Breathing Pattern and Respiratory Mechanics in Sevoflurane-Anesthetized Humans

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In order to determine the respiratory effects of sevoflurane in humans, breathing pattern and mechanical behavior of respiratory system were investigated in ten subjects at anesthetic depth of 1 MAC (minimum alveolar concentration). Average tidal volume and breathing frequency amounted to 275 ml and 20.9 breaths per minute. Arterial carbon dioxide tension amounted to 45.6 mmHg. Duration of inspiration was 1.06s and that of expiration was 1.92s. Mean inspiratory flow rate amounted to 259 $ml \cdot s^{-1}$. Average value of passive respiratory elastance determined by the method of Zin et al. amounted to 21.8 $cmH_2O \cdot l^{-1}$, while those of active respiratory elastance and resistance obtained by the method of Behrakis et al. were 28.0 $cmH_2O \cdot l^{-1}$ and 3.15 $cmH_2O \cdot l^{-1} \cdot s^{-1}$, respectively.

Values of these variables were compared to those reported in halothane and enflurane anesthesia and possible explanations of the differences between the anesthetics are discussed. (Key words: respiration, anesthetics, sevoflurane, elastance, resistance)

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The effects of various anesthetics on the control of breathing have been extensively studied in both animals and humans. However little information is available regarding the effects of sevoflurane, a new inhalational anesthetic, on the pattern and mechanics of breathing in humans.

Recently Behrakis et al.[1] have applied a method introduced by Siafakas et al.[2] to determine active inspiratory impedance in anesthetized patients. They provided detailed data obtained from eight healthy subjects anesthetized with halothane. Therefore we employed a similar study in ten sevoflurane-anesthetized patients and compared the values of respiratory elastance and resistance to those reported by Behrakis et al. during halothane anesthesia. Furthermore we determined the timing and depth of breathing in the same 10 patients and compared the data to those values reported in the literature for halothane[3,4] to elucidate the difference of the effects on the respiratory control mechanisms between the two anesthetics.

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Materials and Methods

Ten patients scheduled for minor gynecological surgery were studied after obtaining an informed consent from each subject. None had any significant cardiorespiratory disorders or took regular medication. The physical characteristics and the values of preoperative pulmonary function tests are listed

Table 1. Anthropomorphic data and pulmonary function tests of ten subjects

Subject No	age years	height cm	weight kg	FVC *l*	$FEV_{1.0}$ *l*
1	51	156	60	3.15	2.73
2	45	164	67	2.30	1.91
3	54	154	50	2.85	2.38
4	29	158	55	2.65	2.40
5	40	154	50	2.71	2.22
6	57	155	56	2.00	1.65
7	26	155	50	2.80	2.66
8	34	160	56	2.82	2.68
9	39	157	52	2.69	2.43
10	46	154	58	2.49	2.37
Median	45	156	56	2.71	2.40
Mean	42.1	156.7	55.4	2.65	2.34
SD	10.4	3.2	5.4	0.32	0.34

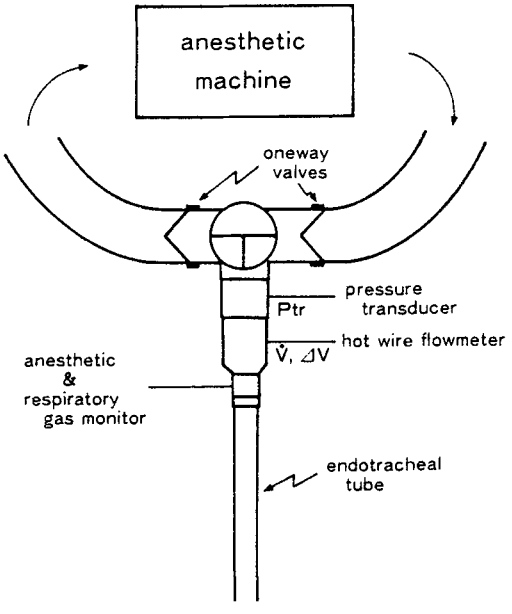

Fig. 1. Schematic illustration of the experimental apparatus. For discription, see text.

in table 1.

No premedication was given prior to the induction of anesthesia. Anesthesia was induced with inhalation of sevoflurane-nitrous oxide (66%)/oxygen by mask. After obtaining an adequate level of anesthesia, respiration was controlled manually and the administration of nitrous oxide was discontinued. Then oral endotracheal tube (ID7.5 mm) was inserted without the aid of muscle relaxant. Following tracheal intubation spontaneous breathing was allowed to resume and the breathing circuit was changed to the one illustrated in figure 1. Fractional concentrations of carbon dioxide and sevoflurane were continuously monitored by an anesthetic/respiratory gas monitor (ALBION INSTRUMENTS RASCAL). Tracheal pressure (Ptr) was measured by a differential pressure transducer (NIHON KODEN TP-603T). Air flow ($\dot{V}$) was measured by a hot-wire flowmeter (MINATO RF-H) and the changes in the lung volume (ΔV) were obtained by an electrical integration of the $\dot{V}$ signal. Ptr, $\dot{V}$ and ΔV were recorded on a four channel recorder (NIHON KODEN Recticorder).

After reaching the steady state condition, defined by the stable $\dot{V}$, ΔV and end-tidal carbon dioxide concentration at endtidal anesthetic concentration of 1 MAC (minimum alveolar concentration), ventilatory variables were recorded for two minutes. Then, five end-inspiratory airway occlusions followed by five end-expiratory airway occlusions were performed every ten breaths. Durations of inspiration (T_I) and expiration (T_E) and the respiratory cycle time (T_{TOT}) were measured from the V signal and the tidal volume (V_T) was determined

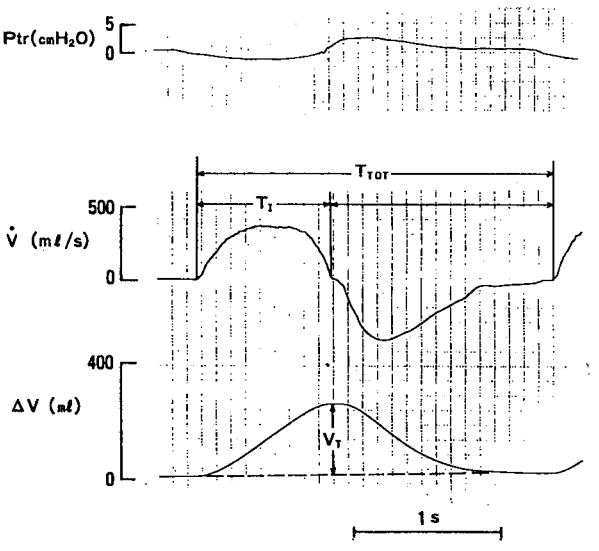

Fig. 2. Experimental records illustrating breathing pattern of subject 4. Ptr, tracheal pressure; $\dot{V}$, airflow; ΔV, changes in the lung volume.

Table 2. Ventilatory variables and Pa_{CO_2} of ten subjects

Subject No	T_I sec	T_E sec	T_I/T_{TOT}	f bpm	V_T ml	V_T/T_I ml·sec	$\dot{V}_E$ $l \cdot min^{-1}$	Pa_{CO_2} mmHg
1	1.35	2.33	0.367	16.3	354	263	5.78	48.6
2	0.97	1.68	0.367	22.7	276	284	6.25	43.6
3	0.97	1.69	0.366	22.6	225	232	5.08	46.8
4	0.97	1.46	0.399	24.7	264	272	6.51	49.5
5	1.00	1.26	0.441	26.6	243	245	6.47	43.9
6	1.06	1.69	0.387	21.9	275	259	6.02	43.9
7	1.10	3.28	0.252	13.7	284	259	3.90	42.2
8	1.07	1.94	0.355	19.9	291	272	5.41	44.6
9	1.14	2.02	0.361	19.0	270	237	4.50	45.8
10	0.98	1.86	0.345	21.1	266	271	5.71	47.3
Median	1.06	1.86	0.367	21.9	275	263	5.78	45.8
Mean	1.06	1.92	0.364	20.9	275	259	5.56	45.6
SD	0.12	0.56	0.048	3.8	34	17	0.86	2.4

from the ΔV signal as shown in figure 2. Using these variables mean inspiratory flow rate (V_T/T_I), duty ratio (T_I/T_{TOT}), respiratory frequency (f) and minute ventilation ($\dot{V}_E$) were calculated. Passive respiratory elastance (Ers) was calculated according to the method described by Zin et al[5]. Active respiratory elastance (E'rs) and resistance (R'rs) were also calculated by the method reported by Siafakas et al.[2], which is based on the following equation of motion:

$$-P^{\circ}tr = R'rs.\dot{V} + E'rs.\Delta V \qquad (1)$$

$P^{\circ}tr$ is tracheal pressure during an inspiratory effort with the airways occluded at functional residual capacity, representing the inspiratory driving pressure. $\dot{V}$ and ΔV are the instantaneous flow and volume changes during the control breath immediately preceding the occluded effort.

Arterial blood samples were drawn at the end of the experimental procedure and the partial pressure of carbon dioxide (Pa_{CO_2}) was measured using the blood gas analyzer (Radiometers; ABL2). All measurements were performed before the start of

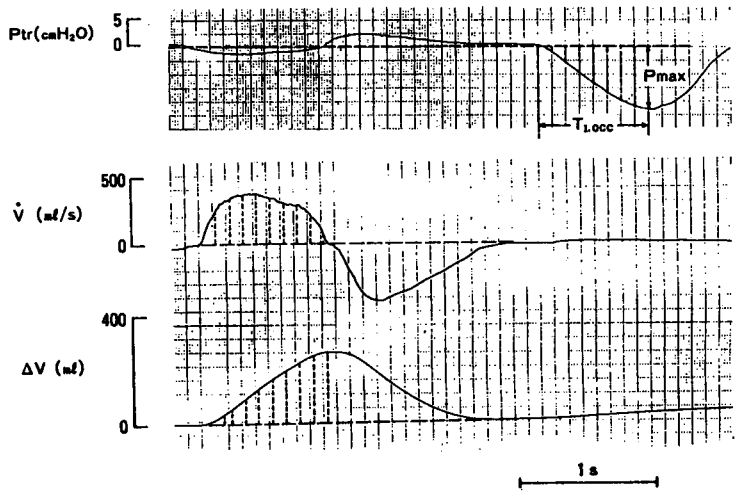

Fig. 3. Tracings demonstrating the changes in tracheal pressure during end-expiratory airway occlusion. Dotted vertical lines are drawn in 0.1s intervals after the onset of inspiratory effort.

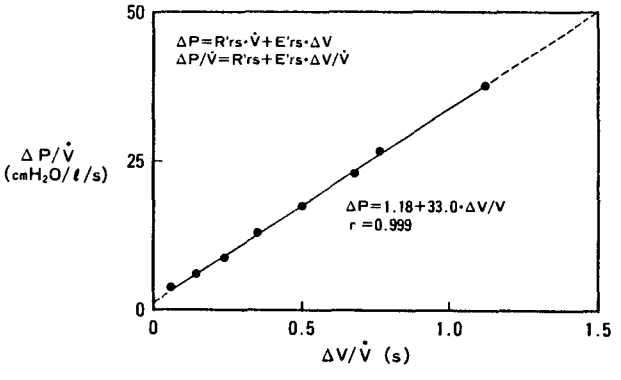

Fig. 4. Relationship between $-P^{\circ}tr/\dot{V}$ and $\Delta V/\dot{V}$ during inspiration, computed from data as in figure 3. Up to $\Delta V/\dot{V}$ of 1.45s a linear relationship is obtained, as shown by *regression line*. For further information and abbreviations see text.

surgical procedures. Results were analyzed using the least square regression analysis.

Results

Individual breathing parameters of each subject are listed in table 2. All reported data are the average values obtained during the 2 minutes of the steady state period.

Tracings of $\dot{V}$, ΔV and Ptr of unoccluded and occluded breaths are shown in figure 3. Occlusion of the inspiratory limb of the breathing circuit was performed during the preceding expiration and maintained during the whole respiratory cycle. During this period, the subject performed an inspiratory effort as indicated by negative Ptr, which was measured at 0.1s intervals after onset of occluded inspiration. $\dot{V}$ and ΔV of the preceding breath were measured in the same way, and data were plotted according to the following equation modified from Eq 1:

$$(-P^{\circ}tr - K_1.\dot{V} - K_2.\dot{V}^2)/\dot{V} = R'rs + E'rs.\Delta V/\dot{V} \quad (2)$$

K_1 and K_2 are Rohrer's constants representing the pressure-flow relationship of the endotracheal tube, hot-wire flowmeter and the connectors. Values of K_1 and K_2 of the equipment used in the present study amounted to 3.4 and 7.7, respectively. Equation 2 was obtained by subtracting the resistive pressure drop due to the equipment (including the endotracheal tube) from $-P^{\circ}tr$ in Eq.1 and dividing both sides of the equation by $\dot{V}$. Equation 2 is a linear function

Table 3. Values of respiratory elastance and active resistance of ten subjects

Subject No	Ers $cmH_2O \cdot l^{-1}$	E'rs $cmH_2O \cdot l^{-1}$	R'rs $cmH_2O \cdot l^{-1} \cdot s^{-1}$
1	18.8	21.1	6.55
2	22.8	27.7	3.54
3	22.2	31.4	3.07
4	23.6	33.5	1.94
5	23.2	25.0	1.63
6	23.9	33.0	2.09
7	17.8	29.2	3.67
8	20.4	23.6	3.24
9	21.6	24.7	2.69
10	23.4	30.4	3.10
Median	22.8	29.2	3.10
Mean	21.8	28.0	3.15
SD	2.1	4.2	1.38

Ers and E'rs, passive and active respiratory elastances; R'rs, active respiratory resistance

of the general type $y = a + bx$, where E'rs is the slope and R'rs is the intercept on the y-axis. Figure 4 depicts such a relationship obtained in a subject. Linear relationships were obtained in all subjects, with correlation coefficients (r) greater than 0.99. Values of active elastance and resistance, along with those of passive elastance, of the ten subjects are listed in table 3.

Discussion

In the present study, we have determined detailed respiratory pattern and the respiratory mechanics in sevoflurane-anesthetized humans.

At 1 MAC of anesthetic depth, a slight increase of Pa_{CO_2} was noticeable, compared to the normal values of awake subjects (35–45 mmHg), which indicates a moderate respiratory depressant effect of sevoflurane. Similarly, Doi et al.[6] have reported average Pa_{CO_2} levels of 48.8 and 54.8 mmHg at 1.1 and 1.4 MAC of sevoflurane, respectively. By applying a linear function to the relationship between the Pa_{CO_2} and MAC value, one would get an extrapolated value of 46.8 mmHg at 1 MAC which is very close to our value of 45.6 mmHg. Doi et al. also provided data for $\dot{V}_E$, V_T and f, amounting to 5.3 $l \cdot min^{-1}$, 247 ml and 21.7 bpm at 1.1 MAC, respectively. These values are again close to ours obtained at 1 MAC (table 2). Unfortunately, they did not report any data relating to respiratory timing, thus we have no comparable values for T_I, T_E and V_T/T_I in sevoflurane anesthesia. Instead, there have been several studies examining the respiratory timing and depth of breathing in enflurane or halothane anesthesia. Drummond et al.[7] have reported values of T_I and T_E amounting to 1.35 and 1.61s in 1.1 MAC of enflurane anesthesia, respectively. Corresponding values in 1 MAC of halothane anesthesia reported by Izumi et al.[3] amounted to 0.90 and 1.52s and those reported by Byrick et al.[4] with 1.4 MAC of halothane amounted to 0.90 and 1.0s, respectively. Therefore our values of T_I obtained in 1 MAC of sevoflurane anesthesia is longer than those obtained in halothane anesthesia, but shorter than those in enflurane anesthesia. T_E on the other hand, is slightly longer than that reported in enflurane anesthesia, probably due to the marked prolongation observed in subject 7. Differences of respiratory timings between the anesthetics may be due to different degrees of strength of Hering-Breuer inflation reflex, which is known to inhibit inspiration

when lung volume is increased. However, it is generally accepted that the reflex is not operative at normal range of tidal volume in humans[8]. Furthermore as demonstrated by Drummond et al.[7] and Izumi et al.[3], duration of occluded inspiration (T_I°) is equal to or slightly shorter than the duration of unoccluded inspiration (T_I) not only in halothane but also in enflurane anesthesia, indicating that Hering-Breuer inflation reflex does not regulate respiratory timing during halothane or enflurane anesthesia. This is also the case in the present study conducted with sevoflurane, in which average value of T_I amounted to 1.06 ± 0.12s while that of T_I° amounted to 1.00 ± 0.12s (mean ± SD).

V_T/T_I obtained from our subjects at 1 MAC of sevoflurane anesthesia (259 $ml \cdot s^{-1}$ is less than that obtained at 1 MAC of halothane anesthesia (328 $ml \cdot s^{-1}$)[3] or at 1.4 MAC of halothane (300 $ml \cdot s^{-1}$)[4] and is higher than in enflurane anesthesia (156 $ml \cdot s^{-1}$)[7]. It is generally accepted that V_T/T_I reflects the central respiratory drive[9]. V_T/T_I, on the other hand, can be affected by several factors including lung volume and thoracoabdominal configuration through its effect on the length-tension relationship of the diaphragm. In addition, alteration of neuromuscular transmission and the contractility of the respiratory muscle itself can also influence the relation between V_T/T_I and the central neural drive. However, changes in FRC have been shown to occur immediately after the induction of anesthesia and do not change any further with increasing depths of anesthesia or with the administration of muscle relaxants[10,11]. Furthermore effects of the three inhalational anesthetics on the contractility of the respiratory muscles would presumably be similar in magnitude at 1 MAC[12]. Taking these points together we believe, at least in the present experimental condition, V_T/T_I accurately reflects central neural drive. Thus current results and those of Izumi et al.[3] and Drummond et al.[7] indicate that the depressant effect of sevoflurane on the central respiratory drive is slightly greater than that of halothane and is less than that of enflurane at 1 MAC.

Mechanical behavior of the respiratory system is another important determinant of the breathing pattern, namely an alteration of elastic and/or resistive component of the respiratory system. This behavior may change the pattern of breathing through its effects on the load compensatory mechanisms[13]. Values of passive and active elastance amounted to, on the average, 21.8 ± 2.1 and 28.0 ± 4.2 and those reported by Behrakis et al. in halothane anesthesia were 23.2 ± 3.7 and 31.2 ± 5.2 $cmH_2O \cdot l^{-1}$, respectively. Our average value of active respiratory resistance (3.2 ± 1.4) was slightly higher than that of Behrakis et al.[1] (2.1 ± 0.7) but close to that of Higgs et al.[14] (2.8 ± 1.0 $cmH_2O \cdot l^{-1} \cdot s^{-1}$). The difference between our value and that of Behrakis et al. is probably due to the effect of atropine given in the latter study. We believe that this small difference of resistance cannot explain the difference of breathing pattern between sevoflurane and halothane.

Considering the absence of Hering-Breuer inflation reflex in humans and the lack of significant differences in mechanical behavior of the respiratory system between the anesthetics, the most likely explanation for the different respiratory patterns is that each anesthetic affects central respiratory regulatory mechanisms in a different way. Although we do not have direct evidence supporting this notion, several animal studies suggest the different sites of action for different anesthetics in the central nervous system[15,16]. For example Shapiro et al.[15] have demonstrated that cerebral glucose utilization in various parts of the central nervous system differs between the anesthetics. Furthermore Gautier et al.[16] have shown that increase of respiratory frequency induced by halothane can be abolished by midcollicular decerebration, indicating that tachypneic properties of halothane originate from the effect of the anesthetic on the suprapontine structures.

In conclusion, we suggest that differences of the pattern of breathing between sevoflurane and halothane or enflurane originates primarily from the different effects on the central respiratory related neural network.

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