Ventricular Arrhythmias and Automaticity following Norepinephrine.* (22832)

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In human subjects norepinephrine was shown to increase peripheral vascular resistance without accelerating the heart rate(1). Norepinephrine has also been reported to be less effective in precipitating ventricular ectopic rhythms(2) and it is being used in treatment of secondary shock when epinephrine is contra-indicated to restore arterial blood pressure. Recently, norepinephrine was observed to increase the vulnerability of the ventricles to fibrillation and the greater safety reported for norepinephrine was considered to be due to its slower rate of infusion in clinical practice(3). Because norepinephrine is employed extensively in treatment of hypotensive states, this study was undertaken to compare its potency relative to that of epinephrine in eliciting experimental, ventricular rhythms. Using cats under pentobarbital, harman methosulfate was given to predispose the heart to ventricular rhythms by a method previously described(4). To extend the quantitative comparison of norepinephrine and epinephrine on cardiac excitability, their actions on isolated cardiac papillary muscle preparation of Cattell and Gold(5) were also investigated.

Methods. Experimental ventricular arrythmias. The electrocardiographic changes produced by epinephrine and norepinephrine were studied in normotensive cats under sodium pentobarbital anesthesia. Harman methosulfate (2.5 mg/kg) was injected 5 minutes before epinephrine or norepinephrine and the ensuing electrocardiographic changes were recorded. *Automaticity studies.* Following the technic of Cattell and Gold(5) isolated, cat, cardiac papillary muscles were mounted in lucite holder and immersed in 75 ml of modified Locke's solution(6). The chordae tendinae were connected by a fine silk thread to a thin steel plate on each side of which a Baldwin SR-4 strain gauge was mounted and contractions were recorded with the strain gauge amplifier of a Sanborn Twin-Viso Cardiette. The muscle was stimulated electrically with a square wave shock from a thyratron stimulator at 60 per minute and the amplitude of contractions and threshold of excitability were noted. The incidence of automaticity (rhythmic contractions without electrical stimulation) was observed following addition of norepinephrine and epinephrine with equilibration period of at least 15 minutes between drugs.

Results. Nodal rhythm (NR), ventricular extrasystoles, tachycardia and flutter (VR) and ventricular fibrillation (VF) occurred following injection of both epinephrine and norepinephrine in cats previously treated with harman methosulfate (Table I). Immediately before the onset of fibrillatory rhythm, a migration of the T-wave into the QRS could be seen (Fig. 1). A similar interruption of T-waves by R-waves was observed by Fastier to occur before "epinephrine syncope" following benzene or furfurin(7). In contrast to larger mammals, cats were able to survive relatively long periods of ventricular fibrillation. Based on both the duration of arrhythmias and the incidence of ventricular fibrillation, norepinephrine was found to be significantly more active than epinephrine in eliciting ventricular ectopic rhythms ($p < 0.05$). *Automaticity of papillary muscles.* A pos-

TABLE I. Incidence and Duration of Arrhythmias in Cats Treated with 2.5 mg/kg Harman Methosulfate.

Drug	Dose, μg/kg	Number				Duration of arrhythmias, sec.*
		Total	NR	VR	VF	
Epinephrine	2.5	10	0	6	3	8.4± 3
	5.0	10	2	9	6	54 ±16
	10.0	11	3	11	5	78 ±20
	20.0	10	4	10	7	66 ± 9
Norepinephrine	1.2	10	1	10	4	82 ±43
	2.5	10	0	9	4	116 ±40
	5.0	10	3	10	6	198 ±30
	10.0	10	4	10	9	162 ±16

* Mean ± S.E.

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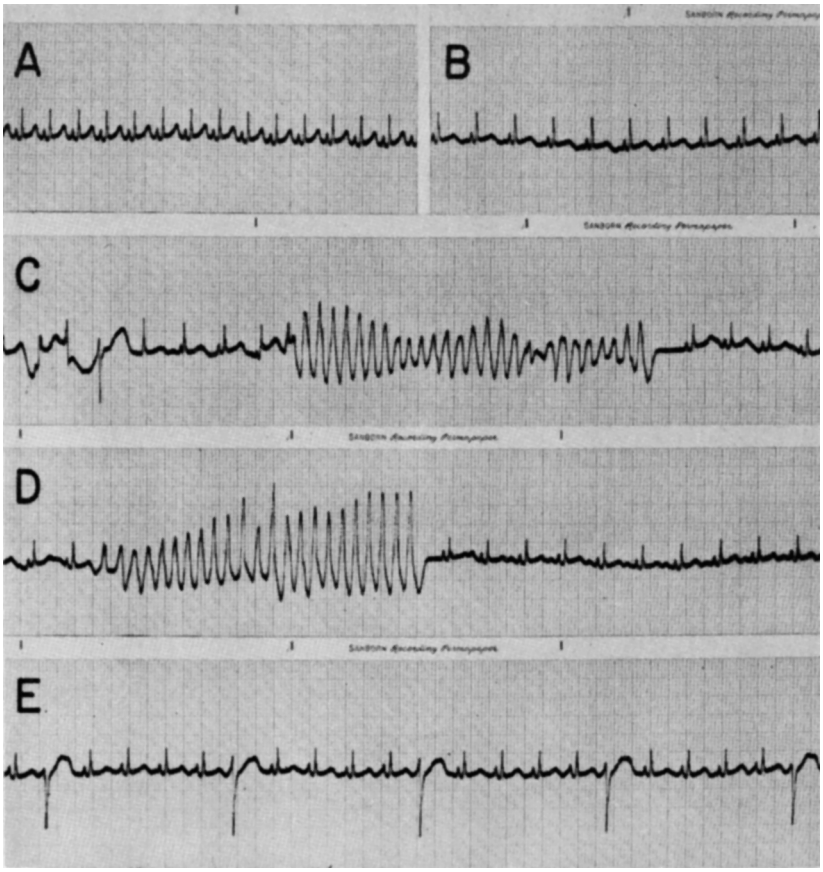

FIG. 1. Electrocardiograms of cat (2.4 kg) under sodium pentobarbital. A, 11:37 a.m., control reading. B, 11:44 a.m., 4 min. after harman methosulfate 2.5 mg/kg intrav. C, 11:45 a.m., 12 sec. after norepinephrine bitartrate 5 μg/kg intrav. D, continuation of C. E, 11:47 a.m., 2 min. after norepinephrine bitartrate.

sible relationship between ability of a substance to initiate automaticity and the property of precipitating ventricular ectopic beats was previously suggested(4). A comparison of the incidence of automaticity in the papillary muscles after addition of epinephrine and norepinephrine was therefore indicated to see whether norepinephrine was also more active in this preparation. As shown in Fig. 2, norepinephrine was found to be effective in increasing contractile force and inducing rapid, automatic contractions of papillary muscle. Although changes of contractile force of the papillary muscle produced by norepinephrine and epinephrine did not differ, the incidence of automaticity after norepinephrine was significantly greater than after epinephrine ($p < 0.05$).

TABLE II. Effects of Epinephrine and Norepinephrine on Cardiac Papillary Muscles.

Drug	Conc.	Incidence of automaticity	Mean % increase in amplitude of contractions
Epinephrine	$.4 \times 10^{-6}$	2/12	60
	1.6 "	6/12	123
Norepinephrine	.2 "	5/12	66
	.8 "	8/ 9	95

To compare the cardioaccelerator properties of epinephrine and norepinephrine with their effects on cardiac excitability, the increases in heart rate in isolated, perfused cats' hearts were determined. The tachycardia following epinephrine was greater than for equivalent doses of norepinephrine although the difference in activity was not significant. Thus, the relative effects of these substances

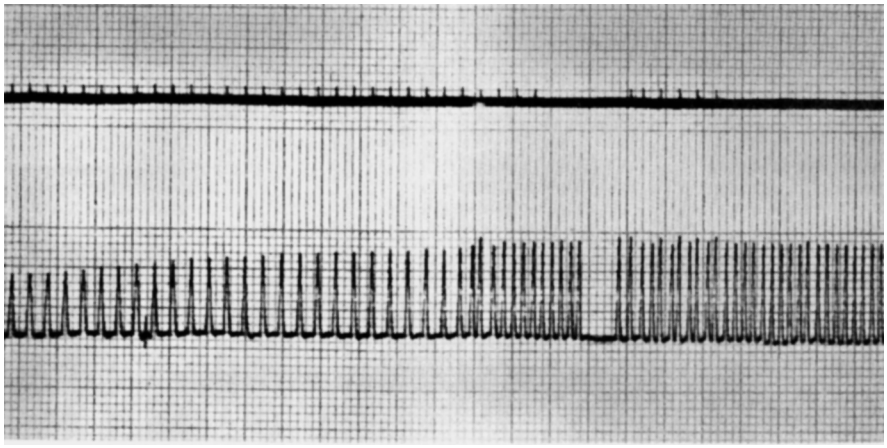

FIG. 2. Increase in contractile force and automaticity induced by norepinephrine bitartrate (1.6×10^{-6}) in the cat's heart papillary muscle. Upper record, stimulus marker (frequency, 1/sec.; duration, 10 millisec.; 15 volts). Lower record, contractions recorded by a strain gauge and amplifier of a Sanborn Twin-Viso Cardiette. Five horizontal lines represent 1 g.

on the sinus node and on ventricular excitability appeared to be separable.

Discussion. Electrocardiographic changes consisting of heart block and supraventricular rhythms were occasionally observed in normal subjects after intravenous norepinephrine(9). In cases of shock, on the other hand, most authors have found no evidence that the drug increased myocardial irritability during the hypotensive phase even after coronary occlusion. Nevertheless, the high potency of norepinephrine in precipitating ventricular rhythms in normotensive cats treated with harman methosulfate as well as in increasing cardiac irritability(8) points to a potential hazard of this pressor amine in clinical practice. Both epinephrine and norepinephrine were found to be less likely to elicit ventricular rhythms including fibrillation in dogs under cyclopropane which were made hypotensive by bleeding(2). The failure of norepinephrine to provoke arrhythmias in the therapy of shock in which the heart is vulnerable to fibrillation may therefore be related to the low blood pressure levels in these cases and not to the fact that norepinephrine lacks the effects of epinephrine on ventricular excitability.

Summary. (1) Nodal rhythm, ventricular extrasystoles, flutter and fibrillation were precipitated by norepinephrine in cats, under pentobarbital anesthesia, treated with harman methosulfate. Migration of the T-wave into the R-wave at onset of ventricular fibrillation was similar to that described before epinephrine induced arrhythmias. (2) The effects of norepinephrine on cardiac excitability were confirmed using isolated papillary muscles in which norepinephrine had a greater potency than epinephrine in eliciting automatic contractile activity.

1. Goldenberg, M., Pines, K. L., Baldwin, E. deF., Greene, D. G., and Roh, C. E., *Am. J. Med.*, 1948, v5, 792.

2. Brockman, H. L., and Huggins, R. A., *Arch. int. pharmacodyn.*, 1954, v99, 395.

3. Hoffman, B. F., Siebens, A. A., Cranefield, P. F., and Brooks, C. McC., *Circulation Res.*, 1955, v3, 140.

4. Hutcheon, D. E., Scriabine, A., and Rapuzzi, A. L., *J. Pharmacol.*, 1955, v113, 29.

5. Cattell, McK., and Gold, H., *ibid.*, 1938, v62, 116.

6. Chenoweth, M. B., and Koelle, E. S., *J. Lab. and Clin. Med.*, 1946, v31, 600.

7. Fastier, F. N., *J. Physiol.*, 1951, v112, 359.

8. Greiner, T. H., and Garb, S., *J. Pharmacol.*, 1950, v98, 215.

9. Moyer, J. H., Skelton, J. M., and Mills, L. C., *Am. J. Med.*, 1953, v15, 330.

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