Aconitine-Induced Auricular Arrhythmias and Their Relation to Circus-Movement Flutter

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Certain characteristics of aconitine-induced auricular arrhythmias in dogs and the responses of aconitine-induced flutter to various experimental procedures and to drugs are described. In certain experiments there was evidence that a secondary flutter mechanism had developed which, in some instances, resembled flutter of circus-movement origin. When aconitine-induced and circus-movement flutters were induced separately and simultaneously in auricles functionally divided by a crush, they responded to drugs in their characteristic manners. Aconitine-induced flutter slowed progressively and recovered gradually to flutter, whereas circus-movement flutter frequently reverted suddenly and permanently to sinus rhythm.

SCHERF and co-workers have reported certain of the phenomena occurring upon the local application of aconitine to the dog's auricle.1-4 These authors gave evidence that the arrhythmias arising from this procedure are maintained by the artificial source of impulse production and not because a circus movement arises. On the other hand, experimental auricular flutter of circus-movement origin has been well-defined by Rosenblueth and García Ramos.5 In spite of the distinct characteristics of these two types of experimental auricular flutter, the existence of the latter is denied.6-5 The present work was undertaken primarily to determine the effects of certain substances on both the aconitine-induced and circus-movement auricular flutters. During the investigation it was found that auricular arrhythmias of two different sources might exist either simultaneously or subsequently in the same auricle, and further, that two flutters of different origins could be induced simultaneously in the same auricle. This report thus deals mainly with the distinctions which can be made between experimental auricular flutters of different origins.

METHOD

The experiments were conducted in dogs, weighing between 15 and 23 Kg., anesthetized by the intraperitoneal injection of 0.7 cc. per kilogram of Dial with urethane solution (Ciba). Blood pressure was recorded from the carotid artery. Auricular electrograms were recorded, and the ventricular complex was taken from pericardial tissue near the ventricular apex. Injections of compounds under study were made into the external jugular vein. The reported results were obtained in dogs in which the blood pressure was at least 60 mm. Hg and rectal temperature was maintained at 37 C. by external heat.

Two methods for inducing auricular flutter were employed. The first was induced according to the method of Scherf in which 0.05 cc. of a 0.05 percent solution of aconite nitrate is injected subepicardially near the tip of the right auricle. Circus-movement flutter was induced according to the method of Rosenblueth and García Ramos in which flutter is initiated by brief, rapid electrical stimulation near a crushed area on the right auricle. The precise method used in the present study has been fully described.6, 11

Changes in electrical activity in the auricle were recorded from pairs of silver electrodes with small interelectrode distance (2 to 3 mm.) which were clipped lightly to the auricular muscle. All recordings were made by means of a four channel ink-writing oscillograph (Grass, model IIA), and were made continuously during all experiments. Differences in rate and wave form between impulses recorded near the aconitine site and those recorded at a distance during aconitine-induced flutter were noted in a number of experiments. In most experiments (except those described in part B, below), the differences were minor and disappeared upon changing the orientation of the distant electrodes. In some instances the relation between position of recording leads and direction of the impulse accounted for apparent irregularity, alternation or even regularly occurring missed beats, since these could be eliminated by changing position of the electrodes.

The effect of stimulation of the cardiac nerves was
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determined during both types of flutter. Maximal nerve stimulation (using a Grass 3C stimulator, square waves) was effected by using the lowest frequency of stimulation which slowed or accelerated the ventricle significantly and a voltage above which no further change could be produced. For the cut central end of the vagus this was stimuli of 0.2 or 0.5 millisecond duration at a frequency of 10 to 30 per second and a voltage of 10 to 20. The sympathetic chain was stimulated by placing the electrodes between the stellate and ganglion of T-2, after freeing the chains of all connections except the postganglionic fibers arising from the stellate ganglion, using a pulse duration of 0.01 millisecond, a frequency of 2 or 60 per second, and a voltage of between 20 and 40.

Observations

A. Characteristics of Aconitine-Induced Auricular Arrhythmias

The auricular changes brought about by the local application of aconitine were studied in 39 dogs. The innervation was intact in most instances. The auricular rate began to increase within 10 to 100 seconds (average of 26 ± 2.2 seconds) after injection of the aconitine in 33 of the experiments, and the total time interval until an auricular rate of 300 beats per minute or more was reached averaged 41 ± 4.2 seconds. In three experiments a rapid arrhythmia occurred immediately after injection of the aconitine, while in three other experiments no increase in auricular rate occurred for several minutes and a rate of 300 or more was not reached for nearly five minutes. The time necessary to reach a steady rate (variation less than 20 beats per minute) averaged 222 ± 21 seconds for all 39 dogs.

The character of onset of the aconitine arrhythmia was different in different dogs and bore no relation to whether a regular flutter or a fibrillation developed. In 17 experiments the most marked increase in auricular rate occurred within one cycle of the previous sinus rate. In 14 of these experiments, the sudden increase appeared 27 ± 4.3 seconds after injection of the aconitine and averaged 148 ± 12.8 beats per minute; in one experiment the sudden increase amounted to 430 beats per minute, in another experiment to 30 beats per minute, whereas in a third dog the rate jumped rapidly and suddenly several times and was not counted. In the remaining 22 experiments, the onset was less sudden, and the arrhythmias developed to their maximal rate over a period of 30 to 90 seconds. Full development of these 22 arrhythmias occurred sometimes as a regular steady increase, sometimes irregularly (ectopic beats, coupling, and runs of fast beating), and sometimes as alternating fast and slow rhythms. The steady rate attained in most experiments was less than the rate developed within the first several minutes.

The criteria for flutter, as the term is used in this paper, are continuing regularity of rapid beating with regular wave form and a variation from the average rate developed of less than 20 beats per minute over a period of 10 to 30 minutes. Regular flutter occurred in 29 of the 39 dogs, and had an average rate of 430 ± 16 beats per minute. The lowest steady flutter rate recorded was 300 beats per minute and the highest was 600 beats per minute.

Auricular fibrillation, defined in terms of high rate and erratic wave form, occurred in 10 of the dogs. Auricular rates in these experiments ranged between 660 and 1080 near the aconitine site. In four experiments a fourth or more of the impulses recorded near the aconitine site could not be obtained at distant electrodes. In eight experiments the fibrillation was persistent; in two it changed to a flutter after a few minutes. The instances of persistent fibrillation could be converted into flutter by the injection of one or another of the substances under study.

Duration of the arrhythmia induced by the standard injection of aconitine was not studied specifically. The regular auricular flutter which occurred in the 29 dogs usually persisted longer than two hours in spite of intermittent slowing produced by the injection of drugs.

The results reported below were obtained in well-stabilized flutter.

Effect of Experimental Procedures. Aconitine-induced flutter responded to changes in the innervation (fig. 1) in the same direction as circus-movement flutter.19 Section of one vagus nerve increased slightly both the flutter and the ventricular rate, and section of the other vagus caused an additional increase. Complete vagotomy occasionally had no effect, while in
some experiments both auricular and ventricular rates were increased by amounts up to 20 per cent. Stimulation of the vagus caused a marked increase when the flutter rate was high (450 or more) but only about a 5 per cent increase when the flutter rate was low. Irregular arrhythmias frequently changed to regular flutter during vagal stimulation. This change to a regular beating was noted by Lewis and co-workers who attributed the change to a shortening of refractory period.\textsuperscript{12, 15}  Stimulation of the sympathetic chain also caused an increased flutter rate of approximately 5 per cent.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Effects of changes in the innervation of the heart on aconitine-induced auricular flutter. In this and other figures A and V indicate auricular and ventricular rates.}
\end{figure}

In confirmation of Scherf,\textsuperscript{1} cooling the site of aconitine injection often decreased the auricular rate (fig. 2). The degree of slowing was dependent upon the intensity of the cold. Stretching the auricle often increased the rate of flutter. Further, it was usually found that, as noted by Scherf,\textsuperscript{1} the arrhythmia disappeared upon isolation of the aconitine-containing portion of the auricle by clamping and reappeared upon removal of the clamp (fig. 4). Often a period of one to two minutes was required before the clamping procedure completely blocked the influence of impulses from the aconitine site on the rest of the auricle. At the same time the rate in the isolated tip often decreased. These changes suggest that interference with circulation plays a part in impulse propagation under these circumstances.

\textit{Effect of Drugs.} The effects of procaine and the related substances, diethylaminoethanol (DEAE) and $\beta$-diethylaminoethyl-2,4-dichlorobenzoate (DCB) and also of quinidine were evaluated in aconitine-induced flutter. Their effects in auricular flutter of circus-movement origin have been reported previously.\textsuperscript{10, 11}  A similar course of events followed the intravenous injection of any one of these compounds and is illustrated in figure 2. The auricular rate began to slow within a minute, and maximal slowing occurred in two to five minutes. The degree and duration of slowing increased as the dose was increased. Doses of 4 mg. per kilogram of all substances except DEAE generally caused slowing to or near to the sinus rate. Doses of 32 mg. per kilogram of DEAE produced similar effects.

In about 50 per cent of the experiments the sinus node became the pacemaker when the rate of impulse formation at the aconitine site was depressed below that of the sinus node. This change of pacemaker was indicated in the electrograms as a reversal of the path of the conduction wave (fig. 3). The positions of the recording electrodes were in a line between the site of aconitine injection and the region of the sinus node. When acute drug effects had worn off, the path of the wave again reversed in di-
rection. Ectopic beats became more frequent until the aconitine site regained control of beating. Recovery to approximately the original flutter rate usually occurred within 15 to 25 minutes. The recovery was gradual and was either regular or irregular regardless of whether or not a change to sinus rhythm had occurred.

These phenomena are in sharp contrast to the sudden and permanent reversion from a high rate of flutter which occurs in circus-movement flutter.10

During recovery from maximal slowing, the response of the aconitine site to application of cold could not be elicited; it remained somewhat depressed after recovery to original flutter rate (fig. 2).

![Auricular electrograms (A1 and A2) illustrating change in direction of conduction of the auricular wave from aconitine site to sinus node following marked slowing of aconitine-induced flutter caused by injection of a drug (at arrow).](image)

The ventricular rate in innervated hearts was decreased by diethylaminoethanol (DEAE) and its dichlorobenzoic acid ester (DCB), but it was frequently increased by procaine and by quinidine in doses which did not cause a rapid decrease in auricular rate.

B. Indications that a Secondary Mechanism May Arise Spontaneously

The responses of aconitine-induced flutter to cooling, stretching, clamping and vagal stimulation were employed by Scherf1.2,4 as evidence that a single focus of rapid impulse formation and not circus-movement was the mechanism responsible for this arrhythmia. As noted in the previous section, confirmatory results were obtained in many experiments. Further, it was demonstrated that the response of aconitine-induced flutter to drugs differs from that of circus-movement flutter in that sudden (within one beat) and permanent reversions do not occur. In certain experiments, however, atypical responses to these procedures were obtained.

Unusual behavior of the aconitine-induced flutter appeared in 10 of the 29 dogs in which a regular flutter was elicited. In 5 of the 10 animals, the rapid injection of DCB or procaine resulted in a sudden (within one beat) reversion to sinus rate from a high rate of flutter (350 to 560 beats per minute)—a characteristic of experimental circus-movement flutter. Although in these five animals the reversions were permanent, occasional ectopic beats sometimes occurred for a short period after reversion, sug-

![Auricular electrograms (A1 and A2) illustrating change in direction of conduction of the auricular wave from aconitine site to sinus node following marked slowing of aconitine-induced flutter caused by injection of a drug (at arrow).](image)

[Fig. 3. Auricular electrograms (A1 and A2) illustrating change in direction of conduction of the auricular wave from aconitine site to sinus node following marked slowing of aconitine-induced flutter caused by injection of a drug (at arrow).]
during a clamping period in one experiment resulted in a prompt and permanent reversion to sinus rate.

The five experiments cited above show that in some instances of aconitine-induced flutter (a) reversions characteristic of circus-movement flutter occur, and (b) isolation of the aconitine-containing auricular tip does not affect flutter in the body of the auricle but eliminates it from the tip. These observations indicate that a flutter mechanism secondary to the original aconitine had developed and was responsible for maintenance of the arrhythmia. The secondary mechanism could be either a second ectopic focus or circus-movement flutter. The sudden and permanent reversions which occurred imply an impulse circuit. In these five experiments the aconitine was no longer the predominant factor maintaining the arrhythmia; it was depressed in its activity to such an extent that it was completely displaced by a secondary flutter mechanism.

A somewhat different situation was found to exist in the other five experiments in which unusual behavior of the aconitine-induced flutter was noted. In three of the experiments, cooling the site of the aconitine injection resulted in an increased rate (rather than a decrease) and stretching the auricle resulted in a decreased rate of flutter (rather than an increase) (fig. 5). The responses were not confined to the aconitine area but were recorded at distant areas as well. These phenomena could result from an unusual response of the auricular tissue at the aconitine site in these animals. The phenomena could also be explained by assuming interaction between impulses spreading from the aconitine site and those from a secondary mechanism, permitted by changes in refractoriness.

More striking evidence that a secondary mechanism may be simultaneously active was encountered in the other two experiments and a third obtained more recently. Auricular elec-
ograms in these experiments showed that the aconitine-induced flutter did not have the same rate in different parts of the auricle. In the experiment graphed in figure 6, a very high (1000) and fairly regular beating was recorded near the site of the aconitine injection (A1). The second lead, about 3 cm. further away, recorded a slower (600) and regular beat (A2). This difference could mean that many of the beats from A1 did not reach A2. In order to test this, A1 was isolated from A2 by clamping. As a result, activity at A1 fell within one minute to about 300 beats per minute and to 120 in the follow-

![Diagram](attachment:image.png)

**Fig. 7.** Development of two arrhythmias in the same auricle. Record A was obtained after injection of aconitine at point A (in diagram) and before dividing the auricle by an encircling crush. Record B was taken after crushing and shows the aconitine flutter recorded at R1 and the return to sinus rate at R2. Record C was taken after brief stimulation at S had resulted in an arrhythmia in the atrial portion removed from the aconitine.

...ing two minutes. The auricular rate at A2 remained at 640 to 660 for one and one-half minutes, then suddenly fell, but was still fluttering at 420 beats per minute. When the clamp was removed, activity at A1 returned in about one minute to its original high level. A2 followed this return until it also reached its original level. The maintenance of flutter rates at A2 during clamping indicates the independent existence of a secondary mechanism. The abrupt change in its rate may be attributed to either (a) a fortuitous change in the mechanism of the secondary arrhythmia, or (b) exclusion of impulses from the aconitine source which had indicated that the secondary mechanism can exist independently and simultaneously with the aconitine flutter.

C. **Circus-movement Flutter and Aconitine Flutter Induced Separately and Simultaneously in the Same Auricle**

These experiments were conducted as indicated in the diagram of figure 7. R1 and R2 are pairs of recording electrodes; S is a pair of stimulating electrodes. Aconitine was injected at site A, and the resulting flutter, recorded at both R1 and R2, is shown in the first record (A). A few minutes later the auricle was di-
vided by an encircling crush made by a large hemostat. Complete isolation of the auricular from the atrial portion was indicated in the electrograms taken from R2 which changed from flutter to a sinus rate (record B, figure 7). Electrical stimulation was then applied at point S to induce a circus-movement arrhythmia in the remaining auricle, atrium or around the great veins. Record C shows the arrhythmia which was initiated by stimulation. It was irregular and rapid, with a rate of 540 beats per minute. At the same time, the aconitine-induced flutter was regular and had a rate of 400 beats per minute.

In these experiments, the rate of the aconitine-induced arrhythmia averaged 410 ± 26 beats per minute in 11 hearts, and the rate of the circus-movement flutter averaged 455 ± 32 in 10 experiments. In one heart the rate of the circus-movement arrhythmia was 1080 beats per minute. Eight of the hearts studied had intact innervation, and three hearts were studied also after decentralization by section of the vagi and upper thoracic sympathetic roots. Brown and Acheson found circus-movement flutter to have an average rate of 472 ± 8.2 in 36 hearts with intact innervation.

The simultaneously existing flutters responded to cooling of the aconitine site or the ventral and lateral walls of the atrium in the same way as when they existed separately in an auricle; the aconitine flutter decelerated while the circus-movement flutter was unaffected. The responses to nerve section and stimulation, however, were variable probably because of damage to nerve pathways by the encircling crush. In general, section of one vagus nerve or stimulation of the sympathetic chain caused no change in rate. For a brief period after section of both vagi episodes of fibrillation of the aconitine-induced flutter occurred, but the circus-movement flutter did not change in rate. Vagal stimulation usually caused an increased rate of the aconitine flutter, but either increased, decreased, or did not change the rate of the circus-movement flutter.

Effects of the drugs described in part A were similar to those obtained when each flutter ex...
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Isted singly in an auricle. A typical record is shown in figure 8. In this experiment the effects of quinidine on both the circus-movement flutter and on the ventricular rate in the innervated heart are the same as those previously described.11 The atrial flutter slowed markedly and suddenly reverted to sinus rate three and one-half minutes after the injection of quinidine. The aconitine-containing portion slowed rapidly and fairly regularly until the rate was below that of the sinus rate. The auricular tip cannot be governed by the sinus node because it is isolated from it. Activity in the aconitine-containing portion eventually returned to the original flutter rate even in experiments where activity had been temporarily reduced to zero by drug injection, whereas the atrial portion remained at sinus rate until subsequent stimulation was employed to reinduce flutter.

Discussion

In the present series of experiments, the arrhythmias induced by local application of aconitine were of higher rate and longer duration, and showed a higher incidence of fibrillation than those of a comparable series reported by Scherf using the same injection site near the auricular tip.1 The discrepancies may be ascribed to the fact that Scherf used a lead II electrocardiogram, whereas in the present experiments two or more direct auricular leads were employed. It has been noted under Method that certain apparent conduction failures were artefacts due to the relation between position of recording leads and the path of the impulses. Further, not all waves from a rapidly firing focus may be conducted as far as distant electrodes. At rapid auricular rates it is unlikely that all the waves produced at the aconitine site are evident in lead II.

The drugs studied slow the rate of flutter induced by aconitine. They also increase the effective refractory period of the auricular wall, but to a degree which still permits the auricle to conduct at a relatively rapid rate of beating.11,14 When the aconitine-induced flutter is markedly slowed, the sinus node becomes the pacemaker because its rate of beating is more rapid. From these facts it seems unlikely that effective refractory period is the principal factor responsible for the slowing of the rate of flutter. The drugs, therefore, may be presumed to decrease the rate of impulse formation at the aconitine site. In addition, in the presence of rapid responses of auricular tissue, acetylcholine can increase impulse production.15 The acceleration of aconitine-induced flutter by vagal stimulation may depend upon this effect. It should be noted that the aconitine site is much more sensitive to all of these effects than is the sinus node.14

In aconitine-induced flutter, changes of conduction velocity would not influence the number of impulses recorded from a given site at a distance from the focus of impulse formation. In contrast, slowing or acceleration of the rate of circus-movement flutter depends upon slowing or acceleration of the conduction velocity of the impulse. During aconitine-induced flutter, an ectopic focus is present as long as the aconitine effect lasts; recovery of rate of flutter following the depression of impulse formation produced by drugs represents simply the disappearance of the drug effect. In contrast, reversion occurs in experimental circus-movement flutter when the circus wave is abolished; there is no ectopic focus. A drug designed to revert circus-movement flutter need act only long enough to produce the appropriate changes of conduction velocity and effective refractory period.

Scherf and co-workers16 have reported that the auricular fibrillation induced by electrical stimulation or by the local application of acetylcholine at the sinus node did not slow on cooling this area, but usually slowed when both the sinus and A-V areas were cooled simultaneously. They suggested that in these instances the fibrillation was due to multiple foci of rapid impulse formation, one or more of these foci being in the area of the A-V node. They noted that multiple foci rarely occurred following induction of fibrillation with aconitine. In contrast to this, the experiments described in part B provide evidence that a secondary mechanism can develop in aconitine flutter and may contribute to or be responsible for maintenance of the arrhythmia. When the nature of the flutter is unknown, as in these instances, it may be deduced from its responses to procedures which have characteristic effects in either aconitine-induced or circus-movement flutter. The
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