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Influence of halothane and catecholamines on heart rate and rhythm in the horse

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Summary

1. Ventricular ectopic beats were recorded in eight of thirteen conscious horses following the intravenous administration of adrenaline in doses of 3 μg/kg. Following pre-treatment with either atropine sulphate (0·1 mg/kg) or propranolol hydrochloride (0·1 mg/kg), the same dose level of adrenaline failed to produce ventricular ectopic beats.

2. Halothane anaesthesia sensitized the equine heart to the arrhythmogenic actions of adrenaline ; the incidence and duration of ventricular arrhythmias being greater than in conscious animals. In comparison with the findings in conscious horses, ether anaesthesia appeared to protect the heart against adrenaline-induced arrhythmias.

3. From a comparison of the arrhythmogenic, chronotropic and pressor actions of adrenaline, noradrenaline and isoprenaline during halothane anaesthesia, it was concluded that sensitization to the arrhythmogenic actions of catecholamines resulted primarily from the action of halothane on the ventricle. The results also indicated that the pressor responses to catecholamines during halothane anaesthesia probably played some part in the genesis of arrhythmias.

4. No " spontaneous " ventricular arrhythmias were recorded in twenty-four horses anaesthetized with halothane or in sixteen animals under ether anaesthesia.

5. The available evidence indicates that a moderate to fairly severe degree of hypercapnia produced little increase in sympathetic control of the myocardium during halothane anaesthesia ; the absence of irregularities in ventricular rhythm during halothane anaesthesia were attributed to this factor.

Introduction

A high incidence of cardiac arrhythmias during halothane anaesthesia has been reported in the cat (Muir, Hall & Littlewort, 1959 ; Purchase, 1966). Arrhythmias have also been recorded during halothane anaesthesia in man (Burnap, Galla & Vandam, 1958 ; Hellewell & Potts, 1965 ; Johnstone, 1966a, b ; Stephen, Grosskreutz, Lawrence, Fabian, Bourgeois-Gavardin & Coughlin, 1957 ; Wyant, Merriman, Kilduff & Thomas, 1958), although the incidence appears to be less frequent than in the cat. Under halothane anaesthesia, irregularities of cardiac rhythm were not recorded in the dog by Raventos (1956), but in the horse arrhythmias were reported by Vasko (1962) and Eberly, Gillespie, Tyler & Fowler (1968). From these, and other reports, it would appear that there may be species

variations in the incidence of cardiac arrhythmias during halothane anaesthesia and that extrapolation of detailed human studies to other species might be unreliable.

Since halothane is used extensively in equine anaesthesia, it appeared that a more detailed investigation of the pharmacology of halothane in horses was needed. For this investigation the effects of halothane have been compared with those produced by ether. Studies of the arrhythmias produced by hydrocarbon anaesthetics in other species have indicated that many factors are involved in the genesis of arrhythmias. With these points in mind, measurements were made of arterial blood pressure, electrocardiogram and arterial blood acid-base balance. As an important element in hydrocarbon anaesthetic arrhythmias is cardiac "sensitization" to catecholamines, the study has included an investigation of the effects of noradrenaline, adrenaline, isoprenaline and appropriate antagonists.

Methods

Horses of either sex, ranging in weight from 197 to 560 kg and in age from 18 months to 15 years, were used. No pre-anaesthetic medication was given in any experiment. The experiments on conscious animals were carried out with the horses standing quietly. In the experiments under general anaesthesia a dose of 10 mg/kg thiopentone sodium (Pentothal, Abbott) in a 10% solution was given as a rapid intravenous injection to induce anaesthesia. After intubation, anaesthesia was maintained with either a halothane/oxygen or an ether/oxygen mixture administered in a closed circle anaesthetic circuit in which the rebreathing bag was replaced by a spirometer. The exhaled carbon dioxide was absorbed by soda lime in a canister incorporated into the spirometer. A steady state of anaesthesia was maintained by means of a constant inflow of oxygen/anaesthetic mixture into the spirometer, the rate of inflow being adjusted to keep the total volume of gas in the spirometer at a constant level.

The technique for collection of arterial blood samples, the measurement of arterial blood P_{O_2}, P_{CO_2} and pH, and the recordings of respiratory rate, tidal and minute volumes, mean arterial blood pressure (1 mmHg≡1·333 mbar) and heart rate and rhythm were obtained by the methods described previously (Lees & Tavernor, 1969).

All the drugs used in this study were dissolved in normal saline and given as a rapid injection into a jugular vein. The doses of the drugs and the strengths of solutions used were as follows: L-adrenaline hydrochloride (May & Baker) 3 μg/kg of the base in a 0·1% solution; DL-isoprenaline hydrochloride (Isupren, Bayer) 0·85 μg/kg of the base in a 0·02% solution; L-noradrenaline bitartrate (Levophed, Bayer) 3 μg/kg of the base in a 0·1% solution; atropine sulphate (Allen & Hanbury) 0·1 mg/kg in a 0·33% solution; DL-propranolol hydrochloride (Inderal, I.C.I.) 0·1 mg/kg in a 1·0% solution.

In the anaesthetized animals the sympathomimetic amines were given in a random order both before and after the administration of propranolol. Between the injection of each amine sufficient time was allowed for the heart rate and blood pressure to return to control levels; the minimum period of time between injections was 10 min.

The doses of atropine and propranolol given in the text refer to the salts. Doses of the sympathomimetic amines refer to the bases.

Results

Experiments in conscious horses

The mean value and standard error for heart rate in forty-five conscious, resting horses was 44·6 ± 3·0 beats per minute. In thirteen of these animals the effects of adrenaline were recorded ; the administration of a dose of 3 μg/kg produced ectopic beats of ventricular origin in eight, but in only two of the horses did the total number of these beats exceed five (Table 1). Both the degree and duration of the sinus tachycardia produced by adrenaline were small in comparison with the responses during anaesthesia with either halothane or ether (Figs. 1 and 2). The effect of the prior administration of propranolol 0·1 mg/kg to six animals was to prevent the arrhythmogenic action of adrenaline and to convert the positive chronotropic action of adrenaline to a bradycardia (Table 2, Fig. 1). In seven animals the administration of adrenaline 3 μg/kg after atropine 0·1 mg/kg produced a marked tachycardia but no arrhythmias were recorded (Table 2). The finding that pre-treatment with either propranolol or atropine prevented the occurrence of ventricular ectopic beats in response to adrenaline, was statistically significant ($P<0·02$ for both propranolol and atropine) when compared with the incidence of such beats produced by adrenaline alone.

Experiments under halothane anaesthesia

In twenty-four horses, recordings of heart rate and rhythm and of blood pressure were made during anaesthesia with a halothane/oxygen mixture. After 60 min anaesthesia, the mean values and standard errors for heart rate and mean arterial

TABLE 1. *Total number of beats of nodal and ventricular origin produced by sympathomimetic amines in the horse*

	Adrenaline	Noradrenaline	Isoprenaline
Conscious	6·8 ± 4·4 (13)*		
Halothane anaesthesia	137 ± 33·8 (11)	10 ± 6·8 (4)†	94 ± 36·3 (6)
Ether anaesthesia	$P_1<0·001$	$P_2<0·05$	$P_2>0·40$
	0 (6)	0 (6)	0 (6)

The values are mean ± standard errors. Figues in parentheses indicate the number of animals.
* No arrhythmias recorded in five of these animals.
† No arrhythmias recorded in two of these animals.

Values of P determined by t tests: P_1, comparison of effect of adrenaline between conscious and halothane anaesthetized animals; P_2, comparison of effect of noradrenaline and isoprenaline with adrenaline in halothane anaesthetized animals.

TABLE 2. *Influence of adrenaline on heart rate before and after the administration of propranolol or atropine in conscious horses*

Time (min)		$-\frac{1}{2}$	0*	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$	3	$3\frac{1}{2}$	4	$4\frac{1}{2}$	5
1. Before	propranolol	52	47	61	60	47	45	50	50	57	56	56	55
After	propranolol	49	45	25	28	31	35	37	39	43	42	41	43
2. Before	atropine	52	47	67	48	39	48	51	58	56	57	59	58
After	atropine	96	97	165	151	147	131	122	114	111	108	107	106

1, Mean values for six animals receiving adrenaline 1 h before and 5 min after propranolol (0·1 mg/kg).
2, Mean values for seven animals receiving adrenaline 1 h before and 5 min after atropine (0·1 mg/kg).
* Adrenaline given at time "0".

blood pressure were 47·7 ± 2·5 beats per minute and 93·2 ± 5·0 mmHg, respectively. In no animal was any irregularity of cardiac rhythm recorded, in spite of the fact that there was a fairly severe respiratory acidosis in some of these animals. The mean values and standard errors for arterial blood pH, P_{CO_2} and P_{O_2} levels in

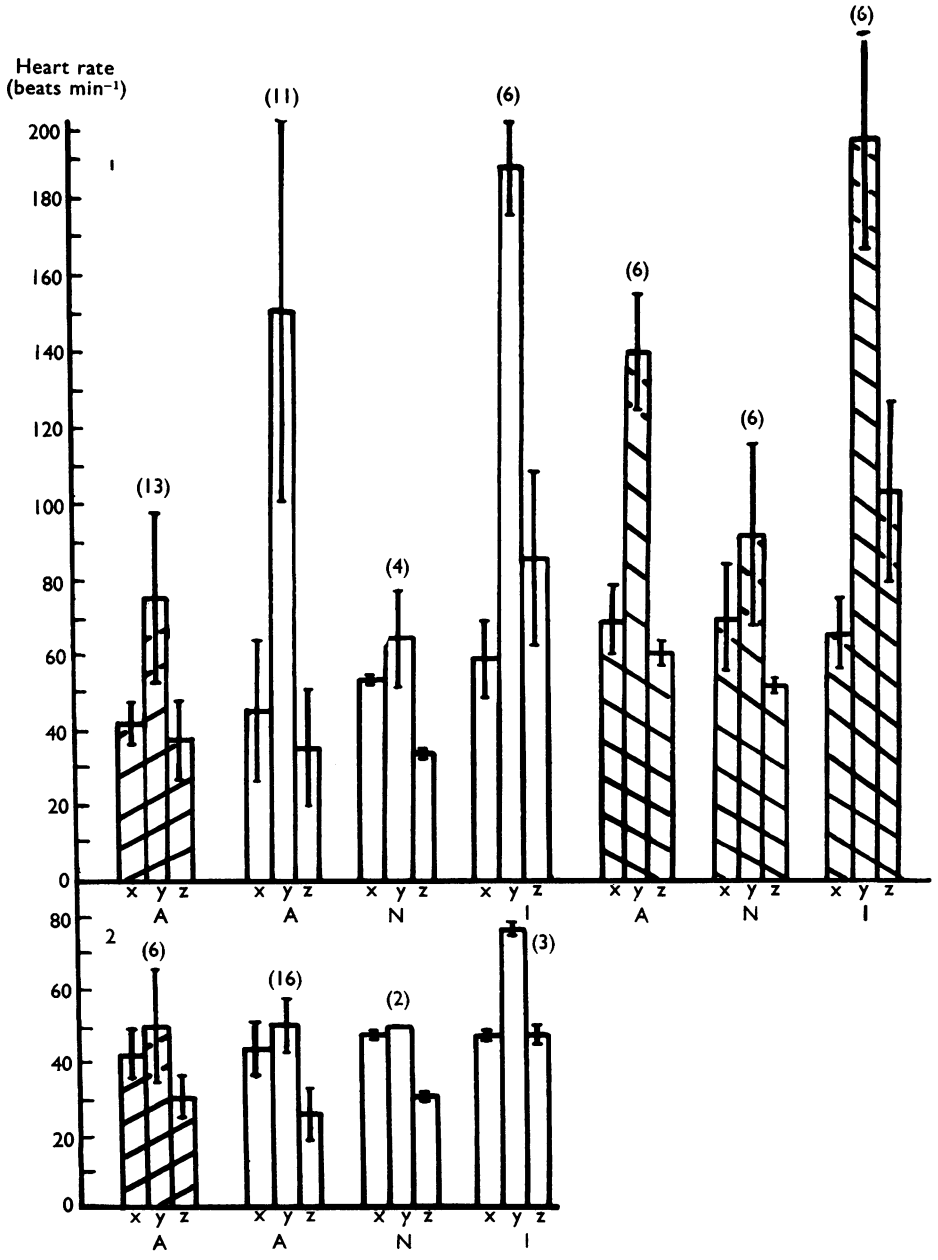

FIG. 1. Influence of catecholamines on heart rate in conscious, halothane-anaesthetized and ether-anaesthetized horses. The heights of the rectangles represent the mean values of heart rate and the bars indicate the standard deviations. ▨, Conscious ; □, halothane-anaesthetized ; ▩, ether-anaesthetized. A, Adrenaline ; N, noradrenaline ; I, isoprenaline ; x, control value ; y, maximum value ; z, minimum value. 1, Before propranolol ; 2, after propranolol. Figures in parentheses indicate number of animals.

eight of the horses were 7·19 ± 0·008, 81·0 ± 5·2 mmHg and 84·8 ± 6·6 mmHg respectively, after one hour's anaesthesia.

The intravenous administration of a dose of 3 μg/kg adrenaline to eleven animals was followed by the appearance of ventricular ectopic beats in all cases, and by either ventricular or nodal tachycardia in four of the animals. The average number of ectopic beats of ventricular and nodal origin was 137 ; this figure was significantly greater than the number recorded in conscious animals (Table 1). After the administration of the drug there was a marked overall increase in heart rate. This was followed by a reduction in rate to levels below the control values in five horses at the time of, or shortly before, the maximal pressor response (Figs. 1 and 2). This reduction in rate was obscured, however, in Fig. 2, as a result of taking mean values. There was a pronounced increase in blood pressure, followed by a return to normal values approximately 8 min after injection, but in no case did the pressure fall below the control value (Fig. 3). The effect of adrenaline on respiratory minute volume was variable, but it may be seen from the mean values (Fig. 3) that there was an overall increase in minute volume shortly after injection of the drug.

The administration of noradrenaline, at a dose level of 3 μg/kg, produced ventricular tachycardia in two of four animals. The average number of beats of ventricular origin for the four animals was only 10 ; this figure was significantly less than that produced by adrenaline (Table 1). Initially, the heart rate increased slightly, and this was followed by a more pronounced bradycardia shortly after the

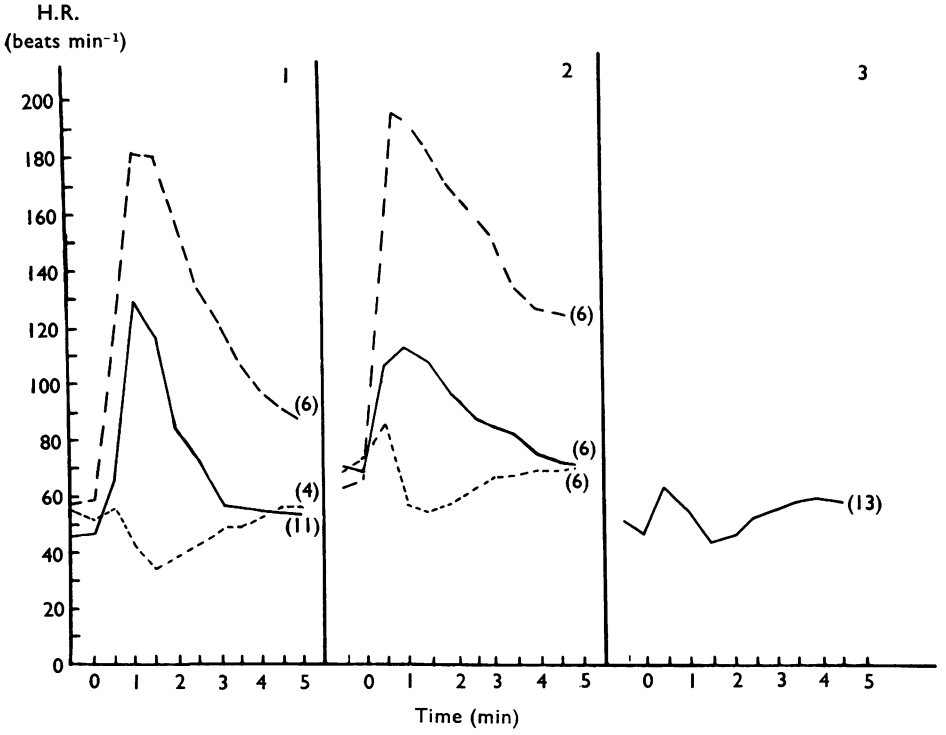

FIG. 2. Influence of adrenaline (——), isoprenaline (– – –) and noradrenaline (- - -) on heart rate of (1) halothane-anaesthetized ; (2) ether-anaesthetized ; (3) conscious horses. Figures in parentheses indicate number of animals.

time of the maximal pressor response (Figs. 1 and 2). There was an increase in mean arterial blood pressure, normally somewhat less pronounced than that produced by adrenaline, and this was followed by a return to control values approximately 6 min after injection (Fig. 3). As with adrenaline, the effects of noradrenaline on respiratory minute volume were variable, the main overall effect being a reduction approximately 1 min after the maximal pressor response (Fig. 3).

The intravenous injection of a dose of 0·85 μg/kg isoprenaline to six horses produced ventricular ectopic beats in all animals, and either ventricular or nodal tachycardia in three cases. The average number of ectopic beats of ventricular and nodal origin was 94; this figure was not significantly different from that produced by adrenaline (Table 1). The heart rate was greatly increased, followed by a much slower return to normal than in the case of adrenaline (Figs. 1 and 2). The effect of isoprenaline on blood pressure usually consisted of a small rise followed by a slight, transient reduction before rising again to a level slightly above the control value (Fig. 3). In all cases isoprenaline caused a slight increase in respiratory minute volume followed by a return to normal values within 4 min.

The effect of the prior intravenous administration of 0·1 mg/kg propranolol was to antagonize completely the arrhythmogenic action of all three catecholamines. The effect of these amines on the heart rate after propranolol is shown in Fig. 1. Adrenaline and noradrenaline produced a reduction in heart rate, whereas isopren-

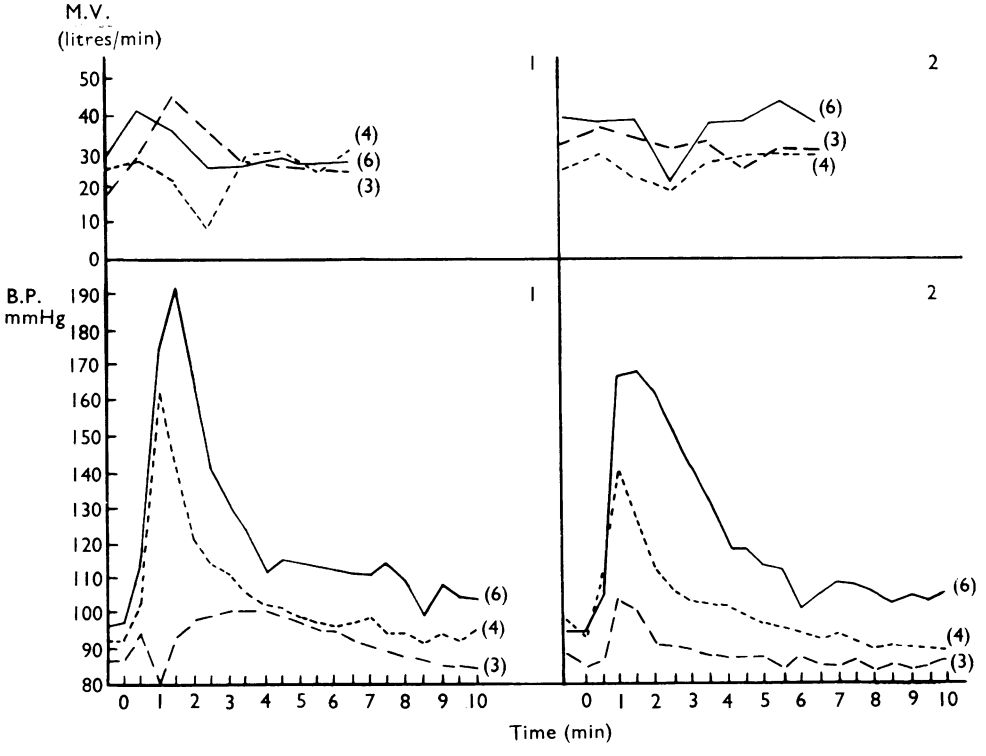

FIG. 3. Influence of adrenaline (——), isoprenaline (– – –) and noradrenaline (- - -) on minute volume (MV) and blood pressure (BP) in halothane-anaesthetized horses (1) before and (2) after the administration of 0·1 mg/kg propranolol. Figures in parentheses indicate the number of animals.

aline still increased heart rate, but this effect of isoprenaline was greatly reduced when compared with the action of the drug before the administration of propranolol. The effects of adrenaline and noradrenaline on blood pressure were similar to the effects before propranolol but of reduced magnitude. Isoprenaline produced a slight rise but no subsequent decrease in pressure (Fig. 3). Respiratory minute volume tended to fall following the injection of each of the catecholamines. Compared with their action before propranolol, the most marked difference was the reduction in minute volume produced by adrenaline.

In a single animal anaesthetized with halothane, the administration of noradrenaline (3 μg/kg) before the administration of atropine produced ventricular ectopic beats, whereas after giving atropine (0·1 mg/kg) the same dose level of noradrenaline resulted in ventricular fibrillation within 20 s followed by death. This was the only case, in all the present experiments, in which ventricular fibrillation was recorded following the injection of any of the catecholamines.

Experiments under ether anaesthesia

In sixteen horses, recordings of heart rate and rhythm and blood pressure were made during anaesthesia with an ether/oxygen mixture. After a period of 60 min anaesthesia, the mean values and standard errors for heart rate and mean arterial blood pressure were 59·5 $\pm$ 4·3 beats/min and 89·0 $\pm$ 7·5 mmHg respectively. In no animal was any irregularity of cardiac rhythm recorded. The mean values and standard errors for arterial blood pH, P_{CO_2} and P_{O_2} levels in six of the horses were

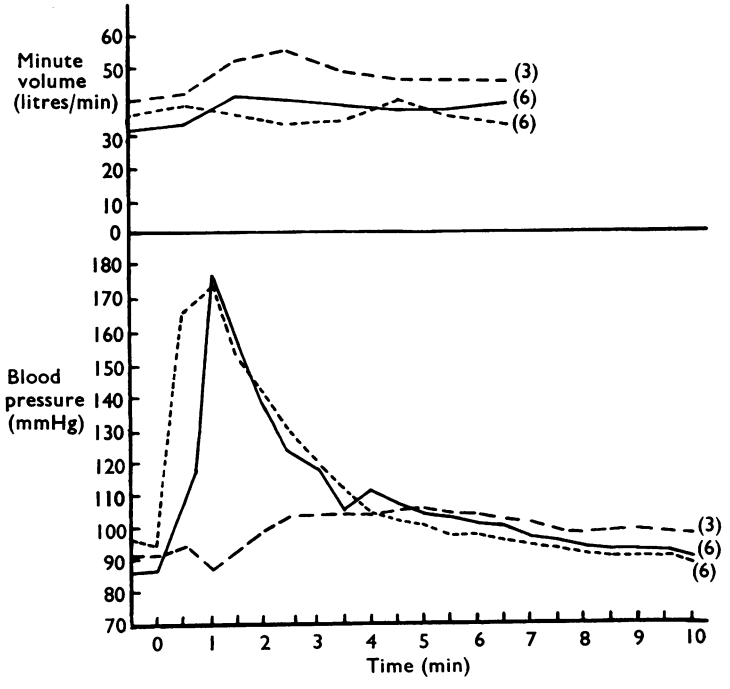

FIG. 4. Influence of adrenaline (——), isoprenaline (– – –) and noradrenaline (- - -) on minute volume and blood pressure in ether-anaesthetized horses. Figures in parentheses indicate the number of animals.

7·255 ± 0·016, 60·0 ± 2·2 mmHg and 119·0 ± 13·5 mmHg respectively, after one hour's anaesthesia.

The administration of each of the three catecholamines, at the same dose levels used during halothane anaesthesia, failed to produce cardiac arrhythmias in six horses during ether anaesthesia (Table 1). In the case of adrenaline, the incidence of ventricular ectopic beats in conscious animals differed significantly ($P<0·02$) from the finding that no such beats occurred in response to adrenaline during ether anaesthesia. The changes in heart rate, blood pressure and respiratory minute volume produced by the catecholamines during ether anaesthesia were essentially similar to those produced in animals anaesthetized with halothane (Figs. 1–4).

Discussion

The results of the present investigation indicate that a 3 μg/kg dose of adrenaline may produce ventricular ectopic beats when given by rapid intravenous injection to conscious, resting horses. In addition, this dose level normally produced an immediate increase in heart rate followed by a period of bradycardia. When adrenaline was given to conscious horses after pre-treatment with atropine there were no ventricular arrhythmias, but a pronounced increase in heart rate occurred. On the other hand, administration of adrenaline after pre-treatment of the horses with propranolol was associated with a marked bradycardia but again there were no ventricular arrhythmias. It was to be expected that propranolol would prevent the occurrence of ventricular arrhythmias for it is well known that this agent will antagonize the direct chronotropic, inotropic and dromotropic actions of adrenaline and other sympathomimetic amines (Shanks, 1966). Since atropine also prevented the arrhythmogenic action of adrenaline in the conscious horse, it would appear that the direct action of adrenaline on the heart is not solely responsible for the occurrence of these arrhythmias. The blocking action of atropine indicates that the arrhythmias may be attributable to an increase in vagal tone to the heart, resulting from the pressor action of adrenaline, and a consequent slowing of pacemaker activity in the sinus node at a time when adrenaline was acting directly on the A-V node and the conducting tissues in the ventricle. Other workers have stressed the importance of increased vagal activity in the generation of heterotopic pacemakers by catecholamines in the cat and dog (Dresel, 1962 ; Riker, Depierre, Roberts, Roy & Reilly, 1955 ; Roberts, Standaert, Kim & Riker, 1956).

A comparison of the changes in heart rate produced by adrenaline in conscious and ether-anaesthetized horses shows that much greater increases in rate occurred in the latter animals. It is likely, therefore, that the reflex increase in vagal tone to the heart, which results from the pressor action of adrenaline, is depressed by ether anaesthesia. Depression of this vagal reflex may account for the " protective " action of ether against the arrhythmogenic action of adrenaline. A protective action of ether against catecholamine-induced arrhythmias has also been recorded in the dog (Detterling, Ngai, Laragh & Papper, 1954 ; Meek, Hathaway & Orth, 1937).

The present study clearly indicates that halothane, in contrast to ether, sensitizes the equine heart to the arrhythmogenic actions of catecholamines. In the first place, it can be seen from a comparison of the actions of adrenaline, noradrenaline and isoprenaline during ether and halothane anaesthesia, that essentially similar changes in heart rate and blood pressure occurred with both anaesthetics, but only in the

halothane-anaesthetized animals did ventricular arrhythmias arise. Second, it is clear that the incidence and duration of ventricular arrhythmias, in response to adrenaline, are much greater during halothane anaesthesia than in the conscious horse. The present experiments indicate that the level of mean arterial blood pressure is a contributory factor in the production of catecholamine-halothane arrhythmias in the horse. Thus, of the catecholamines employed, adrenaline produced the greatest pressor response and the greatest number of ventricular ectopic beats. On the other hand, isoprenaline, which produced much greater increases in heart rate than adrenaline, and caused only small increases in blood pressure, was slightly less potent than adrenaline in the production of ventricular arrhythmias. It is likely, therefore, that the extent to which blood pressure rises in response to catecholamines is related to the production of arrhythmias.

In spite of the significance of blood pressure changes in the genesis of catecholamine–halothane arrhythmias, it is concluded from the present findings that the blood pressure level is not the most important factor. This conclusion is indicated by two lines of evidence. First, noradrenaline, which is the least potent of the three catecholamines studied in its direct chronotropic effects, produced ventricular arrhythmias in only two of four animals anaesthetized with halothane, in spite of the fact that this drug produced a moderate rise in mean arterial blood pressure. Second, isoprenaline was found to be almost as potent as adrenaline in producing ventricular arrhythmias, and yet the pressor action of this drug was only slight. Indeed, in some experiments, isoprenaline produced ventricular ectopic beats at a time when the mean arterial blood pressure was reduced below control levels. It is reasonable to conclude that the increased sensitivity to catecholamine arrhythmias results primarily from an action of halothane on the conducting tissues of the ventricle. This hypothesis is supported by the findings of Moore, Morse & Price (1964) who suggested, on the basis of micro-electrode recordings, that arrhythmias originated distal to the Bundle of His.

A number of authors have recorded the appearance of " spontaneous " arrhythmias during halothane anaesthesia in several species ; these usually having been ascribed to surgical stimulation during light anaesthesia, or to the occurrence of respiratory acidosis. In the cat, cardiac arrhythmias occurred in 69% and in 88% of animals breathing nitrous oxide, oxygen, halothane mixtures in the experiments of Purchase (1966), and Muir *et al.* (1959), respectively. Black, Clarke, Howard & McCullough (1969), on the other hand, recorded extraventricular beats in only two of eleven cats anaesthetized with halothane. Recordings in man indicate that the incidence of arrhythmias during halothane anaesthesia is of the order of 15 to 20% (Burnap *et al.*, 1958 ; Hellewell & Potts, 1965 ; Johnstone, 1966a, b ; Stephen *et al.*, 1957 ; Wyant *et al.*, 1958). It should be noted, however, that two groups of workers state specifically that abnormalities of cardiac rhythm occur in man only in the presence of hypercarbia (Black, Linde, Dripps & Price, 1959 ; Payne & Senfield, 1964). The experiments of Raventos (1956) in the dog indicate that " spontaneous " arrhythmias are unlikely to occur during halothane anaesthesia in this species.

In the horse, on the other hand, Vasko (1962) recorded arrhythmias during halothane anaesthesia whilst Eberly *et al.* (1968) recorded arrhythmias only during periods of respiratory embarrassment. In contrast to the findings of these workers, the present results indicate that " spontaneous " arrhythmias are unlikely to occur in the halothane-anaesthetized horse, in spite of the fact that respiratory acidosis

was a regular feature of the present experiments. In a previous investigation under halothane anaesthesia (Lees & Tavernor, 1969), it was found that a short period of respiratory depression produced in eight horses by the administration of suxamethonium, resulted in mean values for arterial blood pH, P_{CO_2} and P_{O_2} of 7·12, 120 mmHg and 48 mmHg respectively, and failed to produce arrhythmias. The present findings differ not only from those of Vasko (1962) and Eberly *et al.* (1968) in the horse but also with the results of Purchase (1966) in the cat who found that extraventricular beats invariably occurred when P_{CO_2} levels increased above 55 mmHg, provided that haemoglobin saturation was reduced to approximately 90%. The results of this author may be due to the fact that the cat is more sensitive to the arrhythmogenic actions of catecholamines than other species. This is supported by the observation that the doses of adrenaline, noradrenaline and isoprenaline required to produce ventricular arrhythmias were 6 to 10 times greater in the dog than in the cat (Roberts *et al.*, 1956).

From the absence of ventricular arrhythmias in the presence of hypercarbia in the halothane-anaesthetized horse it would appear that a moderate respiratory acidosis produces little increase in the sympathetic control of the myocardium in this species. This suggestion is confirmed by two other findings. First, after a one-hour period of halothane anaesthesia the heart rate did not differ significantly from the rate in conscious animals. Second, the administration of a dose of propranolol (0·1 mg/kg) that greatly reduced the positive chronotropic action of isoprenaline, caused little or no change in heart rate, in either conscious or halothane anaesthetized horses (Tavernor & Lees, 1969). This finding further indicates that the heart is subject to little, if any, sympathetic control by both the conscious and halothane anaesthetized horse. These results contrast with the suggestion of Eberly *et al.* (1968) that sympathetic efferent activity is increased during halothane anaesthesia in the horse; their suggestion was based, however, only upon the evidence that blood pressure was maintained within the normal range and that peripheral resistance was elevated.

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