SUBANAESTHETIC HALOTHANE: ITS EFFECT ON REGULATION OF VENTILATION AND RELEVANCE TO THE RECOVERY ROOM*

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IT IS NECESSARY for the clinical anaesthetist to be aware of both the duration of action of his drugs and their effects in all concentrations. Halothane is one of the most widely used inhalational anaesthetic agents and yet there is little information on the ventilatory effects of sub-anaesthetic levels, such as occur in the recovery room. A commonly held notion is that low concentrations of halothane, which are present in the patient who is awake and ready to leave the recovery room, do not have a significant effect on the chemical control of breathing.

We have recently observed that a sub-anaesthetic concentration of halothane (0.1 MAC), administered to volunteers, markedly depresses the ventilatory response to very brief hypoxaemia.[1] The purpose of the present study was to explore this effect of sub-anaesthetic halothane further and to determine its relevance to patients in the recovery room. Specifically, we posed three questions. First, does sub-anaesthetic halothane reduce the ventilatory response to sustained as well as to brief hypoxaemia? Secondly, if it does, is its effect dose-related? Finally, if small doses of halothane impair the hypoxic reflex, are they present for significant periods of time following clinical anaesthesia?

METHODS

A. *Laboratory study*

Our previous work,[1] as well as a review of the meagre literature on recovery from halothane anaesthesia,[2-4] indicated that end-tidal halothane concentrations of 0.08 per cent and less (0.1 MAC and less) would be the appropriate dosage range to study.

Six male volunteers were studied in a laboratory. All were completely fit, were taking no medications and had no characteristics known to influence ventilatory control.[5] Their mean age, weight and height (±1 standard deviation) were 30 ± 4 years, 69.0 ± 4.5 kg, and 172 ± 6 cm. Each subject was informed of the nature of the study, including a full explanation of potential risks. Tests were performed only after each was acquainted with the experimental apparatus and was relaxed while using it.

Each subject sat in a comfortable chair in a moderately darkened room, with quiet music playing on a radio. With nose clips applied, he breathed through a mouthpiece attached to a non-rebreathing circuit. Incorporated in the circuit were a Rudolph #1400 non-rebreathing valve, a pneumotachograph head in the inspiratory limb and a gas sampling port on the expiratory side of the non-rebreathing valve. Exhaled gas was sampled continuously and analyzed by a Perkin-Elmer #1100 mass spectrometer for oxygen and carbon dioxide tensions. The pneumotachograph coupled with an integrator gave signals of inspired flow and volume. Inspired ventilation and exhaled gas tensions could be recorded on a strip polygraph.

A period of resting ventilation was recorded after the subject had adapted to breathing air from the circuit. Isocapnic hypoxaemia was induced subsequently by replacing the air in the inspired gas with a mixture of air and nitrogen, to reduce the end-tidal oxygen tension to approximately 40 torr (5.32 kPa). To avoid hypocapnia during hypoxic hypernoea, carbon dioxide was added to maintain the control value of end-tidal carbon dioxide. After hypoxaemia (i.e. PET_{O_2} of 40 ± 2 torr [5.32 ± 0.26 kPa]) had been present and constant for at least ten minutes, ventilation and gas tensions were recorded.

After a period of rest, the subjects inhaled 0.1 per cent halothane in air until they reached a steady end-tidal halothane concentration of 0.04

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*A portion of this paper was presented in the Resident's Competition of the Canadian Anaesthetists' Society Annual Meeting in Saskatoon, Saskatchewan in June, 1977.

This work was supported by the Medical Research Council of Canada, Development Grant 150.

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per cent (equivalent to 0.05 MAC), as determined by mass spectrometry. This usually took 15 to 20 minutes. Once this steady end-tidal concentration was achieved, it was probable that alveolar, blood and brain halothane concentrations were equilibrated.[4] To check that the end-tidal value was not falsely high, we reduced the inspired halothane concentration to within 10 per cent of the end-tidal for a minute and ensured that the end-tidal value remained constant.

While the subject inhaled air with halothane at 0.05 MAC, a period of resting ventilation was recorded. With 0.05 MAC halothane continuing, we induced a steady-state of isocapnic hypoxaemia ($P_{ET_{O_2}}$ 40 ± 2 torr [5.32 ± 0.26 kPa]), and after conditions had been stable for at least 10 minutes, we measured ventilation again.

Finally, we repeated the study a third time with the subject inhaling 0.2 per cent halothane and at a steady end-tidal concentration of 0.08 per cent (0.1 MAC).

B. *Recovery room study*

Five healthy patients were investigated in the recovery room after dental surgery. No attempt was made to interfere with the anaesthetic technique employed. All patients had been unpremedicated. Anaesthesia was induced with sodium thiopentone 3–6 mg/kg, followed by paralysis with succinylcholine 0.5–1.5 mg/kg and tracheal intubation. Subsequently, patients inhaled halothane in nitrous oxide and oxygen at various concentrations. At the end of the operation they were transferred to the recovery room, where our assessments of anaesthetic depth began.

During recovery, end-tidal halothane cannot be considered to represent brain anaesthetic depth.[4] To gain some index of minimal brain halothane tension in the recovery room, we used a test of rapid re-equilibration of end-tidal halothane concentration. Knowing that it takes 15 to 20 minutes to reach a stable end-tidal concentration when inhaling halothane during induction, it was arbitrarily decided that if the recovery room patients could reach a stable end-tidal halothane concentration of 0.08 per cent (0.1 MAC) within one minute of being re-exposed to halothane 0.2 per cent inspired and if they could maintain this concentration steady even when inspired halothane was immediately reduced to 0.09 per cent then, at the time of the test, they must have a minimum of halothane 0.08 per cent (converted to tension) in the vessel-rich tissues, including the brain. After each patient became sufficiently conscious to hold a mouthpiece safely this test was performed every 10 to 15 minutes, until either equilibration (i.e. end-tidal concentration stability) was at a level lower than 0.08 per cent or until equilibration failed to occur within one minute.

C. *Data analysis*

(*a*) *Laboratory data.* Values of tidal volume (V_T), ventilatory frequency (f) and inspired ventilation ($\dot{V}_I$) were the average of at least one minute of recorded ventilation. All ventilation and tidal volumes were converted to B.T.P.S.

During hypoxaemia, the value of end-tidal oxygen tension ($P_{ET_{O_2}}$ 40 torr [5.32 kPa]) was taken to represent the stimulus to ventilation. The actual stimulus is more properly the arterial oxygen tension, but in physically fit subjects with oxygen tensions below 80 torr (10.64 kPa) the end-tidal tension is only slightly greater than arterial, the difference being less than 6 torr (0.8 kPa).[6,7] The recorded responses to steady-state hypoxaemia were the increments in tidal volume (ΔV_T), ventilatory frequency (Δf) and inspired ventilation ($\Delta \dot{V}_I$).

A Student's t test for paired data was employed to evaluate possible differences between sedation and awake data, p values of 0.05 or less being regarded as indicative of a significant difference.

(*b*) *Recovery room data.* The time from termination of anaesthesia during which rapid re-equilibration of end-tidal halothane to 0.08 per cent was observed was called P.A.T. 0.1, that is, the post-anaesthetic time at halothane 0.1 MAC or more.

Results

A. *Laboratory study*

There were no untoward effects of these tests. During hypoxaemia, subjects reported variously a sensation of uneasiness, slight mental impairment and/or mild agitation. Electrocardiograms recorded during hypoxaemic periods showed increases in heart rate of about 20 to 30 beats per minute, but neither arrhythmias nor ischaemic changes. Steady-states of halothane sedation were readily achieved by the method described. Volunteers became pleasantly drowsy while inhaling halothane, but were easily rousable and coherent and had full recall of the experiment afterwards. During sedation, symptoms of hypoxaemia were either markedly reduced or totally absent.

TABLE I

	Awake	.05 MAC	.10 MAC
$\dot{V}_I$ (L/min)	7.5 ± 0.6	7.0 ± 0.3	7.5 ± 0.6
V_T (L)	0.59 ± 0.03	0.53 ± 0.03*	0.52 ± 0.02*
f (breaths/min)	13 ± 1	13 ± 1	15 ± 1
RESPONSE TO HYPOXIA ($P_{ET_{O_2}}$ 40 torr)			
$\Delta \dot{V}_I$ (L/min)	12.4 ± 3.4	6.5 ± 1.8*	3.6 ± 1.2*
ΔV_T (L)	0.55 ± 0.14	0.31 ± 0.08*	0.17 ± 0.07*
Δ f (breaths/min)	5 ± 1	3 ± 1	1 ± 1*

Values are mean ± S.E.M.
Values of $\dot{V}_I$ and V_T are at B.T.P.S.
*Indicates significant difference from awake ($p < 0.05$).

Mean values of ventilation and the increment in ventilation associated with isocapnic hypoxaemia are recorded for each state in Table I. Awake values are typical of normocapnic healthy subjects. Neither level of halothane sedation (0.05 MAC and 0.1 MAC) significantly altered resting minute ventilation, but both decreased resting tidal volume slightly. Sedation markedly reduced the ventilatory response to steady-state hypoxaemia, with halothane 0.1 MAC having a somewhat greater effect than 0.05 MAC. This impaired ventilatory response was due to a reduced tidal volume response and, in the case of 0.1 MAC, to a reduced ventilatory frequency response as well.

B. *Recovery room study*

The duration of anaesthesia for patients studied in the recovery room ranged from 45 to 95 minutes with a mean of 59 minutes. The post-anaesthetic time at halothane 0.1 MAC or more (P.A.T. 0.1) varied from 25 to 80 minutes with a mean of 54 minutes (Table II).

TABLE II

RELATIONSHIP BETWEEN ANAESTHETIC TIME AND P.A.T. 0.1

Subject	Anaesthetic time (minutes)	P.A.T. 0.1 (minutes)
1	55	65
2	45	25
3	95	80
4	55	50
5	45	50
Mean	59	54

DISCUSSION

A previous study suggested that patients recovering from clinical anaesthesia might have an important derangement of chemical regulation of ventilation – specifically an obtunded ventilatory response to hypoxia.[1] To confirm this possibility, we considered a study of the regulation of ventilation of patients during emergence, but were deterred by both technical and ethical problems. The nature of spontaneous emergence from anaesthesia precludes "steady-states", which are normally essential to an assessment of regulation of breathing. As the emergence period is somewhat unpredictable, it is difficult to inform potential subjects of probable effects of experimental interventions such as induced hypoxaemia or hypercarbia. As an alternative to this we employed an indirect two-step approach, studying first the ventilatory effects of constant levels of halothane sedation in conscious volunteers and then the persistence of one of these levels of sedation in patients emerging from clinical anaesthesia. Although with obvious deficits, this method was practical and yielded some interesting new information.

To quantify the dosage of halothane in the conscious volunteers, we used the MAC (minimum alveolar concentration) concept of Eger, *et al.*[4,8] The problem of assessing isonarcotic concentrations of inhalational anaesthetics was greatly al-

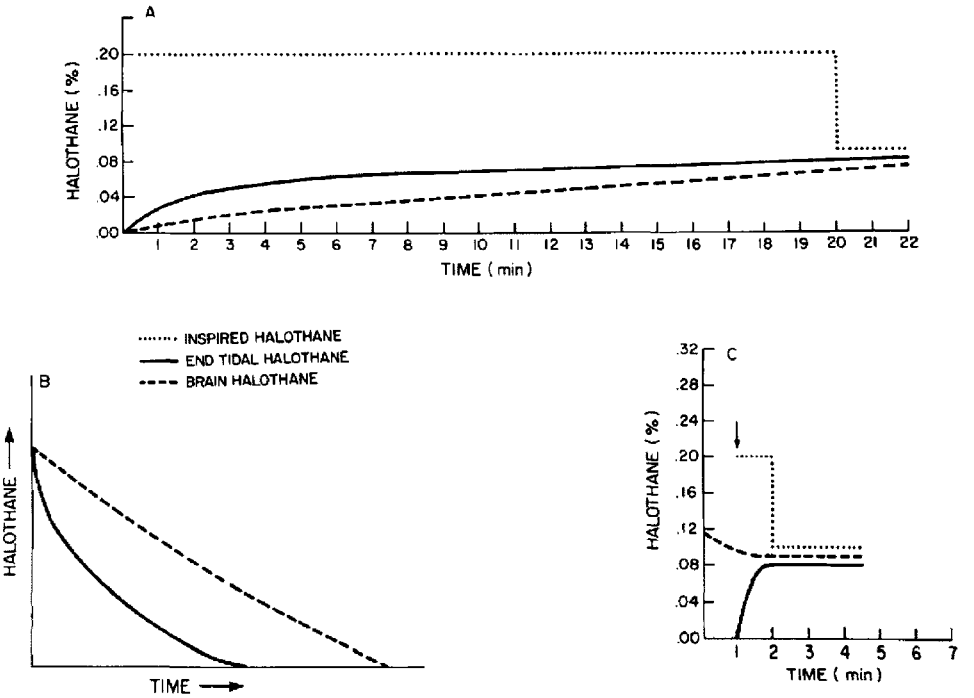

FIGURE 1 Graphic characterization of probable relationships between inspired and end-tidal concentrations and brain halothane levels, depicted as vapour concentrations; A – during induction of sedation in the laboratory; B – during emergence from anaesthesia in the recovery room; C – during a test of re-equilibration. For explanation see text.

leviated by the introduction of MAC. Fundamental to this concept is the assumption that, in the steady-state, the alveolar tension of an anaesthetic, as measured by end-tidal gas sampling, is in equilibrium with blood and, in turn, with brain tissue tensions. It is known that end-tidal and arterial tensions are not identical but, in the absence of gross ventilation/perfusion imbalance, are close enough to make this concept useful.[9] Thus one can estimate brain anaesthetic dose by measuring end-tidal gas concentrations or tensions. In our laboratory studies subjects inhaled 0.1 per cent halothane in air and the end-tidal concentration rose slowly to reach a steady value of 0.4 per cent or 0.05 MAC. Subsequently they inhaled 0.2 per cent halothane in air and the end-tidal concentration rose to 0.08 per cent or 0.1 MAC (graphical depiction in Figure 1-A).*To ensure that this value was not being falsely increased by gas from ventilated but unperfused alveoli, the inspired concentration was reduced to within 10 per cent of the end-tidal value (Figure 1-A) and, if the latter remained constant, it was assumed to reflect reasonably the blood and so the brain anaesthetic tension.[9]

In these steady-states of sub-anaesthetic halothane, resting ventilation remain virtually unchanged from that in the awake subject, but the ventilatory response to several minutes of hypoxaemia ($P_{ET_{O_2}}$ 40 torr (5.32 kPa)) was clearly impaired (Table I). This effect of halothane sedation was potent; only 0.05 MAC reduced the hypoxic response to approximately one half of the awake value. It was also dose-related, 0.1 MAC reducing the response more than 0.05 MAC. There was no apparent difference in the magnitudes of impairment of sustained hypoxaemic responses in this study and brief hypoxaemic responses studied previously.[1]

Figure 2 depicts the depression of the hypoxic chemoreflex (the $\Delta\dot{V}_I$ at P_{ET} 40 torr [5.32 kPa]) over a range of halothane dosages, representing both sedation and anaesthesia. The effect of

*It is recognized that the MAC value for halothane in man is 0.75 per cent[4] and that 0.1 MAC would therefore be 0.075 per cent. However, the best resolution of our mass spectrometer analysis of halothane vapour was to 0.01 per cent.

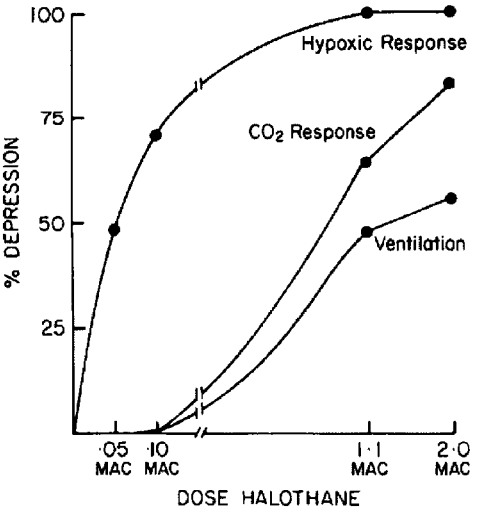

FIGURE 2. Depression of isocapnic ventilation and the ventilatory response to hypoxia and carbon dioxide at four doses of halothane, −0.05, 0.1, 1.1 and 2.0 MAC. Zero depression indicates no change from the conscious state; 100 percent depression means totally abolished. Points were derived from mean values of ventilation and parameters of hypoxic and carbon dioxide responses, taken from this and a previous study. Lines connecting points of the same variable are hand drawn. Halothane depresses ventilation and each response in a dose-related fashion; the most potent effect is on the hypoxic reflex. Halothane sedation (0.05 and 0.1 MAC) selectively reduced the hypoxic response, while halothane anaesthesia (1.1 and 2.0 MAC) totally abolished it.

halothane on ventilation and the ventilatory response to carbon dioxide (slope of $\dot{V}_I$:P_{CO_2} relationship) are also represented for comparison. This figure was constructed from mean data of this study along with mean data from our previous study[1] and unpublished observations. The dose-response curves of this figure clearly point out the selective impact of halothane on the hypoxic ventilatory response.

The carotid body chemoreceptors which mediate the ventilatory response to hypoxaemia have always been considered resistant to the depressive effects of anaesthetic drugs. During progressive depression of the central nervous system by drugs in animals, responsiveness to peripheral chemoreceptor stimuli (hypoxaemia and sodium cyanide) were reported to remain relatively brisk.[11] This apparent ruggedness of the carotid body receptors and their immediate reflex pathways led to their being labeled the "ultimum moriens" – the last to die. In contrast to this concept, our studies indicate that as little as 0.04 per cent halothane depresses the peripheral chemoreceptor-mediated response to hypoxaemia selectively (Figure 2): a similar reduction of the hypoxic chemoreflex has also been observed with sub-anaesthetic nitrous oxide,[12] but not with sub-anaesthetic thiopentone.[13]

Having found a marked depression of the hypoxic chemoreflex in sedated volunteers, we were particularly interested in how relevant this finding was to patients emerging from anaesthesia in the recovery room. For what period of time during emergence from halothane anaesthesia would a dose of halothane 0.1 MAC be present?

The assessment of brain halothane concentration in the recovery room is made difficult by the fact that patients are not in a steady state. Stoelting, *et al.*[3] came to the conclusion that, in patients breathing spontaneously during recovery, end-tidal halothane significantly underestimates the brain level. For this reason we decided to employ a test in which rapid re-equilibration of end-tidal halothane would indicate minimal brain halothane levels. Figure 1 illustrates our rationale, depicting temporal changes in halothane concentrations in inspired gas and end-tidal gas and what we predict would be the simultaneous brain levels expressed as vapour concentrations. Part A represents the induction of sedation, as in our laboratory studies. With a constant inspired halothane of 0.2 per cent, end-tidal concentration rises slowly to a value of approximately 0.08 per cent, where it remains even when inspired concentration is reduced to 0.09 per cent. Note that the brain level lags behind the end-tidal.[4] Part B represents the general situation in the recovery room, where inspired concentration is nil, end-tidal concentration falls quickly to zero and a brain halothane level is still present. Part "C" shows what we predict is occurring with our test of re-equilibration during recovery. At time zero, end-tidal concentrations are virtually nil and an unknown brain level is present. With sudden re-exposure to an inspired concentration of 0.2 per cent (at arrow Figure 1C), end-tidal values rise quickly, in contrast to the situation in Part A. If during this test the end-tidal value reached 0.08 per cent or more within one minute of administration of 0.2 per cent halothane and remained there even when the inspired concentration was decreased to 0.09 per cent briefly, we assumed that the blood and brain level must have been the equivalent of 0.08 per cent or more. The time of one minute was chosen arbitrarily; it is believed

that this time is sufficiently short to prevent re-administration of halothane from establishing a new tissue level.[4]

We observed that the mean duration of halothane 0.1 MAC or more (P.A.T. 0.1) was 54 minutes for clinical anaesthetics of a mean duration of 59 minutes (Table II). This observation is consistent with what was predicted by Stoelting and Eger from animal studies and analog computations.[3,4] How much longer halothane 0.05 MAC would persist is not known.

The occurence of hypoxaemia is not uncommon in patients recovering from halothane anaesthesia[1,4] and small concentrations of halothane which persist in the recovery period may impair the ventilatory reaction to hypoxaemia. The absence of a normal response to hypoxia increases the severity and, therefore, the danger of hypoxic episodes. Our data indicate that this hazard persists for about one hour after a one-hour halothane anaesthetic.

Summary

Ventilation and the ventilatory response to a steady-state of isocapnic hypoxaemia were measured in six healthy volunteers, both awake and while sedated with low doses of halothane (0.05 and 0.1 MAC). Halothane sedation markedly reduced ventilatory responses to sustained hypoxaemia, in a dose-related fashion.

We estimated the length of time after anaesthesia that halothane 0.1 MAC would be present in patients in the recovery room. In five healthy patients who had halothane anaesthesia with a mean duration of one hour, halothane 0.1 MAC or more persisted for approximately one hour.

We conclude that, during emergence from halothane anaesthesia, patients may have a significant impairment of the ventilatory response to hypoxaemia, which persists for some time even after regaining consciousness.

Résumé

Chez six volontaires en bonne santé tantôt éveillés, tantôt sous sédation légère à faible dose d'Halothane (0,05 et 0,1 MAC), on a mesuré la ventilation et la réponse ventilatoire à l'hypoxémie isocapnique soutenue. Proportionnellement à la dose administrée, l'Halothane a fortement réduit la réponse ventilatoire à l'hypoxémie soutenue.

Dans un deuxième temps, nous avons cherché à estimer combien de temps, au sortir d'une anesthésie à l'Halothane, on peut encore déceler en salle de réveil des concentrations d'Halothane de l'ordre de 0,1 MAC. Chez cinq malades en bonne santé pour une heure d'anesthésie à l'Halothane, des concentrations de 0,1 MAC ou plus ont persisté en salle de réveil pendant à peu près une heure.

Nous en concluons qu'au sortir d'une anesthésie à l'Halothane, la réponse ventilatoire à l'hypoxémie peut être nettement réduite et que ce phénomène persiste même après le retour à la conscience.

Acknowledgements

The authors wish to thank patients, residents, nurses and respiratory technologists who took part in this study, Mrs. L. Nolan who helped prepare the manuscript and Miss Jane Clement who assisted invaluably in the performance of the studies.

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