Anesthesiology
82:20–31, 1995

Human Chest Wall Function while Awake and during Halothane Anesthesia

II. Carbon Dioxide Rebreathing

David O. Warner, M.D.,* Mark A. Warner, M.D.*

Background: **Changes in the distribution of respiratory drive to different respiratory muscles may contribute to respiratory depression produced by halothane. The aim of this study was to examine factors that are responsible for halothane-induced depression of the ventilatory response to carbon dioxide rebreathing.**

Methods: **In six human subjects, respiratory muscle activity in the parasternal intercostal, abdominal, and diaphragm muscles was measured using fine-wire electromyography electrodes. Chest wall motion was determined by respiratory impedance plethysmography. Electromyography activities and chest wall motion were measured during hyperpnea produced by carbon dioxide rebreathing while the subjects were awake and during 1 MAC halothane anesthesia.**

Results: **Halothane anesthesia significantly reduced the slope of the response of expiratory minute ventilation to carbon dioxide (from 2.88 ± 0.73 (mean ± SE) to 2.01 ± 0.45 $l \cdot min^{-1} \cdot mmHg^{-1}$). During the rebreathing period, breathing frequency significantly increased while awake (from 10.3 ± 1.4 to 19.7 ± 2.6 min^{-1}, $P < 0.05$) and significantly decreased while anesthetized (from 28.8 ± 3.9 to 21.7 ± 1.9 min^{-1}, $P < 0.05$). Increases in respiratory drive to the phrenic motoneurons produced by rebreathing, as estimated by the diaphragm electromyogram, were enhanced by anesthesia. Anesthesia attenuated the response of parasternal electromyography and accentuated the response of the transversus abdominis electromyography to rebreathing. The compartmental response of the ribcage to rebreathing was significantly decreased by anesthesia (from 1.83 ± 0.58 to 0.48 ± 0.13 $l \cdot min^{-1} \cdot mmHg^{-1}$), and marked phase shifts between ribcage and abdominal motion developed in some subjects. However, at comparable tidal volumes, the ribcage contribution to ventilation was similar while awake and anesthetized in four of the six subjects.**

Conclusions: **Halothane anesthesia enhances the rebreathing response of neural drive to the primary respiratory muscle, the diaphragm. These findings provide direct evidence that, at the dose examined in this study, halothane-induced respiratory depression is caused by alterations in the distribution and timing of neural drive to the respiratory muscles, rather than a global depression of respiratory motoneuron drive. (Key words: Anesthetics, volatile: halothane. Lung: breathing pattern; diaphragm; functional residual capacity; intrathoracic blood volume; ribcage. Measurement technique: electromyography; respiratory impedance plethysmography. Muscle: diaphragm; external oblique; parasternal intercostal; respiratory; transversus abdominis.)**

RESPIRATORY depression produced by halothane and other anesthetic drugs can be quantified by measuring the response of minute ventilation ($\dot{V}_E$) to increases in the arterial carbon dioxide tension (Pa_{CO_2}) produced by the rebreathing of expired gas.[1] The carbon dioxide response is consistently depressed by the volatile anesthetics.[2–8] This depression could result from a proportional decrease in the overall neural output from respiratory centers to all respiratory muscles or an altered distribution of this output to various respiratory muscle groups.

A study by Tusiewicz *et al.*[8] favored the latter explanation. They attributed a major portion of halothane-induced depression of the carbon dioxide response to a preferential suppression of intercostal muscle function, with a relative sparing of diaphragm activity. This conclusion was based on measurements of ribcage and abdominal dimensions in adolescents, and the absence of activity in the parasternal intercostal muscle during quiet breathing in a small separate group of anesthetized adult subjects. However, because chest wall motion normally is determined by the complex interaction of many muscle groups, chest wall motion alone cannot be used to directly infer respiratory muscle activity. For example, in an accompanying communication, we showed that inspiratory ribcage expansion during quiet

* Associate Professor of Anesthesiology.

Received from the Departments of Anesthesiology and Physiology and Biophysics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Submitted for publication June 3, 1994. Accepted for publication August 29, 1994. Supported in part by GM-40909 from the National Institutes of Health. Dr. D. O. Warner is a recipient of the Anesthesiology Young Investigator/Parker B. Francis Investigator Award from the Foundation for Anesthesia Education and Research.

Address reprint requests to Dr. D. O. Warner: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

breathing was relatively well preserved during halothane anesthesia in human subjects, despite the absence of parasternal intercostal muscle activity.[9] Also, halothane anesthesia consistently produces phasic activity in abdominal muscles, so that measurements of abdominal dimensions may not directly reflect diaphragmatic function. Finally, it is possible that the parasternal intercostal muscles (and other extradiaphragmatic muscles that affect chest wall motion) may be recruited during rebreathing. Changes in the electrical activity of the respiratory muscles in response to rebreathing in anesthetized humans have not been studied, so that the factors contributing to halothane-induced depression of the carbon dioxide response remain unclear.

This paper continues the presentation of results obtained in our study of the effects of halothane anesthesia on human chest wall function,[9] focusing on results obtained during hyperpnea induced by carbon dioxide rebreathing. Issues addressed include (1) whether halothane-induced alterations in the pattern of respiratory muscle use during quiet breathing persist during hyperpnea induced by rebreathing, (2) how such alterations affect chest wall motion during hyperpnea, and (3) how the neural activation of the diaphragm, the primary muscle of respiration, adapts to provide increases in $\dot{V}_E$ during wakefulness and halothane anesthesia.

Materials and Methods

This study was approved by the Institutional Review Board. Six healthy male subjects were studied after informed consent. The day before each experiment, each subject was brought to the laboratory for familiarization with experimental procedures, including one trial of rebreathing. In the following section, procedures used to instrument and anesthetize these subjects are summarized (details are found in an accompanying communication[9]), and methods used to produce rebreathing are presented in detail.

All studies were performed with the subject in the supine position. Instrumentation included (1) a radial arterial line for arterial blood pressure and blood gas sampling; (2) respiratory impedance plethysmography (RIP) bands around the upper ribcage and the abdomen, calibrated by standard techniques[10]; (3) bipolar fine-wire electromyogram (EMG) electrodes placed percutaneously into the parasternal intercostal, transversus abdominis, external oblique, and diaphragm muscles[11]; (4) esophageal and gastric balloons placed in the midesophagus and stomach, respectively, after the induction of halothane anesthesia; and (5) a pneumotachograph to measure inspired and expired gas flows, which were integrated to obtain changes in lung gas volume, corrected to body temperature, standard pressure conditions. Imaging of the thorax[9] was not performed because of limits on allowable radiation exposure of volunteers. We have shown in an accompanying communication that RIP is a valid technique to measure chest wall motion during anesthesia, even though it does not measure actual volumes displaced by the surfaces of the ribcage and the diaphragm.[9] All measurements presented in this communication were performed while the subject was breathing through a mouthpiece with a nose clip (awake) or an endotracheal tube (anesthetized) with the arms resting at the subject's side.

After instrumentation, each subject breathed quietly for several minutes to establish a stable pattern of breathing. They were then quickly connected to a 7-l bag containing 7% CO_2 and 93% O_2 (awake measurements) or 8% CO_2 and 91% O_2, plus 1% halothane (anesthetized measurements). Carbon dioxide concentration in the bag was continuously monitored by an infrared analyzer and expressed as carbon dioxide tension (P_{CO_2}, Nelcor N-2500). The different initial carbon dioxide concentrations were used to promote rapid equilibration between blood and bag P_{CO_2} and to standardize the rate of rise of P_{CO_2} in awake and anesthetized conditions. Rebreathing continued until P_{CO_2} in the bag increased by approximately 10–15 mmHg. Arterial blood gases were obtained before and at the conclusion of rebreathing.

After rebreathing while awake, other measurements were obtained as detailed in the accompanying communication. An inhalation induction of halothane anesthesia was performed, and the trachea was intubated with a 9.0-mm endotracheal tube under deep halothane anesthesia. The subjects were allowed to breathe spontaneously, and inspired halothane concentration was adjusted to provide end-tidal concentrations of $0.9 \pm 0.1\%$ (equal to approximately 1 MAC). Rebreathing was then repeated.

Data Analysis

All data were analyzed at 30-s intervals during rebreathing.

EMG signals recorded on tape were processed with a third-order Paynter filter to provide a 100-ms moving time average (MTA).[12] The diaphragm MTA tracings were digitized, and the mean diaphragm MTA activity

per breath ($\bar{E}_{DIA}$) was calculated as the area under the MTA signal divided by the duration of the signal[13] (fig. 1). If EMG activity persisted into expiration, only the portion of the signal before the onset of expiratory flow was used to calculate this mean (see Appendix for discussion of EMG analysis).

Changes in the duration of EMG activity could affect $\bar{E}_{DIA}$, even if the rate of increase in neural output over the course of each breath remained constant. To account for these changes in duration, the average rate of rise of MTA activity ($\dot{E}_{DIA}$) was calculated[14] (fig. 1). This calculation aids in the distinction between alterations in diaphragm activity caused by changes in the duration of activity and alterations caused by changes in the time course of EMG activity development. Only the portion of the signal before the onset of expiratory flow was used to determine the duration of activity and to calculate $\dot{E}_{DIA}$ (see Appendix).

Volume-motion coefficients were calculated for the RIP data according to the method of Mankikian *et al.*[10] Calibrations were performed with the subjects awake and repeated during anesthesia. With these calibrations, tidal volume was partitioned into ribcage and diaphragm-abdomen (referred to hereafter as abdominal) components. Displacements of these compartments approximate but do not equal the actual volumes displaced by motion of the ribcage and diaphragm.[9,15] When used to calculate compartmental contributions to tidal volume, changes in dimensions were measured only over the duration of inspiratory flow. Thus, paradoxic motion of any compartment (*e.g.*, ribcage expansion during early expiration) is not included in the computation of compartmental tidal volumes. Phase relationships between the ribcage and abdominal compartments were displayed as Lissajous plots of ribcage *versus* abdominal dimensions as measured by RIP.

The validity of RIP calibration was assessed as follows. For all subjects, the mean correlation coefficient during rebreathing between tidal volume calculated as the sum of ribcage and abdominal components ($V_{T,RIP}$) and tidal volume measured with the pneumotachograph ($V_{T,pneumo}$) was 0.972 ± 0.012 while awake and 0.994 ± 0.003 while anesthetized. The relative difference between $V_{T,RIP}$ and $V_{T,pneumo}$ was calculated for each patient as $|(V_{T,RIP} - V_{T,pneumo})/V_{T,RIP}| \times 100$. The mean relative difference for all data points during rebreathing was 7.6 ± 1.8% while awake and 3.4 ± 0.9% while anesthetized.

Variables were compared between awake and anesthetized states using paired *t* tests. Linear regressions were used when appropriate to quantify the relationship between two variables. $P < 0.05$ was taken as significant.

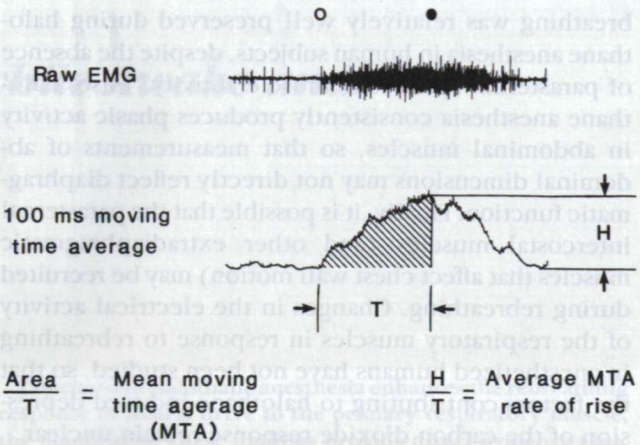

Fig. 1. Methods used to quantify electromyogram (EMG) activity. Open and closed circles represent the beginning and end of inspiratory gas flow, respectively. Activity was quantified as either the mean moving time average (MTA) or the average rate of MTA rise, analyzed only over the period of inspiratory gas flow.

Results

Ventilation and Timing

Halothane anesthesia significantly reduced the slope of the response of expiratory minute ventilation ($\dot{V}_E$) to carbon dioxide (from 2.88 ± 0.73 to 2.01 ± 0.45 $l \cdot min^{-1} \cdot mmHg^{-1}$, fig. 2 and table 1). The $\dot{V}_E$ at an expired P_{CO_2} of 55 mmHg also was significantly reduced by halothane anesthesia (from 37.5 ± 7.7 to 13.1 ± 2.3 l/min). The initial Pa_{CO_2} (measured during quiet breathing immediately before rebreathing) was increased by halothane anesthesia (from 41 ± 2 to 51 ± 3 mmHg). The increase in Pa_{CO_2} produced by rebreathing did not differ significantly between awake and anesthetized conditions (increases of 13 ± 2 mmHg and 13 ± 4 mmHg, respectively). The initial $\dot{V}_E$ was not affected by anesthesia (table 2). The increase in $\dot{V}_E$ produced by rebreathing also did not differ significantly between awake and anesthetized conditions (increases of 25.9 ± 5.2 l/min and 19.5 ± 2.1 l/min, respectively).

Rebreathing changed ventilatory timing in both awake and anesthetized states but in a markedly different manner. The breathing frequency at the onset of

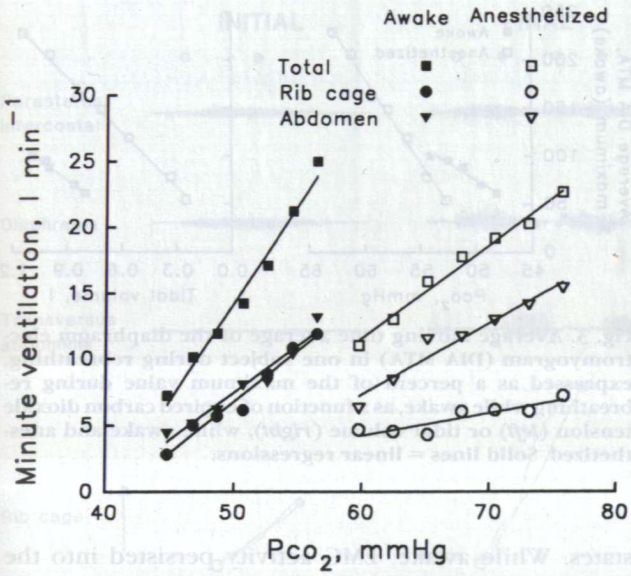

Fig. 2. Response of total minute ventilation (measured with a pneumotachograph) and the compartmental minute ventilation of the ribcage and abdominal compartments (measured with respiratory impedance plethysmography) to changes in inspired carbon dioxide tension while awake and anesthetized for one subject. Data points were obtained at 30-s intervals. Solid lines = linear regressions.

rebreathing was significantly higher while anesthetized (table 2). The inspiratory time (T_I) and expiratory time (T_E) were both significantly lower while anesthetized; the ratio of T_I to the total period of breathing (T_I/T_{TOT}) was not different. During the rebreathing period, breathing frequency increased while awake and decreased while anesthetized (table 2). In other words, T_{TOT} (the reciprocal of breathing frequency) decreased while awake and increased while anesthetized during the rebreathing period. While awake, T_I and T_E decreased and T_I/T_{TOT} increased over the rebreathing period. Thus, decreases in T_{TOT} over the rebreathing period were caused by decreases in both T_I and T_E. During anesthesia, T_E increased over the rebreathing period, whereas T_I and T_I/T_{TOT} did not change significantly. Thus, increases in T_{TOT} over the rebreathing period while anesthetized were caused by increases in T_E.

The response of tidal volume to rebreathing also differed among awake and anesthetized states. The tidal volume at the onset of rebreathing was significantly lower during anesthesia (table 2). As $\dot{V}_E$ increased, tidal volume increased both while awake and while anesthetized. The slope of the linear regression of tidal volume *versus* $\dot{V}_E$ was significantly greater while anesthetized (0.053 ± 0.004 min) than while awake (0.038 ± 0.007 min). Thus, a greater increase in tidal volume was necessary to produce a given change in $\dot{V}_E$ while anesthetized.

Respiratory Muscle Activation

Satisfactory diaphragm EMG data were obtained in five subjects. $\bar{E}_{DIA}$ at the onset of rebreathing, expressed as a fraction of the maximum activity during rebreathing while awake, was not significantly different while awake (0.63 ± 0.05) or anesthetized (0.49 ± 0.13). The effect of rebreathing on $\bar{E}_{DIA}$ was quantified by linear regression of $\bar{E}_{DIA}$ *versus* P_{CO_2} for each subject (fig. 3). The slope of this relationship was significantly

Table 1. Overall and Compartmental Responses to CO_2 Rebreathing

	Awake						Anesthetized					
	Slope (L · min⁻¹ · mmHg⁻¹)			$\dot{V}_{55}$ (L · min⁻¹)			Slope (L · min⁻¹ · mmHg⁻¹)			$\dot{V}_{55}$ (L · min⁻¹)		
Patient No.	$\dot{V}_E$	$\dot{V}_{RC}$	$\dot{V}_{AB}$	$\dot{V}_E$	$\dot{V}_{RC}$	$\dot{V}_{AB}$	$\dot{V}_E$	$\dot{V}_{RC}$	$\dot{V}_{AB}$	$\dot{V}_E$	$\dot{V}_{RC}$	$\dot{V}_{AB}$
1	6.21	4.33	1.88	61.3	39.4	21.9	4.00	1.05	2.95	9.0	2.6	6.4
2	2.50	0.75	1.75	27.1	8.1	19.0	1.91	0.24	1.67	11.6	2.9	8.7
3	1.42	0.74	0.68	20.9	10.2	10.7	0.71	0.17	0.54	8.1	3.4	4.6
4	3.01	1.86	1.15	56.7	32.5	24.2	2.24	0.57	1.67	23.7	5.9	17.8
5	1.28	0.81	0.48	16.3	7.9	8.4	1.52	0.53	0.99	11.6	4.4	7.2
6	2.83	2.49	0.34	42.7	35.9	6.8	1.68	0.31	1.37	14.4	2.9	11.5
Mean	2.88	1.83	1.05	37.5	22.3	15.2	2.01*	0.48*	1.53	13.1*	3.7*	9.4*
SEM	0.73	0.58	0.27	7.7	6.2	3.0	0.45	0.13	0.33	2.3	0.5	1.9

$\dot{V}_E$ = total minute ventilation (sum of $\dot{V}_{RC}$ and $\dot{V}_{AB}$); $\dot{V}_{RC}$ = compartmental ribcage minute ventilation; $\dot{V}_{AB}$ = compartmental abdominal minute ventilation; $\dot{V}_{55}$ = calculated minute ventilation at a P_{CO_2} of 55 mmHg. All values obtained from linear regression of minute ventilations against P_{CO_2} measured in rebreathed gas.

* Significant difference from awake values.

greater during anesthesia (0.185 ± 0.050 $mmHg^{-1}$) compared with the awake state (0.052 ± 0.013 $mmHg^{-1}$). In other words, for a given increase in P_{CO_2} during rebreathing, the increase in $\bar{E}_{DIA}$ was consistently greater during halothane anesthesia compared with the awake condition. When this relationship was used to estimate $\bar{E}_{DIA}$ at a P_{CO_2} of 55 mmHg, there was no significant difference in this activity while awake (1.11 ± 0.11) and while anesthetized (1.07 ± 0.33).

The duration of inspiratory diaphragmatic activity significantly decreased over the rebreathing period while awake (from 2.61 ± 0.95 to 1.66 ± 0.61 s) and significantly increased while anesthetized (from 0.95 ± 0.34 to 1.25 ± 0.18 s). These changes in duration could affect $\bar{E}_{DIA}$, even if the rate of increase in neural output over the course of each breath remained constant. To account for these changes in duration, the average rate of rise of EMG activity ($\dot{E}_{DIA}$) was calculated. $\dot{E}_{DIA}$ at the onset of rebreathing, expressed as a fraction of the maximum $\dot{E}_{DIA}$ during rebreathing while awake, was significantly greater during anesthesia (0.90 ± 0.37) compared with wakefulness (0.37 ± 0.04). The effect of rebreathing on $\dot{E}_{DIA}$ was quantified by the linear regression of this quantity and P_{CO_2} for each subject. The slope of this relationship was significantly greater during anesthesia (0.199 ± 0.064 $mmHg^{-1}$) compared with wakefulness (0.084 ± 0.011 $mmHg^{-1}$). In other words, for a given increase in P_{CO_2} during rebreathing, the increase in $\dot{E}_{DIA}$ was consistently greater during halothane anesthesia. When this relationship was used to calculate $\dot{E}_{DIA}$ at a P_{CO_2} of 55 mmHg, there was no significant difference between awake (1.12 ± 0.15) and anesthetized (1.58 ± 0.56) states.

The temporal relationship of diaphragm EMG activity to airflow also differed between awake and anesthetized states. While awake, EMG activity persisted into the early part of expiration (fig. 4). This postinspiratory activity was present throughout the rebreathing period. This activity was never observed during halothane anesthesia; the cessation of inspiratory diaphragm EMG activity and the onset of expiration were synchronous (fig. 5).

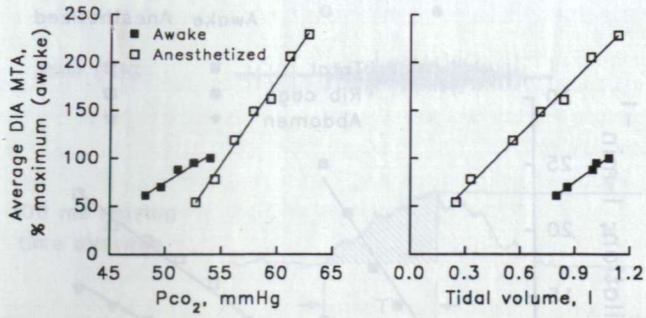

Fig. 3. Average moving time average of the diaphragm electromyogram (DIA MTA) in one subject during rebreathing, expressed as a percent of the maximum value during rebreathing while awake, as a function of expired carbon dioxide tension (*left*) or tidal volume (*right*), while awake and anesthetized. Solid lines = linear regressions.

Because the tidal volume at a given P_{CO_2} differed markedly between the awake and anesthetized states, changes in diaphragm EMG activity during rebreathing were analyzed as a function of tidal volume (fig. 3). The slope of the relationship between $\bar{E}_{DIA}$ and tidal volume during rebreathing was significantly greater during halothane anesthesia (0.657 ± 0.266 l^{-1} awake and 1.89 ± 0.69 l^{-1} anesthetized). The $\bar{E}_{DIA}$ at a tidal volume of 1.2 l also was significantly greater during halothane anesthesia (0.875 ± 0.115 awake *vs.* 2.31 ± 0.81 anesthetized). These results indicate that a

Table 2. Ventilatory Parameters during Rebreathing

	Awake		Anesthetized	
	Initial	Final	Initial	Final
Breathing frequency (min)	10.3 ± 1.4	19.7 ± 2.6*	28.8 ± 3.9†	21.7 ± 1.9*
Period of breathing (T_{TOT}) (s)	6.52 ± 1.06	3.36 ± 0.48*	2.29 ± 0.33†	2.88 ± 0.27*
Inspiratory time (T_I) (s)	2.42 ± 0.36	1.65 ± 0.27*	0.95 ± 0.11†	1.14 ± 0.12
Expiratory time (T_E) (s)	4.10 ± 0.74	1.71 ± 0.24*	1.34 ± 0.23†	1.74 ± 0.18*
T_I/T_{TOT}	0.38 ± 0.02	0.49 ± 0.02*	0.43 ± 0.03	0.39 ± 0.02
Tidal volume (V_T) (L)	0.95 ± 0.17	1.84 ± 0.33*	0.28 ± 0.03†	1.33 ± 0.20*
V_T/T_I ($L \cdot s^{-1}$)	0.39 ± 0.03	1.18 ± 0.19*	0.30 ± 0.02†	1.17 ± 0.09*
Minute ventilation (V_E) ($L \cdot min^{-1}$)	9.0 ± 1.0	34.9 ± 6.2*	7.7 ± 0.7	27.2 ± 1.7*

* Significant difference from initial value.

† Significant difference initial awake *versus* anesthetized values.

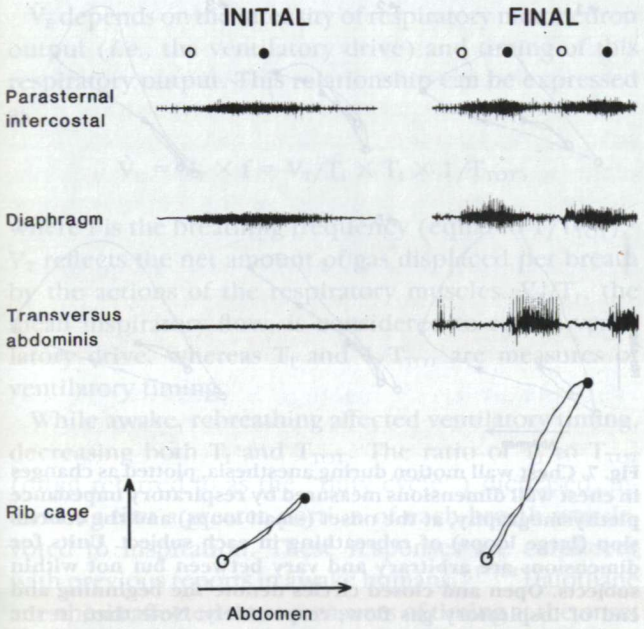

Fig. 4. Electromyogram activity (*top*) and the pattern of chest wall motion plotted as changes in chest wall dimensions measured by respiratory impedance plethysmography (*bottom*) in one awake subject at the onset (*left*) and conclusion (*right*) of rebreathing. Open and closed circles denote the beginning and end of inspiratory gas flow, respectively.

greater mean diaphragmatic MTA activity per breath was required to produce a given V_T while anesthetized. Similar results were found for $\dot{E}_{DIA}$ (data not shown).

Rebreathing significantly increased the average parasternal intercostal MTA activity while awake (fig. 4, a 3.4 ± 1.0-fold increase over initial values). Parasternal intercostal activity developed in subjects 1 and 2 during rebreathing while anesthetized shortly before the conclusion of the rebreathing period (fig. 5). The maximum mean MTA activity during anesthetized rebreathing in these two subjects was relatively small compared with awake values (13% and 16% of awake maximum values in subjects 1 and 2, respectively). The onset of this activity in these two subjects was not associated with perceptible changes in chest wall motion. Like the diaphragm, postinspiratory activity was present in the parasternal intercostal muscle while awake (fig. 4) but not while anesthetized (fig. 5).

Three subjects developed phasic expiratory activity in the transversus abdominis muscle during rebreathing while awake (fig. 4); no phasic activity was observed in the external oblique. During anesthesia, phasic expiratory activity was always present in the transversus abdominis at the beginning of rebreathing and consistently increased throughout the period (fig. 5, a 2.8 ± 1.1-fold increase over initial values). The duration of activity did not change over the rebreathing period (from 1.72 ± 0.24 to 1.87 ± 0.43 s). One subject developed phasic activity in the external oblique during rebreathing; otherwise, phasic activity in this muscle was not observed while anesthetized. Phasic expiratory activity in the diaphragm electrode, probably reflecting activity in the adjacent internal intercostal muscles, was consistently present at the conclusion of rebreathing while anesthetized (fig. 5).

Compartmental Responses

Minute ventilation of the ribcage and abdominal compartments was computed as the product of the compartmental tidal volume (measured by RIP) and breathing frequency. Halothane anesthesia significantly depressed the ribcage response to carbon dioxide, quantified as the slope of the linear regression of this relationship between compartmental minute ventilation and P_{CO_2} measured in the rebreathing bag but did not significantly change the abdominal response (fig.

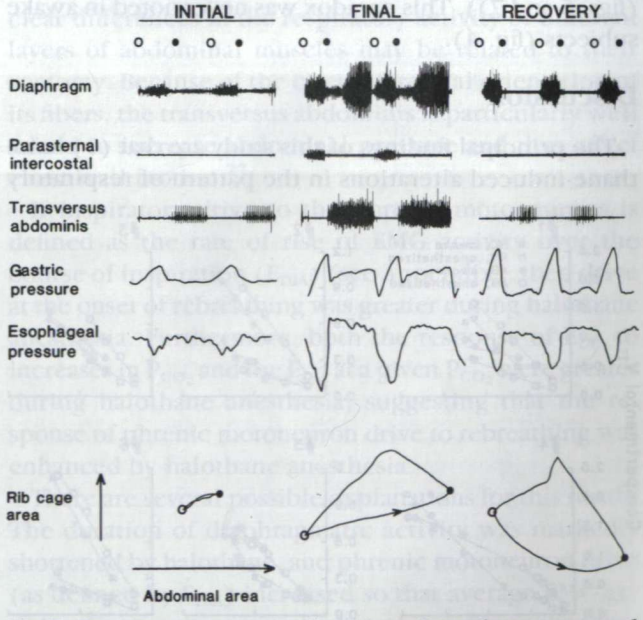

Fig. 5. Electromyograms, gastric and esophageal pressures, and chest wall motion in one anesthetized subject at the onset (*left*) and conclusion (*middle*) of rebreathing. Open and closed circles denote the beginning and end of inspiratory gas flow, respectively. Also shown (*right*) is a unique pattern of breathing that developed in this subject during recovery from rebreathing that demonstrates the possible importance of expiratory muscle activity to ribcage expansion (see text for discussion).

2 and table 1). However, this analysis does not take into account the fact that these responses were measured over different ranges of tidal volumes, with smaller tidal volumes during halothane anesthesia (table 2). To evaluate compartmental contributions at comparable tidal volumes, compartmental tidal volumes were expressed as a function of total tidal volume (fig. 6). At comparable tidal volumes, the ribcage contribution to inspiration was significantly depressed only in subjects 1 and 6. When compartmental volume displacements at a V_T of 1.2 l were estimated using linear regression parameters, the ribcage contribution to tidal volume tended to be less during halothane anesthesia (27 ± 3%) than while awake (42 ± 6%) but not significantly so.

Halothane anesthesia also affected the phase relationship between ribcage and abdominal motion (figs. 5 and 7). Immediately after the onset of rebreathing, ribcage and abdominal movements were relatively synchronous both while awake and while anesthetized (as shown by the narrow loops in figs. 4, 5, and 7). At the end of the rebreathing, all subjects exhibited paradoxic ribcage motion during halothane anesthesia (*i.e.*, the ribcage expanded during the first part of expiration (figs. 5 and 7)). This paradox was never noted in awake subjects (fig. 4).

Discussion

The principal findings of this study are that (1) halothane-induced alterations in the pattern of respiratory muscle activity observed during quiet breathing persist during rebreathing, (2) increases in respiratory drive to phrenic motoneurons produced by rebreathing, as estimated by the diaphragm EMG, were enhanced by halothane anesthesia, and (3) ribcage expansion contributed significantly to the tidal volume during anesthetized rebreathing, despite suppression of parasternal intercostal activity by halothane.

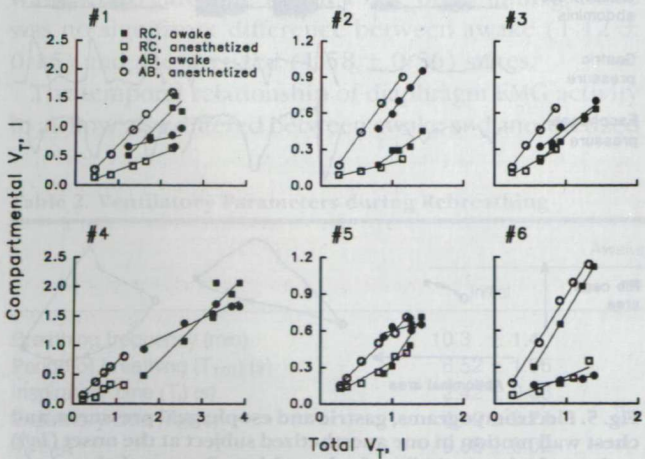

Fig. 6. Compartmental tidal volumes as a function of total tidal volume for each subject while awake and anesthetized. Note that, at comparable tidal volumes, the ribcage volume displacement is decreased during anesthesia only in subjects 1 and 6. Solid lines = linear regressions. Some data points have been omitted for clarity.

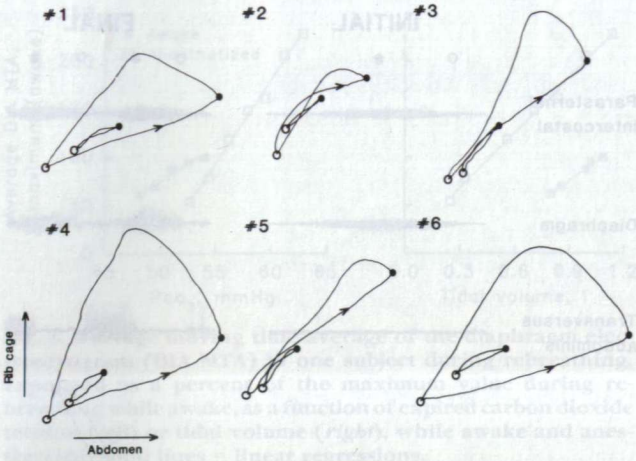

Fig. 7. Chest wall motion during anesthesia, plotted as changes in chest wall dimensions measured by respiratory impedance plethysmography, at the onset (small loops) and the conclusion (large loops) of rebreathing in each subject. Units for dimensions are arbitrary and vary between but not within subjects. Open and closed circles denote the beginning and end of inspiratory gas flow, respectively. Note that, at the conclusion of rebreathing, each subject exhibits paradoxic ribcage motion, with ribcage dimensions continuing to increase during early expiration.

Overall Ventilation and Timing

$\dot{V}_E$ is a useful measure of overall respiratory output that frequently is used to quantify drug-induced respiratory depression. Our results confirm previous findings that halothane, like the other volatile anesthetics, reduces the response of $\dot{V}_E$ to increases in Pa_{CO_2} produced by the rebreathing of expired gas.[2,3,5,6,8] The magnitude of this depression in our study was modest at this moderate dose of halothane (a 26% reduction in slope). We also confirm that halothane decreases the $\dot{V}_E$ maintained at a given Pa_{CO_2}, as estimated by the P_{CO_2} during rebreathing. The $\dot{V}_E$ at the onset of rebreathing was not significantly changed by halothane anesthesia despite a higher Pa_{CO_2}, consistent with previous work showing that halothane anesthesia increases physiologic dead space.[2,3,6,16]

$\dot{V}_E$ depends on the intensity of respiratory motoneuron output (*i.e.*, the ventilatory drive) and timing of this respiratory output. This relationship can be expressed as

$$\dot{V}_E = V_T \times f = V_T/T_I \times T_I \times 1/T_{TOT},$$

where f is the breathing frequency (equal to $1/T_{TOT}$).[1] V_T reflects the net amount of gas displaced per breath by the actions of the respiratory muscles. V_T/T_I, the mean inspiratory flow, is considered to reflect ventilatory drive, whereas T_I and $1/T_{TOT}$ are measures of ventilatory timing.

While awake, rebreathing affected ventilatory timing, decreasing both T_I and T_{TOT}. The ratio of T_I to T_{TOT} (often referred to as the "duty cycle") increased, indicating that a greater portion of each breath was devoted to inspiration. These responses are consistent with previous reports in awake humans.[4,17,18] Halothane anesthesia affected these measures of timing at the onset of rebreathing, reducing T_I and T_{TOT}, findings consistent with previous reports.[2,3,5,6,8] The responses of ventilatory timing parameters to rebreathing were dramatically affected by anesthesia; T_I was unchanged over the rebreathing period, whereas f decreased, because of increases in the expiratory time (T_E). This result differs from previous reports that found no change in f with steady-state increases in inspired carbon dioxide during halothane anesthesia[3,19,20] or during rebreathing with methoxyflurane.[4] This difference may reflect differences in the experimental technique used to increase inspired carbon dioxide (rebreathing *vs.* steady state) or the anesthetic.

The mechanisms responsible for these effects on ventilatory timing are unknown. Most information comes from animal experiments; however, significant species differences may limit application of these insights to humans.[21] During quiet breathing, halothane-induced tachypnea appears to be centrally mediated.[22] The importance of vagally mediated input from pulmonary stretch receptors in the termination of inspiration (the Hering-Breuer reflex) in humans is controversial,[23–25] with at least one study suggesting that this reflex is operative during quiet breathing in enflurane-anesthetized humans.[26] The fact that V_T increased significantly without changing T_I suggests that vagal influences dependent on V_T have little influence on timing during hyperpnea in halothane-anesthetized humans. Similar results have been reported in subjects given intravenous anesthetics.[23]

Respiratory Muscle Activation

As found in previous studies, the parasternal intercostal muscles contributed to the rebreathing response while awake. In contrast, while anesthetized, parasternal intercostal activity was noted during rebreathing in only two subjects, with little apparent effect on the pattern of chest wall motion. Thus, halothane-induced suppression of parasternal intercostal muscle activity, previously noted in quiet breathing,[8,9] persists in most subjects even at high levels of Pa_{CO_2} (mean value of 64 mmHg).

Although the abdominal muscles could contribute to the rebreathing response both while awake and while anesthetized, recruitment was more consistent during anesthesia. Recordings from the diaphragm electrode suggest a similar pattern of results for lateral ribcage expiratory muscles such as the internal intercostal muscles. De Troyer *et al.*[11] found that the transversus abdominis is the predominant abdominal muscle that exhibits phasic respiratory activity in awake humans and that this muscle can participate in the rebreathing response.[11] Our results extend this finding to the anesthetized state. The other abdominal muscle examined, the external oblique, was recruited infrequently. These clear differences in the respiratory activity of different layers of abdominal muscles may be related to their anatomy. Because of the circumferential orientation of its fibers, the transversus abdominis is particularly well suited to increase abdominal pressure and thus affect chest wall motion.[27]

If inspiratory drive to the phrenic motoneurons is defined as the rate of rise of EMG activity over the course of inspiration ($\dot{E}_{DIA}$) (see Appendix), then drive at the onset of rebreathing was greater during halothane anesthesia. Furthermore, both the response of $\dot{E}_{DIA}$ to increases in P_{CO_2} and the $\dot{E}_{DIA}$ at a given P_{CO_2} were greater during halothane anesthesia, suggesting that the response of phrenic motoneuron drive to rebreathing was enhanced by halothane anesthesia.

There are several possible explanations for this result. The duration of diaphragmatic activity was markedly shortened by halothane, and phrenic motoneuron drive (as defined by $\dot{E}_{DIA}$) increased so that average EMG activity ($\bar{E}_{DIA}$) at the onset of rebreathing was unchanged. Thus, increases in phrenic motoneuron drive could be related to the profound changes in timing. Furthermore, because of differences in the response of the breathing frequency, greater increases in V_T were required to produce a given increase in $\dot{V}_E$ while anesthetized. The need for greater increases in V_T should require greater

increases in neural drive to the diaphragm. Finally, the range of tidal volumes generated by respiratory muscle activity was different among the two conditions. It is apparent that, when drive was analyzed as a function of V_T, significantly greater EMG activity was needed to generate a given V_T when anesthetized. Also, a greater change in EMG activity was required to produce a given increase in V_T during anesthetized rebreathing. This finding suggests a decrease in the efficiency of diaphragmatic contraction during halothane anesthesia, *i.e.*, a decrease in the volume of gas displaced for a given neural input to the diaphragm.

Increased drive to the phrenic nerve during halothane anesthesia may compensate for changes in the activity of other respiratory muscles that normal assist respiration. Although the diaphragm is the primary muscle of respiration, even quiet breathing normally requires the coordinated activity of several respiratory muscles.[28] For example, normal inspiratory ribcage expansion requires activation of the parasternal intercostal muscles.[29,30] It is probably simplistic to think of the increase in diaphragm activity as a response to the loss of activity in any single muscle group produced by halothane anesthesia. However, the profound effect of halothane anesthesia on extradiaphragmatic respiratory muscles raises the possibility that the increase in drive to phrenic motoneurons may represent compensation for the loss of normal respiratory muscle coordination.

Analysis of the response of average inspiratory flow (V_T/T_I), previously mentioned as a parameter of overall ventilatory drive, suggests that this compensation was complete. Although V_T/T_I at the onset of rebreathing was significantly lower during anesthesia (table 2), the slope of the linear regression of inspiratory flow *versus* $\dot{V}_E$ was significantly greater while anesthetized (2.82 ± 0.42) than while awake (1.80 ± 0.12). Thus, rebreathing produced a greater increase in inspiratory flow for a given change in $\dot{V}_E$ during anesthesia, despite the lack of parasternal intercostal muscle activity.

Other aspects of phrenic motoneuron control were altered by halothane anesthesia. While awake, activity in the diaphragm and other inspiratory agonists persisted into early expiration throughout the rebreathing period. The physiologic significance of this postinspiratory inspiratory activity (PIIA) is not fully understood, but presumably serves to regulate early expiratory flow and increase mean lung volume. This activity was abolished by halothane. In animals, PIIA is limited to a specific population of phrenic motoneurons that begins to fire early in the phrenic discharge.[31] These motoneurons can be selectively inhibited (*e.g.*, by positive end-expiratory pressure,[32]), and it is possible that halothane could preferentially inhibit these motoneurons. Because PIIA may play a role in producing the normal respiratory rhythm, halothane-induced suppression of PIIA may be related to the halothane-induced changes in ventilatory timing. The absence of PIIA could potentially affect changes in intrathoracic pressure during early expiration, and subsequently, motion of the ribcage (see below).

Compartmental Responses. Both the ribcage and abdominal compartments contributed to increases in V_T during awake rebreathing. As found in previous studies,[8,18,33,34] there was considerable variability in the individual responses of these largely naive subjects. We could not confirm an earlier report[18] that the variability of the ribcage response exceeds that of the abdominal response in humans (the coefficient of variation for ribcage and abdominal responses was 61% and 62% in awake and anesthetized subjects, respectively; table 1). The motion of both compartments remained well synchronized.

Although we previously observed that halothane caused only small changes in the pattern of ribcage and diaphragm motion during quiet breathing,[9] increases in tidal volume produced by rebreathing in the present study revealed more pronounced effects. Several of our findings may be attributed to suppression of activity in ribcage muscles with inspiratory actions. Both human and animal studies show that muscles of the ribcage such as the parasternal intercostals are essential for normal ribcage expansion.[29,30,35,36] Isolated contraction of the diaphragm constricts the upper ribcage during inspiration, caused by decreases in intrathoracic pressure unopposed by the normal expansive force produced by contraction of inspiratory ribcage muscles.

Consistent with the findings of Tusiewicz *et al.* in adolescents,[8] the compartmental response of the ribcage, quantified as the slope of the relationship between compartmental minute ventilation and P_{CO_2}, was significantly reduced by halothane anesthesia. Furthermore, asynchrony developed between ribcage and abdominal motion in some subjects, with ribcage motion lagging that of the abdomen. This asynchrony was most pronounced in subjects 1, 4, and 5 (fig. 7). These three subjects also had the greatest ribcage compartmental responses while awake and experienced the greatest decreases in response while anesthetized. These findings are consistent with the suggestion of Tusiewicz *et al.*[8] that patients with brisk ribcage responses to carbon

dioxide while awake are particularly vulnerable to halothane-induced respiratory depression. The factors responsible for this variability in ribcage responsiveness while awake are unknown.[18]

The ribcage moved outward in early expiration during anesthetized rebreathing in all subjects. This paradoxic motion probably occurred because the expansile forces exerted on the ribcage by inspiratory muscles were reduced during halothane anesthesia. Thus, unlike the normal situation while awake, the position of the upper ribcage (that portion monitored by the RIP) was determined primarily by intrathoracic pressure. Intrathoracic pressure rapidly increased in early expiration as diaphragmatic contraction ended. Thus, although lung volume was decreasing, the ribcage was passively expanded by this increase in intrathoracic pressure until equilibrium was reached between the outward elastic recoil of the ribcage and the inward recoil exerted by the lung. Thereafter, ribcage dimensions again decreased as lung volume and lung elastic recoil continued to decrease. The lack of PIIA activity in inspiratory muscles during halothane anesthesia would accentuate this sudden increase in intrathoracic pressure during early expiration and thus may have contributed to this paradoxic ribcage motion.

Although ribcage motion during halothane anesthesia was not normal, in some respects its motion was well preserved, given the lack of parasternal intercostal muscle activity. The ribcage contributed to increases in tidal volume produced by rebreathing in all subjects. In four subjects, the ribcage contribution to tidal volume was remarkably similar when differences in tidal volume between awake and anesthetized states were considered (fig. 6).

At least two explanations for this partial preservation of ribcage motion are possible. First, inspiratory activity may have been present in other ribcage muscles not monitored in these subjects. Candidates include the levator costae, scalene, sternocleidomastoid, and external intercostal muscles. Although the activity of the parasternal intercostal muscles and other inspiratory agonists such as the scalene muscles often are linked,[35] we cannot exclude this possibility. Second, expiratory activity in ribcage and abdominal muscles could affect ribcage motion. Expiratory activity in the internal intercostal muscles (suggested by phasic activity in the diaphragm electrode during expiration) may actively decrease ribcage dimensions during expiration. The cessation of this activity at the onset of inspiration would allow the ribcage to passively expand and thus contribute to inspiratory expansion. Other ribcage muscles with expiratory actions not monitored in this study, such as the transversus thoracis muscle, could contribute to this action. The importance of similar activity to ribcage expansion has been clearly established in anesthetized dogs[36,37] but is unknown in human subjects. The possible role of abdominal muscles is less clear. These muscles may affect ribcage motion by direct actions *via* their insertions on the ribcage and by indirect effects *via* abdominal pressure on the ribcage through the area of apposition.[27] Relaxation of transversus abdominis muscle activity had a clear mechanical action, producing a transient decrease in gastric pressure at the onset of inspiration (fig. 5); relaxation of expiratory ribcage muscles may contribute to this decrease.[36] However, this decrease in gastric pressure would promote the inward motion of the lower ribcage and tend to hinder inspiratory expansion. The direct effect of transversus abdominis contraction on the human ribcage is unknown. Thus, it is difficult to predict the net mechanical consequences of the combined activity of multiple expiratory muscles.

Two observations in individual subjects support the importance of expiratory muscle activity to ribcage expansion during halothane anesthesia. Rebreathing increased expiratory activity in the diaphragm and the transversus abdominis electrodes in all subjects. However, in one subject, this expiratory activity was absent in the diaphragm electrode and much reduced in the transversus abdominis muscle for a brief period immediately after the conclusion of rebreathing during anesthesia (fig. 5). The reason for this marked transient change in breathing pattern is unknown, but this finding provides insight into the mechanical actions of these respiratory muscles. Before the conclusion of rebreathing, when expiratory activity was present, the ribcage exhibited paradoxic motion during early expiration, but expanded over the course of inspiration (fig. 5). When this expiratory activity was absent (immediately after rebreathing), ribcage dimensions decreased during inspiration, and the paradox in early expiration was exaggerated. Over time, expiratory activity redeveloped, and the pattern of chest wall motion returned to its original pattern (data not shown). In another subject (fig. 8), expiratory activity was absent for a period during the course of anesthetic induction. In the absence of this activity, the ribcage contracted during inspiration. As induction proceeded, expiratory activity developed, first in the diaphragm electrode, then in the transversus abdominis electrode. As activity developed,

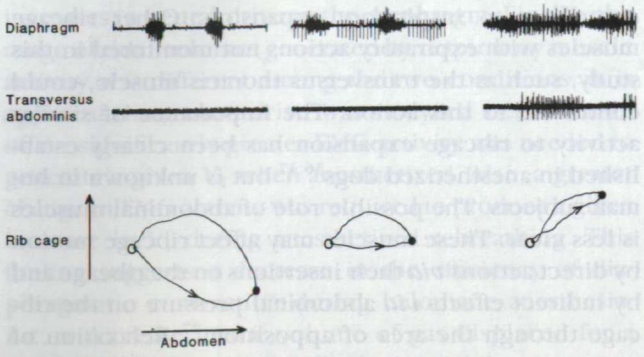

Fig. 8. Electromyograms and chest wall motion, measured with respiratory impedance plethysmography, in one subject during the induction of anesthesia, showing the effects of the development of expiratory muscle activity on the pattern of chest wall motion. Paradoxic ribcage motion in early expiration lessens as expiratory muscle activity becomes more prominent.

the ribcage expanded with inspiration. Thus, in these two subjects, preceding expiratory activity appeared to be required for subsequent inspiratory ribcage expansion. We suggest that cessation of this expiratory activity at the onset of inspiration allows passive expansion of the ribcage and assists its inspiratory motion. However, our present evidence is only suggestive. To better establish this relationship, further studies are needed to (1) document that expiratory muscle activity constricts the ribcage below its passive configuration and (2) determine whether other inspiratory muscles (not monitored in the current study) are active during anesthesia and could contribute to inspiratory ribcage expansion.

Analysis of the effect of halothane on the ventilatory response to carbon dioxide only in terms of changes in $\dot{V}_E$ obscures much of the complexity of its effects. Halothane anesthesia enhances the rebreathing response of neural drive to the primary respiratory muscle, the diaphragm. These findings provide direct evidence that, at the dose examined in our study, halothane-induced respiratory depression is caused by alterations in the distribution and timing of neural drive to the respiratory muscles, rather than a global depression of respiratory motoneuron drive.

The authors thank Kathy Street and Darrell Loeffler, for their technical assistance; Janet Beckman, for secretarial support; Dr. Brad Narr, for performing preanesthetic medical evaluations; Dr. Bill Lichty and Dr. Michael Joyner, for assistance with electromyography techniques; and Dr. Jamil Tajik, for assistance with ultrasonography.

References

1. Pavlin EG, Hornbein TF: Anesthesia and the control of ventilation, Handbook of Physiology. Section 3: The Respiratory System. Volume III. Edited by Fishman AP. Bethesda, American Physiological Society, 1986, pp 793–813

2. Fourcade HE, Larson CP Jr, Hickey RF, Bahlman SH, Eger EI II: Effects of time on ventilation during halothane and cyclopropane anesthesia. ANESTHESIOLOGY 36:83–88, 1972

3. Hornbein TF, Martin WE, Bonica JJ, Freund FG, Parmentier P: Nitrous oxide effects on the circulatory and ventilatory responses to halothane. ANESTHESIOLOGY 31:250–260, 1969

4. Derenne J-P, Couture J, Iscoe S, Whitelaw WA, Milic-Emili J: Occlusion pressures in men rebreathing CO_2 under methoxyflurane anesthesia. J Appl Physiol 40:805–814, 1976

5. Knill RL, Gelb AW: Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. ANESTHESIOLOGY 49:244–251, 1978

6. Munson ES, Larson CP Jr, Babad AA, Regan MJ, Buechel DR, Eger EI II: The effects of halothane, fluroxene and cyclopropane on ventilation: A comparative study in man. ANESTHESIOLOGY 27:716–728, 1966

7. Brandstater B, Eger EI II, Edelist G: Constant-depth halothane anesthesia in respiratory studies. J Appl Physiol 20:171–174, 1965

8. Tusiewicz K, Bryan AC, Froese AB: Contributions of changing rib cage-diaphragm interactions to the ventilatory depression of halothane anesthesia. ANESTHESIOLOGY 47:327–337, 1977

9. Warner DO, Warner MA, Ritman EL: Human chest wall function while awake and during halothane anesthesia: I. Quiet breathing. ANESTHESIOLOGY 82:6–19, 1995

10. Mankikian B, Cantineau JP, Sartene R, Clergue F, Viars P: Ventilatory pattern and chest wall mechanics during ketamine anesthesia in humans. ANESTHESIOLOGY 65:492–499, 1986

11. De Troyer A, Estenne M, Ninane V, Van Gansbeke D, Gorini M: Transversus abdominis muscle function in humans. J Appl Physiol 68:1010–1016, 1990

12. Garland H, Angel RW, Melen RD: A state variable averaging filter for electromyogram processing. Med Biol Eng 10:559–560, 1972

13. Ledlie JF, Pack AI, Fishman AP: Effects of hypercapnia and hypoxia on abdominal expiratory nerve activity. J Appl Physiol 55: 1614–1622, 1983

14. Altose MD, Stanley NN, Cherniack NS, Fishman AP: Effects of mechanical loading and hypercapnia on inspiratory muscle EMG. J Appl Physiol 38:467–473, 1975

15. Mead J, Loring SH: Analysis of volume displacement and length changes of the diaphragm during breathing. J Appl Physiol 53:750–755, 1982

16. Nunn JF, Hill DW: Respiratory dead space and arterial to end-tidal CO_2 tension difference in anesthetized man. J Appl Physiol 15: 383–389, 1960

17. Rebuck AS, Rigg JRA, Kangalee M, Pengelly LD: Control of tidal volume during rebreathing. J Appl Physiol 37:475–478, 1974

18. Pengelly LD, Tarshis AM, Rebuck AS: Contribution of rib cage and abdomen-diaphragm to tidal volume during CO_2 rebreathing. J Appl Physiol 46:709–715, 1979

19. Byrick RJ, Janssen EG: Respiratory waveform and rebreathing in T-piece circuits: A comparison of enflurane and halothane waveforms. ANESTHESIOLOGY 53:371–378, 1980

20. Lindahl SGE, Yates AP, Hatch DJ: Respiratory depression in children at different end tidal halothane concentrations. Anaesthesia 42:1267–1275, 1987

21. Warner DO, Joyner MJ, Ritman EL: Anesthesia and chest wall function in dogs. J Appl Physiol 76:2802–2813, 1994

22. Berkenbosch A, de Goede J, Olievier CN, Quanjer PH: Sites of action of halothane on respiratory pattern and ventilatory response to CO_2 in cats. ANESTHESIOLOGY 57:389–398, 1982

23. Gautier H, Bonora M, Gaudy JH: Breuer-Hering inflation reflex and breathing pattern in anesthetized humans and cats. J Appl Physiol 51:1162–1168, 1981

24. Guz A, Noble MIM, Trenchard D, Cochrane HL, Makey AR: Studies on the vagus nerves in man: Their role in respiratory and circulatory control. Clin Sci 27:293–304, 1964

25. Paskin S, Skovsted P, Smith TC: Failure of the Hering-Breuer reflex to account for tachypnea in anesthetized man: A survey of halothane, fluroxene, methoxyflurane, and cyclopropane. ANESTHESIOLOGY 29:550–558, 1968

26. Polacheck J, Strong R, Arens J, Davies C, Metcalf I, Younes M: Phasic vagal influence on inspiratory motor output in anesthetized human subjects. J Appl Physiol 49:609–619, 1980

27. Mier A, Brophy C, Estenne M, Moxham J, Green M, De Troyer A: Action of abdominal muscles on rib cage in humans. J Appl Physiol 58:1438–1443, 1985

28. Taylor A: The contribution of the intercostal muscles to the effort of respiration in man. J Physiol 151:390–402, 1960

29. Estenne M, De Troyer A: Relationship between respiratory muscle electromyogram and rib cage motion in tetraplegia. Am Rev Respir Dis 132:53–59, 1985

30. De Troyer A, Heilporn A: Respiratory mechanics in quadriplegia: The respiratory function of the intercostal muscles. Am Rev Respir Dis 122:591–600, 1980

31. Prabhakar NR, Mitra J, Overholt JL, Cherniack NS: Analysis of postinspiratory activity of phrenic motoneurons with chemical and vagal reflexes. J Appl Physiol 61:1499–1509, 1986

32. Yamakage M, Aoki M, Namiki A, Ikeda M: The inhibitory effects of positive end-expiratory pressure (PEEP) on phrenic motoneuronal activity in cats. Anesth Analg 76:80–84, 1993

33. Lumb AB, Petros AJ, Nunn JF: Rib cage contribution to resting and carbon dioxide stimulated ventilation during 1 MAC isoflurane anaesthesia. Br J Anaesth 67:712–721, 1991

34. Bickler PE, Dueck R, Prutow RJ: Effects of barbiturate anesthesia on functional residual capacity and ribcage/diaphragm contributions to ventilation. ANESTHESIOLOGY 66:147–152, 1987

35. De Troyer A, Estenne M: Coordination between rib cage muscles and diaphragm during quiet breathing in humans. J Appl Physiol 57:899–906, 1984

36. Warner DO, Brichant J-F, Ritman EL, Rehder K: Chest wall motion during epidural anesthesia in dogs. J Appl Physiol 70:539–547, 1991

37. Schroeder MA, Tao H-Y, Farkas GA: Mechanical role of expiratory muscle recruitment during eupnea in supine anesthetized dogs. J Appl Physiol 70:2025–2031, 1991

38. Kim MJ, Druz WS, Sharp JT: Effect of muscle length on electromyogram in a canine diaphragm strip preparation. J Appl Physiol 58:1602–1607, 1985

39. Brancatisano A, Kelly SM, Tully A, Loring SH, Engel LA: Postural changes in spontaneous and evoked regional diaphragmatic activity in dogs. J Appl Physiol 66:1699–1705, 1989

40. Dureuil B, Viires N, Nivoche Y, Fiks M, Pariente R, Aubier M, Desmonts J-M: Different effects of halothane on diaphragm and hindlimb muscle in rats. J Appl Physiol 63:1757–1762, 1987

41. Clergue F, Viires N, Lemesle P, Aubier M, Viars P, Pariente R: Effect of halothane on diaphragmatic muscle function in pentobarbital-anesthetized dogs. ANESTHESIOLOGY 64:181–187, 1986

42. Kochi T, Ide T, Isono S, Mizuguchi T, Nishino T: Different effects of halothane and enflurane on diaphragmatic contractility in vivo. Anesth Analg 70:362–368, 1990

43. Kochi T, Ide T, Mizuguchi T, Nishino T: Halothane does not depress contractile function of fresh or fatigued diaphragm in pentobarbitone-anaesthetized dogs. Br J Anaesth 68:562–566, 1992

44. Easton PA, Fitting J-W, Arnoux R, Guerraty A, Grassino AE: Costal and crural diaphragm function during CO_2 rebreathing in awake dogs. J Appl Physiol 74:1406–1418, 1993

45. Lourenco RV, Cherniack NS, Malm JR, Fishman AP: Nervous output from the respiratory center during obstructed breathing. J Appl Physiol 21:527–533, 1966

Appendix

The diaphragm was active both while awake and while anesthetized, so that diaphragm EMG response to rebreathing in the two states can be compared. However, such comparisons must be made with caution for several reasons. First, the electrode could have become dislodged between the time of awake and anesthetized measurements. Electrode activity was monitored carefully throughout the experiment, and no sudden changes in activity were observed, as would be expected if electrode position had changed. Second, the electrical environment surrounding the electrode could have changed during anesthesia, because of changes in muscle length or chest wall geometry. These changes can alter the EMG produced for a given neural input to the muscle.[38,39] However, anesthesia had little effect on the position of the diaphragm in these subjects,[9] so that muscle length and structures surrounding the electrode should have changed little. Third, high concentrations of volatile anesthetics can depress neuromuscular transmission and muscle contractility in the diaphragm,[40,41] although these effects are small or nonexistent at physiologic frequencies of stimulation.[42,43] Finally, we monitored diaphragm activity at only one location. The diaphragm is composed of costal and crural portions that may be differentially activated in animals under some conditions,[44] although such difference are minimal for many respiratory behaviors. Regional differences in the activation of the human diaphragm have not been studied. If regional differences in activation exist, then our measurement in the costal portion of the diaphragm may not be representative of the activity of the whole diaphragm. However, in a study of dogs anesthetized with various agents, we noted no differences in the responses of costal and crural portions of the diaphragm during quiet or stimulated breathing.[21] Thus, although some caution is warranted, we believe that our diaphragm EMG measurements are reasonable estimates of the neural drive to phrenic motoneurons[45] and the most direct method possible in intact human subjects.

Many methods have been proposed to quantify EMG activity and to estimate "neural drive." Our technique uses an analog device to provide a signal approximating the average of the rectified EMG waveform for the preceding 100 ms.[12] To quantify inspiratory drive to the phrenic motoneurons, we chose to analyze signals only during the period of inspiratory gas flow for two reasons. First, only this activity contributes to inspiratory gas flow. Second, PIIA, present while awake but not while anesthetized, would make comparisons based on analysis of the entire diaphragm signal problematic.