ENHANCEMENT OF THE ARRHYTHMOGENIC EFFECT OF HYPERCARBIA BY SURGICAL STIMULATION DURING HALOTHANE ANAESTHESIA IN MAN

B.J. ROBERTSON, J.L. CLEMENT AND R.L. KNILL

ABSTRACT

We studied the levels of hypercarbia necessary to induce ventricular extrasystoles in one group of six subjects anaesthetized with halothane 1.3 MAC and in another group of six subjects anaesthetized with a 1.3 MAC combination of halothane and nitrous oxide, both before and during elective surgical procedures. Hypercarbia was induced progressively by total rebreathing to a maximum $P\bar{v}_{CO_2}$ value of approximately 11.0 kPa (83 torr). $P\bar{v}_{CO_2}$ values at which ventricular extrasystoles were first observed were taken as the $P\bar{v}_{CO_2}$ arrhythmic thresholds. During anaesthesia alone in both groups, $P\bar{v}_{CO_2}$ arrhythmic thresholds were achieved in only one of six subjects and the median $P\bar{v}_{CO_2}$ thresholds were therefore greater than 11.0 kPa (83 torr). During halothane anaesthesia with surgery, thresholds were observed in all subjects and the median value was 9.1 kPa (68 torr). During halothane-nitrous oxide with surgery, thresholds were identified in three of six subjects and the median was greater than 10.7 kPa (80 torr). The thresholds during halothane with surgery were significantly less than the threshold or maximum $P\bar{v}_{CO_2}$ values observed in each of the other three states (p values <0.05). The results indicate that during halothane anaesthesia, surgical stimulation markedly enhances the arrhythmogenic effect of added carbon dioxide and that, in the presence of surgery, a nitrous oxide-halothane mixture is less sensitizing than an equi-potent dose of halothane alone.

KEY WORDS: ANAESTHETICS, VOLATILE, halothane; COMPLICATIONS, arrhythmia.

ALTHOUGH HALOTHANE itself rarely causes ventricular arrhythmias in man, it predisposes to ventricular arrhythmias induced by factors not infrequently present in clinical practice, such as tracheal intubation,[1] intravenous atropine,[2] adrenalin infiltration,[3] and acute hypercarbia.[4,5] The level of hypercarbia necessary to elicit ventricular extrasystoles in subjects lightly anaesthetized with halothane and not undergoing surgery has been found to be variable, but generally quite high. Black et al reported arrhythmic threshold PET_{CO_2} values ranging from 8.0 to 18.6 kPa (60 to 140 torr) with a mean of 12.3 kPa (92 torr),[4] Eikard, *et al.*, threshold Pa_{CO_2} values of 10.9 to 14.5 kPa (82 to 109 torr) with a mean of 13.1 kPa (98 torr).[5]

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These experimental observations of very high critical P_{CO_2} values seem inconsistent with clinical experience, which suggests that ventricular arrhythmias in the presence of halothane may be associated with only modest levels of hypoventilation and, presumably, much smaller increments in P_{CO_2}. Accordingly, we wondered if additional factors in the clinical environment might predispose to carbon dioxide related arrhythmias. The purpose of the present study was to explore possible effects of surgical stimulation and nitrous oxide, during controlled levels of halothane anaesthesia and with a reproducible carbon dioxide stimulus.

METHODS

The subjects were 12 patients, six male and six female, booked for elective peripheral orthopaedic surgical procedures. Their ages, heights and weights were respectively 27 ± 7 years, 167 ± 10 cm, 68 ± 17 kg (means ±S.E.M.). Preoperative history and physical examination found all subjects to be fit (A.S.A. Class I). The haemoglobin, urinalysis, 12 lead electrocardiogram, and arterialized capillary blood gas values were all within normal limits. Each subject was informed

of the nature and risks of the study and gave written consent, according to a protocol approved by the University of Western Ontario Human Research Committee.

Subjects were divided into two groups: Group I (n = 6) to be studied during halothane anaesthesia 1.3 MAC, and Group II (n = 6) to be studied during halothane 0.8 MAC with nitrous oxide 0.5 MAC for a total MAC equivalent of 1.3. There were three males and three females in each group. All members of each group were studied both before and during a surgical procedure.

Each unpremedicated subject was placed in the supine position. After pre-curarization with d-tubocurarine 3–4.5 mg intravenously, we induced anaesthesia with intravenous thiopentone 5 mg·kg^{-1} followed by succinylcholine 1.5 mg·kg^{-1} and then intubated the trachea with a cuffed tube of 8 mm I.D. for females and 9 mm I.D. for males. Intravenous atropine and topical anaesthesia of the upper airway were omitted. Breathing spontaneously, each subject inhaled an anaesthetic mixture from a non-rebreathing circuit (incorporating a Rudolph # 1400 non-rebreathing valve) for 30–40 minutes, to reach steady anaesthetic and respiratory states which are defined below. The anaesthetic for Group I was halothane only, administered with oxygen and in concentrations appropriate to achieving the steady end-tidal halothane level equivalent to 1.3 MAC, assuming a MAC value of 0.84 per cent for this group.[6] Group II subjects inhaled halothane, nitrous oxide and oxygen, to achieve steady end-tidal concentrations of halothane 0.8 MAC and nitrous oxide 0.5 MAC, assuming the MAC effect of nitrous oxide in anaesthetic mixtures to be 110 per cent.[7] These anaesthetic states, once attained, were kept constant throughout the study.

Subjects received an intravenous infusion of 5 per cent dextrose in 0.2 per cent normal saline to maintain systolic blood pressure levels at least 70 per cent of awake values. Body temperature was monitored with a nasopharyngeal or axillary temperature probe.

We considered that a steady state existed when ventilation was steady, and end-tidal carbon dioxide and anaesthetic concentrations had been constant for ten minutes. At this point, a sample of arterialized blood was withdrawn from a free-flowing vein on the dorsum of the hand, without the use of a tourniquet, for estimation of Pa_{CO_2} and $[H^+]a$.[8] Arterialization of blood, sampled in this manner from subjects anaesthetized with halogenated vapours, is known to be excellent. In our samples, the P_{O_2} values always exceeded 15 kPa* and the P_{CO_2} and $[H^+]a$ values are therefore reported as arterial. Next, we induced progressive hypercarbia, employing a modification of Read's total rebreathing technique.[9] A circuit of 12 litre capacity was primed with carbon dioxide 7.5–8 per cent in oxygen, and anaesthetic(s) in concentration(s) appropriate to maintaining anaesthetic level constant throughout the rebreathing procedure. The subject's airway was connected to this circuit and his lungs were inflated with three large breaths. After the subject resumed spontaneous breathing, we verified the presence of a P_{CO_2} plateau throughout the respiratory cycle in the tracing of airway P_{CO_2}, indicative of equilibrium of carbon dioxide between mixed venous blood, alveolar gas and the rebreathing circuit.[10] This equilibrated P_{CO_2} value is equivalent to oxygenated mixed venous P_{CO_2} and hereafter is referred to as "$P\bar{v}_{CO_2}$". Rebreathing continued until this $P\bar{v}_{CO_2}$ value reached approximately 11.0 kPa (83 torr) or until the appearance of ventricular extrasystole, whichever was first. At that point the subject was switched immediately to the non-rebreathing system to wash out the carbon dioxide stimulus and to re-establish control values of ventilation and end-tidal carbon dioxide.

Next, the surgical procedure began and proceeded without interference for at least ten minutes. During a period well removed from intense surgical stimuli, – for example, periosteal incisions, bone drilling, – we ensured that end-tidal anaesthetic concentrations were at the same level as pre-surgery and checked that ventilation and end-tidal carbon dioxide were reasonably steady at their new levels. We then withdrew a sample of arterialized blood and proceeded with the rebreathing test as during anaesthesia alone, except that the concentration of carbon dioxide in the circuit prime was reduced to 6.5–7 per cent.

Before and during each test, we monitored systemic arterial blood pressure with an automated Arteriosonde (an instrument which detects systolic and diastolic pressure with a

*Taking this minimum "arterialized" P_{O_2} value in relation to a maximum possible arterial value of 90 kPa, converting both to expected oxygen content and considering a variety of possible values of venous oxygen and carbon dioxide contents, we calculate that the maximum deviation of an "arterialized" P_{CO_2} value from actual arterial would be less than 0.06 kPa (0.5 torr). This maximum possible "arterialization" error for P_{CO_2} is within the error inherent in the measurement technique. Maximum possible $[H^+]a$ error is similarly very small.

sensor responding to Doppler shifts of transmitted ultra-sound), cardiac rate and rhythm with a standard lead II electrocardiogram and end-tidal or airway concentrations of halothane, nitrous oxide and carbon dioxide with a Perkin-Elmer #1100 mass spectrometer. In addition we monitored inspired ventilation by pneumotachography as an index of the steady respiratory state. Blood pressures were taken and recorded every 20 to 30 seconds. The remaining test data were inscribed continuously on a multi-channel time based recorder, with paper speed at 25 mm/sec.

Blood samples were drawn anaerobically into pre-heparinized syringes, capped immediately and placed in ice. Blood gas analysis was done within the hour using a radiometer Copenhagen BMS 3 system calibrated each testing day with both specialty gas mixtures (Canadian Liquid Air) and tonometered blood.

Values of dried airway or end-tidal carbon dioxide concentrations were converted to tensions, employing the measured barometric pressure of the day of testing and assuming that end-tidal gas was fully saturated with water vapour at 37°C. Mean blood pressure was computed as diastolic pressure plus one-third pulse pressure. Individual heart rate values were calculated from recorded ten second intervals. A ventricular extrasystole was defined as a broad QRS complex occurring early in the cardiac cycle and followed by a compensatory pause.

We analyzed the heart rate and blood pressure responses to added carbon dioxide from the point of appearance of the mixed venous P_{CO_2} plateau[10] to the end of the rebreathing run. Heart rate and blood pressure were assumed to relate linearly to $P\bar{v}_{CO_2}$ and responses of these variables were represented by the slopes of least squares linear regressions. The P_{CO_2} arrhythmic threshold was defined as the tension of airway carbon dioxide during rebreathing, i.e. the $P\bar{v}_{CO_2}$, at the time of the first ventricular extrasystole. If extrasystoles were not observed after achieving a $P\bar{v}_{CO_2}$ value of about 11.0 kPa (83 torr), the arrhythmic threshold was assumed to be higher and the $P\bar{v}_{CO_2}$ value at the end of rebreathing was called a "maximum, sub-threshold" value.

Data were analyzed by calculating the means and S.E.M. of each variable in each of the four states studied. Where possible, we determined a group median threshold $P\bar{v}_{CO_2}$, i.e. the $P\bar{v}_{CO_2}$ effective in provoking ventricular extra beats in 50 per cent of subjects. To test for possible differences of data between the four states, we employed the Student's t-test for paired or unpaired data as appropriate.

Results

Each subject recovered from his anaesthetic without complication related to this study. Values of $P_{ET_{O_2}}$ remained above 26.6 kPa (200 torr) throughout all phases of all studies. Axillary or nasopharyngeal temperatures did not drop below 35°C. Ventricular arrhythmias related to hypercarbia did not produce hypotension and they always ceased spontaneously within 40 seconds of discontinuing rebreathing.

Table I shows resting values of Pa_{CO_2}, $[H^+]a$, heart rate and mean blood pressure, along with the slopes of the heart rate and mean blood pressure responses to added carbon dioxide ($\Delta HR/\Delta P\bar{v}_{CO_2}$ and $\Delta\overline{BP}/\Delta P\bar{v}_{CO_2}$) for the ranges of $P\bar{v}_{CO_2}$ values studied. Table II lists individual values of threshold or maximum sub-threshold $P\bar{v}_{CO_2}$.

Halothane 1.3 MAC and halothane-nitrous oxide 1.3 MAC without surgery caused modest elevations of resting Pa_{CO_2}, increments of $[H^+]a$ and reductions of mean blood pressure, compared to expected awake values (Table I). With surgical stimulation resting Pa_{CO_2} and $[H^+]a$ decreased in each group and resting heart rate and mean arterial pressure increased (Table I, p values < 0.05). The increase in mean pressure associated with surgery reflected nearly equal increments in systolic and diastolic values.

During rebreathing, the mean rates of increase of P_{CO_2} were similar in each group, varying from 0.49 to 0.61 kPa/min (3.7 to 4.6 torr/min). In all states, heart rate and mean arterial blood pressure increased with hypercarbia (Table I), the increments in mean pressure being due mostly to increases in systolic pressure with diastolic relatively little affected. Individual heart rate and mean blood pressure responses varied considerably; but all were small and less than usual awake values.[11] Slopes of heart rate and $\overline{BP}$ responses in each state were not significantly different.

P_{CO_2} arrhythmic thresholds were identified in all subjects during halothane 1.3 MAC with surgery, in three subjects during halothane-nitrous oxide with surgery, but in only one subject in each group without surgery (Table II). Arrhythmic thresholds were always preceded by a regular sinus or nodal rhythm and followed by a short run of unifocal or multifocal ventricular premature beats lasting up to 40 seconds. Three subjects displayed short runs of bigeminy; there

TABLE I
RESTING Pa_{CO_2}, $[H^+]a$, HEART RATE AND MEAN BLOOD PRESSURE, WITH RESPONSES OF HEART RATE AND MEAN BLOOD PRESSURE TO ADDED CARBON DIOXIDE

	Group 1 Halothane 1.3 MAC		Group 2 Halothane – N_2O 1.3 MAC	
	No Surgery	Surgery	No Surgery	Surgery
Resting				
Pa_{CO_2} kPa	6.4 ± 0.4	5.5 ± 0.2*	6.4 ± 0.3	5.7 ± 0.1*
(torr)	(48 ± 3.0)	(41 ± 1.5)	(48 ± 2.3)	(43 ± 0.8)
$[H^+]a$ nmol/l	51 ± 2	48 ± 1*	52 ± 1	48 ± 2*
HR beats/min	67 ± 3	75 ± 5*	66 ± 2	76 ± 3*
$\overline{BP}$ kPa	10.0 ± 0.6	11.0 ± 0.8*	9.0 ± 0.4	10.1 ± 0.5*
(torr)	(75 ± 4.5)	(83 ± 6.0)	(68 ± 3.0)	(76 ± 3.8)
CO_2 Responses				
$P\bar{v}_{CO_2}$ range kPa	2.5 ± 0.2	2.0 ± 0.3	2.9 ± 0.2	3.3 ± 0.4
(torr)	(19 ± 1.5)	(15 ± 2.3)	(22 ± 1.5)	(25 ± 3.0)
$\Delta HR/\Delta P\bar{v}_{CO_2}$				
beats/min/kPa	3.5 ± 0.5	4.5 ± 1.6	4.9 ± 1.6	3.4 ± 1.1
(beats/min/torr)	(0.47 ± 0.09)	(0.60 ± 0.20)	(0.65 ± 0.20)	(0.45 ± 0.20)
$\Delta\overline{BP}/\Delta P\bar{v}_{CO_2}$	0.44 ± 0.08	0.47 ± 0.36	0.36 ± 0.12	0.16 ± 0.27

Bracketed values are torr equivalents.
All values are means ± S.E.M.
*Significantly different from no surgery state ($p < 0.05$).

TABLE II
THRESHOLD $P\bar{v}_{CO_2}$ kPa (torr)

Group 1 Halothane 1.3 MAC			Group 2 Halothane – N_2O 1.3 MAC		
Subject	No Surgery	Surgery	Subject	No Surgery	Surgery
1	>11.2 (84)	8.4 (63)	7	>11.4 (86)	>11.4 (86)
2	9.1 (68)	8.5 (64)	8	10.9 (82)	10.2 (77)
3	>10.4 (78)	9.7 (73)	9	>11.0 (83)	10.4 (78)
4	>11.0 (83)	8.8 (66)	10	>11.0 (83)	10.5 (79)
5	>11.2 (84)	10.2 (77)	11	>11.2 (84)	>11.4 (86)
6	>11.0 (83)	9.4 (71)	12	>10.9 (82)	>10.9 (82)
Mean	10.7 (80)	9.2* (69)	Mean	11.1 (83)	10.8 (81)
±S.E.M.	±0.3 (±2.6)	±0.3 (±2.3)	±S.E.M.	±0.1 (±0.8)	±0.2 (±1.6)
Median	>11.0 (83)	9.1 (68)		>11.0 (83)	>10.7 (80)

Bracketed values are torr equivalents.
Values preceded by ">" were maximum sub-threshold values.
*Significantly less than the other three states ($p < 0.05$).

were no instances of ventricular tachycardia. Individual threshold values did not correlate with heart rate, mean arterial blood pressure, rate-systolic pressure product or the change in any of these variables induced by carbon dioxide.

Thresholds during halothane with surgery were significantly less than the combined threshold and maximum sub-threshold values of each of the other three states (Table II, p values < 0.05).

DISCUSSION

The results of this study indicate that surgical stimulation and nitrous oxide can markedly modify the arrhythmogenicity of carbon dioxide during halothane anaesthesia in man. Surgical stimulation reduced the level of P_{CO_2} required to evoke ventricular extrasystoles and the inclusion of nitrous oxide in the anaesthetic mixture increased it during surgery.

We studied carbon dioxide responses in four states; halothane 1.3 MAC, both alone and with surgery, and halothane 0.8 MAC with nitrous oxide 0.5 MAC – for a total MAC equivalent of 1.3, also alone and with surgery. Assuming MAC values to be additive at doses other than 1.0 MAC, the anaesthetic states we studied can be considered equi-potent.[7] A total dose of 1.3 MAC was selected as one which would be satisfactory for surgery in most subjects[7] and thus unlikely to predispose to arrhythmias on the basis of inadequate anaesthesia.[12] We omitted lidocaine spray before tracheal intubation to avoid its potential anti-arrhythmic effect. Intravenous atropine was also withheld, as it is occasionally arrhythmogenic in the presence of halothane,[2] and particularly so if the carbon dioxide level is high.[12] To reduce variables related to anaesthesia and respiration to a minimum we wished to study reasonably steady states. Steady states were achieved with relative ease during anaesthesia alone and the potential problem of moment-to-moment variation of surgical stimulation was mitigated by confining testing to periods of surgery well removed from potent stimuli, such as incisions of skin and periosteum, and drilling of bone.[13]

Hypercarbia was induced progressively by the Read rebreathing technique, in which carbon dioxide increases in a manner which is independent of cardiovascular and ventilatory responses,[14] and at a rate (less than 0.7 kPa/min (5 torr/min)) – which evokes arrhythmic thresholds reproducibly.[4,15] During this test, after carbon dioxide equilibration, the change in airway carbon dioxide (the measured stimulus) is equivalent to the change in tissue P_{CO_2} (the "actual" stimulus).[14] In addition the measured airway carbon dioxide is virtually equivalent to oxygenated mixed venous P_{CO_2}.[14,16] On this basis we, like others,[16] regard airway P_{CO_2} during rebreathing after equilibration as values of $P\bar{v}_{CO_2}$. (However, we did not measure $P\bar{v}_{CO_2}$ directly in these subjects, i.e. in samples of blood from the pulmonary artery). These $P\bar{v}_{CO_2}$ values can be converted to corresponding Pa_{CO_2} values by multiplying by 0.8.*[16] For this study we limited airway or $P\bar{v}_{CO_2}$ values to approximately 11.0 kPa (83 torr), a level which is known to be safely tolerated in healthy young subjects anaesthetized with halothane.[4,5]

*This conversion factor takes into account differences in oxygenated and actual venous $P\bar{v}_{CO_2}$, as well as the increasing $P\bar{v}_{CO_2} - Pa_{CO_2}$ difference as carbon dioxide content rises.[16]

Halothane 1.3 MAC alone produced typical values of resting Pa_{CO_2} $[H^+]a$, heart rate and mean blood pressure (Table I). Substituting nitrous oxide for a portion of the anaesthetic did not detectibly alter these variables, a finding which differs from that of Hornbein, *et al.*, who reported that nitrous oxide 70 per cent included with halothane in spontaneously breathing subjects was associated with slightly lower values of P_{CO_2} and somewhat higher mean arterial pressures than was an equi-potent 1.0 MAC dose of halothane alone.[17] However, these effects of nitrous oxide may depend upon nitrous oxide concentration and the duration of its administration,[18,19] factors which differed between our study and Hornbein's. Not unexpectedly, surgical stimulation reduced Pa_{CO_2} and $[H^+]a$ values, and increased heart rate and both systolic and diastolic pressures in both anaesthetic states (Table I). In agreement with previous reports, heart rate and blood pressure responses to added carbon dioxide were small during halothane 1.3 MAC alone;[11,20] neither the inclusion of nitrous oxide nor surgical stimulation altered these responses consistently (Table I).

The observations of most interest relate to the carbon dioxide arrhythmic thresholds. Due to the limitation of hypercarbia we imposed upon this study ($P\bar{v}_{CO_2}$ 11.0 kPa or 83 torr), we failed to attain threshold in five of six subjects during halothane 1.3 MAC alone (Table II) consistent with the data of Black, *et al.* and Eikard, *et al.* which predict $P\bar{v}_{CO_2}$ thresholds well above this level. Similarly, we did not reach threshold in five of six subjects during halothane-nitrous oxide alone, making it impossible to assess the effect of including nitrous oxide in the anaesthetic mixture in the absence of surgical stimulation. During halothane 1.3 MAC with surgery, all six subjects displayed arrhythmic thresholds (Table II) and, on the basis that these values were significantly less than the combined threshold and sub-threshold values observed during anaesthesia alone, we conclude that surgical stimulation in the presence of halothane enhances carbon dioxide arrhythmogenicity. Whether surgery had a similar effect during halothane-nitrous oxide is not totally clear, as surgery in this group yielded arrhythmic thresholds in only three subjects. However, the thresholds of these three during surgery were less than the corresponding threshold or sub-threshold values during anaesthesia alone (Table II) indicating the possibility of a similar effect.

We have estimated the magnitude of the effect

of surgical stimulation on arrhythmic thresholds by comparing the thresholds we observed during halothane anaesthesia with surgery to the thresholds reported by Eikard, *et al.* for all of their subjects studied during halothane anaesthesia alone.[5] (We were unable to use the data on halothane alone from our study, because a threshold value was identified in only one subject.) The two studies were very similar in terms of anaesthetic technique, halothane dose and rate of induction of the carbon dioxide stimulus. To compare threshold data directly, we converted $P\bar{v}_{CO_2}$ tensions of our study to the estimated corresponding Pa_{CO_2} values.[16] Without surgery, the median Pa_{CO_2} threshold was 13.4 kPa (101 torr), with surgery it was 7.3 kPa (55 torr). Without surgery, individual thresholds ranged from 10.9 to 14.5 kPa (82 to 109 torr); with surgery, from 6.7 to 8.2 kPa (50 to 62 torr). This suggests that surgical stimulation during halothane anaesthesia reduces carbon dioxide arrhythmic thresholds considerably (mean reduction approximately 6 kPa (45 torr)) and reduces them to Pa_{CO_2} values much more likely to be encountered in clinical practise. We believe that this comparison underestimates the potential effect of surgery, since we selected for study periods of surgical stimulation which were relatively quiescent and it was our impression that other periods associated with more potent surgical stimuli would have reduced the threshold even further. In any case, the order of magnitude of surgical effect indicated by this analysis suggests that surgical stimulation is an important factor predisposing to ventricular arrhythmias during halothane anaesthesia in man. The factor of surgery is sufficient to account for the apparent discrepancy between experimental data suggesting a very high critical P_{CO_2} for ventricular arrhythmias during halothane alone[4,5] and the impression gained from clinical practise that only a modest level of hypoventilation is required.

Although we were unable to evaluate the effect of nitrous oxide on thresholds in the absence of surgery, we did observe an effect of nitrous oxide with surgery. The combined threshold and subthreshold values during halothane-nitrous oxide with surgery were significantly greater than thresholds observed during halothane with surgery (Table II), suggesting that in the presence of surgery and hypercarbia, nitrous oxide in the anaesthetic mixture may exert an "anti-arrhythmic" effect.

What is the explanation for these modifying effects of surgery and nitrous oxide on carbon dioxide arrhythmogenicity with halothane? Arrhythmic effects of carbon dioxide during anaesthesia are the result of increased activity of cardiac sympathetic nerves,[21–23] with, perhaps, a contribution from increased levels of circulating adrenal catecholamines,[24] both due apparently to actions of carbon dioxide on reticular fibres of the mid-brain and hind-brain regions.[25,26] Surgical or nociceptive stimuli also activate reticular fibres of the mid-brain and hind-brain[21,27] in a fashion very similar to that of added carbon dioxide[26] and, when sufficiently potent, can themselves evoke ventricular arrhythmias independent of P_{CO_2}[12] through activation of cardiac sympathetic nerves and/or release of adrenal catecholamines.[28] Reticular fibre activation by nociceptive stimuli is greatly magnified by acute hypercapnia.[26] If sympatho-adrenal output behaves similarly, facilitation of carbon dioxide related arrhythmias by surgical stimulation is readily explained. The basis for the protective effect of including nitrous oxide in the anaesthetic is not known: possibilities include a smaller absolute dose of halothane having a lesser "sensitizing" effect and/or an anti-arrhythmic action of nitrous oxide per se which, to our knowledge, has not been described. To investigate these possibilities one would need to determine carbon dioxide thresholds at varying doses of halothane both with and without added nitrous oxide.

In the genesis of ventricular arrhythmias during anaesthesia, the interactive effects of halothane and acute hypercarbia are well-known. The important new observation of this study was that the triad of halothane, hypercarbia and surgery was much more "sensitizing" than halothane and hypercarbia alone. In addition, we observed that including nitrous oxide in the anaesthetic mixture, offered some protection against arrhythmias induced by carbon dioxide.

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ABBREVIATIONS

Pa_{CO_2} – arterial CO_2 tension
$[H^+]a$ – arterial hydrogen ion concentration
$P_{ET_{CO_2}}$ – end-tidal CO_2 tension
$P_{ET_{O_2}}$ – end-tidal O_2 tension
$P\bar{v}_{CO_2}$ – mixed venous CO_2 tension (oxygenated)

H.R. – heart rate
$\overline{B}.\overline{P}.$ – mean blood pressure
S.E.M. – standard error of the mean.

REFERENCES

1. GAUTHIER, J., BOSOMWORTH, P., PAGE, D., MOORE, F. & HAMELBERG, W. Effect of endotracheal intubation on E.C.G. patterns during halothane anesthesia. Anesth. Analg. Curr. Res. *41*: 466 (1962).
2. JONES, R.E., DEUTSCH, S. & TURNDORF, H. Effects of atropine on cardiac rhythm in conscious and anesthetized man. Anesthesiology *22*: 67 (1961).
3. KATZ, R.L. & EPSTEIN, R.A. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. Anesthesiology *29*: 763 (1968).
4. BLACK, G.W., LINDE, H.W., DRIPPS, R.D. & PRICE, H.L. Circulatory changes accompanying respiratory acidosis during halothane (Fluothane) anaesthesia in man. Br. J. Anaesth. *31*: 238 (1959).
5. EIKARD, B. & SKOVSTED, P. Effects of respiratory acidosis on the arrhythmia threshold during fluroxene and halothane anaesthesia. Acta Anaesth. Scand. *19*: 120 (1975).
6. GREGORY, G.A., EGER, E.I. & MUNSON, E.S. The relationship between age and halothane requirements in man. Anesthesiology *30*: 488 (1961).
7. QUASHA, A.L., EGER, E.I. & TINKER, J.H. Determination and applications of MAC. Anesthesiology *53*: 315 (1980).
8. COOPER, E.A. & SMITH, N. Indirect estimation of arterial P_{CO_2}. Anaesthesia *16*: 445 (1961).
9. READ, D.J.C. A clinical method for assessing the ventilatory response to carbon dioxide. Australas. Ann. Med. *16*: 20 (1967).
10. REBUCK, A.S. Measurement of ventilatory response to CO_2 by rebreathing. Chest Suppl. *1*: 118 (1976).
11. PRICE, H.L., LURIE, A.A., BLACK, G.W., SECHZER, P.H., LINDE, H.W. & PRICE, M.L. Modification by general anaesthetics (cyclopropane and halothane) of circulatory and sympathoadrenal responses to respiratory acidosis. Annals of Surgery *152*: 1071 (1960).
12. JOHNSTONE, M. & NISBET, H.I.A. Ventricular arrhythmia during halothane anaesthesia. Br. J. Anaesth. *33*: 9 (1961).
13. LAM, A.M., CLEMENT, J.L. & KNILL, R.L. Surgical stimulation does not enhance ventilatory chemoreflexes during enflurane anaesthesia in man. Canad. Anaesth. Soc. J. *27*: 22 (1980).
14. READ, D.J.C. & LEIGH, J. Blood-brain tissue P_{CO_2} relationships and ventilation during rebreathing. J. Appl. Physiol. *23*: 53 (1967).
15. LURIE, A.A., JONES, R.E., LINDE, H.W., PRICE, M.L., DRIPPS, R.D. & PRICE, H.L. Cyclopropane anaesthesia. I: Cardiac rate and rhythm during steady levels of cyclopropane anaesthesia at normal and elevated end-expiratory carbon dioxide tensions. Anesthesiology *19*: 457 (1958).
16. MCEVOY, J.D.S., JONES, N.L. & CAMPBELL, E.J.M. Mixed venous and arterial P_{CO_2}. Br. Med. J. *4*: 687 (1974).
17. HORNBEIN, T.F., MARTIN, W.E., BONICA, J.J., FREUND, F.G. & PARAMENTIER, P. Nitrous oxide effects on the circulation and ventilatory responses to halothane. Anesthesiology *31*: 250 (1969).
18. SMITH, N.T., EGER, E.I., STOELTING, R.K., WHAYNE, T.F., CULLEN, D. & KADIS, L.B. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology *32*: 410 (1970).
19. HILL, G.E., ENGLISH, J.E., LUNN, J., STANLEY, T.H., SENTKER, G.R., LOESER, E., LIU, W.S., KAWAMURA, R., BIDWAI, A.V. & HODGES, M. Cardiovascular responses to nitrous oxide during light, moderate and deep halothane anesthesia in man. Anesth. Analg. *57*: 84 (1978).
20. MANNINEN, P. & KNILL, R.L. Cardiovascular signs of acute hypoxaemia and hypercarbia during enflurane and halothane anaesthesia in man. Canad. Anaesth. Soc. J. *26*: 282 (1979).
21. PRICE, H.L. Effects of carbon dioxide on the cardiovascular system. Anesthesiology *21*: 652 (1960).
22. PRICE, H.L., LURIE, A.A., JONES, R.E., PRICE, M.L. & LINDE, H.W. Cyclopropane anesthesia: Epinephrine and norepinephrine in initiation of ventricular arrhythmias by carbon dioxide inhalation. Anesthesiology *19*: 619 (1958).
23. KATZ, R.L. Neural factors affecting cardiac arrhythmias induced by halopropane. J. Pharmacol. Exp. Ther. *152*: 88 (1966).
24. MILLAR, R.A. & MORRIS, M.E. Norepinephrine release during respiratory acidosis in adrenalectomized dogs. Anesthesiology *22*: 62 (1961).
25. DELL, P & BONVELLET, M. Contrôle direct et réflex de l'activité du système réticulé activateur ascendent du trône cérébrale par l'oxygène et le gas carbonique de sang. C.r. Soc. Biol. Paris *148*: 855 (1954).
26. GELLHORN, E. On the physiological action of carbon dioxide on the cortex and hypothalamus. Electroenceph. & Clin. Neurophysiol. *5*: 401 (1953).
27. CASEY, K.L. Somatosensory responses of bulboreticular units in awake cats. Science *173*: 77 (1971).
28. BROW, G.R., LONG, C.L.H. & BEATTIE, J. Irregularities of the heart under chloroform. J. Amer. Med. Assoc. *95*: 715 (1930).

RÉSUMÉ

Nous avons étudié les niveaux d'hypercarbie susceptibles de causer des extrasystoles ventriculaires sur un groupe de six sujets anesthésiés à l'halothane à la concentration de 1.3 MAC et sur un autre groupe de six sujets anesthésiés avec un mélange équivalent à 1.3 MAC comprenant halothane et protoxyde d'azote avant et pendant une chirurgie réglée. L'hypercarbie fut induite progressivement par "rebreathing" total à une valeur de $P\bar{v}_{CO_2}$ maximale d'environ 11.0 kPa (83 torr). On a adopté comme seuil arrythmique les premières atteintes valeurs de $P\bar{v}_{CO_2}$ au cours desquelles les extrasystoles ventriculaires ont fait leurs apparitions.

Pendant l'anesthésie seule, dans les deux groupes, les seuils arrythmiques furent atteints dans seulement un des six sujets et les seuils médians de $P\bar{v}_{CO_2}$ ont été alors plus élevés que 11.0 kPa (83 torr). Lors de l'anesthésie à l'halothane pendant la chirurgie, les seuils anesthésiques furent observés chez tous les sujets et la valeur médiane a été de 9.1 kPa (68 torr). Lors de l'anesthésie à l'halothane-protoxyde d'azote administré pendant la chirurgie, les seuils ont été atteints dans trois des six sujets et la médiane a été plus élevée que 10.7 kPa (80 torr). Les seuils obtenus pendant l'anesthésie à l'halothane avec chirurgie furent moins élevés de façon significative que le seuil où les valeurs maximales de $P\bar{v}_{CO_2}$ observé dans chacun des trois autres états ($p < 0.05$). Ces résultats montrent que pendant l'anesthésie à l'halothane la stimulation chirurgicale augmente de façon marquée les effets arrythmogéniques causés par l'addition de gaz carbonique et que pendant la chirurgie un mélange protoxyde d'azote-halothane est moins sensibilisant qu'une dose équipotente d'halothane seule.