CARDIOVASCULAR AND RESPIRATORY RESPONSES TO SEVERE HYPOXAEMIA UNDER ANAESTHESIA

II. Spontaneous and Controlled Ventilation During Methoxyflurane Anaesthesia

I.G. GRAY, M.D., F.F.A.R.C.S., H.I.A. NISBET, M.B., CH.B., F.F.A.R.C.S., F.R.C.P.(C),
P.M. OLLEY, M.B., B.S., M.R.C.P.(Lond.), F.R.C.P.(C),
B.E. WELSH, B.SC., M.B., B.S., D.A., F.F.A.R.C.S., AND
A.E. JOHNSTON, M.D., F.R.C.P.(C), with the technical assistance of G. VOLGYESI

THE EFFECT of varying depths of anaesthesia upon the cardio-respiratory response to severe arterial hypoxaemia has received little attention despite its relevance to clinical practice; the response to hypoxaemia under methoxyflurane has not been studied at all. This agent has been used to induce anaesthesia at concentrations[1] which may cause laryngospasm, to maintain anaesthesia for tonsillectomy[2] where upper airway obstruction is a possibility, and is considered particularly suitable for patients with cardiac disease.[3] In all these circumstances patients may inadvertently be exposed to hypoxaemia at various depths of methoxyflurane anaesthesia, yet our knowledge of the response is limited to the tentative suggestion that myocardial depression may result.[4] The present report concerns the cardiorespiratory effects of severe arterial hypoxaemia in dogs under methoxyflurane anaesthesia at various depths.

The circulatory response to hypoxaemia represents the resultant of direct cardiac-depressant effects and opposing reflex and humorally-mediated alterations in heart rate, vasomotor tone and cardiac contractility.[5] In anaesthetized dogs the nature of the response has been found to vary with the type of ventilation permitted. Numerous reports[6–9] have indicated that if ventilation is controlled, the response is dominated by carotid chemoreceptor stimulation which produces a fall in heart rate, a rise in total systemic vascular resistance and a fall or no change in cardiac output. Such a response, with its deleterious effect upon oxygen transport, would be undesirable in anaesthetized patients.

Since these problems cannot be investigated in patients, a study has been made of the effect of severe arterial hypoxaemia both in spontaneously breathing and artificially ventilated dogs at three different depths of methoxyflurane anaesthesia.

From the Departments of Anaesthesia and Cardiology, The Research Institute, The Hospital for Sick Children, and the Departments of Anaesthesia and Paediatrics, University of Toronto, Toronto, Ontario, Canada.

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Reprint address: Dr. H.I.A. Nisbet, Department of Anaesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto, M5G 1X8.

TABLE I

THE EFFECT OF HYPOXAEMIA ON RESPIRATORY FUNCTION IN SPONTANEOUSLY BREATHING DOGS ANAESTHETIZED WITH METHOXYFLURANE

		0.30% ETM		0.45% ETM		0.60% ETM	
		C*	H†	C	H	C	H
PaO_2, mmHg	Mean	72.00	26.40	70.00	29.80	70.00	21.50
	SD	5.80	3.90	4.00	2.90	7.00	1.50
	P	<0.001		<0.001		<0.001	
$PaCO_2$, mmHg	Mean	41.80	34.80	44.70	35.20	40.20	32.30
	SD	6.30	4.60	9.00	9.00	0.75	2.30
	p	<0.001		<0.01		<0.001	
pH	Mean	7.36	7.41	7.26	7.32	7.33	7.38
	SD	0.05	0.06	0.08	0.09	0.04	0.02
	p	<0.001		<0.005		<0.005	
f, per min	Mean	13.30	26.80	13.40	25.00	20.60	44.20
	SD	5.60	9.80	5.10	9.80	6.70	15.60
	p	<0.001		<0.01		<0.001	
$\dot{V}E$, ml	Mean	1522	2765	1271	2749	1601	3143
	SD	329	871	456	1014	240	788
	p	<0.005		<0.01		<0.005	
VT, ml	Mean	127.0	106.5	95.70	113.6	81.40	71.50
	SD	31.9	24.7	14.50	29.0	18.80	10.60
	p	ns		ns		ns	
$\dot{V}A$, ml	Mean	840	1237	744	1504	865	1316
	SD	216	349	309	582	107	320
	p	<0.005		<0.01		<0.01	
VD/VT	Mean	0.44	0.53	0.42	0.44	0.45	0.58
	SD	0.09	0.14	0.11	0.16	0.09	0.07
	p	<0.02		ns		<0.01	
A-aDO_2, mmHg	Mean	25.10	11.20	20.60	15.80	23.10	14.60
	SD	8.30	7.30	12.70	9.90	7.60	4.10
	p	<0.005		ns		ns	
$\dot{V}O_2$, ml	Mean	51.20	48.90	49.20	41.30	56.40	47.50
	SD	9.70	13.50	9.30	7.20	6.70	12.20
	p	ns		ns		ns	
$\dot{V}co_2$, ml	Mean	39.70	48.90	36.75	57.20	40.20	49.40
	SD	5.50	9.90	10.60	13.00	4.90	10.90
	p	<0.01		<0.001		<0.025	
R	Mean	0.78	1.02	0.73	1.39	0.73	1.06
	SD	0.10	0.22	0.08	0.25	0.13	0.1
	p	<0.05		<0.005		<0.01	

*Values during control period.
†Values during hypoxaemic period.

METHOD

Beagle dogs (10–12 kg in weight) were anaesthetized with a sleep dose of barbiturate and intubated with a cuffed tracheal tube. Anaesthesia was maintained with methoxyflurane at end-tidal concentrations (%ETM) of 0.3 per cent*, 0.45 per cent† and 0.6 per cent‡, representing minimal alveolar concentrations (MAC) of 1.3, 1.9 and 2.5 respectively, according to the data of Regan and Eger.[10]

*Light anaesthesia.
†Moderately deep anaesthesia.
‡Deep anaesthesia.

The dogs were divided into two groups; one group was allowed to breathe spontaneously. In this group seven dogs were under light anaesthesia, five were under moderate anaesthesia, and six were under deep anaesthesia.

The second group was ventilated by a Harvard pump in such a manner as to maintain $PaCO_2$ values within normal limits. In this group 14 dogs were under light anaesthesia, 12 were under moderate anaesthesia, and 13 were under deep anaesthesia.

Under fluoroscopy, catheters were placed in the aorta and the right atrium of each dog. After anaesthesia had been maintained at the appropriate depth for at least one hour, we measured the cardiac output ($\dot{Q}$) by dye dilution, the mean aortic blood pressure (MABP) and the heart rate (HR). Arterial oxygen tension (PaO_2), carbon dioxide tension ($PaCO_2$) and pH were measured and the results corrected for changes in the temperature of the dog as measured by a rectal thermocouple. Temperature changes were minimized by placing the dog on a heated blanket. End-tidal samples of gas were collected from the trachea and the concentrations of methoxyflurane measured by means of a calibrated Ohio gas analyser*. In the spontaneously breathing dogs minute volume ($\dot{V}E$) and respiratory rate (f) were measured, and expired gas was collected and analysed for oxygen and carbon dioxide contents. All these measurements are reported as control (C) throughout the paper.

After the measurements were completed, hypoxaemia was induced by substituting an appropriate mixture of oxygen and nitrogen for the air in the inspired gas mixture. The dogs were subjected to this for 20 minutes until PaO_2 values were close to 30 mmHg, when we repeated all the measurements (hypoxaemia values, H).

From the collected data we determined the response to hypoxaemia as seen in cardiac output, heart rate, mean aortic blood pressure, minute volume, respiratory rate and tidal volume (VT). We calculated the corresponding changes in stroke volume (SV), total systemic vascular resistance (TSVR), oxygen transport (TaO_2), oxygen uptake ($\dot{V}O_2$), carbon dioxide elimination ($\dot{V}_{CO_2}$), alveolar ventilation ($\dot{V}A$), dead space to tidal volume ratio (VD/VT), respiratory exchange ratio (R), and alveolar to arterial oxygen tension gradient ($A\text{-}aDO_2$).

The significance of these changes was assessed by means of a paired t-test.

Results

Respiratory responses to hypoxaemia

At all depths of anaesthesia in the spontaneously breathing dogs (Table I) there were similar and significant changes in pH and blood gas values during hypoxaemia although control values for pH were lower and control values for $PaCO_2$ were higher at 0.45 per cent ETM than at the other ETM values. $\dot{V}E$ rose significantly at all depths of anaesthesia; at 0.6 per cent ETM the rise in respiratory rate and the fall in PaO_2 were greater than at the other ETM values; under light and deep anaesthesia VT fell, but not significantly, although VD/VT was significantly increased. The decrease in $A\text{-}aDO_2$ during hypoxaemia at each depth of anaesthesia

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TABLE II

THE EFFECT OF HYPOXAEMIA ON BLOOD GASES AND pH IN VENTILATED DOGS ANAESTHETIZED WITH METHOXYFLURANE

		0.30% ETM		0.45% ETM		0.60% ETM	
		C*	H†	C	H	C	H
PaO_2, mmHg	Mean	80.00	29.00	83.00	34.70	75.00	25.40
	SD	17.60	6.80	3.80	2.30	3.90	2.30
	p	<0.001		<0.001		<0.001	
$PaCO_2$, mmHg	Mean	36.00	38.00	41.00	40.50	35.40	33.10
	SD	2.00	2.00	2.80	4.30	2.80	3.60
	p	ns		ns		ns	
pH	Mean	7.35	7.33	7.34	7.35	7.36	7.37
	SD	0.04	0.04	0.04	0.04	0.04	0.04
	p	ns		ns		ns	

*Values during control period.
†Values during hypoxaemic period.

was only significant in the lightly anaesthetized dogs. The decreases in $\dot{V}O_2$ accompanying hypoxaemia at each depth of anaesthesia were not significant, although the increases in both $\dot{V}_{CO_2}$ and R were.

All the dogs allowed to breathe spontaneously survived the exposure to hypoxaemia.

In the ventilated dogs no significant changes were measured in pH or $PaCO_2$ during hypoxaemia. The fall in PaO_2 was of similar magnitude to that in the spontaneously breathing dogs, although mean values during hypoxaemia were slightly higher at all depths of anaesthesia (Table II).

Cardiovascular responses to hypoxaemia

The cardiovascular responses to hypoxaemia in spontaneously breathing and artificially ventilated dogs are compared in Table III. A rise in $\dot{Q}$ was measured in each group but in the deeply anaesthetized ventilated group the rise was smaller and insignificant.

Small insignificant changes in TaO_2 were measured in both groups of dogs under light and moderately deep anaesthesia. With deep anaesthesia larger falls in TaO_2 occurred; the greatest reduction was measured in the spontaneously breathing dogs, in whom mean values for PaO_2 were very low.

HR and SV increased in all groups of dogs but under deep anaesthesia the changes in SV were small and insignificant both during spontaneous breathing and artificial ventilation. Significant falls in TSVR occurred only at light and moderate depths of anaesthesia.

DISCUSSION

(a) Respiratory changes

The large increase in minute volume in spontaneously breathing dogs during hypoxaemia at all depths of methoxyflurane anaesthesia was almost entirely attributable to an increase in respiratory rate and was similar to that found by Cullen and Eger[11] using halothane.

TABLE III

COMPARISON BETWEEN THE CARDIOVASCULAR EFFECTS OF HYPOXAEMIA ON SPONTANEOUSLY BREATHING (SB) AND VENTILATED (IPPV) DOGS, BOTH GROUPS ANAESTHETIZED WITH METHOXYFLURANE

		0.30% ETM				0.45% ETM				0.60% ETM			
		IPPV		SB		IPPV		SB		IPPV		SB	
		C*	H†	C	H	C	H	C	H	C	H	C	H
Q, L/min	Mean	1.80	2.80	1.49	2.32	1.37	2.33	1.72	2.48	1.54	1.96	1.91	2.58
	SD	0.47	0.54	0.29	0.53	0.26	0.79	0.53	0.65	0.20	0.74	0.10	0.19
	p	<0.001		<0.01		<0.01		<0.02		ns		<0.001	
TaO_2, ml/min	Mean	320	295	274	247	222	269	288	282	238	170	309	199
	SD	92	90	36	47	35	83	66	118	40	68.8	26	32
	p	ns		ns		ns		ns		ns		<0.001	
HR/per min	Mean	115	142	129	158	154	163	156	170	129	155	150	179
	SD	16	22	11	12	15	18	27	22	19	23.4	6	23
	p	<0.005		<0.005		ns		ns		ns		<0.02	
SV, ml	Mean	16.20	20.20	11.80	14.70	8.80	13.70	11.45	15.00	12.00	12.40	12.80	14.70
	SD	4.90	5.50	3.00	3.10	1.40	2.90	4.40	5.66	1.40	4.00	1.20	2.90
	p	<0.01		<0.001		<0.005		ns		ns		ns	
MABP, mmHg	Mean	104	120	120	132	97	121	124	122	74	92	103	125
	SD	16	17	10.7	21.8	21	23	17.8	34.6	17	32	25	34
	p	<0.02		ns		<0.025		ns		ns		<0.05	
TSVR (dynes cm^{-5})	Mean	4709	3496	6725	4742	5895	4563	6235	4100	3144	3899	4323	3889
	SD	1157	742	1722	1689	1745	1491	2223	1387	1168	830	1063	1018
	p	<0.001		<0.001		<0.05		<0.025		ns		ns	

*Values during control period.
†Values during hypoxaemic period.

The fall in oxygen uptake was minimal (4 per cent) with 0.3 per cent ETM but larger (16 per cent) with the higher concentrations. This result was similar to that reported by Schuurmans-Stekhoven and Kreuzer[12] in dogs anaesthetized with pentobarbitone and subjected to a similar degree of hypoxaemia. On the other hand, with halothane anaesthesia, a rise of 130–180 per cent during hypoxaemia has been reported.[11]

Suwa *et al.*[13] have found that low VD/VT ratios are associated with a high cardiac output and pulmonary artery pressure (PAP). Since both $\dot{Q}$ and presumably PAP are increased during hypoxaemia under methoxyflurane anaesthesia it was surprising to find an increase in the VD/VT ratio, with both 0.3 per cent and 0.6 per cent ETM, indicating that a greater part of the increased minute ventilation was wasted. The increase in VD/VT may be explained by the fall in tidal volume.

Bronchoconstriction resulting from the decrease in P_{CO_2} together with the increased respiratory rate could have caused a disadvantageous redistribution of inspired gas.

The fall in A-aDO_2 in the lightly anaesthetized dogs was similar to that reported by others[12] in dogs under barbiturate anaesthesia.

Although PaO_2 tensions reached fairly constant levels after 10 minutes hypoxaemia, the changes in $\dot{V}_{CO_2}$ and R indicate that a longer period is necessary before a steady state for $\dot{V}_{CO_2}$ is reached.

(b) Cardiovascular response

With halothane, at end-tidal concentrations of 0.75 per cent, 1.0 per cent and 1.25 per cent, Cullen and Eger[11] reported similar but more variable responses to hypoxaemia during light anaesthesia: cardiac and respiratory arrest occurred early in some dogs even with low concentrations of halothane. We did not have this complication either in the present or in our related experiments,[14] possibly because our experimental design was different. Cullen and Eger subjected each dog to moderate and severe hypoxaemia at varying depths of anaesthesia; probably their animals were under more stress than ours. The chemoreceptor response to hypoxaemia in animals under intravenous pentobarbitone or chloralose anaesthesia is primarily depressant[7,8,15] – heart rate falls and total systemic vascular resistance increases. Interestingly, Downing *et al.*[16] have shown that tachycardia never results from local perfusion of the carotid bodies with hypoxic blood. Daly and Scott[8,15] have found that the chemoreceptor response is modified by increased ventilation in spontaneously breathing dogs unless the lungs are denervated. Kontos *et al.*[17] have reported that, unless atropine is given, artificial ventilation prevents the increases in heart rate and cardiac output seen in spontaneously breathing hypoxaemic dogs. Similar results have been reported by Jones *et al.*[9] but Krasney[18] obtained a dramatic increase in heart rate in ventilated dogs subjected to severe hypoxaemia. Kontos *et al.* have suggested that the anaesthetic technique used may modify the response.[17]

Humoral mechanisms may reverse the depressant reflex chemoreceptor response to hypoxaemia; these are diminished or abolished by adrenalectomy and splanchnicectomy.[19]

The response of the myocardium itself is surprisingly well maintained even

during severe hypoxaemia and the cause of death is usually extra-cardiac.[20] Oxygen tensions of 15–40 mmHg are associated with increased contractility in isolated hearts[20] which do not fail until PO_2 values are below 20 mmHg.[21]

Our results with hypoxaemia during light anaesthesia suggest that humoral or other activity overrides the depressant effect of chemoreceptor stimulation, both in spontaneously and artificially ventilated dogs. Nisbet *et al.*[14] have reported a similar response during artificial ventilation with light halothane and trichlorethylene.

The results with hypoxaemia during deep anaesthesia resemble the results obtained by Kontos *et al.*[17] under IPPV, and at first sight might suggest that with deep anaesthesia the chemoreceptor response is more active. However, since at this level of anaesthesia during artificial ventilation the rises in HR and mean $\dot{Q}$ were appreciable if insignificant, it is probable that this apparent similarity between the two series of investigations would cease to exist if the numbers of animals were larger.

There is evidence that the response of both baroreceptors[22] and chemoreceptors[23] is depressed during anaesthesia and it would be surprising if the deepest anaesthesia in our experiment was associated with increased chemoreceptor response.

The sympathetic response on the other hand, may well be depressed during deep anaesthesia,[24] and Eisele *et al.*[25] have shown that anaesthetics produce immediate cardiac depression. Some dogs investigated under deep anaesthesia with methoxyflurane and with other agents[14] have suffered cardiovascular collapse at levels of arterial oxygen tension well above the 15–20 mmHg which result in myocardial failure in the isolated heart. From this it appears likely that direct myocardial depression and diminished sympathetic activity are responsible for the diminished cardiovascular response under deep anaesthesia.

Conclusions

We conclude that the deepest anaesthesia used in these investigations does not interfere with the respiratory signs of hypoxaemia and that at this depth the recognition of hypoxaemia in clinical circumstances is facilitated if respiration is not controlled. While rises in heart and blood pressure do occur in both spontaneously breathing and artificially ventilated dogs, in deep anaesthesia these responses to hypoxaemia are more variable and are therefore less reliable clinical signs of hypoxaemia.

With light and moderately deep methoxyflurane anaesthesia oxygen transport is maintained near control values during hypoxaemia and the cardiovascular responses probably are effective in preventing tissue hypoxaemia. This is less likely to be true with deep anaesthesia.

Summary

The response to hypoxaemia under methoxyflurane has not hitherto been studied although this agent is used in situations where the risk of hypoxaemia is not remote. The present investigations concern the respiratory and cardiovascular

effects of severe arterial hypoxaemia in both spontaneously breathing and artificially ventilated dogs under methoxyflurane anaesthesia at various depths (0.3 per cent, 0.45 per cent, 0.6 per cent ETM).

In the spontaneously breathing dogs even under deep anaesthesia with methoxyflurane the respiratory response to hypoxaemia was well maintained, mainly because of a rise in respiratory rate. Tidal volume decreased during hypoxaemia and this may have contributed to an increase in dead space to tidal volume ratio. Significant reduction of the alveolar to arterial oxygen tension gradient was only observed in the lightly anaesthetized dogs.

In both spontaneously breathing and artificially ventilated dogs under light and moderately deep anaesthesia cardiac output increased significantly when they were subjected to similar degrees of hypoxaemia. A smaller and insignificant rise in cardiac output in the artificially ventilated dogs under deep anaesthesia contrasted with the large rise in the spontaneously breathing group. In spite of this rise in cardiac output a significant fall in oxygen transport during hypoxaemia was measured in the spontaneously breathing group, in which PaO_2 values were very low. Oxygen transport was not significantly changed during hypoxaemia in the other groups of dogs, although the amount of oxygen carried was lower in those deeply anaesthetized.

Heart rate and stroke volume increased in all groups of dogs during hypoxaemia but under deep anaesthesia the increase in stroke volume was small and insignificant. Total systemic vascular resistance fell only at light and moderate depths of anaesthesia.

We conclude that the deepest anaesthesia used in these investigations does not interfere with the respiratory signs of hypoxaemia and that at this depth the recognition of hypoxaemia in clinical circumstances is facilitated if respiration is not controlled. While rises in heart and blood pressure do occur in both spontaneously breathing and artificially ventilated dogs, in deep anaesthesia these responses to hypoxaemia are more variable and are therefore less reliable clinical signs of hypoxaemia.

With light and moderately deep methoxyflurane anaesthesia oxygen transport is maintained near control values during hypoxaemia and the cardiovascular responses are effective in preventing tissue hypoxaemia. This is less likely to be true with deep anaesthesia.

Résumé

La réponse à l'hypoxhémie sous anesthésie au méthoxyflurane n'a pas encore été étudiée bien que cet agent soit utilisé dans des circonstances où le risque d'hypoxhémie n'est pas éloigné. Les études actuelles ont porté sur les effets respiratoirs et cardiovasculaires de l'hypoxhémie artérielle grave chez des chiens, sous ventilation spontanée et sous ventilation artificielle, soumis à une anesthésie au méthoxyflurane à différents niveaux (0.3 pour cent, 0.45 pour cent, 0.6 pour cent ETM).

Chez les chiens sous ventilation spontanée, même sous anesthésie profonde au méthoxyflurane, la réponse respiratoire a l'hypoxhémie s'est bien maintenue, prin-

cipalement à cause d'une élévation de la fréquence respiratoire. L'air courant a diminué durant l'hypoxhémie et cela peut avoir participé à une augmentation du rapport : espace mort/air courant. Une diminution importante de la différence de pression d'oxygène alvéolaire et artérielle a été notée chez les chiens soumis à une anesthésie légère.

Aussi bien chez les chiens sous ventilation spontanée que chez les chiens sous ventilation artificielle soumis à une anesthésie superficielle ou à une anesthésie plus profonde, le débit cardiaque a augmenté de façon importante lorsqu'ils furent soumis à des degrés semblables d'hypoxhémie. Nous avons observé une plus petite et non significative élévation du débit cardiaque chez les chiens sous ventilation artificielle et soumis à une anesthésie profonde comparée à l'élévation considérable observée chez les chiens sous ventilation spontanée. En dépit de cette élévation du débit cardiaque, une chute importante dans le transport de l'oxygène durant l'hypoxhémie a été mesurée chez les chiens du groupe sous ventilation spontanée, chez qui les valeurs de la PaO_2 étaient très basses. Le transport de l'oxygène n'était pas changé de façon significative durant l'hypoxhémie chez les autres groupes de chiens, bien que la quantité d'oxygène transportée était inférieure chez les sujets sous anesthésie profonde.

La fréquence cardiaque et le volume systolique ont augmenté chez les chiens de tous les groupes durant l'hypoxhémie, mais sous anesthésie profonde, l'augmentation du volume systolique était faible et non significative. La résistance vasculaire systémique totale a diminué seulement sous anesthésie légère et modérée.

Nous concluons que l'anesthésie la plus profonde employée au cours de cette étude ne modifie pas les signes respiratoires de l'hypoxhémie et que, à cette profondeur d'anesthésie, le dépistage de l'hypoxhémie, dans des circonstances cliniques, est plus facile si la ventilation n'est pas contrôlée. Alors que l'élévation de la fréquence cardiaque et de la tension artérielle n'apparait pas chez les chiens sous ventilation spontanée et sous ventilation artificielle, sous anesthésie profonde, ces réponses à l'hypoxhémie sont plus variables et, en conséquence, moins fiables comme signes cliniques d'hypoxhémie.

Sous anesthésie légère et modérée au méthoxyflurane le transport de l'oxygène se maintient près des valeurs de contrôle durant l'hypoxhémie et les réponses cardiovasculaires sont efficaces pour prévenir l'hypoxhémie tissulaire. Cela ne semble pas aussi vrai sous anesthésie profonde.

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