Factors Modifying Cyclopropane-Epinephrine Cardiac Arrhythmias

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We have reported that the minimal cardiac arrhythmia due to epinephrine in cyclopropane-anesthetized dogs is a coupled, usually bigeminal rhythm which exhibits a remarkably constant interval between the normal and the abnormal beats. This arrhythmia is elicited only by the simultaneous presence of a sympathomimetic amine with cardiac actions and a critical systemic blood pressure, which is characteristic for each preparation.1, 2

The blood pressure dependence of this arrhythmia and the demonstration by others3, 4 that cyclopropane-epinephrine multifocal ventricular tachycardias are dependent on the level of systemic pressure suggested the possibility that both arrhythmias are due to a similar mechanism. We presented evidence in a previous paper1 that the bigeminal rhythm could not be due to a focus of increased ventricular automaticity. The present work extends our previous studies to show further similarities between multifocal ventricular tachycardia and bigeminal rhythm. In addition, some indication of fundamental differences between epinephrine-induced ventricular fibrillation and the less severe arrhythmias has been obtained, and the site of origin of both bigeminal rhythm and ventricular tachycardias may have been localized.

Methods

The methods used were identical to those described in some detail in our previous publication.1 Briefly, dogs were anesthetized with thiopental 20 mg./Kg. intravenously and maintained on 20 per cent cyclopropane in oxygen administered by positive pressure artificial respiration. Electrocardiograms (usually lead II) and blood pressure from a carotid or a femoral artery (using a Statham P23AA transducer) were recorded on a Grass polygraph. Both vagi were cut in all animals. Tektronix stimulators were used to stimulate the atra and the peripheral ends of the cut right or left vagus nerve. The frequency of stimulation of the vagus varied between 1 and 20/sec, using pulses of 1 msec. duration and voltage sufficient to slow the heart maximally in preliminary runs using a frequency of 5/sec. The atra were driven at rates of 20 to 40/min. greater than the sinus rates, using 1 msec. pulses of twice threshold voltage. The pressure reservoir which was used to control systemic blood pressure was connected to the abdominal aorta at the level of the iliac arteries. This reservoir contained donor blood which, in some cases, was diluted by not more than 50 per cent with 6 per cent dextran in saline. Epinephrine was injected into a femoral vein in doses of 1 to 20 µg./Kg. of the base over a one-minute period, 15 minutes being allowed between injections; 1, 1-isoproterenol was injected in the same manner in doses of 5 to 300 µg./Kg. Epinephrine infusions of up to 15 minutes duration were given through a long polyethylene catheter inserted through a femoral vein to the level of the thoracic vena cava. The rates of infusion varied from 0.5 to 4 µg./Kg./min. A period of at least 20 minutes was allowed between infusions. Atropine sulfate (0.5 mg./Kg.) was injected intravenously, 15 minutes being allowed for the development of an optimal anticholinergic action.

Results

I. Effect of Mechanical Elevation of the Blood Pressure in the Presence of Bigeminal Rhythm or of Ventricular Tachycardia

If the level of the systemic pressure is raised during an infusion of epinephrine sufficient to cause bigeminal rhythm, the bigeminal rhythm is converted to a multifocal ventricular tachycardia which is indistinguishable from that caused by increasing the rate of infusion of epinephrine. This has
been shown in a total of 12 dogs. The pressure was increased by means of occlusion of the thoracic aorta in 3 and by donor blood infusion from the pressure regulator in 9 animals. A typical tracing is shown in figure 1. After confirming our previously reported observation that lowering the blood pressure during bigeminal rhythm restores normal rhythm and that reinfusion of the shed blood to the original blood pressure causes reversion to bigeminy, donor blood was infused to increase further the blood pressure. The beginning of what appears to be multifocal ventricular tachycardia can be seen readily in this figure. The increase in pulse rate (usually accompanied by a decrease in the 2:1 pulse deficit characteristic of bigeminy) was observed in all the animals. These changes could be induced several times during any one infusion of epinephrine.

In no instance were we able to convert bigeminy to ventricular fibrillation by either overtransfusion or occlusion of the aorta. In a further series of four animals, the rate of infusion of epinephrine was increased to yield a stable multifocal ventricular tachycardia. Donor blood was then infused or the aorta occluded to increase further the systemic pressure. In one of two animals in which the pressure regulator was utilized, a maximal systolic pressure of 460 mm. Hg was observed for a brief period. In none of these four animals was ventricular fibrillation induced.

II. Effects of Stimulation of the Vagus on Bigeminy and Multifocal Ventricular Tachycardia Induced by Infusion of Epinephrine

Bigeminal rhythm was induced 19 times in 11 dogs by constant infusion of epinephrine. Stimulation of the right or left vagus nerve at frequencies of 1 to 10/sec. caused conversion of bigeminy to normal sinus rhythm in 24 of 38 attempts. If conversion did not occur within three seconds, the coupling interval between the normal and abnormal beats was lengthened prior to conversion. In 12 of the 14 attempts during which conversion of
Figure 2
Effect of stimulation of right vagus nerve on bigeminy in two dogs. Lead II electrocardiograms. Heavy line indicates period of stimulation at 5/sec. Dog I: Top record, conversion to normal sinus rhythm; bottom record, 15 minutes after atropine. Dog II: Lengthening of the coupling interval is the only effect of stimulation seen in this preparation. The coupling intervals in milliseconds are indicated above the record.

bigeminy to normal did not occur at any time, the coupling interval was lengthened by more than 15 msec. These effects of vagal stimulation were blocked by the administration of 0.5 mg./Kg. of atropine sulfate. The electrocardiograms from two typical experiments are seen in figure 2. The top tracings (dog I) show conversion of bigeminy to normal by vagal stimulation and blockade of this effect by atropine. Dog II responded to vagal stimulation with an increase in the coupling interval to a new stable interval 40 msec. longer than that prior to stimulation.

The efficacy of vagal stimulation in converting bigeminy to normal rhythm was found to be a function of the frequency of stimulation. The relationship is shown in figure 3 (top). It is notable that frequencies of stimulation as low as 2/sec. were effective in some of the experiments. Maintaining the atrial rate by electrical stimulation at rates of 180 to 240/min. rendered vagal stimulation much less effective in converting bigeminy to normal rhythm. Conversion to normal was produced in only 3 out of 13 attempts during the atrial drive. In the remaining experiments, the coupling interval was unchanged in three and, surprisingly, was decreased in seven.

Multifocal ventricular arrhythmias were produced 13 times in 7 dogs by constant infusion of epinephrine. Stimulation of either vagus resulted in conversion of this arrhythmia to normal in 42 of 61 attempts. In 9 of the remaining 19 attempts, vagal stimulation converted the multifocal rhythm to bigeminal rhythm. There was a positive correlation between the rate of vagal stimulation and the success in converting the arrhythmia which is shown in figure 3 (bottom). When the atrial rate was maintained, vagal stimulation caused conversion to normal in 17 out of 35 attempts. Figure 4 illustrates a typical record obtained from one animal. Atropine again blocked the effects of vagal stimulation.
It is notable that conversion of the arrhythmia to normal was accompanied by an increase in blood pressure.

Five dogs were used to determine the effect of vagal stimulation at high frequencies (10 and 20/sec.) on the dose of epinephrine required to produce ventricular fibrillation. The protocol of these experiments was to inject 2 \( \mu \text{g.} /\text{Kg.} \) of epinephrine first during and then in the absence of stimulation of the vagus. The dose was then doubled and the process repeated until fibrillation occurred.

Vagal stimulation did not appear to affect the dose necessary to cause ventricular fibrillation under the conditions of our experiments. We did note, however, that vagal stimulation increased the dose of epinephrine necessary to induce bigeminy and greatly delayed the onset of and decreased the duration of ventricular tachycardia. For example, in one of the animals, a dose of 8 \( \mu \text{g.} /\text{Kg.} \) of epinephrine caused ventricular tachycardia which started 36 seconds after the beginning of the one-minute injection of epinephrine and had a duration of 75 seconds. The same dose, injected during stimulation of the vagus at a frequency of 10/sec., caused a ventricular tachycardia of 11 seconds duration starting 95 seconds after the beginning of the injection. In this animal, the next higher dose (16 \( \mu \text{g.} /\text{Kg.} \)) injected during vagal stimulation caused ventricular fibrillation.

Others have reported that large doses of isoproterenol will induce ventricular arrhythmias in sensitized dogs. In our hands, even very large doses of this agent caused only nodal rhythm in six dogs. Stimulation of either vagus during or after nodal rhythm, or after injections of doses of isoproterenol insufficient to cause this arrhythmia resulted in severe ventricular tachycardia.

**Discussion**

On the basis of the pressure sensitivity both of bigeminal rhythm induced by minimal doses of epinephrine and of multifocal ventricular rhythm induced by larger doses of this agent, we suggested in our previous report that these two arrhythmias may be due to similar mechanisms. The present experiments support this hypothesis by two different lines of evidence. First, we have demonstrated that at any one dose level of epinephrine, the level of the blood pressure determines the presence of and the severity of the arrhythmia. Thus, all of the rhythms observed in these preparations, with the exception of ventricular fibrillation, may be converted one to another by altering either the dose of epinephrine or the blood pressure. Secondly, we have demonstrated that these arrhythmias, again with the exception of fibrillation, are modified greatly by stimulation.

Figure 3

*Top* Incidence of conversion of bigeminy to sinus rhythm plotted against frequency of stimulation of vagus nerve (11 dogs). *Bottom* Incidence of conversion of multifocal rhythm to sinus rhythm plotted against frequency of stimulation of vagus nerve (7 dogs). In both graphs, the dashed curves are drawn through points obtained at constant atrial rates, the solid curves through experiments without control of this parameter; the numbers beside the points are the total number of attempts made at each frequency.
Effects of vagal stimulation on multifocal arrhythmia due to infusion of epinephrine. From top to bottom: Lead II electrocardiogram, signal marker (heavy line indicates period of stimulation at 5/sec.), arterial pressure. (A) Before atropine; note the increase in arterial pressure on conversion to sinus rhythm. The gap in the record represents 5 seconds of normal rhythm during continued vagal stimulation. (B) After atropine; note the change in calibration of the blood pressure record.

of the vagi and that these effects are always blocked by atropine.

There has been one previous report of conversion to normal of epinephrine-induced cardiac arrhythmias by stimulation of the vagi. In the chloroform-sensitized animals used by these workers, conversion was associated with a drastic decrease in the systemic blood pressure. As can be seen in figure 4, our results are not due to a decrease in blood pressure. It is difficult to compare results of vagal stimulation with effects of reflex vagal discharge. However, we feel that the latter also has some effect on the arrhythmia since we found it easier to maintain bigeminy of long duration in vagotomized animals than in animals with intact vagi. Blockade of epinephrine-induced arrhythmias by choline esters has been reported by others. Our observations differ greatly from those of DiPalma, who reported atropine to be effective in preventing the antiarrhythmia action of acetylcholine. Our results appear to be at variance with those reported by Nickerson and Nomaguchi who were unable to affect monofocal ventricular tachycardia by vagal stimulation. This kind of difference, as usual, may be ascribed to differences in technique. These workers used 30 per cent cyclopropane anesthesia and, probably more important, injections of a rather large dose (10 μg./Kg.) of epinephrine.

The exacerbation or induction of arrhythmia by vagal stimulation after isoproterenol stands in contrast to the effects obtained after epinephrine. The difference is due most probably to the absence of a pressor response to isoproterenol. The responses obtained in our experiments are identical to those obtained by Nickerson and Nomaguchi who injected epinephrine after dibenamine in cyclopropane-anesthetized animals and by Roberts et al. who injected isoproterenol into dogs and cats anesthetized with Dial-urethane.

We cannot explain the observation that in the absence of conversion of bigeminy to normal sinus rhythm, stimulation of the vagi decreased the coupling interval when the atria were driven, whereas it was lengthened when the atria were not stimulated electrically.
Adrenergic fibers in the vagus might be involved. Our results appear to localize anatomically the origin of both bigeminy and multifocal ventricular tachycardia. While there is not universal agreement on the point, most investigators presently believe that the vagus does not innervate the ventricles distal to the bundle of His. It is highly improbable that enough acetylcholine is released in the coronary arterioles to cause conversion, and the possibility that acetylcholine released by the vagus reaches the sites of origin of the arrhythmias by way of recirculation is precluded by the rapid conversion. Elimination of these possibilities leads to the conclusion that the arrhythmias originate in the His bundle.

The same types of evidence which relate bigeminal rhythm to multifocal ventricular tachycardia separate these arrhythmias from ventricular fibrillation. Thus, fibrillation cannot be induced by maximal increases in the systemic blood pressure, even in the presence of doses of epinephrine sufficient to induce multifocal ventricular tachycardia. This result is in agreement with previous observations indicating that fibrillation does not depend on a rise in systemic pressure and occurs most frequently before or during the ascending phase of the blood pressure response. In addition, we found that maximal stimulation of the vagus at a high frequency does not appear to affect the threshold dose of epinephrine for the induction of ventricular fibrillation. If, for the moment, our previous conclusion is accepted that bigeminy is not due to a focus of increased ventricular automaticity, along with our present conclusion that multifocal arrhythmias are due to a mechanism identical to that causing bigeminy, then it is attractive to suggest that fibrillation differs from the less severe arrhythmias by being due to foci of increased ventricular automaticity.

Summary

Constantly coupled bigeminal rhythm of long duration induced by infusion of epinephrine into cyclopropane-anesthetized dogs may be converted to multifocal ventricular tachycardia by increasing the blood pressure without changing the infusion rate. Multifocal arrhythmia may be converted to bigeminy or to sinus rhythm by decreasing the blood pressure but is not converted to ventricular fibrillation by an increase in systemic pressure. Stimulation of the peripheral end of either vagus can convert bigeminy to normal rhythm or increase the coupling interval. Multifocal ventricular tachycardia is converted to sinus rhythm or to bigeminy by stimulation of the vagus. The vagal effect, which is blocked uniformly by atropine, also may be demonstrated when the atrial rate is maintained constant. Vagal stimulation does not increase the threshold dose of epinephrine necessary for induction of ventricular fibrillation. It is concluded that multifocal ventricular tachycardia is due to a mechanism similar to that causing bigeminy, which was shown previously not to be due to the emergence of a focus of increased ventricular automaticity. Both of these arrhythmias probably originate in the bundle of His and differ fundamentally from ventricular fibrillation.

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References


BOOK REVIEW


With the ascendency of the concept of neurochemical transmission has come a profligate array of candidates for transmitter agents. The not uncommon practice of uncritically assigning transmitter function to a host of naturally occurring and extracted substances exhibiting activity on excitable tissue elements has contributed to a confusion situation. It can not be denied, however, that despite the premature claims in most instances, one favorable effect has been to stimulate research and increase our factual knowledge about these Stoffe. It should not be surprising, therefore, that the candidacy for inhibitory transmitter was assured for γ-aminobutyric acid (GABA) when it was identified as one of the active constituents of the extracted inhibitory principle of Florey (i.e., Factor I). As a consequence of this early work, GABA subsequently served as a basis for a great deal of research effort. Thus, the conference held at the City of Hope Medical Center, Duarte, California, May 22-24, 1959, to discuss this ubiquitous amino acid and its possible significance in the nervous system was a timely one.

Although the discussions were conducted in the context of inhibitory phenomena, the conference fell somewhat short of its stated purpose because the phenomenon of inhibition, unfortunately, was treated incidentally. Nevertheless, it is to the credit of the organizing committee that such an auspicious endeavor was put forth to assemble the very large group of interdisciplinary investigators to participate in discussions of the pharmacology and biochemistry of GABA and related active substances on the nervous system.

The quality spectrum of the papers presented was quite broad, ranging from “excellent” to “poor.” The subjects of some papers were trivial and of questionable merit; a few were out of context of the symposium, while other papers were very interesting, but poorly developed with a lack of needed expansion and discussion. It is likely, however, that the handicap of time limitation may have been operating in some of the last mentioned instances. Although there were the usual polemics and a small amount of redundancy of reported findings, the general tenor of the symposium was adequately conservative, and a large body of good experimental data were presented. Indeed, it is from the latter standpoint that the book probably offers its greatest value.

It is unfortunate, perhaps, that few conclusions were reached and little in the way of new concepts or elucidation of mechanisms emerged from the symposium. However, synopsia are held in order to survey, to evaluate, to gain perspective, and to reduce confusion. If these objectives are satisfied in some measure, the conference may be termed a success, and as such, the conference on GABA meets these criteria.
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