Abnormal Cardiac Rhythms Caused by Acetylcholine

By David Scherf, M.D., and Forris B. Chick, M.D.

The effect of topical administration of acetylcholine on the auricular and ventricular surface of the dog's heart was studied. The experiments show the appearance of variform arrhythmias, particularly auricular fibrillation. The tendency for the development of these arrhythmias is diminished, but not abolished by atropinization. The experiments confirm previous results of the authors according to which auricular flutter is due to a rapid stimulus formation in a center. They help explain the occasional appearance of extrasystoles and paroxysmal tachycardias during vagus stimulation in experimental and clinical observations.

In addition to the peripherally stimulating action of acetylcholine on structures with cholinergic nerve supply, which is abolished by atropine and known as the muscarinic effect of acetylcholine, Dale, in 1914, demonstrated another action which was similar to that of nicotine. This "nicotinic effect" consists of an intense stimulation of autonomic ganglions and skeletal muscle fibers via the end plates. In recent years there has been increasing evidence that acetylcholine and related compounds also have a stimulating effect on the heart muscle, in distinction to the muscarinic effect which results in cardiac depression.7, 8, 12, 23

Most of these investigations are concerned with a study of acetylcholine on the contractility of cardiac muscle; studies on the influence of acetylcholine on the arrhythmias are rare. In dog experiments, ventricular and auricular extrasystoles were observed after intravenous injection of acetylcholine.6, 16, 19 When acetylcholine was applied to the isolated mammalian auricle, extra contractions appeared.12 Auricular fibrillation following intravenous administration of acetylcholine or Mecholyl was also seen in dogs.6, 9, 16 Auricular fibrillation appeared in man after injection of acetylcholine into the carotid artery.2

In studies undertaken to investigate the mechanism of auricular fibrillation we applied acetylcholine topically on the sinus node.23

These experiments led to observations which demonstrated clearly that acetylcholine has a stimulating effect on the heart, in situ.

Method

Twenty-six dogs were used. They were anesthetized with Nembutal and artificial respiration was instituted by tracheal catheter. The sternum was removed and the pericardium was opened. An electrocardiogram was obtained on lead II. Acetylcholine chloride (Roche) in a 5 per cent solution was applied to the head of the sinus node with the aid of a small square of filter paper according to the method of Langendorff. In some experiments 0.05 cc. of the acetylcholine solution was injected subepicardially in the area of the sinus node. In order to apply the drug to the area of the upper auriculoventricular node (coronary sinus node), the heart was lifted from its pericardial bed and the solution of acetylcholine injected into the coronary sinus node through the wall of the coronary sinus vein. It had been shown before that warming of this area led to the appearance of coronary sinus rhythm.21 The right vagus was exposed in the neck, and, if necessary, stimulated with the aid of a Cambridge Inductorium. Atropine was injected into the superior vena cava in the amount of 0.1 mg. per Kg. of body weight. This is, according to Lewis, adequate for paralysis of the vagus.

Results

Response of Auricles to Acetylcholine in Nonatropinized Animals. The results were uniform in all experiments. Application of acetylcholine by the filter paper method or by subepicardial injection into the head of the sinus node invariably led to the appearance of auricular fibrillation which lasted from a few minutes to 40 minutes. At first there was a brief cardiac standstill and then, suddenly, auricular flutter

From the Department of Medicine, New York Medical College, New York, N. Y.

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appeared which quickly changed to fibrillation, or fibrillation occurred from the start. This standstill was most pronounced when acetylcholine was given by injection and is partly due to reflex action. Single extrasystoles occasionally appeared.

In order to study the mode of onset of the auricular arrhythmia, undisturbed by the activity of the ventricle, we employed faradic stimulation to the right vagus which inhibited the ventricles. The faradic stimulation was applied during the application of filter paper soaked with acetylcholine.

Figures 1A and B show at first cardiac inhibition during stimulation of the vagus and application of acetylcholine (the string moved because of the manipulation necessary for the application of the filter paper). Immediately after the application of the filter paper, abnormal stimuli are formed in the auricle. In figure 1A they appear at first in groups as rudimentary flutter and are then followed by more prolonged periods of flutter and fibrillation. In figure 1B rapid flutter appears immediately with a rate of over 600; this increased to about 1000 and was followed by fibrillation. The rapidity with which fibrillation appeared in these experiments was striking. In some experiments, after the appearance of auricular fibrillation, cooling of the area on which acetylcholine had been applied abolished the arrhythmia. In most experiments however, particularly when fibrillation had persisted for more than 20 seconds it was necessary to cool the whole area of the sinus and A-V node in order to reestablish sinus rhythm. Prolonged attacks of flutter did not occur; fibrillation was the rule.

Injection of acetylcholine into the area of the upper auriculoventricular or the coronary sinus node, was performed in eight experiments. The lifting of the heart caused, as figure 1C shows, some changes in the electrocardiogram which are readily understandable. Here also the stimulation of the right vagus nerve led to cardiac inhibition. A few seconds after the injection of acetylcholine, flutter appeared with a rate of approximately 1000. This was followed by fibrillation. The flutter waves, however, in this instance showed the deep inverted and peaked form which one expects in lead II when stimulus formation takes place in the area of the coronary sinus node. The form of the QRS complexes and T waves shows that the heart was back in its normal position when the flutter started and that the change in the form of the P waves is not due to the change in position of the heart.

Response of the Ventricles to Acetylcholine in the Nonatropinized Animal. Focal application of acetylcholine to the ventricles led only to the appearance of short, but regular, runs of ventricular tachycardia with a slightly higher rate than that of the existing sinus rhythm. These lasted a few seconds. The high ventricular rate of the sinus rhythm was certainly, at least in part, responsible for the short duration of the ventricular ectopic rhythm. Ventricular fibrillation occasionally followed any mechanical stimulus such as striking the ventricles with a blunt instrument or penetration with a fine needle. Ventricular fibrillation appeared readily following mechanical stimulation of the ventricles when three or more applications of acetylcholine had been made previously to the sinus node.

Response of the Auricles to Acetylcholine in the Atropinized Animal. After complete atropinization of the dog, in only 1 of 22 experiments were we able to produce auricular fibrillation merely by cautious application of acetylcholine on filter paper to the sinus node area. Temporary tachycardias with a rate of about 270 appeared. This tachycardia ceased after a few minutes. For about 10 minutes after the application of acetylcholine, the auricles were extremely irritable and readily went into fibrillation or flutter from the slightest mechanical stimulus. Merely touching the auricles, even at a distance from the site where acetylcholine had been applied, brought about auricular fibrillation for a few minutes (fig. 2). Therefore, subepicardial injection of acetylcholine, which made mechanical manipulation unavoidable, often initiated auricular fibrillation. When atropine was administered during auricular fibrillation, the latter was invariably converted into flutter and sinus rhythm.

Response of the Ventricles to Acetylcholine in the Atropinized Animal. The inclination of the ventricles to fibrillate upon mechanical stimula-
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tion disappeared after atropinization. Strong mechanical stimuli, such as striking of the ventricle with a blunt instrument, caused, however, the appearance of ventricular tachycardia. This persisted for 10 to 40 seconds and gradually subsided. It appeared following stimulation at any point of either ventricle. Parasystolic rhythms were often seen.

In the experiment from which figure 3 was taken sinus rhythm was present. Striking the conus area of the right ventricle led to the appearance of ventricular tachycardia with a rate of 130. Figure 3 shows the end of this tachycardia which had lasted 32 seconds.

In five experiments twice as much atropine (0.2 mg. per Kg.) was injected after the intravenous administration of 0.04 Gm. of acetylcholine. Under these conditions mechanical stimuli applied to the auricles or ventricles did not cause abnormal rhythms in three experiments; they were much shorter in two.

**DISCUSSION**

The experiments described in this paper demonstrate an excitatory effect of acetylcholine on stimulus formation in the heart. The appearance of auricular fibrillation on application of acetyl-β-methylcholine to the dog's auricle in the area of the sinus node has been reported by Nahum and Hoff. These authors, in "some instances," could provoke auricular fibrillation by the application of the drug alone, but it always could be evoked by additional mechanical stimulation of the auricles. We found that the use of larger concentrations of acetylcholine produced auricular fibrillation regularly without the addition of other stimuli. While in the experiments of Nahum and Hoff atropine did not affect the arrhythmia once it had been produced, we could always convert auricular fibrillation into sinus rhythm by the intravenous injection of atropine. Finally, in the experiments of Nahum and Hoff, locally applied atropine prevented all effects of acetylcholine. In our experiments the intravenous injection of atropine definitely diminished the tendency to the development of auricular fibrillation, but did not abolish the appearance of auricular fibrillation and of heterotopic auricular and ventricular tachycardias on mechanical stimulation. The differences between our results and those by Nahum and Hoff may be partly due to the fact that acetyl-β-methylcholine has practically no nicotinic action.29

Of great interest is the appearance of fibrillation or occasionally flutter following mechanical stimulation. Because of the depolarizing effect of a strong mechanical stimulus leading to the appearance of injury currents, it is understandable that extrasystoles appear for a few minutes after striking the heart with a blunt instrument. In our experiments even the most gentle touching of the auricles after atropinization elicited fibrillation when the heart was under the effect of acetylcholine. Smith and Wilson28 found that, in the presence of Mecholyl and anoxia, stimulation of the dog's auricle with a feather precipitated auricular fibrillation, while in the absence of anoxia, strong mechanical stimuli were necessary to induce fibrillation. In our experiments, using acetylcholine, slight mechanical stimuli without anoxia had the same effect. Stretch and pressure lead to rapid stimulus formation in skeletal muscle fibers1 and in the dog's auricle in situ under the influence of aconitine.55

The experiments supply support for our contention that auricular flutter and fibrillation are due to rapid stimulus formation and not to a circus movement.18, 26, 25 It is difficult to believe that the short abortive attacks of flutter shown in figure 1, consisting of only a few beats, are caused by a circus movement, because a circus movement cannot start after a pause.

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**Fig. 1. A.** Application of acetylcholine to the sinus node during stimulation of the right vagus caused two attacks of rudimentary flutter followed by a short period of fibrillation which changed into flutter and sinus rhythm. B. Same procedure as in fig. 1A; very rapid flutter appears immediately on application of acetylcholine and fibrillation follows. C. Same procedure as in figures 1A and B; here the auricular flutter which precedes the fibrillation exhibits deeply inverted P waves following application to the A-V node.

**Fig. 2.** Gentle touching of the auricles results in fibrillation after the administration of acetylcholine.

**Fig. 3.** End of paroxysm of ventricular tachycardia which had appeared in an atropinized animal after striking the conus area of the right ventricle.
without the presence of a center producing stimuli. At least the first beat of each group must be due to an ectopic stimulus. It may be objected that this ectopic stimulus leads to a circus mechanism, but then the form of the following auricular waves should differ from the first one because the spread of the excitation over the auricles is necessarily different. The slight differences in form of the waves in figure 1 are fully explained by changes in the rate. Furthermore, if auricular flutter were due to a circus movement around the orifice of the great veins independent from the focus of stimulation, as Lewis postulated, the flutter waves, after application of acetylcholine to the auriculoventricular node, should be the same as after application to the sinus node; figure 1C shows, however, that the flutter waves always assume the form which one would expect if the stimulus originated at the specific site on which acetylcholine had been applied. One of us has shown earlier that faradization of the auricles leads to auricular flutter exhibiting flutter waves which strikingly resemble the P waves of the prevailing rhythm before faradization.

The experiments demonstrate that after injection of atropine, which prevents any effect of faradization of the vagus nerves on the heart, mechanical stimuli lead to the appearance of auricular fibrillation or ventricular abnormal rhythms, respectively. If larger amounts of atropine were given, mechanical stimulation of the heart was less effective or without results. It is known that large doses of atropine have a direct damaging action on the heart which is probably responsible for this observation.

While there seems to be general agreement that acetylcholine may, under certain circumstances, have a positive inotropic and chronotropic effect, the mechanism of this action still is not clear. Some reports speak in favor of a release of epinephrine-like substances in the heart under the influence of acetylcholine, but certain experimental data obtained by McDowell and Spadolini cannot be fully explained by this mechanism. Our observations do not supply an answer to this problem, but it is interesting to note that local application of epinephrine on the sinus node and ventricle in the concentration of 1:1000 and 1:10,000, following intravenous injection of 0.01 Gm. of acetylcholine in the atropinized dog, did not lead to heterotopic rhythms.

The results of these experiments are of interest to the clinician because they explain certain experiences which are often termed paradoxic. The appearance of ventricular extrasystoles during carotid sinus pressure is so common and so well known that quotation of references does not seem necessary. The appearance of ventricular and auricular tachycardias also has been observed on carotid pressure. Similar tachycardias have been observed in animals during vagal stimulation. Auricular fibrillation was seen to appear on deep breathing or swallowing. These and other paradoxic effects of vagus stimulation on stimulus formation and conduction are more readily understandable when the fact is known that acetylcholine may elicit heterotopic rhythms.

Conclusions

The effect of topical application of acetylcholine to the heart of dogs was studied.

Auricular flutter and fibrillation appeared immediately when a 5 per cent solution of acetylcholine was applied to the sinus node area.

When acetylcholine was injected into the region around the orifice of the coronary sinus vein the flutter waves were negative. This experience and the analysis of the arrhythmias observed at the beginning of the flutter, immediately after application of acetylcholine, are in agreement with the results of previous experiments of the authors according to which flutter and fibrillation were not considered to be the result of a circus movement.

Atropine invariably abolished an existing auricular fibrillation caused by application of acetylcholine.

After atropinization, acetylcholine rarely caused fibrillation; however, the slightest mechanical stimulus applied to the auricles, in form of stretch or pressure, elicited transient fibrillation before and after atropinization which abolished the effect of vagus stimulation. After injection of larger doses of atropine these effects of mechanical stimuli applied to the auricles or ventricles diminished or disappeared.

The ventricles responded in a similar way before and after atropinization but only short periods of tachycardia appeared. Fibrillation
was seen only on mechanical stimulation in the presence of acetylcholine and before atropinization.

Epinephrine applied locally in a concentration of 1:1000 did not cause arrhythmias in the atropinized heart.

The importance of these results for the understanding of the appearance of paroxysmal tachycardias and fibrillation on vagal stimulation in man is discussed.

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