Cardiac Arrhythmias Induced by Minimal Doses of Epinephrine in Cyclopropane-Anesthetized Dogs

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It is believed generally that the phenomenon of hydrocarbon sensitization of the myocardium to the production of aberrant rhythms by sympathomimetic amines involves an increased susceptibility of ventricular tissue to pacemaker formation. This concept clearly emerges from most papers and reviews on this subject. Several of these authors point out, nevertheless, that the known actions of the sensitizing agents on the myocardium are depressant and that increased susceptibility to the formation of foci of automaticity is difficult to reconcile with these actions. Several suggestions have been made which attempt to integrate the 2 sets of observations. Thus Riker et al. suggest that multiple ventricular foci of automaticity emerge because the primary ectopic pacemaker located in the A-V node is depressed by the hydrocarbon, while DiPalma and Schultz advanced the hypothesis that the effect of epinephrine is greater on local depressed areas than on more normal areas of myocardium.

We have shown recently that the potency of epinephrine for inducing ventricular arrhythmias in barbiturate-anesthetized dogs is not changed by maintaining the atrial rate electrically at a frequency greater than the ectopic rate. In this preparation, each episode of ventricular rhythm was shown to be preceded by slowed or blocked A-V nodal conduction, leading to sufficient ventricular slowing to allow the emergence of the ventricular focus of automaticity.

If hydrocarbon sensitization to the production of cardiac arrhythmias by sympathomimetic amines is due to facilitation of ectopic pacemaker formation, it is necessary that the rate of the new ventricular pacemaker(s) be greater than the atrial rate, or that A-V nodal block intervene as it does in the barbiturate-anesthetized animal. It seemed of interest, therefore, to determine the effects of changes in atrial rate on the dose of epinephrine necessary to induce ventricular tachycardia in animals under cyclopropane anesthesia. Since it is known that vagotomy has no effect on the induction of arrhythmia in sensitized preparation although it protects barbiturate anesthetized animals, vagal effects on A-V nodal conduction were eliminated by bilateral vagotomy. In attempting to determine the threshold dose, we found that the nature of the arrhythmia produced changed from ventricular tachycardia to a coupled rhythm as the dose of epinephrine was reduced. Observations on the nature of this coupled rhythm and on factors involved in its genesis provide the basis of this report.

Methods

Fifty-seven healthy mongrel dogs of both sexes, weighing from 4 to 11 Kg., were anesthetized initially with 20 mg./Kg. of sodium thiopental, intravenously. The trachea and right carotid artery were cannulated, the vagi sectioned bilaterally, and the right femoral vein exposed for injection. In 31 of these animals, the thorax was opened, using a midline, sternum-splitting incision. A small incision in the pericardium was made and stimulating electrodes placed on the right atrial appendage. Positive pressure artificial respiration was administered using a Palmer pump supplying 100 per cent oxygen. After completion of most of the operative procedures, the gas mixture in the semielosed system was changed to 20 per cent cyclopropane in oxygen. After completion of the operative procedures, the gas mixture in the semielosed system was changed to 20 per cent cyclopropane in oxygen.

Thirty minutes were allowed for equilibration of the animal with the gas mixture, the rebreathing bag being emptied frequently to prevent nitrogen accumulation. A carbon dioxide absorber pre-
vented the development of hypercapnia. Because of the reported "adrenolytic" effect of cyclopropane after prolonged administration, all experiments were terminated after less than 3 hours of cyclopropane anesthesia.

Lead II electrocardiograms were taken on all dogs using subcutaneous needle electrodes, and in many of the open-chest animals atrial electrograms were recorded as well. A Statham transducer was used to measure the carotid blood pressure. All parameters were recorded on a Grass polygraph.

In experiments in which the heart was driven by electrodes on the atrial appendage, a Tektronix stimulator supplied rectangular stimuli of 1.0 msec, duration and approximately twice threshold intensity. The driving rate was set 25 to 45 beats/min. greater than the sinus rate. In some experiments, systemic arterial pressure was held constant or altered by a pressure regulator. This consisted of a reservoir connected to a large pressure tank, and primed with blood from a donor dog diluted not more than 50 per cent with 6 per cent dextran in saline. In these experiments, the abdomen was opened by a midline incision, the abdominal aorta exposed and cannulated with large bore tubing below the renal vessels. In most dogs, only the proximal segment of the aorta was cannulated.

Epinephrine (0.1 to 2.0 μg./Kg. of the base in 3 ml. of 0.9 per cent NaCl) was injected into a femoral vein over a period of 60 seconds. A period of at least 15 minutes was allowed between injections. Isoproterenol, phenylephrine, and methoxamine, in doses of 0.5 to 60 μg./Kg., 25 to 50 μg./Kg., and 0.8 mg./Kg., respectively, were given by the same method. Sufficient time was allowed between injections of phenylephrine for the blood pressure to return to control levels. Methoxamine was not injected repeatedly. Dichloroisoproterenol was administered intravenously in doses of 2.0 to 10.0 mg./Kg. over a 5- to 10-minute period and 30 minutes were allowed for the maximal effect to develop before further administration of epinephrine. Intravenous infusions of epinephrine at rates varying from 0.063 to 3.0 μg./Kg./min. were administered by means of a Palmer slow injection apparatus. The duration
of the infusions was 7 to 22 minutes, and 20 to 30 minutes were allowed between infusions.

Intervals on the electrocardiograms were determined by means of a measuring magnifier graduated to 0.1 mm. This allowed an accuracy greater than ± 4 msec. at the paper speed of 25 mm./sec. used in recording. The “coupling interval” has been defined as the time between the beginning of the R wave of the normal and that of the abnormal complex. Because of the difficulty in determining this point in some abnormal complexes, it is probable that our measurements were not more accurate than ± 10 msec.

Results

I. Electrocardiographic Changes Induced by Minimal Doses of Epinephrine

Small doses of epinephrine were injected slowly in an attempt to determine the threshold for multifocal ventricular tachycardia in the cyclopropane-sensitized vagotomized dog. Instead of the expected arrhythmia, a coupled rhythm was induced consistently. The coupling usually took the form of a bigeminal rhythm, characterized by alternation of normal and abnormal QRS complexes, in which the interval between the normal and the abnormal beats was constant or varied within very narrow limits. Because the abnormal QRS occludes the next expected normal beat, a “compensatory pause” always follows the abnormal beat. This type of rhythm has been termed a “fixed-interval bigeminy.”

In 42 of 47 dogs, sustained fixed-interval bigeminy maintained for 12 seconds to several minutes was produced by 0.1 to 2.0 µg./Kg. of epinephrine injected over a period of 1 minute. In most of these animals, the minimal effective dose was 0.25 to 1.0 µg./Kg. Of the 5 dogs in which this arrhythmia was not produced by doses in the range of 0.1 to 2.0 µg./Kg., 2 showed isolated coupling, and 3 were resistant to even very large doses of epinephrine (4 to 20 µg./Kg.). Induction of bigeminy was accomplished with equal ease in open- or closed-chest animals. The characteristic bigeminy also was produced in 3 non-vagotomized dogs. Typical records are shown in figure 1.

In figure 1A, the signal artefact indicates the beginning of the injection of 2.0 µg./Kg. of epinephrine. The control arterial pressure was approximately 100/75 mm. Hg and the rate of the undriven heart 150/min. The 60-second intravenous injection was completed 7 seconds before the first abnormal complex. Immediately before the bigeminal rhythm, the arterial pressure had reached 200/165 mm. Hg and the heart rate 180/min. In this, as in most experiments, the coupling interval tended to shorten slightly after the first 2 or 3 coupled beats, but remained constant thereafter.

Figure 1B shows the response to 1.0 µg./Kg. of epinephrine in an open-chest animal whose atrial rate was regulated at 120/min. The bigeminy began 5 seconds after completion of the injection. At this point, the arterial pressure had risen from 135/110 to 270/185 mm. Hg. The pulse deficits seen in figure 1 were associated with the bigeminy in all but 2 experiments. They usually were complete, but occasionally a pulsus alternans was observed. The missing or attenuated pulse wave always corresponded to the abnormal QRS complex.

At an atrial rate of 170/min. (360 msec. interval), the coupling interval varied between 196 and 332 msec. in different bigeminal rhythms, and similar variability was noted at other atrial rates. However, the coupling intervals seen after any 1 injection were remarkably constant, varying by no more than ±10 msec. after the first 2 or 3 coupled beats, which usually had a somewhat
longer interval. In approximately 80 per cent of injections, the QRS complexes of the abnormal beats were identical or extremely similar throughout the response. In some cases, particularly where the coupling interval was relatively long, the upstroke of a P wave was observed before the beginning of the abnormal complex. The time interval was such as to indicate that this was the P wave of the replaced normal beat.

In 20 per cent, or less, of the injections, some variation in the appearance of the abnormal QRS complexes was noted, usually associated with a change in the coupling interval. However, the coupling interval corresponding to each configuration remained constant. Some of the variations in the fixed-interval bigeminy are illustrated in figure 2. Figure 2A shows an unusual alternation of 2 types of coupled beats, each with a characteristic coupling interval (about 285 and 350 msec., respectively). Figure 2B shows a very rare arrhythmia during which the configuration of the abnormal QRS changed without a significant concomitant change in the coupling interval (about 240 msec.). It must be emphasized that figure 2 illustrates relatively uncommon types of bigeminal rhythm. The typical fixed-interval bigeminy is that shown in figures 1 and 5.

II. Effects of Other Sympathomimetics

Phenylephrine, a pressor amine which has been shown to induce multifocal ventricular tachycardia when relatively large doses are administered to sensitized preparations, produced a fixed-interval bigeminy in all of 4 dogs tested when injected intravenously in doses of 25 to 50 µg./Kg. Methoxamine, a pressor amine with minimal or no direct cardiac action, caused bigeminy in only 1 of 6 dogs when injected in a dose of 0.8 mg./Kg. despite the prolonged pressor response which was always at least equal to that induced by effective doses of epinephrine. This compares with an incidence of electrical alternation of 10 per cent in animals under barbiturate anesthesia, as reported by Ellis. Isoproterenol, a depressor sympathomimetic with strong cardiac actions, which has been shown to cause multifocal ventricular arrhythmias when given in large doses to sensitized preparations, did not induce bigeminy in doses of 0.5 to 60 µg./Kg. in 7 dogs (17 injections).

III. Role of Ectopic Foci of Automaticity in the Production of Bigeminal Rhythm

At constant atrial rates, it is improbable that a fixed-interval coupled rhythm could be due to the emergence of a focus of increased automaticity in the ventricle, discharging at a rate synchronous with the atrial rate. However, one of the more plausible mechanisms of bigeminy due to ectopic focus formation would involve a parasystolic focus with an entry block to prevent depolarization of the focus by the sinus beat. The interval between the 2 abnormal QRS complexes would then represent the rate of firing of the parasystolic focus.

Figure 3 illustrates results which make ectopic focus formation an untenable explanation for the production of the bigeminy. In these experiments, bigeminy was induced by epinephrine, both in the normally beating
and in the driven heart. In figure 3A, the atrial drive was stopped abruptly; in figure 3B, the drive was started suddenly. The change in heart rate had no effect on the coupling interval, although the duration of the “compensatory pause” after the abnormal systole was changed considerably. This constancy of the coupling interval with sudden alterations in the heart rate was a consistent finding in all of the 7 open-chest animals in which these maneuvers were attempted. If the fixed-interval bigeminy were due to a focus of increased automaticity, parasystolic or not, the coupling interval should change with the altered heart rate.

IV. Effects of Arterial Blood Pressure and of Heart Rate on the Induction of Bigeminy

Because epinephrine-induced bigeminy usually was associated with a considerable rise in blood pressure, and because only pressor amines with direct cardiac actions caused this irregularity, it appeared probable that the bigeminy was causally related to the hypertension and possibly to the tachycardia.

A fixed-interval bigeminy of long duration was induced in 9 of 10 dogs by a constant infusion of epinephrine in doses of 0.063 to 3.0 μg./Kg./min. This arrhythmia could be converted to a normal sinus rhythm by lowering the systemic arterial blood pressure with the pressure regulator, and could be induced at will by again raising the pressure. Although the blood pressure level at which bigeminy was induced or reinduced varied in different experiments, it appeared to be quite constant during any one infusion of epinephrine. This blood pressure “threshold” is strikingly illustrated in figure 4. In this animal, the thorax had not been opened and there was considerable rhythmic variation of the blood pressure in phase with the artificial respiration. Infusion of 3.0 μg./Kg./min. of epinephrine resulted in an increase in pressure just sufficient to associate the bigeminy with the phasic changes in arterial pressure. Bigeminy occurred whenever the systolic pressure reached 235 mm. Hg during expiration. Conversion to sinus rhythm occurred when the systolic pressure decreased with inspiration. Controlled alteration of the arterial pressure by means of the pressure regulator during another epinephrine infusion had the same effect in this dog: bigeminy appeared at a systolic pressure of 235 mm. Hg and conversion to sinus rhythm was below this level.

In 3 dogs, the threshold dose of epinephrine for the induction of bigeminy was determined. No change in threshold was seen when the atrial rate was controlled by stimulation at a frequency of 25 to 35 beats/min. greater than the preinjection sinus rate.

Blood pressure and/or heart rate also were altered without injection of a sympathomimetic. Tachycardia induced by stimulation of the atrial appendage caused bigeminal rhythm of short duration in only 3 of 31 open-chest dogs. An increase in blood pressure comparable to that induced by an effective dose of epinephrine, but achieved by rapid infusion of a blood-dextran mixture from the pressure stabilizer, induced bigeminy in only 1 of 9 trials in 3 dogs. When this increase in blood pressure was combined with tachycardia, bigeminy was induced in 6 of 14 trials in the same animals.

When the depressor response to isoproterenol was reversed by use of the pressure
regulator, by constriction of the thoracic aorta, or by prior infusion of 200 ml. of 6 per cent dextran in saline, this drug induced bigeminy in 3 of 6 animals.

V. Effect of Dichloroisoproterenol (DCI)

We have shown previously that dichloroisoproterenol (DCI) is a very potent antagonist of ectopic pacemaker induction by epinephrine in barbiturate-anesthetized dogs. Consequently, it was of interest to compare the effects of this blocking agent on the major arrhythmias (ventricular tachycardia and ventricular fibrillation) and on bigeminy induced by epinephrine in the sensitized preparation. Relatively large amounts of DCI were used to insure considerable blockade of the several cardiac actions of epinephrine. A dose of 4.0 mg./Kg. was used most commonly because this appears to be close to the largest dose with which blocking specificity is retained without significant nonspecific cardiac depression.

After determining the threshold for bigeminy, DCI was injected intravenously, and the threshold redetermined a half hour later. The effect of a large dose (20 mg./Kg.) of epinephrine, causing fibrillation in most unprotected animals, was subsequently observed. Representative records from 1 of 5 such experiments are shown in figure 5, which also illustrates the expected sinus tachycardia due to the intrinsic sympathomimetic activity of the blocking agent. It is evident that the threshold for bigeminy was unchanged by 4.0 mg./Kg. of DCI, whereas the major arrhythmia expected in response to the larger dose of epinephrine was prevented, bigeminy of long duration being the only abnormal rhythm produced. In 3 of 5 dogs, the threshold for bigeminy was unaltered. In the remaining 2 animals, the dose required to induce this arrhythmia was doubled. In 2 animals, bigeminy due to the large dose of epinephrine was interrupted by brief runs of multifocal ventricular tachycardia.

Discussion

During the past 3 decades, the cyclopropane-epinephrine preparation has been used extensively in the study of major cardiac arrhythmias and of the induction of ventricular automaticity. Little or no attention has been given to the minimal effects produced by the injection of small doses of epinephrine. Moe et al., in the course of an investigation into the effects of arterial pressure on the major ventricular arrhythmias, reported a bigeminal rhythm following the rapid injection of 0.5 mg./Kg. of epinephrine into a dog anesthetized with cyclopropane. From their illustration, it appears that this bigeminy had a constant coupling interval. This appears to be the only notation of bigeminal rhythm following small, "ineffective" doses of epinephrine, although bigeminy has been observed commonly during recovery from multifocal ventricular tachycardia in sensitized, and occasionally or under special circumstances in nonsensitized, preparations.

We have found the epinephrine-induced bigeminal rhythm to be pressure-sensitive, as is the case of the major ventricular arrhythmias. This dependence on the level of systolic pressure appears to be so exact that we feel justified in suggesting that the coupling mechanism responsible for the bigeminy also is responsible for the pressure sensitivity of the major arrhythmias. The finding of a systolic...
pressure threshold for induction of bigeminy supports the conclusion previously reached in connection with the major arrhythmias that it is the blood pressure level reached rather than the extent of the pressure rise which is decisive in the induction of arrhythmias.\textsuperscript{19}

We feel there is strong evidence that the minimal effects of epinephrine described are not due to induction of a focus of automaticity in the ventricle. Such a focus must have its own intrinsic rate, and the changes in atrial rate induced were of sufficient magnitude to cause major changes in the coupling interval if this mechanism were involved. In addition, the differential blockade of major and minor arrhythmias by dichloroisoproterenol, a compound previously shown effectively to inhibit ectopic focus formation in barbiturate-anesthetized animals,\textsuperscript{15} also suggests that the mechanism of the coupled rhythm is different from that of focus formation. However, results with this blocking agent are complicated by the fact that it has considerable intrinsic sympathomimetic activity and potentiates the pressor response to epinephrine. It is quite likely that the blood pressure threshold, the intensity of intrinsic adrenergic action, and the degree of adrenergic blockade on the heart are independent variables, and further work will be necessary to clarify this picture.

Although a fixed-interval bigeminal rhythm is a not uncommon clinical finding, the experimental production of this arrhythmia has heretofore been difficult. We are aware of the induction of bigeminy in 3 other situations. The first involves injection of potassium phosphates into the cisterna magna,\textsuperscript{20} presumably evoking a maximal autonomic discharge. The second method is that of injecting hypertonic saline, barium chloride and other agents into the ventricular myocardium,\textsuperscript{21} which occasionally induces bigeminy. The third involves infusion of the antimalarial amodiaquin, a potent myocardial depressant.\textsuperscript{22}

The mechanism of the bigeminal rhythm cannot be defined with any certainty. Scherf and Schott\textsuperscript{23} recently suggested oscillatory afterpotentials in an area or cell as the mechanism for the production of such rhythms, but were unable to present any direct evidence in support of this hypothesis. We consider the development of a re-entry type of conduction defect to be at least as attractive an hypothesis to explain the genesis of the coupled beats. The recent measurement of a conduction velocity of 0.02 M/sec. in the superior portion of the A-V node of the normal rabbit heart, and the re-emergence of the concept of decremental conduction in cardiac tissue in general\textsuperscript{24} decreases the importance of one of the major arguments against the re-entry theory, namely, the time factor.

Summary
Very small doses (0.1 to 2.0 \(\mu g/Kg.\)) of epinephrine injected in 1 minute into dogs anesthetized with 20 per cent cyclopropane cause a coupled rhythm which is usually bigeminal and characterized by an exceptionally constant interval between the coupled beats. Phenylephrine also causes this arrhythmia, methoxamine does so rarely, but isoproterenol does not. An elevation in systolic pressure and possibly a tachycardia are required for the appearance of bigeminy. However, this arrhythmia can be elicited consistently by these factors only in the presence of a sympathomimetic amine with cardiac stimulant actions. A focus of automaticity has been ruled out in the genesis of the abnormal ventricular beat by demonstrating the constancy of the coupling interval despite sudden changes in the atrial rate. Dichloroisoproterenol appears to attenuate the induction of bigeminy by epinephrine to a considerably lesser extent than the major arrhythmias expected on injection of large doses of this sympathomimetic.

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Summario in Interlingua
Micrissime doses de epinephrine (0.1 a 2.0 \(\mu g/\text{Kg.}\)) injicite intra 1 minute in canes anesthesiato con 20 pro cento de cyclopropane causa un rhythmo copulate que es usalmente bigeminal e...
characterized per un exceptionally constant intervallo inter le copulate pulsos. Pharyngephrina etiam causa iste arrhythmia. Methoxamina lo face ramenta. Isoproterenol non lo face del tuto. Un elevation del tension systolique o possibilmente lo presentia de un tachycardia es requisito pro le esse bigeminia pot apparer. Tamen, iste arrhythmia pote esser evocate expectate post injectiones de grande doses de iste.

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References
1. MEEK, W. J.: Some cardiac effects of the inhalant anaesthetics and the sympathominetic amines. Harvey Lec. 30: 188, 1941.
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