Significance of the Sino-Atrial Node on Mechanism of Occurrence of Atrial Fibrillation

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SUMMARY

The authors have studied the participation of the sinus node in the occurrence of atrial fibrillation.

In the experiments on dog hearts in situ, an electrical stimulation given to the right atrium easily induced atrial fibrillation in the presence of the normal sinus node.

When the sinus node was injured, atrial fibrillation was very much reduced in frequency of occurrence and duration.

Also in the case of aconitine induced atrial fibrillation, the occurrence of fibrillation was very late when the sinus node had been injured.

Application of aconitine on preparations of the rabbit's right atrium including the sinus node easily induced fibrillation, but by application of aconitine on preparation of right and left atrial common muscle devoid of spontaneous activity fibrillatory contraction has never been observed.

Recently, we have made the studies on aconitine-fibrillation of the right atrium of the rabbit with 2 microelectrodes by means of the isolation technique.

In them, aconitine was administered to the common muscle chamber in which the solution had been separated from the sinus node chamber with glycerin-soaked cotton. An ectopic pacemaker was produced after aconitine administration. Then the sinus node became a latent pacemaker. As the ectopic impulses increased in frequency, the action potential of the sinus node was a little more reduced in duration than that of the pectinate muscle, showed a marked decrease, and could not synchronize with that of the pectinate muscle, then changed into the fibrillatory potential. Subsequently, the fibrillation occurred to the common muscle.

Authors further demonstrated a clinical case report. The patient was 23 years old male, whose cardiac rhythm alternated to atrial fibrillation with A-V nodal rhythm. We have observed successively ECG alternation by the system of long term recording. It was found that the sinus rhythm apparently appeared every time before the onset of atrial fibrillation.

From the results mentioned above, it was considered that the sinus node dominantly participates in the occurrence and the duration of atrial fibrillation.

Additional Indexing Words:
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SINCE about 15 years we compared the mechanism of occurrence of atrial fibrillation. From the results of animal experiments as well as clinical observations and based on their mutual considerations, we are now in the firm belief that sinus node plays an important role in occurrence of atrial fibrillation. The following reports are chief points of our recent studies concerning this problem.

I. Comparison in Frequency of Onset of Atrial Fibrillation between Normal and Injured Sinus Node Group

METHOD

Mongrel dogs were anesthetized by intravenous administration of 30–50 mg./Kg. thiopental sodium. The chest was opened by a midline or right chestwall incision and the pericardium was incised.

Sinus nodes was injured by the injection of 10% trichloroacetic acid or blocked by clamping and ligation.

To produce atrial fibrillation, right atrium was stimulated electrically (15 v., 50 cycle per sec., for 5 sec.) and also applied 0.2 per cent aconitine solution.

Fig. 1. The frequency of occurrence of atrial fibrillation and flutter in the intact sinus group and the injured sinus group.

In the vertical line marked the frequency of occurrence of atrial fibrillations and flutters, according to their duration marked in the horizontal line. The cases stimulated upon the atrial body were illustrated in A and the cases stimulated upon atrial appendage in B. Open bars illustrated the group of intact sinus node; and shaded bars illustrated the group of injured sinus node.
Fig. 2. Delay of the onset of atrial fibrillation and flutter produced by aconitine application. Marked the time from aconitine application in the horizontal line and the experimental dog No. on the vertical line.

RESULTS

Fig. 1 shows clearly that by electrical stimulation on the right atrium of dogs atrial fibrillation hardly occurs in injured sinus node group, and by occurrence it reveals delay of onset and an eminent decrease of duration as compared with normal sinus node group. Fig. 2 shows delay of the onset of atrial fibrillation produced by aconitine application on dog atrium. In normal sinus node group atrial fibrillation occurs in all cases within 15 to 98 sec., whereas in injured sinus node group delays to the onset of atrial fibrillation are markedly prolonged (from 1 min. 15 sec. to 6 min. 30 sec.); moreover, in 5 out of 13 cases atrial fibrillation does not occur; in these cases all remain in a state of atrial tachycardia.

II. Correlation between Normal Sinus Impulse and Atrial Fibrillation. Experimental Studies on Atrial Fibrillation with Micro-electrodes

METHOD

In order to clarify the bearing of the sino-atrial node on atrial fibrillation, occurrence of atrial fibrillation was tested with 2 microelectrodes by means of the
Fig. 3. Apparatus of the experiment:
- **r.e.**: recording electrode
- **i.e.**: indifferent electrode
- **Tm**: thermometer
- **S.P.**: suction pipette
- **H.**: heater
- **Ts.**: thermostat
- **G.**: gate of the J-FET preamplifier

Fig. 4. Sketch of the atrial preparation in a lucite double chamber:
- **G.**: gate of J-FET preamplifier
- **G.C.**: glycerin-soaked cotton
- **r.e.**: recording electrode
- **V.C.S.**: vena cava superior
isolation technique.

The right atrium including the sino-atrial node (ca. 5 mm. × 15 mm.) was excised from adult rabbits and fixed in a lucite double chamber (Fig. 3). The preparations were continuously perfused with Tyrode's solution saturated with a mixture of 95% O₂ and 5% CO₂ and maintained at a temperature of 36±0.5°C.

Aconitine was added to the common muscle chamber in a final concentration of 10⁻⁶ Gm./ml., which solution was separated from the sino-atrial node chamber with glycerin-soaked cotton (ca. 3 mm. in width) (Fig. 4). In some experiments, Tyrode's solution containing Tetrodotoxin* in a concentration of 10⁻⁶ Gm./ml. was used to the common muscle chamber.

In all experiments, 2 micropipettes filled with 3 Mol-KCl were simultaneously impaled into the sino-atrial nodal cell and the pectinate muscle by suspension method for potential recording. The membrane potentials were led to 2 transistorized preamplifier and displayed on 2 beams of a dual beam oscilloscope. In some experiments, the potentials were recorded simultaneously by a pen-recorder through a DC amplifier.

**RESULTS**

**Effects of aconitine on right atrium including the sino-atrial node**

Fig. 5A shows spontaneous activity. The upper trace was recorded from the pectinate muscle and the lower from the sino-atrial nodal region. As seen in Fig. 5B, when aconitine was added to the bathing fluid of the common muscle chamber in a final concentration of 10⁻⁶ Gm./ml., an ectopic rapid activity was suddenly initiated in the common muscle and the sino-atrial node became a latent pacemaker. The amplitude of the resting and the action potential decreased not only in the pectinate muscle, but also in the sino-atrial nodal region. The sino-atrial nodal action potential could not follow the pectinate muscle, as the rate of excitation increased. Then the irregularity in size and configuration of the action potential was observed as seen in Fig. 5C. Within a few minutes, the changes became more prominent and atrial fibrillation ensued as seen in Fig. 5D.

**A phasic relation of the action potentials between the sino-atrial nodal cell and the pectinate muscle**

In Fig. 6, A showed the control. The action potential duration in the sino-atrial node was longer than in the pectinate muscle. B to F were the changes after aconitine administration to the common muscle chamber. An ectopic pacemaker was induced in the common muscle. As seen in B, C and D, with an increase of the frequency of the ectopic excitations, the action poten-

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* Tetrodotoxin is a crystalline toxin isolated from the ovaries of Japanese puffer-fish, genus Fugu, and manufactured by Sankyo Co., Ltd.
Fig. 5. Membrane action potentials in aconitine-induced atrial fibrillation. Aconitine was administered to the common muscle chamber. The upper trace was recorded from the pectinate muscle and the lower trace from the sino-atrial nodal region.

A: Control, B: 2 min. after aconitine administration, aconitine-induced tachycardia was observed in the common muscle. C: Several minutes later than B. D: Aconitine-induced atrial fibrillation was observed in both side of the sino-atrial node and the common muscle.

tial duration of the pectinate muscle was markedly shortened in contrast to that of the sino-atrial node.

Consequently the sino-atrial nodal action potential could not follow the rapid activity of the ectopic pacemaker and showed local block, graded re-
Interaction between the sino-atrial nodal pacemaker and the aconitine-induced ectopic pacemaker

In order to clarify this problem, the aconitine treated preparation was irrigated with Tetrodotoxin Tyrode's solution, and then re-irrigated with normal Tyrode's solution. In Fig. 7 A the repetitive excitations of high frequency (420/min.) recorded from the pectinate muscle (upper strip) showed its regularity in rate, but its slight irregularity in the amplitude of the action potential. However, the sino-atrial nodal action potentials were now irregular in rate, size and configuration and showed fibrillatory potentials. B, C and D were successive changes of the action potentials after irrigating with Tetrodotoxin Tyrode's solution, 4, 8 and 14 min. respectively. When the aconitine induced ectopic pacemaker activity ceased gradually, the sino-atrial nodal action potential became gradually synchronous with that of pectinate muscle. Then the sino-atrial node took over its pacemaker activity, when the aconitine induced ectopic pacemaker failed to produce an impulse by Tetrodotoxin. The pectinate muscle was excited by propagated impulses from the sino-atrial node.

Fig. 8 (A to D) was successive changes of 4, 8, 11 and 16 min. after perfusing with normal Tyrode's solution respectively. When Tetrodotoxin Tyrode's solution was replaced by normal Tyrode's solution, an ectopic pace-
Fig. 7. Changes of the action potentials when the aconitine-treated preparation was irrigated with Tetrodotoxin Tyrode’s solution. The upper trace was recorded from the pectinate muscle and the lower from the sino-atrial node.

A: Aconitine-induced repetitive excitations of high frequency observed in the common muscle. However, the sino-atrial node showed the fibrillatory potentials. B, C, D: Successive changes of the action potentials after irrigating with Tetrodotoxin Tyrode’s solution, 4, 8 and 14 min. respectively.

maker activity recovered gradually. In this condition the rate of the ectopic pacemaker was faster than that of the sino-atrial nodal pacemaker. Then the sino-atrial nodal action potential could not follow the ectopic activity. At first it became like a latent pacemaker and then a fibrillatory potential. Effect of Tetrodotoxin was reversible, but that of aconitine was irreversible.
Fig. 8. Changes of the action potentials when the same preparation as Fig. 7 was re-irrigated with normal Tyrode's solution. The upper trace was recorded from the pectinate muscle and the lower trace from the sino-atrial node.

A-D: Successive changes of 4, 8, 11 and 16 min. after perfusing with normal Tyrode's solution respectively.

Interaction between the sino-atrial nodal pacemaker and the aconitine-induced ectopic pacemaker was observed more clearly on the rapid speed film. Fig. 9 A was control. The sino-atrial nodal pacemaker took over, when the aconitine-induced ectopic pacemaker failed to produce an impulse. However, the sino-atrial node became to function as a latent pacemaker, when the aconitine-induced ectopic pacemaker developed (Fig. 9 B).
III. Clinical Observation

A case has been experienced which showed alternate appearance of sinus rhythm, atrial fibrillation and atrio-ventricular rhythm and their ceaseless continuation.

This case was 23 years old man who had no special finding except alternately successive appearance of arrhythmias and bradycardia. By continuous tracing of electrocardiogram for 275 hours we found that in this case 3 different types of rhythm appeared, though in regular alternation, but continuously. Fig. 10 shows analysis diagram of this tracing during admission (from September 1969 to July 1970). Portion of sinus or atrial rhythm is with the hatched, that of atrial fibrillation with the open, and that of atrio-ventricular nodal rhythm with the shaded line visualized. The alternate change of rhythm is schematically seen. By electrocardiogram analysis the period of bradycardia corresponds to atrioventricular nodal or sinus rhythms, and that of arrhythmia to atrial flutter or fibrillation, respectively. Furthermore, presence of sinus rhythm just before appearance of each atrial fibrillation is an almost constant finding. Fig. 11 shows an ECG portion of this case, especially just before commence of atrial fibrillation. In the upper strip are visible series of P waves, PR interval of 0.20 sec., shapes of each P wave being almost similar; these indicate clearly presence of sinus rhythm. In the lower (last) strip, together with irregular RR interval and absence of P wave, atrial fibrillation is now established. And then in the middle (from the second to the third) strips presence of nodal escaped beat, atrial P and sinus P waves (expression of atrial contraction by excitation of sinus origin), waves considered as fusion of T and P waves; these
Fig. 10. Alternation of cardiac rhythm during admission in a clinical case (23 y. male).

Fig. 11. ECG alternation during long term recording. Onset of atrial fibrillation (23 y. male).

First strip is visible series of P waves, P-R interval of 0.20 sec. These indicate clearly presence of sinus rhythm.

Second strip shows presence of A-V nodal escaped beat, atrial P and sinus P waves.

Third strip shows onset of atrial fibrillation at the 6th beat.

Fourth strip shows atrial fibrillation.
altogether seem to be a conversion stage from sinus rhythm to atrial fibrillation. Fig. 12 shows each rhythm change in fragments of ECG tracing.

We have experienced another similar case.

**DISCUSSION**

Many studies have so far been conducted on the mechanism of the maintenance and the occurrence of atrial fibrillation, however, there are many problems unclarified.

As for the main theories of fibrillation, there have been advocated circus movement theory, ectopic focus theory, and multiple re-entries theory. Each hypothesis of these theories may be acceptable in part for the phenomena of some experimental fibrillations, however, it is impossible to explain the whole phase of atrial fibrillation.

Moreover, in spite of many studies performed on atrial fibrillation, there are few noticeable investigations made on the relationship between atrial fibrillation and the sinus node as an origin of normal impulse. Only Scherf conjectured that the sinus node in the acetylcholine-induced atrial fibrillation would be a part of the sustaining centers.
The authors, therefore, have noticed on this point and supposed that the sinus node is related to the atrial fibrillation and is actively taking part in the fibrillation. Thus, we have made experimental studies on the occurrence and maintenance of atrial fibrillation in the intact sinus node group of dogs and injured sinus node group devoid of sinus function. And we observed the difference between these 2 groups. As a result, it was clarified that in the injured sinus node the occurrence of atrial fibrillation was difficult and its duration was shortened as compared with normal sinus rhythm by the electrical atrial fibrillation. Moreover, in the studies on aconitine atrial fibrillation, the intact sinus group showed the occurrence of fibrillation in all the cases, however, the injured sinus group showed the delay up to the appearance of atrial fibrillation. Furthermore, there were cases revealing only atrial tachycardia. Nadeau et al.\(^5\) have reported entirely the similar experimental results as the authors, but in acetylcholine induced atrial fibrillation.

In order to confirm these results, we have further conducted the follow-up experimental studies by means of microelectrode in the atrial muscle of rabbits' hearts. In the right atrial muscle strip including the sinus node, the fibrillation was easily observed by the application of aconitine, however, no occurrence of fibrillation was observed in the common muscle devoid of sinus node by aconitine application alone. Thereafter, the electrical stimulation was repeatedly given, but fibrillation never appeared, only tachycardia was observed. And also, the isolation technique was employed for further investigation on the right atrial muscle of rabbits' hearts by separating chamber into the part including sinus node and the part of the common muscle. In such manipulations, the application of aconitine to the common muscle chamber caused the occurrence of tachycardia on the side of the common muscle, but no fibrillation was observed, and only after the appearance of fibrillatory potential in the sinus node area, the side of the common muscle showed fibrillation. From a series of the above experimental results, the authors considered that the sinus node seemed to take part actively in the occurrence of atrial fibrillation.

As for the mechanisms of the influence of sinus node on the occurrence of the atrial fibrillation, there is a possibility of the occurrence of the local block, graded response, and spatial summation, from the specific histological structure and electro-physiological properties of sinus node region. Such mechanisms seem to cause the susceptibility to atrial fibrillation (see Fig. 13).

On the other hand, there is a report\(^6\) on the pathological alterations of the sinus node in the autopsies of the patients with atrial fibrillation, however, no clarification has been made on the relationship between the histological change and the occurrence of atrial fibrillation. Concerning this problem,
the complete extinction of the function of sinus node would hardly induce atrial fibrillation, while a partial injury of sinus node seems to cause a susceptible condition to induce atrial fibrillation. We, therefore, are now investigating these problems with microelectrode by making injuries to the sinus node.

Recently, several studies have been made on the role of the sinus node acting to atrial fibrillation. Hashimoto et al.\textsuperscript{7)} have reported that they observed easy occurrence of atrial fibrillation in sinus rhythm, but they could not observe atrial fibrillation in all the cases in A-V nodal rhythm after injecting acetylcholine into the sinus node of dog-hearts on their experiments. Moreover, Sano et al.\textsuperscript{8)} have reported that the action potential of the sinus node induced the spontaneous atrial fibrillation at the strip of the right atrial muscle of rabbits' hearts in hypopotassium solution, but not in the strip of the left atrial muscle of rabbits. The fibrillation of the latter was induced only after giving the repetitive electrical stimulations similar to sinus rhythm. These experimental results seem to suggest the role of the sinus node in playing the action to the occurrence of atrial fibrillation.

Furthermore, clinical observations revealing the alternate occurrence of sinus rhythm, A-V nodal rhythm and atrial fibrillation have been rarely reported. And also, it is difficult to confirm the transferred part at the time of occurrence of atrial fibrillation in these cases. In our case, however, the oc-
currence of atrial fibrillation was confirmed following the interposing sinus rhythm under A-V nodal rhythm. From this observation, we considered to have confirmed that also in clinical cases the sinus rhythm is taking part in the occurrence of atrial fibrillation.

As mentioned above, the authors have reached a conclusion that the role of the sinus node to the occurrence of the atrial fibrillation is established by the experimental results on aconitine and electrical atrial fibrillations in dog hearts in situ, by the experimental results of aconitine atrial fibrillation by means of microelectrode technique in the strip of atrial muscle of rabbits’ hearts and by the result on the observation of a clinical case.

References