An Analysis of Arrhythmias Induced by Ouabain in Intact Dogs

By Mario Vassalle, M.D., Kalman Greenspan, Ph.D., and Brian F. Hoffman, M.D.

The mechanism of cardiac arrhythmias induced by digitalis compounds has been investigated recently by the microelectrode technique. Coraboeuf et al. found that the automaticity of the canine 'tissu nodal' was enhanced by administration of digitalis. This finding was confirmed by Dudel and Trautwein for canine Purkinje fibers. Also, the action of glycosides on transmembrane potentials of ventricular muscle fibers has been studied extensively. In a comparative study canine Purkinje fibers and ventricular muscle fibers were exposed to ouabain in vitro under identical experimental conditions. It was found that the transmembrane potential of the Purkinje fibers is markedly modified by ouabain and that this tissue quite often develops a fast rhythm at a time when the transmembrane action potentials of ventricular muscle fibers show only minor changes. No electrophysiological evidence that ventricular muscle fibers develop automaticity under the influence of ouabain was found. The sensitivity of the specialized conducting system to ouabain suggested that a similar increase in automaticity of Purkinje fibers might be observed in vivo at an early stage of ouabain administration. Since ventricular muscle fiber action potentials showed little change when Purkinje fibers exhibited fast rhythms, one could expect an increase in automaticity of the specialized system of the ventricles at a time when no marked changes were present in the electrocardiogram. Indeed, Rothberger and Winterberg had demonstrated that, in animals given strophanthidin, a fast ventricular rhythm often could be unmasked by means of vagal stimulation. However, this finding was not present in every instance and some animals died in cardiac arrest resulting from failure of ventricular pacemakers. These authors attributed such a failure to the fact that the hearts of their experimental animals were denervated. In view of recent conflicting findings bearing on the relationship between cardiac glycosides and epinephrine, it was thought desirable to study the effects of ouabain administration in animals with intact cardiac sympathetic innervation. Also, evidence was sought for the occurrence, in vivo, of two types of arrhythmias seen in vitro, namely: an increase in automaticity of Purkinje fibers and coupled extrasystoles. The influence of sinus rhythm on the latter type of arrhythmia was investigated since, in vitro, coupled beats disappeared on interrupting the driving stimulus.

Methods

The automaticity of the ventricular specialized conducting system was studied by means of vagal stimulation which resulted in either A-V block or cardiac standstill. The rate of ventricular escape during vagal stimulation was taken as a measure of the automaticity of the specialized tissues of the ventricles. Graded vagal stimulation which slowed the sinus rhythm, without suppressing it, also was employed when re-entry type beats were present.

The experimental animals were mongrel dogs of either sex weighing 9.5 to 21.8 kg. The animals were anesthetized with sodium pentobarbital (30 mg/kg intravenously) and additional amounts of anesthetic were administered intravenously as required. The dogs were placed in supine position. A tracheotomy was performed and a cannula inserted. Blood pressure was recorded through a
catheter inserted in the left carotid artery and connected to a Statham transducer. An intravenous infusion of isotonic saline was administered through a catheter placed in either the external jugular or femoral vein. The electrocardiogram was recorded as lead I or II. The recording apparatus was either a GME mini-polygraph model M4P or Sanborn 4-channel recorder. The distal end of a crushed vagus, usually the right, was employed for stimulation. No difference between the effects of right and left vagus was noted. The duration of the stimulus was 0.05-1 msec and the frequency was 20 impulses per second. Stimulation was maintained for one minute, except in the first four experiments (table 1).

After vagal stimulation had been repeated three times under control conditions, a priming dose of ouabain (0.25 mg) was injected intravenously; this was followed by an infusion of ouabain in isotonic saline in a concentration of 1:400,000. The rate of infusion varied in different experiments from 0.10-0.15 μg of ouabain/kg per min and, at these rates, several hours elapsed before ventricular arrhythmias developed. Initially, vagal

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Exper. no. = number of experiments. Basal R. = control heart rate per minute. Escape = idioventricular escape beats during vagal stimulation. The number of escape beats is indicated by "none" and their rate per minute by "R." The rate reported was the maximal rate present and usually was measured toward the end of the period of vagal stimulation. P. V. R. = fastest sinus rate per minute after the end of vagal stimulation. Stimul. time = duration of vagal stimulation in seconds throughout the experiment. The values of the escape beats during the control period and during ouabain administration are those found during the period of stimulation indicated. Escape max. decr. = maximal decrease in the number (no.) and rate (R) of the idioventricular escape beats after the beginning of the ouabain infusion. The word "none" indicates that there was a steady increase of the idioventricular escape beats. Escape max. incr. = maximal increase of the number and rate of the idioventricular escape beats when the sinus rhythm was still present and no arrhythmias were apparent. Slowest sinus R. = maximal decrease of the sinus rate after the administration of ouabain. Both the rate values before (basal) and after vagal stimulation (P. V.) are reported. The occurrence of extrasystoles is marked by the abbreviation "extras." Fastest sinus R. = fastest sinus rate during the ouabain infusion before the appearance of arrhythmias. Ventr. arrhythm. = rate of the heart when the ventricular arrhythmias were present. Bigem. = the occurrence of bigemini is marked with the sign +. Atrial fibrill. = the occurrence of atrial fibrillation after one of the first idioventricular beats is indicated by the sign +. A circle around the sign + shows that the same phenomenon also occurred during the control period prior to ouabain administration.

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stimulation was repeated every 30 or 45 minutes and subsequently at shorter intervals as changes in ventricular escape beats were noted. Graded vagal stimulation was employed when coupled extrasystoles were present. In a number of animals, once the stage of multifocal arrhythmias was attained, the ouabain infusion was stopped and an isotonic solution of KCl infused. The effects of the KCl infusion on ouabain will be reported elsewhere.30

Quite often a coupled extrasystole appeared at such a time that it was preceded by a short P-R interval. Therefore, it was difficult to decide whether the altered morphology of the coupled complex was the result of its ventricular origin or rather the result of disturbed intraventricular conduction of a supraventricular beat. One way to solve the problem was to implant a recording electrode over the His bundle; when the excitation process invades the His bundle from the atrioventricular node an action potential is recorded. If excitation of the ventricles proceeds from a ventricular site, activity in the His bundle propagates in the opposite direction and the polarity of His action potential is reversed. In this way supraventricular beats with disturbed intraventricular conduction (normal His complex) can be distinguished with certainty from ventricular extrasystoles (reversed His complex). For this reason, silver electrodes were chronically implanted over the His bundle in two dogs (for details of the technique.11*12 These dogs also had other electrodes sewn to the epicardial surface of the right atrium and the ventricles at locations indicated for each figure. The recording apparatus for these two dogs was an 8-trace switched beam oscilloscope (Electronics for Medicine). Records were photographed on 7-inch paper moving at speeds indicated in the illustrations. In other animals atrial activity was recorded through a unipolar endocavitary lead placed in the right atrium through the external jugular vein.

In five experiments a control dog was prepared in a manner identical to the experimental animals with the exception that the saline infusion did not contain ouabain. These control animals were subjected to vagal stimulation of the same duration and at the same intervals as the experimental dogs.

Results

A. CONTROL DOGS

The number and rate of the ventricular escape beats appearing during vagal stimulation varied in different dogs. However, no significant changes were found on repeated stimulation in each control animal throughout an experiment. The minor changes countered showed no directional trend. A transient sinus acceleration was observed at the end of vagal stimulation. In three dogs, atrial fibrillation was seen during vagal stimulation; this arrhythmia disappeared rapidly once the vagal stimulation ended. This finding will be described below in some detail.

B. EXPERIMENTAL DOGS

Prior to ouabain administration the ventricular escape beats recorded from each animal during vagal stimulation were fairly consistent with respect to both number and rate. The average value obtained from three control stimulations and the sinus rate prior to and following vagal stimulation are given in table 1. No changes were observed after injection of the priming dose of ouabain. During the infusion of ouabain there was, over a period of several hours, a progressive decrease in the sinus rate (table 1).

The arrhythmias induced by ouabain were rather complex and, in an attempt to facilitate the description, we shall separate the findings into two groups. In the first group, changes in idioventricular automaticity which eventually resulted in arrhythmias will be described. This type of arrhythmia is characterized by independence of the activity of the ventricular focus from the sinus rhythm. If the rate of the ventricular pacemaker is higher than that of the sinus node, the former will drive the ventricles. To the second group belong the extrasystoles which depend on an initiating beat, usually of sinus origin, in order to appear. These extrasystoles may or may not exhibit a constant coupling with the preceding beat. If sinus activity is suppressed by vagal stimulation these extrasystoles also disappear.

1. Changes in Idioventricular Automaticity

On successive stimulation of the vagus during ouabain infusion, changes in both the rate and number of ventricular escape beats were noted. In some instances the number of the escape beats increased from the beginning of the ouabain infusion because of an increased frequency of the ventricular pacemaker. A representative example is illustrated in figure
The control tracing (A) and the tracings recorded during ouabain infusion (B, C and D) show only the electrocardiogram (lead I). A. Stimulation of the right vagus was begun at the upright arrow and terminated at the downward arrow. B. On stimulation of the vagus (upright arrow) the escape beats start earlier than in the control tracing and appear at a faster rate. Stimulation of the vagus continued for 72 sec. C. As soon as vagal stimulation was started a fast rhythm appears but subsides shortly thereafter. Predominantly negative complexes appear intermingled with the complexes seen previously. Vagal stimulation lasted 90 seconds. D. The idioventricular rhythm seen in A, B and C is intermingled with sinus rhythm and P waves are at times fused with the QRS complexes. The onset of vagal stimulation (upright arrow) is followed by the disappearance of P waves while the fast ventricular rhythm continues. Because of the spontaneous slowing of the idioventricular rhythm, at the end of vagal stimulation the sinus node is the pacemaker for a short period of time. Paper speed in all four traces is 10 mm/sec.

1. The control tracing is shown in figure 1A; at the arrow vagal stimulation was started and, after a pause, ventricular escape beats became apparent. During the last third of the vagal stimulation a new escape rhythm, somewhat faster than the preceding one, assumed dominance. Upon cessation of vagal stimulation, sinus rhythm showed a transient acceleration before reverting to the prestimulation rate. Later on, during ouabain infusion (fig. 1B), the escape rhythm started sooner. Its rate was faster than that of the preceding escape rhythms but still slower than the sinus rhythm. A few sinus escape beats were intermingled with the ventricular rhythm but they are easily recognizable. At a later stage of ouabain administration (fig. 1C), as soon as vagal stimulation inhibited the sinus rhythm,
a fast ventricular rhythm appeared. It subsided shortly thereafter but was seen once more toward the end of the tracing intermingled with activity originating from a new ventricular pacemaker not present previously. With the progression of intoxication, the ventricular rhythm which previously had been unmasked by means of vagal stimulation appeared intermingled with sinus beats (fig. 1D), in the absence of vagal stimulation. On vagal stimulation, the sinus node was inhibited and the ventricular rhythm became uniform. In most animals, as the ouabain infusion continued, the duration and the amplitude of the ventricular complexes increased. Finally, activity of the dominant ventricular pacemaker became discontinuous for short periods of time and during these intervals, ventricular complexes of different shape appeared. On a rare occasion the fast ventricular rhythm converted for short periods of time into the pattern of ventricular flutter.

The sequence of the changes described above was rather common. However, an unexpected finding was quite obvious in many experiments. This was a progressive slowing of the idioventricular rhythm which preceded its acceleration (table 1). Early during the ouabain infusion the escape beats were of the same shape as during the control period but on successive vagal stimulations they appeared at a progressively lower rate. Also, the interval between beats showed increasing irregularity. Sometimes the depression of the automaticity of the ventricular pacemaker was so marked that there was no escape during vagal stimulation of one minute duration (table 1).

2. Re-entry Type Arrhythmias

In most animals, as mentioned above, the initial depression of ventricular automaticity was followed by enhancement; in some, however, automaticity never increased appreciably. Nevertheless, arrhythmias also were present in this latter group of animals; the disturbance of the rhythm belonged to the second group of arrhythmias and was due to extrasystoles which may or may not have demonstrated a constant coupling to an initiating beat which usually was of sinus origin. Regardless of whether or not there was constant coupling, all extrasystoles disappeared when the sinus rhythm was suppressed by vagal stimulation. An example of this type of arrhythmia is shown in figure 2. The first and third complexes are sinus beats and the second and the fourth are extrasystoles with fixed coupling to the sinus beat. As in most of the other dogs in which this arrhythmia appeared, the bigeminal beat appeared after the P wave that followed a normal beat. This is possibly the result of the fast heart rate. The coupling interval (0.41 sec in fig. 2) is well within the range commonly found for bigemini (0.35 to 0.6 sec according to Sherf and Schott). The inverted polarity of the His complex, when compared to the His electrogram which precedes the QRS of a sinus beat, proves that the ventricles were not activated from the atrium but rather from a ventricular site. Also, both the interval between atrial activity and the His complex and between the His complex and the beginning of the QRS are shortened; this is what one would expect for a premature ventricular beat. The dependence of these coupled beats on the initiating beat appears clearly in figure 3A. Extra beats regularly alternate with sinus beats. At the arrow the vagus was stimulated: there is one sinus beat followed by two extrasystoles neither one of which was preceded by evidence of atrial activity in the atrial lead. A period of cardiac standstill followed and, upon cessation of vagal stimulation, there was resumption of the sinus rhythm. The extrasystoles reappeared after a few beats and showed the same coupling as before.

The relationship between the sinus rhythm and the extrasystoles could be modified merely by slowing the sinus rhythm. Figure 3B illustrates this finding: on graded vagal stimulation the extrasystoles appear after every second sinus beat instead of being coupled to each of them. The sinus rate was reduced from 140 to 111 as a consequence of the vagal
stimulation initiated at the arrow. Also, the coupling interval was increased from 0.42 to 0.47 second. Therefore, for a 21% decrease in the rate, the coupling interval increased by 11%. Perhaps more surprising was the disappearance of the extrasystoles when the sinus rhythm was slowed further by means of a graded increase in the strength of vagal stimulation (fig. 3C). The fact that on graded vagal stimulation the coupled extrasystoles appeared after every third sinus beat instead of every second one, or disappeared altogether, indicated that a definite relationship existed between the appearance of the extra beats and the sinus rate. An obvious corollary was that an increase in cardiac rate should increase the number of extrasystoles. Such an increase in rate was produced in the same dog by driving the heart through an atrial electrode. This procedure resulted in an increase of the number of extrasystoles (fig. 3D). Prior to the stimulation, extrasystoles appeared regularly after every second sinus beat; the first driven beat (appearing earlier than the sinus beat) was followed by three extrasystoles, the fourth driven beat by three extrasystoles. Shortly after the stimulation was stopped the extrasystoles returned to their original pattern of appearance. In this connection it is interesting to note that, in most dogs, a spontaneous acceleration of sinus rate was present at the end of the period of vagal stimulation. During ouabain administration this acceleration often was accompanied by extrasystoles. These results will be referred to in greater detail later on in this section. Although the coupled extrasystoles required an initiating beat, evidence was obtained to support the possibility that the same extrasystoles might be self-sustaining. That
All the traces in this figure are taken from the same experiment as in figure 2. Only the peripheral leads of the original tracings are shown here. Tracings have been retouched to show rapid upstrokes. In A, B and D, paper speed is 25 mm/sec; in C 10 mm/sec. Time lines at intervals of 1 sec. A. At the arrow, maximal vagal stimulation was started. Suppression of sinus activity is accompanied by disappearance of bigeminal rhythm. B. Graded vagal stimulation started at the arrow: extrasystoles appear after every second sinus beat instead of every sinus beat as was the case prior to vagal stimulation. C. Sinus rate has slowed from 140/min (B) to 125/min and the extrasystoles appear after every second sinus beat. The P wave which preceded the extrasystoles in trace B is now fused with the beginning of the extrasystolic QRS complex (see also trace D). Graded vagal stimulation started at the upright arrow provoked slowing of the sinus rhythm: the slowing was accompanied by disappearance of the extrasystoles. Extra beats reappeared at the end of the stimulation (downwards arrow). D. The heart was driven through an electrode chronically implanted on the atrium. The stimulus artifact, visible in lead 2, marks the period during which driving stimuli were applied. Number of extrasystoles increased during this period.

is, once the extrasystoles are started they can act as initiating beats themselves (fig. 4). The second sinus beat in this record is followed by a run of extrasystoles which have the same shape as the bigeminal complexes seen previously: however, their rate is faster than the atrial rate and any relationship with the sinus rhythm is lost. The run of extrasystoles shown in figure 4 ceased spontaneously and then started once more after a few sinus beats. If the vagus was stimulated during one of these runs of extrasystoles, the extrasystoles were not affected. However, by inhibiting the sinus activity, vagal stimulation succeeded in preventing the start of a new run of arrhythmia. Therefore, although vagal stimulation does not affect the extrasystoles themselves, it suppresses them through inhibition of the initiating beat. The different effects of vagal stimulation applied at different times are shown in records from another experiment (figs. 5 and 6). Runs of extrasystoles of alternating polarity appear in figure 5: the interval separating these complexes, however,
is not perfectly regular and the interval between the positive and negative complexes is shorter than the interval between the negative complexes and the following positive ones. The last two complexes of the run are of sinus origin; this is shown by the fact that they are preceded by atrial activity and a His complex of control configuration. Vagal stimulation started at the arrow lead to ventricular standstill. A few minutes later the vagus was stimulated again (fig. 6). This time, however, stimulation was started during a run of extrasystoles: ventricular arrest ensued only when the run of extrasystoles ceased spontaneously. With advanced ouabain intoxication polymorphic extrasystoles succeeded each other in a chaotic fashion. At this time there was no apparent effect of vagal stimulation.

In two dogs the inhibition of sinus activity by vagal stimulation revealed a marked depression of idioventricular automaticity. As a consequence of ouabain intoxication a complete atrioventricular block subsequently developed in these two animals and they died in ventricular arrest. The two types of arrhythmias described, namely, those due to an enhanced idioventricular automaticity and those due to re-entry type beats, might both be present at the same time in the same animal.

3. Effects on Atrial Rate and Rhythm

An interesting finding was the onset of atrial fibrillation during vagal stimulation. This finding was unusual in that the atrial fibrillation was initiated by retrograde transmission of one of the ventricular escape beats: generally it was the first one but sometimes the second or the third. Such an event is illustrated in figure 7. Shortly after the beginning of vagal stimulation there was an atrial escape beat followed by a QRS of altered configuration. The ventricular complex was in turn followed by another atrial beat which appears to result from retrograde conduction from the ventricles to the atria. In other instances two or three atrial complexes in close succession followed one ventricular complex. Of particular interest are the events following the second ventricular beat. This complex was not preceded by any atrial activity and represented the beginning of a series of ventric-
Continuous tracing has been divided in two parts which have been photographed one on top of the other. Carotid blood pressure is indicated by the letters BP. The calibration of the blood pressure in mm Hg is shown in the left upper corner. Second trace (unlabeled) is the zero reference line for the blood pressure. RA refers to the third trace which displays the bipolar electrogram recorded from the right atrial appendage. On the His lead, the dots mark the His electrogram of control configuration and the squares are located below the His electrogram complexes which result from ventricular activation. The rest of the lettering is as in figure 2. The beginning of the left vagal stimulation is indicated by the arrow. Some of the complexes in the His lead have been retouched to show rapid deflections. Paper speed is 100 mm/sec; time lines at intervals of 1 sec.

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Continuous tracing has been divided into two parts which have been photographed one on top of the other. Symbols are the same as in figure 6. Left vagal stimulation started at the arrow during a run of extrasystoles. Letter F indicates fusion complexes: they are identified by the control configuration of the His electrogram, normal A-H interval and shortened H-S interval. Paper speed 100 mm/sec; time lines at intervals of 1 sec.

Continuous tracing has been divided in two parts which have been photographed one on top of the other. Symbols are the same as in figure 5. Left vagal stimulation started at the arrow during a run of extrasystoles. Letter F indicates fusion complexes: they are identified by the control configuration of the His electrogram, normal A-H interval and shortened H-S interval. Paper speed 100 mm/sec; time lines at intervals of 1 sec.

Upon cessation of vagal stimulation the atrioventricular block disappeared and the ventricles then followed the stimuli reaching them from the atria. The last part of the tracing shows restoration of sinus rhythm. In other instances in which idioventricular automaticity initially was depressed by ouabain administration, no ventricular escape beat appeared during vagal stimulation. In this case (fig. 8) there was no atrial fibrillation during stimulation of the vagus. However, as soon as the stimulation ended a nodal or possibly His bundle pacemaker initiated excitation of the ventricles and atrial fibrillation resulted.
Continuous tracing has been divided into two parts which have been photographed one on top of the other. Trace labeled EL was recorded through a unipolar intracavity lead placed in the right atrium. Both atrial and ventricular activity are recorded. Curved blood pressure is marked BP; 100 mm Hg indicates the calibration with respect to the line of zero pressure at the bottom of this same strip. Peripheral electrocardiogram lead is indicated by L₂. Insert magnifies the intracavity record and shows in greater detail the onset of atrial fibrillation. Vagal stimulation was initiated at the upright arrow and terminated at the downwards arrow. Tracing L₂ is distorted by stimulus artifact. Paper speed 10 mm/sec.

In this same animal, at a later stage of ouabain administration, when ventricular escape beats appeared once more during vagal stimulation, the first of such beats provoked atrial fibrillation. In one dog, stimulation of the left vagus produced atrioventricular block with persisting atrial activity; during the period of stimulation no ventricular escape beats appeared. Atrial fibrillation started only after the cessation of the vagal stimulation and after the first QRS not preceded by a P wave. In four of the experimental animals atrial fibrillation followed a ventricular escape beat even during the control period.

While referring to the results obtained from the control dogs we mentioned that, at the end of vagal stimulation, the sinus rhythm showed a transient acceleration. This same
acceleration was observed in the experimental dogs and the per cent change was even larger, probably in relation to the ouabain-induced sinus slowing. Often the transient post-vagal acceleration was accompanied by irregularly appearing ventricular extrasystoles. Usually the extrasystoles subsided after a short period of time as the sinus rhythm slowed. These extrasystoles required the presence of the sinus rhythm to appear as demonstrated by their onset after the cessation of vagal stimulation. If vagal stimulation was started once more while the extrasystoles were present, the suppression of the sinus rhythm resulted in their abolition.

Discussion

The diphasic action of ouabain on the automaticity of the ventricular Purkinje fibers demonstrated in these studies has interesting implications. The mechanism by which cardiac glycosides modify idioventricular automaticity has not been elucidated. However, data bearing on the action of cardiac glycosides at a cellular level have been accumulating. It has been shown that digitalis glycosides inhibit active transport of sodium and potassium ions across the cell membrane.14-18 As a result, the intracellular concentration of K+ falls while that of Na+ increases. The frequently demonstrated interrelationship between changes in K+ concentration and likelihood of digitalis-induced arrhythmias emphasizes the importance of this ion rather than Na+. Also, it has been demonstrated19 that a decrease of [K+] in the perfusion fluid, in vitro, causes an increased automaticity of Purkinje fibers while an increase of the K+ concentration has the opposite effect. If the loss of fiber potassium is related to an increased automaticity of Purkinje fibers, it would not be unreasonable to suppose that the initial slowing of the idioventricular rhythm is due to initial stimulation of active transport by ouabain. In fact Nagen,20 Boyer and Pointdexter21 and more recently Tuttle et al.22 and Brown et al.23 found that, with "therapeutic" concentrations of digitalis compounds, the fiber potassium increased above control values while with "toxic" concentrations fiber potassium was lost. However, there is no agreement on the subject since Wedd24 and Sanyal and Saunders25 found that intracellular potassium content was unaltered with "therapeutic" and a loss occurred with "toxic" concentrations of digitalis while Blackman26 found a loss of potassium even with "therapeutic" doses. Whatever the role of potassium ions, the initial depression of idioventricular automaticity appears to be of considerable interest in relation to the known ability of cardiac glycosides to abolish extrasystoles in patients not previously treated with these drugs.

It could be argued that the slowing of the idioventricular rhythm is brought about through effects of vagal activity on the His bundle and its branches, a mechanism in part verified for the sinus node. Although such a
possibility cannot be ruled out with certainty, it should be pointed out that vagal innervation of the specialized conducting system of the ventricle is generally denied. In addition, it has been demonstrated in vitro that the automaticity of Purkinje fibers is unaffected by acetylcholine. Obviously, slowing could be provoked by an antiadrenergic action of ouabain such as that described by Méndez et al. for the sinus and atrioventricular nodes. Unfortunately, studies on the relationship between ouabain and catecholamines have yielded contradictory results.

The initial slowing of the idioventricular rhythm is followed by a progressive acceleration. This acceleration appears when no signs of toxicity are apparent in the electrocardiogram and can be demonstrated only by temporary suppression of the sinus rhythm. This result is in agreement with the findings of Rothberger and Winterberg obtained for acutely denervated dog hearts. Increased automaticity in the absence of apparent signs of toxicity agrees with the in vitro demonstration that, on administration of ouabain, the action potential and automaticity of Purkinje fibers change markedly at a time when the action potential of ventricular muscle exhibits only a moderate degree of shortening.

In the in vitro study referred to above not all preparations of Purkinje fibers developed a fast spontaneous rhythm when exposed to ouabain. Some, after developing an enhanced diastolic depolarization, showed a rapid decline of the resting potential and became irreversible to electrical stimulation without developing a spontaneous activity. In the present investigation it was found that, in a few animals, depression of ventricular automaticity was not followed by an increase. If, at the same time, ouabain provoked atrioventricular block, ventricular arrest followed. This failure of ventricular pacemakers was attributed tentatively by Rothberger and Winterberg to the suppression of tonic discharge of the sympathetic nerves to the ventricles due to the section of these nerves. This explanation appears doubtful since in our experiments the sympathetic innervation of the heart was intact. It rather appears that, as a manifestation of ouabain toxicity, in some cases Purkinje fibers may exhibit a decrease in resting potential and loss of automaticity.

Cardiac glycosides enhance automaticity of more than one pacemaker site as is shown by the new ventricular rhythms which appear during vagal stimulation. The sudden shift in polarity of the electrocardiographic complexes and the associated change in rate (fig. 1C) supply evidence for multiple pacemaker sites. As the rates of discharge of the ventricular foci increase, the fastest becomes dominant. Apparently such a focus discharges rhythmically and continuously. As long as the sinus rhythm is faster, the sinus pacemaker will activate the ventricles. However, evidence of the continuous pacemaker activity of the ventricular focus is the following: on inhibition of the sinus rhythm by vagal stimulation a regularly firing ventricle pacemaker is immediately apparent. As the rate of the idioventricular pacemaker increases, it exceeds the sinus rate and drives the ventricles. Vagal stimulation at this time suppresses only the atrial activity.

The increase in duration and amplitude of the ventricular complexes noted with the progression of intoxication probably is the result of a disturbance in intraventricular conduction. The tachycardia itself is, of course, a contributing factor; however, it has been shown that cardiac glycosides depress conduction in the specialized conducting system of the ventricle before conduction in the muscle fiber is affected.

The uniformity of the ventricular tachycardia does not signify that only one focus is active but merely that the faster one uniformly drives the ventricles. That other latent pacemakers exist becomes apparent when, as a consequence of the progressive intoxication, the dominant pacemaker drops out for short periods of time. During these pauses the ventricles are activated from other foci. The interruptions in the fundamental rhythm represent a more severe degree of ouabain.

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intoxication than the uniform tachycardia. The mechanism of such a phasic discharge from the ventricular pacemaker is uncertain but an analysis of the behavior of Purkinje fibers exposed to ouabain in vitro is interesting in this respect. It has been shown that Purkinje fibers which are markedly poisoned by ouabain and which exhibit a rapid spontaneous rhythm periodically show a rapid and progressive decline in resting potential. The fibers then become unresponsive to electrical stimulation and spontaneous activity ceases. During the resulting pause the membrane potential progressively increases until the fiber once more becomes responsive to electrical stimuli or spontaneously active. This behavior was thought to be the result of poisoning of the active transport mechanism by ouabain. During the period of electrical quiescence, the impaired transport mechanism might restore to some extent the normal concentration gradients across the cell membrane; as a result, the resting potential would increase and excitability and automaticity would be restored.

The present studies have shown that those arrhythmias requiring initiating beats to appear are clearly separated from the arrhythmias due to enhanced automaticity of the specialized conducting system. The former group of disturbances of the rhythm is characterized by the fact that, whatever their mechanism of production, no intrinsically automatic centers are necessarily involved. The distinction between these two types of arrhythmia has been stressed by Scherf and Schott. They believe that the mechanism for production of coupled beats cannot be thought of as a re-entry mechanism; rather, the extra beat originates in a "center" in which cells, under certain conditions, depolarize twice for each sinus beat. The second depolarization is the cause of the extrasystoles with a constant coupling. However, the cells in the "center" do not develop automatic properties of their own. Goldenberg and Rothberger, experimenting with dogs given glycosides and breathing CO₂ in high concentration, showed that, during vagal stimulation producing cardiac arrest, coupled beats also are suppressed. The present investigation has shown that it is possible to elicit extrasystoles with constant coupling by administration of ouabain by the intravenous route without the administration of excess CO₂. The relationship between this type of extrasystole and the initiating beat indicates clearly that no intrinsically automatic center need be involved. However, the coupled extrasystoles are dependent not only on the presence of an initiating beat but also on the heart rate. The suppression of coupled extrasystoles when the sinus rhythm merely is slowed indicates that the sinus rate is related in a crucial manner to production of coupled extra beats. The rate of the initiating beat will determine whether the extrasystoles will be present or not and, if they are present, how often they will appear in relation to the initiating beat.

It is indeed interesting, again stressing the importance of the rate of the initiating beat, that driving the heart at a rate faster than the sinus rate multiplies the number of extrasystoles that follow an atrial beat. The spontaneous sinus acceleration which followed vagal stimulation often was accompanied by extrasystoles and these usually disappeared when the sinus rhythm slowed to the pre-vagal stimulation rate. The extrasystoles that appeared after vagal stimulation usually did not have constant coupling; still they required an initiating beat in order to appear. Such a finding implies a few consequences. First of all, the distinction between extrasystoles with constant coupling and those with variable coupling loses much of its meaning since both are shown to depend on the same conditions; namely, an initiating beat at a certain rate. Certainly, extrasystoles with variable coupling may be the result of enhanced idioventricular automaticity. However, the fact that some of the extrasystoles recorded at the end of vagal stimulation do not result from increased automaticity shows that a single mechanism can produce extrasystoles with and without constant coupling. This point of view is supported by the fact that extrasystoles with constant coupling may
become irregular in their appearance. Another and perhaps more important consequence is that a self-sustaining tachycardia may exist without any increase in automaticity of any part of the heart. Figure 4 is particularly instructive in this respect. It shows that, with progression of ouabain intoxication, sinus beats are followed not by one but by several extrasystoles.

These extrasystoles occurring in runs are indistinguishable from the previous bigeminal beat as far as shape of the complexes is concerned. The only difference is their occurrence at a rate faster than that of the sinus. It could be suggested here that a parasystolic focus is responsible for these extrasystolic beats. However, such an interpretation is ruled out by findings such as those shown in figure 5. None of the extrasystoles present prior to vagal stimulation was present during stimulation although they reappeared when the sinus rhythm resumed. If the extrasystoles were of parasystolic origin, since by definition a parasystolic focus is independent of the sinus beat, they would have persisted during vagal stimulation. It could be proposed that stimulation of the vagus depressed activity of the site of origin of the extrasystoles. Such a possibility is, however, dispelled by the results of vagal stimulation initiated during a run of extrasystoles (fig. 6). Clearly, vagal stimulation had no effect on the existing run of extras although inhibition of the sinus beat prevented reappearance of the extras after the run had ceased spontaneously. Therefore, it can be concluded that the extrasystoles occurring in runs are not the result of a parasystolic focus, are unaffected by vagal stimulation, and that the whole run may be started by one single sinus beat. The fact that the extrasystoles appear in the absence of enhanced automaticity or even when automaticity is depressed suggests that they are self-sustaining. In other words, the present investigation has shown that each extrasystole may initiate the following extra just as a sinus beat initiates the first extrasystole of the run. However, the extrasystolic runs have a tendency to subside spontaneously and a sinus beat is required to start them anew. The mechanism by which the extrasystoles are triggered by an initiating beat is still a matter of speculation and an adequate explanation cannot be formulated on the basis of available evidence.

Initiation of atrial fibrillation by the first ventricular escape beat during vagal stimulation is an interesting phenomenon shown in the present studies. The fact that it occurred in control dogs as well as after ouabain administration demonstrates that the factors involved were operating in the absence of toxicity. However, the administration of ouabain caused the atrial fibrillation to occur during vagal stimulation in dogs which had not shown this arrhythmia during the control period. The factors thought to play a role in causing atrial fibrillation include shortening of the action potential and a slowing of conduction. Vagal stimulation has been shown to decrease markedly the duration of the action potential of atrial fibers, although the conduction velocity in the atria is slightly increased. In addition, vagal stimulation as well as digitalis administration are known to transform auricular flutter into fibrillation. As shown by the work of Wedd et al., both a slowing of conduction and a shortening of the action potential of atrial tissue occur as digitalis toxicity develops. Therefore, the action of ouabain contributes to the establishment of conditions favoring the process of fibrillation and would account for the more frequent onset of fibrillation as compared with the control period. It is interesting that atrial fibrillation required an escape beat to be initiated but, surprisingly, the initiating escape beat had to be ventricular in origin. Atrial beats were ineffective in this respect. The explanation for such a phenomenon is not obvious. However, certain hypotheses can be evaluated by considering the factors thought to be of importance in the genesis of atrial fibrillation and determining how they might be affected by the atrial and ventricular escape beats. The role played by the shortening of the action potential of atrial fibers does not change whether the atria are activated.
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from the sinus node or from the ventricles since the shortening of the action potential is not related to the direction of activation but to prevailing conditions at the cell membrane. However, if the process of activation of the atria from the sinus node utilizes specialized paths, it might be completed in a shorter time than when the atria are activated from the ventricles. Electrophysiological evidence has been provided that specialized paths exist in the atria and these paths would permit a coordinated activation of the atrial muscle fibers.32 If activation of the atria from the ventricles spreads in an inhomogeneous manner, the time required for complete activation would be prolonged. Such a condition might permit reactivation of tissue that has already repolarized and lead to a self-sustaining arrhythmia.

Summary

The results of this study show that ouabain administration quite often causes idioventricular automaticity to undergo an initial depression and a subsequent enhancement. When the electrocardiogram shows normal sinus rhythm these changes in ventricular automaticity can be unmasked by vagal stimulation which causes either sinus arrest or atrioventricular block. On occasion, the depression of idioventricular automaticity is permanent; if ouabain produces complete atrioventricular block at this time, ventricular arrest ensues. When, on the contrary, the automaticity of Purkinje fibers is progressively enhanced, an extra beat appears during slow intravenous administration of ouabain and that they disappear not only on suppression but also on slowing of the sinus rhythm. Furthermore, it was shown that bigeminal rhythm may be transformed into extrasystoles occurring after every second sinus beat by means of vagal stimulation which slows the sinus rate. If, however, the heart was driven at faster rate, several extrasystoles followed one atrial beat. At a more advanced stage of ouabain intoxication these extrasystoles lose their fixed relationship with the sinus beat and runs of self-sustaining tachycardia appear. Such runs of ventricular tachycardia are unaffected by vagal stimulation but have a tendency to subside, spontaneously, and start anew after another initiating sinus beat. If vagal stimulation inhibits the initiating beat, the run of tachycardia also is suppressed. At an advanced stage of intoxication, however, when polymorphic ventricular complexes are present, vagal stimulation no longer produces any apparent effects.

Finally, this investigation has shown that, during vagal stimulation which produces sinus arrest or A-V block, atrial fibrillation can be initiated by retrograde transmission of ventricular escape beats even though atrial escape beats are ineffective in eliciting the same phenomenon.

References


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