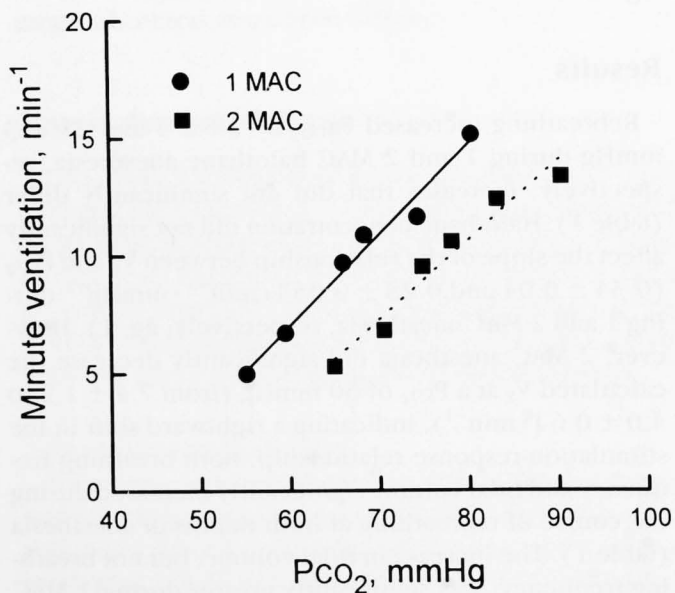
the relationship between MTA rate of increase and Pco_2 for each inspiratory muscle, such that the MTA rate of increase was significantly less at a given Pco_2 (table 2). However, the slope of this relationship was decreased at 2 MAC only for the parasternal intercostal muscle; the responses of both portions of the diaphragm were

Fig. 1. Expired minute ventilation as a function of Pco_2 in the rebreathing bag during CO_2 rebreathing in one dog during 1 and 2 MAC halothane anesthesia (*circles* and *squares*, respectively). Lines denote linear regressions used to calculate parameters for statistical analysis.
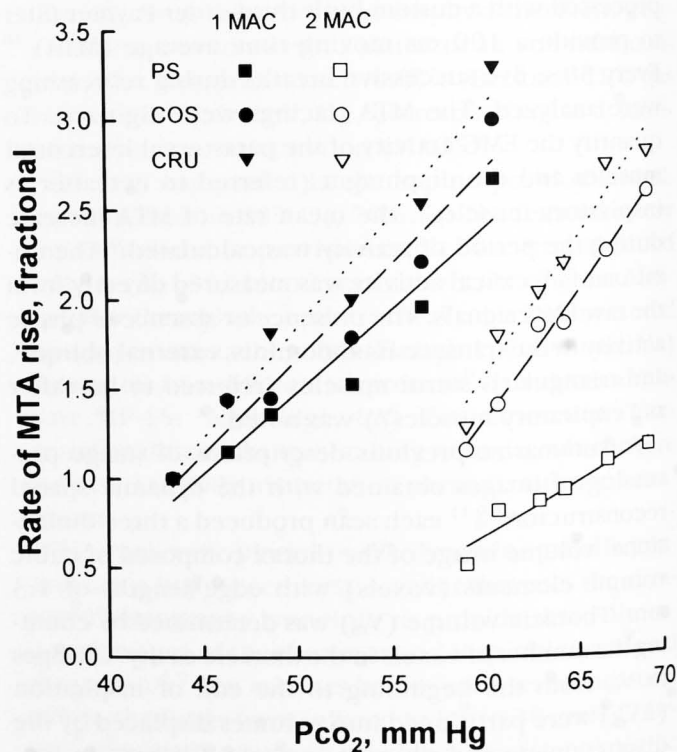

Fig. 2. Rate of increase of moving time average (MTA) activity for the parasternal intercostal (PS), costal diaphragm (COS), and crural diaphragm (CRU) as a function of Pco_2 in the rebreathing bag.

Table 2. Electromyogram Activity of Inspiratory Muscles

	1 MAC Halothane		2 MAC Halothane	
	Slope (mmHg^{-1})	MTA$_{60}$	Slope (mmHg^{-1})	MTA$_{60}$
Parasternal intercostal	0.16 ± 0.04	3.01 ± 0.51	0.10 ± 0.02*	1.13 ± 0.39*
Costal diaphragm	0.19 ± 0.04	3.57 ± 0.59	0.19 ± 0.03	1.82 ± 0.47*
Crural diaphragm	0.24 ± 0.06	4.19 ± 0.69	0.21 ± 0.05	2.34 ± 0.47*

Values are mean ± SE and represent coefficients from linear regressions performed on the data from individual dogs. These regressions describe the relationship between the rate of rise of moving time average (MTA) electromyogram activity, expressed as a fraction of activity during quiet breathing under 1 MAC anesthesia, and the P_{CO_2}. MTA$_{60}$ is the MTA rate of increase at a P_{CO_2} of 60 mmHg.

* Significant difference from value during 1 MAC anesthesia, paired t test.

not altered (table 2). The duration of EMG activity decreased during the course of rebreathing for each inspiratory muscle (table 3). This decrease did not differ among 1 and 2 MAC anesthesia for any muscle.

At the onset of breathing, no EMG activity was observed in any muscles with expiratory actions (the triangularis sterni, the external oblique, and the transversus abdominis). During 1 MAC anesthesia, activity was present at the conclusion of rebreathing in the triangularis sterni of two dogs, the external oblique of one dog, and the transversus abdominis of one dog (table 4). During 2 MAC anesthesia, activity was present in the triangularis sterni of two dogs at the conclusion of rebreathing; no activity was noted in the transversus abdominis or external oblique muscles.

Rebreathing significantly increased the inspiratory change in total thoracic volume (ΔV_{th}) measured with the dynamic spatial reconstructor (table 5), an increase that was greater during 1 MAC anesthesia. Rebreathing did not affect the inspiratory change in thoracic liquid volume. Rebreathing significantly increased the inspiratory volume displacement of the rib cage, an increase that was significantly less during 2 MAC anesthesia. Accordingly, the relative contribution of the rib cage to ΔV_{th} was significantly increased by rebreathing during

1 MAC, but not 2 MAC, halothane anesthesia. Rebreathing also significantly increased the volume displacement of the diaphragm, an increase that did not depend on anesthetic depth. Rebreathing did not significantly change the end-expiratory thoracic volume (table 5), even in those dogs that developed phasic activity in expiratory muscle groups at the conclusion of rebreathing. Thus, this expiratory activity, when present, did not have a significant mechanical action to actively reduce end-expiratory thoracic volume.

Discussion

We found that halothane-induced suppression of expiratory muscle activity, previously observed in dogs during quiet breathing, persisted at high levels of central respiratory drive produced by increases in Pa_{CO_2}. In contrast, the parasternal intercostal muscles were briskly recruited by rebreathing. This recruitment was reflected in the significant contribution of the rib cage to increases in tidal volume produced by rebreathing. These and several other features of the rebreathing response differ significantly from previous reports in halothane-anesthetized humans.

Table 3. Duration of Electromyogram Activity of Inspiratory Muscles

	1 MAC Halothane		2 MAC Halothane	
	Initial	Final	Initial	Final
Parasternal intercostal	1.24 ± 0.15	0.84 ± 0.06*	0.98 ± 0.09	0.69 ± 0.04*
Costal diaphragm	1.04 ± 0.09	0.83 ± 0.07*	1.00 ± 0.06	0.67 ± 0.03*
Crural diaphragm	0.91 ± 0.08	0.80 ± 0.08*	0.84 ± 0.08	0.65 ± 0.04*

Values are mean ± SE (seconds).

Initial = values measured during quiet breathing; Final = values measured at the conclusion of rebreathing.

* Significant difference from initial value.

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Table 4. Incidence of Expiratory Muscle Activity during Rebreathing

Dog No.	1 MAC Halothane			2 MAC Halothane		
	Triangularis Sterni	External Oblique	Transversus Abdominus	Triangularis Sterni	External Oblique	Transversus Abdominus
1	+	+	−	−	−	−
2	−	−	−	+	−	−
3	+	−	+	+	−	−
4	−	−	−	−	−	−
5	−	−	−	−	−	−
6	−	−	−	−	−	−

+ = presence of phasic activity at some point during rebreathing; − = absence of phasic activity during rebreathing.

To examine these species differences (table 6), we refer primarily to our previous study of the rebreathing response in anesthetized humans.[6] In many ways, the experimental protocol followed in the current study of dogs was similar, including: (1) subject positioning, (2) halothane induction without the use of other drugs, and (3) bypassing of the upper airway (by orotracheal intubation in humans and tracheostomy in dogs). Differences between the two studies include: (1) the inclusion of measurements at 2 MAC in the dogs, and (2) a greater increase in Pa_{CO_2} during the course of rebreathing in the dogs (20 ± 4 mmHg in dogs $vs.$ 13 ± 2 mmHg in humans during 1 MAC anesthesia). However, the relative increase in minute ventilation produced by rebreathing was not significantly different in humans and dogs (3.7 ± 0.4 and 2.9 ± 0.4 fold, respectively).

First, we consider overall ventilatory timing. Halothane produces tachypnea in both humans and dogs during quiet breathing, an effect that is apparently centrally mediated.[12–14] Rebreathing increased breathing frequency in these halothane-anesthetized dogs, an effect also noted in awake and pentobarbital-anesthetized dogs,[15–19] and in awake humans.[20] These increases in breathing frequency are associated with decreases in the duration of inspiration. These changes in duration may be caused by increases in tidal volume that terminate inspiration via vagally mediated input from pulmonary stretch receptors. In contrast, breathing frequency decreases during the course of rebreathing in human subjects, associated with no change in the duration of inspiration, but rather a prolongation of expiration.[6,21] That V_T increases significantly without changing inspiratory time in humans, but not in dogs, may suggest that vagal influences dependent on V_T may be more important in halothane-anesthetized dogs compared with halothane-anesthetized humans. Other studies have also noted similar significant differences

Table 5. Chest Wall Volumes

	1 MAC Halothane		2 MAC Halothane	
	Initial	Final	Initial	Final
ΔV_{th} (ml)	160 ± 11	$368 \pm 37^*$	131 ± 4	$286 \pm 42^{*\dagger}$
ΔV_{liq} (ml)	18 ± 5	25 ± 7	9 ± 5	28 ± 13
Volume displaced by rib cage				
ml	56 ± 12	$177 \pm 23^*$	$18 \pm 2\ddagger$	$69 \pm 28^{*\dagger}$
$\%\Delta V_{th}$	33 ± 6	$48 \pm 2^*$	$14 \pm 2\ddagger$	$23 \pm 6\dagger$
Volume displaced by diaphragm				
ml	104 ± 6	$190 \pm 15^*$	113 ± 6	$202 \pm 17^*$
$\%\Delta V_{th}$	67 ± 6	$52 \pm 2^*$	$86 \pm 2^*$	$77 \pm 6\dagger$
End-expiratory thoracic volume (ml)	779 ± 41	805 ± 43	784 ± 46	787 ± 47

ΔV_{th} = inspiratory change in thoracic volume; ΔV_{liq} = inspiratory change in thoracic liquid volume.

* Significant difference from initial value.

† Significant interaction between depth and condition.

‡ Significant difference in initial value *versus* 1 MAC.

Table 6. Comparison of Rebreathing Responses in Dogs and Humans during 1 MAC Halothane Anesthesia*

Changes over the Rebreathing Period	Dogs	Humans
Recruitment of parasternal intercostals	Yes	No
Recruitment of transversus abdominis	No	Yes
Tidal volume	↑	↑
Breathing frequency	↑	↑
Duration of inspiratory electromyogram activity	↓	↑
Contribution of rib cage expansion to tidal volume	↑	↓

↑ = increases over the course of rebreathing; ↓ = decreases over the course of rebreathing.

* Data from Warner and Warner.[6]

between the effects of intravenous anesthetics on ventilatory timing during rebreathing in animals and humans.[22,23]

We found that increasing anesthetic depth from 1 to 2 MAC did not change the slope of the relationship between $\dot{V}_E$ and P_{CO_2}. In contrast, Brandstater *et al.*[24] found in four halothane-anesthetized dogs that increasing anesthetic depth from 1 to 2 MAC profoundly depressed this slope. However, their values for MAC, determined individually in each dog studied, exceeded those used in our study (0.98% *vs.* 0.86% halothane, respectively). Perhaps related to this difference, they found that their dogs became apneic at 2.1 MAC, behavior clearly different from that noted in this and other studies. Analysis of inspiratory muscle EMG activity shows that the preservation of the slope of the $\dot{V}_E$ response with increases in anesthetic depth is associated with preservation of the response of the electrical activity of the diaphragm in these dogs. Consistent with these measurements, increases in volume displaced by the diaphragm were preserved as depth increased. These findings are consistent with those of Stuth *et al.*,[25] who found in vagotomized, isoflurane-anesthetized dogs that the response of phrenic nerve activity to steady-state changes in Pa_{CO_2} over a similar range was not affected by changing anesthetic depth from 1 to 2 MAC. The EMG responses of the costal and crural portions of the diaphragm to rebreathing were similar, unlike previous reports in pentobarbital-anesthetized dogs.[19,26]

In contrast to these findings in dogs, Fourcade *et al.*[27] found that increasing anesthetic depth from 1 to 2 MAC significantly decreased the slope of the relationship between $\dot{V}_E$ and P_{CO_2} in halothane-anesthetized humans. If this slope is interpreted as a measure of the overall gain of the respiratory controller in response to in-creases in central respiratory drive, this finding suggests that the human respiratory controller is more sensitive to halothane's effects over this range of anesthetic dose. The effect of increasing anesthetic depth on the responses of individual respiratory muscles to CO_2 rebreathing in human subjects is unknown.

In contrast to the preservation of the EMG response observed in the diaphragm, the slope of the relationship between parasternal EMG activity and P_{CO_2} was depressed in dogs when anesthetic depth was increased from 1 to 2 MAC. Consistent with this finding, increases produced by rebreathing in the volume displaced by the rib cage were attenuated as anesthetic depth increased. During quiet breathing, increasing the halothane dose from 1 to 2 MAC also preferentially decreases parasternal activity in dogs[1] and cats[28] during quiet breathing.

No quantitative measurements are available in dogs comparing activity in the parasternal intercostal muscle while awake, with activity while anesthetized, although all of the dogs in the current study demonstrated marked phasic inspiratory activity while awake.[1] Human parasternal intercostal muscle activity is clearly more sensitive to halothane-induced depression compared with the dog. During quiet breathing, halothane abolishes parasternal intercostal activity in humans.[2,4] During 1 MAC halothane anesthesia, rebreathing produces minimal recruitment of parasternal muscle activity in humans,[6] whereas we noted brisk recruitment in the dog under similar conditions. These differences in the pattern of parasternal intercostal muscle activity are correlated with differences in the pattern of chest wall motion between the two species. During the course of rebreathing at 1 MAC halothane anesthesia, the relative contribution of rib cage expansion to tidal volume increased in these dogs, but decreases in humans.[6]

Possible mechanisms responsible for this marked species difference in the sensitivity of parasternal intercostal muscle activity to halothane-induced depression are unclear. It has been proposed that suppression of such activity in human subjects is related to depression of proprioceptive feedback from muscle spindles in the parasternal intercostal muscles.[4,29] However, these spindles are also present in the intercostal muscles of the dog. Furthermore, in the human, the abdominal muscles, which also have many muscle spindles, are recruited by halothane anesthesia.[2,3] In animals, evidence exists for separate premotor pathways controlling phrenic and intercostal motoneurons, so

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that the source of differential suppression of phrenic and intercostal activities by halothane could be in the respiratory controller itself in addition to possible effects on motoneurons.[30] There are no comparable data in humans, other than to note that phrenic and intercostal motoneurons can be differentially activated by voluntary effort, suggesting separate premotor control systems that may be differentially affected by halothane.

Pronounced species differences were also noted in the effect of halothane on the responses of rib cage and abdominal muscles with expiratory actions. Phasic activity was absent at the onset of rebreathing, and developed in only a minority of dogs. In dogs, when activity did develop, it had no measurable mechanical effect, as measured by end-expiratory thoracic volume. If a mechanical effect had been present, the end-expiratory thoracic volume would be decreased compared with quiet breathing[9,11]; however, this was not observed. In contrast, expiratory muscle activity increases significantly during rebreathing in halothane-anesthetized humans, with marked mechanical effects.[6]

The mechanism responsible for the profound suppression of expiratory muscle activity in dogs is unclear. The central respiratory rhythm generator controls separate groups of medullary inspiratory and expiratory neurons that drive the motoneurons of inspiratory and expiratory muscle groups.[30] Activity of these neurons is also influenced by afferent activity from peripheral receptors. For example, vagotomy profoundly depresses expiratory muscle activity in the dog and other quadrupeds, suggesting that vagal input has an important facilitatory influence on expiratory motoneuron activity in anesthetized animals.[31,32] Halothane could exert differential effects on separate medullary neurons or motoneurons to inspiratory and expiratory muscle groups. Stüth et al.,[25] however, found that expiratory bulbospinal neurons were more resistant to isoflurane-induced suppression compared with the phrenic nerve; inspiratory bulbospinal nerves were not examined. Steady-state increases in Pa_{CO_2} increased activity in both the phrenic nerve and expiratory bulbospinal nerves. Because in these dogs vagotomy and pneumonectomy had been performed to eliminate afferent activity from lung and chest wall receptors, this finding suggests a differential sensitivity of inspiratory and expiratory bulbospinal neurons to isoflurane. Similar findings have been reported in a similar feline preparation for halothane.[33] The very different pattern of results observed in the EMG activities of the intact animals in the current study suggests that halothane-

induced suppression of expiratory muscle activities may by modulated via peripheral afferent activity.

We have little insight into the mechanisms responsible for these species differences in the response of expiratory muscle groups. Humans and quadrupeds such as dogs use very different strategies of breathing while awake. For example, awake quadrupeds exhibit prominent phasic expiratory activity in rib cage and abdominal muscles in all body positions, so that expiration is an active process, even during quiet breathing.[15,16,34] This activity provides an important mechanical contribution to the tidal volume in dogs in the following manner.[9,11,35,36] During expiration, this activity constricts the chest wall, so that thoracic volume is less than it would be in the absence of muscle activity (i.e., less than its relaxed volume). At the onset of inspiration, this activity ceases, and thoracic volume passively increases to approach relaxed volume. Muscles with inspiratory activity, such as the parasternal intercostal muscles and diaphragm, then are activated and complete the inspiration. In contrast, the expiratory muscles of humans demonstrate phasic activity only during hyperpnea, such as produced by exercise.[37] In other words, in humans, expiration is usually a passive process. These fundamental differences in breathing strategies may reflect adaptations to the differing gravitational challenges posed by the predominant positions maintained by each species (upright in humans and prone in dogs). These alternative strategies imply significant species differences in systems controlling the extradiaphragmatic muscles of respiration, systems that respond quite differently to anesthetic drugs.

It is important to note that we studied primarily the individual effectors of an overall system to maintain chemical homeostasis. The presence of species differences in the control of individual respiratory muscles does not necessarily imply the presence of such differences in all other elements of the system (e.g., chemoreceptors). However, some global measures of overall ventilatory control (such as the response of ventilatory timing parameters) differ significantly between dogs and humans, suggesting species differences in anesthetic effects at sites other than just individual effector muscles.

We conclude that in the dog, CO_2 rebreathing during halothane anesthesia significantly increases the activity of the parasternal intercostal muscles, whereas activity in respiratory muscles in the rib cage and abdomen with expiratory actions remains absent. These findings are markedly different from those observed in previous

studies in humans, and provide further evidence that the dog, and perhaps other quadrupeds, is not a suitable model to study anesthetic effects on human respiratory muscle control.

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