

THE CARDIOVASCULAR EFFECTS OF CONTINUOUS
INTRAVENOUS INFUSION OF NOREPINEPHRINE,
EPINEPHRINE AND NEOSYNEPHRINE DURING
CYCLOPROPANE AND ETHER ANESTHESIA
IN THE DOG * †

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INTRODUCTION

It has been desirable in certain circumstances to use dilute solutions of norepinephrine or neosynephrine® as continuous intravenous infusions to maintain arterial pressure during anesthesia and operation (1). The immediate onset and short duration of their pressor action make the administration easy to control as a continuous intravenous infusion in appropriate concentrations. However, Orth *et al.* (2) have shown that norepinephrine, epinephrine and other sympathomimetic amines with a catechol nucleus can precipitate serious ventricular arrhythmias when administered intravenously as a single dose of 0.01 mg. per kilogram of body weight to experimental animals during cyclopropane anesthesia. Consequently, the simultaneous administration of single doses of epinephrine or norepinephrine with cyclopropane has been contraindicated clinically. On the other hand Storni (3) found that intravenous injection of epinephrine into dogs produced no other electrocardiographic alteration than those interpreted as due to the action of epinephrine itself if the concentration of cyclopropane was not high enough to produce respiratory paralysis. He emphasized the need of caution in the combined use of cyclopropane and epinephrine but reported no harmful cardiac effects on 300 patients in whom these agents were used together. These discrepancies in findings may be explained in part by the difference in species, the small doses of epinephrine, or the relatively lower concentrations of cyclopropane ordinarily employed in clinical patients (4).

Norepinephrine has been used clinically as a continuous intravenous infusion in a concentration of 2 to 4 mg. per liter of normal saline or 5 per cent dextrose solution. The rate of infusion to achieve the desired pressor effect is usually 0.1 to 0.3 microgram of the free base per

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kilogram of body weight per minute. Obviously, the blood concentration of norepinephrine under such conditions would differ from that following a single large intravenous injection. It was the purpose of this study to determine the incidence of alterations in cardiac rhythm during continuous intravenous infusions of norepinephrine, epinephrine and neosynephrine in various concentrations during cyclopropane or ether anesthesia in the dog. The pressor effects of these sympathomimetic amines were also compared and correlated with electrocardiographic tracings.

METHODS

Seven dogs weighing between 7 to 11 kg. were used for the present study. Each dog was challenged with continuously infused vasopressor amines during anesthesia. The same experiments were repeated on each dog after a rest period of one week. Ether or cyclopropane was employed during the first experiment, to be followed by the other anesthetic agent the following week. Thus each dog served as its own control. Induction of anesthesia was achieved with 10 to 20 mg. per kilogram of thiopental sodium given intravenously to minimize excitement. A cuffed endotracheal tube was inserted through which ether or cyclopropane was administered with oxygen. The endotracheal tube was connected to a closed to-and-fro rebreathing absorption system and anesthesia was carried to the third plane of surgical anesthesia, that is, absence of the wink reflex. The anesthesia was maintained at this plane for about thirty minutes for equilibration before any of the vasopressor amines was given. Solutions of 1-epinephrine hydrochloride, 1-norepinephrine bitartrate and neosynephrine hydrochloride were prepared by dissolving the respective crystalline salts in 5 per cent dextrose in water in appropriate concentrations for convenient adjustments of flow rates. The infusion was administered through a cannula inserted in the femoral vein. A constant rate of infusion was maintained with a Graubard-Peterson flowrate[§] calibrated for 5 per cent dextrose in water at 20 C. The range of dosages studied varied from 0.3 to 0.9 microgram of the free base per kilogram of body weight per minute. Each test infusion lasted from ten to twenty minutes. An infusion of 5 per cent dextrose in water was administered during rest periods of fifteen minutes or longer between test periods to allow recovery from any change in cardiac rhythm and arterial pressure. From 0.1 to 0.25 mg. per kilogram of body weight of epinephrine or norepinephrine was given intravenously as a single dose at the end of each final experiment.

The arterial pressure from the femoral artery was recorded continuously with a capacitance electromanometer (Sanborn). The electrocardiogram in standard limb leads was recorded simultaneously with a direct writing Sanborn twin visio-cardiette. In a few early experi-

[§] Fisher and Porter, Hatboro, Pa.

ments the mean arterial pressure was measured with a mercury manometer.

RESULTS

I. Pressor Effects

A. *Cyclopropane Anesthesia*.—Norepinephrine in the dosage ranging from 0.3 to 0.9 microgram per kilogram of body weight per minute caused a rise in the mean arterial pressure of 20 to 40 mm. of mercury. Only in one instance when the dosage was 0.3 microgram per kilogram per minute was the rise less than 20 mm. of mercury. Both systolic and diastolic pressures were elevated (fig. 1, table 1).

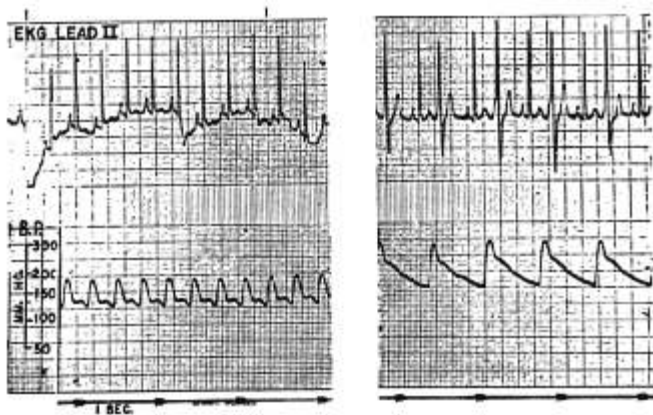


FIG. 1. Dog weighed 10.9 kg. Cyclopropane anesthesia. Left record: control period—heart rate was 200 per minute; arterial pressure, 180/120 mm. of mercury (normal sinus rhythm). Right record: during intravenous infusion of 0.5 microgram per kilogram per minute of norepinephrine bitartrate—arterial pressure rose to 290/150 mm. of mercury; heart rate was 180 per minute with alternating ventricular extrasystoles.

The pressor effects of epinephrine which occurred in dosage ranges of from 0.7 to 0.9 microgram per kilogram per minute were similar to those of norepinephrine in this range. With lower dosage, the mean arterial pressure rise was usually less than 20 mm. of mercury and the diastolic pressure was not altered or only elevated slightly (table 1). Indeed in one instance when the dosage of epinephrine infusion was 0.3 microgram per kilogram per minute the systolic pressure was depressed from a control of 155 mm. to 105 mm. of mercury and the diastolic pressure from 100 mm. to 70 mm. of mercury (fig. 2).

With neosynephrine in the dosage of 3 to 6 micrograms per kilogram per minute the pressor effect was quite marked. Elevation of the mean

arterial pressure exceeded 40 mm. of mercury (fig. 3). Since the animals of all groups had intact baroreceptors and reflex mechanisms, the heart rate was usually decreased during elevation of the arterial pressure unless ventricular tachycardia supervened.

B. *Ether Anesthesia*.—Infusion of norepinephrine of the same dosage as in the experiments with cyclopropane did not cause a comparable elevation of arterial pressure. In half of the experiments the rise was less than 20 mm. of mercury.

During 11 epinephrine infusions of similar dosages to those with cyclopropane the mean arterial pressure was elevated in only 3 in-

TABLE I
EFFECTS OF NOREPINEPHRINE, EPINEPHRINE AND NEOSYNEPHRINE ON ARTERIAL BLOOD PRESSURE DURING ETHER AND CYCLOPROPANE ANESTHESIA

Vasopressor Amines	Dosage, $\mu\text{g./kg./min.}$	Cyclopropane						Ether					
		Experiments	Incidence of					Experiments	Incidence of				
			Mean Arterial Pressure Changes						Mean Arterial Pressure Changes				
			Fall	No. Change	Rise (mm. Hg)				Fall	No. Change	Rise (mm. Hg)		
0-20	20-40	40			0-20	20-40	40+						
Norepinephrine	0.3	3			1	2		2			1	1	
	0.5	4			4	3		3			1	2	
	0.7	4			3	1		4			2	2	
	0.9	3			3			2			1		1
Epinephrine	0.3	2	1		1			2	1	1			
	0.5	3			2	1		2		2			
	0.7	4			1	3		5	1	2	2		
	0.9	3				3		2		1		1	
Neosyneprine	3	1				1							
	6	2					2	1				1	

stances. In 6 animals there was no detectable change in the arterial pressure and in another 2 the arterial pressure fell.

One test infusion of neosyneprine of 6 micrograms per kilogram per minute caused a rise in mean arterial pressure from 155 to 175 mm. of mercury. The heart rate was not significantly changed unless the arterial pressure was elevated. In such cases the heart rate became slower.

II. Cardiac Rhythm

A. *Cyclopropane*.—The simultaneous administration of cyclopropane and norepinephrine or epinephrine provoked marked changes in the cardiac rhythm. During cyclopropane anesthesia a large number of test infusions of these two vasopressor amines resulted in ventricular

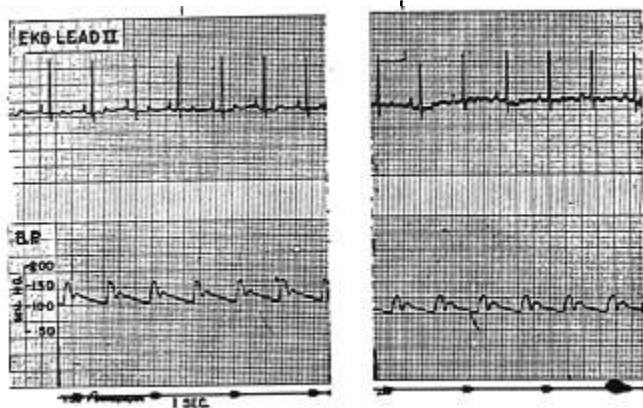


FIG. 2. Dog weighed 9.7 kg. Cyclopropane anesthesia. Left record: control period—heart rate was 110 per minute; normal sinus rhythm; the arterial pressure, 155/100 mm. of mercury. Right record: during intravenous infusion of 0.3 microgram per kilogram per minute of epinephrine hydrochloride—heart rate remained at 110 per minute; normal sinus rhythm; arterial pressure dropped to 105/70 mm. of mercury.

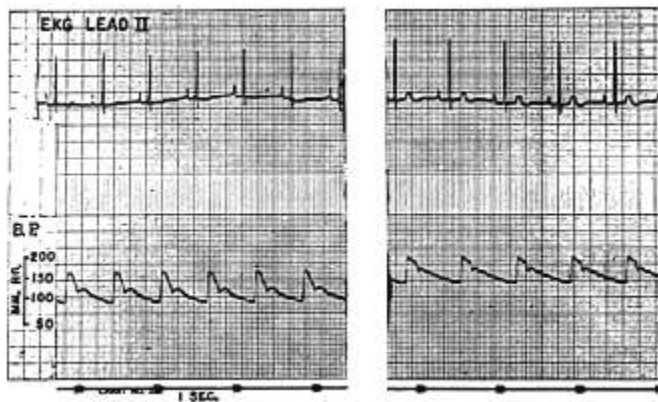


FIG. 3. Dog weighed 10.9 kg. Cyclopropane anesthesia. Left record: control period—heart rate was 100 per minute; normal sinus rhythm; arterial pressure, 160/85 mm. of mercury. Right record: during intravenous infusion of 6 micrograms per kilogram per minute of nesynephrine hydrochloride—heart rate was 90 per minute; normal sinus rhythm; arterial pressure rose to 200/130 mm. of mercury.

arrhythmias (table 2). The most frequent form of ventricular arrhythmia was premature ventricular contractions, usually multifocal in origin. In 4 instances these premature ventricular contractions preceded runs of idioventricular rhythm and ventricular tachycardia. The ventricular arrhythmias usually disappeared promptly after termination of the test infusion but sometimes they disappeared even during the infusions. It is interesting to note that with norepinephrine, ventricular arrhythmias in some form occurred in all experiments whereas with epinephrine normal sinus rhythm was maintained throughout 7 of 12 periods. In all three trials of neosynephrine infusions during

TABLE 2
INCIDENCE OF VENTRICULAR ARRHYTHMIAS DURING NOREPINEPHRINE, EPINEPHRINE AND
NEOSYNEPHRINE INFUSION WITH CYCLOPROPANE AND ETHER ANESTHESIA

Vasopressor Amines	Dosage, mg./kg./ min.	Cyclopropane					Ether						
		Experi- ments	Incidence of Ventricular Arrhythmia					Experi- ments	Incidence of Ventricular Arrhythmia				
			None	P.V.C.	I.V.R.	V.T.	V.F.		None	P.V.C.	I.V.R.	V.T.	V.F.
Norepinephrine	0.3	3		2	2	1		2	2				
	0.5	4		4		1		3	3				
	0.7	1		3	1			4	4				
	0.9	3		3				2	2				
Epinephrine	0.3	2	1			1*		2	2				
	0.5	3	1	2				2	2				
	0.7	4	3	1		1		5	5				
	0.9	3	2			1		2	2				
Neosynephrine	3	1	1										
	6	2	2					1	1				

* The idioventricular rhythm was followed by asystole. Sinus rhythm resumed promptly after the cyclopropane and epinephrine infusions were withdrawn.

Abbreviations: P.V.C.—premature ventricular contractions, I.V.R.—idioventricular rhythm, V.T.—ventricular tachycardia, V.F.—ventricular fibrillation.

cyclopropane anesthesia there was no disturbance in the cardiac rhythm.

Ventricular fibrillation was not observed with norepinephrine and epinephrine administered as a continuous intravenous infusion. When these amines were given intravenously as single injections at the end of our experiments, 3 animals responded with prompt onset of ventricular fibrillation. In two instances the challenging drug was norepinephrine, 0.1 and 0.25 mg. per kilogram respectively, and in the third, 0.1 mg. per kilogram of epinephrine. In the fourth animal transient ventricular tachycardia was the response to intravenous administration of 0.01 mg. per kilogram of epinephrine and later of norepinephrine.

B. Ether.—Intravenous infusion of norepinephrine, epinephrine and neosynephrine to animals during ether anesthesia did not alter the basic normal sinus rhythm. The dosage of infusion was the same as in the case of cyclopropane, ranging from 0.3 to 0.9 microgram per kilogram per minute for norepinephrine and epinephrine, and 6 micrograms per kilogram per minute for neosynephrine (table 2).

At the end of one experiment with ether anesthesia a single dose of 0.32 mg. per kilogram of norepinephrine was injected intravenously. It first caused runs of ventricular premature contractions which soon changed into ventricular tachycardia. However, the ventricular tachycardia subsided spontaneously after a few minutes and evolved into sinus tachycardia at a rate of 260 per minute which persisted until the animal was killed.

DISCUSSION

The results obtained in this study confirm and extend the findings of Orth and his co-workers (2). Although the number of experiments is too small to warrant any statistical analysis, it can be stated on the basis of these data that norepinephrine and epinephrine infusions in the dosages studied can produce arrhythmias of ventricular origin during cyclopropane anesthesia in the dog. Certainly, the significance of a transient ventricular premature contraction is questionable, but the frequency of ventricular rhythm is comparable to the results reported previously for single injections of these vasopressor amines (2).

It is interesting to note that in comparable dosage, norepinephrine provoked ventricular arrhythmias more frequently than epinephrine during cyclopropane anesthesia. Norepinephrine also raised the arterial pressure more than did epinephrine. It is obvious that elevation of the arterial pressure is not the most important factor in the production of arrhythmias since significant increases in pressure occurred with neosynephrine without ventricular arrhythmia. This seems to agree with the conclusion drawn by Murphy *et al.* (5) that a rise of blood pressure *per se* is not the cause of irregularity but may predispose to the production of ventricular tachycardia.

The use of thiopental sodium for induction before the establishment of cyclopropane anesthesia is of considerable help in minimizing excitement and consequent endogenous secretion of adrenal medullary pressor substances. It probably did not alter the incidence of ventricular arrhythmias as Orth *et al.* (6) reported that a variety of barbiturates, including thiopental, did not protect the animals from epinephrine-cyclopropane arrhythmias. Indeed, in many cases these authors observed a longer duration of ventricular tachycardia during the action of barbiturates.

The absence of ventricular arrhythmia during continuous intravenous infusion of norepinephrine and epinephrine with ether anesthesia agrees with the findings of Orth *et al.* (2) and Meek and his co-

worker (7). Ether does not sensitize the specific tissue of the heart so that the challenging doses of norepinephrine and epinephrine (as continuous intravenous infusion or single injections) failed to produce any significant cardiac irregularity. Furthermore, it has been claimed that the presence of ether vapor in the anesthetic mixture, even in a very small concentration, can protect the heart against cyclopropane-epinephrine arrhythmias (8).

SUMMARY AND CONCLUSIONS

The cardiovascular effects of continuous intravenous infusions of norepinephrine, epinephrine, and neosynephrine given to dogs during cyclopropane and ether anesthesia were studied.

The simultaneous administration of cyclopropane and norepinephrine or epinephrine resulted frequently in serious ventricular arrhythmias, whereas a sinus rhythm was maintained during the combined administration of ether and these vasopressor amines.

In contrast, neosynephrine infusions did not cause ventricular arrhythmias during cyclopropane anesthesia.

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