Chemical regulation of ventilation during isoflurane sedation and anaesthesia in humans

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To assess the effects of isoflurane on chemical regulation of ventilation, we studied the ventilatory responses to (1) hyperoxic hypercarbia, (2) isocapnic hypoxaemia, and (3) a single half vital capacity breath of carbon dioxide 20 per cent in oxygen in 12 human subjects, awake and sedated or anaesthetized with isoflurane, 0.1 or 1.1 MAC. Sedation did not alter ventilation nor the ventilatory response to hypercarbia but reduced the responses to hypoxaemia and to the half vital capacity breath of CO_2. Anaesthesia reduced ventilation and the response to hypercarbia and nearly abolished the responses to hypoxaemia and to the breath of CO_2. The results indicate that isoflurane reduces ventilatory responses to several chemical drives and that it selectively impairs those responses mediated by peripheral chemoreceptors. In these respects, isoflurane is similar to halothane and enflurane.

Key words

ANAESTHETICS, VOLATILE: isoflurane; RECEPTORS: chemoreceptors; VENTILATION: carbon dioxide response, hypoxic response, regulation.

General anaesthetic agents that depress ventilation have two fundamental effects on the chemical regulation of ventilation. First, they cause ventilation to be totally dependent upon chemical stimulation – since reduction of stimuli below a critical threshold with passive hyperventilation results in apnoea. Second, they reduce ventilatory responses to added chemical stimuli.

Isoflurane, in anaesthetizing doses, depresses ventilation,[1-3] renders ventilation dependent upon chemical stimuli[2] and reduces the ventilatory response to added carbon dioxide.[1] However, its effect on responses to other chemical stimuli, in particular the response to hypoxaemia, is not known. Activity of the hypoxaemia response is of some interest, since halothane and enflurane impair it markedly,[4,5] with important clinical implications.[6]

The purpose of this study was to examine the effects of a sedating and an anaesthetizing dose of isoflurane on the ventilatory responses to hyperoxic hypercarbia, isocapnic hypoxaemia and a single breath of carbon dioxide. The first of these responses is mediated primarily by central chemoreceptors, the remaining two by peripheral chemoreceptors.

Methods

The protocol for this study was approved by the Human Research Committee of the University of Western Ontario.

We studied 12 fit subjects while they were awake and while in a steady-state of either isoflurane sedation 0.1 MAC (n = 5) or isoflurane anaesthesia 1.1 MAC (n = 7).* Subjects who were sedated were either anaesthetists or anaesthetic residents.

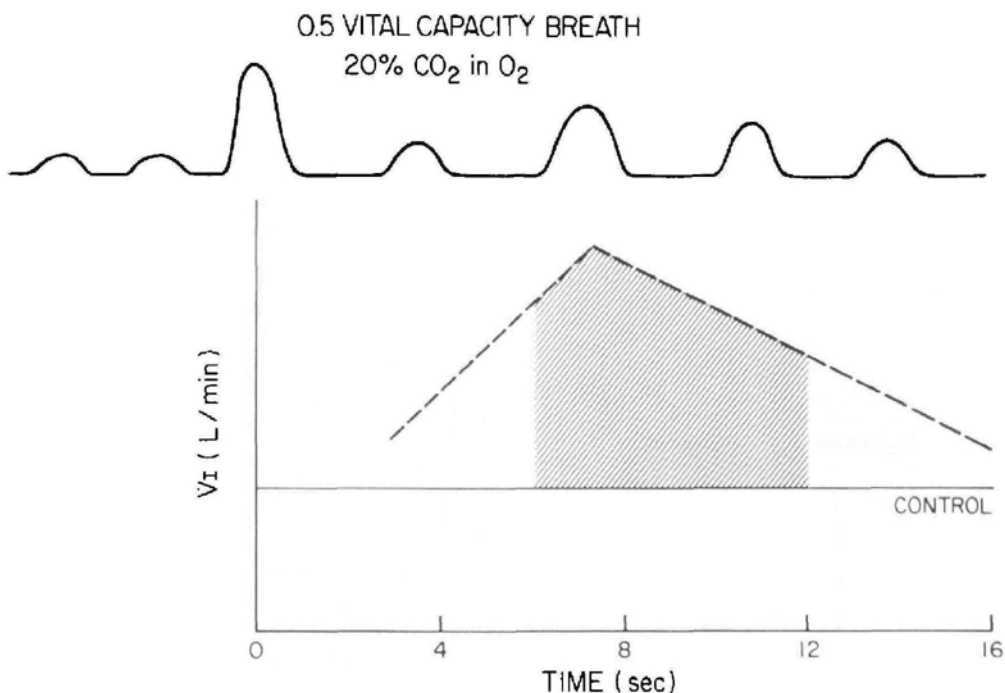*The isoflurane MAC value used was 1.28 per cent.

FIGURE 1   The single breath carbon dioxide test and its analysis. The upper trace is a typical spirogram record showing resting ventilation, the half vital capacity breath consisting of CO_2 20 per cent in oxygen and the subsequent hyperpneic response. The broken line of the graph is a diagrammatic representation of the response based upon a breath-by-breath determination of instantaneous ventilation. The "$\Delta \dot{V}_{ICO_2}$" was the average increment of instantaneous ventilation above control in those breaths taken within 12 seconds of the breath of CO_2, excluding the first (indicated by shaded area).

Subjects who were anaesthetized were patients who had agreed to an extra period of anaesthesia before undergoing an elective orthopaedic or dental surgical procedure. There were seven males and five females. Together, their ages, heights and weights were respectively 27 ± 5 years, 172 ± 8 cm and 68 ± 12 kg (means ± S.D.).

For the awake study, each subject relaxed in a comfortable chair in a darkened room and breathed through a mouthpiece with a nose-clip in place. He began by inhaling oxygen from a non-rebreathing system. When values of ventilation and end-tidal carbon dioxide concentration had been steady for five minutes, we recorded ventilation for a one minute period.

Next, the ventilatory response to each of the three chemical drives was tested. Individual tests were separated by at least five minutes. We induced

hyperoxic hypercarbia progressively, using the Read rebreathing technique[7] and allowing the equilibrated airway CO_2 concentration to increase 2.0 per cent. We induced isocapnic hypoxaemia by the method of Weil, reducing end-tidal oxygen concentration to 6.0 per cent over 8–10 minutes.[8]

The response to a single breath of carbon dioxide was tested with a modification of the method of Sorensen *et al.*[9] (Figure 1). The subject initially breathed quietly from a non-rebreathing system to establish his resting values of ventilation and end-tidal CO_2 concentration. At the end of an expiration, he voluntarily and quickly inhaled a volume equivalent to half his measured vital capacity, the achievement of this volume being indicated by an audio signal activated by the pneumotachograph. He then exhaled to his end-expiratory position and relaxed. Circuits and valves were arranged

so that the half vital capacity breath was 20 per cent carbon dioxide in oxygen and all other breaths were oxygen. The response was monitored for 30 seconds. This test was repeated twice.

Isoflurane sedation was induced and maintained with sub-anaesthetic concentrations of isoflurane in oxygen while the subject sat comfortably in the same darkened room. After 25 minutes of inhalation and with end-tidal isoflurane steady at 0.1 MAC, we repeated ventilatory measurements and tests as in the awake state.

Each subject to be studied during anaesthesia was positioned supine. Anaesthesia was induced with isoflurane in oxygen. The glottis and upper trachea were sprayed with lidocaine four per cent and the trachea was intubated with an 8 or 9 mm cuffed orotracheal tube. Inspired isoflurane concentrations were set to achieve 1.1 MAC end-tidal, allowing 40 minutes to reach equilibrated and steady anaesthetic and respiratory states. The subject breathed spontaneously from a non-rebreathing system throughout. Five per cent dextrose in 0.2 per cent saline was infused as necessary to keep systolic arterial pressures at least 70 per cent of awake values.

When ventilation and end-tidal concentrations of isoflurane and carbon dioxide had been constant for ten minutes, we recorded a one minute period of ventilation. Duplicate samples of arterial blood were withdrawn anaerobically for determination of arterial isoflurane tension[10] and arterial blood gas values. Ventilatory responses to chemical stimuli were then tested, using minor modifications of the procedures employed in studies of the awake and sedation states.[4,5] During induction of hypoxaemia in anaesthetized subjects, we monitored arterial haemoglobin saturation continuously, using a Hewlett-Packard #47201A ear oximeter, to prevent saturation from falling below 70 per cent.[11] To assess more precisely the relationship between end-tidal and arterial oxygen tensions during hypoxaemia, samples of arterial blood were withdrawn at intervals throughout hypoxaemia tests for subsequent blood gas analysis. The single half vital capacity breath of carbon dioxide was delivered from a collapsible bag under positive pressure.

During all tests in all states, exhaled gas was continuously sampled from a port close to the airway and analyzed for its carbon dioxide, oxygen and isoflurane concentrations by a Perkin-Elmer #1100 mass spectrometer, calibrated as in our previous studies.[4,5] End-tidal concentrations were read from a time-based recording and were converted to tensions, using the measured barometric pressure of each testing day. Arterial isoflurane tension was determined using a multiple gas phase equilibration technique[10] and a Hewlett-Packard #5730 gas chromatograph. Arterial blood gas values were determined with a Radiometer Copenhagen BMS 3 System calibrated with Canadian Liquid Air Specialty Gases. The values of duplicate samples were averaged.

Inspired ventilation was measured with a pneumotachograph calibrated as previously described.[4,5] Values of instantaneous ventilation, determined in the responses to hypercarbia and hypoxaemia, were based upon the averaged tidal volumes and respiratory cycle lengths of three consecutive breaths. Values of instantaneous ventilation, determined in the single breath CO_2 responses, were based upon breath-by-breath calculations. All ventilatory volumes were expressed at body temperature and ambient pressure, saturated.

To depict the response to hyperoxic hypercarbia, we calculated the slope of the linear ventilation: PET_{CO_2} relationship, using the method of least squares. The hypoxaemia response was represented by values of instantaneous ventilation found at PET_{O_2} values of 53.2, 13.3, 9.3 and 6.0 kPa (400, 100, 70 and 45 mmHg) and also by the "$\Delta \dot{V}I_{45}$," the measured increment of instantaneous ventilation between PET_{O_2} values of 53.2 kPa and 6.0 kPa. To depict the response to the single breath of carbon dioxide, we calculated the "$\Delta \dot{V}I_{CO_2}$" (see Figure 1). Results of repeated single breath tests were averaged.

To check for possible differences between awake and sedation states, and between awake and anaesthesia states, we compared observations made in the same subjects using the two-tailed t-test for paired data. We considered a p value of 0.05 or less as indicative of a significant difference.

Results

There were no important complications of these studies. Induction of anaesthesia with isoflurane was frequently accompanied by episodes of sneezing, coughing and/or breath-holding. However, these episodes were minor and short-lived. A steady-state of anaesthesia reduced systolic blood pressure modestly (average drop from awake to lowest stable anaesthetic value, 2.5 kPa) and in-

TABLE

	Isoflurane 0.1 MAC (n = 5)	
	Awake	Sedation
$\dot{V}_I$ (L·min^{-1})	6.9 ± 0.4	6.5 ± 0.4
V_T (L)	0.62 ± 0.04	0.52 ± 0.04
f	11 ± 1	13 ± 2
PET_{CO_2} (kPa)	5.5 ± 0.1	5.3 ± 0.1
(mmHg)	(41 ± 0.7)	(40 ± 0.7)
Responses:		
Hypercarbia, slope		
(L·min^{-1}·kPa^{-1})	15.0 ± 3.0	19.5 ± 6.0
(L·min^{-1}·mmHg^{-1})	(2.0 ± 0.4)	(2.6 ± 0.8)
Hypoxaemia, $\Delta\dot{V}_{I45}$		
(L·min^{-1})	9.7 ± 1.1	4.1 ± 1.1*
Single breath CO_2, $\Delta\dot{V}_{I_{CO_2}}$		
(L·min^{-1})	7.7 ± 1.0	5.6 ± 0.8*

	Isoflurane 1.1 MAC (n = 7)	
	Awake	Anaesthesia
$\dot{V}_I$ (L·min^{-1})	6.8 ± 0.7	4.9 ± 0.4*
V_T (L)	0.54 ± 0.06	0.17 ± 0.01*
f	13 ± 1	29 ± 2*
PET_{CO_2} (kPa)	5.1 ± 0.1	5.9 ± 0.4*
(mmHg)	(38 ± 0.4)	(44 ± 2.8)
Pa_{CO_2} (kPa)		6.5 ± 0.4
(mmHg)		(49 ± 2.7)
Responses:		
Hypercarbia, slope		
(L·min^{-1}·kPa^{-1})	13.5 ± 1.5	4.5 ± 0.7*
(L·min^{-1}·mmHg^{-1})	(1.8 ± 0.2)	(0.6 ± 0.1)
Hypoxaemia, $\Delta\dot{V}_{I45}$		
(L·min^{-1})	11.4 ± 2.2	0.3 ± 0.3*
Single breath CO_2, $\Delta\dot{V}_{I_{CO_2}}$		
(L·min^{-1})	8.4 ± 1.7	1.2 ± 0.5*†

All values mean ± S.E.M.
*Significantly different from awake values p < 0.05.
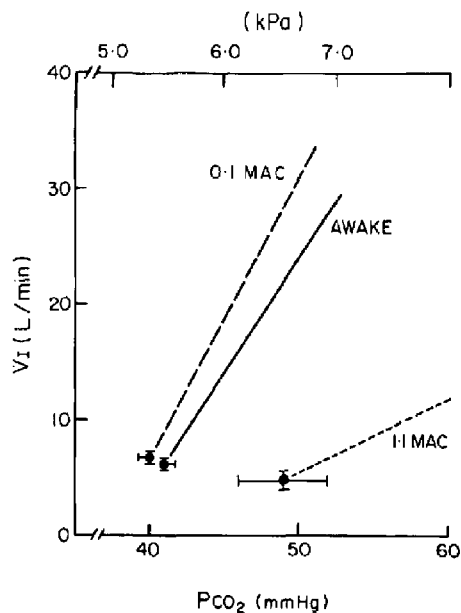†n = 5.

FIGURE 2 Ventilatory responses to hypercarbia of subjects sedated with isoflurane (0.1 MAC) and anaesthetized with isoflurane (1.1 MAC). Dots represent mean values of ventilation at mean resting PET_{CO_2} values of awake and sedated subjects and at mean resting Pa_{CO_2} values of anaesthetized subjects. Bars are ± S.E.M. Lines extending from dots depict mean slopes of responses to hypercarbia. The awake response is that of the sedation group.

creased heart rate slightly (average increase from awake to stable anaesthetic value, 6 beats/min). During anaesthesia, end-tidal and arterial tensions of isoflurane were respectively 1.30 ± 0.1 and 1.26 ± 0.4 kPa (9.8 ± 0.1 and 9.5 ± 0.3 mmHg, means ± S.E.M.).

Ventilatory findings are summarized in the Table and in Figures 2 and 3. Sedation did not detectably alter minute ventilation, tidal volume, breathing frequency nor values of PET_{CO_2}. Anaesthesia reduced minute ventilation and tidal volume, increased breathing frequency and elevated values of PET_{CO_2}. During anaesthesia, there was a modest $P(ET-a)_{CO_2}$ gradient.

Sedation did not detectably alter the ventilatory response to hyperoxic hypercarbia, but reduced the responses to hypoxaemia and to the single breath of CO_2. Anaesthesia reduced the response to hyperoxic hypercarbia, virtually abolished the response to isocapnic hypoxaemia and markedly reduced the response to the single breath of CO_2.

During anaesthesia and tests of the response to hypoxaemia, differences between end-tidal and arterial tensions of oxygen were as follows: at PET_{O_2} values 13.0–13.6 kPa (98–102 mmHg), 1.4 ± 0.2 kPa (11 ± 2 mmHg); at PET_{O_2} values 9.0–9.6 kPa (68–72 mmHg), 0.3 ± 0.3 kPa (2 ± 2 mmHg); and at PET_{O_2} values 6.0–6.7 kPa (45–50 mmHg), 0.1 ± 0.1 kPa (1 ± 1 mmHg) (means ± S.E.M.).
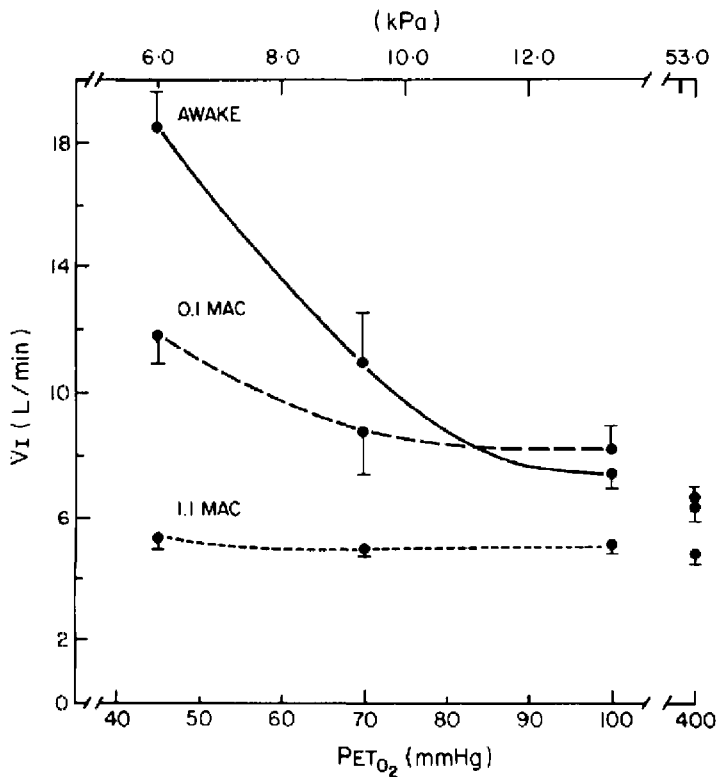
FIGURE 3   Ventilatory responses to isocapnic hypoxaemia of subjects sedated with iso-
flurane (0.1 MAC) and anaesthetized with isoflurane (1.1 MAC). Dots represent mean values
of ventilation at $P_{ET_{O_2}}$ values of 53.2, 13.3, 9.3 and 6.0 kPa (400, 100, 70 and 45 mmHg).
Bars are ± S.E.M. Lines through dots were hand drawn. The awake response is that of the
sedation group.

Discussion

Experimental conditions were identical for studies
of awake and sedation states, but there were several
variables added during anaesthesia. These included
the supine position, tracheal intubation, and, of
potential relevance to testing responses to hypox-
aemia, increased differences between end-tidal and
arterial tensions of oxygen and elevated values of
$P_{ET_{CO_2}}$. We doubt that any of these affected our
results in an important way. The supine position
does not alter ventilation and ventilatory responses
to chemical stimuli in awake subjects.[12,13] Tracheal
intubation does not affect the response to hyper-
carbia in subjects lightly anaesthetized with halo-
thane.[4] Increased end-tidal to arterial oxygen ten-

sion differences during anaesthesia might have
decreased the validity of the end-tidal value as the
measured stimulus of the response to hypoxaemia.
However, at end-tidal tensions of 9.6 kPa and less,
where the ventilatory response to hypoxaemia is
normally observed, these differences in anaesthe-
tized subjects were small and quite similar to those
found in awake subjects.[8] An elevated carbon
dioxide tension, as was present during anaesthesia,
may have augmented the response to hypoxaemia.[8]
However, such an effect would have acted only to
underestimate the magnitude of the depressive
effect of isoflurane.

Isoflurane anaesthesia 1.1 MAC in our subjects
reduced ventilation and tidal volume, increased

breathing frequency and elevated values of PET_{CO_2}. The relative magnitudes of these effects were similar to those previously reported.[1-3] Isoflurane sedation 0.1 MAC had no detectable effect on values of ventilation and PET_{CO_2}.

The ventilatory response to progressive or steady-state hyperoxic hypercarbia is effected by two sets of CO_2-[H^+] sensitive receptors, the central chemoreceptors located in the medulla and the peripheral chemoreceptors located in the carotid bodies of man. However, the contribution of the peripheral receptors is normally small (<30 per cent of total)[14,15] and, accordingly, the response is considered to be primarily central chemoreceptor mediated. Isoflurane anaesthesia 1.1 MAC in our subjects reduced the response to progressive hyperoxic hypercarbia modestly, in keeping with previous observations.[1] Isoflurane sedation 0.1 MAC had no detectable effect. In this respect, isoflurane is similar to several other anaesthetic agents.[16]

The increment of ventilation in response to isocapnic hypoxaemia is mediated exclusively by peripheral chemoreceptors.[14,15] This response was selectively and markedly impaired by isoflurane. Sedation 0.1 MAC, which had no detectable effect on ventilation and the response to hyperoxic hypercarbia, reduced the hypoxaemia response to less than half of awake values. Anaesthesia 1.1 MAC virtually abolished it. Halothane and enflurane produce a similar disproportionate impairment of the response to hypoxaemia in human subjects.[3,4] Interestingly, other anaesthetics, such as thiopentone and nitrous oxide, do not.[16]

The ventilatory response to a single large breath of carbon dioxide has been proposed as a test of the peripheral chemoreceptor mediated response to CO_2-[H^+] that excludes a central chemoreceptor mediated contribution.[9,17] In this test, the subject voluntarily inhales a single large breath of CO_2 and the result is an immediate, large and transient increment of CO_2 in the blood. The added carbon dioxide is delivered sooner and much more rapidly to peripheral than to central chemoreceptors, due to different circulatory lag times and rates of local blood flow. Accordingly, the initial 11–15 seconds of the response can be considered to be mediated primarily, if not entirely, by peripheral chemoreceptors.[9,17-19] As originally described, the test requires that the subject inhale a full vital capacity breath of carbon dioxide 15 per cent in oxygen.[9,17]

Because a vital capacity breath cannot be delivered safely in anaesthetized subjects, we reduced the size of the breath to one half a vital capacity and increased its CO_2 concentration to 20 per cent.*

The effect of isoflurane on the response to a single breath of CO_2 was similar to its effect on the response to hypoxaemia. Sedation 0.1 MAC diminished it moderately; anaesthesia 1.1 MAC reduced it markedly. The results suggest that the depression of the single breath response may have been slightly less than the impairment of the response to hypoxaemia. However, this difference was not statistically significant. Whatever the relative magnitude of effect, isoflurane appears to be a potent depressant of both these physiological ventilatory reflexes mediated by peripheral chemoreceptors.

The results of the present study, together with other data, indicate that modern halogenated anaesthetics may be powerful depressants of several peripheral chemoreceptor mediated ventilatory reflexes in humans. Halothane, enflurane and isoflurane, in light anaesthetizing doses, virtually abolish the hyperpneic response to hypoxaemia.[4,5,16] Halothane reduces the ventilatory response to hyperoxaemia and delays the response to a sudden CO_2 stimulus generated by an intravenous bolus of sodium bicarbonate in a manner that suggests no contribution from peripheral chemoreceptors.[19] Isoflurane greatly impairs the peripheral chemoreceptor mediated response to a single breath of CO_2. Halothane and enflurane severely reduce the response to a pharmacological stimulus of peripheral chemoreceptors – a small dose of doxapram.[4,5] Thus, in several respects, human subjects anaesthetized with halogenated agents behave almost as if lacking peripheral chemoreceptors. Although halothane is a direct and potent depressant of carotid body chemoreceptors in the cat,[20] the site and mechanism of action of these agents on the peripheral chemoreflex pathway in humans remains unknown.

We conclude that with respect to chemical regulation of breathing, isoflurane is similar to halothane and enflurane. It reduces ventilatory

*Although these changes may have altered the magnitude of the stimulus and the response, they did not affect the essential nature and the validity of this test. This modification of the single breath test was used throughout this study.

responses to several chemical stimuli, especially those responses mediated by peripheral chemoreceptors.

The most important clinical implications of these findings relate to the effect on the response to hypoxaemia.[6] Abolition or marked depression of this reflex is a serious hazard to spontaneously breathing patients since it permits hypoxaemia to develop more readily, more quickly and to a more severe level than would otherwise be the case. Furthermore, loss of the hyperpneic response to hypoxaemia means loss of a useful clinical sign. These implications apply not only to patients anaesthetized with isoflurane, but also to patients recovering from isoflurane anaesthesia for as long as sedating doses of the agent persist.

Acknowledgements

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Résumé

Afin d'étudier les effets de l'isoflurane sur la régulation chimique de la ventilation nous avons étudié la réponse ventilatoire à: 1) l'hypercarbie hyperoxique; 2) l'hypoxémie isocapnique; 3) l'inspiration d'un mélange gazeux contenant 20 pour cent de CO_2 dans l'oxygène. La quantité de ce mélange inhalé était équivalente à la moitié de la capacité vitale inspirée en une seule fois.

Ce travail a été effectué chez 12 volontaires d'abord éveillés, ensuite sous sédation et enfin anesthésiés à l'isoflurane à 0,1 et 1,1 MAC.

La sédation à l'isoflurane n'a pas modifié la ventilation, non plus que la réponse ventilatoire à l'hypercarbie mais a réduit la réponse à l'hypoxémie et à l'inspiration de haute concentration de CO_2. Pour sa part, l'anesthésie a réduit la ventilation et la réponse à l'hypercarbie et, à toutes fins utiles, a aboli la réponse à l'hypoxémie et à l'inspiration de CO_2. Ce résultat indique que l'isoflurane diminue la réponse ventilatoire à plusieurs des stimulants chimiques et qu'il prévient de façon sélective les réponses qui s'effectuent par les chémorécepteurs périphériques. En ceci, l'isoflurane est semblable à l'halothane et à l'enflurance.