Ventricular Arrhythmias Induced by Sympathomimetic Amines in Unanesthetized Dogs Following Coronary Artery Occlusion

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Epinephrine and norepinephrine, in doses which cause little ectopic activity in unanesthetized normal dogs, produce exaggerated ectopic responses about the fourth day after coronary ligation, when the arrhythmias caused by the ligation per se have subsided. These responses persist for approximately 12 days after ligation and suggest reactivation of latent ectopic foci. Observations with methoxamine, isoproterenol, and atropine indicate that ventricular tachycardia is easily induced after occlusion by drugs which simultaneously stimulate the myocardium and slow the sinus node rate.

Harris1 has shown that dogs develop ventricular ectopic rhythms 3 to 10 hours after coronary artery ligation if immediate ventricular fibrillation is prevented by following a two-stage occlusion procedure. The delayed ventricular ectopic activity reaches a maximum within the first 24 hours and then progressively declines, disappearing in 3 to 5 days. Harris postulated that ischemic cells in a zone surrounding the central necrotic area of infarct act as hyperexcitable ectopic foci discharging impulses spontaneously, and that other factors such as released epinephrine,1 norepinephrine,2 histamine,1 and potassium3 might contribute to the hyperactive state of the ectopic foci.

During a study of the effects of antiarrhythmic drugs on the delayed ventricular ectopic activity in dogs following two-stage occlusion of the anterior descending coronary artery, it was noted that intravenous injections of epinephrine, in doses which cause little ectopic activity in normal dogs, produce marked ventricular tachycardia even several days after the arrhythmias induced by the ligation have disappeared. These exaggerated responses to epinephrine indicate the existence of hyperexcitable ectopic foci for a period longer than the 3 to 5 days described by Harris. Epinephrine-induced ventricular tachycardia after coronary artery occlusion has also been noted by Clark and Cummings.4 The present study was initiated, therefore, to study the electrocardiographic responses to several sympathomimetic amines in unanesthetized dogs before and after coronary artery ligation.

Methods

Mongrel dogs 6 to 22 Kg. were anesthetized with sodium pentobarbital and the heart exposed. In 24 dogs the anterior descending coronary artery was ligated by the two-stage occlusion procedure of Harris1 at the level of the tip of the left atrium, 1.5 to 3 cm. from the ostium. In 2 dogs, the marginal branch of the circumflex artery was ligated by the same technic approximately 1 cm. from its junction with the circumflex trunk. Two dogs were subjected to sham operations. Penicillin was administered daily for 4 days following operation. At least 20 hours elapsed before the testing of drugs.

Electrocardiograms were recorded either with a Sanborn Viso-Cardiette or a Grass four-channel oscillograph using standard or augmented limb leads. In some experiments potential differences between the right arm and a pericardial electrode was also recorded. Femoral arterial pressure was recorded by a Statham transducer connected to an indwelling polyethylene catheter.

Responses to drugs were determined in each dog before and at varying times after ligation of the anterior descending coronary artery. All drugs were injected intravenously in a constant volume (2 ml.) followed by a saline wash (2 ml.) during an interval of about 10 sec. 1-Norepinephrine and l-epinephrine

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were administered as bitartrates (Levophed and Suprarenin) and methoxamine (Vasoxyl) and isoproterenol (Isuprel) as the hydrochlorides. Dilutions were made daily from the commercial solutions. Doses are expressed in terms of the free bases.

A quantitative comparison of the effects of epinephrine and norepinephrine was made using the following procedure: Three or more days prior to coronary artery ligation, the electrocardiographic responses to graded equimolar doses of the two drugs were obtained in 13 unanesthetized dogs. There was an interval of from 15 to 60 min. between successive injections. In 7 dogs each injection of norepinephrine was followed by the equimolar dose of epinephrine, while in the remaining 6 dogs this order was reversed. Whenever doses greater than 90 μg./Kg. were tested at least 10 days elapsed between the control injections and coronary artery ligation. On the fourth postoperative day, i.e., after subsidence of "spontaneous" ectopic activity, electrocardiographic responses to the same graded doses of epinephrine and norepinephrine were again determined.

The response to each dose was analyzed by counting the total heart rate and the rate of all ectopic beats for each successive 30 sec. interval over a period of 2 min. before and 5 or more min. after injection (fig. 1). The fastest ectopic rate recorded was considered to be the maximum produced by a given dose. The number of ectopic beats during the first 5 min. following an injection was defined as the "5 min. ectopic response." The mean, maximum and 5 min. ectopic responses, were plotted on semilogarithmic paper to obtain dose-response curves.

**RESULTS**

*Direct Effects of Coronary Artery Ligation.* Within 24 hours after coronary artery ligation all dogs developed ventricular and atrioventricular nodal arrhythmias which then progressively declined until about the fourth postoperative day when little ectopic activity remained, a pattern similar to that described by Harris. Little difference in type or severity of arrhythmias was noted between the 24 dogs with ligation of the anterior descending coronary artery and the 2 dogs with occlusion of the marginal branch of the circumflex artery. The absence of exaggerated ectopic responses in the sham-operated dogs demonstrated that coronary artery occlusion is the causal factor in the production of hyperexcitable ectopic foci.

**Effects of Ligation on Responses to Epinephrine and Norepinephrine.** Following ligation of the anterior descending coronary artery or the marginal branch of the circumflex artery, marked cardiac arrhythmias resulted from the intravenous injections of epinephrine and norepinephrine. These drug-induced arrhythmias were superimposed on the ligation-induced "spontaneous" ectopic activity until the disappearance of the latter around the fourth postoperative day. The drug-induced arrhythmias continued to be exaggerated until about the twelfth day, even though there was usually no spontaneous ectopic activity after the fourth day. Within a minute after the injection of either epinephrine or norepinephrine, runs of ventricular tachycardia appeared, which usually alternated among several foci. A-V nodal rhythm frequently preceded the ventricular rhythm. Interference dissociation became prominent during the decline of the ectopic activity. Within 5 to 10 min. sinus rhythm usually had returned, although with large doses the ectopic activity sometimes lasted 20 min. or more.

The absence of exaggerated ectopic responses in the sham-operated dogs demonstrated that coronary artery occlusion is the causal factor in the production of hyperexcitable ectopic foci. That epinephrine and norepinephrine produced exaggerated ectopic responses after ligation is evident from figure 1, which is a graphical comparison of the electrocardiographic and arterial pressure responses to equimolar doses of the two drugs before and on the fourth day after ligation of the anterior descending coronary artery. The responses of the two drugs were similar before ligation, consisting of a rise in arterial pressure, cardiac
slowing, and moderate ectopic activity, which was usually atrioventricular nodal in origin. After ligation, the same doses produced ventricular tachycardia. Records with well-defined P-waves obtained with pericardial electrodes indicated that epinephrine and norepinephrine produced marked reflex slowing of the sinus node both before and after coronary artery ligation.

Dose-response curves to the two compounds were obtained in 13 unanesthetized dogs before and on the fourth day after coronary occlusion when there was no appreciable spontaneous ectopic activity. The maximum ectopic rate and the 5 min. ectopic response were found proportional to the dose for both drugs before and after ligation (fig. 2). Before ligation the maximum ectopic rates produced by epinephrine and norepinephrine were alike; 4 days after occlusion the maximum ectopic rate produced by norepinephrine exceeded that produced by the equimolar dose of epinephrine by approximately 24 beats/min., a significant difference (p<0.001). This difference is even more evident in the case of the 5 min. ectopic responses. As seen in the lower half of figure 2, in the range of 0.02 to 0.2 μM/Kg., norepinephrine produced 150 to 250 more ectopic beats during the first 5 min. than epinephrine, a difference due both to the greater maximum intensity and the longer duration of action of norepinephrine.

Doses of epinephrine and norepinephrine greater than 0.1 μM/Kg. produced highly variable responses before ligation, as seen by the large standard errors of the means for the maximum ectopic rates in figure 2.

The difference between the potency of epinephrine and norepinephrine after ligation does not seem to be correlated with the level of arterial pressure (fig. 1).

Duration of Ectopic Process Determined by Responses to Norepinephrine. The persistence of the ectopic process after the disappearance of the spontaneous ectopic activity was apparent from the continued exaggerated ectopic responses to a standard dose of norepinephrine (0.056 μM/Kg. = 9.5 μg/Kg.). Figure 3 compares the temporal decline of the spontaneous activity...
and norepinephrine-induced ectopic activity after ligation. The maximum ectopic rate produced by norepinephrine was greatest on the first postoperative day, as was the spontaneous ectopic rate. Both types of ectopic activity then progressively declined, the spontaneous one more rapidly. Thus, by the fourth postoperative day, the spontaneous arrhythmias had virtually disappeared, whereas the electrocardiographic responses to norepinephrine persisted 12 days after occlusion.

Electrocardiographic Responses to Methoxamine and Isoproterenol. Since the drug-evoked arrhythmias might have resulted from a combination of myocardial stimulation and slowing, two other sympathomimetic amines with different properties were tested. Methoxamine, a pressor amine with negligible cardiac stimulant action, caused marked sinus bradycardia with only moderate ectopic activity, both before and 4 days after ligation. Ventricular tachycardia did not occur with methoxamine. Isoproterenol, a vasodepressor amine with strong myocardial stimulant action, produced marked sinus acceleration and almost no ectopic activity, either before or 4 days after ligation.

Effect of Atropine on Arrhythmias. Atropine, in dose of 0.1 to 0.3 mg./Kg. intravenously, which caused acceleration to levels equal or greater than the ectopic rates, reduced or abolished both the spontaneous and drug-induced arrhythmias after occlusion. Other investigators have reported a similar action of atropine against epinephrine arrhythmias in conscious normal dogs and anesthetized cats.

Discussion
An analysis of the effects of several drugs indicates that ventricular tachycardias are most easily induced after occlusion by drugs which stimulate the myocardium and also produce sinus bradycardia. Thus, epinephrine and norepinephrine induce a reflex slowing of the sinus node rate concomitant with myocardial stimulation. Both drugs elicit ventricular tachycardia after coronary artery occlusion. In contrast, isoproterenol, although a strong myocardial stimulant, induces a pronounced acceleration of the sinus node rate, both directly and reflexly as a result of the fall in blood pressure.

Isoproterenol causes only negligible ectopic activity in the unanesthetized dog before or 4 days after coronary ligation. Methoxamine, on the other hand, produces a rise in blood pressure and reflex bradycardia, but no myocardial stimulation, and causes only moderate ectopic activity after occlusion. Finally, atropine, by blocking vagus nerve impulses, produces sinus tachycardia and abolishes the spontaneous arrhythmias induced by coronary artery ligation per se as well as those elicited by norepinephrine.

Two aspects of the present study warrant mention in connection with myocardial infarction in human beings. First, the total period of exaggerated drug-induced ectopic activity in the dog is approximately 12 days, a close correspondence with the clinical observation that the first 2 weeks following myocardial infarction in man is the most likely period for the development of paroxysmal ventricular tachycardia. Secondly, the use of large doses of norepinephrine in the treatment of shock resulting from myocardial infarction may involve a risk of inducing arrhythmias. In general, however, since the concentrations and rates of infusion of norepinephrine used clinically are much less than those used in the present study, the potential danger is probably slight.

The close correspondence in potency between epinephrine and norepinephrine in regard to eliciting ventricular arrhythmias after coronary artery occlusion agrees with the demonstrations of the equipotency of the two drugs on cardiac excitability, cardiac contractile force, and the production of atrioventricular rhythms during vagal stimulation.

Summary
Two-stage occlusion of either the anterior descending coronary artery or the marginal
branch of the circumflex artery produces both "spontaneous" ventricular arrhythmias and exaggerated ectopic responses to epinephrine and norepinephrine. Both spontaneous and drug-induced ectopic activity reach a maximum intensity within 24 hours after ligation. The spontaneous ectopic activity gradually disappears over a period of about 4 days, while the exaggerated drug-induced ectopic activity persists for about 12 days. Observations with isoproterenol, methoxamine, and atropine indicate that ventricular tachycardias are easily induced after occlusion by drugs which simultaneously stimulate the myocardium and slow the sinus node rate. A quantitative comparison suggested that norepinephrine is slightly, but significantly more active than epinephrine in producing arrhythmias after coronary artery ligation.

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