**EPINEPHRINE-INDUCED DYSRHYTHMIAS:
COMPARISON DURING ANAESTHESIA WITH NARCOTICS AND WITH HALOGENATED
INHALATION AGENTS IN DOGS**

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IT IS GENERALLY BELIEVED that the use of a narcotic-nitrous oxide-muscle relaxant technique, popularly known as "balanced anaesthesia", is better tolerated by patients with labile cardiovascular function than is general anaesthesia with halogenated inhalation agents, nitrous oxide and muscle relaxants. Epinephrine-induced cardiac dysrhythmias have been widely studied with halogenated inhalation agents and oxygen as the anaesthetic regimen,¹⁻⁵ without the addition of nitrous oxide, which is a frequent adjunct in clinical anaesthesia. The purpose of this study was to evaluate the arrhythmogenicity of epinephrine in dogs anaesthetized with morphine, fentanyl or meperidine with nitrous oxide and pancuronium and to compare this with a second group of animals anaesthetized with halothane, enflurane or methoxyflurane with nitrous oxide and pancuronium.

METHOD

In sixteen mongrel dogs weighing 15–20 kg anaesthesia was induced with intravenous thiopentone 15–20 mg·kg⁻¹ to facilitate tracheal intubation and the lungs were ventilated mechanically to maintain a P_{aCO_2} of 4.6–5.33 kPa (35–40 torr). Eight animals in Group 1 received 1.2 MAC halothane (1.0 per cent), enflurane (2.6 per cent) or methoxyflurane (0.28 per cent) in 50 per cent nitrous oxide with oxygen at a flow rate of five litres per minute, according to the MAC concentrations of these anaesthetics reported by Eger.⁶ The end tidal PCO_2 , halothane and enflurane were measured continuously by Beckman Infra-red Analyzers. Eight animals in Group

two received two intravenous doses of each narcotic administered 60 minutes apart: morphine 1 and 2 mg·kg⁻¹, fentanyl 0.01 and 0.02 mg·kg⁻¹ and meperidine 10 and 20 mg·kg⁻¹, also with an inspired gas mixture of nitrous oxide 50 per cent with oxygen. Both groups received intravenous pancuronium 0.2 mg·kg⁻¹. Each animal in Group 1 or Group 2 was studied three times, but only once a week and one anaesthetic regimen per study. The order of administration of the anaesthetic regimen was randomized for both groups.

Lead II of the electrocardiogram, oesophageal temperature and arterial pressure were monitored continuously. Oesophageal temperature was maintained at $37 \pm 1^\circ\text{C}$ throughout the study. Heating pads were used when necessary. The arterial pressure was taken from a two-inch catheter inserted percutaneously into the femoral artery from which blood gases and serum sodium (Na) and potassium (K) were determined before epinephrine infusion when the preparation was stabilized, during the peak pressure response from epinephrine infusion and every 30 minutes for the rest of the experiment. Five per cent dextrose in lactated Ringer's solution was infused to maintain a mean arterial pressure of 10.66 ± 1.33 kPa (80 ± 10 torr) during the anaesthetic course. This varied from 7 to 22 ml/kg with a mean of 12 ml/kg. When the preparation became stable in 30–45 minutes, epinephrine 5 µg/ml was infused at a rate of 1 µg·kg⁻¹·min⁻¹ up to ten minutes, with a Harvard syringe pump. In eight of 24 experiments in Group 1 the epinephrine infusion was stopped after about five minutes because of the development of ventricular tachycardia (VT) or ventricular fibrillation (VF). All but one of the 48 epinephrine infusions in Group 2 went to completion with a total of 10 µg·kg⁻¹·min⁻¹⁰ (see RESULTS). The occurrence of three or more consecutive dysrhythmic beats was used as the endpoint of the epinephrine arrhythmogenic dose.

Statistical comparisons were made using the Student's *t*-test for paired and unpaired data. *P* values less than 0.05 were considered significant.

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RESULTS

The peak mean arterial blood pressure increases from epinephrine infusion in all treatment groups varied from 6.6–10.66 kPa (50–80 torr) and were not significantly different among groups. However, the mean arterial blood pressures of animals anaesthetized with meperidine-nitrous oxide-pancuronium, before epinephrine infusion, were generally 1.33–4.0 kPa (10–30 torr) lower than the animals anaesthetized by the other regimen; therefore, larger quantities (15–20 ml/kg) of 5 per cent dextrose in lactated Ringer's solution were infused to maintain the mean arterial pressure of 10.66 kPa (80 torr).

Arterial blood gases showed minimal changes in both groups, and there were no significant differences among groups during the course of the experiment. The pooled values ($N = 216$, mean $\pm$ SD) were P_{aO_2} 24 ± 2.13 kPa (180 $\pm$ 16 torr), P_{aCO_2} 4.8 ± 0.4 kPa (36 $\pm$ 3 torr) and cH^+ 43.65 ± 0.14 nmol/l (pH 7.36 ± 0.07). Control serum sodium was 142 ± 5 mmol/l and serum potassium was 4.1 ± 0.3 mmol/l. Serum sodium did not change significantly during the course of the experiments, but serum potassium increased to a peak concentration of 6.5 ± 0.4 mmol/l at 4.3 ± 1.2 minutes following the infusion of epinephrine (4.3 ± 0.9 $\mu\text{g}\cdot\text{kg}^{-1}$). The peak serum potassium changes were not significantly different among groups during the epinephrine infusion.

The dose of epinephrine that induced dysrhythmias during narcotic-nitrous oxide anaesthesia is summarized in Table I. The arrhythmogenic dose tended to be higher for morphine in comparison with fentanyl or meperidine, but not statistically significant. We were not able to demonstrate a dose-response relationship at the doses studied. The ventricular dysrhythmia dose was generally higher than the corresponding supraventricular dose for each anaesthetic regimen. Out of 48 epinephrine challenges in the eight dogs anaesthetized with narcotics and nitrous oxide ventricular tachycardia was observed only once during fentanyl-nitrous oxide anaesthesia (Table I).

The dose of epinephrine that induced dysrhythmias during anaesthesia with the halogenated agents and nitrous oxide is summarized in Table II. There was no significant difference between the arrhythmogenic doses among the halogenated agents studied. The ventricular dysrhythmic doses were generally higher than their corresponding supraventricular dysrhythmic doses during the same anaesthetic regimen. The

incidence of ventricular dysrhythmias was less during methoxyflurane-nitrous oxide anaesthesia (4/8) than with halothane-nitrous oxide (8/8) and enflurane-nitrous oxide (8/8) anaesthesia (Table II). The ventricular dysrhythmias observed during halothane-nitrous oxide or enflurane-nitrous oxide anaesthesia were multifocal and associated with bigeminy to quadrigeminy, whereas those observed during methoxyflurane-nitrous oxide were usually unifocal dispersed with bigeminy only. The arrhythmogenic doses in the halogenated anaesthesia groups were significantly higher than in the narcotic anaesthesia groups; however, the incidence of ventricular dysrhythmias was greater in the halogenated anaesthesia groups (20/24 vs 20/48). Ventricular tachycardia and/or ventricular fibrillation occurred in five out of eight epinephrine challenges in the halothane group, three out of eight in the enflurane group and in none of the eight in the methoxyflurane-nitrous oxide group (Table II).

DISCUSSION

Intravenous epinephrine was first used as a method of inducing cardiac dysrhythmias in dogs in the classic publication of Meek, *et al.* in 1937.¹ More recently, others have used the appearance of ventricular extrasystoles as the end point following incremental doses of epinephrine.²⁻⁴ The use of epinephrine for evaluating the arrhythmogenic potential of anaesthetics is clinically meaningful because intraoperative cardiac dysrhythmias are frequently associated with imbalance of the autonomic nervous system, usually a preponderance of sympathetic activity, and epinephrine is still commonly used to reduce surgical bleeding.

Factors⁵ which are known to potentiate catecholamine-induced cardiac dysrhythmias are hypoxia, hypercarbia, hypertension and electrolyte imbalance, especially hyper- or hypokalaemia.⁷ The arterial blood gases obtained during this study would tend to eliminate hypoxia and hypercarbia as contributing factors. Hypertension during epinephrine infusion was not controlled in our study, but blood pressure elevations were not significantly different among the groups. The combination of meperidine and nitrous oxide tended to be more hypotensive than the other anaesthetic regimen in the dog, but the hypotension was easily overcome by intravascular infusion. Once stabilized, the blood pressure of all animals was well maintained throughout the experimental period. Epinephrine is known to re-

TABLE I
DOSE OF EPINEPHRINE ($\mu\text{g/kg}$) THAT INDUCED DYSRHYTHMIAS DURING NARCOTIC-NITROUS
OXIDE ANAESTHESIA

		Supraventricular	Ventricular	VT or VF
Morphine	1 $\text{mg}\cdot\text{kg}^{-1}$	1.1 $\pm$ 0.4 (4/8)	1.9 $\pm$ 0.3 (3/8)*	(0/8)
	2 $\text{mg}\cdot\text{kg}^{-1}$	0.9 $\pm$ 0.4 (4/8)	2.3 $\pm$ 0.0 (2/8)*	(0/8)
Fentanyl	0.01 $\text{mg}\cdot\text{kg}^{-1}$	1.0 $\pm$ 0.3 (3/8)	1.5 $\pm$ 0.8 (4/8)	(0/8)
	0.02 $\text{mg}\cdot\text{kg}^{-1}$	1.0 $\pm$ 0.2 (3/8)	1.6 $\pm$ 0.8 (5/8)	1.9 (VT, 1/8)
Meperidine	10 $\text{mg}\cdot\text{kg}^{-1}$	1.2 $\pm$ 0.6 (4/8)	1.7 $\pm$ 0.7 (3/8)	(0/8)
	20 $\text{mg}\cdot\text{kg}^{-1}$	0 (0/8)	1.6 $\pm$ 0.6 (3/8)	(0/8)

Mean $\pm$ SD (N = 8); numbers in parentheses represent incidence of occurrence.

*Significantly larger ($P < 0.05$) than the corresponding doses required to produce supra-ventricular dysrhythmias. Ventricular dysrhythmias are usually unifocal, not associated with bigeminy, and without pulse deficits.

TABLE II
DOSE OF EPINEPHRINE ($\mu\text{g/kg}$) THAT INDUCED DYSRHYTHMIAS DURING ANAESTHESIA WITH
HALOGENATED INHALATION AGENTS AND NITROUS OXIDE

	Supraventricular	Ventricular	VT or VF
Halothane	2.9 $\pm$ 1.8 (6/8)	3.6 $\pm$ 1.7 (8/8)	5.6 $\pm$ 1.5 (5/8)
Enflurane	2.3 $\pm$ 1.5 (6/8)	3.2 $\pm$ 1.4 (8/8)	5.5 $\pm$ 1.6 (3/8)
Methoxyflurane	3.0 $\pm$ 1.1 (4/8)	3.9 $\pm$ 1.9 (4/8)	0 (3/8)

Mean $\pm$ SD (N = 8); numbers in parentheses represent incidence of occurrence. None of the arrhythmogenic doses are significantly different from each other ($P > 0.05$), but they are larger ($P < 0.05$) than the corresponding supraventricular and ventricular doses of Table I; ventricular dysrhythmias are frequently multifocal and associated with bigeminy to quadrageminy with pulse deficits.

lease endogenous potassium from the liver,⁸ and cardiac dysrhythmias are potentiated by hyperkalaemia.⁵ A mean peak serum potassium concentration of 6.5 mmol/l was obtained in this study following epinephrine infusion. None of the serum potassium measurements were higher than 7.0 mmol/l in any group. It has been reported that serum potassium between 6–9 mmol/l is a cardiac stimulant^{9,10} and would exert an insignificant dysrhythmic effect on the heart below 6 mmol/l. Therefore, changes in serum potassium among groups in this study do not appear to be an influential factor in the genesis of dysrhythmias induced by epinephrine.

In a preliminary report where halothane, enflurane, fluroxene and methoxyflurane were studied with nitrous oxide and oxygen or nitrogen and oxygen as inspired gas mixtures, the data suggested that the addition of nitrous oxide to the halogenated anaesthetics was more arrhythmogenic than the addition of nitrogen during epinephrine-induced ventricular dysrhythmias.⁷ The present study did not demonstrate significant differences of the arrhythmogenic doses among the halogenated-nitrous oxide

anaesthetics (Table II). This lack of arrhythmic dose differences among halothane, enflurane and methoxyflurane is different from published reports.²⁻⁴ However, it should be noted that all of these published studies were done without the addition of nitrous oxide. The addition of nitrous oxide to these halogenated general anaesthetics significantly decreased the arrhythmogenic dose of epinephrine in this study as compared with the previous studies.²⁻⁴ Nitrous oxide is known to have an α -adrenergic stimulating action when administered with oxygen.^{11,12} This α -adrenergic stimulating action of nitrous oxide is also evident when administered with other inhalation anaesthetics¹³⁻¹⁵ or morphine.¹⁶ However, whereas morphine-oxygen produced cardiac stimulation, the addition of nitrous oxide to morphine-oxygen produced cardiac depression.¹⁶ Pancuronium has also been shown to have a vagolytic effect on the heart in animals¹⁷ and cardiovascular stimulating effects in man.¹⁸ The interaction of nitrous oxide with the anaesthetics or narcotics is not well understood and is probably more complex with the addition of pancuronium. Failure to demonstrate different arrhythmic potentials of the haloge-

nated agents to epinephrine infusion may be related to the addition of nitrous oxide and pancuronium. Methoxyflurane-nitrous oxide anaesthesia was not only associated with a lower incidence of ventricular dysrhythmias (4/8) in comparison with halothane-nitrous oxide (8/8) and enflurane-nitrous oxide (8/8), but also was not associated with any occurrence of ventricular tachycardia or ventricular fibrillation. When methoxyflurane was administered without the addition of nitrous oxide to dogs² and goats,⁴ the arrhythmic doses of epinephrine were higher than those required during halothane anaesthesia, but the same as those required during enflurane anaesthesia. Methoxyflurane and enflurane are both ether derivatives and possess pharmacological actions similar to diethyl ether, which has potent cardiac stabilizing qualities against epinephrine-induced dysrhythmias.¹ The addition of nitrous oxide appears to antagonize the cardiac stabilizing effects of enflurane more than of methoxyflurane. Methoxyflurane with nitrous oxide has been advocated for anaesthetic management of pheochromocytoma,¹⁹ where epinephrine-induced ventricular arrhythmias are a problem. In the present study, methoxyflurane-nitrous oxide anaesthesia was as effective as narcotic-nitrous oxide anaesthesia in preventing the occurrence of ventricular tachycardia and ventricular fibrillation.

The narcotic doses used in this study were aimed at meaningful doses for clinical anaesthesia and represent equipotent doses of morphine, fentanyl and meperidine. There are no published data on the "MAC" of narcotics. The preliminary report of Fraioli, *et al.* tend to suggest that $1 \text{ mg} \cdot \text{kg}^{-1}$ of morphine sulfate and 60 per cent nitrous oxide are required to prevent movement of 50 per cent of patient in response to a skin incision; this is defined as the 0.5 MAC equivalent of morphine.²⁰ The lack of dose-response relationship in the present study would suggest that the doses chosen were on the nearly flat portion of the dose-response curve. The complex interaction of nitrous oxide, pancuronium and narcotics noted above could also have influenced the results. The narcotic-nitrous oxide groups consistently required smaller doses of epinephrine to induce cardiac dysrhythmias as compared with the halogenated-nitrous oxide groups, which was an unexpected finding. However, the ventricular dysrhythmias observed in the halogenated anaesthesia group were frequently multifocal with bigeminy to quadrigeminy, with greater distortion of the QRS

FIGURE 1 Arrhythmogenicity of epinephrine in dogs anaesthetized with morphine, $2 \text{ mg} \cdot \text{kg}^{-1}$, and halothane, 1.2 MAC, with 50 per cent nitrous oxide with oxygen and pancuronium, $0.2 \text{ mg} \cdot \text{kg}^{-1}$. A, Control. B, Onset of ventricular dysrhythmias following $3.9 \mu\text{g} \cdot \text{kg}^{-1}$ epinephrine infusion (halothane-nitrous oxide); following $2.3 \mu\text{g} \cdot \text{kg}^{-1}$ (morphine sulphate-nitrous oxide). C, Following $5.7 \mu\text{g} \cdot \text{kg}^{-1}$ epinephrine infusion: halothane-nitrous oxide associated with bigeminy and pulse deficit; morphine sulphate-nitrous oxide associated with ventricular dysrhythmia without pulse deficit.

complexes and with pulse deficits (Figure 1). This type of rhythm led to more frequent ventricular tachycardia or fibrillation except during methoxyflurane-nitrous oxide anaesthesia. In contrast, the ventricular dysrhythmias of the narcotic groups were of slower heart rate, with less distortion of the QRS complexes and without pulse deficits (Figure 1). The latter type of rhythm rarely led to ventricular tachycardia or ventricular fibrillation. The onset of ventricular dysrhythmias in the narcotic-nitrous oxide group was not usually preceded by bradycardia; whereas those observed in the halogenated-nitrous oxide groups were usually preceded by bradycardia. Since there was no significant difference in peak blood pressure between the two groups, these findings tend to suggest that reflex bradycardia was blocked by narcotics with nitrous oxide, but not blocked by halogenated anaesthetic agents with nitrous oxide. Suppression of supraventricular pacemakers with bradycardia allows emergence of ventricular pacemakers. It is possible that anaesthesia with halothane or enflurane and nitrous oxide may also produce intrinsic ventricular conduction defects that potentiate ventricular dysrhythmias during epinephrine infusion. That larger doses of epinephrine are required before the onset of ventricular dysrhythmias in the halogenated nitrous oxide groups may possibly explain the increased incidence of ventricular tachycardia and ventricular fibrillation when they occurred. These results suggest that anaesthesia with narcotics or methoxyflurane, nitrous oxide and relaxants may

stabilize the heart against serious epinephrine-induced ventricular dysrhythmias better than anaesthesia with halothane or enflurane with nitrous oxide and relaxant.

SUMMARY

The effects of epinephrine-induced dysrhythmias were evaluated in sixteen 15–20 kg mongrel dogs anaesthetized with halogenated inhalation agents, nitrous oxide and pancuronium and with narcotics, nitrous oxide and pancuronium. Group 1 consisted of eight animals which received 1.2 MAC halothane, enflurane or methoxyflurane in nitrous oxide and oxygen (2.5/2.5 litres) and Group 2 of eight animals which received morphine (1 and 2 mg·kg⁻¹), fentanyl (0.01 and 0.02 mg·kg⁻¹) and meperidine (10 and 20 mg·kg⁻¹) with nitrous oxide and oxygen (2.5/2.5 litres). Pancuronium (0.2 mg·kg⁻¹) was administered to both groups. Each animal in Group 1 or 2 was studied three times but only once a week and one anaesthetic regimen per study. The order of administration of the anaesthetic regimen was randomized for both groups.

Lead II of the electrocardiogram, oesophageal temperature and arterial pressure were monitored continuously. Arterial blood gases and serum sodium and potassium were determined during control, during the peak pressure response from epinephrine infusion and every 30 minutes for the rest of the study. Epinephrine (5 µg/ml) was infused at a rate of 1 µg·kg⁻¹·min⁻¹ up to ten minutes. The persistence of three or more consecutive dysrhythmic beats was used as the endpoint of the epinephrine arrhythmogenic dose. Arterial blood gases showed minimal changes in both groups during the course of the experiment with PaO₂ 24 ± 2.13 kPa (180 ± 16 torr), PaCO₂ 4.8 ± 0.4 kPa (36 ± 3 torr) and cH⁺ 43.65 ± 0.14 nmol/l (pH 7.36 ± 0.07). Serum sodium did not change significantly during the experiment, but serum potassium increased to a peak concentration of 6.5 ± 0.4 mmol/l during the epinephrine infusion. The ventricular dysrhythmic dose of epinephrine was generally higher than the corresponding supraventricular dysrhythmic dose for each anaesthetic regimen for both groups. The arrhythmogenic doses for the halogenated-nitrous oxide anaesthesia groups were significantly higher than for the narcotic-nitrous oxide groups; however, the incidence of ventricular arrhythmias was greater in the halogenated-nitrous oxide groups (20 of 24 vs 20 of

48). The incidence of ventricular arrhythmias was less in the methoxyflurane-nitrous oxide group (4/8) than in the halothane-nitrous oxide (8/8) or enflurane-nitrous oxide (8/8) groups. Ventricular tachycardia and ventricular fibrillation occurred in five of eight in the halothane group, three of eight in the enflurane group and in none of the eight in the methoxyflurane group, compared with an occurrence of one out of 48 epinephrine challenges in the narcotic-nitrous oxide groups. These results suggest that anaesthesia with narcotics or methoxyflurane with nitrous oxide and relaxants may stabilize the heart against serious epinephrine-induced ventricular dysrhythmias better than anaesthesia with halogenated inhalation agents, nitrous oxide and relaxant.

RÉSUMÉ

Cette étude porte sur les dysrythmies provoquées par l'épinéphrine sur 16 chiens de race commune anesthésiés aux halogénés et aux narcotiques. Un premier groupe de huit animaux a reçu de l'halothane, de l'enflurane ou du méthoxyflurane à une concentration équivalente à 1.2 fois la concentration alvéolaire minimale, alors que le deuxième groupe recevait de la morphine à la dose de 1 et 2 mg·kg⁻¹, du fentanyl à 0.01 et 0.02 mg·kg⁻¹ ou de la mépéridine 10 et 20 mg·kg⁻¹. Du protoxyde d'azote et de l'oxygène à 50 pour cent ainsi que du pancuronium ont été administrés aux deux groupes avec les produits mentionnés. Chacun des animaux a été étudié trois fois mais jamais plus d'une fois par semaine et un seul produit a été employé par séance. L'ordre d'administration des agents a été randomisé pour les deux groupes.

La dérivation II de l'électrocardiogramme, la température œsophagienne et la pression artérielle ont été suivies de façon continue. On a analysé les gaz du sang ainsi que la concentration du sodium et du potassium pendant la période de contrôle, pendant l'infusion d'épinéphrine et à toutes les trente minutes jusqu'à la fin de l'étude. Une solution d'épinéphrine (5 µg/ml) a été perfusée à la vitesse de 1 µg·kg⁻¹·min⁻¹ pendant dix minutes ou moins. Le temps d'arrêt de la perfusion a été déterminé par la persistance de trois battements dysrythmiques ou plus. Les gaz du sang et le sodium ont été peu modifiés pendant l'expérience alors que le potassium s'élevait à une concentration de 6.5 ± 0.4 mmol/l au cours de la perfusion. Dans les deux groupes d'animaux, la dose d'épinéphrine requise pour pro-

voquer une dysrythmie ventriculaire était en générale plus forte que celle requise pour une dysrythmie supraventriculaire. La dose arythmogène pour le groupe halogéné-protoxyde d'azote a été de façon significative plus élevée que pour le groupe narcotique-protoxyde; cependant l'incidence d'arythmies ventriculaires a été plus marquée dans le groupe qui avait reçu un agent halogéné (20 chiens sur 24 comparativement à 20 sur 48). L'incidence d'arythmies ventriculaires a été moindre pour les chiens anesthésiés au méthoxyflurane-protoxyde d'azote (4 sur 8) qu'à l'halothane-protoxyde (8 sur 8) ou l'enflurane-protoxyde (8 sur 8). De la tachycardie et de la fibrillation ventriculaires sont survenues sur cinq des huit chiens du groupe halothane, sur trois sur huit du groupe enflurane et sur aucun sur huit du groupe méthoxyflurane, comparativement à un seul chien du groupe des narcotiques sur 48. Ces résultats permettent de conclure que l'anesthésie produite par un narcotique ou du méthoxyflurane auxquels on associe du protoxyde d'azote et un myorésolutif protège le cœur contre les dysrythmies ventriculaires graves provoquées par l'épinéphrine mieux que les autres halogénés associés aux mêmes produits.

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