

CARDIOVASCULAR STUDIES OF ADRENERGIC AND GANGLIONIC STIMULATING DRUGS ADMINISTERED DURING CYCLOPROPANE

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THAT an anesthetic may sensitize the heart to the administration of an adrenergic or a ganglionic stimulating agent was appreciated years ago by Levy (1, 2), who carried out a study on the combined action of chloroform and epinephrine in regard to the production of ventricular fibrillation. More recently, cyclopropane has replaced chloroform in this type of investigation concerned with experimental cardiac arrhythmias. The technique most often employed consists of injecting 10 μ g. per kg. of epinephrine into a dog anesthetized with 30 per cent cyclopropane which results in a run of ventricular tachycardia (3). McMillen, Hampton, and Drill (4) modified this method by selecting as their end point the appearance of multiple extrasystoles induced by injecting intravenously 1 μ g./kg./ml./20 sec. of epinephrine into a dog anesthetized with cyclopropane in a concentration of 16 per cent. The slow injection of epinephrine to a defined end point eliminates the possibility that the fixed dose may be just insufficient to evoke a response and permits the plotting of a distribution curve which includes animals both unusually sensitive and refractory to ventricular arrhythmias. In addition, the observation of Stutzman and Allen (5) that dogs became resistant to epinephrine-induced arrhythmias after an hour or more of 30 per cent cyclopropane anesthesia has not been observed when 16 per cent cyclopropane was employed for the same period of time (6).

Although reports have appeared on the cardiovascular effects during cyclopropane anesthesia of several of the adrenergic and ganglionic stimulating agents used in this investigation (7-9), no single laboratory has made a systematic study on the relative effectiveness of all of these drugs to produce changes in cardiac rhythm under conditions of minimal stress. Such conditions were established by using the smallest concentration of cyclopropane which still maintained stage III, plane 2 surgical anesthesia, a minimal amount of epinephrine to elicit ventricular arrhythmias, and equipressor doses of the test drugs. In addition, from the studies of Walton and Brodie (10) and Goldberg *et al.* (11), it became apparent that there was a possibility that the force of heart contraction produced by certain adrenergic

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agents might be a factor in the production of ventricular arrhythmias during cyclopropane anesthesia. Therefore, drugs were selected which were known to have different inotropic actions in order to test this concept.

METHODS

All dogs were anesthetized initially with thiopental sodium, 20 mg. per kg., in order to allow passage of the endotracheal tube with an inflatable cuff. Cyclopropane, in a concentration of 16 per cent, was usually sufficient to maintain the animals in plane two or three anesthesia. Occasionally it was necessary to increase the concentration in order to establish the desired level of anesthesia. Blood pressure was recorded from the common carotid artery by means of an Anderson membrane manometer. All electrocardiographic tracings were taken from lead II on a direct writing Sanborn cardiette.

After equilibrating the animal on the cyclopropane mixture for at least forty minutes, epinephrine was administered in a concentration of 1 μ g. per kg. per ml. and infused into the external jugular vein at a constant rate of 1 ml. per twenty seconds until multiple extrasystoles appeared. This procedure was repeated at intervals of fifteen minutes until it was certain that the epinephrine response was uniform. Provided that the dose of epinephrine was within normal limits, the test drug was then injected. By omitting the control injection in at least 2 experiments on each drug, it was found that initial administrations of epinephrine did not in any way alter the response of the test adrenergic or ganglionic stimulating agent. The concentration for each drug was such that the total volume injected was 2 ml. and, with the exception of isopropylnorepinephrine, doses were selected which produced a rise in systolic blood pressure equivalent to or greater than the arrhythmia-producing dose of epinephrine. A dose of 10 μ g. per kg. of isopropylnorepinephrine was administered because this amount, under different conditions of cyclopropane anesthesia, had been reported to induce ventricular arrhythmias (12).

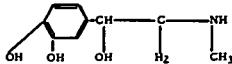
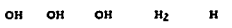
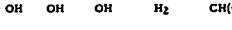
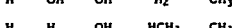
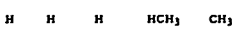

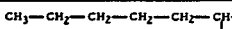
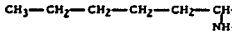
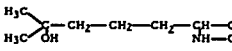
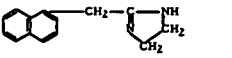
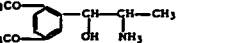
RESULTS

Thirteen compounds were studied in 65 dogs under cyclopropane anesthesia. Of these, 11 were adrenergic agents: epinephrine (Adrenalin®), 1.4 to 2.4 μ g. per kg.; levarterenol (Levophed®), 1.4 to 1.8 μ g. per kg.; isopropylnorepinephrine (Isuprel®), 10 μ g. per kg.; phenylephrine (Neo-Synephrine®), 25 to 250 μ g. per kg.; desoxyephedrine (Desoxyn®), 1 mg. per kg.; mephentermine (Wyamine®), 0.1 to 3 mg. per kg.; methoxamine (Vasoxyl®), 1 to 1.5 mg. per kg.; methylaminoheptane (Oenethyl®), 0.5 mg. per kg.; methylaminomethylheptanol (Aranthol), 5 to 7 mg. per kg.; naphazoline (Privine®), 25 to 50 μ g. per kg.; and ephedrine, U.S.P., 1 to 2 mg. per kg. The chemical structure of these compounds is presented in table 1. Two ganglionic stimu-

lating agents, nicotine, U.S.P., 0.25 mg. total dose, and dimethylphenyl-piperazinium iodide (DMPP), 20 μ g. per kg., were also included in these studies.

ADRENERGIC DRUGS: Epinephrine. In 56 animals, the average amount of epinephrine required to induce multiple ventricular extrasystoles during 16 per cent cyclopropane anesthesia was 1.98 μ g. per kg. with a standard of ± 0.24 , a finding which is in agreement with earlier reports (4, 6). Ventricular tachycardia was observed in 2 animals, and in one of these experiments, the second injection of 1.6 μ g. per kg. of epinephrine resulted in arrhythmias which progressed within a few seconds to fatal ventricular fibrillation. Other electrocardi-

TABLE 1

					NAME
					Epinephrine
					Levarterenol
					Isuprel
					Phenylephrine
					Ephedrine
					Desoxyephedrine
					Mephentermine
<hr/>					
					Oenethyl
					Aranthol
					Naphazoline
					Methoxamine

ographic changes produced by epinephrine during cyclopropane anesthesia included acceleration of heart rate, reflex sinoauricular bradycardia, and an elevation of the T wave in the majority of the animals. The latter change was most evident immediately before the appearance of cardiac arrhythmias.

In order to demonstrate more clearly the role of the anesthetic agent in the production of epinephrine-induced arrhythmias, 5 experiments were carried out in which the same animal received both cyclopropane and ether. In a typical experiment (fig. 1), 1.6 μ g. per kg. of epinephrine produced a series of multiple extrasystoles when cyclopropane was the anesthetic agent. When ether was substituted, how-

ever, no arrhythmias appeared and 10 times the standard dose also failed to elicit ventricular irregularities. At this point, cyclopropane was reinstituted and after a 2-hour equilibration period, 5 and 16 μg . per kg. of epinephrine produced ventricular extrasystoles and ventricular tachycardia, respectively. The standard dose of 1.6 μg . per kg., though, produced only a sinus tachycardia, a difference which might be accounted for by the incomplete recovery from ether anesthesia.

Levarterenol. The electrocardiographic effects of injected levarterenol during cyclopropane anesthesia were similar to those previously described for epinephrine. In comparison with the latter drug, it was found in the 6 experiments in which levarterenol was employed that a slightly smaller amount of this compound induced cardiac irregularities.

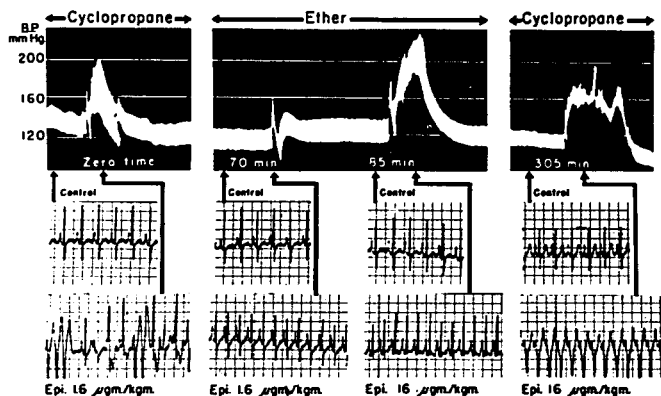


FIG. 1. Effect of small and large doses of epinephrine in a dog anesthetized with both cyclopropane and ether.

Isopropylnorepinephrine, unlike epinephrine and levarterenol, produced a fall in blood pressure with a dose of 10 μg . per kg. in 5 animals. A marked increase in cardiac rate and multiple extrasystoles, ventricular tachycardia, or ventricular fibrillation occurred as the pressure fell. The hypotensive phase was of fairly short duration, returning to normal in ten to fifteen minutes (fig. 2, Dog A), and repeated injections of isopropylnorepinephrine produced essentially the same type of response. Because of the appearance of ventricular arrhythmias during the period of vasodilation with isopropylnorepinephrine, 3 dogs were given an adrenergic blocking agent and then epinephrine. A dose of 0.5 mg. per kg. of Dibozane was employed to produce adrenergic blockade, and thirty minutes later the usual concentration

of epinephrine was administered. Although with the adrenergic blocking agent there was a dose-time sequence and large doses could both reverse blood pressure and prevent arrhythmias after an injection of epinephrine, it may be noted in figure 2, Dog B, that ventricular extrasystoles developed while the systemic blood pressure was reduced. A fall in blood pressure *per se* was ruled out as an etiological factor in these arrhythmias because equal vasodepression was produced by acetylcholine, histamine, and nitroglycerin without the appearance of ectopic rhythms.

Ephedrine- and desoxyephedrine-induced cardiovascular effects in 8 animals anesthetized with cyclopropane were similar inasmuch as,

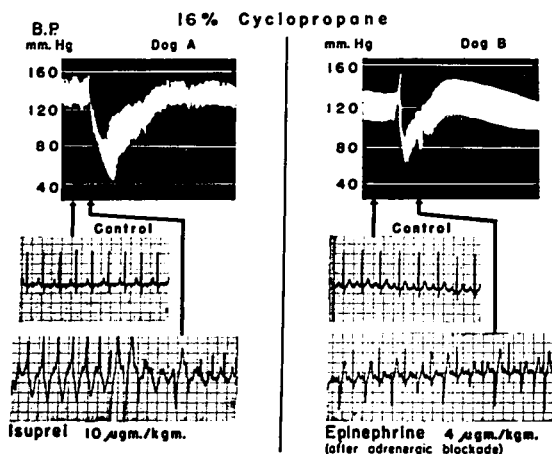


FIG. 2. Hypotension and ventricular arrhythmias in 2 different animals resulting from an injection of Isuprel and an injection of epinephrine 30 minutes after adrenergic blockade by Dibozane, 0.5 mg. per kg.

with the initial injection, both produced a prolonged hypertension, acceleration of the heart rate, and ventricular arrhythmias; while, after subsequent injections, diminished vasopressor responses and absence of ectopic rhythm occurred. The only quantitative differences noted between the 2 drugs were a greater positive chronotropic effect and a more rapidly developing tachyphylaxis after the initial injection of desoxyephedrine.

Mephentermine. An initial intravenous administration of 0.3 mg. per kg. of mephentermine resulted in multiple ventricular extrasystoles in 6 out of 7 dogs and a second injection of this same amount produced arrhythmias in 3 instances. Four other dogs were given doses of 0.1 to 0.2 mg. per kg., and cardiac irregularities were produced in half of the

experiments with the initial injection. Large doses of 3.0 mg. per kg. of the drug were injected into 4 animals, resulting usually in a long duration of multiple ventricular extrasystoles and increased heart rate. In one of these dogs, the only abnormality was sinoauricular tachycardia, the heart rate changing from 160 to 280 beats per minute. Vasopressor changes were similar to those produced by ephedrine and desoxyephedrine, except that the time required for the blood pressure to return to normal was more prolonged and tachyphylaxis developed more slowly. Another point of dissimilarity between mephentermine and the 2 phenylisopropylamines is that the presence or the absence of ventricular arrhythmias after repeated injection of the former drug

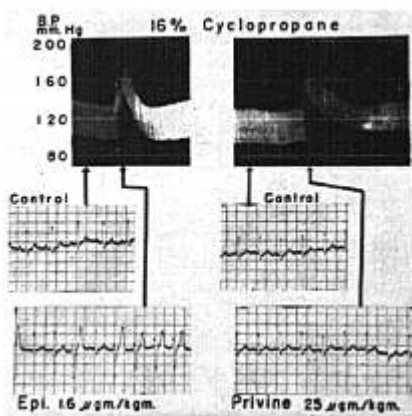


FIG. 3. Effect on blood pressure and the electrocardiogram of equipressor doses of epinephrine and naphazoline (Privine).

was unpredictable, while ectopic beats never developed with subsequent administrations of the latter compounds.

Methylaminoheptane produced sinoauricular tachycardia, ventricular extrasystoles, and ventricular tachycardia in 3 dogs anesthetized with cyclopropane. The ventricular arrhythmias were of relatively long duration, lasting 96, 480, and 700 seconds after the initial injection. Subsequent administrations of methylaminoheptane usually produced cardiac disturbances, but they lasted a shorter period of time and were less severe. After approximately 3 injections, the drug neither elevated blood pressure nor altered cardiac rhythm.

Methylaminomethylheptanol. In the 5 dogs used, the first few injections usually elicited an ectopic rhythm; ventricular tachycardia, however, was never observed. Three to 5 repeated injections of

methylaminomethylheptanol at 45-minute intervals resulted in a diminished vasopressor response. These experiments also supported the contention that, during the time when tachyphylaxis is slowly developing, one cannot predict with certainty whether or not arrhythmias will occur with any given dosage.

Phenylephrine in an amount which was the pressor equivalent to the control "arrhythmia" dose of epinephrine never produced ventricular irregularities in 5 dogs under cyclopropane anesthesia. After administering the compound intravenously, blood pressure remained elevated for approximately fifteen minutes, and repeated injections resulted in equipressor responses. Chronotropic changes were variable, but usually the heart rate decreased about 10 beats per minute.

TABLE 2
EFFECT OF REPEATED NICOTINE INJECTIONS DURING CYCLOPROPANE ANESTHESIA

	Time of Inject. in Min.	Dose, mg.	Syst. B.P. mm. Hg	Arrhy.*	
				Type	Dur., sec.
Dog 1	15	0.3	+70	+	240
	30	0.3	+65	(+)	—
	45	0.3	+75	0	—
	60	0.3	+70	0	—
	75	0.3	+70	0	—
	90	0.5	+85	+	180
	105	0.5	+85	(+)	—
Dog 2	15	0.5	+86	+	36
	30	0.5	+80	+	30
	45	0.5	+105	+	84
	60	0.5	+80	+	81
	75	0.5	+85	+	108
	90	0.5	+70	+	78
	105	0.5	+110	+	33
	120	0.5	+90	+	24
	135	0.5	+75	(+)	—

* + = multiple extrasystoles, (+) = occasional ectopic beats, 0 = absence of arrhythmias.

Large amounts of phenylephrine (250 μ g. per kg.) produced occasional ventricular extrasystoles and a positive chronotropic effect in the 3 animals tested.

Methoxamine. The average initial rise in systolic pressure produced by this compound in the 5 dogs under cyclopropane anesthesia was 50 mm. Hg, a hypertension which equalled or surpassed the peak response of the control epinephrine. The only change in rhythm was a moderate slowing of heart rate; ventricular arrhythmias were never observed. The phenomenon of tachyphylaxis was apparent and occasionally repeated injection of methoxamine resulted in a hypotensive response.

Naphazoline. The effect of equipressor doses of naphazoline and

epinephrine are compared in figure 3. Similar results were recorded in 2 other experiments using 16 per cent cyclopropane. Tachyphylaxis occurred with the doses of naphazoline employed, and usually the third or fourth successive injection failed to elicit a marked rise in blood pressure. Heart rate was either unchanged or slowed.

GANGLIONIC STIMULATING AGENTS: Nicotine. The observation of Drill and Hays (13) that repeated injections of nicotine may fail to produce ventricular arrhythmias at a time when the pressor response had only slightly decreased was confirmed. This finding probably is due to the small, fixed dose of nicotine which was employed rather than to nicotinic paralysis of the sympathetic ganglion, since slightly larger amounts of the drug produced multiple extrasystoles after repeated minimal doses failed to do so (dogs 1, 2; table 2). Typical blood pressure and electrocardiographic responses to injections of nicotine during cyclopropane anesthesia were an initial hypotension and bradycardia followed by a marked hypertension and tachycardia which, after a few seconds, suddenly changed to multiple ventricular extrasystoles. Occasionally, the arrhythmia terminated in fatal ventricular fibrillation.

Dimethylphenylpiperazinium iodide (DMPP). The minimal dose of DMPP which consistently produced ventricular arrhythmias in 4 experiments was found to be 15 μ g. per kg., and a dose between 50 and 100 μ g. per kg. always induced fatal ventricular fibrillation. Like nicotine, repeated injections of a sufficient constant dose of DMPP produced equipressor responses and ventricular arrhythmias.

DISCUSSION

Although Moe and co-workers (14) have demonstrated with an abdominal aorta pressure stabilizer that systemic hypertension may be a factor in the production of arrhythmias induced by adrenergic or ganglionic stimulating agents during cyclopropane anesthesia, experience in this laboratory suggests that a rise in blood pressure *per se* is not a requisite. Evidence was accrued from the present investigation that there is no definite correlation between the ability of adrenergic drugs to elevate blood pressure and to induce ventricular irregularities, for methoxamine, phenylephrine and naphazoline produced a hypertension which equalled that of an arrhythmia-producing dose of epinephrine without altering cardiac rhythm. Furthermore, it was observed that cardiac arrhythmias were produced during a period of hypotension by isopropylnorepinephrine and epinephrine following adrenergic blockade.

In the present study, it seemed desirable for the purpose of discussion to divide the drugs into 3 classes. Class I consists of those compounds which induced ventricular arrhythmias (both multiple extrasystoles and ventricular fibrillation) and brief sinus tachycardia. Drugs included in this category are epinephrine, levarterenol, isopropylnorepinephrine, nicotine, and DMPP. In Class II are those com-

pounds which produced ventricular multiple extrasystoles (but no ventricular fibrillation) and a long sinus tachycardia only after the first few injections. Drugs which make up this class are ephedrine, desoxyephedrine, mephentermine, and the 2 aliphatic amines, methylaminoheptane and methylamino methylheptanol. Compounds which neither produced ventricular arrhythmias nor accelerated the heart rate have been grouped as Class III drugs. In this category are methoxamine, naphazoline, and phenylephrine. This classification of adrenergic and ganglionic stimulating agents according to their electro-

TABLE 3

THE INOTROPIC ACTION OF DRUGS (CLASSIFIED ACCORDING TO THEIR ELECTROCARDIOGRAPHIC EFFECTS DURING CYCLOPROPANE ANESTHESIA) IN DOGS UNDER BARBITURATE ANESTHESIA OR IN ISOLATED RABBIT HEARTS

Drug	Inotropic Response Initial Injections	Subsequent Response*	Reference
Class I (consistent ventricular arrhythmias; brief tachycardia)			
Epinephrine	+++	+++	11, 15
Levarterenol	+++	+++	11, 16
Isuprel	+++	+++	15
DMPP	+++	+++	17**
Class II (arrhythmias only at first; long sinus tachycardia)			
Ephedrine	+++	+++, +, -	11, 10
Oenethyl	+++	+++, +, -	18
Aranthol	+++	+++, +, -	19, 10
Desoxyephedrine	+++		11
Mephentermine	+++		11
Class III (neither ventricular arrhythmias nor sinus tachycardia)			
Methoxamine	±	±	11
Phenylephrine	±	±	11, 20
Naphazoline	±	±	21**

* +++ = marked increase in force of contraction; ++, +, - = progressive decrease; ± = slight or no increase.

** = isolated perfused rabbit heart experiment.

cardiographic effects during cyclopropane anesthesia is in agreement with a division made by Goldberg and associates (11) which was based on relative inotropic effects during barbiturate anesthesia. There is a correlative indication from this latter study and other investigations that drugs which induce ventricular arrhythmias in a myocardium sensitized by cyclopropane may do so by increasing the heart contractile force, and conversely, drugs which do not elicit cardiac irregularities exert no positive inotropic action (table 3). Preliminary experiments have supported the concept that there is a direct relationship between (a) the positive inotropic effects of epinephrine, iso-

propylnorepinephrine, and ephedrine and the production of arrhythmias, and (b) the negligible inotropic effects of phenylephrine and the absence of arrhythmias. These experiments were performed using a strain gauge arch attached to the right ventricle of closed chest dogs anesthetized with 16 per cent cyclopropane, the results of which will be published at a later date.

It was mentioned previously that repeated injections of compounds represented in Class II usually resulted in tachyphylaxis to both blood pressure and multiple extrasystoles. Associated with this change is a decrease in heart contractile force (table 3), and this effect might explain the failure of arrhythmias to develop following repeated injections of ephedrine, desoxyephedrine, mephentermine, methylaminoheptane, and methylaminomethylheptanol.

Since there are definite indications that drugs which increase the force of heart contraction induce ventricular arrhythmias, the problem arises as to why this correlation should exist. From a cellular standpoint, loss of potassium from cardiac muscle cells may be an important factor. Research is now in progress to investigate the role of potassium and other cations in the production of cardiac irregularities.

SUMMARY

The average amount of epinephrine that induced ventricular extrasystoles in 36 dogs anesthetized with 16 per cent cyclopropane was 1.98 μ g. per kg. with a standard error of ± 0.24 . Neither this nor a dose 10 times this amount resulted in ventricular arrhythmias when ether was substituted as the anesthetic agent.

Repeated injections of epinephrine, levarterol, isopropylnorepinephrine, nicotine, and DMPP produced multiple extrasystoles.

Ephedrine and desoxyephedrine always induced arrhythmias after the first administration but subsequent injections resulted in tachyphylaxis, as exemplified by diminished blood pressure responses and absence of cardiac irregularities.

Injections of mephentermine, methylaminoheptane, and methylaminomethylheptanol usually produced ventricular extrasystoles while repeated injections resulted in a slowly developing tachyphylaxis, during which period the electrocardiographic changes were variable.

An amount of phenylephrine, methoxamine and naphazoline which gave a vasopressor response equal to the arrhythmia-dose of epinephrine did not alter heart rhythm.

The role of contractile force as a factor involved in the production of cardiac arrhythmias is discussed.

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