An Experimental Study on the Mechanism of Atrial Flutter and Fibrillation by Means of the Microelectrode Method

KAZUO ISHIKAWA†

Aconitine was administered to the isolated right atrium of the rabbit, and atrial flutter and fibrillation were induced. The action potentials of unipolar lead electrogram regularly appeared in atrial flutter, and their configuration was different from that in sinus rhythm. In the initial stage of atrial fibrillation, both appearances of the action potentials of unipolar lead and intracellular lead electrograms were regular and synchronous in some degree. In atrial flutter and fibrillation, the membrane resting and action potentials decreased to various degree. The rising velocity of upstroke of action potential decreased, and the duration of action potential shortened. The steepness of diastolic slow depolarization increased. It may be concluded that atrial flutter results from rapid impulse formation in a single focus. Atrial fibrillation would be caused by rapid impulse formation in multiple ectopic foci.

THERE ARE various theories concerning the mechanism which produce atrial flutter and fibrillation — namely, the theory of circus movement¹⁻⁴, the theory of multiple re-entries⁵⁻⁸, and the theory of focal or multifocal impulse formation⁹⁻¹². These arrhythmias have generally been supposed to be essentially the same in their mechanisms and still remain as subjects of continuous controversy¹³.

Most of the studies on atrial flutter and fibrillation have hitherto been performed by means of electrocardiogram. Since the electrocardiogram is a manifestation of the summarized electrical events of the entire heart muscles, the ordinary electrocardiogram, even the direct lead electrocardiogram, does not make clear the electrical event of individual muscle cell of the spot under the exploration.

Since the advent of the microelectrode method made it possible to clarify the electrical event of individual cell, the present experiments were performed through the combination use of the microelectrode method and the ordi-

nary unipolar lead electrogram to have a better understanding for the mechanism of atrial flutter and fibrillation. In the present paper, these arrhythmias were artificially induced by the administration of aconitine onto the isolated rabbit atrium.

METHOD

Thirty-nine adult rabbits weighing 2.0–2.5 Kg were used in the present experiments. Each rabbit was anesthetized with methylhexabital sodium of 40–70 mg per Kg of body weight, administered intravenously. The chest was then opened and the heart was removed. The heart was immediately moved out into a thermostatic bath filled with oxygenated Tyrode's solution kept at a constant temperature of 32–34°C. Both right and left ventricles and the left atrium were cut away from the specimen (right atrium). The specimen was then opened by making a cut through the anterior free wall along the atrial septum up to the vena cava superior. The specimen was constantly irrigated at a rate of 20–30 cc/min with Tyrode's solution. The chemical composition of the Tyrode's solution was as follows: NaCl, 137 m mol; NaHCO₃, 4.8 m mol; dextrose,

(Received for Publication, April 19, 1967)

† The First Department of Internal Medicine, School of Medicine (Director: Prof. S. Hibino), and the Research Institute of Environmental Medicine (Director: Prof. H. Toyoshima), Nagoya University, Nagoya

Fig. 1. Schematic representation of the experimental apparatus.

5.5 m mol; CaCl_2 , 1.9 m mol; KCl , 2.7 m mol; MgCl_2 , 0.5 m mol; NaH_2PO_4 , 3.6 m mol; pH was 7.2 at the temperature range mentioned above.

Atrial flutter or fibrillation was induced by the administration of aconitine. Two methods of administration were used: 1) diffuse administration, and 2) local administration. In the diffuse administration, 0.1 per cent solution of aconitine crystal was added dripping into the Tyrode's solution until the fibrillation occurred. The concentration of aconitine at the final stage was $0.9\text{--}1.5 \times 10^{-6}$ g/cc. The irrigation was temporally discontinued during the dripping of the drug. The oxygen supply and the temperature of Tyrode's solution were kept constant throughout the entire course of the experiment. In the experiments of the local administration, 0.04–0.08 cc of a 0.1 per cent aconitine solution was administered injecting into a part of the tissue with a fine glass needle of 0.1–0.2 mm in diameter.

A unipolar surface lead electrogram and an intracellular lead electrogram through the use of microelectrode were simultaneously recorded from various spots of the endocardium of the specimen. In most cases, the unipolar lead electrogram was recorded from a spot in the sinoatrial area or its vicinity, and the intracellular lead electrogram, from the various spots in the right atrium apart more than 5 mm from the unipolar surface electrode. The electrode for unipolar lead was made of Ag-AgCl wire of about 0.2 mm in diameter. The wire was insulated by coating enamel, excepting a tip of one end. The

tip was contacted to the aimed spot of the endocardial surface. For intracellular lead electrogram, a capillary glass tube electrode was used. The tip of the capillary tube was less than 0.5μ in diameter. The capillary tube was filled with 3 mol KCl , and the electrical resistance of the microelectrode thus prepared ranged from 10 to 30 meg ohms. The indifferent electrodes for unipolar lead and intracellular lead electrograms placed at a corner of the thermostatic bath.

The preamplifier for the intracellular lead electrogram was type MZ-1B made by the Nihonkoden Kogyo Co. That for the unipolar lead electrogram was type ADB-1 made by the same company. The output voltage from each preamplifier was introduced into a two-beam cathode ray oscilloscope made by the Saneisokki Co. both tracings on the screen were simultaneously photographed at a constant film speed of 10 cm/sec with a continuous recording camera made by the Saneisokki Co. (Fig. 1).

The concentrations of potassium and sodium of the muscle specimen from the right atrial free wall were measured with a flame photometer, type FPF-2 made by the Hitachi Co. The specimen was prepared by the technique reported by JENNINGS and associates¹⁴.

RESULTS

(1) Development of atrial flutter and fibrillation

Atrial flutter was induced by the adminis-

Fig. 2. A series of progressive changes in unipolar lead and simultaneous intracellular lead electrograms produced by the diffuse administration of aconitine solution. Unipolar lead electrogram (the upper tracing in each row) was recorded from the proximal part of the right branch of crista terminalis, and intracellular lead electrogram (the lower tracing), from the right subendocardium of the atrial septum. A; control. B; 4 min. after aconitine administration. C; 7 min. after the administration. D; 8 min. after the administration. The rhythm gradually changed from flutter to fibrillation.

tration of aconitine in all cases. Atrial fibrillation occurred always through a stage of the flutter, though it was sometimes very short. In the cases of the local administration of aconitine solution, the incidence of fibrillation was observed in 5 cases out of 17, whereas the incidence in the cases of the diffuse administration was observed in 15 cases out of 17.

Atrial flutter was abruptly induced within a few minutes after the administration of aconitine to the specimen beating under the normal sinus rhythm. Two different courses were observed in the development of flutter in the cases of diffuse administration of aconitine. In one course, the flutter occurred abruptly. The amplitude of the action potential of unipolar lead electrogram became smaller in accordance with the occurrence of flutter. The configuration, however, remained almost unchanged. In another course, flutter occurred after several runs of extrasystole. In this course, the configuration and magnitude of the

action potential in flutter remained almost the same as those seen in extrasystole. The local administration of aconitine to the specimen, excepting to the sinoatrial nodal region, showed the latter course. The action potential of unipolar lead electrogram occurred regularly at a constant rate of from 250 to 450 per minute. The action potential in intracellular lead electrogram simultaneously recorded from various spots was synchronous with that in unipolar lead electrogram.

In the unipolar lead electrogram, the action potential became gradually irregular in the rhythm within 4 to 17 minutes after the occurrence of the flutter. There was also gradual alteration in configuration and magnitude of action potential in accordance with the gradual change of the rhythm, giving rise to atrial fibrillation. The frequency of the action potential in the fibrillation ranged from 350 to 900 per minute.

In the intracellular lead electrogram, the

Fig. 3. A series of progressive changes in two simultaneous intracellular lead electrograms produced by the diffuse administration of aconitine solution. The upper tracing in each row was recorded from the free wall of the right atrium near the right branch of crista terminalis. The lower one, from the right subendocardium of the atrial septum. A; control. B; 10 min. after aconitine administration. C; 13 min. after the administration. In row C, the upper tracing was regular in the rhythm, but that in the lower one was quite irregular.

membrane action potential in the fibrillation was also irregular in the rhythm and the frequency ranged from 270 to 600 per minute. In the fibrillation, the frequency in the intracellular electrogram was usually less than that in the unipolar lead and intracellular lead electrograms were completely irregular in their rhythms and there was no time correlation between these two electrograms.

In the initial stage of fibrillation, however, there was some regularity of the rhythm in the unipolar lead electrogram. This was also observed in the intracellular lead electrogram. Some of the action potentials showed synchronism between these two lead electrograms.

The followings are the description about the representative cases.

Fig. 2 reproduces a series of unipolar lead and simultaneous intracellular lead electrograms during an experiment of diffuse administration of aconitine. The unipolar lead electrogram showed atrial flutter in row B. As may be seen in the figure, the configuration of the action potential of unipolar lead electrogram

was quite different from that under sinus rhythm. In row C, showing the transitional stage from flutter to fibrillation, the action potential of unipolar lead electrogram was irregular in the rhythm and showed various configurations. The membrane action potential, however, was synchronous with the action potential of unipolar lead electrogram. In row D, action potentials in both lead electrograms were quite irregular in their rhythms, but there was relatively good time correlation between their spikes.

In order to further study the nature of the fibrillation, two intracellular electrograms were simultaneously recorded from different spots. In Fig. 3, aconitine was administered diffusely to a specimen. Penetrations were made at two spots 8 mm apart each other. In row B, action potentials of intracellular lead electrograms showed slight irregularity and asynchronism. In row C, the action potential seen in the upper tracing was regular in the rhythm, whereas that in the lower one was quite irregular. There was no synchronism between these two tracings.

Fig. 4. A series of progressive changes in unipolar lead and simultaneous intracellular lead electrograms produced by the local injection of aconitine solution into a basal part of the orifice of superior vena cava. Unipolar lead electrogram (the upper tracing) was recorded from a proximal part of the right branch of crista terminalis. Intracellular lead electrogram (the lower tracing), from a middle part of the right branch of crista terminalis. A; 10 min. after aconitine administration. B; 17 min. after the administration. Analytical diagram was shown beneath each row (see text).

It was generally observed that the synchronism between different two spots gradually disappeared as the stage of fibrillation advanced. Generally, the more the distance of two spots, the earlier was the onset of the disappearance of the synchronism.

Fig. 4 reproduces simultaneous unipolar lead and intracellular lead electrograms obtained from the experiment in which aconitine was injected into a basal part of the orifice of superior vena cava. Row A in Fig. 4 is from the transitional stage from flutter to fibrillation. In this row, the unipolar lead electrogram showed two patterns of action potential, i.e., one was the large wave (shaded bar in the analytical diagram) and another was the small wave (open bar in the diagram).

In the intracellular lead electrogram, the action potential represented by open bar in the diagram was synchronous with the small wave in the unipolar lead electrogram. In addition to this group of the action potentials, another

group of the action potentials represented by stippled bars in the diagram showed no definite time correlation with the waves in the unipolar lead electrogram. Row B reproduces simultaneous recordings taken 5 minutes after A. In this row, the unipolar lead electrogram showed still two patterns of action potential. The action potential of the intracellular lead electrogram was irregular. However, it kept good time correlation with the small wave.

Fig. 5 reproduces the continuous recordings obtained from the experiment in which aconitine was injected into a proximal part of the right branch of crista terminalis. As may be seen in this figure, both the unipolar lead and intracellular lead electrograms displayed the condition of fibrillation. The rhythms of both action potentials were quite irregular and their waveforms were in wide variation. Careful observation, however, revealed that there were two constant patterns of action potential in the unipolar lead electrogram. These two

Fig. 5. Unipolar lead and simultaneous intracellular lead electrograms obtained during atrial fibrillation induced by the local injection of aconitine solution into a proximal part of the right branch of crista terminalis. In the analytical diagram, three types of action potential in the unipolar lead electrogram were schematized by open, stippled and shaded bars. Among of these three bars, open and stippled bars were presented with regular interval and constant patterns, respectively. The analogous relationships were also observed between the intracellular lead electrogram and analytical diagram. (see text).

patterns of action potential occurred relatively regularly as shown by open and stippled bars in the underlying analytical diagram. In some instances, these action potentials displayed sometimes escape from their appearance. In such cases, the succeeding action potential with same pattern appeared with the interval of whole number multiples of the expected cycle length. In the intracellular lead electrogram, there were also two wave groups. These two groups appeared correspondingly to those two groups in the unipolar lead electrogram.

(2) Changes in membrane potential in atrial flutter and fibrillation.

In the stage of atrial flutter, the main changes in the membrane potential of atrial proper muscle cell were the decreases of the amplitudes of membrane resting and action potentials, the shortening of the action potential duration, and the decrease of the rising velocity of the sharp depolarization upstroke. Membrane resting and action potentials ranged from

44 to 80 mV and from 46 to 102 mV, respectively. The overshoots were less than 22 mV and lacked in some cases.

Even in the stage of fibrillation, the membrane resting potentials continued to decrease, but not markedly. During the fibrillation, they ranged from 43 to 65 mV with an average of 56 mV. The membrane action potential also continued to decrease even in the fibrillation. It varied in amplitude and configuration from excitation to excitation. It was less than 58 mV in amplitude and lacked overshoot. The rising velocity of the sharp depolarization upstroke decreased markedly. (Fig. 2-5).

The changes in amplitude and duration of the membrane action potential had also been observed with the atrial specimen under the artificial tachycardia due to electrical stimulation. In order to distinguish the effect of aconitine from that of tachycardia, two types of experiment were performed in the present paper; (1) inducement of the flutter by diffuse

Fig. 6. Relationship between the frequency of excitation of atrial muscle cell and the amplitude of membrane resting potential. Solid line represents the case of aconitine administration, whereas dash line, the case of electrical stimulation.

Fig. 7. Unipolar lead and simultaneous intracellular lead electrograms before and after the local injection of aconitine solution into the atrial proper muscle. Unipolar lead electrogram (the upper tracing) was recorded from a site in sinoatrial node. Intracellular lead electrogram (the lower tracing), from the site of the injection. A; control. B; 30 min. after aconitine injection. Note the appearance of diastolic slow depolarization in intracellular lead electrogram after aconitine injection.

administration of aconitine and (2) high frequent, electrical stimulation. The changes in aconitine-induced flutter were compared with those in high frequent, electrical stimulation. Electrical stimulation was applied to the specimen with various high frequencies using a square wave pulse of 4 to 6 volt in potential and 2 msec in duration.

As may be seen in Fig. 6, the membrane resting potential in the aconitine-induced flutter usually markedly decreased beyond the frequency level of 300 per minute. In the electrical tachycardia, however, the decrease in the membrane resting potential was not so marked as seen in the aconitine-induced flutter. In the experiments of aconitine administration, fibrillation started to occur at the frequency level of 350 to 400 per minute in most cases, and average amplitude of the membrane resting potential at this stage was 54 mV. In the experiments of electrical stimulation, however, fibrillation did not occur even at the high level of 500 per minute.

In some cases of the local administration of aconitine to the atrial proper muscle, the appearance of diastolic slow depolarization was noted when the recording was made from the spot of local administration, as may be seen in Fig. 7.

Aconitine provoked also membrane potential changes in sinoatrial node. The changes

Fig. 8. A series of progressive changes in unipolar lead and simultaneous intracellular lead electrograms by the diffuse administration of aconitine solution. Intracellular lead electrogram (the lower tracing) was recorded from sinoatrial node. A; control. B; 2 min. after aconitine administration. C; 2.5 min. after the administration. D; 12 min. after the administration. The steepness of the diastolic slow depolarization increased from 5° in row A to 7° in row B.

Fig. 9. Relationship between the frequency of excitation of atrium and the conduction time of activation. Specimens were driven electrically and the conduction time was measured between the fixed two spots in the right atrium through an experiment. Dash and chain lines represents the cases of the diffuse administration of aconitine solution, whereas solid line, the case of non-aconitine administration.

were the decrease of the rising velocity of sharp depolarization upstroke, the increase of the steepness of diastolic slow depolarization, the shortening of the action potential duration, and so on. In fibrillation, the membrane action potential of sinoatrial node also varied in amplitude and configuration from excitation to excitation (Fig. 8).

(3) Intra-atrial conduction velocity in flutter.

The intra-atrial conduction velocity was investigated in the case of the diffuse administration of low concentration of aconitine solution, and also in the case of electrical stimulation alone. As may be seen in Fig. 9, the conduction time in which the activation propagated a certain distance was gradually prolonged, as the frequency increased. The conduction in the case of aconitine application was markedly delayed, as compared with that in the case of non-aconitine application. Especially, the discrepancy became pronounced when the frequency exceeded over 350 per minute.

(4) Changes in potassium and sodium concentrations of atrial muscle tissue.

Potassium and sodium concentrations of the muscle specimen from the right atrial free wall were shown in Table I. In fibrillatory tissue, potassium concentration decreased markedly, whereas that of sodium increased.

TABLE I POTASSIUM AND SODIUM CONCENTRATIONS OF THE RIGHT ATRIAL TISSUE

	K n=16	Na n=19
<i>Control</i>	0.072 ± 0.010	0.099 ± 0.021
<i>Fibrillation</i>	0.049 ± 0.009	0.132 ± 0.033

mEq/g wet weight

DISCUSSION

Recently, the widely accepted hypothesis by LEWIS¹ that there is a circular sequence of excitation around the ostia of the two vena cava as the mechanism responsible for atrial flutter and fibrillation has been questioned by SCHERF^{11,15}, and by PRINZMETAL¹². SCHERF and associates concluded from their experiments in which atrial flutter and fibrillation were induced by the injection of aconitine into the atrial muscle that these arrhythmias were caused by a rapidly discharging ectopic focus. PRINZMETAL and

associates reached the same conclusion from their studies by means of electrocardiograph and high-speed cinematograph. More recently, however, ROSENBLUETH and GARCIA RAMOS¹⁰ supported the circus movement theory basing on their study on atrial flutter induced by electrical stimulation. MATSUDA and associates¹⁶ reported that aconitine produced ectopic, spontaneous, and repetitive activity of the cardiac muscle cell when it was applied to the specimen.

In the present experiments, the local administration of aconitine to any locale of the specimen induced extremely rapid, regular beating of the atrium in the early stage of the administration. In some cases of the local administration of aconitine to the atrial proper muscle, the appearance of diastolic slow depolarization was noted when the recording was made from the spot of the local administration. The configuration of action potential of the unipolar lead electrogram in atrial flutter was almost uniform, but different from that in control. The action potentials of unipolar lead and simultaneous intracellular lead electrograms were synchronous throughout the flutter. Synchronism of the membrane action potentials was also observed in two simultaneous intracellular lead electrograms led from the different parts. These findings may suggest that the local administration of aconitine induces a rapidly discharging, ectopic focus, and that the whole atrium responses coordinately to the impulse originated in the ectopic focus.

SANO and associates^{17,18} emphasized the total incoordination of muscles as the characteristics of fibrillation from their studies by means of multiple direct lead electrograms and micro-electrode method. In the initial phase of atrial fibrillation, however, they observed that the interval between excitations tended to be constant, and that a propagation pattern could be plotted which seemed to start from the origine of local firing. By the use of autocorrelation technique, BATTERSHY¹⁹ demonstrated the presence of a periodic component in the atrial waveform of patients with chronic atrial fibrillation.

In the present experiments, the regularity and synchronism in the appearances of action potentials of unipolar lead and intracellular

lead electrograms were also transiently observed, though it was very short in some cases, in the initial stage of atrial fibrillation. The tracings seen in row C of Fig. 2 are those in the transitional stage from flutter to fibrillation. In this stage, synchronism between the action potentials of unipolar lead and intracellular lead electrograms was still observable, though both action potentials became irregular in their rhythms and various in their configurations. These findings may suggest that the specimen still activates coordinately, in spite of the disturbance of conduction and the unfixed pattern of propagation of activation.

As may be seen in Fig. 3, there was a stage in which a part of specimen was activated regularly, while the another part was activated irregularly. This means the fibrillation is occurring at a limited region of the specimen, and suggests that there is a possibility of occurrence of two or more foci in the specimen.

As may be seen in Fig. 4, there were two different types of action potential in unipolar lead electrogram, one remained regular and another became irregular in their rhythms with the advancement of the fibrillation. This case may suggest that the aconitine administration induces at least two foci, and one of these foci became irregular in the rhythm while the other remained regular.

As may be seen in Fig. 5, some of the action potentials in unipolar lead and intracellular lead electrograms occurred regularly and synchronously each other in the early stage of fibrillation, and these action potentials of unipolar lead electrogram exhibited uniformity of the pattern. When these action potentials of two electrograms displayed escape from their appearance at the expected time, the succeeding action potential in the same pattern occurred with the interval of whole number multiples of the expected cycle length. These findings may suggest that multiple ectopic foci are induced by aconitine administration. It may also suggest that at least two foci originate impulses regularly, and these impulses are conducted by a fixed pattern of propagation with an almost constant velocity. Sometimes, the conduction is blocked or interfered. That would be a reason why the action po-

tentials of unipolar lead and intracellular lead electrograms occur in a rhythm of the whole number multiples of the basic cycle length, when they fail to occur with the basic cycle length.

According to HOFFMAN and SUCKLING²⁰, an increase in the frequency of excitation of the atrial muscle cell caused a decrease in the amplitude of membrane resting and action potentials, a shortening in the action potential duration, and a decrease in the rising velocity of the sharp depolarization upstroke. According to WEIDMANN²¹, a reduction in the resting potential led to a reduction in the steepness and amplitude of the sharp depolarization upstroke. In the present experiments of the diffuse administration of aconitine solution, the membrane resting potential began to markedly decrease beyond the frequency level of 300 per minute, and the fibrillation started to occur at the frequency level of 350 to 400 per minute in most cases. In the experiments of electrical stimulation, however, a decrease in the resting potential was not so marked as seen in the experiments of the diffuse administration of aconitine solution, and the fibrillation did not occur even at the high frequency level of 500 per minute. Based on these findings, it may be reasonable to presume that a decrease in the membrane resting potential plays an important role to the occurrence of the fibrillation.

It has been supposed that the gradient of potassium ion across the cell membrane is most directly concerned with the origination of the membrane resting potential^{22,23}. Since the composition of Tyrode's solution irrigating the specimen was constant in the present experiments, it is considered that the extracellular potassium concentration was also almost constant, and that the change in potassium concentration of the tissue resulted from that in intracellular potassium concentration. Comparison between the potassium concentrations in normal and fibrillatory atrial muscle tissues revealed that the potassium decreased markedly in the fibrillatory tissue. This finding seems to indicate that aconitine may bring about the change in the cell metabolism, and thus intracellular concentration of potassium may de-

crease markedly. It seems likely that the fibrillation occurs whenever the membrane resting potential decreases down to a certain level. HOLLAND^{24, 25} reported that fibrillation began to occur at the time when the rate of potassium ion loss exceeded a certain critical rate and that the onset of fibrillation may result from a sudden transient increase in cell membrane permeability to the potassium ion. The present experiments also seem to suggest that the occurrence of atrial fibrillation is closely related to the change in the potassium ion concentration of the muscle cells.

It has been known that if the membrane resting potential is lowered towards the threshold potential, all other factors remaining constant, the ease with which the tissue can be stimulated is increased²⁶. The decrease in the membrane resting potential of atrial muscle cell during atrial flutter may suggest that the excitability of atrial cell becomes increased.

It has been also known that there are at least three important factors for the determination of the frequency of pacemaker discharge; namely, (1) the steepness of the diastolic slow depolarization, (2) the level of the membrane resting potential, and (3) the level of the threshold potential²⁷. According to SCHMIDT²⁸ and other investigators¹⁶, aconitine caused the increase in the steepness of the diastolic slow depolarization and the decrease in the membrane resting potential of the Purkinje fiber. In the present experiments, the result in sinoatrial node was essentially the same with that observed in Purkinje fiber. It is surmised that the increasing of the frequency of discharge of the pacemaker is largely due to above mentioned factors, factors (1) and (2).

As the reason of occurrence of multiple foci, the followings will be considered. In the right atrium, there are a variety of sites which exhibit latent pacemaker activity²⁷. Both the increase in the steepness of the diastolic slow depolarization and the decrease in the membrane resting potential of the cell with automaticity may suggest increasing possibility for the spontaneous firing of latent pacemaker. Thus multiple ectopic foci would be induced.

In addition, the conduction disturbance may contribute to the occurrence of ectopic foci. If

the impulse is delayed or blocked on the way to the latent pacemaker, the spontaneous firing of the latent pacemaker will be manifested. As may be seen in Fig. 9, the conduction delay in the cases of diffuse administration of aconitine solution became marked when the frequency exceeded over 350 per minute. This finding may suggest that the conduction disturbance is one of the factors contributing to the occurrence of atrial fibrillation, considering of the fact that the frequency of atrial excitation ranged from 350 to 400 per minute for the initiation of atrial fibrillation in the cases of the diffuse administration of aconitine solution.

It may be concluded that the aconitine-induced atrial flutter results from rapid impulse formation in a single focus evoked by aconitine solution. When the focus is ectopic, the pacemaker in the sinoatrial node would behave as usual latent pacemaker. The aconitine-induced atrial fibrillation would be caused by rapid impulse formation in multiple ectopic foci evoked by aconitine solution.

SUMMARY

1. Aconitine was administered to the isolated right atrium of the rabbit to induce atrial flutter and fibrillation. Unipolar surface lead and intracellular lead electrograms were simultaneously recorded from the endocardium of the specimen.

2. The action potential of unipolar lead electrogram in the atrial flutter was quite regular in the rhythm. The configuration was different from that in sinus rhythm. The action potential of intracellular lead electrogram was also regular in the rhythm and was synchronous with that of simultaneous unipolar lead electrogram.

3. In the atrial fibrillation, the action potentials of unipolar lead and simultaneously recorded intracellular lead electrograms were irregular and asynchronous each other. They exhibited a wide variation in amplitude and configuration. In the initial stage of the fibrillation, however, some of the action potentials in both lead electrograms appeared regularly and synchronously each other, though it was very short in some cases.

4. In the atrial flutter and fibrillation, the

membrane resting and action potentials decreased to various degree. The rising velocity of the sharp depolarization upstroke of membrane action potential became decreased, and the duration became shortened. The steepness of diastolic slow depolarization became increased.

5. The diffuse administration of aconitine brought about the decrease of membrane resting potential. It was especially marked at the frequency level beyond 300 per minute. In most cases, the fibrillation started to occur at the frequency level of 350 to 400 per minute.

6. In some cases of the local administration of aconitine to the atrial proper muscle, the appearance of diastolic slow depolarization was noted when the recording was made from the spot of local administration.

7. Intra-atrial conduction velocity in the case of the diffuse administration of low concentration of aconitine solution was gradually decreased, as the frequency increased. The decrease of conduction velocity became marked when the frequency exceeded over 350 per minute.

8. In fibrillatory atrium, intracellular potassium decreased markedly, whereas intracellular sodium increased.

9. It may be concluded that the atrial flutter results from rapid impulse formation in a single focus. When the focus is ectopic, the pacemaker in sinoatrial node would behave as a usual latent pacemaker. The atrial fibrillation would be caused by rapid impulse formation in multiple ectopic foci. The conduction disturbance may also contribute to the occurrence of the fibrillation.

Acknowledgement

The author wishes to express his gratitude and appreciation to professor Susumu Hibino, professor Hideo Toyoshima, and assistant professor Kazuo Yamada for their helpful and valuable instructions.

The author is grateful to Dr. Yasushi Mizuno and Dr. Mitsuharu Okazima.

The author is indebted to Dr. Yukio Sakaida, Dr. Akira Nonogawa, Dr. Hiroshi Oishi, and Dr. Toshiji Kobayashi for their cooperation.

REFERENCES

1. LEWIS, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3. London, Shaw & Sons, 1925.
2. DE BOER, S.: *Ergebn. Physiol.* **21**: 1, 1923.
3. DECHERD, G. M., RUSKIN, A. AND HERRMANN, G.: *Am. Heart J.* **29**: 20, 1945.
4. ROSENBLUETH, A. AND GARCIA RAMOS, J.: *Am. Heart J.* **33**: 677, 1947.
5. GARREY, W. E.: *Physiol. Rev.* **4**: 214, 1924.
6. BRAMS, W. A. AND KATZ, L. N.: *Am. Heart J.* **7**: 249, 1931.
7. KATZ, L. N. AND PICK, A.: Clinical electrocardiography: The arrhythmias, Philadelphia, Lea & Febiger, 1956.
8. TENNEY, S. M. AND WEDD, A. M.: *Circulation Res.* **2**: 28, 1954.
9. WINTERBERG, H.: *Pflüger's Arch. ges. Physiol.* **117**: 233, 1907.
10. ROTHBERGER, C. J. AND WINTERBERG, H. L.: *Pflüger's Arch. ges. Physiol.* **160**: 42, 1914.
11. SCHERF, D., ROMANO, F. J. AND TERRANOVA, R.: *Am. Heart J.* **36**: 241, 1948.
12. PRINZMETAL, M., CORDAY, E., BRILL, E. C., OBLATH, R. W. AND KRUGER, H. E.: The Auricular Arrhythmias, Springfield, Ill., Charles C. Thomas, 1952.
13. HECHT, H., KATZ, L. N., PICK, A., PRINZMETAL, M. AND ROSENBLUETH, A.: *Circulation* **7**: 591, 1953.
14. JENNINGS, R. B., CROUT, J. R. AND SMETTERS, G. W.: *A.M.A. Arch. Path.* **63**: 586, 1957.
15. SCHERF, D.: *Proc. Soc. Exper. Biol. & Med.* **64**: 233, 1947.
16. MATSUDA, K., HOSHI, T. AND KAMEYAMA, S.: *Jap. J. Physiol.* **9**: 419, 1959.
17. SANO, T., TSUCHIHASHI, H. AND SHIMAMOTO, T.: *Circulation Res.* **6**: 41, 1958.
18. SANO, T. AND SCHER, A. M.: *Circulation Res.* **14**: 117, 1964.
19. BATTERSHY, E. J.: *Circulation Res.* **17**: 296, 1965.
20. HOFFMAN, B. F. AND SUCKLING, E. E.: *Am. J. Physiol.* **179**: 123, 1954.
21. WEIDMANN, S.: *J. Physiol.* **127**: 213, 1955.
22. HODGKIN, A. L.: *Biol. Rev. Cambridge Phil. Soc.* **26**: 339, 1951.
23. BURGEN, A. S. V. AND TERROUX, K. G.: *J. Physiol.* **120**: 449, 1953.
24. HOLLAND, W. C.: *Am. J. Physiol.* **190**: 63, 1957.
25. HOLLAND, W. C. AND TINSELY, B.: *Am. J. Physiol.* **193**: 235, 1958.
26. JENERICK, H. P. AND GERARD, R. W.: *J. Comp. Physiol.* **42**: 79, 1953.
27. HOFFMAN, B. F. AND CRANFIELD, P. F.: Electro-physiology of the Heart, New York, McGraw-Hill Co. 1960.
28. SCHMIDT, R. F.: *Pflüger's Arch. ges. Physiol.* **271**: 526, 1960.