Lack of the Mechanoreceptor Influences on Ventilatory Control during Halothane Anesthesia in Humans

Tetsuo KOCHI, Toru IDE, Shiro ISONO
and Tadanobu MIZUGUCHI

Mechanical influences independent of chemoreceptor function on ventilatory control were studied in halothane-anesthetized, artificially ventilated patients using the technique reported by Altose et al. (Respir Physiol 66: 171–180, 1986). Contribution of mechanical factor was indirectly assessed by comparing the values of arterial carbon dioxide tension at which the subjects started breathing efforts during CO_2 loading induced by the following two methods. 1) Partial rebreathing of expired gas and 2) Mechanical hypoventilation (successive decrease in inflation volume). These two maneuvers resulted in a similar rate of increase in end-expiratory carbon dioxide tension. However, contrary to the observation made by Altose et al. in awake volunteers, we found comparable values of ventilatory recruitment threshold for Pa_{CO_2}. Thus, we speculate that halothane anesthesia and/or loss of consciousness impair transmission of afferent information from the lung and/or chest wall musculature. Such effects may be responsible for the depression of load compensatory mechanism during anesthesia. (Key words: halothane, ventilatory recruitment threshold, carbon dioxide tension, mechanoreceptor afferent)

(Kochi T, Ide T, Isono S, et al.: Lack of the mechanoreceptor influences on ventilatory control during halothane anesthesia in humans. J Anesth 6: 387–394, 1992)

It has been shown in animals and awake humans that the afferent information originating from the lung and/or the chest wall musculature plays a significant role in the determinant of the level and pattern of breathing during quiet breathing[1,2], and is responsible for the compensatory increses in respiratory activity during ventilatory loading[3,4]. Remmers et al. have demonstrated in cats that lateral cervical lesions significantly changed tidal volume and increased respiratory frequency[5]. Similarly, diaphragmatic afferents can also modify respiratory controller since stimulation of the afferent traffic of the phrenic nerve has been shown to change the efferent phrenic discharge[6,7].

In mechanically ventilated humans, Altose and his colleagues demonstrated that end-expiratory carbon dioxide level at which the subjects started breathing effort was significantly lower when inflation volume was gradually

Department of Anesthesiology, Chiba University School of Medicine, Chiba, Japan

Address reprint requests to Dr. Kochi: Department of Anesthesia, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa-shi, Chiba, 277 Japan

decreased than when CO_2 was added to the inspired gas while ventilator settings were held constant[4]. All of these results indicate that the mechanoreceptor afferents can modify the respiratory controller independent of the chemoreceptor activities.

In this regard, it has been demonstrated that during REM sleep intercostal muscles are totally inactive and afferent messages initiated by the passive elongation of spindles constitute only a proprioceptive information[8]. If anesthesia and sleep share common mechanism of depressing afferent traffic from the mechanoreceptors, then the contribution of the afferent influences on the respiratory controlling mechanism becomes less important during anesthesia compared to awake state.

To test this hypothesis we examined the ventilatory recruitment threshold for carbon dioxide in fourteen mechanically ventilated subjects anesthetized with 1.4 MAC of halothane and compared the results to those reported by Altose et al. in awake human subjects[4].

Methods

Fourteen patients 20–56 yr of age, scheduled for elective ophthalmic or minor orthopedic surgery were studied. None of them had clinical evidence of respiratory, cardiovascular, or neuromuscular disorders. Forced vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_{1.0}$) were measured preoperatively. All values were greater than 80% of values predicted for height and age. No subject was on regular medication at the time of the study. The protocol was approved by our institutional ethics committee and each patient gave informed consent. All the patients were intramuscularly premedicated 30 min prior to the induction of anesthesia with 0.5 mg of atropine and 50 mg of hydroxyzine. Anesthesia was induced with thiopental (4–5 $mg \cdot kg^{-1}$ iv) followed by succinylcholine chloride (1 $mg \cdot kg^{-1}$ iv), and the trachea was intubated with a cuffed endotracheal tube (Portex, ID 7.5 mm). Anesthesia was maintained with 33% O_2 in N_2O and halothane (1–1.5%) for approximately 1 hr and the surgery was started during this time period. Then administration of N_2O was discontinued and the inspired concentration of halothane was adjusted so as to maintain constant end-expired concentration (1%; 1.4 MAC) using a Datex anesthetic gas monitor (Normac).

Ventilatory airflow ($\dot{V}$) was measured through a hot-wire flowmeter (Minato RF-2), and tidal volume (V_T) was obtained by electrical integration of the $\dot{V}$ signal. Airway opening pressure (Pao) was measured with a differential pressure transducer (Nihon Kohden TP 603-T). Partial pressure of expiratory carbon dioxide ($P_{E_{CO_2}}$) was monitored continuously with an infrared CO_2 analyzer (Datex Normocap). All these signals were continuously recorded on a four channel recorder (Nihon Kohden RJG 4124). A radial artery was cannulated with a 22 gauge teflon catheter (Viggo, Viggo Japan) to obtain arterial blood samples.

Baseline ventilator settings were as follows: V_T 10 $ml \cdot kg^{-1}$, ventilatory frequency 10–12 breaths per minute, inspiratory to total duration of a breath 0.3–0.4. This resulted in an end-expired carbon dioxide tension ($P_{ET_{CO_2}}$) of 35–40 mmHg.

The experimental procedure was started after achieving at least 1 hr of stable end-expired halothane level with stable cardiovascular status. The protocol was as follows. An arterial blood sample subjected for control measurement was withdrawn while keeping the baseline ventilatory parameters. Then V_T was decreased by 50 ml every 30 second allowing $P_{ET_{CO_2}}$ to rise. By doing this $P_{ET_{CO_2}}$ increased at a rate of

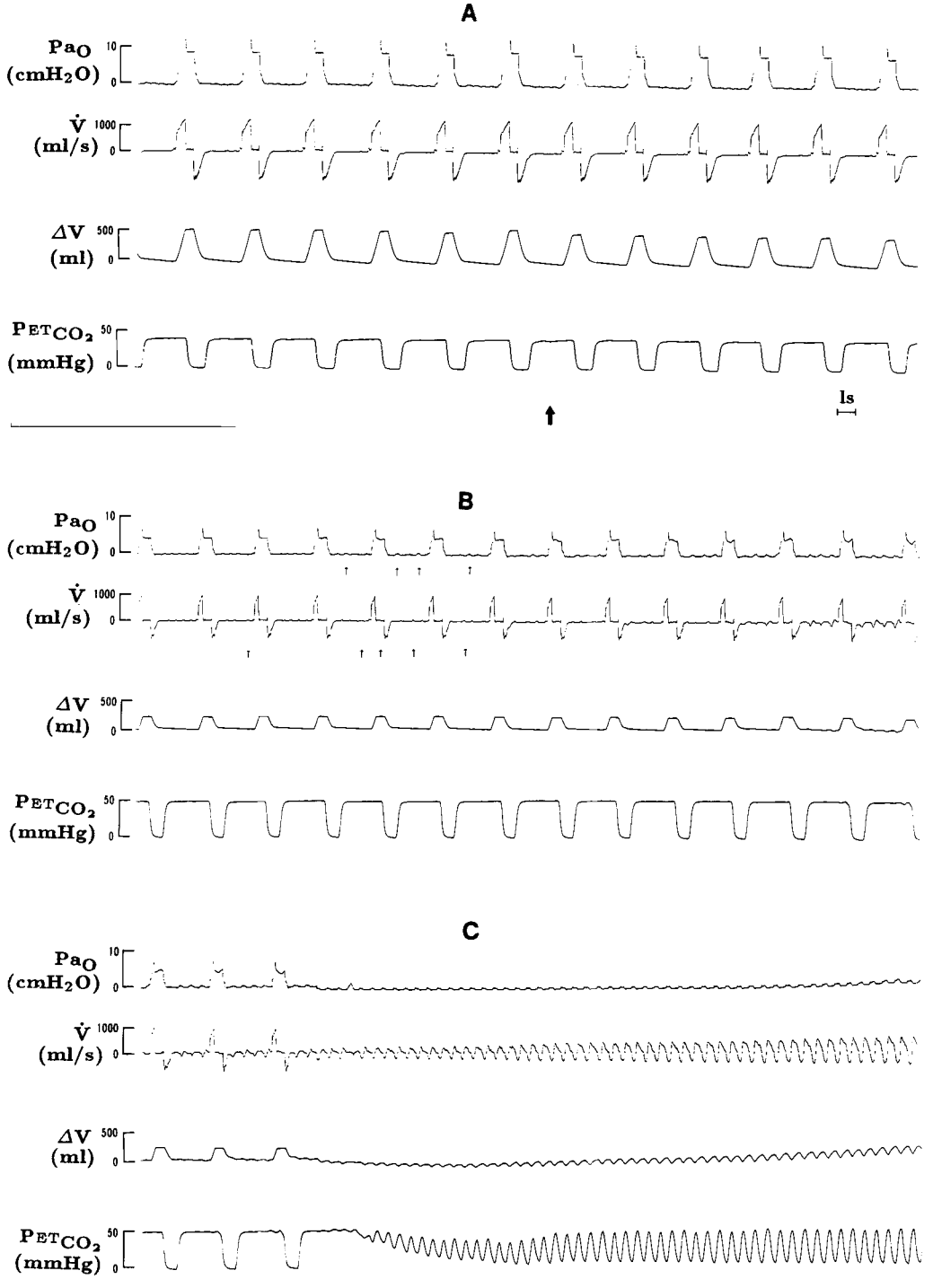

Fig. 1. Representative tracing obtained in a subject during mechanical hypoventilation protocol. A: Before the onset of spontaneous inspiratory effort; B: Initiation of inspiratory effort; C: Spontaneous breathing. Pao; airway opening pressure, $\dot{V}$; airflow, ΔV; changes in the lung volume, $P_{ET}CO_2$; partial pressure of end-tidal carbon dioxide.

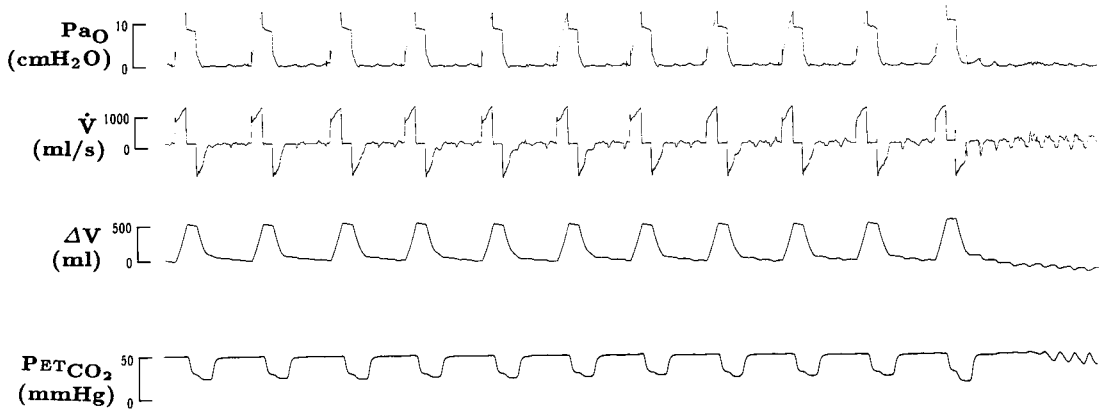

Fig. 2. Recording obtained during rebreathing protocol in the same subject as in figure 1. For abbreviations see figure 1.

Table 1. Patient characteristics and the values of recruitment threshold for CO_2 of fourteen subjects

Subject #	Age (years)	Height (cm)	Weight (kg)	RT-CO_2 (mmHg) VT $P_{ET}CO_2$	VT Pa_{CO_2}	Rebreathing $P_{ET}CO_2$	Rebreathing Pa_{CO_2}
1	43	169	65	42.8	46.9	43.3	45.8
2	20	180	62	56.0	59.5	57.4	59.2
3	56	164	64	42.1	46.6	44.1	47.6
4	38	165	68	45.1	47.1	40.1	43.6
5	43	160	80	55.7	57.4	48.3	50.8
6	48	167	66	56.8	59.3	58.9	61.4
7	58	157	60	57.7	61.7	70.0	72.7
8	24	183	70	50.3	54.8	43.0	44.2
9	23	168	59	40.9	43.1	41.0	43.4
10	23	168	76	48.8	51.9	57.2	59.9
11	35	158	48	49.6	52.3	54.6	57.2
12	36	163	56	42.6	46.0	45.9	46.8
13	43	152	43	41.0	43.6	44.9	45.4
14	20	174	62	50.0	52.6	51.3	55.4
Mean	36.4	166.3	62.8	48.5	51.6	50.0	52.4
SD	12.5	8.3	9.4	6.2	6.0	8.6	8.5

2–2.5 mmHg·min^{-1}. As soon as the inspiratory effort of the subject was detected from the V̇ or Pao signal, arterial blood sample was withdrawn from the arterial line for blood gas analysis (Ciba Corning, model 288). Subsequently ventilatory parameters were put back to the original settings. After allowing thirty minutes of stabilization, CO_2 level was again raised at approximately similar rate of increase in $P_{ET}CO_2$ (2–2.5 mmHg·min^{-1}) by partial rebreathing of the expired gas. This was accomplished by adjusting the amount of bypass flow to the CO_2 absorber in the expiratory line of the anesthetic circuit. An arterial blood sample at the initiation of the inspiratory effort was similarly obtained as in hypoventilation protocol. The sequence

of the above protocol was followed in seven subjects, and in the remaining seven subjects the order of the procedures was reversed.

The value of Pa_{CO_2} at which spontaneous breathing occurs is hereafter termed as ventilatory recruitment threshold for CO_2 (RT-CO_2). Statistical analysis was performed using Wilcoxon's rank test. P value < 0.05 was considered to be statistically significant.

Results

Baseline values of end-expiratory P_{CO_2} were not different between the two protocols and amounted to 35.3 ± 3.7 and 35.1 ± 3.8 mmHg, (mean ± SD). Thus, control arterial blood samples were withdrawn just before starting the first protocol. Average value of Pa_{CO_2} was 38.9 ± 2.6 mmHg.

Figure 1 illustrates an actual tracing obtained in a subject during mechanical hypoventilation protocol. In figure 1A, tidal volume was reduced from 500 ml to 450 ml. However, spontaneous breathing was not detected yet. When tidal volume was further reduced to 200 ml, inspiratory effort gradually occurred as indicated by arrows (fig. 1B). To ascertain that such changes in $\dot{V}$ or Pao are indeed reflections of inspiratory efforts, mechanical ventilation was halted for about 30 seconds and the development of spontaneous breathing was confirmed (fig. 1C).

Figure 2 shows similar tracing recorded during the rebreathing protocol in the same subject as in fig. 1. In this particular subject inspiratory effort occurred at $P_{ET_{CO_2}}$ of 51 mmHg during rebreathing and at 50 mmHg during mechanical hypoventilation. Average rate of rise of $P_{ET_{CO_2}}$ observed during mechanical hypoventilation (2.1 mmHg·min^{-1}) was not significantly different from the corresponding value obtained in the rebreathing protocol (2.3 mmHg·min^{-1}).

Table 1 depicts patient characteristics and the values of RT-CO_2 determined in the two protocols for individual subjects. Mean (± SD) value of RT-CO_2 during mechanical hypoventilation amounted to 51.6 ± 6.0 mmHg and was not statistically different from the corresponding value of 52.4 ± 8.5 mmHg obtained in the rebreathing protocol. The difference of RT-CO_2 values between the two protocols in each subject was also calculated and amounted to 0.75 ± 5.5 mmHg, which was not significantly different from 0.

Discussion

The main finding of the present results is that the ventilatory recruitment threshold for a given rate of increase in $P_{ET_{CO_2}}$ is not different between mechanical hypoventilation and rebreathing. To the extent that the two protocols produce different degree of stretching of the lung and the chest wall, the lack of difference in RT-CO_2 suggests that the contribution of the afferent information to the inspiratory drive is minimal in halothane anesthetized humans.

Critique of the methods

Although we determined the initiation of inspiratory effort during mechanical ventilation from the changes in the patterns of ventilatory airflow and airway opening pressure, this may not be sensitive enough to detect CO_2 threshold of the respiratory center. Central neural output is transformed to the pressure changes at the airway opening and hence generation of airflow through several steps, namely neuromuscular junction, contraction of the respiratory muscles and the generation of negative intrathoracic pressure. Therefore, conceivably, the initiation of the inspiratory activities of the various inspiratory nerves and muscles may precede that of airflow or changes in pressure. However this can-

not influence our results since we used same criteria for the ventilatory recruitment of CO_2 in the two protocols. Besides, Prechter and colleagues have demonstrated that the measurement of airway opening pressure and airflow is as sensitive as the measurement of diaphragmatic electromyogram (EMGdi) for detecting the initiation of inspiratory effort[9].

It has been demonstrated that apneic threshold of CO_2 during surgery is lower than that determined in the absence of surgical stimulation[10]. Since our measurements were all done during the course of surgery, possible differences of the surgical stress during the two protocols may have influenced our results. However, we selected surgical procedures those minimally affect respiration and randomized the sequence of the two protocols between subjects. Therefore we believe that surgical stimulation did not influence our results.

In the present experimental conditions, brain tissue P_{CO_2} may not be the same as Pa_{CO_2} by the following reasons. First, decrease in tidal volume during mechanical ventilation may augument cardiac output through its effects on the venous return, while rebreathing of expired gas will not exert any mechanical influences on circulation. Secondly, since we determined arterial blood gas during gradual increase in $P_{ET_{CO_2}}$ from normocapnia, both end-tidal to arterial and arterial to brain tissue CO_2 gradients may not have achieved steady state condition. Taking these two points together, even if Pa_{CO_2} values are comparable actual CO_2 tension at the central chemosensitive area during rebreathing might be slightly higher than during hypoventilation protocol. This possibility may have produced an error in estimating brain tissue P_{CO_2} from the measurement of Pa_{CO_2} by about 2 mmHg.

Results

Our finding of identical levels of CO_2 ventialtory threshold between the two protocols is contradictory to the observation reported by Altose et al. who found lower RT-CO_2 value during mechanical hypoventilation than during rebreathing in awake humans (37.0 ± 1.4 vs 43.1 ± 0.7 mmHg)[4]. The following three mechanisms may be applied to explain the discrepancies of the results.

First, Altose et al. detected inspiratory effort of the awake subjects from the reduction of peak inspiratory airway pressure. By contrast, in the present study, the initiation of inspiratory airflow during the expiratory phase of the ventilator cycles always preceded the reduction of peak inspiratory pressure. This may be related to the increase in intrinsic respiratory rate during halothane anesthesia and to the respiratory entrainment phenomenon during wakefulness. Whatever the mechanism is, different pattern of initiating inspiration during wakefulness and anesthesia could be responsible for the difference of the results.

Second, wakefulness state influences the perception of the thoracic movement at the cortical level. It has been demonstrated that the changes in respiratory activity during ventilatory loading are blunted by anesthesia[11], during sleep[12] and following the administration of opiate drungs[3]. There is an evidence indicating that the mechanical influences on breathing, other than those produced by ventilatory loading, are also critically dependent on the wakefulness state. In this connection, during high frequency oscillation the inhibition of rhythmic ventilation appears to be greater with sedation and anesthesia than in a state of full awakefulness[13]. Similarly, posthyperventilation apnea can regularly be produced during sleep

but the apneic response at comparable P_{CO_2} levels is absent or variable during wakefulness[14]. By contrast, Daubenspeck and Bennet have reported compensatory responses to ventilatory loads below the perceptual threshold[15]. Similarly, Altose et al. also noticed that changes in respiratory activity first occurred before there was any awareness of a difference in respiratory sensation[4]. This suggests that mechanical factors' influences on breathing can be initiated subconsciously and may involve only simple neural reflexes without modulation by cortex. In this regard, Jones and colleagues have shown that the electromyographic activity (EMG) of the inspiratory intercostal muscles is more sensitive to halothane than diaphragm[16]. They attributed the different sensitivity of the two muscles to the depressant effect of halothane on the spinal interneuronal pool. Thus, halothane may diminish the contribution of mechanoreceptor influences on breathing efforts by inhibiting the neuronal transmission of the afferent traffic from the lungs and/or chest wall either at the receptor site or at the synaptic level. In order to ellucidate the precise site of action of halothane in the afferent traffic from the mechanoreceptor, detailed neurophysiological study would be needed.

In conclusion, influences from the mechanoreceptor in the lung and/or the chest wall on the respiratory control are depressed during halothane anesthesia most probably due to the inhibitory effects of halothane on the afferent traffic. This may be related to the blunted load compensatory mechanisms during halothane anesthesia[17].

Acknowledgement: The authors wish to thank Dr. Ayumi Watanabe for her technical assistance.

(Received Dec. 16, 1991, accepted for publication Feb. 24, 1992)

References

1. Remmers J and Marttila I: Action of intercostal muscle afferents on the respiratory rhythm of anesthetized cats. Respir Physiol 24:31–41, 1975
2. Easton PA, Jadue C, Arnup ME, et al: Effects of upper and lower airway anesthesia on hypercapnic ventilation in humans. J Appl Physiol 59:1090–1097, 1985
3. Kryger MH, Yacoub O, Dosman J, et al: Effect of meperidine on occlusion pressure responses in hypoxia and hypercapnia. Am Rev Respir Dis 114:333–340, 1976
4. Altose MD, Castele RJ, Connors AF Jr, et al: Effects of volume and frequency of mechanical ventilation on respiratory activity in humans. Respir Physiol 66:171–180, 1986
5. Remmers JE, Tsiaras WG: Effects of lateral cervical cord lesions on the respiratory rhythm of anesthetized decerebrated cats after vagotomy. J Physiol (Lond) 233:63–74, 1973
6. Jamme Y, Buchler B, Delpierre S, et al: Phrenic afferents and their role in inspiratory control. J Appl Physiol 60:854–860, 1986
7. Duron B: Intercostal and diaphragmatic muscle endings and afferents. In: Hornbein TF eds. Regulation of Breathing, part I. Lung Biology in Health and Disease vol. 17. New York, Marcel Dekker 473–540, 1981
8. Duron B: La fonction respiratoire pendant le sommeil physiologique. Bull Physiol Pathol Respir 8:1031–1057, 1972
9. Prechter GC, Nelson SB, Hubmayr RD: The ventilatory recruitment threshold for carbon dioxide. Am Rev Repir Dis 141:758–764, 1990
10. Eger EI, Dolan WM, Stevens WC, et al: Surgical stimulation antagonizes the respiratory depression produced by forane. Anesthesiology 36:544–549, 1972
11. Whitelaw WA, Derenne JP, Couture J, et al: Adaptation of anesthetized man to breathing through an inspiratory resistor. J Appl Physiol 41:285–291, 1976
12. Iber C, Berssenbrugge A, Skatrud

JB, et al: Ventilatory adaptations to resistive loading during wakefulness and non-REM sleep. J Appl Physiol 52:607–614, 1982
13. Butler WJ, Bohn DJ, Bryan AC, et al: Ventilation by high-frequency oscillation in humans. Anesth Analg 59:577–584, 1980
14. Skatrud JB, Dempsey JA: Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. J Appl Physiol 55:813–822, 1983
15. Daubenspeck JA, Bennett FM: Immediate human breathing pattern responses to loads near the perceptual threshold. J Appl Physiol 55:1160–1166, 1983
16. Jones JG, Faithfull D, Jordan C, et al: Rib cage movement during halothane anaesthesia in man. Br J Anaesth 51:399–407, 1979
17. Freedman S, Campbell EJM: The ability of normal subjects to tolerate added inspiratory loads. Respir Physiol 10:213–235, 1970