ON THE LOCALIZATION OF CYCLOPROPANE-ADRENALINE CARDIAC ARRHYTHMIAS

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Betty Irene Sasyniuk

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B.I. Sasyniuk

ABSTRACT

Atrioventricular block due to destruction of the bundle of His has been shown to prevent the typical bigeminal rhythms produced by adrenaline in thiopental-cyclopropane anaesthetized dogs. Bigeminal rhythms could still be elicited, however, after atrioventricular block due to destruction of the A-V node. These results support the hypothesis that the bundle of His is important in the genesis of this arrhythmia.

Destruction of the bundle of His did not prevent multifocal rhythms but did increase the dose of adrenaline required to induce them. The multifocal arrhythmias produced by larger doses of adrenaline after destruction of the bundle of His were unaffected by stimulation of the vagus nerves. When these same doses of adrenaline produced multifocal rhythms in the intact heart, they were also unaffected by stimulation of the vagus nerves. Arrhythmias produced by destruction of the His bundle were unaffected by injections of acetylcholine into the left circumflex coronary artery but were usually affected by injections into the anterior descending coronary artery. The evidence indicates that multifocal arrhythmias produced by larger doses of adrenaline both in intact hearts and in animals with complete A-V block may be due to a mechanism different from that produced by smaller doses of adrenaline in the intact heart. It is suggested that this mechanism may be an increase in automaticity in the lower portions of the ventricular conducting system.

Destruction of the bundle of His, while affecting the nonfatal arrhythmias, had no effect on the dose of adrenaline required to produce ventricular fibrillation.

It has been shown that conversion of both bigeminal and multifocal arrhythmias in the intact heart by stimulation of the vagus nerves may be largely indirect. Such conversion may be brought about through decreases in either the blood pressure or heart rate or through a slowing or block of conduction through the A-V node. Conversion of these arrhythmias by injections of acetylcholine into the posterior septal artery may be largely a result of the effects of such injections on conduction through the A-V node.

Simultaneous recordings from the bundle of His, the right atrium and the right and left ventricular surfaces, together with a lead II electrocardiogram, indicate that the site of origin of bigeminal rhythms may be the left septal region of the heart. The results support the hypothesis that the bigeminal beat is a type of "fusion" complex resulting from simultaneous activation of the heart by stimuli originating above and below the bundle of His.

To

Mom and Dad

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INTRODUCTION

A. ADRENALINE-INDUCED ARRHYTHMIAS

The phenomenon of "sensitization" of the heart to sympathomimetic amines by hydrocarbon anaesthetics has been the subject of numerous investigations. Early studies concerned mainly the development of ventricular fibrillation as a result of sensitization of the heart by chloroform. More recently, interest has centered around the less severe cardiac arrhythmias resulting from small doses of sympathomimetic amines in the presence of cyclopropane or halothane.

Despite the voluminous literature on the subject, the exact nature of "sensitization" remains unresolved. It is clear, however, that certain basic differences exist between arrhythmias produced by adrenaline in sensitized animals and those produced in nonsensitized animals (i.e. animals anaesthetized with agents such as pentobarbital, chloralose, etc.). One of the major differences is the marked reduction in the dose of adrenaline required to produce arrhythmias in the sensitized preparation. Doses of adrenaline which merely increase the sinus rate in pentobarbital or chloralose anaesthetized dogs may cause severe arrhythmias in dogs anaesthetized with chloroform or cyclopropane. The characteristics of the arrhythmias produced in the two preparations also differ. In sensitized animals the type of arrhythmia produced varies with the dose of adrenaline injected. Low doses of adrenaline (0.1-2.0 μg/kg) result in bigeminal rhythm. Higher doses (2.0-8.0 μg/kg) produce multifocal ventricular tachycardia. Doses of adrenaline greater than 8.0 μg/kg usually result in fatal ventricular fibrillation. The predominant arrhythmia in nonsensitized animals is monofocal ventricular tachycardia. Multifocal arrhythmias or ventricular fibrillation are rare occurrences.

Arrhythmias in sensitized and nonsensitized animals differ in their response to vagotomy, stimulation of the vagus nerves and elevation of the blood pressure. It is recognized generally that reflex vagal activity plays an important role in the induction of cardiac arrhythmias by adrenaline in nonsensitized animals. Elevation of the blood pressure is important to the genesis of these arrhythmias only because of its effect on reflex activation of the vagus nerves. Thus, stabilization of the blood pressure, section of the vagi or the administration of atropine in the nonsensitized preparation protects in large measure against adrenaline-induced arrhythmias although these arrhythmias may still be obtained if sufficiently large doses are employed (1,2).

The mechanism of arrhythmias in the nonsensitized preparation is generally attributed to increased ventricular automaticity. Riker et al. (2) suggested that adrenaline stimulates all centres of automaticity including the sinoatrial node, the atrioventricular node and potential ventricular pacemakers, the lower centres manifesting their activity when the higher centres are depressed by vagal activity. Roberts et al. (3,4) demonstrated that adrenaline, noradrenaline and isoproterenol could "raise the pacemaker automaticity" sufficiently to allow the emergence of a ventricular pacemaker when either vagus nerve was stimulated in bilaterally vagotomized animals anaesthetized with chloralose. Dresel (5) has shown that the effect of the vagus on conduction through the atrioventricular node is of sufficient magnitude that artificial maintenance of the atrial rate does not change the threshold dose of adrenaline necessary to induce cardiac arrhythmias in barbiturate-anaesthetized animals. In his experiments A-V nodal block always

preceded initiation of arrhythmia when the atria were driven, and occasionally in the absence of drive. Thus, it is agreed that ventricular slowing must occur before a ventricular pacemaker may emerge in the non-sensitized preparation.

Vagotomy or the injection of atropine does not protect against ventricular arrhythmias produced by adrenaline in the sensitized preparation (6-9). Vagal stimulation will abolish or prevent arrhythmias other than ventricular fibrillation in animals anaesthetized with chloroform or cyclopropane. The level of the blood pressure affects these arrhythmias directly. The role of all these factors have been delineated, recently, by Dresel and coworkers (10,11). Their investigations began with a study of the arrhythmias produced by minimally effective doses of adrenaline in dogs anaesthetized initially with thiopental followed by a mixture of 20% cyclopropane in oxygen. These doses of adrenaline produced bigeminal rhythms in which the interval between the normal and abnormal complexes was constant for any one arrhythmia. Each coupled beat was followed by a compensatory pause of greater duration than the coupling interval. They concluded that the bigeminal beat could not be due to a focus of increased ventricular automaticity firing at a rate greater than the sinus rate because the compensatory pause following the abnormal complex was of a duration sufficient to allow another such automatic beat to occur. They showed, therefore, that the mechanism of these arrhythmias differs from that in nonsensitized animals. An increase in automaticity of a parasystolic focus was excluded by showing that sudden changes in atrial rate affected the duration of the compensatory pause without affecting the coupling interval. Having ruled out a focus

of automaticity in the genesis of the abnormal ventricular beat, they suggested the development of a reentry type of conduction defect to explain the coupled beat (vide infra).

Increasing the dose of adrenaline changes bigeminal rhythms to multifocal ventricular rhythms. Dresel and Sutter (10) have shown a clear-cut dependence of these two arrhythmias upon the level of the systolic blood pressure. They demonstrated that at any one dose level of adrenaline, the level of the blood pressure determines the presence of and the severity of the arrhythmia. Thus, normal sinus rhythm, bigeminal rhythm and multifocal ventricular tachycardia were found to be interconvertible by changes in the arterial pressure. Maximal increases in blood pressure, however, could not convert multifocal rhythms to ventricular fibrillation. This confirmed previous work (9,12) which showed that pressure plays little or no role in the etiology of ventricular fibrillation in sensitized animals. Dresel and Sutter also showed that bigeminal and multifocal rhythms were affected similarly by vagal stimulation which converted both arrhythmias to normal sinus rhythm. Stimulation of the vagus had no effect on the dose of adrenaline required to produce ventricular fibrillation. They concluded that multifocal ventricular tachycardia was due to a mechanism similar to that causing bigeminy which was shown previously not to be due to a focus of increased ventricular automaticity.

There is no general agreement concerning the site of origin of adrenaline-cyclopropane arrhythmias. Riker et al. (2) believe that this site is in the ventricles. They suggested that a depression of A-V nodal automaticity by hydrocarbon would impede the usual pacemaker stabilization at this site and allow a multitude of myocardial foci, released from

nodal domination, to respond to adrenaline directly.

MacCannell and Dresel (13) have shown that injections of acetylcholine into the left circumflex coronary artery were successful in converting bigeminal and multifocal rhythms to normal sinus rhythm. Similar injections into the left anterior descending coronary artery were without effect. On the basis of this evidence and that obtained previously with stimulation of the vagus they suggested that these arrhythmias originate in the atrioventricular node or the bundle of His. Their conclusions were based on the premise that the atrioventricular node and bundle of His are the lowest structures innervated by the cardiac vagus (vide infra) and that injections of substances into the left circumflex coronary artery also reach these areas of the heart.

Moore et al. (14,68) disagreed with the above hypothesis on the basis of direct electrical recordings from the bundle of His during cyclopropane-adrenaline arrhythmias. They reported that ventricular depolarization preceded the His potential during the bigeminal beat and that the latter was of reversed polarity. This suggested to them that the ventricles were not activated normally and that activity was originating from below the bundle of His. The same sequence of events occurred during the monofocal ventricular tachycardia.

The conclusions of Moore et al. (14,68) concerning the site of origin of the arrhythmias was supported by Vick (15). He showed that the induction of both bigeminal rhythm and multifocal ventricular tachycardia is dependent upon the atrial rate. Since conversion of adrenaline arrhythmias with stimulation of the vagus was accompanied by slowing of the atrial rate and since restoring the atrial rate by electrical driving reestablished the arrhythmia, Vick concluded that the

action of the vagus was not a direct one at a site of cholinergic transmission, but was secondary to the decrease in heart rate. Vick agreed with Dresel and Sutter that reentry may be a possible mechanism for the arrhythmias, but suggested that the site of reexcitement may be the Purkinje-myocardial junction thus bringing his results in line with the observations of Moore and his group.

The controversy concerning the site of origin of adrenaline-hydrocarbon arrhythmias is, therefore, two-fold: 1) if the effect of the vagus nerve on the arrhythmias is indeed only secondary to changes in rate or to other indirect effects of the vagus, then no conclusions can be made concerning a probable site of vagal action; 2) if the vagus nerve converts the arrhythmias by a direct effect on a reentry site, then this site must either be high in the conducting system or the vagus must reach lower portions of the ventricular conducting system.

B. INNERVATION OF THE VENTRICLES BY THE VAGUS NERVES

" The influence exerted by the vagi on the functions of rhythmicity and conductivity is not only exceedingly complex, but very variable in different animals. In general, however, it may be said: 1) that the magnitude of the influence of both nerves on nodal tissue decreases as these are traced downward, and 2) that the gradient of the left vagus influence is, on the whole, of a lower order than that of the right". This statement, made by Wiggers in 1923 (16), still applies to what is known today about the effects of the vagus nerves on the heart.

The profound depressant influence of the vagus nerves upon pacemaker cells of the sinus node, the A-V node and atrial myocardium is well documented (17-20). Their effects on the ventricles, however, are still controversial.

Numerous workers have studied the effect of the vagus nerves upon ventricular contractility in the mammalian heart. Many of these investigators (21-28) concluded that vagal stimulation has little or no influence on the contractility of the ventricles; others (29-32) deduced that it elicits a negative inotropic effect.

Interpretation of some of the earlier studies has been complicated by the simultaneous actions of the parasympathetic nerves upon heart rate, coronary perfusion pressure and the time relationship of atrial and ventricular contractions. In many of the earlier studies in which it was reported that vagal stimulation evoked a negative inotropic effect upon the mammalian ventricle, heart rate was not held constant. Several investigators who concluded that vagal stimulation has no effect upon ventricular contractility also failed to keep heart rate constant.

Rushmer (26) observed a definite, depressant effect upon ventricular performance during vagal stimulation in only one of thirteen experiments. In the remainder only small reductions in left ventricular systolic pressure were found. Schreiner et al. (25) assessed ventricular contractility during vagal stimulation on the basis of ventricular function curves in which the stroke work of paced hearts was plotted as a function of left atrial mean pressure. They detected no significant difference between such curves obtained before, during and after vagal stimulation. They concluded, therefore, that efferent vagal stimulation exerts no appreciable influence upon ventricular contractility. The conclusions derived by Sarnoff and his coworkers (27), also on the basis of ventricular function curves, were identical to those of Schreiner et al. (25). Similarly, Brockman (33) could find no significant change in ventricular function curves obtained before and during vagal

stimulation in dogs with complete A-V block. Wang et al. (31), however, observed that vagal stimulation diminished the external work performed by the paced left ventricle.

Recently, DeGeest et al (34,35) studied vagal effects upon ventricular contractility in a preparation in which the heart rate and coronary perfusion pressure were kept constant. They used a paced, innervated left ventricle preparation in which the ventricle contracted against a fixed volume of incompressible fluid (the so-called isovolumetric preparation). Using this preparation, DeGeest et al. have shown that electrical stimulation of the distal ends of the cervical vagi diminished left ventricular systolic pressure. This was interpreted as signifying a depression of left ventricular contractility by vagal stimulation.

DeGeest and his group evaluated previous work on the effects of vagus nerves upon ventricular contractility. In their experiments heart rate was kept constant by simultaneous pacing of the right atrial appendage and ventricle. Other workers paced either the atria or the ventricles, not both. In Rushmer's experiments only the atria were paced. DeGeest suggested that a greater depression of ventricular contractility might have been obtained by Rushmer if he had also paced the ventricles because a higher frequency of vagal stimulation could have been used without causing atrioventricular block. Wang et al. (31) paced the ventricles but not the atria. The effects of vagal stimulation in their experiments could have been due, thought DeGeest, to the vagal effects on atrial systole, resulting in a decrease in ventricular filling and consequently, in a decrease in external work. In an earlier study by Ullrich et al.(28), also using the paced, canine, isovolumetric left ventricle preparation, the vagus had no effect on ventricular contractility even though both

atria and ventricles were paced. DeGeest suggested that the discrepancy between their results and those of Ullrich may have been due to the failure of the latter to keep coronary perfusion pressure constant.

Levy et al. (36) demonstrated that the negative inotropic effect on ventricular contractility is mediated, at least in part, by antagonism of the positive inotropic influence of the prevailing sympathetic nervous activity. They interpreted this as suggesting that in the intact animal the vagi exert a tonic, negative inotropic effect upon the ventricular myocardium and play a role in the nervous control of ventricular performance. In a later paper Levy et al. (37) demonstrated that the reflex negative inotropic effect upon ventricular performance elicited by stimulation of the carotid sinus baroreceptors is mediated to a large extent by the vagus nerves. In this study sudden elevation of pressure in the isolated carotid sinus still elicited a depression of left ventricular systolic pressure in the isovolumetric left ventricle preparation after blockade of sympathetic neuroeffector junctions by bretylium tosylate. This response was abolished by atropine sulfate and by cooling of the cervical vagi. Similar conclusions concerning vagal mediation of reflex effects upon ventricular performance were reached by Salem et al. (38) and by DeGeest et al. (39). Brockman (33), however, reached a different conclusion. In his experiments an increase in pressure within the carotid sinus reflexly induced a decrease in ventricular contractility in dogs with complete A-V block. However, this negative inotropic effect was not altered following bilateral cervical vagotomy but was abolished after division of the cardiac sympathetics. He concluded, therefore, that the reflexly induced negative inotropic effect arising from the carotid sinus must be a consequence of inhibition

of cardiac sympathetics. Three other studies (40-42) which showed a reflex relationship between baroreceptors and ventricular contractility, reached the conclusion that the reflex must occur in part via the sympathetic system. It has not been established, therefore, what role, if any, the vagus nerves play in the control of ventricular performance.

The demonstration of a negative inotropic effect of vagal stimulation on the ventricles presupposes the presence of cholinergic fibres. However, the exact distribution of the cardiac nerves in the heart has not been adequately defined anatomically.

The early anatomical evidence for a parasympathetic innervation of the mammalian ventricles is contradictory. Tcheng (43) described intramural ganglia in the substance of the right ventricle of young dogs and concluded that parasympathetic fibres reach the ventricles. The existence of such fibres was doubted by Nonidez (44) who failed to demonstrate their presence. Davis et al. (45) denied the presence of nerve cells in the ventricles of most mammals while Mitchell et al. (46) reported the existence of subepicardial nerve cells in the ventricles of the monkey and rabbit.

Recent anatomical evidence using more advanced histological techniques favors parasympathetic innervation of the ventricles. Hirsch et al. (47) studied the distribution of nerves, their ganglia and terminals in the septal myocardium of the dog and human heart. They demonstrated that septal cardiac tissues, including the specialized myocardium of the conducting system, have many large and small nerves which are associated with ganglia. The association of ganglia with nerves in an organ or tissue innervated, according to present concepts of the autonomic nervous system (48), is characteristic of vagal

structures. On this premise they concluded that the septal tissues are innervated abundantly by postganglionic vagal fibres. Nerves with ganglia were also demonstrated in ventricular myocardium but their numbers were appreciably smaller. In a subsequent study Hirsch et al. (49) demonstrated the occurrence of morphological changes in the intrinsic cardiac nerves after bilateral cervical vagotomy, bilateral cervical sympathectomy, or total extrinsic denervation in the canine heart. After bilateral cervical vagotomy there was degeneration of the septal nerves associated with ganglia. There was also degeneration of nerves distributed with arteries deep in ventricular myocardium. After bilateral thoracic sympathectomy cardiac nerves with and without ganglia, identified previously as vagal nerves, remained intact. After total extrinsic denervation of the heart there remained numerous intact ganglion cells with fibres and fibrils. This, according to Hirsch et al. (49) suggested the survival of appreciable amounts of postganglionic vagal innervation of cardiac tissues. This study is supported by electron microscopic studies of Napolitano et al. (50). They demonstrated the presence of C fibres in the atria and ventricles of the canine heart after total extrinsic cardiac denervation. They concluded that these must arise from ganglion cells within the heart, and are thus by definition intrinsic and postganglionic. On the premise that intrinsic cardiac nerves represent postganglionic parasympathetic elements, this study provides additional evidence for vagal innervation of the ventricles. Although, it can not be stated conclusively that such fibres are cholinergic, Cooper et al. (51) have demonstrated the absence of catecholamines in the extrinsically denervated heart suggesting the absence of adrenergic fibres.

The above morphological evidence of vagal nerve penetration into ventricular muscle impinges upon the controversy among physiologists concerning the existence of significant functional vagal innervation of ventricular muscle. There is somewhat less controversy concerning the significance of vagal innervation on the electrical properties of the ventricular conducting system and the muscle fibres.

Although acetylcholine and vagal stimulation have been shown to accelerate repolarization of frog or toad ventricle (52,91), their effect on mammalian ventricular tissue is not great. Recently, Greenspan et al. (53) have presented evidence that in the dog heart vagal activity may alter the pattern of ventricular repolarization as well as atrial repolarization. This alteration was found to be more marked when the vagi were stimulated during a hyperkalemic state. The electrocardiographic change was an increase in the amplitude of the T wave. A similar observation has been reported by Fisch et al. (54) with intracoronary injection of acetylcholine. Greenspan et al. suggested that the electrocardiographic changes observed with vagal stimulation might be explained by a release of acetylcholine from the sinoatrial area and the atrium and not to a direct effect of the vagus nerves on the ventricles. This would account for the failure of acetylcholine to act on isolated mammalian ventricular tissues.

There is no direct evidence which suggests that stimulation of the vagus influences the velocity of conduction in the ventricles. Hoffman et al. (55,56), recording from multiple sites in the intact dog heart, have shown that stimulation of the vagus sufficient to cause complete atrioventricular dissociation has no measurable effect on conduction velocity in the bundle of His, the bundle branches or the

Purkinje fibres of the ventricular conducting system. The conducting fibres of the His-Purkinje system were also found by Hoffman and Suckling (20) and by Cranefield et al. (19) to be relatively insensitive to acetylcholine. These results were confirmed by the studies in situ of Mendez et al. (69) who showed that neither the diastolic excitability nor the time course of recovery of the His bundle were altered by stimulation of the vagi at intensities sufficient to greatly prolong the atrial-His bundle functional refractory period. Alanis et al. (67), however, contends that acetylcholine reduces the excitability of fibres of the His bundle. His conclusions are based on the observation that the N potential (which represents electrical activity of the A-V node) did not appear to be attenuated by acetylcholine injected in amounts sufficient to block the His responses. However, the significance of this observation is questionable. DeGeest et al. (35) did not observe any changes in the duration of the QRS complex during stimulation of the vagus sufficient to have a negative inotropic effect. Eliakim et al. (57) reported that the ventricular rate may diminish when the vagi are stimulated in dogs with complete atrioventricular block. However, this effect was neither consistent nor marked. A slight decrease in ventricular rate was also found by Brockman (33) in animals with complete heart block.

It should be noted that negative inotropic effects occur when high concentrations of acetylcholine (10^{-4}-10^{-5} g/ml) are applied to excised ventricular strips (20) or are administered intravenously to the dog (25). However, Hoffman and Suckling (20) could detect no changes in membrane potentials when these high doses were applied to mammalian myocardial fibres. It is possible then that the surface membrane of the

ventricular fibre has no receptive sites at which acetylcholine can increase potassium permeability, but that acetylcholine can reach sites which control contractility. This direct effect on the contractile process would occur only when higher concentrations of acetylcholine are used or when vagal activity is intense. This may indeed be the case since significant decreases in ventricular contractility have been observed only in preparations in which the ventricles were paced (31,34,35). This may mean that only those intensities of vagal activity which arrest sinus activity and block conduction through the atrio-ventricular node affect ventricular contractility.

The present status of the controversy concerning vagal innervation of the ventricles may be summed up as follows: vagal fibres probably do innervate the ventricles. However, the functional significance of this innervation is questionable, expecially in terms of possible electrophysiologic effects.

C. REENTRY (OR REEXCITATION) - A MECHANISM INVOLVED IN THE GENESIS OF CARDIAC ARRHYTHMIAS

Basically, two mechanisms have been invoked to account for the majority of cardiac arrhythmias. These are reentry and automaticity. Neither mechanism can be considered as the exclusive explanation of all varieties of abnormal impulse generation. Assuming that potential pacemaker activity is widely distributed throughout cardiac tissue, it follows that increased automaticity is a possible source of premature systoles and various other arrhythmias. On the other hand, the development of reentrant rhythms under appropriate conditions is firmly established and one cannot deny the possibility of such arrhythmias as circus movement flutter, clearly a conduction disturbance. The object

of this review is to point out the arguments which have been put forth for and against a reentry mechanism and to show the interrelationships that exist between it and disturbances in automaticity.

Differential conduction is the basis of experiments dating from Schmitt and Erlanger (58) which led to the formulation of the concept of reentry in the mammalian heart. Schmitt and Erlanger demonstrated that, when the central portion of a long strip of turtle heart muscle was depressed by various means, e.g. compression, cooling, etc., an impulse initiated at one end of the strip having traversed the strip in one direction, returned to reexcite that part of the strip from which it had originated. They explained these observations by assuming a functional longitudinal dissociation in the muscle strip over a certain distance. They assumed that the impulse was conducted with delay in one direction through one section of the strip and returned in the opposite direction to its point of origin through a different part of the strip through which conduction in the original direction had been blocked. This was one of the first demonstrations of both localized slowing of conduction and unidirectional block, factors now considered basic to the phenomenon of reentrant excitation.

The concepts of reentry put forward by various early authors differ only in detail. Wenckebach and Winterberg (59) postulated a block in the peripheral twig of the conducting system. Thus, the portion of myocardium supplied by this twig was assumed to be activated by adjacent portions of myocardium so that the excitation wave passed retrogradely with delay through the affected twig to reexcite the unaffected twig. The unaffected twig could conduct the wave a second time giving rise to an extrasystole. Ashman and Hull (60) assumed the

existence of a portion of the myocardium with a prolonged refractory phase through which excitation is conducted with delay.

An essentially similar concept has been put forward by Katz and Pick (61). However, they were the first to suggest that both a prolongation of the refractory phase in some part of the heart and the presence of unidirectional conduction were necessary for a reentry mechanism to occur. They invoked a reentry mechanism to account for the common variety of extrasystoles which occur at a fixed time interval after dominant beats. This is identified by the constancy of the R-R intervals between the preceding dominant beat and the premature systole; a relationship called fixed coupling. The phenomenon of coupling suggests that the coupled beat is in some way related to and initiated by the activity of the preceding normal beat and does not arise de novo from an independently discharging pacemaker. In order to explain the relatively long interval between the normal and abnormal beats one of the following assumptions had to be made: (a) the conduction rate through the reentry path is greatly retarded; (b) the impulse meanders through a very long and necessarily tortuous route back to the point at which it was stopped; or, (c) two or more sweeps occur through the reentry path before one such impulse succeeds in penetrating a branch which is no longer refractory. Recent evidence suggests that their first assumption is probably the correct one (vide infra).

Several objections have been raised against the reentry theory as a mechanism for coupled extrasystoles. Some of these have been enumerated by Scherf and Schott (62). The main argument against a reentry mechanism, which was responsible for lack of acceptance of this theory for some time, has been the length of the coupling interval

(which is usually between 0.3 and 0.6 sec). The measurements of conduction velocities in the myocardium or His-Purkinje system allowed calculation of the length of the path an impulse would have to travel before reentering with a given coupling interval. All these calculations indicated that the path lengths were unrealistically long (90). However, such an argument becomes less compelling with the recent measurements of conduction velocities on the order of 0.02-0.05 meters/sec in the superior portion of the atrioventricular node (83,84) and of the renewed interest in the concept of decremental conduction in cardiac tissues in general. Propagation of an impulse at greatly reduced velocities in relatively refractory tissue and at junctions between fibre bundles is well documented (18,63,79,93). The concept of, and the demonstration of decremental conduction not only explains the occurrence of functional block in any part of the conducting system but also, because of the great reduction in conduction velocity, removes any requirement for a minimum path length in reentry. The relevence of decremental conduction to the genesis of arrhythmias by a reentry mechanism has been emphasized recently by Hoffman and associates (64-66).

Another objection is provided by the lengths of coupling with increasing heart rates. According to Scherf and Schott (62), if a reentry mechanism were to account for coupled extrasystoles, lengthening of the coupling interval with increasing heart rates should be expected, since, according to them, impairment of conduction would be more pronounced with higher heart rates. This objection is not valid since an increase in the frequency of activity in cardiac tissues has been shown to decrease the duration of the action potential and shorten the refractory period (18). Thus, if a change does occur with increasing heart rates it would be

toward a decrease in the coupling interval. In fact, the lack of change in the coupling interval with changes in heart rate has been taken as a necessary attribute of true "fixed coupling" (11).

An observation which Scherf and Schott (62) feel is incompatible with a reentry mechanism involves the effect of warming the site of origin of experimentally induced extrasystoles. By injection of various drugs (among them sodium or barium chloride, strophanthin or digitoxin) into heart muscle Scherf et al. (70) produced ventricular premature systoles of constant contour which showed fixed coupling to the preceding beats. That each premature systole was induced by the preceding sinus impulse was shown by the fact that the premature systoles disappeared when sinus standstill was produced by stimulation of the vagi. When such extrasystoles had subsided they reappeared when the site of application of the substance was warmed. They reasoned that were such extrasystoles due to a reentry mechanism, warming, which improves conduction velocity and shortens the refractory phase, should abolish the arrhythmia rather than cause an increase in the rate and number of ectopic beats. They believed, then, that this observation favored a mechanism whereby the premature systole originates as a new stimulus from an ectopic focus which is in some way activated by the preceding beat. In addition, they observed that ventricular premature systoles produced in the above manner retained their original contour not only after sinus beats but also after artificially stimulated beats. Scherf felt that the retention of their original contour argued conclusively for the idea that these premature systoles arose from one sharply circumscribed area and this, according to him, spoke against reentry. Mack and Langendorf (71), however, offer a different explanation for the results observed by Scherf. They suggested

that, if the subepicardial injection of strophanthin or digitoxin produced a localized area of prolonged conductivity (as these drugs are known to do) where the reentry phenomenon could occur, then heating this area would, indeed, have the effects Scherf discovered. Because this area remained in the same location the impulse coming out of this area would be conducted through the heart along the same pathway and the form of the extrasystole would thus remain constant. Furthermore, a study by Dresel (unpublished) of the extrasystoles produced by subepicardial injections of sodium chloride (2-20%) has shown that these extrasystoles are not constantly coupled. It may be that this arrhythmia is not due to a reentry mechanism but to some other mechanism (aconitine-like?). It would follow then, that the objections of Scherf and Schott is not a valid one as pertains to reentry arrhythmia.

A general objection to the reentry theory has been the lack of the actual demonstration of the path of a reentering impulse. However, such a pathway has been demonstrated recently by Watanabe and Dreifus (72), using ultramicroelectrode techniques. They studied conduction in the A-V node and demonstrated that the presence of inhomogeneity in this region of the heart permitted a slow but successful transmission of an impulse in one region of the node while decrementing in another. This caused the impulse to travel preferentially through the left side of the node, turn and be transmitted in a retrograde fashion along the right side of the A-V junction, where forward conduction was blocked. Re-excitation followed in the wake of prolonged A-V conduction and occurred in an area of the A-V transmission system in which conduction was most severely depressed. These findings are compatible with the concept of reentry. Watanabe and Dreifus suggested that, under certain experimental

conditions, an impulse originating either in the sinus or A-V node may decrement in one portion of the A-V junctional tissues while being conducted slowly in another portion, turn and reenter the region of decremental conduction, giving rise to concealed or manifest conduction (an extrasystole). This would support reentry as a mechanism of return extrasystoles.

The present views on reentry differ from earlier concepts only in degree. The present day proponents of this theory consider a number of factors to be favorable to a reentry mechanism. These include: (a) nonuniform recovery of excitability in adjacent tissues; (b) differences in refractory periods in adjacent tissues; (c) differences in action potential durations, particularly at junctional points between muscle and Purkinje tissue; (d) differences in conduction velocities in various parts of the heart; (e) differential effects of a single agent on different parts of the heart, particularly on different parts of the specialized conducting tissue, or differential effects of several agents, administered simultaneously, on the same part of the heart; (f) development of phase-4 depolarization and its effect upon conduction; and (g) a combination of some or all of the above factors. A large number of these disturbances are thought to occur in regions of the specialized conducting system, especially those areas having a low safety factor such as the A-V node, its junction with the common bundle, the branching of the common bundle or the Purkinje-myocardial junction. The above factors are considered in detail below.

The relevance of nonuniform recovery of excitability in the heart to the concept of reentry has been emphasized recently by Han and Moe (75), Han et al. (77) and Surawicz et al. (99). When nonuniformity

of recovery occurs, a succeeding impulse can initially be blocked in areas which have not yet recovered, but later enter such areas during their relatively refractory period. As has been pointed out above, conduction through relatively refractory areas may be extremely slow. If conduction is sufficiently slow, adjacent myocardium could recover, and the slowly propagating impulse could emerge from the depressed zone to initiate the extrasystole. The concept of a reentrant circuit created by nonuniform recovery of excitability has gained credence as a result of recent experiments by Moe et al. (76). They demonstrated that the refractory period of the right bundle branch often exceeded that of the left bundle branch. When an appropriately timed premature stimulus was applied to the bundle of His, the impulse was blocked in the proximal right bundle branch but propagated to the ventricles over the left bundle branch. After excitation of the ventricles the right bundle branch was activated retrogradely and the retrograde impulse returned to reenter the bundle of His. Although the exact course of the reentrant pathway could not be established, the circuit required participation of both bundle branches, and was established when the two branches were dissociated by a premature impulse which took advantage of their unequal refractory periods.

Han and Moe (75) found that temporal dispersion of recovery of excitability in the dog ventricle was increased after an early premature beat. They also demonstrated that those agencies which predisposed to arrhythmias increased the temporal dispersion of recovery of excitability, whether the average refractory period was reduced (sympathetic nerve stimulation, ouabain intoxication, ischemia) or increased (chloroform, quinidine in high dosage, hypothermia).

Wallace and Mignone (73) have demonstrated that focal cooling of the left ventricle can create a local area of nonuniform recovery within the intact ventricle and result in the production of extrasystoles. The nonuniform recovery of this area could be exposed by premature excitation. With slow basic driving rates the impulse travelled normally. However, when a sufficiently premature impulse was applied to the atrium, the ventricular response reached the endocardium normally but was conducted to the epicardium with delay. When the local delay was sufficiently great, coupled extrasystoles appeared, strongly supporting the reentry theory. Scherf and his associates (74) had shown previously that focal cooling of the heart can cause multiple extrasystoles, bigeminal rhythm and ventricular fibrillation. They suggested the possibility that these arrhythmias resulted from the formation of ectopic impulses, perhaps as a consequence of a large negative after-potential. It is evident that their results may have been due to reentry.

The differential effects of agents on various parts of the conducting system and on muscle versus conducting tissue may lead to inhomogeneity of conduction and cause local reentry to occur. Adrenaline, for example, reduces the refractory periods of all parts of the conducting system but affects the refractory period of the A-V node to a considerably greater extent than that of the His bundle or its branches. Moe et al. (76) showed that the infusion of adrenaline reduced the refractory period of the A-V node to a value less than that of the right bundle branch and permitted the exposure of intraventricular conduction aberration during the transmission of premature atrial responses.

Han and Moe (76) have demonstrated that a hydrocarbon (chloroform) alone or in combination with adrenaline can create conditions

which can be considered to favor reentry. They found that chloroform uniformly prolonged the refractory period of ventricular muscle and increased the degree of nonuniformity of recovery. When adrenaline was administered in the presence of chloroform the ventricular refractory period was significantly abbreviated but the dispersion of recovery of excitability was still present. Abbreviation of the refractory period by adrenaline would increase the time interval during which reentry may occur in the presence of chloroform.

Cyclopropane has been found to affect the repolarization of Purkinje fibres producing a significant increase in the rate of repolarization during the plateau portion of the action potential accompanied by a decrease in the rate of the rapid terminal repolarization phase (78). This effect of cyclopropane results in an increase in the total duration of the action potential but in a significant decrease in the time required to repolarize to minus 60 millivolts i.e. a decrease in the absolute but an increase in the relative refractory period. Hoffman et al. (79) have shown that Purkinje fibres are capable of reexcitation when repolarized to this value. This action of cyclopropane would therefore increase the time during which an impulse could invade the tissue and be conducted with decrement.

Thus, it is evident that an agent (adrenaline) which has been shown to increase ventricular automaticity (85) and an anaesthetic (cyclopropane) which can sensitize the heart to this increase in automaticity (82) may also produce a reentry type of conduction disturbance as had been suggested previously by Dresel et al. (11).

Throughout the above discussion disturbances in conduction have been emphasized as opposed to changes in automaticity. However,

recent evidence indicates that changes in automaticity need not be entirely dissociated from changes in conduction. Singer et al. (92) have demonstrated that phase-4 depolarization of automatic cells can result in significant alterations in conduction and excitability in the isolated canine false tendon preparation. The magnitude of these changes was related to the decrease in diastolic membrane potential. Appreciable slowing of conduction usually appeared first when the action potential upstroke was initiated at a membrane potential between -75 and -70 mv. Severe conduction disturbances, including decremental conduction, unidirectional and bidirectional block and alterations in the sequence of activation occurred only when the cells conducting the action potentials had become depolarized to -65 mv or less. The most marked abnormalities occurred in conjunction with generalized diastolic depolarization (i.e. a loss of maximum diastolic potential with the result that membrane potential was reduced throughout phase 4). They also demonstrated the occurrence of reentrant beats in conjunction with development of phase-4 depolarization due to increased stretch in the preparation. They suggest conduction disturbances due to phase-4 depolarization as a possible cause of reentrant excitation and arrhythmias in situ. Since both localized slowing of conduction and unidirectional block are thought to underlie the occurrence of reentrant excitation, and since automatic cells are so widely distributed throughout the heart, it seems reasonable to suppose that phase-4 depolarization may, in some cases, be a significant factor in the development of reentrant rhythms. This mechanism is likely to be operative in circumstances known to enhance automaticity and increase the extent of depolarization of the involved cells. These include: (a) increased stretch of specialized fibres; (b) exposure to toxic

concentrations of ouabain; (c) exposure to sympathomimetic amines; (d) ischemia and hypoxia; (e) reduction in serum potassium and ionized calcium concentrations; and (f) low heart rates with resultant long diastoles.

Development of conduction abnormalities is often a rate-dependent phenomenon. Such abnormalities can develop with either increases in rate and shortening of the cycle length or decreases in the rate and prolongation of the cycle length. Aberration of the QRS complex resulting from early atrial premature systoles or a rapid supraventricular tachycardia is an example of conduction abnormalities at shorter cycle lengths. Singer et al. (92) feel that such conduction disturbances can be readily explained in terms of impulse spread through incompletely repolarized fibres (i.e. fibres still in phase 3). On the other hand, ectopic beats have been shown to occur more frequently when the basic rate is relatively slow (95,96). Several explanations have been proposed to explain this phenomenon. Han et al. (97) demonstrated a greater range of refractory periods at various points on the ventricular surface when the basic frequency was low. They proposed that early ectopic activity could be the result of reentrant excitation of already repolarized elements by the flow of current from still depolarized neighboring elements. Other studies also indicate that the differences in refractory periods in ventricular tissues increases as the heart rate decreases. Moe and associates (76) showed that the difference in refractory periods between the bundle of His and the right bundle branch is greater at slow frequencies. Moore et al. (98) demonstrated that the duration of action potentials and the refractory periods of false tendon, essentially equal to those of papillary muscle at high driving rates,

greatly exceeded the latter at frequencies of 1/sec. These observations suggested to them that the likelihood of the development of reentrant ectopic activity is enhanced not necessarily within ventricular muscle itself, but perhaps at junctions between two different tissues, as between ventricular fibres and the specialized conducting fibres. Singer et al. propose a different explanation. They feel that the tendency for ectopic rhythms to develop during periods of low heart rate could be explained in terms of the development of reentrant excitation in conjunction with enhancement of phase-4 depolarization during the long diastolic intervals.

It is evident, then, that such a large number of factors can create the conditions necessary for a reentry mechanism that its occurrence in the mammalian heart in the genesis of arrhythmias is not only possible but probable.

SECTION II

METHODS

A. ANAESTHESIA

Mongrel dogs unselected as to sex and weighing from 4 to 21 kg were anaesthetized initially with 20 mg/kg of sodium thiopental administered into a cephalic vein. Most of the required operative procedures were performed under the barbiturate anaesthesia. Additional doses of sodium thiopental were administered into an exposed femoral vein to maintain anaesthesia in animals showing premature wakening. Before the chest was opened, the animals were connected by means of a tracheal cannula to a Palmer Ideal respiration pump which delivered 20 percent cyclopropane in oxygen at 18 cycles per minute and a tidal volume of 20-25 ml/kg. However, if additional lengthy surgery had to be performed after opening the chest, the animals were artifically respired with 100% oxygen for some time before changing maintenance anaesthesia to 20% cyclopropane.

Cyclopropane, U.S.P., and oxygen, U.S.P. were supplied by a Heidbrink anaesthesia machine, the flow meters of which were calibrated periodically by measuring the volume of water displaced by the gases delivered. A semi-closed system was used. The gases were led to a mixing bag and thence to the Palmer pump. Expired air was returned to the bag through a CO_2 absorber containing fresh barium hydroxide, U.S.P. (Baralyme). The rebreathing bag was emptied frequently to prevent accumulation of nitrogen. A period of at least thirty minutes of cyclopropane administration preceded any experimental procedures to allow for adequate tissue equilibration with the gas. All experiments were terminated within three hours following the initiation of cyclopropane anaesthesia.

B. SURGICAL PROCEDURES

1. Exposure of the Heart

The following technique was used in most of the experiments: The sternum was exposed by heat cautery and cleaved in the midline over its entire length. The pericardium was incised and the edges were sutured to the chest wall to form a cradle; occasionally a small incision was made only over the right atrial appendage.

In those experiments in which injections were made into the main branches of the left coronary artery and the bundle of His was destroyed in the same animal an additional incision was made through the fourth intercostal space of the left thorax to facilitate injections into the artery.

Additional approaches used in the other experiments are described in the pertinent sections below.

2. Mechanical Control of the Systemic Blood Pressure

Mechanical elevation of the systemic blood pressure was achieved by reversible occlusion of the thoracic aorta. A loose ligature was placed around the descending thoracic aorta and the ends were brought out through a stiff rubber tube. Reversible occlusion of the vessel was achieved by compression of the rubber tubing against the vessel.

3. Destruction of the Bundle of His or the Atrioventricular Node

The procedure for destruction of the bundle of His was a modification of that described by Guzman *et al.* (81). The azygos vein was ligated and loose ligatures were placed around the superior and inferior venae cavae, extrapericardially. The veins were occluded and

the right atrium was opened widely along a line just above the atrioventricular groove. Residual blood in the right side of the heart and continuing drainage from the coronary sinus were removed by suction. 0.2 to 0.4 ml of 10-40% formaldehyde solution was injected directly into the bundle of His. An attempt was made to destroy the bundle at the lowest possible point of its path along the atrioventricular groove. The venae cavae were usually occluded for less than two minutes and never for more than five minutes. In some animals in which atrioventricular block was not produced readily, it was necessary to reenter the heart one or more times. The procedure was well tolerated in most dogs. Otherwise, the animals were discarded.

After the formaldehyde solution had been injected into the His bundle, the edges of the atrial incision were approximated in a non-crushing clamp and the venae cavae were released allowing the right heart to fill with blood. The incision was then closed and the clamp was left on the heart.

Heparin (2.5 mg/kg) was administered intravenously to all animals prior to destruction of the His bundle. Whenever the right atrium had to be entered several times, blood loss in excess of 50 ml was replaced with dextran in saline (Intradex, supplied by Glaxo Laboratories). At least 20 minutes was allowed for recovery before any experimental procedures were undertaken.

The technique for destruction of the A-V node alone was a modification of that employed by Pruett and Woods (100) using heat cautery. A fine cautery tip (less than 1 mm wide) was used in an attempt to produce as localized destruction as possible. The cautery tip was placed just anterior to the ostium of the coronary sinus and

just above the septal attachment of the tricuspid valve. This technique was much more reliable than that described above for destruction of the His bundle. Complete A-V dissociation was produced readily and it was seldom necessary to enter the heart a second time.

C. TECHNIQUES FOR INJECTING SUBSTANCES INTO THE CORONARY ARTERIES

1. Main Branches of Left Coronary Artery

Injections into the main branches of the left coronary artery were made by the method described in detail by MacCannell (80). Briefly, the anterior descending and left circumflex branches of the left coronary artery were exposed and loose nylon ligatures were placed around the vessels. The arteries were entered in the direction of blood flow with 27 gauge hubless needles connected to 3-way stopcocks by means of 20 cm lengths of polyethylene tubing (0.16 mm I.D.) filled with heparin-saline. A physiological tissue adhesive (methyl 2-cyanoacrylate monomer) supplied by Ethicon Laboratories was used to anchor the needles to the vessels.

2. Posterior Septal Artery

The technique for injection of substances into the posterior septal artery has been described in detail by Nadeau and Amir-Jahed (101). The chest was opened through the right fifth intercostal space. The pericardium was incised along the right phrenic nerve and sutured to the chest wall. The animal was lying on its back but was slightly turned to the left. The heart was slightly rotated and the posterior septal artery was exposed by dissecting carefully in the region of the atrioventricular groove beneath the terminal portion of the coronary sinus. The short 2 to 3 mm extramyocardial segment of the posterior septal artery was dissected free. A fine cotton ligature was tied at its origin, i.e.

where it branches off from the posterior descending branch of the left circumflex artery, care being taken not to compromise the circulation of this latter artery. The animal was given heparin (2.5 mg/kg) prior to cannulation of the artery. The artery was then incised with a pair of iris scissors close to the ligature and a No. 10 (0.011" I.D.; 0.024" O.D.) polyethylene cannula filled with heparin-saline was inserted 2 to 3 mm within the artery. A second ligature was tied around the artery to secure the cannula. The other end of the cannula was connected to a 27 gauge needle.

If the posterior septal artery gave off a right ventricular branch this was ligated. If two vessels were present instead of one the preparation was not used because they were usually too small for cannulation. Injections were made by means of a tuberculin syringe in volumes of 0.1 to 1.0 ml within 5 to 60 seconds. Control injections of acetylcholine, 0.01 to 10 μg, were made routinely in all experiments to test whether adequate perfusion of the region of the A-V node was obtained. If 10 μg or less of acetylcholine did not affect the regular sinus rhythm it was assumed that the wrong artery had been cannulated and the preparation was discarded.

3. Sinus Node Artery

The technique used for perfusion of the sinus node artery was a modification of that described previously by James and Nadeau (102). The artery was exposed by dissecting carefully about 1 cm from its point of origin, i.e. where it branches off from the distal half of the main right coronary artery and traverses the sulcus terminalis to supply the sinus node. It was ligated at this point and cannulated in the manner described above for the posterior septal artery. Cannulation was

attempted only in those animals in which the artery was large enough to cannulate at this point. The position of the cannula was determined by simple visual inspection and by observing the artery during injection, the blood disappearing from the artery as it filled with the injected solution. Injections were made in a volume of one millilitre over a period of one minute.

D. STIMULATION TECHNIQUES

Light steel clip electrodes attached to the margin of the right atrial appendage were used to pace the heart. A Tektronix pulse generator or a Grass model SD4 stimulator supplied rectangular pulses of 1.0 or 5.0 msec duration and approximately twice threshold intensity. All pulses were passed through isolation units. Small silver ring electrodes were sewn to the epicardial surface of the right or left ventricle in those experiments in which the ventricles were driven after the bundle of His was destroyed.

Bilateral vagotomy was performed at a mid-cervical level in all experiments. The distal end of either the right or left vagus nerve (occasionally both) was placed in a stimulating electrode and bathed in mineral oil. The nerve was stimulated with rectangular pulses of 1.0 msec duration at a frequency and voltage sufficient to produce maximal cardiac slowing without loss of sinus dominance. A Grass model SD5 stimulator was used.

E. RECORDING TECHNIQUES

1. General

The systemic blood pressure was taken as the end pressure

recorded in the left common carotid artery. This vessel was cannulated with polyethylene tubing (Portland No. 54) having an internal diameter of 0.059 inch which was connected to a P23AC Statham pressure transducer. In a few experiments blood pressure was monitored from the left femoral artery.

Lead II electrocardiograms were taken in all dogs using subcutaneous needle electrodes. In those animals in which atrial and ventricular electrograms were recorded, bipolar clip or ring electrodes were attached to the right atrial appendage and to the anterior surface of the right ventricle.

All parameters were recorded on a Grass ink-writing polygraph at a paper speed of 25 mm/sec (with the exception of those experiments in which records were obtained from the bundle of His as described below).

2. Technique for Recording from the Bundle of His

The recording electrodes consisted of fine platinum-iridium wires (0.010" in diameter) embedded in epoxy plaques. Each plaque contained from 3 to 5 contacts situated in the center of the plaque and separated by distances of approximately 1 mm. The wires projected from the surface of the plaque by about 0.1 to 0.2 mm since much better recordings could be obtained than if the wires were polished smooth with the surface of the plaque. The plaque was rectangular in shape (8 mm in width and 12 mm in length) and contained four holes, one in each corner.

The position of the animal and exposure of the heart were the same as that used for the cannulation of the posterior septal artery.

Placement of the electrode over the bundle of His was as follows:

The right atrium was opened during total venous inflow occlusion and two fine silk sutures (size 000) were passed through two portions of atrial endocardium less than $\frac{1}{2}$ mm deep and approximately 3 to 5 mm wide. One of the sutures was placed near the center of the base of the septal cusp of the tricuspid valve and the other approximately 5 mm away from and parallel to it. Thus, the sutures were situated parallel to the conducting system and several millimeters from the actual recording site. The ends of the silk threads were brought out through the opening in the atrium and the atrial incision was closed with a non-crushing clamp after releasing venous occlusion. Fifteen to 20 minutes were allowed for recovery. The ends of the silk threads were passed through the four holes in the electrode plaque outside the heart and the first, slip-free, knot was made. The heart was then entered a second time, the electrode was lowered into position and the knots were tightened. When the electrode was in position second knots were tied to secure it in place. The atrial incision was again closed with the noncrushing clamp and another 15 to 20 minutes were allowed for recovery. The venae cavae were occluded for less than two minutes each time. Care was taken to prevent damage to the lead wires by the clamp approximating the cut edges of the atrium. This was accomplished by placing the leads at a point along the edge such that no bleeding occurred despite the fact that this portion of the muscle was not grasped by the clamp.

Similar electrode plaques were attached to the surfaces of the right and/or left ventricles. Records from the bundle of His were obtained simultaneously with records from the right atrial appendage and right or left ventricle together with a lead II electrocardiogram.

Bipolar leads were employed for all recordings. The low

frequency components of the bundle of His electrogram were filtered in order to increase baseline stability and to facilitate identification of the His potential. The low- and high-filter settings for the His electrogram were either 40/500 or 40/2000. The presence of the His potential was confirmed in all experiments by stimulation of the vagus nerves, a procedure which has been shown previously to lengthen only the atrium-His bundle interval.

The records were displayed on an Electronics for Medicine recorder and photographed on 7-inch paper moving at a speed of 200 mm/sec.

In a few experiments the recording electrodes were used for stimulating the His bundle. In these experiments the bundle of His was stimulated after the A-V node had been destroyed with heat cautery.

F. ANALYSIS OF RECORDS

1. Grass Polygraph Records

Intervals on the electrocardiogram were determined by means of a measuring magnifier graduated to 0.1 mm. The "coupling interval" has been defined previously (11) as the time between the beginning of the R wave of the normal and that of the abnormal complex. The heart rate was read directly from the electrocardiogram or electrogram.

2. Electronics for Medicine Oscillograph Records

Intervals between the various complexes were determined by first measuring the distance between them with the magnifier and then converting the distance to milliseconds on the basis of the time lines provided by the recorder. Local activation time was taken as the peak of monophasic electrogram complexes or, with diphasic complexes, the instant at which the intrinsic deflection crossed the line of zero

potential. Coupling intervals were measured with a millimeter ruler. The basic cycle length was determined by measuring the A-A intervals in an atrial electrogram or the distance between the "a" potentials in an electrogram obtained from the bundle of His.

G. DRUGS EMPLOYED

0.25 to 32 μg/kg of l-adrenaline diluted to 3.0 ml with 0.9 percent sodium chloride were injected into a femoral vein over the course of 60 seconds. At least 15 minutes was allowed between injections. Intravenous infusions of adrenaline (0.5-20 μg/kg/min) were administered at rates of 0.5-20 ml/min by a Harvard infusion pump. The infusions were of 3 to 24 minutes duration; 20 to 30 minutes were allowed between infusions. The tartaric acid salt of adrenaline was employed in all experiments but doses are expressed as the base.

2.5 to 60 μg of acetylcholine was injected into the two branches of the left coronary artery. 0.01 to 20 μg of acetylcholine was injected into the posterior septal artery. The chloride salt of acetylcholine was employed. Doses are again expressed as the base.

10 to 20 μg of atropine was injected into the sinus node artery. The sulfate salt of atropine was used and the dose is expressed as the base.

The dose of heparin was 2.5 mg/kg. Solutions of heparin were prepared in 0.9 percent sodium chloride in a concentration of 110 Units/mg.

The standard 40% formaldehyde solution supplied by Fisher Scientific Co. was used for injection into the bundle of His. Ten percent solutions were obtained by dilution of the 40% solution with distilled water.

SECTION III

THE EFFECT OF DESTRUCTION OF THE BUNDLE OF HIS OR THE ATRIOVENTRICULAR NODE ON CYCLOPROPANE-ADRENALINE ARRHYTHMIAS

Attention has been focused recently on the site of origin of the arrhythmias arising when adrenaline is injected during cyclopropane anaesthesia. Riker et al. (2) had suggested that the arrhythmias originate in ventricular myocardium outside of vagal influence. Later, Dresel et al. (11), Dresel and Sutter (10) and MacCannell and Dresel (13) presented evidence indicating that the site of origin is located in the atrioventricular node or the bundle of His or at least within an area of the heart supplied directly by the cardiac vagus and within the distribution of the left circumflex coronary artery. Recent studies of Moore et al. (14), however, again suggest that cyclopropane arrhythmias originate in the ventricular conducting system below the His bundle.

The investigations reported here were undertaken in an attempt to delineate further the site of origin of these arrhythmias. If Dresel's hypothesis is correct and the bundle of His is indeed important in the genesis of the arrhythmias, then it should be possible to prevent the arrhythmias by destroying this structure.

A. INCIDENCE OF ARRHYTHMIA AFTER DESTRUCTION OF THE BUNDLE OF HIS

1. Characteristics of Rhythm after Destruction of the Bundle of His

The procedure used for the destruction of the bundle of His was a modification of that used by Guzman et al. (81). Following A-V dissociation there was usually a regular ventricular rhythm which ranged from 38 to 75 beats per minute. The form and duration of the QRS complex varied but was usually constant in any one experiment. The P-Q interval changed with each ventricular beat indicating that the atria and ventricles were beating independently. The atrial frequency remained

essentially the same as that prior to A-V block. Stimulation of the vagi intense enough to produce atrial arrest had no effect on the rate of the idioventricular pacemaker.

2. Failure of Adrenaline to Induce Bigeminy after A-V Block

The following protocol was used in 15 animals: control injections of adrenaline were given in order to determine the minimal dose of adrenaline required to produce bigeminy. The bundle of His was destroyed and this minimal dose of adrenaline was again administered. The dose was then increased, each subsequent dose being double the previous one, until ventricular fibrillation occurred. Since it has been shown previously (10,11) that bigeminal rhythms are extremely sensitive to the level of the systemic blood pressure, an attempt was made to obtain equivalent pressor responses after complete A-V block by raising the pressure if necessary with reversible occlusion of the thoracic aorta.

A typical result is shown in Fig. 1. The top panel shows a typical constantly-coupled bigeminal rhythm produced by 1 μg/kg of adrenaline. The level of the systolic blood pressure was approximately 200 mm Hg with a typical pulse deficit. The injection of 40% formaldehyde into the bundle of His produced complete A-V block with an idioventricular rate of approximately 50 beats/min. Injection of twice the control dose of adrenaline increased the rate of the idioventricular pacemaker but failed to elicit bigeminal rhythm. The level of the systolic blood pressure was equivalent to that obtained during the control injection.

The results of these experiments are summarized in Table I. On no occasion was a bigeminal rhythm elicited by doses of adrenaline which had produced this arrhythmia when the conducting system had been intact.

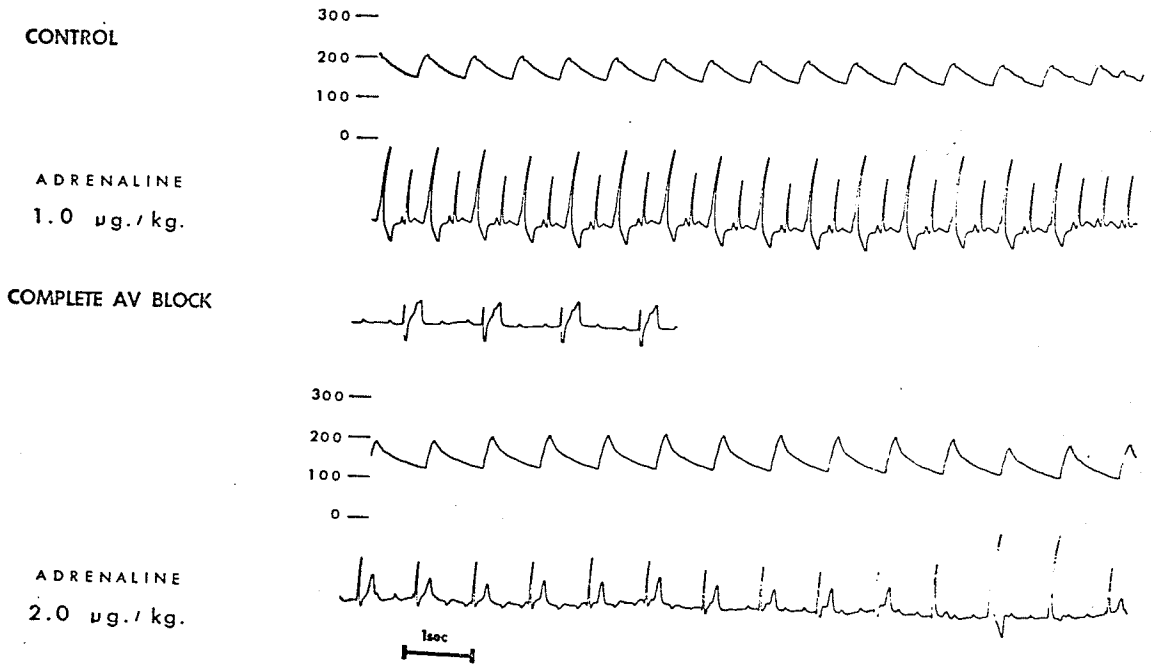


Fig. 1. Prevention of bigeminal rhythm by destruction of the bundle of His. First panel: a typical constantly-coupled bigeminal rhythm produced by 1 µg/kg of adrenaline. Second panel: complete A-V block produced by injection of 40% formaldehyde into the bundle of His. The apparently constant P-Q interval is coincidental. Third panel: absence of bigeminy after complete A-V block following the injection of twice the control dose (2 µg/kg) of adrenaline. Note: Blood pressure response is equivalent to that obtained in the control record.

TABLE I

INCIDENCE OF ARRHYTHMIA BEFORE AND AFTER DESTRUCTION OF THE BUNDLE OF HIS

	Intact Heart		Bundle of His Destroyed				
Dog No.	Bigeminy	Multifocal	Bigeminy		Multifocal		VF
			Blood Pressure				
			Adeq. *	Inadeq. **	Control Dose	Larger Dose	
1	+	+		-	-	-	
2	+		-				
3	+	+	-		-	+	+
4	+	+	-		-		
5		+			-	+	
6		+			+	+	+
7	+	+	-		-	+	+
8	+	+	-		+	+	+
9	+		-				+
10	+		-				
11	+	+	-		-	#	+
12	+	+	-		-	#	+
13	+	+	-		-	#	+
14	+		-				+
15	+			-			+
16		+			+	+	
17	+			-			+
18	+	+	-		-		+
19	+	+	-		-		
20		+			-	+	+
Total:	16/16	14/14	0/13	0/3	3/14	7/8	13/13

* The level of the systolic blood pressure was equivalent to that obtained during the control injection.

** The blood pressure level was below that obtained in the control injection.

\# Control dose was such that administration of the next higher dose caused VF.

In all cases twice the control dose of adrenaline also failed to elicit this arrhythmia after complete A-V nodal block. The administration of these doses of adrenaline increased the rate of the idioventricular pacemaker by 35 to 45 beats/min. In 13 of the 16 experiments the level of the systolic blood pressure was equivalent to that obtained in control injections. In only 3 of the experiments could the absence of arrhythmia be attributed to an inadequate pressor response.

In one animal, the first injection of formaldehyde destroyed only a portion of the His bundle resulting in a 4:1 A-V block. Injection of adrenaline caused first a change to normal sinus rhythm and then bigeminal rhythm. A second injection of formaldehyde established complete A-V block and injection of adrenaline now failed to cause this arrhythmia.

3. Incidence of Multifocal Arrhythmias after A-V Block

Destruction of the bundle of His increased the dose of adrenaline necessary to induce multifocal arrhythmias but did not prevent them. A typical record is shown in Fig. 2. Panel A shows a rather slow but multifocal rhythm in the intact heart in response to 2 μg/kg of adrenaline. This dose caused only acceleration of the ventricular pacemaker after the bundle of His had been destroyed (Panel B) although the pressor response was equivalent to that seen in the control. Panel C shows a multifocal arrhythmia of substantially the same severity as that in Panel A but in response to twice the control dose. However, the onset and offset of this arrhythmia differed from the control in the manner discussed below. The blood pressure during this arrhythmia is also lower than in the control.

The results of all the experiments are summarized in Table I. Previously effective doses of adrenaline failed to cause multifocal

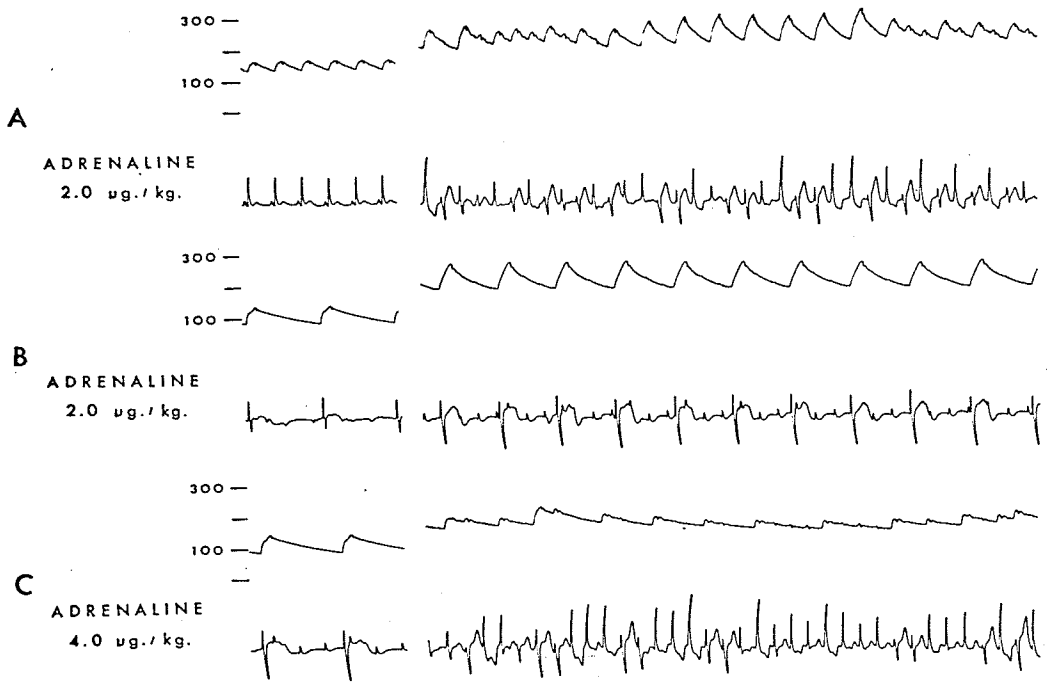


Fig. 2. Effect of destruction of the bundle of His on the dose of adrenaline required to produce multifocal ventricular tachycardia. Panel A: a slow multifocal rhythm produced by 2 μg/kg of adrenaline in the intact heart. Panel B: acceleration of the idioventricular pacemaker after destruction of the bundle of His in response to the same dose of adrenaline as in A. Note: Pressure is equivalent to that obtained in the control injection. Panel C: a multifocal arrhythmia produced by twice the control dose of adrenaline. Note: Pressure is lower than in the control injection. The extreme left of each panel indicates the rhythm present just prior to the injection of adrenaline.

arrhythmias in 11 of 14 dogs with A-V block. Arrhythmia occurred in the other 3 dogs but was much less severe. Four animals responded with multifocal arrhythmias to larger doses of adrenaline. In 3 of the animals the minimal effective dose in intact hearts was such that after destruction of the bundle of His, injection of the next higher dose caused ventricular fibrillation (see below). A record from one of these animals is shown in Fig. 3. Larger doses were not tried in 3 of the dogs. In only one animal did the larger doses fail to elicit arrhythmia. However, in this one animal difficulty was encountered in destroying the bundle of His and the blood pressure was quite low.

Multifocal rhythms elicited after destruction of the bundle of His usually began suddenly and terminated abruptly. Abrupt termination of the arrhythmia was followed occasionally by a period of asystole before the idioventricular pacemaker resumed. This is in contrast to control conditions where multifocal ventricular tachycardia is often preceded and usually followed by a bigeminal rhythm or by isolated nodal or ventricular beats. These properties of multifocal arrhythmias during A-V block resemble closely the sudden onset and termination of the monofocal arrhythmia caused by adrenaline in non-sensitized dogs.

4. Effect of Destruction of the Bundle of His on the Dose of Adrenaline Required to Produce Ventricular Fibrillation

Dresel and Sutter (10) reported that 90% of dogs with intact conducting systems fibrillate after injection of adrenaline at doses of 8 to 16 μg/kg. These same doses caused ventricular fibrillation in animals in which the bundle of His had been destroyed. Fig. 3 shows fibrillation in response to a dose of 8 μg/kg of adrenaline in

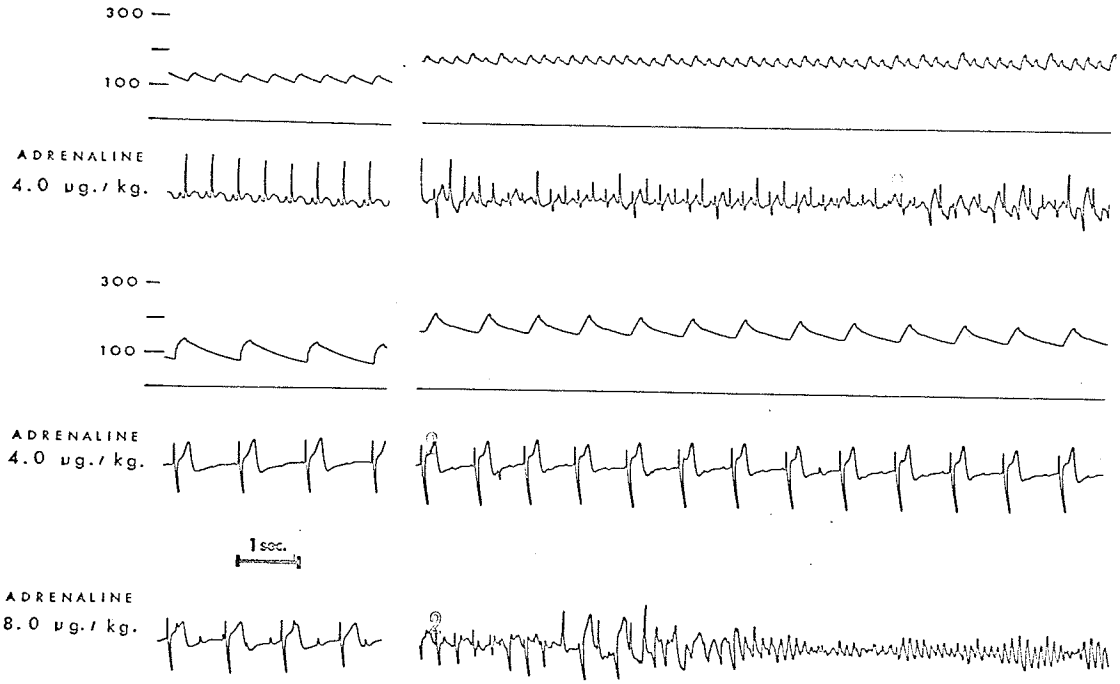


Fig. 3. Effect of destruction of the bundle of His on the dose of adrenaline required to produce ventricular fibrillation. First panel: multifocal ventricular tachycardia produced by 4 µg/kg of adrenaline in the intact heart. Second panel: acceleration of idioventricular pacemaker after same dose of adrenaline but no arrhythmia after destruction of the bundle of His. Third panel: ventricular fibrillation after the next higher dose (8 µg/kg) of adrenaline.

a dog with complete A-V block. This response was obtained in each of 13 animals to which these higher doses (8 to 16 μg/kg) were administered (Table I). Destruction of the bundle of His therefore does not change the dose of adrenaline necessary to produce ventricular fibrillation.

B. EFFECT OF STIMULATION OF THE VAGUS ON BIGEMINY AND MULTIFOCAL VENTRICULAR TACHYCARDIA IN THE INTACT ANIMAL AS COMPARED WITH ITS EFFECT ON ARRHYTHMIAS PRODUCED IN ANIMALS WITH A-V DISSOCIATION

Dresel et al. (82) have shown that injection of sympathomimetic amines into the left anterior descending coronary artery, which reaches the lower portions of the ventricular conducting system, does not cause arrhythmias in nonsensitized animals but does cause arrhythmias in animals under cyclopropane anaesthesia. This difference was attributed to a qualitative change in the sensitivity of the ventricle to increased automaticity induced by these amines. It appeared possible that the larger doses of adrenaline which caused multifocal arrhythmias after A-V block in the present investigations were sufficient to cause foci of increased automaticity in the ventricles and that therefore multifocal arrhythmias after A-V block differ in mechanism from those seen with lower doses of adrenaline before A-V block.

It is well known that stimulation of the vagus nerves in nonsensitized animals causes induction of arrhythmia after subeffective doses of adrenaline and prolongs the monofocal arrhythmia seen after effective doses (3,4,5). In sensitized preparations, on the other hand, stimulation of the vagus nerves converts bigeminal and multifocal rhythms to normal sinus rhythm (10). The former arrhythmia is generally attributed to increased ventricular automaticity, the

latter to other factors (3,10). The effect of stimulation of the vagus nerves might therefore serve to distinguish between the two mechanisms.

The infusion of 1 or 2 μg/kg/min of adrenaline produced a multifocal ventricular tachycardia in each of 8 intact dogs. This arrhythmia was converted to normal sinus rhythm by stimulation of the vagi at various frequencies 18 times in 26 attempts in the 8 dogs. Usually a lower frequency of stimulation was effective shortly after the onset of the arrhythmia while a greater frequency of stimulation was necessary when the arrhythmia was well established. Five of the 8 times in which vagal stimulation was ineffective could be attributed to an inadequate frequency or intensity of stimulation used since conversion occurred each time either parameter was increased. However, sometimes the atrial rate had to be decreased considerably before conversion occurred. On the remaining 3 occasions the arrhythmia was unaffected by stimulation of the vagus nerves and conversion occurred only after the rate of infusion of adrenaline was decreased. On these occasions the rate of the arrhythmia also decreased.

On 2 occasions stimulation of the vagus increased the severity of the arrhythmia. This effect may have been due to the stimulation of cardiac sympathetic fibres present in the canine vagosympathetic nerve trunks.

In agreement with the results obtained previously (Section A-3), the infusion of adrenaline at rates which had produced multifocal arrhythmia in the intact animal failed to produce this arrhythmia in 6 of 8 dogs with complete A-V block. Increasing the rate of infusion, however, did produce arrhythmia. Usually a multifocal rhythm was

produced; monofocal tachycardia appeared occasionally. The effect of vagal stimulation on these arrhythmias was redetermined. The frequency and intensity of stimulation used was equal to or greater than that which had been effective when the conducting system was intact. Conversion was not attributed to vagal action unless the arrhythmia resumed when vagal stimulation had been terminated.

In 19 of 28 attempts in the 8 dogs vagal stimulation was ineffective in converting the arrhythmia after A-V block. Fig. 4 illustrates the response to stimulation of the right vagus before and after destruction of the bundle of His. The infusion of 1 μg/kg/min of adrenaline produced first a bigeminal rhythm (upper panel) and then a multifocal ventricular tachycardia (middle panel). Stimulation of the vagus nerve converted both of these arrhythmias to normal sinus rhythm. After the bundle was destroyed, infusion of twice the control dose of adrenaline produced a multifocal rhythm which was unaffected by vagal stimulation.

The 9 successful conversions can be explained on the following bases: on 6 occasions (4 dogs), conversion to the previously existing slow idioventricular rhythm occurred after the infusion of adrenaline had been stopped but before the termination of arrhythmia. The arrhythmia did not return after stopping nerve stimulation and the possibility of spontaneous recovery could not be ruled out. The arrhythmia did return after stopping nerve stimulation on 3 other occasions (2 dogs). In each of these cases, however, conversion was accompanied by a decrease in blood pressure which, as is known, causes conversion even in the absence of nerve stimulation. The arrhythmias returned only after a considerable delay which may have been due to the

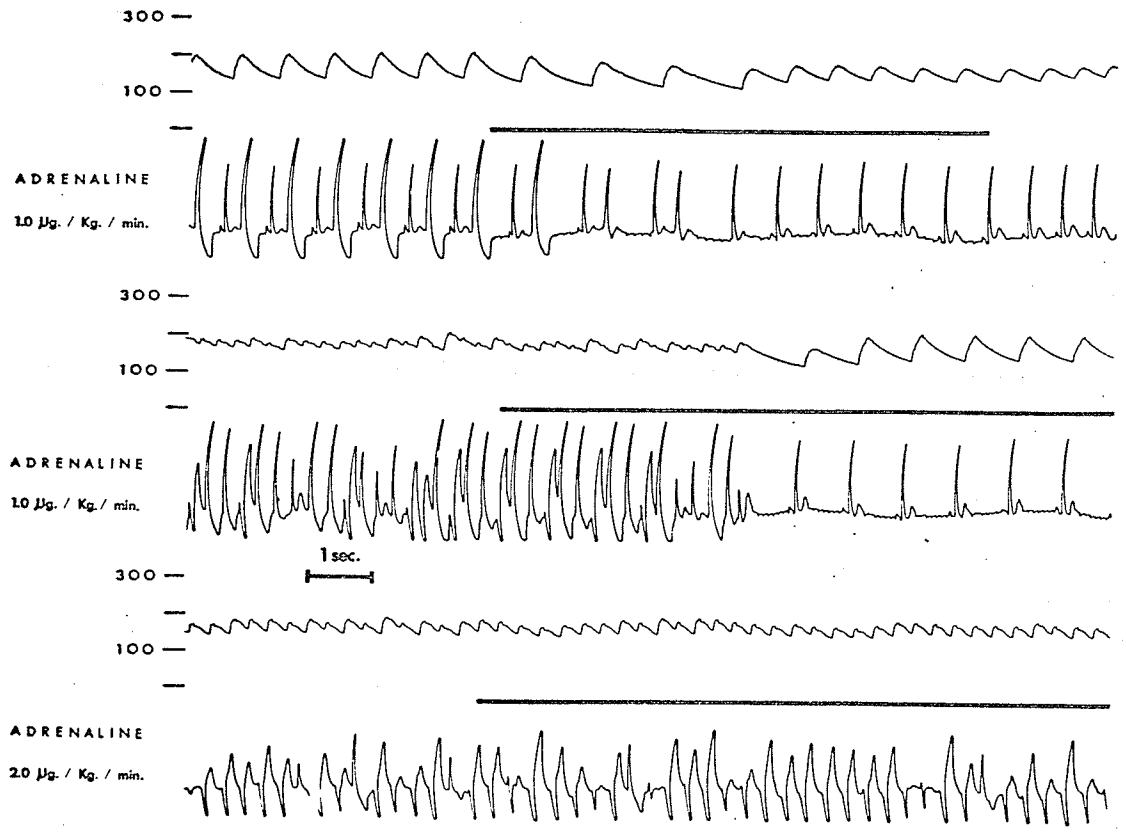


Fig. 4. Effect of stimulation of the vagus nerve during arrhythmias produced by adrenaline before and after destruction of the bundle of His. Upper and Middle panels: stimulation of the right vagus nerve converts both bigeminal and multifocal rhythms produced by the infusion of 1 µg/kg/min of adrenaline to normal sinus rhythm. Bottom panel: lack of effect of vagal stimulation on arrhythmia produced by the infusion of twice the control dose (2 µg/kg/min) of adrenaline after destruction of the bundle of His.

slow recovery of blood pressure to the previous level. No effect of nerve stimulation was seen in all other attempts in these 2 animals and there was also no effect on the blood pressure. It is possible therefore that the fall in blood pressure in these animals was due to a depression of ventricular contractility by the vagal stimulation as suggested by DeGeest et al. (35). The decrease in blood pressure may also have been due to a decrease in the atrial rate and hence reduction of the atrial contribution to cardiac output.

C. EFFECT OF ACETYLCHOLINE INJECTED INTO THE MAJOR BRANCHES OF THE LEFT CORONARY ARTERY ON MULTIFOCAL RHYTHMS ARISING BEFORE AND AFTER DESTRUCTION OF THE BUNDLE OF HIS

Although the procedure used for destruction of the bundle of His was designed to produce only localized damage, it seemed possible on anatomical grounds (57) that preganglionic vagal fibres were also being destroyed.

MacCannell and Dresel (13) had shown that cyclopropane-adrenaline arrhythmias were abolished by injection of acetylcholine into the left circumflex, but not into the left anterior descending coronary artery. If multifocal arrhythmias due to large doses of adrenaline after A-V block were due to induction of foci in the lower portions of the ventricles, acetylcholine should be effective only when injected into the anterior descending artery. This provided another method for differentiating the two mechanisms.

1. The Effect of Acetylcholine Injected into the Left Circumflex Coronary Artery

Acetylcholine, in doses of 2.5 to 60 μg, was injected into

the left circumflex coronary artery of 10 dogs during sustained bigeminal or multifocal rhythms produced by constant infusion of adrenaline. The bigeminal rhythms were uniformly converted to sinus rhythms and the multifocal rhythms were either converted to sinus or to bigeminal rhythms in each of the dogs. After the bundle of His had been destroyed, injections of acetylcholine in doses of 10-60 μg were ineffective in 9 of the animals (Table II). The responses to acetylcholine, 20 and 50 μg, injected into the circumflex artery before and after production of A-V block are illustrated in Fig. 5. In this particular experiment the control multifocal ventricular tachycardia was converted first to a bigeminal rhythm and then to a normal sinus rhythm. The arrhythmia obtained after destruction of the His bundle was unaffected by a large dose of acetylcholine.

On 2 occasions injection of the highest dose (60 μg) of acetylcholine into the circumflex artery appeared to lessen the severity of the arrhythmia after A-V block although smaller doses had been ineffective.

2. The Effect of Acetylcholine Injected into the Left Anterior Descending Coronary Artery

Ten to 60 μg of acetylcholine were injected into the left anterior descending coronary artery during multifocal arrhythmias obtained before and after destruction of the bundle of His. The results are summarized in Table II. The arrhythmia was converted in only 1 of 9 attempts in 5 dogs with intact hearts. In this single instance, conversion occurred after a delay (recirculation ?) and was accompanied by a considerable decrease in the systemic blood pressure.

Fig. 6 shows conversion of multifocal arrhythmia by injection

TABLE II

CONVERSION OF MULTIFOCAL RHYTHMS AFTER INJECTION OF ACETYLCHOLINE INTO MAIN BRANCHES OF LEFT CORONARY ARTERY BEFORE AND AFTER A-V BLOCK

LEFT CIRCUMFLEX ARTERY:	
Before	17/17 (10 dogs)
After	2/16 (10 dogs)
LEFT ANTERIOR DESCENDING ARTERY:	
Before	1/9 (5 dogs)
After	16/30 (10 dogs)

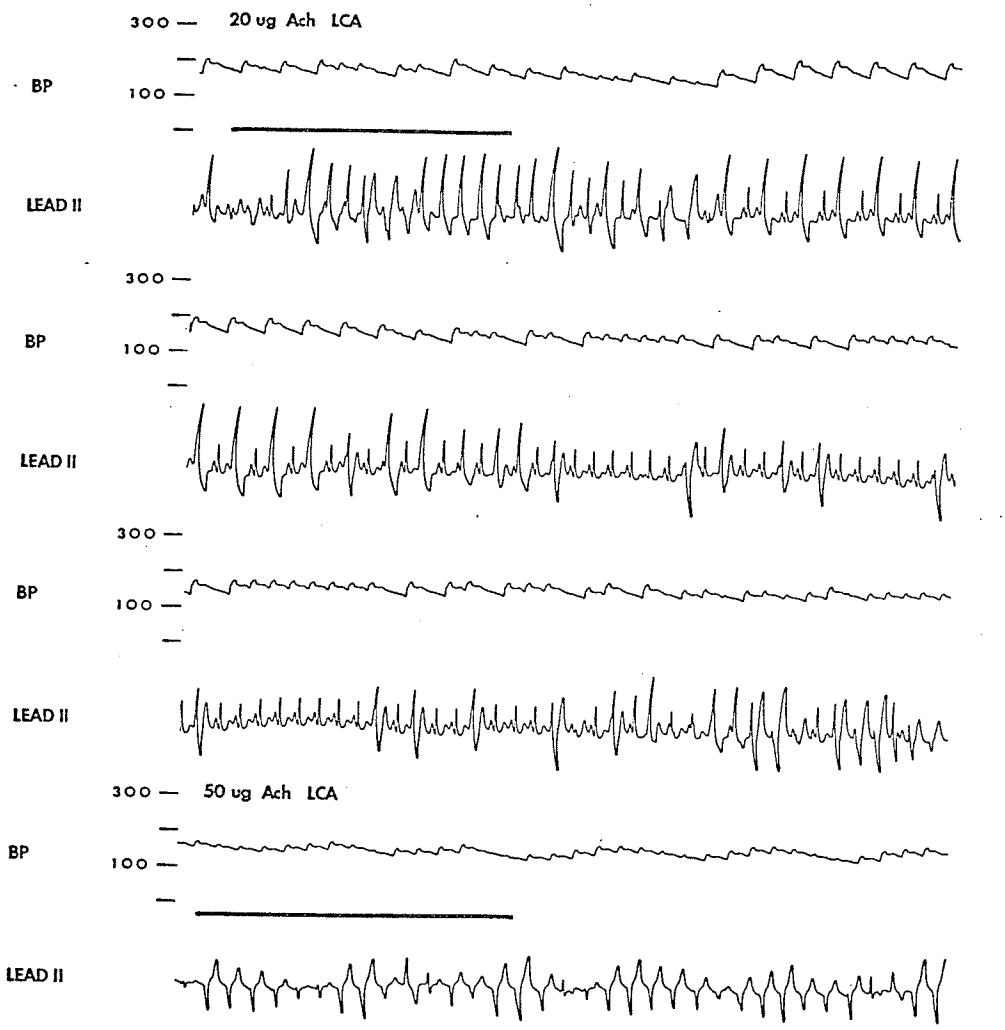


Fig. 5. Effect of injection of acetylcholine into the left circumflex coronary artery during arrhythmias produced by adrenaline before and after destruction of the bundle of His. First, Second and Third panels: injection of 20 μg of acetylcholine converts multifocal ventricular tachycardia in the intact heart first to a bigeminal rhythm and then to a normal sinus rhythm. Eight seconds of bigeminy have been deleted to show the conversion to normal sinus rhythm and the return of the arrhythmia. Fourth panel: injection of 50 μg of acetylcholine has no effect on the multifocal arrhythmia after destruction of the bundle of His.

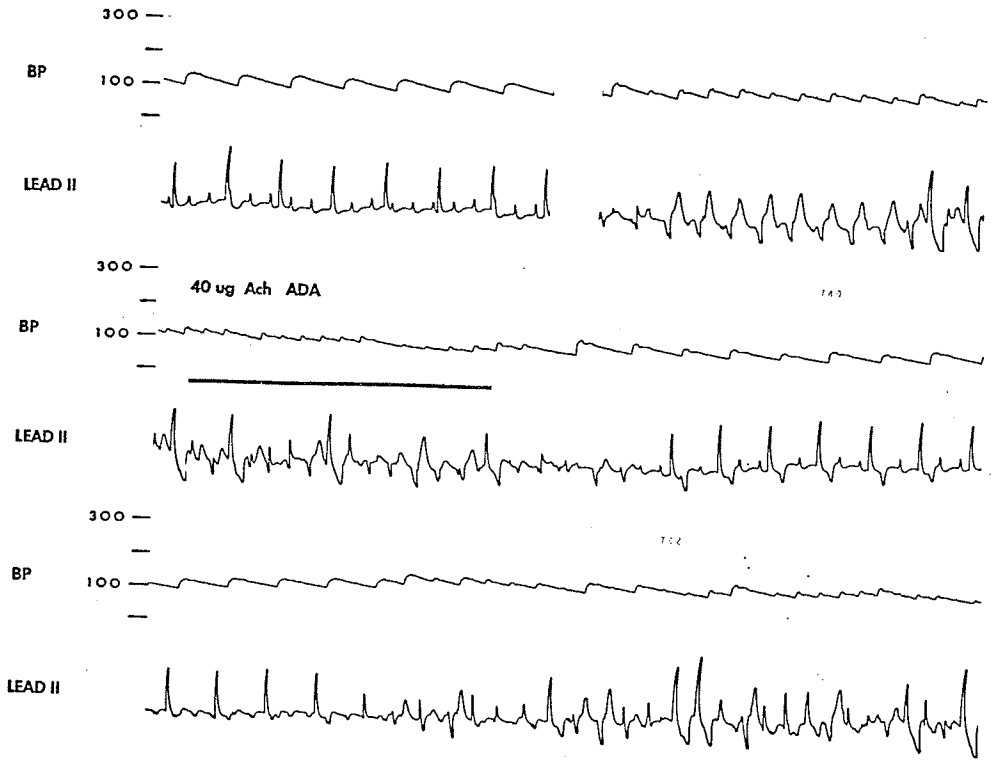


Fig. 6. Effect of injection of 40 μg of acetylcholine into the left anterior descending coronary artery during multifocal rhythm produced by infusion of 4 μg/kg/min of adrenaline in a dog in which the bundle of His had been destroyed. Upper panel: complete A-V block present prior to the start of multifocal arrhythmia. Middle and Bottom panels: conversion of multifocal arrhythmia to previous idioventricular rhythm. Twelve seconds of this rhythm have been deleted to show the return of the arrhythmia.

of 40 μg of acetylcholine into the left anterior descending coronary artery after destruction of the bundle of His. There is some decrease in pressure at the time of conversion. This was seen in 16 of 30 attempts in 10 dogs. In addition, there was a decrease in the severity of the arrhythmia on 4 occasions. Generally, large doses (30-60 μg) were needed to convert the arrhythmia.

No control injections were given in 5 of these animals. The lack of control injections should not change the interpretation of the results because only 1 of 9 such injections was effective in the other animals.

In one experiment, injection of acetylcholine made simultaneously into the left circumflex and anterior descending arteries was effective in converting arrhythmia after A-V block although injections into either artery alone were ineffective.

D. EFFECT OF VENTRICULAR DRIVE IN INDUCING ARRHYTHMIAS IN DOGS WITH COMPLETE A-V BLOCK

It has been reported by Vick (15) and confirmed by the present work (see Section IV) that rate is an important factor in the induction of bigeminal rhythms. Since idioventricular pacemaker rates are generally low the absence of bigeminal rhythms after destruction of the bundle of His might be attributed to this factor. If this is so, then an increase in rate should be effective in inducing bigeminal rhythms after destruction of the bundle of His.

The increase in rate was achieved by pacing the ventricles electrically. The driving rates used were equal to or greater than those at which bigeminy had occurred in the intact heart. Stimulating

electrodes were attached to either the anterior surface of the right ventricle or to the apex of the left ventricle. The following protocol was used: the dose of adrenaline causing bigeminy in the intact heart was determined. The bundle of His was destroyed and the control dose of adrenaline was injected. The same dose was then administered while the ventricles were being driven. This procedure was repeated with increasing doses of adrenaline.

When the control dose of adrenaline was administered no arrhythmia was produced in any of 4 dogs after destruction of the bundle of His whether or not the ventricles were driven. Twice the control dose of adrenaline had no effect in the absence of ventricular drive in any of the animals but produced multifocal arrhythmia in one dog during drive. Four times the control dose produced ventricular fibrillation in one of the remaining 3 animals but had no effect in the other 2 in the absence of drive. After successful defibrillation the administration of the same dose in the presence of ventricular drive produced multifocal rhythm in this animal but still had no effect in the other two animals. The next higher dose of adrenaline produced ventricular fibrillation in these two animals in the absence of drive and no attempt was made to defibrillate them.

In one other dog the ventricles were paced after conversion of a bigeminal rhythm in the intact heart by stimulation of the vagus. Ventricular pacing (either right or left ventricle) failed to reinduce arrhythmia although right atrial pacing had done so. The interpretation of these experiments is complicated by the fact that ventricular pacing usually decreased the blood pressure.

E. INDUCTION OF ARRHYTHMIA AFTER A-V BLOCK DUE TO DESTRUCTION OF THE ATRIOVENTRICULAR NODE

The atrioventricular node was destroyed with heat cautery in 7 dogs. Adrenaline was infused before and after production of A-V block. The idioventricular rate was usually greater than that obtained in the previous series of experiments after destruction of the bundle of His, and accelerated more under the influence of adrenaline.

Infusion of adrenaline induced coupled rhythms in 5 of 7 dogs after destruction of the A-V node. A typical result is shown in Fig. 7. The top panel shows bigeminal rhythm produced in the intact heart by 0.5 μg/kg/min adrenaline. The bottom panel shows bigeminal rhythm obtained in response to 1 μg/kg/min adrenaline after destruction of the A-V node. The increase in the dose of adrenaline might be attributed to the presence of a lower absolute pressure just prior to the infusion of adrenaline. No attempt was made to raise the pressure by occlusion of the aorta during the infusion of the lower dose (0.5 μg/kg/min). The coupled rhythm obtained after destruction of the A-V node had a variable coupling interval in contrast to the constant coupling interval characteristic of bigeminal rhythm obtained in the intact heart. This might be attributed, partly, to the variable configuration of the coupled beat. However, the coupling interval did remain constant for several beats at a time and at such times was the same as the constant interval of the bigeminal rhythm obtained before the A-V node was destroyed. The coupling intervals were variable and longer than in the control arrhythmia in 4 of the 5 dogs in which a coupled rhythm was obtained after A-V dissociation. The bigeminy in the other dog had a

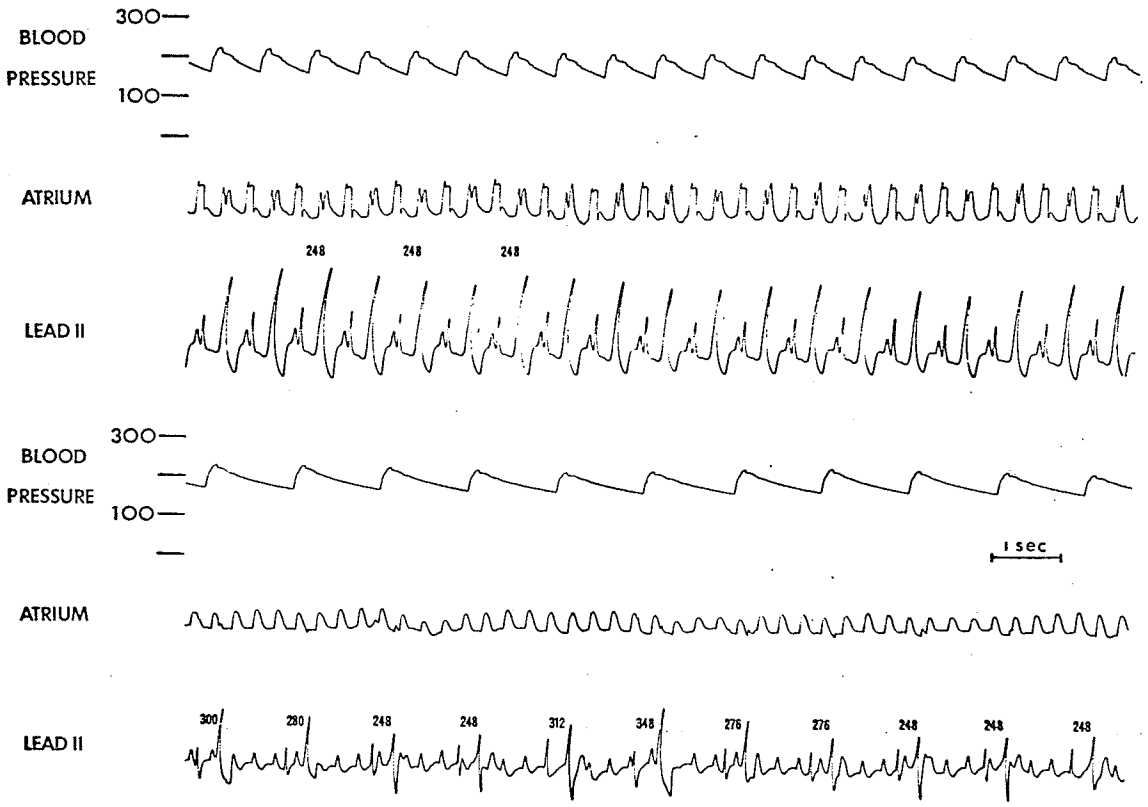


Fig. 7. Induction of bigeminal rhythm after destruction of the A-V node with heat cautery. Upper panel: bigeminal rhythm produced in the intact heart by the infusion of 0.5 μg/kg/min adrenaline. Coupling interval of bigeminal rhythm is constant at 248 msec. Lower panel: coupled rhythm obtained after destruction of the A-V node after the injection of 1 μg/kg/min adrenaline. Coupling intervals vary and are longer in most cases than in the control bigeminy. These are indicated in the diagram.

constant coupling interval which was longer than the interval before A-V block.

Bigeminal rhythm induced after A-V block was not a stable, reproducible arrhythmia and could not be studied in the same manner as the arrhythmia in the intact heart. In 2 of the 5 experiments in which bigeminy was induced coupling continued for 30 seconds or less and then either reverted to A-V block or was replaced by multifocal rhythm. In the other 3 experiments coupling was maintained and the effect of stimulation of the vagus on the arrhythmia could be studied. Such stimulation produced effects which were variable and inconclusive. Stimulation of the vagus intense enough to decrease the atrial rate below the rate at which conversion occurred in the control situation had no effect on the arrhythmia induced after destruction of the A-V node in one of the 3 dogs. In the other 2 dogs stimulation of the vagus converted the arrhythmia to the pre-existing rhythm but only after a decrease in pressure. However, in both dogs the arrhythmia did not return although the pressure had again reached preconversion values; an increase in the dose of adrenaline in one of these dogs produced multifocal rhythm.

The dose of adrenaline required to produce arrhythmia after A-V dissociation was the same as the control dose in 2 of the dogs, twice the control dose in 2 more dogs and four times the control dose in the fifth dog. This increase in dose in 3 of the dogs could be attributed partly to the lower pressure present just prior to the infusion of adrenaline after A-V block as compared to the blood pressure before the control injection. Moe et al. (7) have shown that the threshold dose for the induction of arrhythmia in the intact heart

is inversely related to the level of the arterial blood pressure present just prior to the administration of adrenaline.

Bigeminal rhythm could not be induced after cauterizing the A-V node in 2 of the 7 experiments. The QRS complex in these experiments was wide and notched and resembled bundle branch block. It was assumed that structures other than the A-V node had been cauterized, probably the common His bundle or one of its branches. Adrenaline caused only multifocal rhythms in these animals (as shown previously with destruction of the bundle of His). This was not unexpected since in the dog the A-V node and common His bundle may be as short as a few millimetres (106) and precise localization of the A-V node can be difficult.

The bundle of His was paced in the two experiments in which only a transient coupled rhythm was elicited after destruction of the A-V node. In one of these experiments such pacing induced multifocal rhythm at a dose of adrenaline which failed to induce arrhythmia in the absence of pacing. Pacing was ineffective in the other experiment. However, the QRS configuration during pacing was abnormal indicating that structures other than the bundle of His were being stimulated.

SECTION IV

EFFECT OF ALTERED HEART RATE ON CYCLOPROPANE-ADRENALINE ARRHYTHMIAS

It has been reported by Dresel and Sutter (10) and confirmed by the present work (see Section III) that bigeminy and multifocal ventricular tachycardia can be converted to normal sinus rhythm by stimulation of the vagus nerves. This was interpreted by Dresel and Sutter to mean that these arrhythmias originate in an area of the heart directly under vagal influence, i.e. the A-V node or upper bundle of His. Vick (15) also confirmed the observation but disagreed with Dresel and Sutter's interpretation. He suggested that the influence of the vagus on the arrhythmia was indirect, mediated by the decrease in atrial rate which accompanied conversion.

Dresel and Sutter had already shown that it was more difficult but not impossible to convert the arrhythmia with stimulation of the vagus when the atrial rate was held constant by electrical pacing. Additional experiments were required, however, to delineate further the role of heart rate in the induction, maintenance and conversion of the arrhythmia.

A. EFFECT OF STIMULATION OF THE VAGUS ON BIGEMINAL RHYTHMS AFTER TREATMENT OF THE SINUS NODE WITH ATROPINE

The canine sinus node is supplied with blood by a branch of the right coronary artery. The sinus node branch is clearly visible in a large percentage of animals and can be cannulated. Substances injected directly into this artery affect the function of the sinus node without affecting other parts of the heart. This provided a method for selective treatment of the sinus node with atropine in an attempt to keep atrial rate constant during stimulation of the vagus nerve.

The sinus node artery was cannulated in 5 dogs. A transient

bradycardia was seen in one of the animals after ligation of the artery. The basic sinus rhythm was unaffected in all other dogs. This is in accord with previous work of James (103,104) who showed that ligation of the sinus node artery has no significant effects on sinus rhythm largely because of the extensive arterial anastomoses there.

The following protocol was used: Bigeminy was produced by a constant infusion of adrenaline and the effect on the arrhythmia of stimulation of the vagus nerves was determined. Atropine (10-20 μg) was injected into the sinus node artery either during the adrenaline infusion or just prior to a second infusion. This dose of atropine was used because it was shown previously by James and Nadeau (105) to block the response of the sinus node to stimulation of the vagus for one hour. The effect on the arrhythmia of stimulation of the vagus nerves was redetermined. Injection of atropine into the sinus node artery during an adrenaline infusion did not affect an existing arrhythmia.

Stimulation of the vagus was always successful in converting bigeminal rhythm to normal sinus rhythm when the atrial rate was allowed to decrease. However, the rate had to be decreased considerably in some experiments before conversion occurred. Stimulation of the vagus after atropine was injected into the sinus node artery had one of the following effects: 1) conversion of bigeminal rhythm directly to normal sinus rhythm accompanied by an increase in the P-R interval of the normal beat; the blood pressure on these occasions bordered the threshold value for induction of arrhythmia; 2) prolongation of the P-R interval of the normal beat with no conversion; the blood pressure on these occasions was well above the threshold pressure; 3) production of a 2:1 to 4:1 A-V block with continued coupling; coupling stopped only after A-V block

became more complete (e.g. 6:1); 4) production of A-V block with continued coupling as above but eventual conversion at the same degree of A-V block.

An example of the first type of response is illustrated in Fig. 8. Sustained bigeminal rhythm was produced by the constant infusion of 1 μg/kg/min adrenaline. Atropine (10 μg) had been injected into the sinus node artery prior to the adrenaline infusion. Stimulation of the vagus nerve (10/sec) caused conversion of the bigeminal rhythm to normal sinus rhythm. There was a slight decrease in the atrial rate indicating that the blockade of the sinus node by atropine was not complete. However, the decrease is so small that the preparation can still be considered as a constant rate preparation. There was a change in the configuration of the bigeminal beat just prior to conversion of the arrhythmia and after its return following conversion. The altered bigeminal beat continued for 30 seconds before reversion to the type of bigeminal beat present prior to stimulation of the vagus. Conversion of the bigeminal rhythm was accompanied by a prolongation of the P-R interval of the normal beat. Although the drop in blood pressure during stimulation of the vagus is small, the pressure is bordering the threshold value at which conversion occurred without any experimental intervention. Therefore, a pressure effect cannot be completely ruled out. In this experiment conversion to normal sinus rhythm occurred on 3 additional occasions. Conversion was always accompanied by an increase in the P-R interval of the normal beat and the blood pressure was bordering the threshold value and could not be ruled out as a contributing factor to conversion.

In 9 out of 15 attempts in one other animal, stimulation of

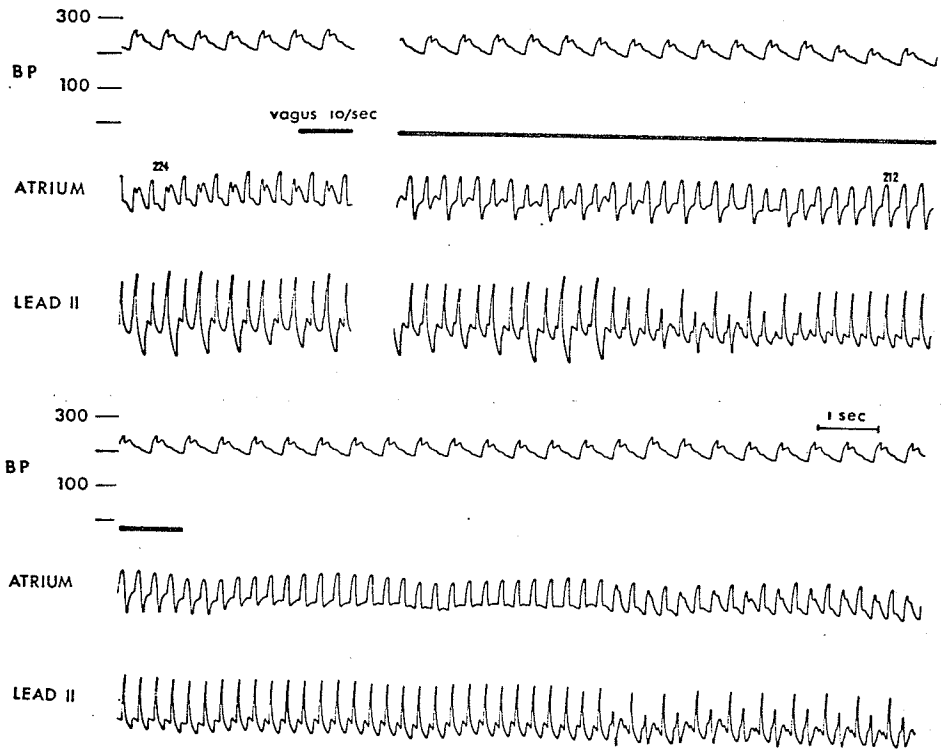


Fig. 8. Effect of stimulation of the vagus on bigeminal rhythm after injection of atropine (10 μg) into the sinus node artery. Stimulation of the vagus at a frequency of 10/sec converted the arrhythmia to normal sinus rhythm accompanied by an increase in the P-R interval of the normal beat at the time of conversion. The atrial rate is decreased from 224 beats/min prior to stimulation to 212 beats/min at the time of conversion. The blood pressure at the time of conversion is bordering the threshold value for induction of arrhythmia. Sixteen seconds of the record (during which stimulation had no effect) have been removed.

either the right or left vagus at various frequencies also caused conversion of the arrhythmia to normal sinus rhythm after the sinus node had been treated with atropine. On all 9 occasions conversion was accompanied by a prolonged P-R interval of the normal beat and the blood pressure was bordering the threshold value for induction of arrhythmia. In the 6 unsuccessful attempts there was also a prolonged P-R interval but the blood pressure was very much above the threshold value.

An example of the third type of response is illustrated in Fig. 9. Bigeminal rhythm was produced in this animal by the infusion of 0.5 μg/kg/min adrenaline. Atropine (20 μg) was injected into the sinus node artery during the adrenaline infusion. Stimulation of the vagus nerve (9/sec) produced a 3:1 A-V block but coupling still continued with a lengthened coupling interval. Conversion was accompanied by a greater degree of A-V block (5:1). The 5:1 A-V block was changed to a 2:1 A-V block after the coupled beat had disappeared. Termination of nerve stimulation was followed by a few nodal beats, nodal bigeminy and then resumption of sinus bigeminy. Stimulation of the vagus caused a small decrease in the atrial rate from 167 beats/min to 158 beats/min. There is also a drop in blood pressure of 45 mm Hg at the time of conversion. Stimulation of the vagus was successful in producing conversion of the arrhythmia in 3 other attempts in this experiment and unsuccessful in 2 attempts. On all successful occasions stimulation produced A-V block with continued coupling, followed by a greater degree of A-V block prior to conversion. On the 2 unsuccessful occasions A-V block was present with continued coupling. Conversion, in this experiment, seemed to be related largely to the greater degree of A-V block present

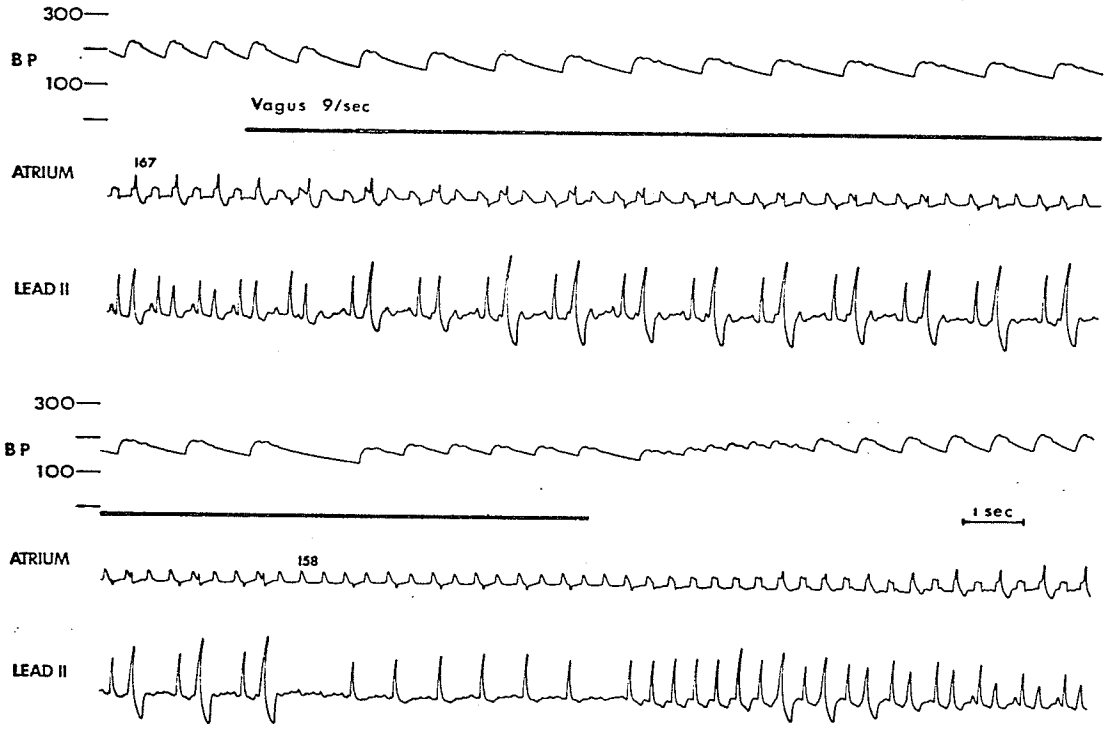


Fig. 9. Conversion of bigeminal rhythm to A-V block by stimulation of the vagus after injection of atropine (20 μg) into the sinus node artery. Stimulation of the vagus at a frequency of 9/sec produced first a 3:1 A-V block with continued coupling, then a 5:1 A-V block followed by termination of coupling and immediate change to a 2:1 block. The atrial rate decreased from 167 beats/min prior to stimulation to 158 beats/min at the time of conversion. The blood pressure decreased 45 mm Hg during stimulation.

prior to conversion. In this experiment, stimulation of the vagus before injection of atropine into the sinus node artery caused conversion of bigeminal rhythm only after a considerable decrease in the atrial rate.

In one other animal A-V block always accompanied conversion of the arrhythmia. In this animal, conversion occurred on 4 of 7 attempts. In 2 of the unsuccessful attempts, the degree of A-V block was less than that present during the successful attempts. However, in the one other unsuccessful attempt stimulation of the vagus produced the same degree of A-V block as when conversion had occurred. The only factor which differed was the frequency of vagal stimulation, which was less during the unsuccessful attempt. The blood pressure at conversion in the 4 successful attempts was about 10 mm Hg above the threshold value. Unlike the example described above where a greater degree of A-V block occurred prior to conversion, in this animal, the same degree of A-V block persisted throughout stimulation of the vagus until coupling eventually stopped.

Conversion to normal sinus rhythm occurred without an accompanying increase in the P-R interval in one animal. However, conversion occurred only after the blood pressure had been decreased to the threshold value and could always be attributed to this factor.

B. EFFECT OF STIMULATION OF THE VAGUS ON BIGEMINAL RHYTHMS AT CONSTANT HEART RATES PRODUCED BY ATRIAL PACING

Bigeminy could be converted to supraventricular rhythm in each of 5 experiments. A typical result is illustrated in Fig. 10. The upper left panel shows a control bigeminal rhythm obtained by the

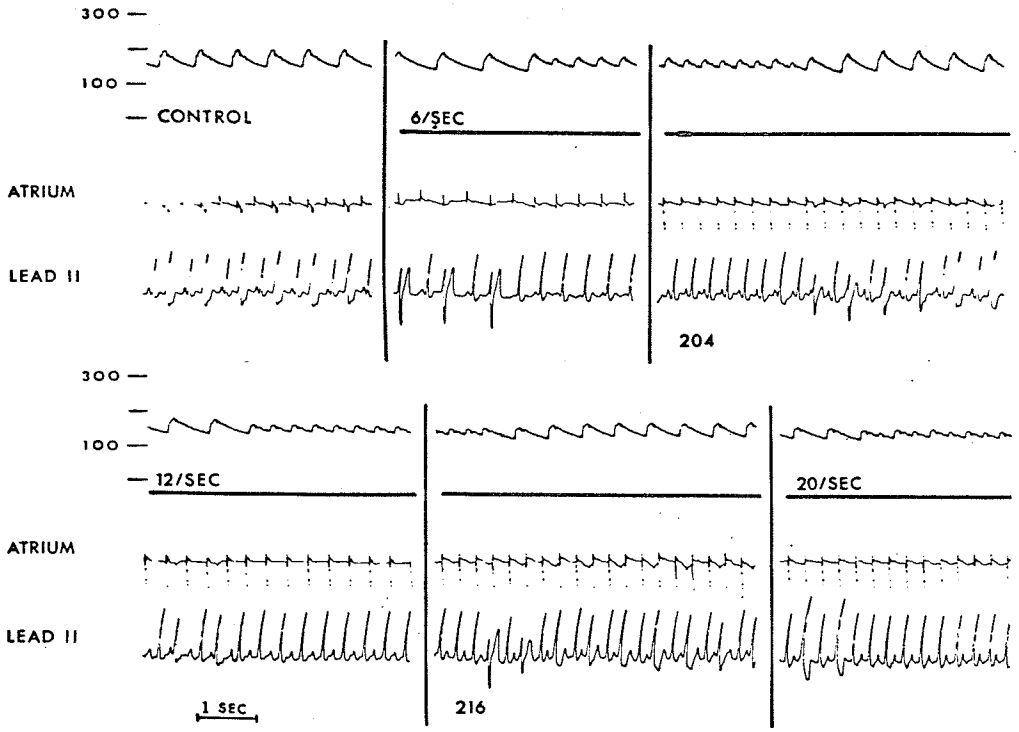


Fig. 10. Conversion of bigeminal rhythm to supraventricular rhythm by stimulation of the vagus during maintained atrial drive. First panel: control bigeminal rhythm produced by infusion of 2 μg/kg/min adrenaline. Atrial rate is 200/min. Second panel: stimulation of the right vagus nerve at a frequency of 6/sec converted the bigeminal rhythm to supraventricular rhythm. Atrial rate is 160/min. Third panel: reinduction of bigeminy with atrial drive at a rate of 204/min. Fourth panel: stimulation of the vagus at a frequency of 12/sec reconverts bigeminal to supraventricular rhythm after a decrease in the blood pressure to the threshold value and an increase in the P-R interval. Fifth panel: bigeminy was reestablished by increasing the rate of atrial drive to 216/min. Sixth panel: an increase in the frequency of stimulation to 20/sec reconverted the arrhythmia after a further decrease in pressure.

intravenous infusion of 2 μg/kg/min adrenaline. The atrial rate is 200/min. During stimulation of the right vagus nerve at a frequency of 6/sec the atrial rate slowed and normal sinus rhythm began at a rate of 160/min. Restoring the faster heart rate during continued stimulation by driving the atrium at a rate approximately equal to the rate at which bigeminy had occurred previously (204/min) resulted in bigeminal rhythm. This confirms the results obtained by Vick (15). An increase in the frequency of nerve stimulation to 12/sec during atrial drive reconverted the bigeminal rhythm to a supraventricular rhythm. However, conversion was accompanied by a marked increase in the P-R interval and occurred only when the blood pressure was decreased to the threshold value for induction of the arrhythmia. At this pressure level arrhythmia could still be reinduced by increasing the rate of atrial stimulation to 216/min. A further increase in the frequency of vagal stimulation again caused conversion to normal sinus rhythm after a further decrease in pressure. However, the normal sinus rhythm was not maintained although stimulation was continued.

Bigeminal rhythms were converted to supraventricular rhythms during maintained atrial drive in each of the 5 experiments for a total of 18 times in 21 attempts. However, on all occasions in which conversion occurred the blood pressure was either bordering the threshold value or atrioventricular block preceded the conversion to normal sinus rhythm. A higher frequency of vagal stimulation was required to convert the arrhythmia when the atrial rate was maintained than when it was allowed to decrease. Frequencies greater than 10/sec were necessary and usually approached 20/sec during successful conversions.

Atrial driving was not always successful in reestablishing

bigeminal rhythms, especially if greater than minimal frequencies of vagal stimulation were used. In some of these cases an increase in the atrial driving rate resulted in a change from sinus rhythm to partial A-V block or to a more disorganized rhythm. However, bigeminy could be reinduced by a decrease in the frequency of vagal stimulation.

C. CONVERSION OF MULTIFOCAL VENTRICULAR TACHYCARDIA BY STIMULATION OF THE VAGUS NERVES AT CONSTANT HEART RATES

Multifocal arrhythmias obtained in the intact heart could not always be converted to normal sinus rhythm by stimulation of the vagus nerves. Occasionally a multifocal rhythm was obtained which persisted during stimulation of the vagus (with or without a decrease in ventricular frequency) despite a considerable decrease in the atrial rate (to approximately one-half or less of the ventricular rate). Thus, only those multifocal rhythms which could be converted readily to normal sinus rhythm by stimulation of the vagus nerves were studied at constant heart rates.

Conversion of multifocal rhythms at constant heart rates by stimulation of the vagus nerves was obtained in 7 of 8 attempts in 3 dogs. On only one of these occasions was the arrhythmia converted directly to normal sinus rhythm. The blood pressure was bordering the threshold value on this one occasion and the arrhythmia reverted spontaneously to normal sinus rhythm shortly thereafter. Therefore a pressure effect alone could not be ruled out. In all other attempts atrioventricular block preceded conversion of the arrhythmia.

D. INFLUENCE OF CHANGES IN THE ATRIAL RATE ON BIGEMINAL RHYTHM IN THE PRESENCE OF VAGAL STIMULATION

The following protocol was used: A dose of adrenaline was infused which produced sustained bigeminal rhythm. The bigeminal rhythm was converted to normal sinus rhythm by stimulation of the vagus nerves. During vagal stimulation bigeminy was reinduced by atrial drive. The atrial rate was decreased by small successive decreases in the driving rate (5-10 beats/min/decrement) until normal sinus rhythm was again restored.

Fig. 11 shows a typical example of changes in the atrial driving rate after conversion with vagal stimulation. The upper left panel indicates a control bigeminal rhythm the atrial rate of which is 180/min. Stimulation of the right vagus nerve slowed the atrial rate to 145/min and converted the arrhythmia. During stimulation of the vagus, increasing atrial rate to 150, 156, 162 and 168 beats/min failed to reestablish the arrhythmia but bigeminy returned within seconds when the driving rate was increased to 174/min. When the driving rate was then decreased to 168, 162, 156 and 150/min bigeminal rhythm was still maintained although these same driving rates had not been effective in reinducing arrhythmia. When the driving rate was slowed to 144/min (the rate at which the vagus had previously converted the arrhythmia) bigeminy reverted to normal sinus rhythm.

The above result was confirmed in 4 other dogs. Maintenance of bigeminal rhythms during small successive decrements in the atrial driving rate was a consistent finding in all of the experiments. However, in all cases bigeminy reverted to normal sinus rhythm at the

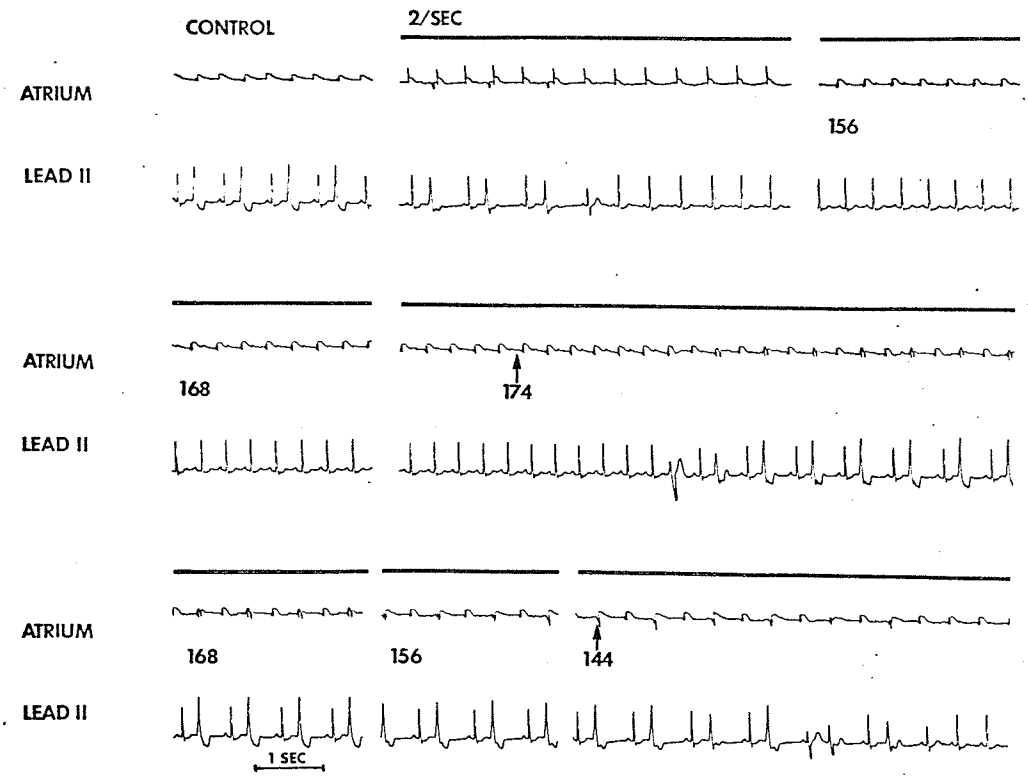


Fig. 11. The influence of changes in atrial rate on bigeminal rhythm during stimulation of the vagus. Upper panel: bigeminal rhythm at a rate of 180/min converted to normal sinus rhythm by stimulation of the right vagus nerve at a frequency of 2/sec. Middle and Bottom panels: during stimulation of the vagus an increase in atrial rate returned bigeminal rhythm when a rate of 174/min was reached. Bigeminal rhythm was maintained despite small successive decreases in the driving rate by 6 beats/min to rates at which the arrhythmia could not be reinduced initially. The arrhythmia reverted to normal sinus rhythm when the rate was decreased to 144/min, the rate at which stimulation of the vagus had caused conversion initially.

same rate at which the vagus had initially converted the arrhythmia.

E. INFLUENCE OF CHANGES IN ATRIAL RATE ON BIGEMINAL RHYTHM DURING THE INFUSION OF A SUBEFFECTIVE DOSE OF ADRENALINE

The following protocol was used: adrenaline was infused at a rate producing stable bigeminy. The rate of infusion was then decreased until sinus rhythm returned. Bigeminy was reinduced by stimulation of the right atrial appendage. After reinduction of bigeminy the driving rate was decreased by small successive decrements in the rate (5-10 beats/min/decrement) until normal sinus rhythm returned.

The influence on bigeminal rhythms of changes in the atrial rate was studied in 5 dogs. A typical result is illustrated in Fig. 12. In this experiment normal sinus rhythm resumed at an atrial rate of 180. Bigeminy reappeared after an increase in the atrial rate to 204/min (upper panel). This is a rate similar to that at which bigeminy had occurred previously during an effective dose of adrenaline. During the subsequent decrease in the atrial driving rate by small successive decrements in the rate (6 beats/min/decrement), bigeminal rhythm was maintained until the driving rate was decreased to 174/min (at which rate two pacemakers are evident). This is a slightly lower rate than that at which bigeminy reverted spontaneously to normal sinus rhythm. When the pressure had fallen below the threshold value for induction of bigeminy, increasing the rate of atrial stimulation to 216/min (bottom panel) could still reinduce arrhythmia. When the pressure had decreased to still lower values no amount of drive could induce arrhythmia. At the lower pressures in which arrhythmia was reinduced

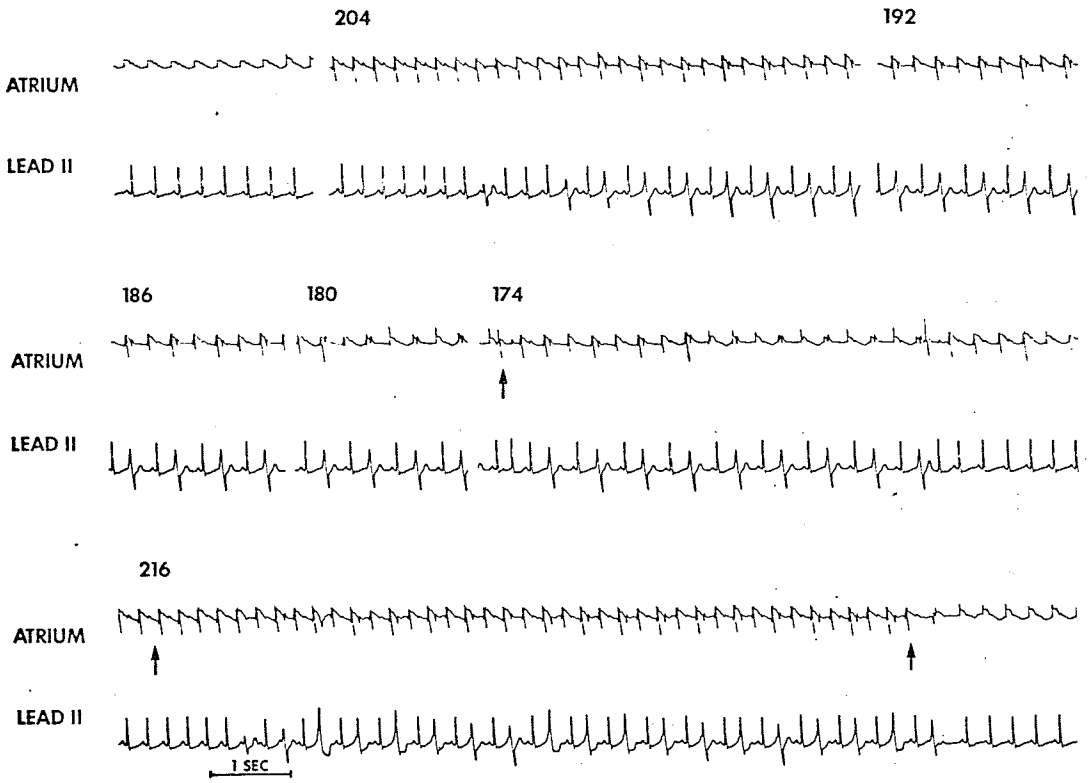


Fig. 12. The influence of changes in atrial rate on bigeminal rhythm during infusion of a subeffective dose of adrenaline. Upper and Middle panels: driving the atria at a rate of 204/min reinduces bigeminal rhythm. Bigeminy is maintained during small successive decreases in the atrial driving rate (6 beats/min) until an atrial rate of 174/min is reached. Bottom panel: bigeminy is reinduced at a driving rate of 216/min when the blood pressure falls below the threshold value for induction of bigeminy. Termination of the drive (indicated by the arrow) returns sinus rhythm immediately.

at the higher rates, the arrhythmia also reverted to normal sinus rhythm at a higher rate.

This result indicates that there exists a range of atrial rates for each particular animal during which bigeminal rhythm may be present or absent. After induction of bigeminal rhythm at some particular driving frequency, the arrhythmia is maintained despite the successive deceleration by small decrements to driving rates at which it had been shown that the arrhythmia could not be reinduced. There also appears to be an interrelationship between rate and pressure in that bigeminy could still be induced at pressures below the threshold value if a greater atrial driving rate was used.

SECTION V

EFFECT ON BIGEMINAL AND MULTIFOCAL RHYTHM OF THE INJECTION OF ACETYLCHOLINE INTO THE POSTERIOR SEPTAL ARTERY

In the dog the posterior septal artery supplies blood to the atrioventricular node, the bundle of His and the posterosuperior portion of the interventricular septum (89,106,107). Therefore, the injection of acetylcholine into this artery has two major advantages, viz.,

1) It provides a means of studying the effect of acetylcholine on the arrhythmia when injected locally into that part of the heart which has been suggested as a possible site of origin of the arrhythmia, and

2) The drug may be delivered in concentrations and volumes so small that systemic effects are not elicited, and other sensitive regions of the heart, especially the sinus node, or significant areas of atrial or ventricular myocardium are not affected.

We studied, therefore, the effect on bigeminal and multifocal arrhythmias of the injection of acetylcholine into this artery.

A. EFFECT ON BIGEMINAL RHYTHMS OF THE INJECTION OF ACETYLCHOLINE INTO THE POSTERIOR SEPTAL ARTERY

The posterior septal artery was ligated and cannulated in seven dogs. Ligation of this artery did not change the basic sinus rhythm in 6 of the 7 dogs and produced a transient nodal rhythm in one dog. This is consistent with the lack of effect of ligation on the basic sinus rhythm observed by Nadeau and Amir-Jahed (101).

Control injections of acetylcholine (0.01 to 2.0 μg) into this artery produced either an increase in the P-R interval or a partial or complete atrioventricular block.

Acetylcholine, in doses of 0.01 to 10 μg, was injected into the posterior septal artery during sustained bigeminal rhythms produced by constant infusion of adrenaline. A total of 88 injections were made.

In 2 of the 7 dogs bigeminal rhythms were converted directly to normal sinus rhythm. A typical result is illustrated in Fig. 13. This figure shows the effect of the injection of 0.65 μg of acetylcholine into the posterior septal artery during bigeminal rhythm produced by the infusion of 0.5 μg/kg/min adrenaline. Conversion to normal sinus rhythm was accompanied by a prolonged P-R interval. The interval between the last bigeminal beat and the first beat of the series of normal beats is longer than the compensatory pause at any time previous to conversion indicating that a single sinus beat has been blocked. The blood pressure remained constant; however, the bigeminal rhythm was present at a blood pressure bordering the threshold level, i.e. the level at which arrhythmia was first induced. In these two dogs conversion to normal sinus rhythm following injections of acetylcholine into the posterior septal artery occurred only when the bigeminal rhythm was present at a blood pressure bordering the threshold level characteristic for that animal. Initially when bigeminy was present at a high pressure, injections of acetylcholine into this artery were either without effect or resulted in one of the following: 1) production of a 2:1 to 3:1 A-V block with continuation of coupling; 2) continuation of coupling with block as in (1) but eventual termination of coupling; or, 3) production of A-V block with immediate termination of coupling. After repeated intracoronary injections of acetylcholine during the adrenaline infusion the blood pressure gradually declined, probably due to the adrenaline becoming less effective. When the blood pressure reached values bordering the threshold level, injections of acetylcholine now converted the arrhythmia to normal sinus rhythm usually accompanied by an initial increase in the P-R interval. Eventually the blood pressure declined to the threshold level and bigeminal rhythm

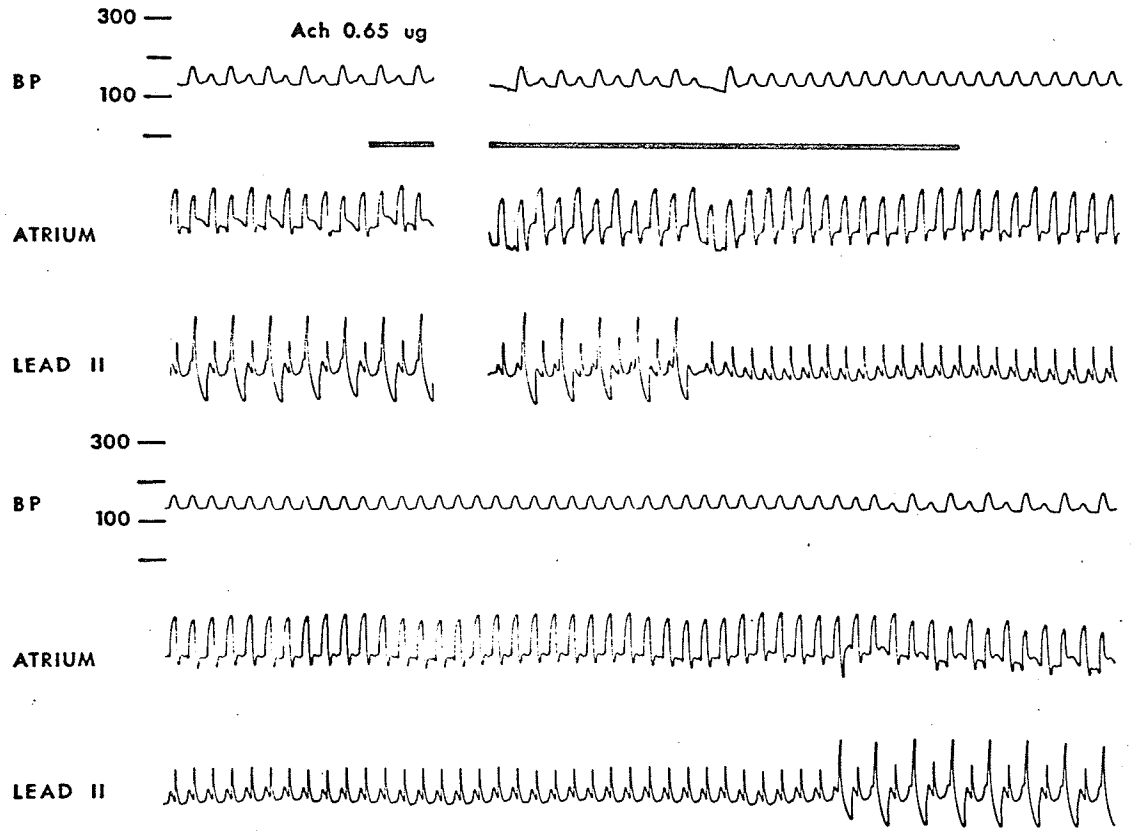


Fig. 13. Effect on bigeminal rhythm of the injection of acetylcholine into the posterior septal artery. Acetylcholine (0.65 µg) converted the bigeminal rhythm to normal sinus rhythm. Conversion was accompanied by a prolonged P-R interval. The blood pressure did not change; however, the blood pressure is bordering the threshold value at which the arrhythmia was initially induced. Thirty-nine seconds of the record during the acetylcholine infusion have been removed.

reverted spontaneously to normal sinus rhythm. The dose of adrenaline was then increased and bigeminy returned but was now present at a higher rate and pressure. Doses of acetylcholine (1 μg or less) which had been effective earlier were now without effect and larger doses (5 to 10 μg) were required to produce conversion. After repeated ineffective doses the blood pressure declined again and when the pressure reached a value approximately 20 mm Hg above threshold, injection of the larger doses of acetylcholine decreased the pressure another 10 to 15 mm Hg and converted the arrhythmia to normal sinus rhythm. It is not clear how these small doses of acetylcholine, injected locally, can cause small decreases in the blood pressure.

In 2 other animals injections of acetylcholine converted the arrhythmia only after first producing A-V block. In one of these animals the arrhythmia consisted of a nodal bigeminy. Injections of acetylcholine changed the nodal bigeminy to a sinus bigeminy (at a lower rate) and then produced a 2:1 to 6:1 A-V block. Coupling still continued and stopped only after a yet greater degree of A-V block had occurred. A-V nodal block preceded conversion on all successful attempts at conversion in these two animals.

In two more animals injections of acetylcholine into the posterior septal artery caused a change in the bigeminal rhythm to a monofocal tachycardia which appeared to originate high up in the conducting system. This latter rhythm sometimes changed either to a normal sinus rhythm, to a nodal rhythm or to a more disorganized rhythm before the reestablishment of bigeminy. Occasionally A-V block preceded the emergence of the tachycardia. A typical example is illustrated in Fig. 14. This figure shows the effect of the injection of 0.1 μg acetylcholine into the

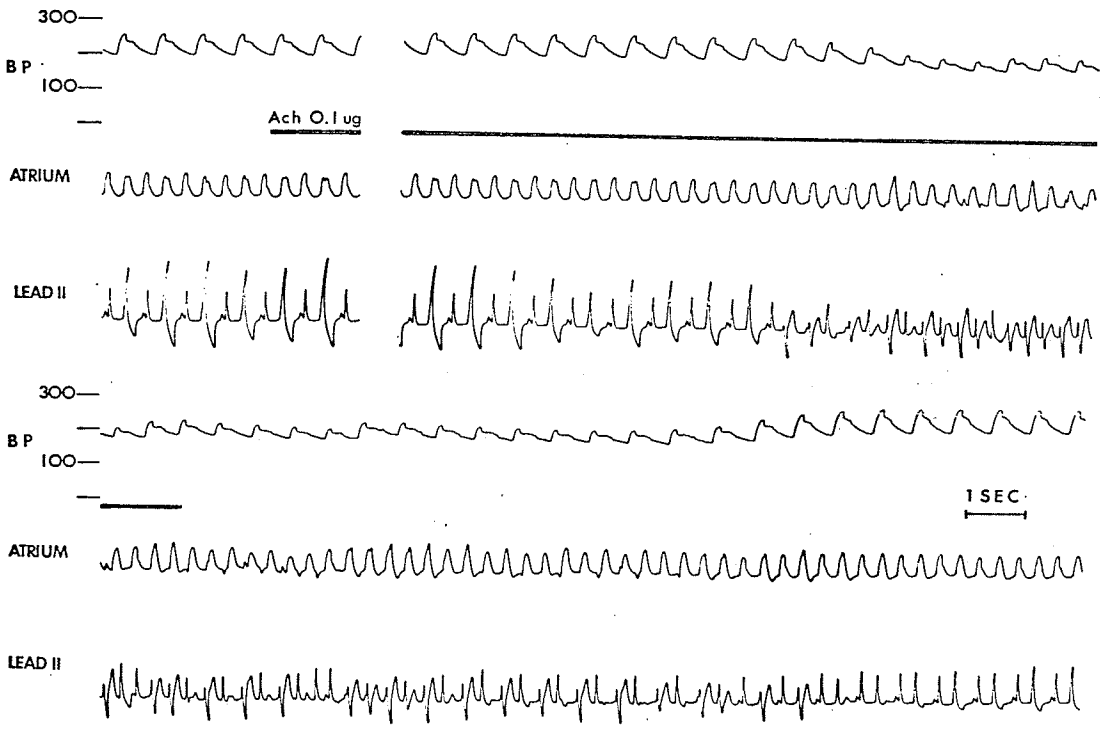


Fig. 14. Effect on bigeminal rhythm of the injection of acetylcholine into the posterior septal artery. 0.1 μg of acetylcholine changed the arrhythmia to a predominantly monofocal rhythm with a QRS complex of negative polarity but very short duration which appears to be originating high up in the conducting system. This was followed by a mixture of sinus beats and abnormal beats. The blood pressure is decreased considerably during this rhythm. Twenty-three seconds of bigeminy during the acetylcholine infusion have been deleted from the record.

posterior septal artery on bigeminal rhythm produced by the infusion of 1 μg/kg/min adrenaline. This dose of acetylcholine changed the bigeminal rhythm to a predominantly monofocal rhythm which then changed to a mixture of sinus beats, bigeminal beats and monofocal beats with coupling of abnormal beats after which sinus bigeminy was reestablished. This type of rhythm was obtained during most attempts at producing conversion in these two animals. The lower effective doses of acetylcholine in each animal usually produced only the monofocal rhythm and immediate resumption of bigeminy. Doses of acetylcholine which were not effective in producing conversion occasionally changed the configuration of the bigeminal beat.

In the only other animal in which injections of acetylcholine were made the bigeminy was converted either to a nodal bigeminy, a nodal tachycardia, a 2:1 A-V block or to a more disorganized rhythm, but never to a normal sinus rhythm.

B. EFFECT ON MULTIFOCAL RHYTHMS OF THE INJECTION OF ACETYLCHOLINE INTO THE POSTERIOR SEPTAL ARTERY

Acetylcholine, in doses of 0.25 to 20 μg, was injected into the posterior septal artery of 3 dogs during multifocal rhythm produced by the infusion of 1 to 4 μg/kg/min adrenaline. In one of the dogs such injections were made during multifocal rhythm produced in the intact heart; in the second, during multifocal rhythm obtained after destruction of the A-V node; and, in the third, both in the intact heart and after destruction of the A-V node.

When the conducting system was intact injection of acetylcholine into the posterior septal artery was successful in converting the arrhythmia

only when A-V block preceded the conversion. A typical result is illustrated in Fig. 15. Acetylcholine (0.3 μg) injected into the posterior septal artery during multifocal rhythm produced by the infusion of 1 μg/kg/min adrenaline in the intact heart produced first an A-V block followed by several normal sinus beats before the return of the arrhythmia. The atrial rate remained constant (with a few seconds of flutter) and the blood pressure increased during the conversion. There appeared to be a change in the nature of the arrhythmia at the start of the injection. On one occasion in this animal the multifocal arrhythmia was converted to a bigeminal rhythm with 2:1 A-V block.

Multifocal rhythms obtained after destruction of the A-V node were unaffected by injections of acetylcholine at doses up to 20 μg in one of the dogs. In the other dog such injections converted the arrhythmia to the previously existing rhythm followed by a period of a very fast monofocal tachycardia before resumption of the arrhythmia. When the dose of acetylcholine was decreased the arrhythmia was changed only to the fast monofocal tachycardia.

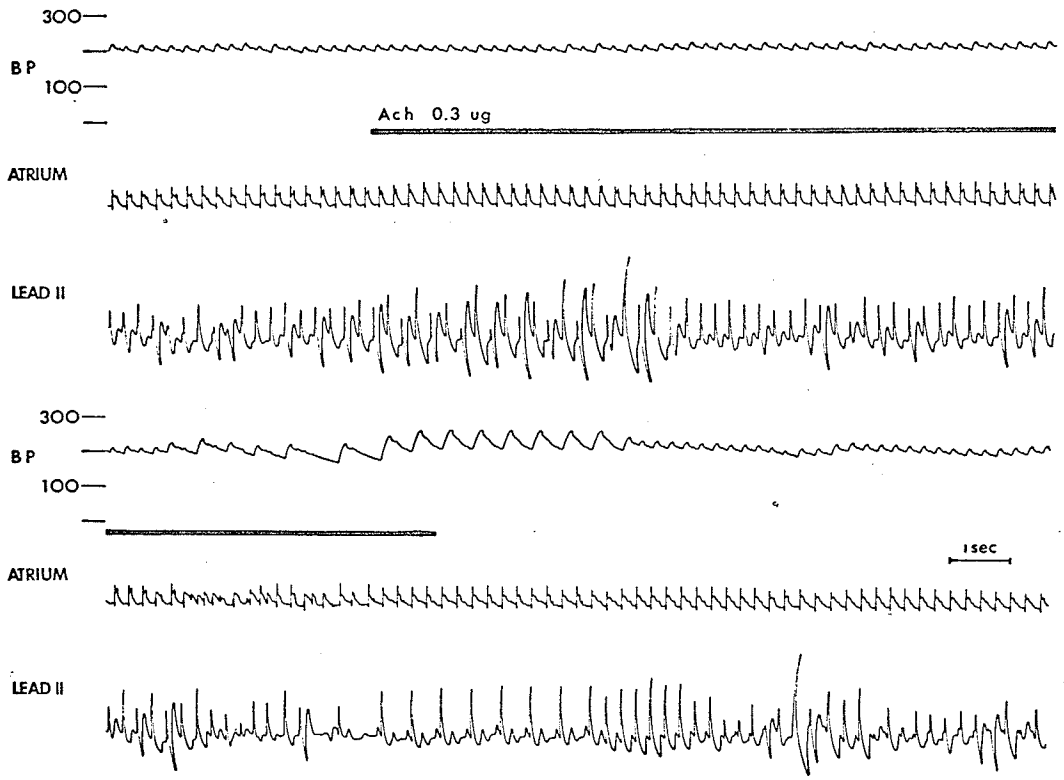


Fig. 15. Effect on multifocal rhythm of the injection of acetylcholine into the posterior septal artery. 0.3 μg acetylcholine converted the arrhythmia to 2:1 A-V block followed by several normal sinus beats before resumption of the arrhythmia. There is no change in the atrial rate and the blood pressure is increased during conversion. The multifocal rhythm was obtained in the intact heart.

SECTION VI

MULTIPLE RECORDINGS FROM THE HEART DURING CYCLOPROPANE-ADRENALINE ARRHYTHMIAS

The evidence implicating the bundle of His as the site of origin of bigeminal and multifocal arrhythmias has been largely indirect. Specifically, the effectiveness of the vagus and of injections of acetylcholine into the left circumflex coronary artery in causing conversion of the arrhythmias has been interpreted by Dresel and Sutter (10) and by MacCannell and Dresel (13) as indicating a site of origin within an area of the heart directly under vagal influence and supplied by the left circumflex artery. Since recent work of Vick (15) and the present experiments indicates that stimulation of the vagus and injections of acetylcholine into the posterior septal artery (which is a branch of the left circumflex coronary artery) may convert the arrhythmias by indirect mechanisms, i.e. actions on either heart rate, atrioventricular conduction or blood pressure, it seemed possible that the arrhythmias might be originating at a site below the bundle of His.

Simultaneous recordings from the right atrium, the bundle of His and the right and left ventricles were made in an attempt to obtain more direct evidence concerning the site of origin of the arrhythmias. The records were analyzed for absolute times and sequences of activation and their relation to the QRS complex.

A. BIGEMINAL RHYTHMS

Recordings from the bundle of His, the right atrium, the epicardial surfaces of the right and/or left ventricles together with a lead II electrocardiogram were made at fast paper speeds on an Electronics for Medicine multichannel oscilloscopic recorder. Records were obtained during coupled bigeminal rhythms produced by the infusion of 0.5 to 4 μg/kg/min adrenaline in 9 dogs. The following comprises a detailed

analysis of the various types of responses recorded.

During the bigeminal beat the His potential was either normal, retrograde or absent and the onset of the R wave of the electrocardiogram either preceded or occurred simultaneously with the His potential. The most consistent finding was early septal activation during the bigeminal beat. The sequence of ventricular activation was either unchanged (right earlier than left) or reversed when compared to the normal beat. Figs. 16 to 19 show examples of typical responses obtained in those experiments in which the His potential was normal.

Fig. 16 shows electrograms recorded from the bundle of His, the anterior surface of the right ventricle (near the region where the free running Purkinje fibres extend from the base of the anterior papillary muscle to the wall of the right ventricle) and the apex of the left ventricle, together with a lead II electrocardiogram. Both ventricular sites have been shown to be sites of early activation. The record was obtained during bigeminal rhythm produced by the infusion of 2 μg/kg/min adrenaline. The bundle of His electrogram is composed of three potentials, viz., an atrial potential (a) due to depolarization of atrial muscle beneath the electrode, the His potential (h) due to depolarization of the bundle of His and the septal potential (s) due to depolarization of the superior portion of the interventricular septum bordering the common bundle. This portion of the septum is one of the last areas of the heart to be activated (108,109). Therefore, during normal conduction the septal potential always occurs during and after the S wave of the electrocardiagram.

The atrial-His (a-h) interval is constant and the His bundle complexes are identical in both the normal and bigeminal beats. However,

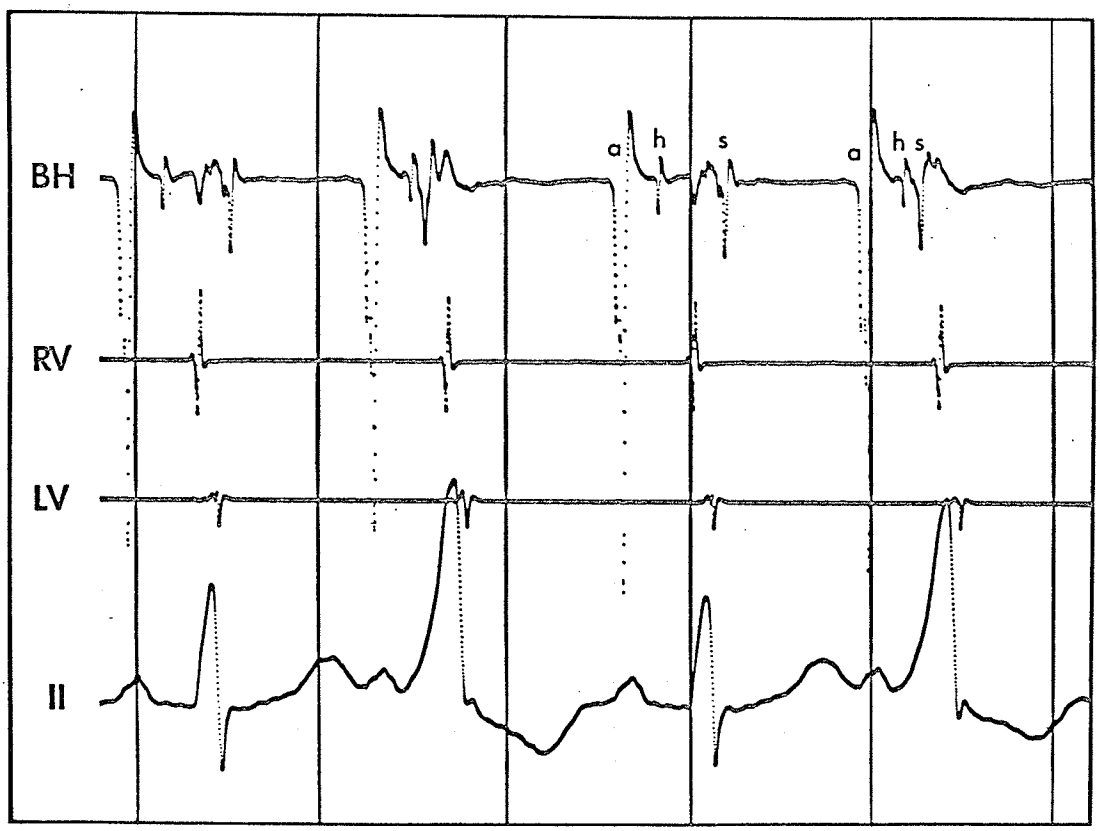


Fig. 16. Bipolar electrograms from the bundle of His (BH), anterior surface of right ventricle (RV), apex of left ventricle (LV), and a lead II electrocardiogram obtained during bigeminal rhythm. In the bundle of His electrogram, a indicates local atrial activity, h indicates electrical activity in the common bundle, and s indicates electrical activity in the interventricular septum. Low- and high-pass filter settings for His electrogram 40/2000; for right and left ventricles 40/500; and for lead II 0.1/100. In this and all subsequent figures, time lines indicate intervals of 200 msec. The measured intervals (in msec) are indicated below:

	Normal Beat		Bigeminal Beat
a-h.....	38.5	.....	38.5
h-RV.....	40.0	.....	40.0
h-LV.....	60.0	.....	60.0
h-s.....	73.0	.....	20.0

during the normal beat depolarization of the His bundle appears midway in the P-R interval of lead II whereas, in the bigeminal beat, the His potential occurs during the onset of the R wave in lead II. Small amplitude potentials precede and follow the His bundle complex in the bigeminal beat suggesting that activity is occurring elsewhere in the heart simultaneously with the activation of the bundle of His. The small potential which precedes the "h" potential coincides with the start of the R wave of the electrocardiogram. The His-right ventricular (h-RV) and the His-left ventricular (h-LV) intervals are 40 and 60 msec, respectively, in both the normal and bigeminal beats. However, right ventricular activation in the normal beat occurs at the onset of the R wave of the QRS complex whereas, in the bigeminal beat right ventricular activation occurs almost at the peak of the QRS complex; similarly, left ventricular activation occurs during the S wave in the normal beat but after completion of the S wave in the bigeminal beat. The most striking difference between the bigeminal beat and the normal beat is the early activation of the septum in the former. The septal potential in the bigeminal beat precedes both right and left ventricular activation by 20 and 40 msec, respectively, and occurs shortly after the onset of the R wave of the electrocardiogram. This is in contrast to the normal beat where septal activation follows all ventricular activation and occurs after completion of the QRS complex.

These results suggest that the bigeminal beat is originating in the upper portions of the interventricular septum. It is unlikely that septal activation could have occurred as early as it did if the abnormal beat were originating in the ventricles as suggested previously by Moore et al. (14). This is also supported by the fact that both right

and left ventricles are activated later with relation to the QRS complex of the bigeminal beat as compared to the normal beat. The fact that both right and left ventricular activation times are normal (at least at those points on the ventricular surface from which records were obtained) suggests a double excitation of the ventricles by both the normal and the abnormal impulses with the early part of the bigeminal beat representing largely abnormal septal activation.

Fig. 17 illustrates a bigeminal rhythm in which the left ventricle is activated abnormally. As in the previous figure, both a-h and h-RV are constant and the His potential is identical in both the normal and abnormal beats. Once again, septal activation occurs early and precedes both right and left ventricular activation. However, unlike the previous figure, the left ventricle is activated earlier than the right during the bigeminal beat, i.e. the sequence of ventricular activation is reversed. The h-LV interval is decreased from 59 msec in the normal beat to 35.5 msec in the first bigeminal beat. The h-s interval of the second bigeminal beat in the record is greater than that in the first bigeminal beat; h-LV changes in the same direction so that LV appears 2.5 msec after RV but is still relatively earlier when compared to the normal beat. The configuration of the left ventricular complex is slightly altered in both bigeminal beats. Despite the fact that the left ventricle is activated relatively earlier than the right in the bigeminal beats, the activation of both ventricles occurs after the completion of the S wave of the QRS complex, later than in the normal beat.

These results again suggest that the origin of the bigeminal beat is in the upper portions of the interventricular septum, more

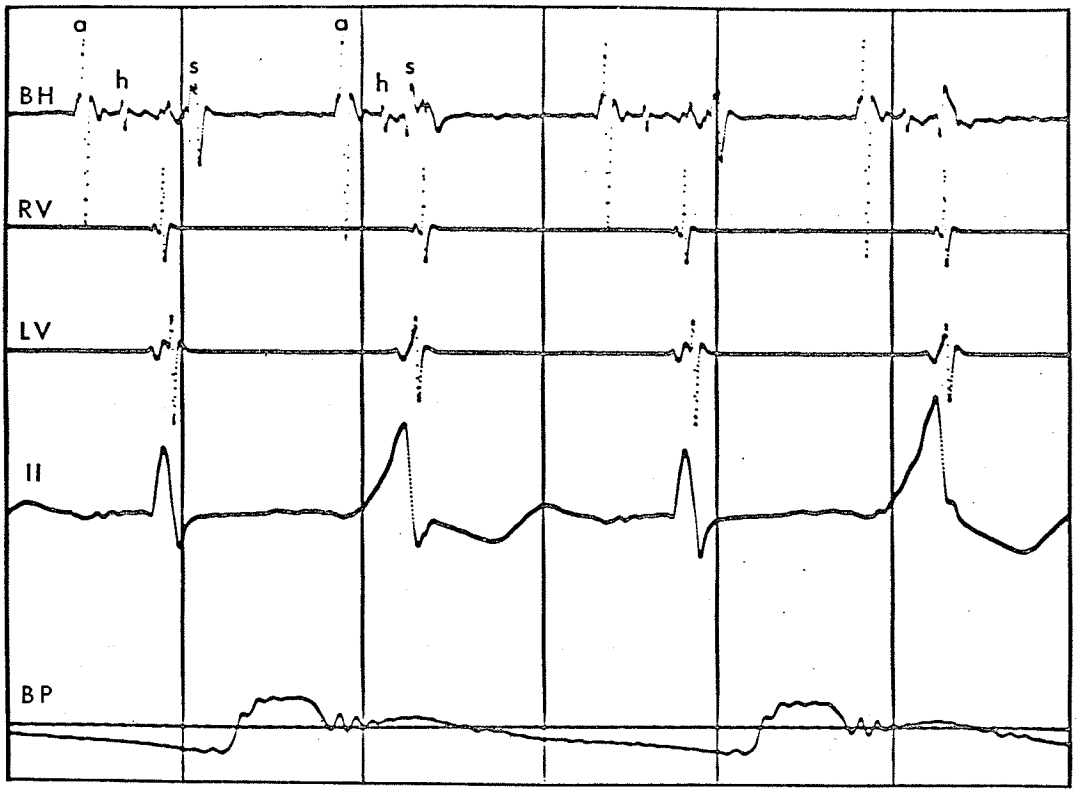


Fig. 17. Symbols as in Fig. 16. Filter settings for BH and lead II as in Fig. 16; for RV and LV 40/200. Record obtained during bigeminal rhythm produced by the infusion of 2 µg/kg/min adrenaline. The intervals (in msec) are indicated below:

	Normal Beat		Bigeminal Beat
a-h.....	45.0	.....	45.0 (45.0)
h-RV.....	44.0	.....	44.0 (44.0)
h-LV.....	59.0	.....	35.5 (46.5)
h-s.....	82.5	.....	27.5 (40.0)

The numbers in parentheses represent the intervals for the second bigeminal beat in the record.

specifically in an area of the left upper septum. It appears that the right ventricle is being activated normally from above via the A-V node and bundle of His (since h-RV is constant) whereas the left ventricle is being activated by both the normal and the abnormal impulses. Similar records were obtained in three additional experiments.

Fig. 18 illustrates a third type of response. As in Fig. 17, a-h is constant and the septum is activated early during the bigeminal beat. However, unlike Fig. 17, both h-LV and h-RV intervals in the bigeminal beat are shorter than in the normal beat. The h-RV interval is decreased from 40 msec in the normal beat to 27.5 msec in the abnormal beat; the h-LV interval is decreased from 60 msec in the normal beat to 39 msec in the abnormal beat. This indicates that neither ventricle could have been activated normally by the atrial impulse. Although the sequence of ventricular activation is the same as in the normal beat (i.e. right still precedes left) the left ventricle is again activated relatively earlier in the bigeminal beat. Right ventricular activation precedes left ventricular activation by 20 msec in the normal beat but by only 11.5 msec in the bigeminal beat. As in the previous two figures, ventricular activation in the bigeminal beat occurs relatively later in the QRS complex when compared to the normal beat, thus indicating that the bigeminal beat could not have originated at a ventricular site. These results again support a site of origin in the upper portions of the left septum. The right ventricle must have been activated by the abnormal impulse originating on the left side of the heart. Such an impulse could reach the right ventricle by two pathways, viz., via the common His bundle or through the interventricular septum. If the pathway followed by the impulse were via the common His bundle one would expect

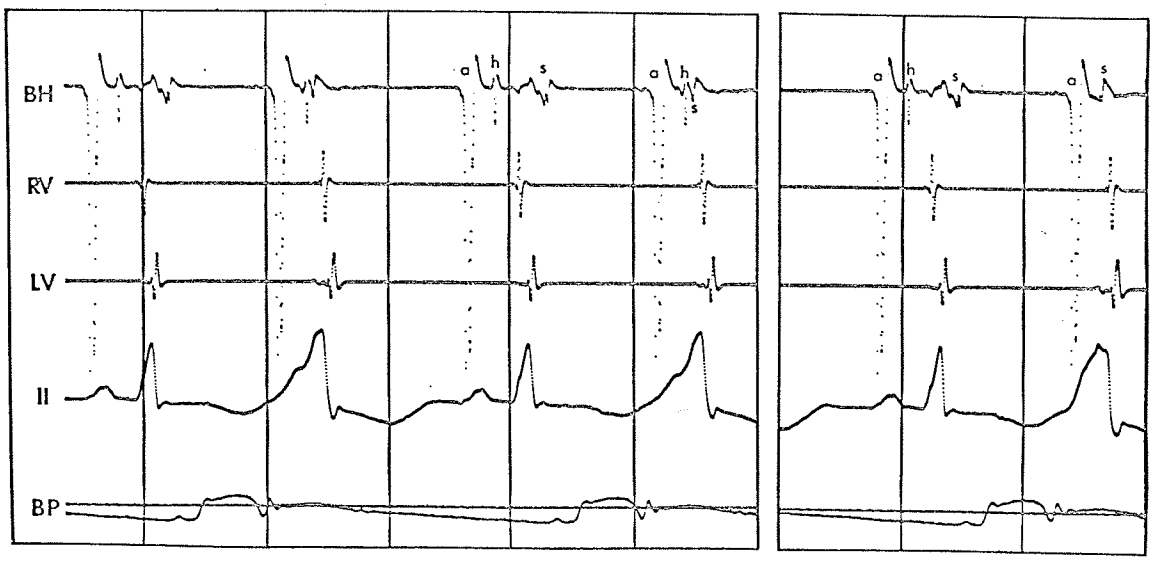


Fig. 18. Symbols and filter settings as in Fig. 17. Bigeminal rhythm produced by the infusion of 1 μg/kg/min adrenaline. The intervals (in msec) in the two bigeminal beats shown in the left panel are indicated below:

	Normal Beat		Bigeminal Beat
a-h.....	49.0	.....	49.0
h-RV.....	40.0	.....	27.5
h-LV.....	60.0	.....	39.0
h-s.....	85.0	.....	14.0

The right panel shows a bigeminal rhythm obtained in the same experiment but at the start of the arrhythmia (in contrast to the bigeminy shown on the left which was obtained later). It differs from the bigeminy in the left panel by having a slightly longer basic cycle length and a slightly shorter coupling interval. The His electrogram shows only an "a" potential and an altered "s" potential. The "h" potential has disappeared.

some effect on the "h" potential. Since the a-h interval is constant and the "h" potential is normal this could only occur if there was simultaneous activation of the His bundle from above and below resulting in a mutual cancellation of electrical forces below the recording electrode. A critical timing for activation from above and below would be necessary. It is also possible that the right ventricle is being activated from the left via the septum. Since right ventricular activation still precedes left ventricular activation the position of the right ventricular recording electrodes would be critical. If one records from various sites on the right ventricular surface during an induced right bundle branch block it can be shown that at several sites on the right ventricle the time of activation does not change when compared to activation times during normal conduction (110). If the recording electrodes were placed at one such site in the present experiment the result obtained can be explained. The right panel of Fig. 18 tends to support activation via the common His bundle rather than through the septum. This panel shows a bigeminal rhythm obtained in the same animal but at the start of the arrhythmia. This bigeminal rhythm differs from the one shown on the left by having a slightly longer basic cycle length and a shorter coupling interval. The His electrogram now shows only an "a" potential and a modified "s" potential. The "h" potential has disappeared perhaps due to simultaneous activation of the His bundle and the septum since the septal potential occurs at the time that the His potential would normally occur.

Fig. 19 shows a bigeminal rhythm with a long coupling interval. The record shows progressive changes in the h-s interval of the bigeminal beat. As the h-s interval becomes shorter the coupling interval

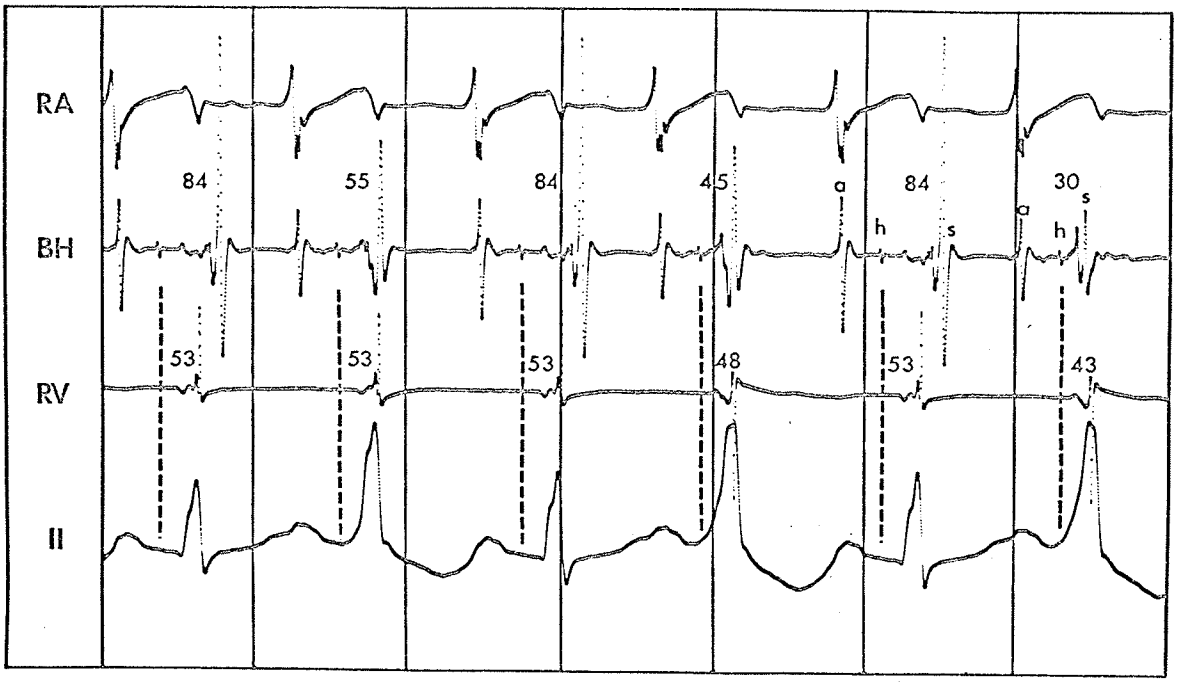


Fig. 19. A bigeminal rhythm characterized by a long coupling interval produced by the infusion of 2 μg/kg/min adrenaline. RA indicates the electrogram recorded from the right atrial appendage; other symbols as in previous figures. Filter settings for RA and RV 4/200; for BH 40/2000; and for lead II 0.1/100. The h-s and h-RV intervals are indicated on the record. The a-h intervals are constant at 50 msec. As the h-s interval of the bigeminal beat decreases the h-RV interval decreases together with a shortening of the coupling (R-R) interval.

(R-R interval) of the bigeminy decreases. The decrease in the coupling interval is due to the fact that the R wave of the QRS complex begins sooner; the S wave remains stationary so that the resultant effect is a wider bigeminal beat. This supports the view that the early part of the bigeminal beat represents largely abnormal septal activation. The right ventricle is either activated normally from above (the h-RV interval of the first bigeminal beat is the same as in the normal beats) or abnormally depending upon how early the septum is activated, and consequently, which impulse reaches the recording electrodes first. In this experiment the left ventricle (not shown on record) was activated relatively earlier, as in the previous two figures.

Fig. 20 shows a bigeminal rhythm in which the "normal" beat originates in the A-V node or the upper bundle of His. In the A-V nodal beat the right ventricular complex precedes the left ventricular complex by 18 msec and the latter, in turn, precedes septal activation by 8 msec. In the bigeminal beat the His potential disappears and the "s" potential precedes ventricular activation by 17 msec. (Records were also obtained in the same experiment in which the "h" potential was clearly retrograde and preceded the "s" potential). Whereas in the normal beat right ventricular activation precedes left ventricular activation, they occur simultaneously in the abnormal beat; hence the left ventricle is activated relatively earlier. Right ventricular activation occurs later in the QRS complex of the bigeminal beat than of the normal beat. These results again support a site of origin in the left septal region of the heart.

Fig. 21 illustrates a bigeminal rhythm in which septal activation occurs later in relation to the QRS complex of the bigeminal beat when compared to the bigeminal rhythms described above. Again,

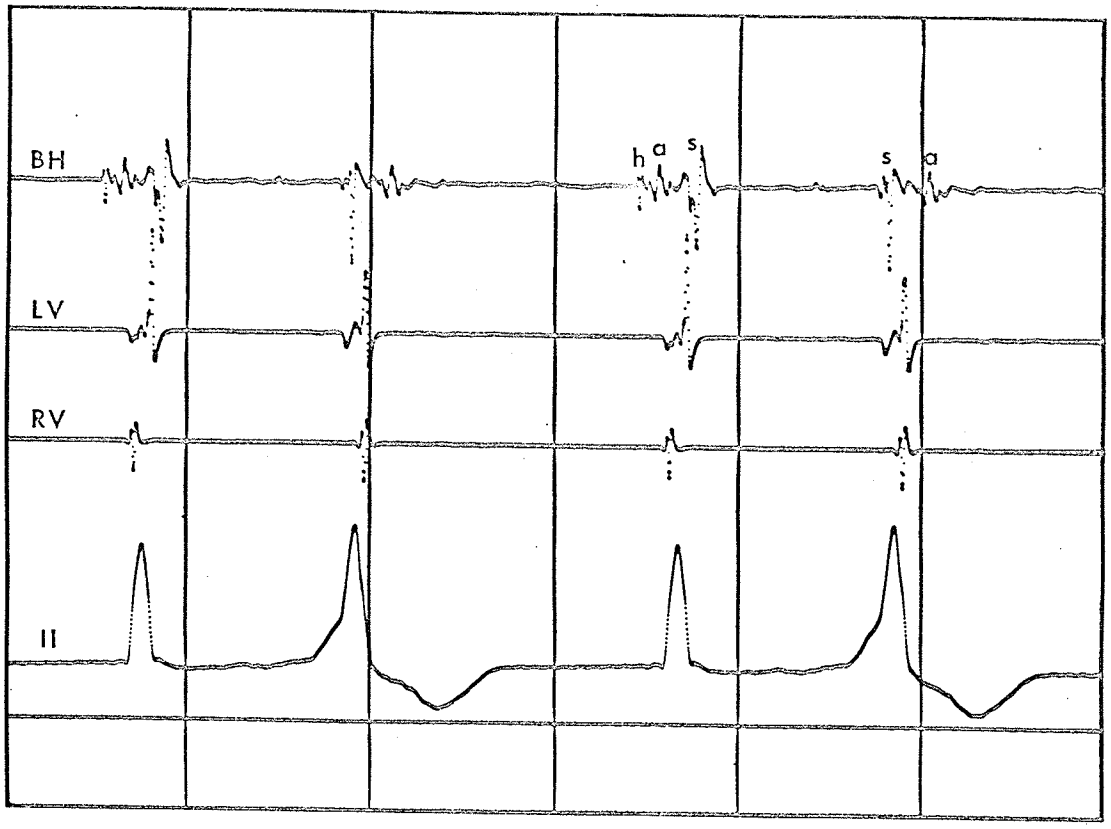


Fig. 20. A nodal bigeminy produced by the infusion of 4 μg/kg/min adrenaline. Symbols as in Fig. 16. Filter settings for BH 40/2000, LV 40/200, RV 4/200 and lead II 0.1/100. In the normal beat the "h" potential precedes RV by 35 msec, LV by 53 msec and septal activation by 61 msec. In the bigeminal beat the "h" potential has disappeared and septal activation now precedes LV by 17 msec. LV is simultaneous with RV.

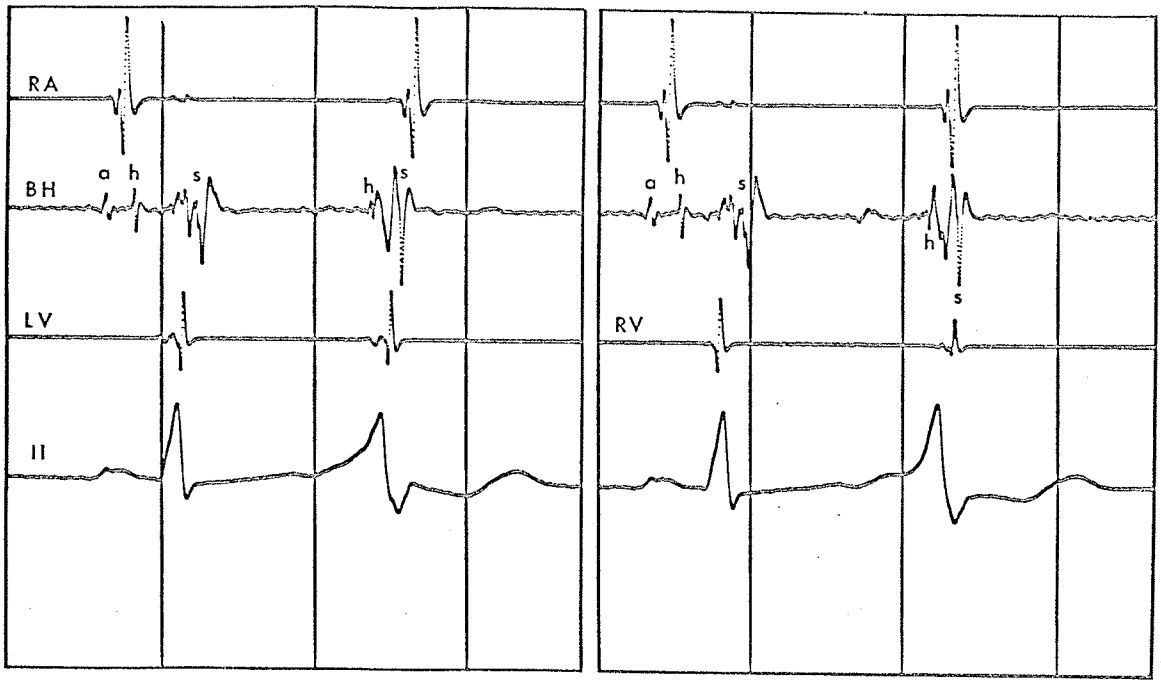


Fig. 21. Bigeminal rhythm produced by 1 μg/kg/min adrenaline showing late septal activation. Symbols as in previous figures. Filter settings for RA, LV and RV 40/200; for BH 40/500; and for lead II 0.1/100. In the left panel the third channel recording was obtained from the left ventricular surface; in the right panel, from the right ventricular surface. In the normal beat right ventricular activation precedes left ventricular activation by 11.5 msec; in the bigeminal beat the sequence of ventricular activation is reversed, left now preceding right by 13.5 msec. The bundle of His is activated abnormally in the bigeminal beat. Septal activation occurs late in the QRS complex of the bigeminal beat but still earlier than septal activation in the normal beat.

however, the sequence of ventricular activation is reversed, left preceding right in the bigeminal beat. The R wave of the electrocardiogram begins before any activity in the His electrogram. In this record the right atrial electrogram does not coincide with the "a" potential of the His electrogram. This is probably due to a conduction block between the sinus node and the recording electrodes on the right atrial appendage, possibly related to the placement of the clamp on the right atrium. Although septal activation occurs relatively later in this bigeminal rhythm in comparison to the other records, it still occurs relatively earlier when compared to septal activation in the normal beat. Right ventricular activation occurs very late in the QRS complex of the bigeminal beat. It occurs during the upward deflection of the R wave of the normal beat but after completion of the S wave in the bigeminal beat suggesting that the right ventricle was activated from the left via the septum. These results suggest that this bigeminal rhythm may be originating in the lower portions of the left septum.

B. EFFECTS OF STIMULATION OF THE VAGUS

Records were obtained from the right atrium, the bundle of His and the right and/or left ventricles, together with a lead II electrocardiogram during conversion of bigeminal rhythms by stimulation of the vagus nerves and during return of the arrhythmia after stopping nerve stimulation. Such records were obtained in 5 animals. Conversion of the arrhythmia in response to stimulation of the vagus could be attributed only to the accompanying decrease in the atrial rate and lengthening of the coupling interval in 3 of the animals.

A typical example of the results obtained with stimulation of

the vagus in these 3 dogs is illustrated in Fig. 22 a and b. The upper left panel of Fig. 22a shows the control bigeminal rhythm present prior to stimulation of the vagus. During the bigeminal beat the "h" potential was similar to that present in the normal beat and the a-h interval was constant; the septum was activated early. The basic cycle length was 285 msec. At the start of vagal stimulation (upper right panel) the cycle length increased to 305 msec with no change in the coupling interval. The His electrogram contains an "a" and an "s" potential. Whether a retrograde "h" potential is present is questionable. A somewhat similar His electrogram was obtained during bigeminal rhythm present normally in this experiment at a greater cycle length (see Fig. 18). When the cycle length increased still further to 360 msec (lower left panel) the coupling interval increased slightly. Both the "h" and "s" potentials disappeared and only the "a" potential was present in the His electrogram during the bigeminal beat. This might be attributed to the fact that the rate has decreased by a greater amount than the corresponding increase in the coupling interval. Disappearance of both the "h" and "s" potentials might be due to activation of these structures during the inscription of the "a" potential, perhaps resulting in low amplitude potentials which were not recorded (the "a" potential is slightly altered). As nerve stimulation was continued there was only a slight further increase in the cycle length (lower right panel) with a greater increase in the coupling interval. The "s" potential was again present in the His electrogram during the bigeminal beat. When the coupling interval increased another few milliseconds (upper left panel of Fig. 22b) the His electrogram contained an "a" potential, an altered "h" potential and an "s" potential. This type of rhythm continued for several seconds with a slight further

Fig. 22a. Conversion of bigeminal rhythm to normal sinus rhythm by stimulation of the vagus nerve and return of arrhythmia after stopping nerve stimulation. Upper left panel: Control bigeminal rhythm, at basic cycle length of 285 msec. Upper right panel: Bigeminal rhythm immediately after beginning of nerve stimulation. The basic cycle length has increased to 305 msec with no change in the coupling interval. His electrogram contains an "a" and an "s" potential; early portion of "s" potential may be a retrograde "h" potential. Lower left panel: Basic cycle length has increased to 360 msec with a slight increase in the coupling interval. His electrogram contains only an "a" potential. Lower right panel: Minor increase in basic cycle length (363 msec) but a greater increase in coupling interval. His electrogram contains both "a" and "s" potentials.

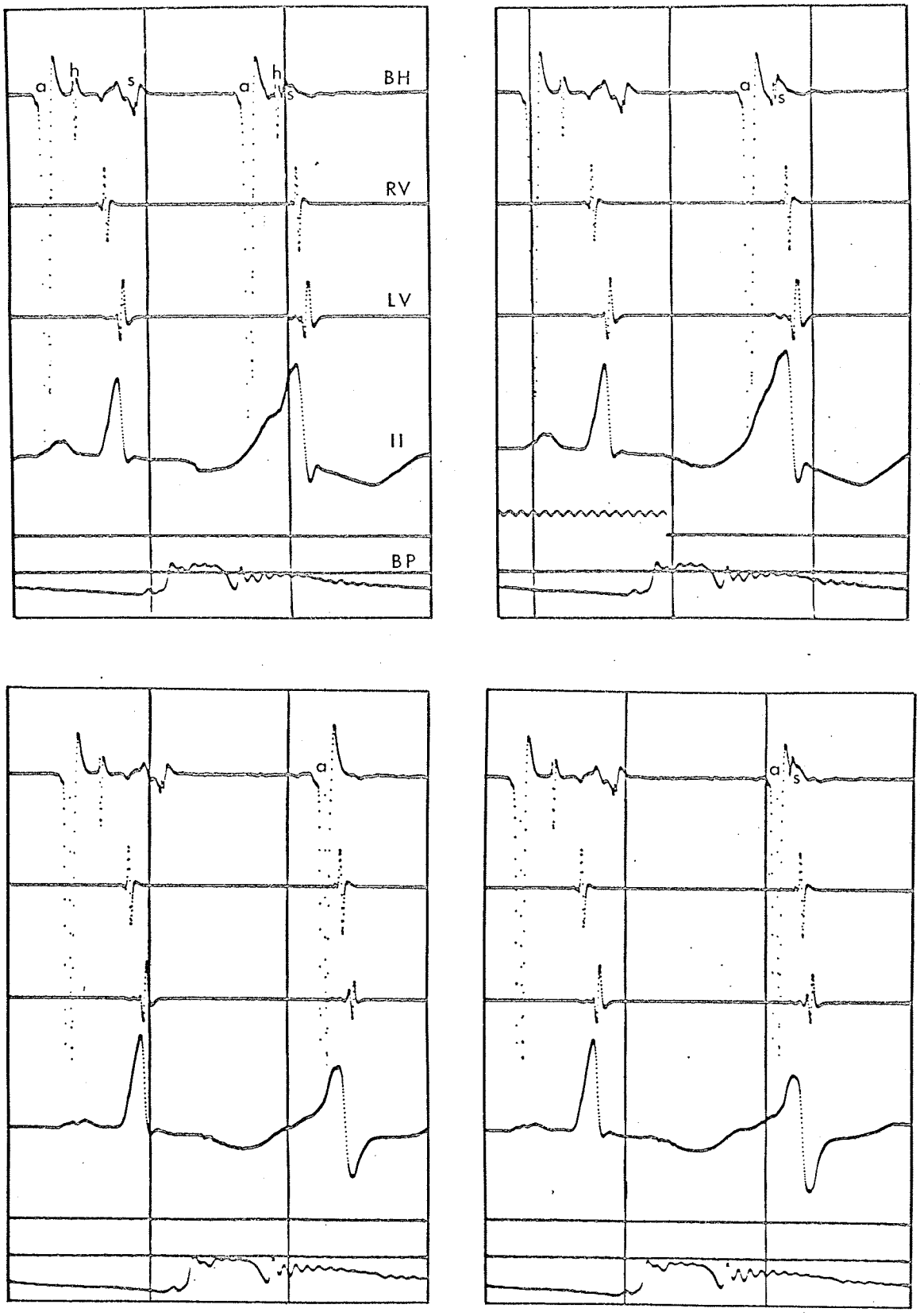
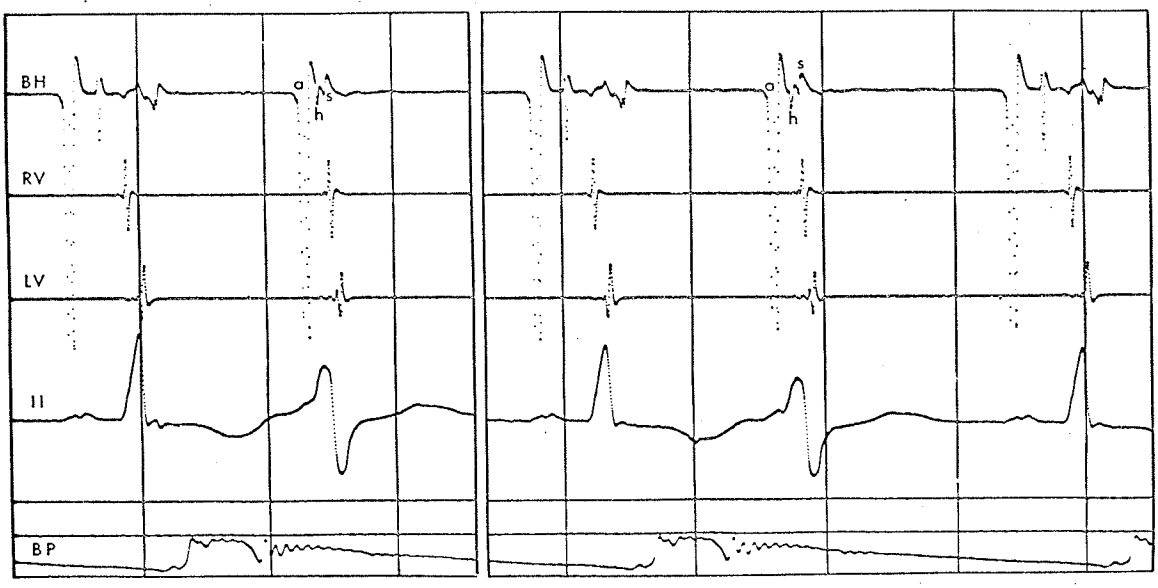
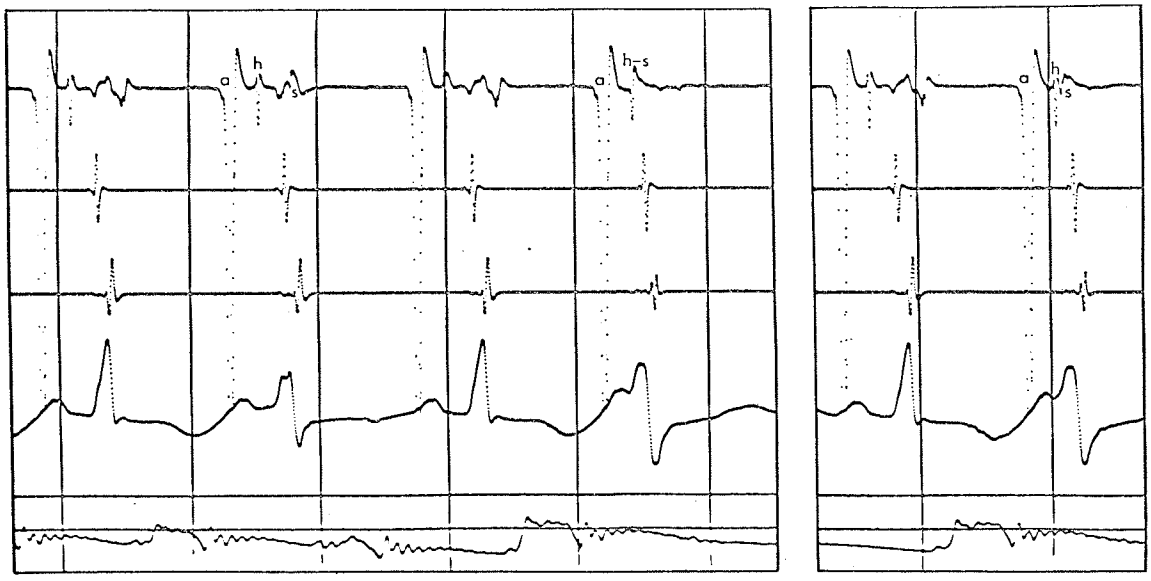

a
h
s
BH
RV
LV
II
BP

Fig. 22b Continuation from lower right panel of Fig. 22a. Upper left panel: Slight further increase in the coupling interval with no further increase in the cycle length. His electrogram contains an "a" potential, an altered "h" potential and an "s" potential. Upper right panel: Last bigeminal beat prior to conversion. His electrogram similar to that in left panel except that the "h" and "s" potentials occur later. Lower left panel: Return of arrhythmia after stopping nerve stimulation. The first and second bigeminal beats at start of arrhythmia are shown. First bigeminal beat differs only by short h-s interval. In the second bigeminal beat the "h" and "s" potentials appear as one complex; ventricles are activated early. Lower right panel: Bigeminal rhythm present several seconds later showing clear separation of "h" and "s" potentials, as in control bigeminy (see upper left panel of Fig. 22a).


BH
RV
LV
II
BP
a
h
s


a
h
s
h-s

increase in the coupling interval (and slightly later "h" and "s" potentials in the His electrogram) until coupling eventually stopped (upper right panel - only the last bigeminal beat is shown). The configuration of the bigeminal beat was altered during stimulation of the vagus, from a positive QRS complex to one with a predominantly negative complex. Conversion appeared to be largely a function of the accompanying decrease in the atrial rate and increase in the coupling interval, with changes in the His electrogram occurring as a result of the relative changes in these two parameters. The a-h interval of the normal beat was increased by only 5 msec during stimulation of the vagus.

The lower left panel of Fig. 22b shows return of arrhythmia after stopping nerve stimulation. The first abnormal beat at the start of arrhythmia showed early septal activation. The ventricular activation times were the same as in the previous normal beat. In the next bigeminal beat septal activation appeared to occur almost simultaneously with His bundle activation, resulting in a potential having characteristics of both the "h" and "s" potentials. The h-RV and h-LV intervals were both decreased as in the control bigeminy. As the rate accelerated there was a clear separation between the "h" and "s" potentials (lower right panel) as in the control bigeminy. The fact that early septal activation was the first abnormality present at the start of arrhythmia would support the interpretation given in the previous section, suggesting a septal site of origin for the arrhythmia. Early septal activation characterized the first abnormal beat at the start of bigeminal rhythm in all 5 dogs.

In the fourth dog stimulation of the vagus produced conversion of bigeminal rhythm without any consistent changes in any of the parameters measured. In the first attempt such stimulation produced no change in the

atrial rate (as determined from the a-a intervals of the His electrograms) but increased the a-h interval by 5 msec. The h-s interval and coupling interval changed throughout stimulation. However, the changes were not consistent, both increases and decreases in these intervals occurring at random throughout stimulation until coupling eventually stopped. Later stimulation of the vagus again produced no changes in rate but doubled the a-h interval (from 45 to 90 msec) without causing any changes in the coupling interval. Conversion occurred only after A-V block of the normal beat.

In the fifth dog stimulation of the vagus decreased the atrial rate and increased the coupling interval of the bigeminal rhythm with little or no change in the a-h interval. There was a progressive lengthening of the h-s interval and of the coupling interval throughout stimulation until conversion occurred.

C. EFFECTS OF CHANGES IN THE ATRIAL RATE ON THE TIME AND SEQUENCE OF HIS BUNDLE, SEPTAL AND VENTRICULAR ACTIVATION DURING THE BIGEMINAL BEAT

In 2 experiments the atria were driven at rates greater than the spontaneous rate at which bigeminy had occurred and the effects of such changes in rate on the time and sequence of His bundle, septal and ventricular activation was determined. Typical records from one of these experiments are illustrated in Fig. 23. The left panel shows a bigeminal rhythm at the spontaneous rate of 196/min. The middle and right panels show bigeminal rhythms obtained when the atria were driven at rates of 206 and 230/min, respectively. The coupling intervals of the bigeminal rhythms at the spontaneous and lower driven rate were identical whereas

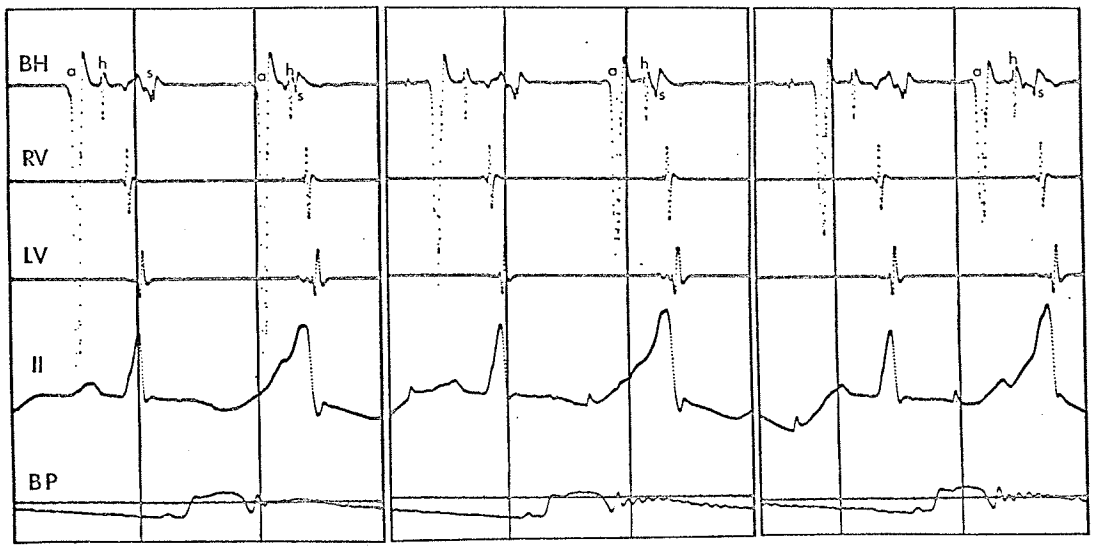


Fig. 23. Effects of changes in the atrial rate on the time and sequence of His bundle, septal and ventricular activation during bigeminal rhythm. The left panel shows a bigeminal rhythm at the spontaneous rate of 196/min. The middle panel shows a bigeminal rhythm in which the atria were driven at a rate of 206/min; the right panel at a rate of 230/min. The various intervals (in msec) for both the normal (N) and the bigeminal (B) beats are indicated below:

	Left Panel		Middle Panel		Right Panel	
	N	B	N	B	N	B
a-h	50.0	51.5	55.0	56.0	60.0	62.5
h-RV	39.5	28.0	41.0	35.5	41.5	42.5
h-LV	59.0	38.0	59.5	45.5	60.0	60.0
h-s	85.0	10.0	86.0	17.5	87.0	34.0
RV/LV	19.5	10.0	18.5	10.0	18.5	17.5

Symbols and filter settings as in Fig. 18.

this interval was shorter by 10 msec at the higher driven rate. The a-h, h-RV, h-LV and h-s intervals in the normal beat were all prolonged with increases in the atrial rate. However, the increases in the last three intervals are small and probably not significant. During the bigeminal beat at the spontaneous rate the septum was activated early and both h-RV and h-LV intervals were decreased. Although the sequence of ventricular activation was the same as that in the normal beat, i.e. right still preceded left, the left ventricle was activated relatively earlier. During the bigeminal beat at the driven rate of 206/min this same sequence of septal and ventricular activation was still present except that the intervals (i.e. h-RV, h-LV and h-s) were all increased by 7.5 msec, thus approaching the values for the normal beat. At the highest driven rate ventricular activation times were the same in both bigeminal and normal beats and the septum in the bigeminal beat was activated still later than at the lower rate (but still characteristically early when compared to the normal beat). Thus, when the atrial rate is increased to 230/min the normal impulse appears to reach the ventricles before the abnormal impulse does, hence reestablishment of the normal sequence and times of ventricular activation.

In the one other experiment in which changes in rate were studied, the spontaneous arrhythmia consisted of a nodal bigeminy with retrograde activation of the His bundle and early septal and left ventricular activation during the bigeminal beat. During periods of atrial drive at rates greater than the spontaneous rate, the nodal bigeminy was changed to a sinus bigeminy and now the a-h interval was constant, the "h" potential was identical in both normal and bigeminal beats, and both right and left ventricles were activated normally. The early septal

activation was maintained. Thus, at the slow A-V nodal rate the abnormal impulse (presumably originating in the left septum) appeared to have reached the bundle of His or lower A-V node before it could discharge spontaneously; at the higher driven rates the impulse from above appeared to activate the common bundle and also both ventricles before the abnormal impulse was able to reach these areas.

These results support the hypothesis that the bigeminal beat is a type of "fusion" beat resulting from activation of the heart simultaneously by stimuli originating above and below the bundle of His. Depending upon the atrial rate and the earliness of septal activation, His bundle and ventricular activation may be normal or abnormal during the bigeminal beat.

D. SUPRAVENTRICULAR AND VENTRICULAR TACHYCARDIA

In a few experiments the blood pressure fell to levels below control after the first infusion of adrenaline and did not recover. In such cases, a second infusion of adrenaline (at a dose less than 4 μg/kg/min) if coupled with aortic occlusion to raise the blood pressure to the arrhythmic threshold, would result in a bigeminal rhythm. However, without aortic occlusion, a dose of adrenaline which is normally considered a fibrillatory dose in the sensitized preparation (10-20 μg/kg) resulted only in a supraventricular tachycardia with aberration of the QRS complex although these high doses of adrenaline were sufficient to raise the blood pressure up to and beyond the arrhythmic threshold.

Fig. 24 illustrates an example of a supraventricular tachycardia produced by the infusion of 20 μg/kg/min adrenaline. In this experiment the threshold dose of adrenaline for induction of bigeminy was 2 μg/kg/min.

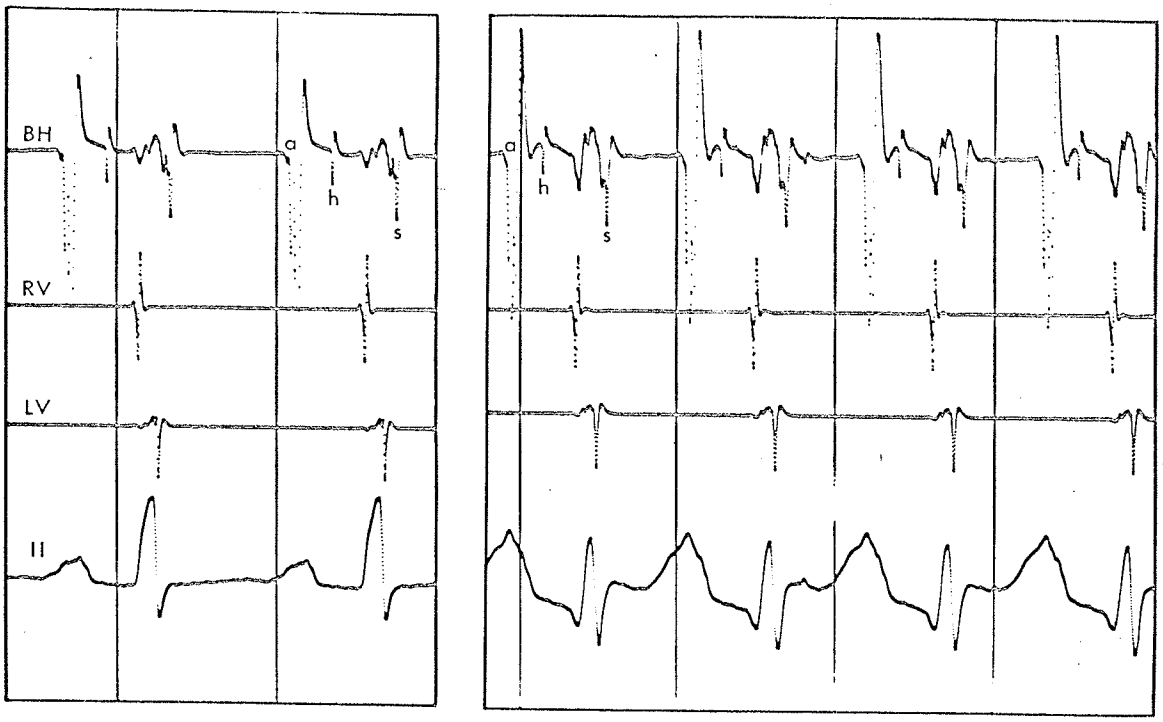


Fig. 24. Supraventricular tachycardia produced by the infusion of 20 µg/kg/min adrenaline. Normal rhythm at left; tachycardia at right. The changes in the intervals (in msec) are indicated below:

	Normal Rhythm		Tachycardia
a-h.....	54	.....	45
h-RV.....	41	.....	43
h-LV.....	65	.....	68.5
h-s.....	80	.....	81.5

The rate has increased from 210/min to 265/min.

The tachycardia occurred during a second infusion of adrenaline. A bigeminal rhythm could be obtained initially during a second infusion of 4 μg/kg/min if the aorta was occluded. The infusion of the higher dose of adrenaline (without aortic occlusion) produced blood pressure levels similar to those obtained with aortic occlusion during the infusion of the lower dose; yet no arrhythmia could be obtained. Occlusion of the aorta during the infusion of the higher dose produced an even greater increase in pressure, but no arrhythmia. Thus, the inability to induce either a bigeminal or multifocal arrhythmic could not be due to an inadequate pressor response. The absence of arrhythmia might be attributed to the presence of a rapid atrial rate. This would reemphasize the importance of rate in the genesis of this arrhythmia. It would appear that the arrhythmia can be induced only at a critical range of rates characteristic for each animal; rates above (or below) this range appear ineffective.

In those experiments in which high doses of adrenaline resulted in a rapid supraventricular tachycardia, stimulation of the vagus and thereby suppression of the tachycardia would always induce a monofocal ventricular tachycardia such as occurs with stimulation of the vagus in the nonsensitized preparation (5). A typical example of monofocal ventricular tachycardia obtained after stimulation of the vagus is illustrated in Fig. 25. This record shows monofocal ventricular tachycardia originating in the right ventricle; the right ventricular complex occurs at the start of the R wave of the electrocardiogram and clearly precedes both septal and left ventricular activation. Activity originating above the bundle of His is independent of activity originating in the right ventricle, hence the altered h-RV and H-s intervals. The

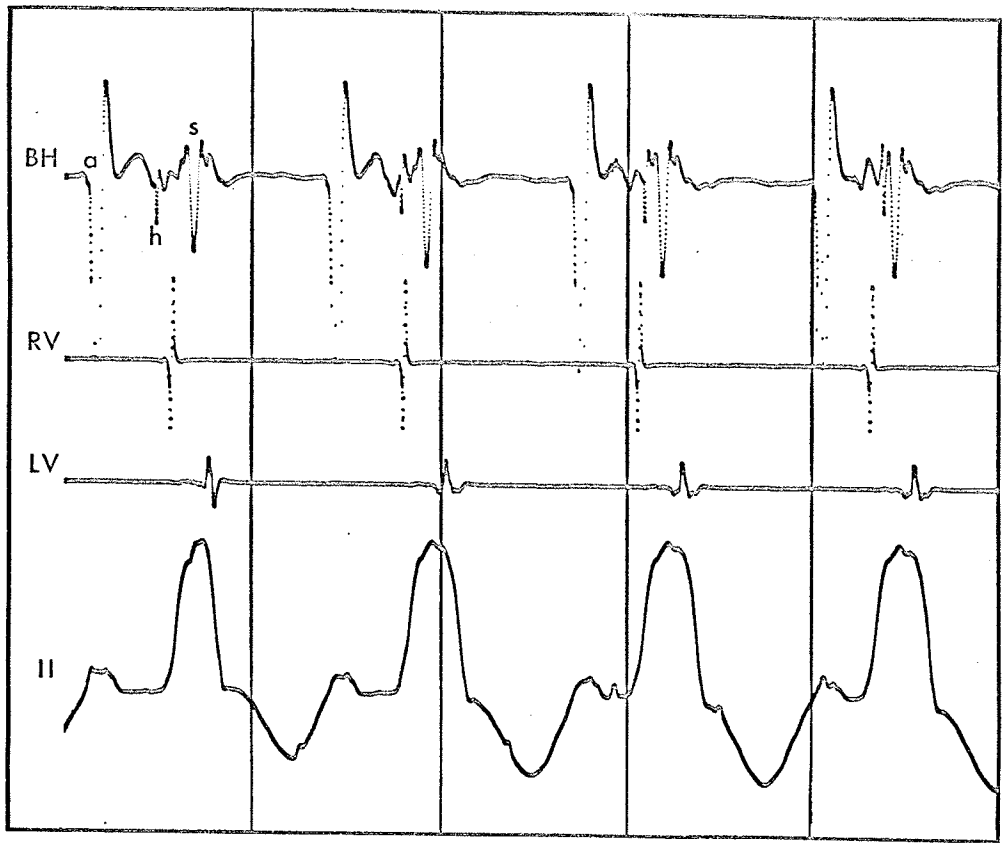


Fig. 25. Monofocal ventricular tachycardia induced by stimulation of the vagus nerve during the supraventricular tachycardia shown in Fig. 24. The arrhythmia is originating in the right ventricle; the right ventricular complex occurs at the start of the R wave of the electrocardiogram and precedes both septal and left ventricular activation. Activity originating above the bundle of His is independent of activity originating in the right ventricle, hence the altered h-RV and h-s intervals. The RV-s intervals are constant indicating that the septum is activated by the impulse originating in the right ventricle.

RV-s interval is constant indicating that the septum was activated by an impulse originating in the right ventricle. The His potential is modified when RV begins to precede it and the a-h interval is slightly decreased in the last complex shown in the record. This record shows a clear distinction between an arrhythmia originating in the ventricles and one originating in the septum (see bigeminal rhythms above). It also indicates that these high doses of adrenaline can increase the automaticity of ventricular pacemakers. The monofocal ventricular tachycardias observed originated in both ventricles, but usually in the left. Monofocal ventricular tachycardias were observed repeatedly by Moore et al. (14) in the cyclopropane-sensitized preparation. They were never observed by us except in a few animals subjected to the experimental intervention of attachment of an electrode over the bundle of His and in some animals in which the bundle of His had been destroyed.

E. EFFECTS OF AORTIC OCCLUSION ON SEPTAL ACTIVATION

The administration of a high dose of adrenaline (10-20 μg/kg/min) produced only a supraventricular tachycardia in animals in which bigeminal rhythms could not be obtained after a second infusion of adrenaline (as described in the previous section). In such cases occlusion of the aorta to raise the blood pressure did not cause arrhythmia but shortened the h-s interval in the His electrogram without changing any of the other parameters measured. This is illustrated in Fig. 26. The left panel shows a supraventricular tachycardia produced by the infusion of 20 μg/kg/min adrenaline. Occlusion of the aorta during the adrenaline infusion decreased the h-s interval in the His electrogram (right panel) without changing any of the other intervals. The configuration of the

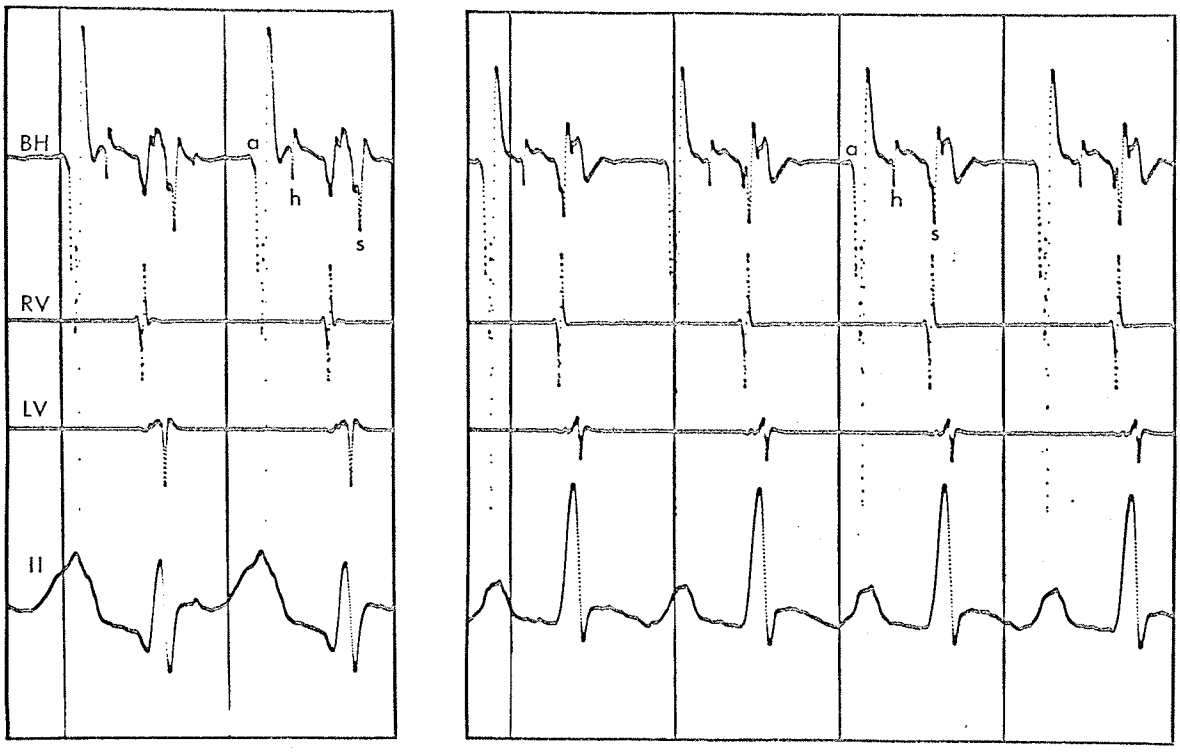


Fig. 26. Effects of aortic occlusion on septal activation. Left panel shows a supraventricular tachycardia produced by the infusion of 20 μg/kg/min adrenaline. Right panel shows rhythm present after aortic occlusion during the tachycardia shown at left. The His electrogram shows a shortened h-s interval. There is no change in any of the other intervals. The configuration of the QRS is altered.

QRS complex was altered. A decrease in the h-s interval (without resulting in arrhythmia) suggests that pressure is in some way related to the early septal reactivation which occurs during bigeminal rhythms since such rhythms are dependent upon the level of the arterial blood pressure.

SECTION VII

DISCUSSION

A. THE ROLE OF THE BUNDLE OF HIS IN THE GENESIS OF CYCLOPROPANE-ADRENALINE ARRHYTHMIAS

The results clearly show that destruction of the bundle of His prevents bigeminal rhythms produced by adrenaline in thiopental-cyclopropane anaesthetized dogs. The absence of arrhythmia could not be attributed to an inadequate pressor response as care was taken to obtain equivalent pressor responses after destruction of the bundle of His.

The rate factor was also eliminated (albeit by indirect means). Previous work of Vick (15) and the present experiments indicate that rate is an important factor in the genesis of bigeminal rhythms. An attempt was made to eliminate rate as a contributing factor in the absence of bigeminal rhythm after destruction of the bundle of His by electrical pacing of either ventricle. It was found that this procedure was occasionally successful in inducing multifocal rhythm, confirming previous work of Vick (15). However, bigeminal rhythms could not be elicited. The interpretation of these experiments is complicated by the effect of ventricular pacing on the blood pressure. Such pacing usually caused a decrease in blood pressure. This is in accord with previous experiments of Lister et al. (86) who showed that pacing of the heart from several ventricular sites causes a significant decrease in cardiac output and a corresponding fall in aortic pressure when compared to right atrial pacing at the same rate. The changes in cardiac performance when the heart is paced from various ventricular sites may be explained by the alterations in ventricular conduction resulting in various degrees of asynchrony during ventricular contraction and changes in the active atrial contribution to ventricular stroke volume due to the altered position of the atrioventricular valves early in ventricular systole.

Since direct stimulation of ventricular muscle results in an abnormal sequence of ventricular activation, the failure of ventricular pacing to induce bigeminal rhythm after destruction of the bundle of His does not eliminate the rate factor. Hence the problem was approached in a different manner. If the rate is indeed the only factor responsible for the absence of bigeminal rhythm, then one should be able to test this possibility by producing an atrioventricular block high up in the conducting system (i.e. by destroying the A-V node) and electrically pacing the bundle of His. Pacing the ventricles from this region of the heart maintains normal sequential ventricular activation.

When the atrioventricular node was destroyed, it was found that coupled rhythms could still be elicited at the slower heart rates. This result suggests that rate is probably not the only reason for the absence of arrhythmia after A-V block produced by the destruction of the bundle of His (although the rates were slightly higher after destruction of the A-V node). The fact that coupled rhythm could still be elicited after destruction of the A-V node suggests that the more important factor is that the "normal" impulse should originate at a site above the bifurcation of the common His bundle, i.e. normal sequential activation of the ventricles has to be maintained. These results indicate, then, that the bundle of His is important in the genesis of bigeminal rhythms. They do not suggest that the bundle of His is a site of origin of the arrhythmia. The difficulty in inducing this arrhythmia at the slow heart rates still supports the view that heart rate is important in the genesis of the arrhythmia. The reason for the variable coupling interval in most of the coupled rhythms present after A-V block is not entirely clear. It may be related to the general instability of the arrhythmia at the slow

heart rates, to the altered configuration of the coupled beat (due in some cases to the superposition of P waves over QRS complexes) or to a different mechanism. The longer coupling interval is probably related to the slow rate.

Larger doses of adrenaline were sometimes required to produce coupled rhythms after destruction of the A-V node. This may, in part, be due to a lower absolute pressure present after A-V block. Moe et al. (7) have shown that the threshold dose of adrenaline required to produce arrhythmia depends upon the absolute pressure present just prior to the administration of adrenaline. However, a larger dose may also be required, in some cases, to initiate arrhythmia when the rate is slow.

In those cases in which coupled rhythm could be obtained only transiently, an attempt was made to induce arrhythmia by pacing the His bundle. This proved unsuccessful. The failure can be attributed largely to the stimulating technique. In the dog the bundle of His is a very small structure and its direct stimulation, particularly in the intact preparation, is difficult. The chances of stimulating the His bundle directly would have been greatly increased if we had had at our disposal the type of electrode used by Stuckey and Hoffman (94) containing as many as 16 contacts in a small area.

One additional point should be made. When we speak of destruction of the A-V node versus destruction of the bundle of His, we do not delude ourselves in thinking that our destructions were precise. It is not unlikely that in our attempt to destroy the bundle of His at the lowest possible point of its course along the atrioventricular groove we were also destroying one of the bundle branches. Similarly, our attempt to destroy the A-V node could have damaged parts of the His

bundle. However, the important point is that an attempt was made to produce an A-V block as high up (or as low down) as possible so that the spontaneous pacemaker arose above or below the bifurcation of the common bundle. Hence, destruction of parts of the His bundle along with the A-V node would not change the interpretation of the results as long as enough of the His bundle was intact to maintain normal sequential ventricular activation.

The importance of the bundle of His to the genesis of multifocal rhythms appears to depend upon the severity of multifocal rhythm which is, in turn, related to the dose of adrenaline required to induce them. This is discussed in detail below.

Dresel and Sutter (10) have postulated that ventricular fibrillation is due to a mechanism different from that causing the non-fatal arrhythmias. Their theory was based on the evidence that stimulation of the vagus did not change the dose of adrenaline required to produce ventricular fibrillation and that this arrhythmia was not pressure sensitive. The present experiments support their view in that destruction of the bundle of His while affecting the nonfatal arrhythmias had no effect on the dose of adrenaline required to produce ventricular fibrillation.

B. ON THE MECHANISM OF MULTIFOCAL VENTRICULAR TACHYCARDIA

Destruction of the bundle of His did not abolish multifocal arrhythmias but did increase the dose of adrenaline required to induce them. Stimulation of the vagus nerves did not affect multifocal rhythms produced by larger doses of adrenaline after destruction of the bundle of His. However, multifocal arrhythmias produced by these larger doses of adrenaline in the intact heart were also unaffected by stimulation

of the vagus nerves. At moderate doses of adrenaline in the intact heart multifocal rhythm was obtained which was not converted to normal sinus rhythm by stimulation of the vagus nerves but which slowed in rate. At still higher doses of adrenaline multifocal arrhythmia was obtained which was unaffected by stimulation of the vagus despite considerable decreases in the atrial rate. Vick (15) was also unable to convert multifocal rhythms produced by these larger doses of adrenaline in chloroform anaesthetized dogs. Nickerson and Nomaguchi (9) were unable to affect ventricular tachycardia by stimulation of the vagus in dogs anaesthetized with 30% cyclopropane and given a rather large dose (10 μg/kg) of adrenaline.

Multifocal arrhythmias produced by small doses of adrenaline in the intact heart were uniformly affected by injections of acetylcholine into the left circumflex coronary artery. Injections of acetylcholine into this artery after the bundle of His had been destroyed failed to affect the arrhythmia in the majority of animals. On the other hand, injections of acetylcholine into the left anterior descending coronary artery were ineffective in converting the arrhythmia in intact hearts but were effective in approximately one-half of the animals after destruction of the bundle of His.

These findings suggest that multifocal arrhythmias produced by larger doses of adrenaline both in intact hearts and in animals with the bundle of His destroyed differ in mechanism from those arrhythmias produced by smaller doses of adrenaline in animals with intact hearts. It is apparent that, at the lower doses of adrenaline in intact hearts, multifocal rhythm is dependent upon the atrial rate and the level of the arterial blood pressure and in this way resembles bigeminal rhythm in

mechanism. The possible mechanism of bigeminal rhythms is discussed below. With increasing doses of adrenaline in the intact heart an arrhythmia is obtained which is independent of the atrial input and, therefore, must be due to a different mechanism. After destruction of the bundle of His the idioventricular pacemaker rates are slow and normal sequential activation of the ventricles is no longer maintained. Consequently, adrenaline is unable to produce arrhythmia in these animals by a mechanism requiring a fast rate and normal ventricular activation but can still induce arrhythmia by another mechanism if larger doses are administered.

We suggest that this second mechanism may be an increase in automaticity in the lower portions of the ventricular conducting system. The likelihood of such a mechanism occurring is supported by previous work. It has been shown (85) that low concentrations of chloroform cause a slight decrease in the threshold concentration of adrenaline or isoproterenol necessary for induction of automatic beating in isolated cat papillary muscles. In vivo, injections of isoproterenol or adrenaline into the anterior descending coronary artery caused arrhythmias in dogs anaesthetized with cyclopropane but not in nonsensitized animals (82). The threshold for inducing nodal pacemaker activity by injections into the left circumflex coronary artery did not differ in the two preparations. Hence, cells in the lower portions of the ventricular conducting system can respond to sympathomimetic amines with an increase in automaticity in the sensitized preparation. Intravenous injections of large doses of isoproterenol have been shown to cause multifocal rhythms in the sensitized preparation, despite a fall in the systemic blood pressure (2,9). Dresel and Sutter (10) found, however, that the administration

of large doses of isoproterenol in sensitized animals resulted in multifocal rhythms only after stimulation of the vagus nerves. Induction of adrenaline arrhythmias after stimulation of the vagus nerves occurs readily in the nonsensitized animal and is generally attributed to increased ventricular automaticity (5). The present experiments show that large doses of adrenaline can also increase the automaticity of ventricular pacemakers in the sensitized preparation (see Fig. 25).

The relative effectiveness or ineffectiveness of injections of acetylcholine into the two branches of the left coronary artery requires further comment. An arrhythmia which is dependent upon atrial rate (as the less severe multifocal rhythms appear to be) will be affected by injections of acetylcholine into the left circumflex coronary artery as such injections slow or block conduction through the A-V node, and unaffected by injections into the anterior descending coronary artery which do not. Much larger doses of acetylcholine were required to convert multifocal arrhythmias produced after destruction of the bundle of His when injected into the anterior descending coronary artery. This suggests a direct action of acetylcholine at the site of origin of the arrhythmia (i.e. in the lower portions of the ventricle) versus an effect on A-V conduction. However, it is not readily apparent how acetylcholine can convert the arrhythmia through a direct action on the ventricular conducting system since under normal circumstances acetylcholine has been shown to have little or no effect on conduction below the bundle of His even at high doses (see Introduction). However, effects on automaticity may differ from those on conduction. It may also be that acetylcholine affects these tissues in the presence of adrenaline and/or cyclopropane. In other words, the specialized conducting tissue becomes more sensitive

to acetylcholine under the conditions of our experiments. It would be interesting to test this possibility. There is some evidence in the literature to suggest that this might be the case. Dresel and Schluter (87) have shown that small concentrations of acetylcholine blocked conduction in cooled, isolated Purkinje fibres reactivated by adrenaline but had no effect (in larger concentrations) on conduction in normally conducting Purkinje fibres. Hollenberg et al. (88) showed that intracoronary infusions of acetylcholine in doses ranging from 0.5 to 20 μg/kg/-min had little or no effect on myocardial contractility but inhibited strikingly the positive inotropic effect of stellate ganglion stimulation or infusions of sympathomimetic amines. They attributed this antagonism to a direct action of acetylcholine on the ventricular myocardium.

C. THE ROLE OF THE VAGUS NERVES IN CONVERSION OF BIGEMINAL AND MULTIFOCAL RHYTHMS - A DIRECT OR INDIRECT EFFECT?

One aspect of the controversy concerning the site of origin of bigeminal and multifocal arrhythmias is the effectiveness of stimulation of the vagus nerves in converting these arrhythmias to normal sinus rhythm. Dresel and Sutter (10) have suggested that the vagus has a direct effect at the site of origin of the arrhythmias. Vick (15), however, disagreed with this interpretation and suggested, instead, that the effect of the vagus was secondary to changes in rate. He showed that after conversion to normal sinus rhythm by stimulation of the vagus, both bigeminy and multifocal ventricular tachycardia could be reinduced by driving the atria to rates at which arrhythmia occurred previous to stimulation.

Vick's results have been confirmed in the present investigations.

Furthermore, it was found that when the atrial rate was held constant (either by electrical pacing of the right atrial appendage or by injection of atropine into the sinus node artery), stimulation of the vagus was successful in converting the arrhythmia only if: 1) the blood pressure was bordering the threshold value for induction of arrhythmia and conversion was accompanied by an increase in the P-R interval of the normal beat, or 2) atrioventricular block preceded conversion. The importance of heart rate in conversion is further supported by the fact that following conversion of bigeminal rhythm by stimulation of the vagus and its subsequent reinduction by atrial pacing, decreases in the driving rate during stimulation resulted in reversion to normal sinus rhythm at the same rate at which the vagus had previously caused conversion.

When records were obtained from the bundle of His and right and left ventricles together with a lead II electrocardiogram during bigeminal rhythms, stimulation of the vagus decreased the atrial rate and increased the coupling interval in most experiments. The changes observed in the His electrogram appeared to result only from the relative changes in atrial rate and coupling interval. The increases in the coupling interval may be a result of the decrease in the atrial rate. Such increases in the coupling interval can occur normally with decreases in the atrial rate, in the absence of any nerve stimulation.

These results suggest that the major action of the vagus in converting the arrhythmias is an indirect one. This indirect action may be brought about in one of three ways, viz. 1) by decreasing the blood pressure, 2) by decreasing the atrial rate, or 3) when the atrial rate is held constant, by slowing or blocking conduction of the normal beat through the A-V node. At constant atrial rates, when bigeminal

rhythm is present at a pressure bordering the threshold value for induction of arrhythmia, a decrease in the conduction velocity of the normal impulse through the A-V node (i.e. an increase in the P-R interval) is sufficient to bring about conversion. However, if pressure is well above the threshold value, A-V block is necessary to cause conversion.

It is possible that the vagus may still play a direct role (albeit a minor one) in the conversion of the arrhythmia. Hirsch et al. (47,49) have demonstrated rich vagal innervation to the septum. The functional significance of this innervation is not known but it is conceivable that if the vagus does, in some instance, have a direct action on the arrhythmia this is where its effect would be exerted. The present experiments show that bigeminal rhythms may originate in the septum (see below). Whenever the arrhythmia originates low down in the ventricles (and the results of Moore et al. (14) would seem to indicate that it can) the vagus would convert the arrhythmia only by an indirect means. When the arrhythmia originates high up in the septum, conversion may be due to both direct and indirect means with the major effect being the latter.

It is not clear how stimulation of the vagus decreases the blood pressure at constant heart rates. Several lines of evidence suggest that it may do so either by decreasing ventricular contractility, or by decreasing atrial contractility resulting in less complete atrial emptying. Kumada et al. (111) have shown that stimulation of the vagus nerves at constant heart rates results in moderate decreases in stroke volume, cardiac output and peak flow velocity. These changes were accompanied by a slight decrease in blood pressure and end diastolic

volume of the ventricles. Since the above changes were not observed when the ventricle was paced, they attributed the decrease to a decline in the atrial contribution to the degree of ventricular filling. Sarnoff et al. (27) support this conclusion. DeGeest et al. (34,35), on the other hand, were able to obtain marked depression of ventricular contractility when both atria and ventricles were paced.

D. THE ROLE OF ACETYLCHOLINE INJECTED INTO THE POSTERIOR SEPTAL ARTERY IN CONVERTING BIGEMINAL AND MULTIFOCAL RHYTHMS - A DIRECT OR INDIRECT EFFECT?

MacCannell and Dresel (13) have shown that injections of acetylcholine into the left circumflex coronary artery were successful in converting both bigeminal and multifocal rhythms to normal sinus rhythm. Similar injections into the anterior descending artery were without effect. These results were used as evidence supporting a site of origin in the atrioventricular node or upper bundle of His. Thus, a direct action of acetylcholine at the site of origin of the arrhythmia was assumed.

The posterior septal artery (which is a branch of the left circumflex coronary artery) supplies blood to the A-V node and proximal three-fourths to seven-eights of the A-V bundle in the dog (107). MacCannell and Dresel's hypothesis could be tested more directly by injections of acetylcholine into this artery. Firstly, such injections are much more localized and secondly, very much smaller doses of acetylcholine are required.

The results indicate that injections of acetylcholine into the posterior septal artery may convert bigeminal and multifocal rhythms

largely by slowing or blocking conduction through the atrioventricular node. Bigeminal rhythms could be converted directly to normal sinus rhythm only if the blood pressure was bordering the threshold value for induction of arrhythmia and conversion was accompanied by a prolongation of the P-R interval. If the blood pressure was well above the threshold value conversion was always preceded by A-V block. Multifocal rhythms could be converted only if A-V block preceded conversion. Atrioventricular block was also seen by MacCannell (80) after injections of acetylcholine into the left circumflex artery. The typical responses selected by MacCannell (his Figs. 9 and 10) to illustrate the conversion of both bigeminal and multifocal arrhythmias by injections of acetylcholine into the circumflex artery indicate that on both occasions such conversions were preceded by atrioventricular block and a decrease in the arterial blood pressure. He commented that "the interpretation of the response to acetylcholine is complicated by the occurrence of transient atrioventricular block and of hypotension when injections were made into the circumflex artery". He excluded the decrease in pressure stating that the "bigeminal rhythm recurred after 18 seconds at the lower pressure". However, a closer examination of his record shows that the blood pressure had, in fact, returned to the previous high level before reversion to bigeminal rhythm had occurred.

The present experiments show that bigeminal rhythms may originate in the septum (see below). Since the posterior septal artery gives off branches which pass through the annulus fibrosus to end in the uppermost part of the interventricular septum, it is possible that in some instances injections into this artery might have a direct effect at the site of origin of the arrhythmia. However, it is unlikely that

the arrhythmia originates this high up in the septum unless the activation of an extra septal pathway is responsible for induction of the arrhythmia (see below).

E. ON THE SITE OF ORIGIN OF BIGEMINAL RHYTHMS

The evidence derived from simultaneous electrograms from the right atrium, bundle of His and right and left ventricles, together with a lead II electrocardiogram indicates that bigeminal rhythms originate below the bundle of His. The R wave of the electrocardiogram of the bigeminal beat preceded or occurred simultaneously with the "h" potential in the His electrogram indicating that activity below the bundle of His must have been responsible for the inception of the bigeminal beat. The exact site of origin is not known. However, the available evidence indicates that this site may be in the left septum. The evidence supporting such a site is as follows:

1) septal activation during the bigeminal beat usually occurred before the activation of either ventricle;

2) left ventricular activation usually preceded that on the right;

3) ventricular activation usually occurred late in relation to the QRS complex of the abnormal beat and therefore, could not have been responsible for its initiation;

4) early septal activation was the first abnormality present at the start of a bigeminal rhythm.

The results suggest that the bigeminal beat is a type of "fusion" complex resulting from simultaneous excitation of the heart by both the normal and the abnormal impulses, and that the early part of the

bigeminal beat represents largely abnormal septal activation. It would appear that an area of ventricular muscle (probably the left septum) is depolarized early by an abnormal impulse (a reentry beat?). However, due to early reactivation of the septum, the impulse spread is probably so slow that propagation is only partially successful and normal atrio-ventricular conduction results in the excitation of the remainder of the ventricular myocardium. The evidence for this is as follows:

1) occasionally a bigeminal rhythm was obtained in which ventricular activation was the same as in the normal beat;

2) in most experiments the right ventricle was activated normally from above during the bigeminal beat;

3) whether activation of the bundle of His was normal or abnormal appeared to depend upon the atrial rate and the length of the coupling interval and hence upon the relative timing of the two impulses originating above and below the bundle of His;

4) the sequence and times of ventricular activation appeared to depend upon the atrial rate and the earliness of septal activation;

5) during stimulation of the vagus (see Fig. 22 a and b) the configuration of the bigeminal beat changed from a positive QRS complex with a slurred upstroke to a predominantly negative QRS complex suggesting that as the atrial rate decreased more of the heart was being activated from below during the abnormal beat;

6) Fig. 19 indicates that the earliness of septal activation is responsible for the early upstroke of the bigeminal beat.

Our results differ from those of Moore et al. (14). Only one of their records (their Fig. 1) is similar to ours in that it shows early septal activation and normal right ventricular activation during the

bigeminal beat. However, they did not record from the left ventricle so we do not know whether this ventricle was activated normally or abnormally. They deduce on the basis of other records that the left ventricle in this record was activated abnormally. However, our Fig. 16 (showing early septal activation but normal activation in both ventricles) indicates that they were not completely justified in drawing this conclusion. They have shown both right and left ventricular electrograms in only one of their figures (their Fig. 4). This record shows that left ventricular activation precedes that on the right during the coupled beat (indicating to them that activity was originating in the left ventricle). Yet, on closer examination of their record, it can be seen that left ventricular activation during the coupled beat occurred later in relation to the QRS complex than it did in the normal beat. It occurred at the peak of the QRS complex in the normal beat but after completion of the S wave in the coupled beat. Thus, activity could not have originated in the left ventricle (but probably originated in the left septum as in our experiments). In their Figs. 2 and 3 right ventricular activation clearly preceded both His bundle and septal activation and the latter occurred during the S wave of the electrocardigram of the bigeminal beat. Although they suggest that the origin of the abnormal beat is in the left ventricle (and the inverted polarity of the QRS complex would appear to suggest that this may be the case), right ventricular activation occurs in these two figures at the start of the R wave of the bigeminal beat. It is not clear how the right ventricle can be activated this early if the arrhythmia is originating in the left ventricle. These two figures show a type of bigeminal rhythm (characterized by a negative R wave) which was never observed in the present experiments when multiple recordings from the heart were made. However,

such bigeminal rhythms do occur in thiopental-cyclopropane anaesthetized dogs, but in a very small percentage of animals.

The similarity between the bigeminal beats illustrated in Figs. 16, 18 and 19 and the type of complexes which occur in the Wolff-Parkinson-White syndrome is noteworthy. These latter rhythms are also characterized by a shortened P-R interval with a slurred and widened QRS complex, usually followed by abnormal T waves. They differ from the bigeminal beats in having a constant S-S interval. One of the theories postulated to explain this syndrome is that the atrial impulses are conducted over an anomalous, accessory atrioventricular pathway, circumventing the A-V node (112). The short P-R interval is thought to be due to the passage of the impulse through the direct pathway from atrium to ventricle. The early part of the W-P-W complex (called the delta wave) is thought to represent abnormal septal activation. This is the same portion of the bigeminal beat which we believe to represent largely abnormal septal activation. It is remotely possible that such an extra pathway (which has been shown to exist in some humans with the W-P-W syndrome) may be present normally in all hearts and be activated under the conditions of our experiments. However, if this were the case one would expect the extra pathway to be disengaged with changes in rate. This does not occur. The more important feature of the similarity of bigeminal rhythm to W-P-W complexes is that it lends weight to our hypothesis suggesting a septal (rather than a ventricular) site of origin for this arrhythmia.

Although multiple recordings from the heart were not made during multifocal rhythms it is not unlikely that the less severe multifocal rhythms originate in the same part of the heart as bigeminal

rhythms. It would be difficult to determine the site of origin from such recordings since the activation of the His bundle, the septum and the ventricles would be altered in many ways depending on which impulse (normal or abnormal) reached which part of the heart first. Moore (68) made such recordings during multifocal arrhythmia. However, his record shows a coupling of two abnormal beats rather than a true multifocal rhythm.

F. ON THE MECHANISM OF CYCLOPROPANE-ADRENALINE CARDIAC ARRHYTHMIAS

Dresel and Sutter (10) suggested that bigeminal and multifocal rhythms are due to a reentry mechanism in the A-V node or upper bundle of His. We still consider reentry as the most likely mechanism for coupled bigeminal rhythms and the less severe multifocal rhythms but believe that such a mechanism is more likely to occur at Purkinje-myocardial junctions below the bundle of His, be this site high up in the septum or in the peripheral portions of the ventricular conducting system.

Bigeminal and multifocal ventricular rhythms are caused by the interaction of several factors or agencies which together or singly affect the conduction characteristics of the ventricular conducting system. These agencies include: 1) the sensitizing effect of the hydrocarbon anaesthetic; 2) the potentiation of the sensitizing effect by thiobarbiturate; 3) the multiple effects of adrenaline, including indirect peripheral actions and direct effects on conduction and excitability in the heart; 4) the arrhythmogenic effect of pressure on the specialized conducting tissue; and 5) the frequency of excitation of the ventricles. Each of these factors probably produce changes in excitability and conduction which are subthreshold but which are of

sufficient magnitude to augment the arrhythmia producing actions of the other factors. There appears to be an interrelationship between these factors such that a decrease in one of them can be overcome (within limits) by a corresponding increase in one or more of the other four. Thus, if rate is maintained constant at a low value, bigeminy can still be induced but at a higher pressure [see Fig. 1 in Dresel *et al.* (11)]; or conversely, as is borne out by the present experiments, if the pressure is lower a higher rate is required for induction of arrhythmia. If the concentration of cyclopropane is increased arrhythmia can be produced in the absence of exogenous adrenaline. Bigeminal rhythm can also be produced in the absence of adrenaline by increasing the pressure mechanically (10).

The known facts about the different agencies involved in the genesis of this arrhythmia which may be conducive to a reentry mechanism are discussed below. Hoffman and Cranefield (66) have pointed out that two aspects of the electrical activity of specialized cardiac fibres appear to be involved in the production of arrhythmias due to conduction disturbances. These include decremental conduction and unidirectional block. Thus, any agency which produces changes favoring the above conduction disturbances may cause a reentry mechanism to occur.

Cyclopropane (at concentrations that produce spontaneous arrhythmias in dogs) has been found to affect the repolarization of Purkinje fibres producing a significant increase in the rate of repolarization during the plateau portion of the action potential accompanied by a decrease in the rate of the rapid terminal repolarization phase (78). This effect of cyclopropane results in an increase in the total duration of the action potential but in a significant decrease

in the time required to repolarize to minus 60 millivolts, i.e. a decrease in the absolute but an increase in the relative refractory period. Hoffman et al. (79) have shown that Purkinje fibres are capable of reexcitation and can elicit conducted responses when repolarized to this value. This action of cyclopropane would therefore increase the time during which an impulse could invade the tissue and be conducted with decrement. However, this effect may not be present at the lower concentration of cyclopropane which produce arrhythmias in combination with adrenaline. It has been shown (75) that chloroform, another hydrocarbon, prolongs the refractory period of ventricular muscle and increases the degree of nonuniformity of recovery of this tissue. It is likely that cyclopropane has the same effect. Adrenaline counteracts the effects of chloroform on the refractory period but does not counteract its effects on the temporal dispersion of recovery of excitability. Smith et al. (113) found that cyclopropane causes a decrease in ventricular excitability. A shortening of the refractory period (adrenaline) coupled with a depression of excitability and conduction velocity could lead to decremental conduction and increase the likelihood of reexcitation.

The potentiation of the sensitizing action of cyclopropane by thiopental cannot be explained fully. Most of the studies on cardiac effects of barbiturates have been done with pentobarbital. However, effects of pentobarbital do not necessarily reflect those of thiopental since not all barbiturates have this sensitizing effect. Only the ultrashort-acting barbiturates (thiopental, thiamylal) possess this action. Thiopental has been shown to initially cause an increase in heart rate and a decrease in the action potential duration of rabbit

atrial fibres (114). The subsequent effect was one of depression. No studies have been done on Purkinje or ventricular fibres. There is some evidence indicating that a part of the action of thiopental may be through release of catecholamines, either from the adrenal medulla or from adrenergic nerve endings (115). This may explain the initial increases in rate seen with thiopental administration.

A part of the action of adrenaline on the arrhythmia is an indirect one on blood pressure. However, its direct cardiac actions are important since MacCannell (80) showed that only sympathomimetic amines with direct cardiac actions consistently produced bigeminal rhythm in thiopental-cyclopropane anaesthetized dogs (methoxamine, for example, was seldom effective).

The most characteristic and clearly defined effect of catecholamines on the electrical activity of normal cardiac fibres is to increase the slope of spontaneous phase 4 depolarization of cardiac cells. The cyclic decrease in membrane potential occurring in automatic cells of the His-Purkinje system can result in changes in the rising velocity of the action potential, excitability and conduction similar to those observed during repolarization if a response is initiated at comparable levels of membrane potential. Catecholamines, by increasing the rate of phase 4 depolarization, may therefore decrease the amplitude and maximum rate of rise of the action potentials elicited from automatic cells and thus slow conduction. In normal Purkinje fibres, the effects on conduction are usually minimal. The maintenance of conduction probably reflects the fact that the normal Purkinje cell is able to generate an effective action potential at levels of membrane potential as low as the normal threshold potential. However, it is not

inconceivable that such decreases in conduction velocity, depression of excitability and conduction disturbances ranging from simple slowing to complete unidirectional block could occur in Purkinje fibres under the influence of thiopental and cyclopropane.

Under normal conditions in situ catecholamines increase the speed of A-V conduction but have little effect on conduction on fibres of the His-Purkinje system or on ventricular muscle, unless accompanied by an increase in serum potassium levels. Thus, if A-V conduction is enhanced more than conduction in the His-Purkinje system it is conceivable that the normal impulse can arrive at the peripheral Purkinje fibres before these fibres have completely repolarized. This could result in a slowing of conduction or block in a unidirectional manner.

It is not known what effect increases in blood pressure have on conduction and excitability in the heart. It may be that the effects of such increases in pressure are produced by stretch of the tissue. It has been shown that cardiac pacemaker tissue in general responds to stretch with enhanced activity. Innes and Sanders (116) showed that a sufficiently quick stretch produces subthreshold changes in excitability of ventricular myocardium as indicated by a decrease in the concentration of adrenaline required to induce automaticity. They studied cat papillary muscle and it is likely that the effects they observed were the result of activity of the terminal twigs of the Purkinje system which pervade the myocardium. Dudel and Trautwein (117) found that moderate stretch (35%) of Purkinje fibres has no effect on the resting potential but causes a considerable reduction in the steepness of phase 0 of the action potential. The most interesting observation, however, was that even slight stretch (10%) produced a tendency toward arrhythmia

associated with an increase in the slope of phase 4 depolarization. Multiple foci of spontaneous activity were seen to develop in such fibres. The eventual consequence was the development of multiple local foci none of which gave rise to propagated activity. The development of phase 4 depolarization due to increased stretch of the canine false tendon preparation was also observed by Singer et al. (92).

The significance of the above observations may be appreciated if one considers the anatomical arrangement of the false tendons and small bundles of Purkinje fibres which run free in the cavity of the ventricle and are thus susceptible to stretch during filling. It is more difficult to conceive of such an effect of stretch on the subendocardial Purkinje fibres high up in the septum, if the arrhythmia does indeed originate this high up in the septum in some instances, and the results would seem to indicate that it may.

Another effect of increased blood pressure may be an increased myocardial oxygen consumption (and a decreased myocardial efficiency) produced by the increased force of contraction required to expel blood against an elevated aortic pressure resulting in relative hypoxia of the conducting fibres. The catecholamines have also been shown to cause a marked increase in oxygen consumption of cardiac tissue. Hypoxia has been shown to enhance the extent of phase 4 depolarization of Purkinje cells, a change which may lead to premature discharge or could contribute to decremental conduction (118). Furthermore, Hoffman and Cranefield (66) have shown that hypoxic automatic cells are more sensitive to the diastolic depolarizing effects of catecholamines.

Perhaps the most puzzling and least understood feature of this arrhythmia is its dependence on rate. There appears to exist a

critical range of rates above or below which the mechanism inducing the arrhythmia cannot be activated. Once the arrhythmia is induced at a certain critical rate at the upper end of the range, it is maintained despite decreases in the rate to values at which it could not be previously induced, until a critical rate at the lower end of the range is reached. An increase in the rate would shorten the relative refractory period of heart tissues in general. However, the Purkinje fibres are the most susceptible to changes in rate and exhibit the most marked effects (18). This may lead to a greater shortening of the Purkinje fibre action potential than that of ventricular muscle and lead to block or slowing of conduction in a unidirectional manner.

It is most likely that such block occurs at the Purkinje-myocardial junction. Matsuda et al. (119) recorded action potentials from the Purkinje-ventricular junctional fibre in a preparation of canine ventricular subendocardial muscle. They found that the action potentials from such junctional fibres consisted of two components: an initial spike and a second slow rising plateau component, the two components being separated by about 5 to 10 msec with a more or less distinct dip. The dip was shown to be due to a local conduction delay at the Purkinje-ventricular junction. This conduction delay was only present in orthodromic impulse conduction. Alanis and Benitez (120) also showed in the papillary muscle-false tendon preparation that a considerable delay of conduction existed at the Purkinje-myocardial (P-M) junction and that this latency was again much more marked in a unidirectional manner (the P-M latency was 32 msec compared with an M-P latency of 18 msec). Furthermore, P-M latency was particularly sensitive to anoxia and an increase in the frequency of stimulation,

both factors causing an increase in P-M conduction time. When the false tendon was stimulated block of conduction at the P-M junction occurred at an average frequency of 4.7/sec although the Purkinje fibres themselves could follow much higher frequencies. If block of conduction in normally conducting fibres occurs at such a frequency, it is not inconceivable that a considerable depression or block of conduction can occur at the P-M junction under the experimental conditions at the frequencies of stimulation (3-4/sec) at which bigeminal rhythms usually occur. This might very well be the role which an increase in rate plays in the genesis of bigeminal rhythms. A decrement in conduction at multiple P-M junctions may cause multiple reentries to occur and hence result in multifocal rhythms.

It is evident, then, that all the factors involved in the genesis of this arrhythmia can ultimately result in a shortening of the refractory period and decremental conduction in a unidirectional manner, the latter resulting in a localized block (P-M junction) and the former permitting reexcitation to occur.

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