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Speed of Onset and Offset and Mechanisms of Ventilatory Depression from Sevoflurane

An Experimental Study in the Cat

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Background: **Inhalational anesthetics depress breathing dose dependently. The authors studied the dynamics of ventilation on changes in end-tidal sevoflurane partial pressure. To learn more about the mechanisms of sevoflurane-induced respiratory depression, the authors also studied its influence on the dynamic ventilatory response to carbon dioxide.**

Methods: **Experiments were performed in cats anesthetized with α chloralose–urethane. For protocol 1, step changes in end-tidal sevoflurane partial pressure were applied and inspired ventilation was measured. Breath-to-breath inspired ventilation was related to the sevoflurane concentration in a hypothetical effect compartment based on an inhibitory sigmoid Emax model. For protocol 2, step changes in the end-tidal partial pressure of carbon dioxide were applied at 0, 0.5, and 1% end-tidal sevoflurane. The inspired ventilation–end-tidal partial pressure of carbon dioxide data were analyzed using a two-compartment model of the respiratory controller, which consisted of a fast peripheral and slow central compartment. Values are the mean ± SD.**

Results: **In protocol 1, the effect-site half-life of respiratory changes caused by alterations in end-tidal sevoflurane partial pressure was 3.6 ± 1.0 min. In protocol 2, at 0.5% sevoflurane, the central and peripheral carbon dioxide sensitivities decreased to 43 ± 20% and 36 ± 18% of control. At 1% sevoflurane, the peripheral carbon dioxide sensitivity decreased further, to 12 ± 13% of control, whereas the central carbon dioxide sensitivity showed no further decrease.**

Conclusions: **Steady state inspired ventilation is reached after 18 min (*i.e.,* 5 half-lives) on stepwise changes in end-tidal sevoflurane. Anesthetic concentrations of sevoflurane have, in addition to an effect on pathways common to the peripheral and central chemoreflex loops, a selective effect on the peripheral chemoreflex loop. Sevoflurane has similar effects on ventilatory control in humans and cats. (Key words: Central chemoreceptors; control of breathing; Hill equation; modeling; peripheral chemoreceptors; pharmacodynamics; respiration; ventilation.)**

INHALATIONAL anesthetics depress breathing dose dependently as a result of effects at several sites: a reduction in peripheral and central chemoreceptor drive, general depression of the central nervous system, and inhibitory actions on the respiratory muscles.[1–8] At high inspired concentrations, they cause the cessation of phrenic nerve action in vagotomized dogs and decerebrate cats, regardless of the arterial carbon dioxide tension.[1,8]

Previous studies of the influences of anesthetics on breathing were not designed to measure the temporal profile (speed of onset and offset) of ventilatory depression. In this study, we evaluated the dynamics of inspired breath-to-breath ventilation ($\dot{V}_I$) related to changes in end-tidal sevoflurane partial pressure ($P_{ET_{SEVO}}$) in a feline model. We analyzed the data using an empiric model consisting of one part that describes the time lag between end-tidal sevoflurane and "effect-site" partial pressures and a second part that translates the effect-site partial pressure into ventilation using an inhibitory sigmoid Emax model (for more information, see references 9–13). The time lag (defined by the rate constant k) reflects the speed at which ventilatory changes occur. This approach enables us to study the rate of change of sevoflurane-induced respiratory depression independent of its lung uptake and removal.

We also evaluated the dynamic ventilatory response to

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carbon dioxide at two $P_{ET_{SEVO}}$ values (resulting in end-tidal concentrations of 0.5 and 1%). The responses were analyzed using a two-compartment model of the respiratory controller, reflecting the peripheral and central chemoreflex pathways.[14,15] These studies provided information about the sites of action of sevoflurane with respect to its dynamic and steady state effects on the ventilatory carbon dioxide response curve.

Materials and Methods

Animals and Apparatus

Experiments were performed in 12 adult cats of either sex (body weight, 2.5–3.6 kg). The Ethical Committee for Animal Experiments of the Leiden University Medical Center approved the use of the animals. Experiments were performed with the animals during light anesthesia. Anesthesia was induced with 10 mg/kg ketamine given intramuscularly, followed by sevoflurane inhalation. Subsequently, the right femoral vein was fitted with a cannula and 20 mg/kg α-chloralose and 100 mg/kg urethane were slowly administered intravenously, and the volatile anesthetic was withdrawn. Thereafter, a continuous infusion of 1 or 2 $mg \cdot kg^{-1} \cdot h^{-1}$ α-chloralose and 5–10 $mg \cdot kg^{-1} \cdot h^{-1}$ urethane was started. With this regimen, the level of anesthesia is sufficient to suppress the pain withdrawal reflex but light enough to preserve the corneal reflex. The anesthetic regimen has little effect on the ventilatory response to hypercapnia compared with the awake state and does not yield systematic changes in respiratory variables over time (>6 h).[16–19] The right femoral artery was fitted with a cannula to allow continuous measurement of blood pressure.

The trachea was fitted with a cannula at the mid cervical level and connected to a Fleisch number 0 flow transducer (Lausanne, Switzerland) to measure inspiratory and expiratory flow. The flow transducer was connected to a T piece of which one arm received a continuous fresh gas flow of 5 l/min. Three computer-controlled mass flow controllers (High-Tec, Veenendaal, The Netherlands) composed desired inspiratory gas mixtures of oxygen, carbon dioxide, and nitrogen. A sevoflurane vaporizer (Vapor 19.3; Dräger, Lubeck, Germany) was used to administer the volatile anesthetic. Sevoflurane, oxygen, and carbon dioxide concentrations were measured using a Capnomac Ultima monitor (Datex, Helsinki, Finland). Temperature was controlled within 1°C in each cat and ranged among the cats between 38 and 39°C.

All signals were recorded (sample frequency, 100 Hz) and processed using a PDP minicomputer (Digital Equipment Co., Maynard, MA). Ventilation, end-tidal carbon dioxide pressure ($P_{ET_{CO_2}}$), end-tidal oxygen pressure ($P_{ET_{O_2}}$), and $P_{ET_{SEVO}}$ were determined and collected on a breath-to-breath basis.

Experimental Design and Data Analysis

$P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ were controlled using the "dynamic end-tidal forcing" technique.[14,15] Studies started when the cat showed a regular breathing pattern. This was generally reached 1.5 h after the start of the continuous α-chloralose infusion.

Protocol 1. Stepwise changes in $P_{ET_{SEVO}}$ were performed with constant levels of $P_{ET_{CO_2}}$ (clamped at 5 mmHg above resting pressure) and $P_{ET_{O_2}}$ (clamped at 110 mmHg) in seven cats. The $P_{ET_{SEVO}}$ pattern applied consisted of (1) 5–10 min at 0 mmHg, (2) a stepwise increase to a specified target level, (3) 10–20 min at the target level, and (4) 20–30 min at 0 mmHg. In four cats, a single study was performed. To obtain information on intrasubject variability, three to seven studies were performed in the three remaining cats. Target $P_{ET_{SEVO}}$ ranged among the cats from 3.8 mmHg (~0.5%) to 7.5 (~1%), 11.3 (~1.5%), and 15 mmHg (~2%).

The $\dot{V}_i$-$P_{ET_{SEVO}}$ data were analyzed using an empiric model consisting of two parts. The first part (part 1) postulates a hypothetical effect compartment and describes the time lag between end-tidal and effect-site partial pressures. The second part (part 2) consists of an inhibitory sigmoid Emax model that translates effect site partial pressure into ventilation (fig. 1).[9–13]

The effect-site concentration is described by part 1 of the model:

$$\frac{dP_{EC}(t)}{dt} = k \cdot [P_{ET_{SEVO}}(t) - P_{EC}(t)] \qquad (1)$$

where k is a first-order rate constant, $P_{ET_{SEVO}}(t)$ is the imposed end-tidal sevoflurane tension at time t (*i.e.,* the input function), and $P_{EC}(t)$ is the effect-site partial pressure at time t. We report the effect-site equilibration half-life ($t_{1/2}$), which equals ln2/k. Note that parameter k describes the hysteresis, which may result from more than pharmacokinetics (see Discussion). Part 2 of the model is described by

$$E(t) = E_{min} + (E_{max} - E_{min}) \cdot \frac{P_{EC}(t)^{\gamma}}{P_{EC}(t)^{\gamma} + P_{EC_{50}}{}^{\gamma}} \qquad (2a)$$

where $E(t) = \dot{V}_i$ (inspired ventilation) at time t, minimal

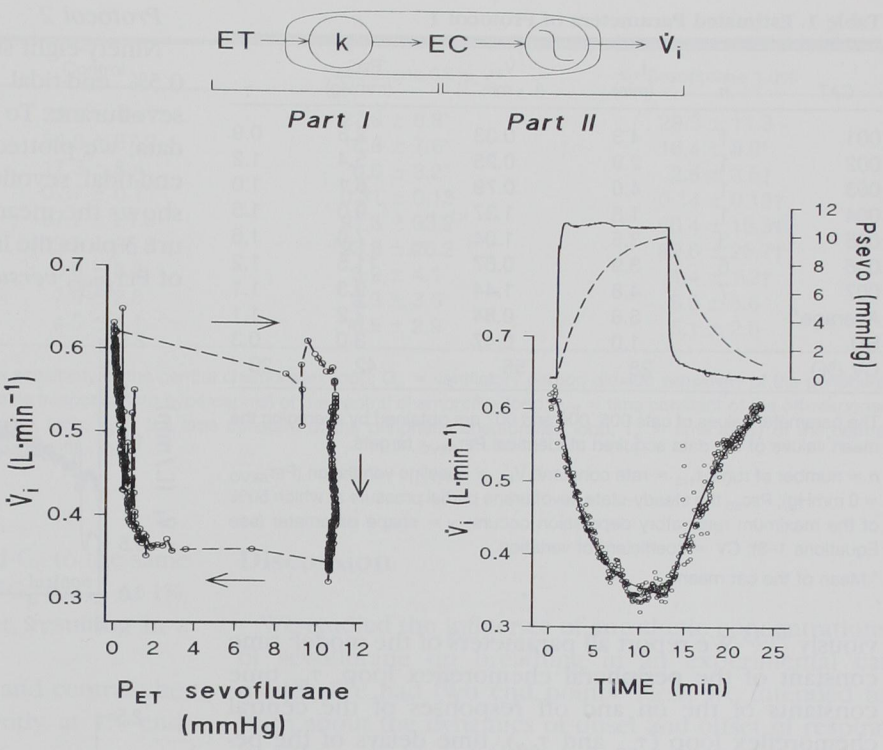

Fig. 1. (*Top*) The two parts of the empiric model used in protocol 1. Part 1 describes the time lag between the end-tidal (ET) sevoflurane and effect-site partial pressures (EC). The time lag is defined by a rate constant, k (or $t_{1/2}$, which equals ln2/k). Part 2 translates the effect-site concentrations *via* an inhibitory sigmoid Emax model (the Hill equation) into ventilation ($\dot{V}_i$). (*Left, bottom*) A typical example of hysteresis of the ventilation–end-tidal sevoflurane partial pressure relation. Each circle represents one breath. The arrows indicate the time course. To guide the eye, a broken line connects the data points. The data fit is plotted in the adjoining diagram. (*Right, bottom*) In the upper panel, the input function (end-tidal sevoflurane partial pressure, continuous line) is plotted with the estimated sevoflurane partial pressure at the effect site (broken line). Note the time lag between the two. In the lower panel, each circle represents one breath. The line through the breaths is the model fit. Estimated parameter values ± SD: $t_{1/2}$, 2.9 ± 0.5 min; $\dot{V}_{BL}$, 0.617 ± 0.003; $P_{EC_{50}}$, 18.1 ± 0.22 mmHg; and γ, 1.34 ± 0.04. $P_{EC_{50}}$ *versus* γ: correlation coefficient = −0.45; γ *versus* $t_{1/2}$: correlation coefficient = 0.36. Data are from cat 006.

effect E_{min} = estimated baseline $\dot{V}_i$ or $\dot{V}_{BL}$, and $E_{max} = \dot{V}_i$ at maximal respiratory depression from sevoflurane or $\dot{V}_{DEP}$. $P_{EC_{50}}$ is the partial pressure that results in 50% of maximal effect and γ is a shape parameter. Substitution results in

$$\dot{V}_i(t) = \dot{V}_{BL} + (\dot{V}_{DEP} - \dot{V}_{BL}) \cdot \frac{P_{EC}(t)^{\gamma}}{P_{EC}(t)^{\gamma} + P_{EC_{50}}{}^{\gamma}} \quad (2b)$$

Because inhalational anesthetics can cause apnea, $\dot{V}_{DEP}$ is set at zero and thus

$$\dot{V}_i(t) = \frac{\dot{V}_{BL}}{1 + (P_{EC}(t)/P_{EC_{50}})^{\gamma}} \quad (3)$$

Parameters of the E_{max} model were estimated using nonlinear regression based on the actual $P_{ET_{SEVO}}$ waveform. On and off responses were analyzed simultaneously. We did not observe systematic differences in parameter estimates in the same cat among the different sevoflurane target groups. Therefore, we pooled the data in cats 005, 006, and 007 by averaging the mean values of the data obtained at identical $P_{ET_{SEVO}}$ targets.

Protocol 2. In eight cats, the dynamic ventilatory responses to stepwise changes in $P_{ET_{CO_2}}$ were determined before and during two constant end-tidal sevoflurane concentrations (0.5 and 1%). The $P_{ET_{O_2}}$ was maintained at 110 mmHg during the studies. Three of these cats participated also in protocol 1. After a period of steady state $\dot{V}_i$ when $P_{ET_{CO_2}}$ was increased slightly above resting values, $P_{ET_{CO_2}}$ was increased by 7–10 mmHg in a stepwise manner and held constant for 7 or 8 min. Thereafter, the $P_{ET_{CO_2}}$ was decreased to its original level and kept constant for another 7 or 8 min. Four to six control studies were performed in each cat. Subsequently, three to four steps at 0.5% end-tidal sevoflurane and three to four steps at 1% end-tidal sevoflurane were performed. The order of sevoflurane studies was random. They started after approximately 30 min of steady state end-tidal sevoflurane concentration.

The steady state relation between $\dot{V}_i$ and $P_{ET_{CO_2}}$ at constant $P_{ET_{O_2}}$ in the cat is linear down to apnea and described by

$$\dot{V} = (G_C + G_P)(P_{ET_{CO_2}} - B) \quad (4)$$

where G_c and G_p are the central and peripheral ventilatory carbon dioxide sensitivities and B represents the apneic threshold or extrapolated $P_{ET_{CO_2}}$ at zero $\dot{V}_i$. To estimate G_p, G_c, and B, we fitted the ventilatory responses to a two-compartment model, as described pre-

Table 1. Estimated Parameters of Protocol 1

CAT	*n*	$t_{1/2}$ (min)	$\dot{V}_{BL}$ (L · min^{-1})	$P_{EC_{50}}$ (mmHg)	γ
001	1	4.3	0.33	2.8	0.9
002	1	2.9	0.25	5.4	1.2
003	1	4.0	0.79	5.1	1.0
004	1	1.8	1.37	9.0	1.5
005	3	3.5	1.04	7.0	1.6
006	6	3.9	0.67	11.5	1.2
007	7	4.8	1.44	9.3	1.1
Average*		3.6	0.84	7.2	1.1
SD		1.0	0.47	3.0	0.3
CV (%)		28	55	42	23

The parameter values of cats 005, 006 and 007 are obtained by averaging the mean values of the data acquired at identical $P_{ET_{SEVO}}$ targets.

n = number of runs; $t_{1/2}$ = rate constant; $\dot{V}_{BL}$ = baseline ventilation ($P_{ET_{SEVO}}$ = 0 mmHg); $P_{EC_{50}}$ the steady-state sevoflurane partial pressure at which 50% of the maximum respiratory depression occurs; γ = shape parameter (see Equations 1–3); CV = coefficient of variation.

* Mean of the cat means.

viously.[14,15] We report all parameters of the model: time constant of the peripheral chemoreflex loop, τ_p, time constants of the on and off responses of the central chemoreflex loop (τ_{on} and τ_{off}), time delays of the peripheral and central chemoreflex loops (T_p and T_c), G_c, G_p, and B. Parameter estimates of the two-compartment model were obtained using a least-squares method.

To compare the control and sevoflurane data, a two-way analysis of variance was performed on the estimated parameters using a fixed model. *Post hoc* comparisons were made using the Newman-Keuls test. The level of significance was set at 0.02. All values reported are the mean ± SD, unless otherwise stated.

Results

Protocol 1

A total of 20 studies was obtained. In all studies we observed rapid changes in $\dot{V}_i$ on the introduction and withdrawal of sevoflurane, with an evident time lag between $\dot{V}_i$ and $P_{ET_{SEVO}}$ (see fig. 1, bottom left where the arrows represent the time course). Inspection of the individual data fits showed that the model adequately describes the ventilatory dynamics of sevoflurane at constant $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$. An example of data fitted to the model is given in figure 1 (bottom right). Table 1 shows parameter mean values of individual cat means. Overall, parameter $t_{1/2}$ averaged 3.6 ± 1.0 min. A sensitivity analysis of the empiric model is presented in Appendix 1.

Protocol 2

Ninety-eight studies were performed: 44 control, 27 at 0.5% end-tidal sevoflurane, and 27 at 1% end-tidal sevoflurane. To get an appreciation of the quality of the data, we plotted typical runs obtained at 0, 0.5, and 1% end-tidal sevoflurane in one cat in figure 2. Table 2 shows the mean values of all estimated parameters. Figure 3 plots the individual parameter values. The relations of $P_{ET_{SEVO}}$ *versus* G_p and G_c were not linear (figs. 3 and

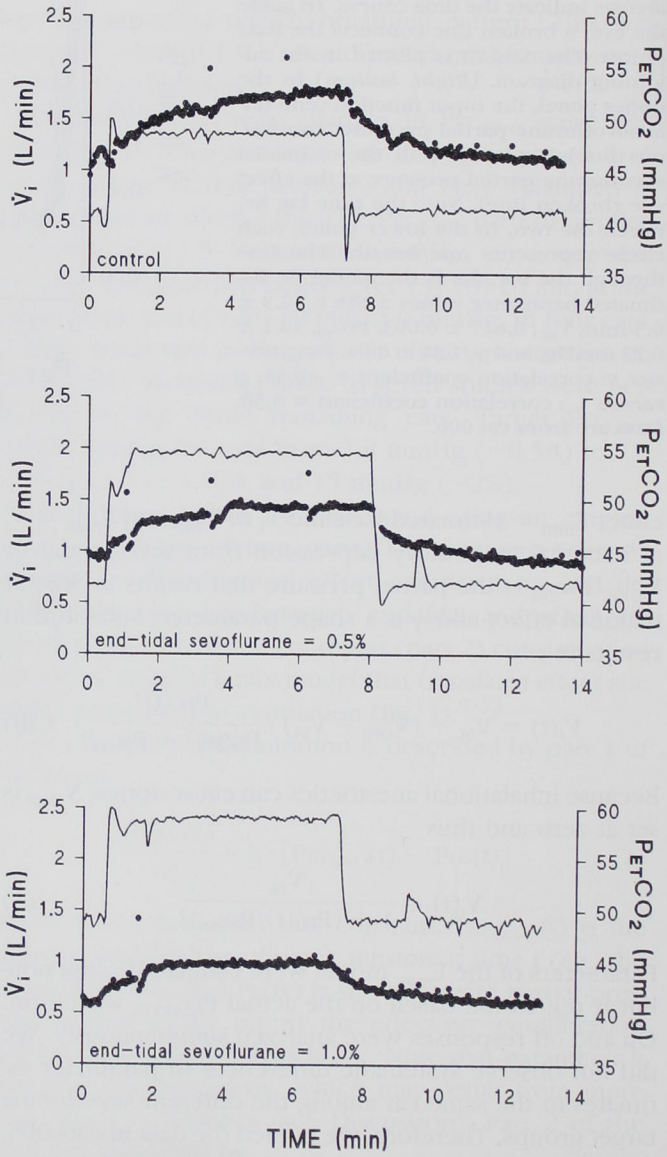

Fig. 2. Three typical carbon dioxide runs of protocol 2 obtained in one cat at 0 (top), 0.5 (middle), and 1% (bottom) end-tidal sevoflurane. Each dot represents one breath. The continuous line is the end-tidal sevoflurane partial pressure input function. Note the larger step sizes of end-tidal carbon dioxide partial pressure during sevoflurane inhalation.

Table 2. Dynamic Parameters of Protocol 2

	Control	Sevoflurane 0.5%	Sevoflurane 1.0%
B (mmHg)	32.3 ± 4.1	27.8 ± 6.8*	29.3 ± 11.3
G_c (ml · min^{-1} · mmHg^{-1})	54.8 ± 37.2	18.8 ± 7.6*	16.4 ± 8.9*
G_p (ml · min^{-1} · mmHg^{-1})	17.3 ± 8.4	6.0 ± 3.2*	2.5 ± 3.5†
G_p/G_c	0.37 ± 0.11	0.31 ± 0.13	0.14 ± 0.13†
τ_{on} (s)	87.2 ± 21.6	91.3 ± 33.2	60.4 ± 18.3†
τ_{off} (s)	113.5 ± 35.9	93.8 ± 26.2	69.6 ± 26.7†
τ_p (s)	9.6 ± 3.9	5.9 ± 4.1	1.4 ± 1.2†
T_c (s)	7.9 ± 2.5	9.3 ± 3.5	8.5 ± 3.6
T_p (s)	4.5 ± 1.1	6.5 ± 2.9	5.1 ± 2.8

B = apneic threshold; G_c = ventilatory carbon dioxide sensitivity of the central chemoreflex loop; G_p = ventilatory carbon dioxide sensitivity of the peripheral chemoreflex loop; τ_{on} = time constant of the on-response (response into hypercapnia) of the central chemoreflex loop; τ_{off} = time constant of the off-response (response out of hypercapnia) of the central chemoreflex loop; τ_p = the time constant of the peripheral chemoreflex loop; T_c = time delay of the central chemoreflex loop; T_p = time delay of the peripheral chemoreflex loop.

* $P < 0.01$ *versus* control.

† $P < 0.01$ *versus* control and sevoflurane 0.5%.

4). At 0.5%, sevoflurane reduced G_p and G_c to the same extent, causing no change in the ratio of G_p to G_c. At 1%, in contrast to G_c, G_p decreased further, resulting in a decrease in the G_p:G_c ratio (fig. 4).

The time constants of the peripheral and central chemoreflex pathways decreased significantly at 1% end-tidal sevoflurane (table 2).

Discussion

We studied the influence of anesthetic concentrations of sevoflurane on breathing in an experimental cat model. We had two end points. First, we intended to learn about the dynamics of onset and offset of respiratory depression; and second, we wanted to identify the

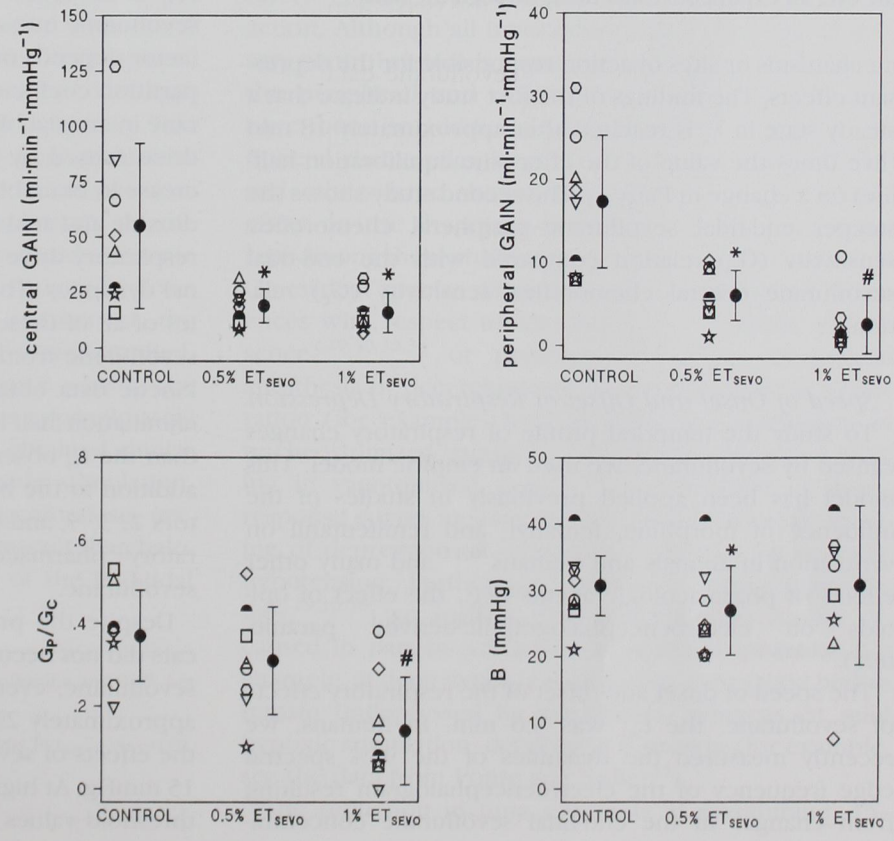

Fig. 3. Estimated parameter values of the central ventilatory carbon dioxide sensitivity (central gain), peripheral carbon dioxide sensitivity (peripheral gain), ratio of G_p to G_c, and the apneic threshold (B) of individual subjects (symbols denote individual cats) in protocol 2. Mean values are ± SD. *$P < 0.01$ *versus* control, #$P < 0.01$ *versus* control and 0.5% sevoflurane.

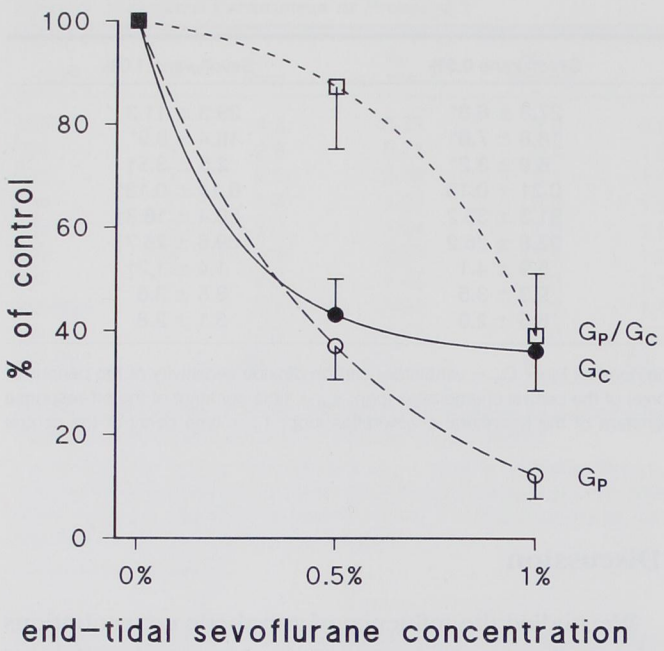

Fig. 4. Dose–response curves of peripheral ventilatory carbon dioxide sensitivity (G_p, ○), central carbon dioxide sensitivity (G_c, ●), and the ratio of G_p to G_c (□) *versus* the end-tidal sevoflurane concentration. Data (the mean of individual means ± SE) are presented as percentages of control. To guide the eye, an exponential was fitted through the data.

mechanisms or sites of action responsible for the depressant effects. The findings of the first study indicate that a steady state in $\dot{V}_i$ is reached after approximately 18 min (five times the value of the effect-site equilibration half-life) on a change in $P_{ET_{SEVO}}$. The second study shows the steeper end-tidal sevoflurane–peripheral chemoreflex sensitivity (G_p) relation compared with the end-tidal sevoflurane–central chemoreflex sensitivity (G_c) relation.

Speed of Onset and Offset of Respiratory Depression

To study the temporal profile of respiratory changes caused by sevoflurane, we used an empiric model. This model has been applied previously in studies of the influence of morphine, fentanyl, and remifentanil on ventilation in animals and humans[10,11] and many other effects of pharmacologic agents (*e.g.*, the effect of opioids on electroencephalographic-derived parameters).[9,12,13]

The speed of onset and offset of the respiratory effects of sevoflurane, the $t_{½}$, was 3.6 min. In humans, we recently measured the dynamics of the 95% spectral edge frequency of the electroencephalogram resulting from changes in the end-tidal sevoflurane concentration.[20] The mean value of $t_{½}$ obtained in 12 patients averaged 3 min. When we extrapolate the results of this study to patients after sevoflurane anesthesia, the time course of sevoflurane-induced ventilatory dynamics would be of the same order as the time course of electroencephalograph dynamics. However, inhalational anesthetics significantly affect ventilatory control at values less than the concentration at which patients "wake up" (the so-called minimum alveolar concentration [MAC]-awake). For example, in humans, isoflurane, 0.13%, reduces the hypoxic ventilatory response by approximately 50%.[21] This is well below the MAC-awake of 0.36%.[22] The latter indicates that respiratory depression from inhalational anesthetics persists for some time after patients awaken from general anesthesia.

The time lag or hysteresis between the $P_{ET_{SEVO}}$ and ventilation depends on several factors. These include (1) the end-tidal to arterial sevoflurane gradient; (2) cardiac output–dependent delivery of sevoflurane to sites relevant to ventilatory control, such as carotid bodies, brain, medulla, respiratory muscles, and lung; (3) changes in blood pressure at the carotid sinus baroreceptors causing (fast) changes in ventilation (independent of arterial P_{O_2} and P_{CO_2})[23,24]; (4) the wash-in and wash-out of sevoflurane into and out of the brain compartment (this factor depends on cerebral blood flow, the blood–brain partition coefficient, and the partial pressure of sevoflurane in arterial blood); (5) changes in central respiratory drive caused by alterations in brain blood flow (an increase in brain blood flow causes the washout of carbon dioxide and acid metabolites, and, consequently, central respiratory drive will diminish)[25]; and (6) central neuronal dynamics. The rate constant k combines the dynamics of all of these factors. We simulated the washout of sevoflurane from the brain (factor 4) using elimination kinetic data obtained from rats.[26] The estimated brain elimination half-life ($t_{½}$elim) was a factor of two faster than the $t_{½}$ observed in protocol 1. This implies that in addition to the brain or effect-site partial pressures, factors 2, 3, 5, and 6 play an appreciable role in the respiratory pharmacokinetics and pharmacodynamics of sevoflurane.

Despite the presence of background anesthesia, the cats did not become apneic during the administration of sevoflurane, even at the highest $P_{ET_{SEVO}}$ (15 mmHg or approximately 2%). We cannot draw conclusions about the effects of sevoflurane at partial pressures more than 15 mmHg. At high sevoflurane concentrations, nonlinear threshold values may cause the respiratory oscillator to

stop abruptly and cause irregular or cyclic breathing and apnea (see references 1 and 8).

Sites of Action of Sevoflurane-induced Respiratory Depression

We used a mathematic two-compartment model of the respiratory controller incorporating gains (ventilatory carbon dioxide sensitivities), time constants, and time delays to estimate the relative contributions and dynamics of the fast peripheral and slow central chemoreflex loops.[14,15] This model has been validated extensively in the anesthetized cat. For example, DeGoede *et al.*[18] showed that the steady state contributions of the peripheral and central chemoreflex loops obtained with the technique of artificial brain stem perfusion closely reflect values derived from the two-compartment model in intact cats. Furthermore, studies using artificial brain stem perfusion to measure the dynamic ventilatory responses to changes in $P_{ET_{CO_2}}$ at constant central (*i.e.,* brain stem) P_{CO_2} and to changes in P_{CO_2} of the blood perfusing the brain stem at constant $P_{ET_{CO_2}}$ obtained values for time constants and delays that corresponded closely with the control values observed in this study.[27,28]

The decrease in G_c and G_p at anesthetic levels of sevoflurane indicates an appreciable depressant effect on the ventilatory control system. However, even at the highest sevoflurane concentration studied, a peripheral response to carbon dioxide was observed. Although small, G_p could be identified in seven of eight cats. This observation corresponds with recent findings of Stuth *et al.*[29] They studied the influence of the anesthetic concentrations of halothane (0.45–1.8% end-tidal)‖ on the canine peripheral chemoreceptor-mediated phrenic nerve response to acute hypoxia. They observed a dose-dependent depression, but not abolishment of the phrenic nerve response to hypoxia for the range studied. The authors calculated that at halothane, 1.8%, the phrenic nerve response to hypoxia was approximately 20% of the awake value. Stuth *et al.*[30] obtained similar results using carotid body carbon dioxide stimulation. Sevoflurane (in cats anesthetized with α-chloralose–urethane) is a more potent respiratory depressant than halothane (in vagotomized dogs) in terms of the end-tidal concentration. How this translates into equal MAC conditions remains unknown, because the MAC value of sevoflurane in our feline preparation (with background anesthesia) was not determined.

At 0.5% sevoflurane, the values of G_c and G_p were 43 ± 20% and 37 ± 18% of control, respectively. At sevoflurane, 1%, the respective values of G_c and G_p were 37 ± 22% and 12 ± 13% of control (table 2, fig. 4), indicating that only G_p decreased further. We interpret these findings as a steeper dose–response relation for G_p *versus* $P_{ET_{SEVO}}$ than for G_c *versus* $P_{ET_{SEVO}}$.# This suggests that in addition to an effect of the anesthetic concentrations of sevoflurane at pathways common to both chemoreflexes (causing relatively equal reductions in G_p and G_c), there is an additional effect on the peripheral chemoreflex loop (which causes a further reduction in G_p). The pathways common to both chemoreflexes are the respiratory integrating centers in the brain stem and the neuromechanical link between the brain stem and ventilation. The latter consists of efferent nerves, spinal respiratory motoneurons, neuromuscular junctions, the diaphragm, intercostal muscles, and the lungs and airways.

Animal studies of the influence of anesthetics on respiratory control are equivocal with respect to sites of action. Although all investigators agree that the ventilatory control system is depressed at pathways common to the peripheral and central chemoreflex loops, some have found an additional selective effect within the peripheral chemoreflex loop,[4,30–32] some have not,[19,29,33,34] and others have shown a dependency of a selective effect on the (hypoxic) stimulus intensity.[35] Comparisons among these studies are difficult to make because of (1) evident species differences, (2) methodologic differences with respect to anesthesia (for example, the absence[4,29,30,32,34] or presence[19,33,35**] of background anesthesia or decerebration[31]), (3) differences in preparation (for example, artificial brain stem perfusion in tracheostomized animals[19,33] *versus* phrenic nerve reading in vagotomized dogs[29,30]), (4) absence of dose-response curves in some studies, and (5) possible masking of depression of peripheral responses by systemic hypotension. Furthermore, similar to other investigators,[29,30,35] we suggest that differences in results are caused in part by variations in stimulus intensity. For example, at deep hypoxic stimulation, the carotid bodies remain undepressed by anesthetics, whereas, at mild hypoxic stimulation, depression is present (for example, see the data from Ponte and Sadler[35]).

The reduction in time constants at sevoflurane, 1%,

‖ Canine and feline MAC values are 2.4% for sevoflurane and 0.9% for halothane.

The slope of the linear relation of $\log G_p$ *versus* $P_{ET_{SEVO}} = -0.91$ against -0.44 for $\log G_c$.

** This study.

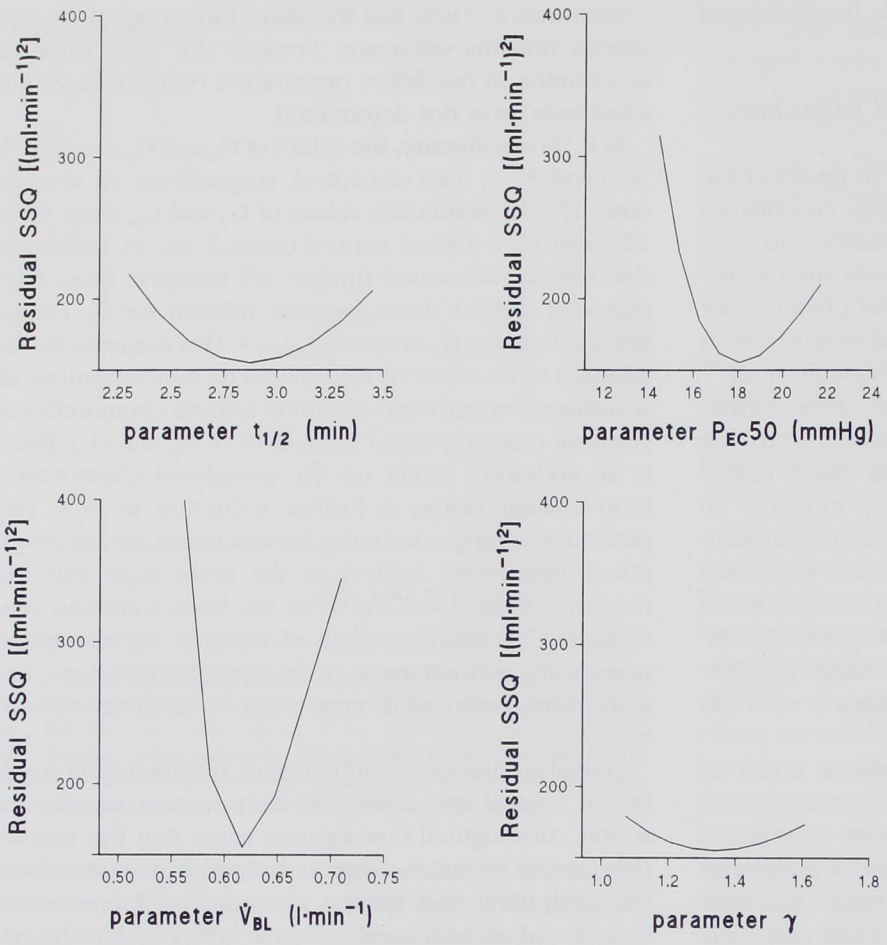

Fig. 5. Results of the sensitivity analysis performed on the data presented in figure 1 (protocol 1). SSQ = sum of squares.

may be related to several mechanisms: an increase in baseline brain blood flow, an increase in the reactivity of brain blood flow to carbon dioxide, and inactivation or suppression of central neuronal ventilatory dynamics, or short-term potentiation.[5] The latter refers to respiratory activity at a higher level than expected just from the dynamics of the peripheral and central chemoreceptors. It is thought to originate at the pontomedullary region of the brain stem and exhibits slow dynamics.[5] Human studies indicate that inhalational anesthetics cause the reduction of time constants as a result of the inactivation of short-term potentiation.[5] More studies are needed to clarify the underlying mechanisms and the relation between the absence of short-term potentiation and respiratory instability during inhalation anesthesia.

When we compare our current results with those from human studies of the influence of sevoflurane and halothane on ventilatory control,[5,36–38] we observe quantitative rather than qualitative differences. In humans already at 0.1 MAC sevoflurane and halothane, investigators have observed a selective peripheral effect (30–50% depression of the peripheral chemoreflex loop)[5,36–38] and, at 0.1 MAC halothane, a reduction of the central time constants.[5] The MAC fraction of sevoflurane in our cats anesthetized with α-chloralose–urethane is not known. Because of the interaction that exists between anesthetics in reducing the MAC value, we argue that a MAC fraction much larger than 0.1 produced a degree of depression of G_p and a reduction of central time constants in our cats of similar magnitude as in humans at 0.1 MAC. The cause of these quantitative differences may simply be the species difference in anesthetic potency. Comparison of the MAC for skin incision in humans, cats, and dogs indicates that sevoflurane, halothane, isoflurane, and enflurane are more potent in humans.[39] There is no reason to doubt that this would not also apply to the effects of these anesthetics on the peripheral chemoreflex loop (G_p).

Conclusions

We determined the temporal profile of sevoflurane-induced respiratory depression in a feline model. More studies are required to compare our data with those from other anesthetics and from humans. Our results indicate that depression of minute ventilation is appreciable, which may persist postoperatively beyond the time that wakefulness has been regained. We further determined the "respiratory" sites of action of sevoflurane and observed an effect at the pathways common to both chemoreflex loops and a selective effect within the peripheral chemoreflex loop. These latter findings indicate that in addition to the species difference in anesthetic potency, similar modes of action of sevoflurane exist in humans and cats.

Appendix 1: Sensitivity Analysis

A sensitivity analysis of a proposed model (*i.e.,* the empiric model of protocol 1) is important to determine whether, in practice, the parameter values of the model can be estimated with finite precision from the measured data. Parameters may not be identifiable for various reasons: because of the model structure, dependence on other parameters, or the specific input function chosen. The model is fitted to the data by choosing those parameter values that minimize the "cost" function, which is the sum of the squares of the difference between the measured ventilation data and the model prediction, on a breath-to-breath basis. We performed an *a posteriori* sensitivity analysis of the data shown in figure 1. The sensitivity analysis was performed by fixing one parameter (*i.e.,* by not allowing it to be estimated) at a time to a series of values (±20%) around the "best" value (in the sense of minimal residual sum of the squares). The other parameters were estimated by minimizing the residual sum of the squares.[40] This method will show whether any of the parameters are or are not estimable using the specific $P_{ET_{SEVO}}$ input function. If not, the curve of the residual sum of the squares *versus* the fixed parameter (*i.e.,* the cost surface) will be flat. Because we performed an analysis of actual data, which evidently incorporates some breath-to-breath noise, we will also identify the existence of so-called local minima.

Figure 5 shows the results of the sensitivity analysis for each of the parameters of the empiric model: $t_{½}$, $\dot{V}_{BL}$, $P_{EC_{50}}$, and γ. The cost function shows that all four parameters could be identified and that the estimation accuracy was acceptable for all parameters. The most accurately estimated parameter was $\dot{V}_{BL}$, and the least sensitive parameter was γ. The latter is not surprising considering the single-step input function that we used (fig. 1). Using a different input function shape may increase the estimation accuracy of γ.[40] Correlations between the estimated values of $P_{EC_{50}}$ and γ (correlation coefficient = −0.45) and γ and $t_{½}$ (correlation coefficient = 0.36) were low. This indicates that we were able to estimate these parameters independently.

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