A Study on the Experimental Production of Atrial Fibrillation

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Although atrial fibrillation and flutter have been studied for many years, the pathogenesis and the mechanism of these arrhythmias have not been established as yet. However, it is generally accepted that many factors might be responsible for the initiation of the arrhythmias; some of them have been proved in clinical and/or experimental studies. It is interesting that both atrial fibrillation and flutter can be obtained experimentally by various methods, because a method producing the atrial arrhythmias may suggest some of the contributing factors to initiate these arrhythmias. This study was attempted to produce atrial fibrillation experimentally by means of new methods. The author observed that atrial fibrillation could be obtained by vagal stimulation or epinephrine injection during vagal stimulation after intravenous infusion of the aqueous solution of sodium bicarbonate, and also of sodium lactate.

Atrial fibrillation is one of the most common arrhythmias observed clinically. Atrial flutter and fibrillo-flutter are also observed clinically, but less frequent than atrial fibrillation. These atrial arrhythmias are seen in patients suffering from various underlying diseases. According to the reports of UEDA and TSUNEOKA, ANDO and NOHARA, atrial fibrillation is caused in half by mitral valvular disease, and the rest is caused by hypertension, coronary arteriosclerosis, aortic valvular disease, combined valvular disease, hyperthyroidism and so forth. Atrial fibrillation has also been found in such cases as below: myocardial infarction, after toxic doses of digitalis, in acute intoxication of alcohol, by carotid sinus and/or eye ball pressure, after surgical operations in the thorax and in the abdominal cavity. Familial occurrence has also been rarely reported for this arrhythmia. Although atrial fibrillation is generally associated with severe organic heart diseases, it is occasionally seen in patients without underlying cardiac affections, as described in detail by FRIEDBERG and EVANS and SWANN.

There have been many theories or hypotheses proposed to the pathogenesis and the mechanism of the arrhythmias, but it has not yet come to a definite conclusion generally accepted. Atrial fibrillation and flutter in man might not be always similar in the pathogenesis and the mechanism to the arrhythmias experimentally produced in animals, nevertheless, the investigation for the latter has played an important role in the studies of the pathogenesis and the mechanism of atrial fibrillation and flutter in man.

ROSENBLOETH and GARCIA RAMOS induced atrial flutter by the combination of crushing and electrical stimulation of the auricular muscle. SCHERF et al. induced atrial flutter and fibrillation by the topical application of aconitine to the auricle, and also SCHERF and his co-workers found that atrial flutter or fibrillation could be obtained by vagal stimulation after subepicardial injection of hypertonic solution of sodium chloride in the area of the sinus node. JAMES and HERSHEY induced atrial fibrillation by vagal stimulation after administration of either calcium salt or catecholamines to dogs.
whose sinus node arteries were ligated. Scherf and Chick produced atrial fibrillation by the topical application of acetylcholine to the auricle. Burn et al. induced atrial fibrillation by stimulation of the right atrium during the infusion of acetylcholine into the heart-lung preparation. Holland and Burn induced atrial fibrillation by electrical stimulation in the presence of acetylcholine in isolated rabbit atrium suspended in a dilute solution of potassium salt. Leveque produced atrial fibrillation by administration of thyroid extract and intravenous acetylcholine. Winterberg, Robinson and other workers found that the arrhythmias might occasionally take place as a result of mere vagal stimulation. These experimental methods of producing the atrial arrhythmias have facilitated the studies on the pathogenesis or the mechanism of these arrhythmias, though in most cases, the arrhythmias were induced by some kinds of mechanical stimulation applied directly to the heart.

This study was attempted to obtain atrial fibrillation experimentally without mechanical stimulation to the heart; and the experiments were performed with closed chest preparations.

**Materials and Methods**

Experiments were performed in 69 healthy mongrel dogs of both sexes weighing from 5 to 18 kg. The dogs were anesthetized with Nembutal (20 to 40 mg per kg, intravenously), and then most of them were heparinized for the femoral catheterization. Electrocardiograms of standard L2 and esophageal leads or direct unipolar atrial leads were recorded simultaneously with a direct-writing oscillograph, and in most cases the femoral arterial blood pressure was also recorded. Since the direct atrial surface electrodes would stimulate mechanically the atrial myocardium, esophageal electrodes were employed except for 2 cases. The experiments were performed with closed chest preparations except for 2 cases in which the direct atrial electrodes were used.

Vagal stimulation and intravenous injection of epinephrine were applied several times before and after infusion of each of those six aqueous solutions described below. After control observations, intravenous infusion of each solution was performed to predispose the heart to atrial fibrillation.

The six groups of solutions were the following:

- a) 2% sodium lactate,
- b) 5% sodium lactate,
- c) 2% sodium lactate with 0.2% of sodium bicarbonate,
- d) 2% lactic acid,
- e) 2% sodium bicarbonate,
- f) 0.86% sodium chloride.

The volume of the infused solution ranged from 30 to 120 cc per kg, but in most cases about 40 cc per kg of solution was used. Each solution was heated up to the body temperature before the infusion. The infusions were performed at various volume velocities which will be described later in detail.

Vagal stimulation was made with an electronic stimulator to the left or the right side portion of the thyroid cartilage. The cervical vagi were not cut in most cases. The voltage for the vagal stimulation ranged from 0.3 to 4 volts, the shape of the stimulating wave was square and the frequency used was about 20 cycles per second.

When atrial fibrillation or flutter did not occur by vagal stimulation, in addition, injection of 0.03 to 0.08 cc of 1:1,000 epinephrine per kg was performed within an interval of 15 seconds.

The experiment in each dog lasted 4 to 9 hours.

**Results**

I) Procedures before and after Infusion

The results of this experiment are summarized in Tables I and II.

i) Control Procedures: As shown in Table I, vagal stimulation was performed 100 times in 67 dogs before infusion and atrial fibrillation was induced 4 times in 4 dogs. Epinephrine was intravenously injected 70 times in 67 dogs during vagal stimulation and atrial fibrillation was induced 2 times in 2 dogs. It is clear from the results that vagal stimulation or epinephrine injection during vagal stimulation in untreated dogs may produce atrial fibrillation, but the incidence is rather low. In control procedures, only one dog died of ventricular fibrillation occurred about 70 seconds after injection of epinephrine during vagal stimulation; this case is not being included in those 69 dogs described above.

ii) Procedures after Infusion (Table II)

a) 2% sodium lactate: Thirty-seven dogs were used for this experiment. 2% sodium lactate in doses of 29–80 cc/kg (average 41 cc/kg) was infused intravenously. The infusion was performed in most cases taking 1–3 hours and in 3 exceptional cases it was finished within 25 minutes. In the electrocardiograms recorded...
after infusion, it was found no definite tendencies in the change of the P-Q interval as compared with control electrocardiograms. In half of this group the P-Q interval was slightly

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<th>Table I  Procedures before infusion</th>
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<tr>
<td>a) 2% sod. lact.</td>
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<td>b) 5% sod. lact.</td>
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<td>c) 2% sod. lact. with 0.2% of sod. bic.</td>
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<td>d) 2% lactic acid</td>
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<td>e) 2% sod. bic.</td>
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<td>f) 0.86% sod. chloride</td>
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* a.f. means atrial fibrillation or flutter, or fibrillo-flutter.

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* a.f. means atrial fibrillation or flutter, or fibrillo-flutter.
prolonged after infusion, whereas for the rest no considerable change was observed except for 2 cases in which the P-Q interval was slightly shortened. Vagal stimulation was made 122 times after infusion and atrial arrhythmias (the term "atrial arrhythmias" in this report means atrial fibrillation, flutter or fibrillio-flutter, it does not include sinus tachycardia, wandering pacemaker, A-V block and other supraventricular arrhythmias) were induced

Fig. 1. Procedures 1 hour after intravenous infusion (38 cc/kg/50 min.) of 2% sodium lactate. The figures written above the loci of blood pressure denote the time elapsed after the initiation of vagal stimulation.

A. atrial flutter induced by vagal stimulation.
B. spontaneous conversion of atrial flutter to fibrillation during vagal stimulation.
C. restoration of sinus rhythm, occurred shortly after the cessation of vagal stimulation. Stimulation was discontinued at the point shown by the arrow.

10 times in 6 dogs. An example, in which atrial flutter and fibrillation was induced, is illustrated in Figs. 1-A, B and C. In this case atrial flutter with an atrial rate of about 660 per minute was induced immediately after vagal stimulation (Fig. 1-A). After 18 seconds, it converted spontaneously to atrial fibrillation (Fig. 1-B). Vagal stimulation was discontinued 128 seconds after the onset of atrial flutter, and sinus rhythm was restored a few seconds later (Fig. 1-C).

Intravenous injection of epinephrine during vagal stimulation was made 96 times and atrial arrhythmias were observed 16 times in 11 dogs. The electrocardiograms immediately before the onset of the arrhythmias exhibited various patterns. There were several cases in which the occurrence of the arrhythmia was indistinct at the onset, but it became apparent a few minutes later (Figs. 2-A, B and C). That shown in Fig. 2 is an example of atrial fibrillation induced by epinephrine injection during vagal stimulation in a dog in which 2% sodium lactate was infused. A-V block with a marked ventricular slowing occurred by vagal stimulation (Fig. 2-A), and then 5 μg per kg of epinephrine was injected intravenously. As it is seen in Fig. 2-B, ventricular tachycardia occurred 35 seconds after the termination of epinephrine injection and also atrial fibrillation occurred, although the onset of the arrhythmia was not clear because of the overlapping of f-waves and rapid QRS complexes. But, after the appearance of normal QRS complexes f-waves became to be
clearly discriminated (Fig. 2–C).

In total, atrial fibrillation was produced 5 times in 5 of 37 dogs before infusion and in 2 of these 5 dogs atrial fibrillation was not obtained after infusion, and atrial arrhythmias were produced after infusion in 15 of the 37 dogs.

b) 5% sodium lactate: 5% sodium lactate was infused in 3 dogs. Doses ranged from 36 to 80 cc/kg (average 63 cc/kg) and infusion was intermittently performed in 2 or more times in each dog taking 3–6 hours. In the electrocardiograms after infusion, prolongation of the P-Q interval (20 per cent or more longer than that of the control electrocardiograms) was observed in all 3 cases. Atrial arrhythmias were not obtained by mere vagal stimulation in 13 attempts in 3 dogs. By epinephrine injection during vagal stimulation, atrial fibrillation was obtained in all 3 dogs.

c) 2% sodium lactate with 0.2% of sodium bicarbonate: Four dogs were used in this experiment. After anesthesia a thoracotomy was used to expose the heart and the breathing was controlled by the respirator in 2 of the 4 dogs. In these 2 dogs direct unipolar atrial lead was recorded. The dogs to which direct atrial electrode was applied were only 2 out of all 69 dogs. In the group which consisted of 2 thoracotomized and 2 non-thoracotomized dogs, the amount of infused solution was larger than those in other groups; the total amount of infusion ranged from 57 to 127 cc/kg (average 85 cc/kg). Infusion was performed in the same way as described in group b. In electrocardiograms, P-Q interval after infusion was slightly (10–20 per cent) longer than that before in all 4 cases. Vagal stimulation induced atrial fibrillation 3 times (in 2 dogs) in 19 attempts. An example of atrial fibrillation by vagal stimulation is shown in Fig. 3. After vagal stimulation R-R interval lengthened slightly, and then abruptly atrial fibrillation occurred. Epinephrine was injected 13 times during vagal stimulation and atrial fibrillation was produced 10 times in these 4 dogs. The incidence of atrial fibrillation by vagal stimulation with epinephrine injection after infusion was markedly higher than that of control procedures.

d) 2% lactic acid: 2% lactic acid in doses of 64 to 86 cc/kg (average 72 cc/kg) was infused into 4 dogs. The P-Q interval did not change considerably before and after infusion in all 4 cases. Both vagal stimulation (10 attempts) and injection of epinephrine during vagal stimulation (9 attempts) did not produce atrial arrhythmias. In 3 of these 4 dogs, the breathing

Fig. 2. Procedures 2 hours and 50 minutes after intravenous infusion (33 cc/kg/75 min.) of 2% sodium lactate. The figures written above the loci of blood pressure denote the time elapsed after the termination of injection of epinephrine.

A. A-V block by vagal stimulation.
B. Conversion of ventricular tachycardia to atrial fibrillation occurred by intravenous injection of epinephrine during vagal stimulation.
C. Spontaneous change in normal sinus rhythm during vagal stimulation. Atrial fibrillation stopped at the point shown by the arrow.

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stopped 1–2 hours after the termination of infusion, and the dogs died.

e) 2% sodium bicarbonate: Eighteen dogs were used for this experiment. The amount of infused solution ranged from 30 to 80 cc/kg (average 43 cc/kg). Infusion was performed within a period of about 3 hours in 7 of the 18 dogs, and in 10 of the rest within about 1 hour. Rapid infusion was applied to one dog to see whether atrial arrhythmias could be induced immediately after the termination of rapid infusion. As already been described before, rapid infusion was also applied to 3 cases with 2% sodium lactate. The relationship between the occurrence of atrial arrhythmias and the time elapsed after the termination of rapid infusion will be described in later section. The P-Q interval was prolonged slightly after the infusion of 2% sodium bicarbonate in 7 of the 18 cases, but for the rest no changes were observed. When vagal stimulation was made after infusion, atrial arrhythmias occurred 19 times (in 7 dogs) in 86 attempts (in the 18 dogs). Intravenous injection of epinephrine during vagal stimulation was performed 43 times and the arrhythmias were produced 17 times in 12 of the 18 dogs. One of these positive cases is presented in Fig. 4 as an example. A-V block occurred after epinephrine injection during vagal stimulation, and then suddenly occurred atrial fibrillation with a marked ventricular slowing. In total, atrial arrhythmias were obtained in 17 of 18 dogs.

f) 0.86% sodium chloride: Three dogs were used. After infusion, the P-Q interval was slightly prolonged in 2 cases, and did not change in the other. Vagal stimulation was performed 14 times in the 3 dogs to whom 88–123 cc/kg (average 100 cc/kg) of 0.86% sodium chloride was being infused, but atrial arrhythmias did not occur at all. Vagal stimulation was followed by injection of epinephrine 11 times, but there were no episodes of atrial arrhythmias. This experiment was attempted to ascertain whether the increase in circulating blood volume caused by massive dose of infusion might predispose the heart to atrial arrhythmias. Accordingly the amount infused in this group was larger than that in any other group.

The above mentioned descriptions can be summarized as follows:

1) Both vagal stimulation and the combination of vagal stimulation and epinephrine injection rarely initiated atrial fibrillation in normal untreated dogs.

2) Atrial arrhythmias were obtained by fairly large possibilities after infusion in groups a, b, c and e; infusion of sodium lactate and/or sodium bicarbonate predisposed the dog heart to atrial arrhythmias.

3) The incidence of the arrhythmias pro-

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Fig. 3. Procedure immediately after intravenous infusion (57 cc/kg/30 min.) of 2% sodium lactate with 0.2% of sodium bicarbonate. The electrocardiograms demonstrate atrial fibrillation induced by vagal stimulation. The onset of the arrhythmia was indicated by the arrow upon the direct unipolar lead in the upper strip.
duced after infusion of 2% sodium bicarbonate was higher than that of 2% sodium lactate.

II) Observations of Atrial Arrhythmias obtained experimentally

i) Onset of arrhythmias

Vagal stimulation: Cervical vagus was not cut in most of the dogs used, but it was cut in 3 cases of 0.86% sodium chloride group, in 2 cases of 2% sodium bicarbonate group, in 5 cases of 2% and 5% sodium lactate groups, and in 4 cases of 2% sodium lactate with 0.2% of sodium bicarbonate group. In the dogs in which 0.86% sodium chloride was infused, vagus was not cut in the first half of the experiment and after several procedures it was cut and then the rest of the experiment was continued. In the dogs in which the right vagus was cut, its distal end was stimulated. Vagal stimulation changed normal sinus rhythm to sinus bradycardia, various degrees of A-V block or sinus arrest. These changes appeared to be little affected by the cut of the right vagus. Since only in few cases the right vagus was cut and further these cases consisted of those from the 4 groups (a, b, c and e) among which the incidence of atrial arrhythmias varied, it is difficult to estimate the effect of the cut of the vagus on the incidence of arrhythmias. In 3 of the 11 dogs atrial fibrillation was induced 5 times by vagal stimulation, but in one of those eleven dogs arrhythmia was induced also in a control procedure.

In one dog (No. 37) in which 5% sodium lactate was infused, the right vagus was cut and stimulated at the distal end in the first half of the experiment, but after then the stimulation became ineffective somehow by accident. Consequently the left vagus was utilized for electrical stimulation without cutting. In this case atrial fibrillation was induced 2 times by epinephrine injection during left vagal stimulation.

It was generally observed that the effects of vagal stimulation decreased with time. It was also observed that atrial arrhythmia occurred either during vagal stimulation (Fig. 5-A), or immediately after the cessation of vagal stimulation (Fig. 5-B). The electrocardiograms shown in Figs. 5-A and B were obtained in the same dog (No. 127). Atrial arrhythmias occurred 4 times after the cessation of vagal stimulation in 4 out of all 69 dogs. As to these 4 cases, vagal stimulation was discontinued after atrial standstill of about 3 seconds in 2 cases, after second degree A-V block of 41

Fig. 4. Procedures 1 hour and 20 minutes after intravenous infusion (46 cc/kg/2 h) of 2% sodium bicarbonate. The electrocardiograms demonstrate atrial fibrillation induced by vagal stimulation and intravenous injection of epinephrine. The figures written above the esophageal lead denote the time elapsed after the termination of injection of epinephrine.

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seconds in one case and after ventricular ectopic beats of 56 seconds in one case, and then atrial arrhythmias occurred abruptly within a second. As to the other cases in which atrial arrhythmias occurred during vagal stimulation, mostly (18 times in 25 attempts) the arrhythmia occurred 3–30 seconds after the beginning of vagal stimulation. The electrocardiograms immediately before the onset of atrial arrhythmias showed sinus bradycardia, various degrees of A-V block, sinus arrest or ventricular premature beat.

It was observed that atrial fibrillation generated by vagal stimulation mostly began shortly after a QRS complex with a normal P wave or shortly after a QRS complex of a supraventricular or a ventricular premature beat. It was also true that sometimes atrial fibrillation began during complete asystole following vagal stimulation.

Vagal stimulation and epinephrine injection: Intravenous injection of epinephrine was performed several times after vagal stimulation in each dog. The electrocardiograms before epinephrine injection showed various degrees of sinus bradycardias with or without A-V block. When the pacemaking function in the sinus node was extremely suppressed by the strong vagal stimulation, epinephrine was not injected, because the effect of epinephrine was not expected much in such a case.

The electrocardiographic changes following injection of epinephrine are diversified as follows; sinus tachycardia, wandering pacemaker, ventricular tachycardia, frequent multiple multifocal extrasystoles, A-V nodal rhythm and in a few cases transient ventricular flutter which occurs during ventricular tachycardia. On the contrary, there are many cases which showed inhibition of pacemaking function in the sinus node with inhibition of stimulus conduction in the A-V node, such as sinus brady-

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**Fig. 5.** Procedures after intravenous infusion (41cc/kg/1h) of 2% sodium bicarbonate.

A. atrial fibrillation occurred at the point shown by the arrow in the upper strip during vagal stimulation (45 minutes after the infusion).

B. vagal stimulation was discontinued at the point shown by the arrow in the lower strip, and then atrial fibrillation occurred. This experiment was performed 2 hours and 10 minutes after the infusion.
cardia and various degrees of A-V block including A-V block with or without ventricular extrasystoles. In some of these cases no remarkable increase is observed in femoral arterial blood pressure after injection of epinephrine.

In total, atrial fibrillation was generated 47 times in groups a, b, c and e by epinephrine injection during vagal stimulation after infusion. Atrial arrhythmias were observed in both groups which showed different responses to epinephrine, as seen in Figs. 2 and 4.

Intravenous injection of epinephrine was performed within an interval of 15 seconds in each experiment. In the cases in which atrial arrhythmias were obtained, it took 9–120 seconds (mostly 10–20 seconds) to reach the onset of the arrhythmia from the termination of epinephrine injection. Atrial arrhythmia mostly began shortly after a QRS complex with or without a P wave, however there were not a few cases in which the onset of the arrhythmia was not clear because of overlapping of rapid QRS complexes upon atrial waves.

Asphyxia: In 2 thoracotomized dogs in which 2% sodium lactate with 0.2% of sodium bicarbonate was infused, asphyxia was produced by stopping the respirator connected to endotracheal cannula. In these 2 dogs, atrial fibrillation was induced both by vagal stimulation and by epinephrine injection during vagal stimulation after the infusion. After several procedures, the respirator was stopped and atrial fibrillation occurred (Fig. 6–A, B, C

Fig. 6. Procedures after intravenous infusion (78 cc/kg) of 2% sodium lactate with 0.2% of sodium bicarbonate. The electrocardiograms demonstrate atrial fibrillation occurred during asphyxia.

A. asphyxia was initiated at the point shown by the arrow.
B. atrial fibrillation occurred at the point shown by the arrow, 1 minutes and 26 seconds after the initiation of asphyxia.
C. rebreathing began at the point shown by the arrow, 54 seconds after the onset of atrial fibrillation.
D. sinus rhythm was restored at the point shown by the arrow, 28 second after the initiation of rebreathing.

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and D). In the case shown in Fig. 6–B, (No. 32) atrial fibrillation occurred 1 minutes and 26 seconds after the initiation of asphyxia. Air-breathing was re instituted 54 seconds after the onset of atrial fibrillation, and sinus rhythm was restored 28 seconds after the initiation of rebreathing (Fig. 6–C and D). Asphyxia was once more produced about 3 minutes after the above experiment; the respirator was stopped for 4 minutes, but there was no episode of fibrillation. In the other dog (No. 31), the respirator was stopped and atrial fibrillation occurred after 20 seconds. It continued for 8 seconds and then converted to sinus rhythm, while asphyxia being still maintained. Atrial fibrillation once again occurred 27 seconds after the conversion of atrial fibrillation to sinus rhythm. Rebreathing was performed 3 minutes and 40 seconds after the onset of the arrhythmia and fibrillation stopped 1 minute and 50 seconds after the initiation of rebreathing. In this dog, asphyxia was again produced a few minutes later and atrial fibrillation occurred, it continued for about 5 minutes and changed to sinus rhythm without reinstatement of air breathing. In total, atrial fibrillation was observed in 3 out of 4 asphyxia experiments in 2 dogs, but it must be remembered that these asphyxia experiments were performed after many procedures as described above.

Spontaneous atrial fibrillation: Spontaneous atrial fibrillation was observed only in one dog (No. 36) in which 2% sodium lactate was infused. In this dog, atrial fibrillation was induced both before and after the infusion. After the above experiment it happened a complete irregularity of the pulse, and the electrodes were connected again to record the electrocardiograms. It showed distinct atrial fibrillation. The arrhythmia had continued for more than 20 minutes until it changed spontaneously to sinus rhythm.

In other dog (No. 31) in which 2% sodium lactate with 0.2% of sodium bicarbonate was infused, atrial fibrillation was induced by vagal stimulation. The stimulus was discontinued 230 seconds after the onset of atrial fibrillation, but the arrhythmia lasted out for 309 seconds. Then it changed to A-V block which continued for 10 seconds and converted spontaneously to atrial fibrillation which

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<th>Table III Duration of atrial fibrillation, flutter or fibrillo-flutter after infusion</th>
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<td>b) 5% sod. lact.</td>
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<td>38 248</td>
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<td>34 126, 77+2.5, 51</td>
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<td>d) 2% sod. bic.</td>
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* The cases where atrial fibrillation occurred spontaneously and in asphyxia experiments are not included in this table.

Key to designations:

*: Arrhythmia terminated immediately after the cessation of stimulation.
**: Arrhythmia occurred after the cessation of stimulation.+ : Figures following ‘+’ sign represent duration of arrhythmia after the cessation of stimulation or after the removal of ‘voltage of stimulation’.

*: Arrhythmia was observed also in control procedure.
continued for 675 seconds.

In the first case (No. 36) the electrocardiograms were being recorded for a while after the last experiment, accordingly it is clear that the onset of spontaneous atrial fibrillation was more than 10 minutes after the last experiment. As to the second case, however, it should be realized that the changes in cardiac rhythm were rather momentary restoration of pacemaking function in sinus node occurred during atrial fibrillation than the onset of atrial fibrillation during A-V block.

ii) Duration of the Arrhythmias

Duration of the arrhythmias was various as illustrated in Table III. The shortest was 0.5 second and the longest was 58 minutes. The arrhythmia might continue much longer in the case of the longest duration, unless the stimulus of vagus had been interrupted, since in this case the arrhythmia converted to sinus rhythm immediately after the cessation of vagal stimulation. When the stimulus was discontinued during atrial arrhythmias which were induced by vagal stimulation or by the combination of the stimulus and epinephrine injection, the arrhythmia changed to sinus rhythm within 1 second in 5 of 23 attempts, while it continued over 10 seconds in 8 of the 23 attempts. In one case (No. 31) in which atrial fibrillation was induced by vagal stimulation after infusion of 2% sodium lactate with 0.2% of sodium bicarbonate, the arrhythmia continued for 309 seconds after the cessation of vagal stimulation. The duration of atrial arrhythmia before the cessation of vagal stimulation was not so long in the above case, but the duration of the arrhythmia after the cessation of the stimulus was long. In 4 cases in which atrial arrhythmia was induced immediately after the cessation of vagal stimulation, the durations were found to be 0.5 second in 1 case, 5 seconds in 2 cases and 76 seconds in 1 case. A case of momentary atrial fibrillo-flutter, occurred after the cessation of the stimulus, is illustrated in Fig. 7. The atra were beating regularly at a rate of about 1100 per minute.

The duration of the arrhythmias occurred spontaneously and induced by asphyxia after infusion was described in the last section.

It was observed that momentary wandering

Fig. 7. An example of momentary atrial fibrillo-flutter induced after the cessation of vagal stimulation in a dog in which 2% sodium lactate was infused. Vagal stimulation began at the first arrow and was interrupted at the second arrow written above the esophageal lead. Note that a brief paroxysm of fibrillo-flutter is perceptible from the third to fourth arrow (black out) written above the esophageal lead, and that then it changed to wandering pacemaker (shown by small paralleled arrows), and finally to A-V nodal rhythm.

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pacemaker lay between atrial fibrillation and normal sinus rhythm in many cases, and that abrupt restoration of sinus rhythm occurred sometimes. It was also observed that f-waves became coarse and relatively regular near the end of atrial fibrillation and that sinus rhythm was restored after then in some cases.

iii) Rapid Infusion:

Rapid infusion was performed in 4 dogs. In 3 of them 2% sodium lactate was infused and 2% sodium bicarbonate was for the rest. In 4 cases, neither vagal stimulation nor epinephrine injection during vagal stimulation produced atrial arrhythmia before and immediately after the rapid infusion. In one of the 3 cases in which 2% sodium lactate was infused, atrial arrhythmia was not induced, notwithstanding that epinephrine was injected 4 times during vagal stimulation. Atrial arrhythmias were induced 6 times in 3 of all 4 cases 40 minutes or more after the termination of rapid infusion. In contrast with these results, atrial arrhythmias were often produced immediately after infusion in dogs when infusion was performed slowly.

DISCUSSION

It was observed in this experiment that infusion of solutions of both sodium bicarbonate and sodium lactate over a certain dose would predispose the heart to atrial fibrillation, fibrilllo-flutter or flutter. However, the arrhythmias were not induced by mere infusion of these drugs. Only once in all 69 cases, atrial fibrillation occurred spontaneously in a dog to which a large amount of sodium lactate solution was administered. In this case, however, atrial fibrillation was also obtained by vagal stimulation both before and after infusion. In control experiments (Table I) atrial fibrillation was induced 6 times in 6 dogs (including this particular one) by vagal stimulation or epinephrine injection during vagal stimulation.

It is generally accepted that the extrinsic nerves of the heart play an important role in the pathogenesis of atrial fibrillation. On rare occasions atrial fibrillation occurs after emotional stress. A number of clinical and experimental investigations have been reported on atrial fibrillation caused by vagal stimulation. UEDA et al. observed that atrial fibrillation was produced by electrical stimulation of vagal nuclei. WOLPERT, Cannata and NARBONE, Nahum and Hoff and Fujii et al. reported interesting clinical cases in which paroxysms of atrial fibrillation or fibrillo-flutter were induced by carotid sinus and/or eye ball pressure. WINTERBERG, ROBINSON, LEWIS et al. reported that in animals atrial fibrillation was induced by only electrical stimulation of the vagus.

It is apparent from the present results that atrial fibrillation is induced by vagal stimulation not only after but also before the infusion, and that vagal stimulation is one of the important factors to initiate atrial arrhythmias. However, the incidence of atrial arrhythmias induced by vagal stimulation in control experiments was extremely low; 4 times in 100 attempts. (4 per cent).

As to the effects of vagal stimulation of the heart, there have been numerous experimental studies. In this experiment the right vagus was utilized for electrical stimulation in all cases except one.

It is commonly known that the right vagus mainly affects the sino-atrial node and the left does mainly the atrio-ventricular node. In one dog in which 5% sodium lactate solution was infused, the left vagus was stimulated and then epinephrine was injected intravenously, and atrial fibrillation was obtained 2 times in 4 attempts. As to the electrocardiograms, however, no significant difference was observed between the right and left vagus stimulation.

BROOKS et al. described that no significant or consistent difference was observed between the right and left vagus with respect to the changes produced in atrial excitability and conductivity and that cutting both vagi had no appreciable effect on excitability of the atrium.

In this experiment, the electrocardiographic changes caused by vagal stimulation were found to be little affected by the cut of vagus.

It is generally accepted that vagal stimulation increases the membrane permeability of potassium ion, shortens the action potential duration and the refractory period in atrial
myocardium, and that these changes prepare the grounds for atrial fibrillation. Alessi, et al.\textsuperscript{30} reported that the effects of vagal stimulation were not uniformly distributed in atrium. In many studies\textsuperscript{30}, that nonuniformity of the effect of vagal stimulation results in fibrillation has been mentioned rather affirmatively.

With respect to atrial fibrillation and its relation to the sinus node function, James and Hershey\textsuperscript{5,34,35} confirmed from the clinicopathologic and experimental studies that ischemia or injury of the sinus node was one of the factors which influence the onset of atrial fibrillation.

Atrial arrhythmias were obtained 4 times in all 69 dogs immediately after the cessation of vagal stimulation. In 3 of the 4 cases, pacemaker function in the sinus node was strongly inhibited by vagal stimulation. In all 4 cases the arrhythmias occurred within a second after the cessation of the stimulus. The fact that the complicated neurovegetative disorder after the cessation of stimulation would affect the occurrence of atrial arrhythmias should be more carefully considered in these 4 cases.

In this experiment, epinephrine was injected during vagal stimulation in order to produce neurovegetative disorders. Epinephrine injection during vagal stimulation resulted in atrial fibrillation 2 times in 70 attempts in control experiments. As described above, in groups a, b, c and e atrial arrhythmias were induced at a high percentage by the combined application of vagal stimulation and epinephrine injection after infusion.

It is a well known fact that epinephrine results in various kinds of atrial and/or ventricular arrhythmias. However, in the control procedures atrial fibrillation was produced only twice by epinephrine injection during vagal stimulation while in most of the other cases ventricular tachycardia or multiple ventricular premature beats were observed, and in some of the cases various degrees of A-V block and wandering pacemaker etc. were observed. It was noted that the effects of epinephrine varied from dog to dog and were considerably influenced by vagal activity.

With regard to neurovegetative balance, an interesting clinical case has been reported by Smith and Moody\textsuperscript{30}. Whenever the patient was extremely nervous, momentary atrial fibrillation was induced by forced breathing, but, when he was calm, the arrhythmia was not induced by forced breathing without epinephrine administration.

There is a disagreement in opinions concerning the effects of epinephrine on the atrium. According to Webb and Hollander\textsuperscript{37}, epinephrine generally produce the opposite effects to acetylcholine, slowing the repolarization rate and depressing slightly both the resting and action potentials of rat atrium. On the other hand, Brooks et al.\textsuperscript{31} described that both the absolute and relative refractory periods of atrium were decreased by l-epinephrine.

But either of the two different opinions should not be discarded at once, because epinephrine may produce different effects depending upon both the concentration and the state of the responding tissue. It is quite possible that these different opinions are consistent with each other.

From this experiment it is conceivable that the onset of atrial fibrillation might be influenced not only by parasympathetic tonus but also by sympathetic tonus. It might be rather said that neurovegetative disorders result in the arrhythmia in certain condition.

In the dogs in which the solutions of sodium lactate and/or sodium bicarbonate were infused (groups; a, b, c and e), atrial fibrillation were often produced as written below; by vagal stimulation 10 times in 122 attempts in group a, 3 times in 19 attempts in group c, 19 times in 86 attempts in group e, and by epinephrine injection during vagal stimulation 16 times in 96 attempts in group a, 4 times in 11 attempts in group b, 10 times in 13 attempts in group c and 17 times in 43 attempts in group e. On the other hand, neither vagal stimulation nor epinephrine injection during vagal stimulation produced atrial arrhythmias in groups d (2% solution of lactic acid, 4 dogs) and f (physiological solution of sodium chloride, 3 dogs). If the infusion of solution of lactic acid or sodium chloride does not prevent atrium from fibrillating, atrial fibrillation would occur also after

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the infusion of these substances at an incidence as low as that observed in control experiment. It should also be mentioned here that not all of the atrial arrhythmias which occurred after the infusion of sodium lactate and/or sodium bicarbonate solution were predisposed by the infusion, since the arrhythmias were also induced, even rarely though, in control experiments.

Generalized cooling of the heart results often in spontaneous arrhythmias\(^{39,40}\). The refractory period of atrium is affected by cooling the heart\(^{41}\). According to HOLLAND and KLEIN\(^{42}\), the changes in temperature of the heart influence the efflux and the influx rates of potassium. Taking into consideration of these effects of cooling the heart the solution was heated up to the body temperature when infusion was performed in this experiment.

It is generally accepted that atrial distension predisposes the heart to atrial fibrillation. DINBAUM and his co-workers\(^{43}\) observed that the refractory period shortened when the atria were stretched. A large amount of infusion would result in an transitory increase of circulating blood volume and consequently dilatation or stretch of atrial muscle would be produced. Therefore, the effect of the increase of circulating blood volume occurred after infusion should be carefully checked in this experiment. Atrial arrhythmias were obtained neither by vagal stimulation nor by epinephrine injection during vagal stimulation after a large amount of infusion of physiological sodium chloride solution. Therefore it may be said that the increase of circulating blood volume is not an important predisposing factor in the production of the arrhythmias, at least in this experiment.

Intravascular hemolysis in alkalosis created by 5\% sodium bicarbonate solution in dogs was reported by BINDSLEV\(^{44}\). If intravascular hemolysis occurred, potassium content in serum would increase and it would more or less influence the heart, but hemolysis was not observed in the dogs of groups a, b, c, e and f.

In considering the facts mentioned above, it is concluded that the infusions of both sodium lactate and sodium bicarbonate solutions (over a certain dose) predispose the heart to atrial arrhythmias. Furthermore, from the results of this experiment, it can be stated that the incidence of the arrhythmias induced after infusion of 2\% sodium bicarbonate was higher than that of 2\% sodium lactate.

With regard to the changes in acid-base balance following a rapid intravenous infusion of hypertonic solution of sodium bicarbonate, a detailed investigation has been reported by SINGER and his co-workers\(^{45}\). And as to the metabolism and the effects of sodium lactate to the heart, there have been many observations performed by BELLET and his associates\(^{46-49}\), LEE\(^{50}\), FUJITA\(^{60}\), MASUMURA\(^{61}\), WATANABE\(^{62}\) and others. The infusions of sodium bicarbonate and of sodium lactate solutions result in changes in concentration of serum electrolytes, O\(_2\), CO\(_2\), lactic and pyruvic acid and hydrogen ion (pH) in blood to various extents. The results of this experiment suggest that one or more of these changes predispose the heart to atrial arrhythmias.

HOLLAND and BURN\(^{51}\) induced atrial fibrillation by electrical stimulation in the presence of acetylcholine in isolated rabbit atria suspended in medium of low potassium. HOLLAND and his co-workers\(^{52,53,54}\) have emphasized that fibrillation begins at a time when the rate of transmembrane efflux of potassium, and possibly transmembrane influx of sodium, exceeds a certain critical value.

A decrease in concentration of serum potassium caused by the infusion of sodium lactate or sodium bicarbonate might be considered to be one of the predisposing factors in the occurrence of atrial arrhythmias in this experiment.

In asphyxia experiment after infusion of 2\% sodium lactate with 0.2\% of sodium bicarbonate, atrial fibrillation was observed. It has been shown both clinically\(^{55,56}\) and experimentally\(^{57}\) that asphyxia or hypoxia predisposes the heart to atrial fibrillation. DINBAUM and his associates\(^{58}\) observed that atrial flutter which was produced in open chest preparations changed to fibrillation during asphyxia, and they stated that a shortening of the refractory period by stretching the atria occurred during asphyxia might be a contributing factor in the
production of the arrhythmia.

Throughout these experiments, most of atrial arrhythmias occurred shortly after a QRS complex with or without a P wave of the electrocardiogram. ANDRUS and his co-workers\(^{36}\) and ORIAS et al.\(^{30}\) found that atrial fibrillation could be initiated by a single electrical stimulus applied to the atrium during its relative refractory period. WIGGERS and WEGRIA\(^{30}\) found that the latter part of systole constitutes a “vulnerable period” during which stimuli are effective in producing ventricular fibrillation. It is conceivable that one ventricular contraction can initiate atrial fibrillation when atrial myocardium is in the state liable to fibrillate as a result of the infusion of sodium lactate or sodium bicarbonate solution, and in addition, the contraction falls on the vulnerable phase of atrium.

The duration of atrial arrhythmias in this experiment (Table III) ranged from 0.5 second to 58 minutes. If vagal stimulation was not discontinued, the duration of the arrhythmias would be much longer in some cases. LEVEQUE\(^{20}\) produced atrial fibrillation by the administration of acetylcholine in thyrotoxic dogs. According to his experiment, the average duration of fibrillation was 26 seconds (ranged from 7 to 48 seconds in 12 cases). KLEIN and HOLLAND\(^{40}\) believed that the initiation and maintenance of atrial fibrillation were governed by separate physiochemical processes.

At the beginning or at the end of atrial arrhythmias in this experiment, fibrill-flutter was often observed. Fig. 8–A demonstrates the onset of atrial fibrillation with rapid, small, irregular atrial waves and Fig. 8–B shows fibrillo-flutter with relatively regular and coarse atrial waves. The arrhythmia changed to sinus rhythm several seconds after this tracing.

Only once, typical atrial flutter was observed following vagal stimulation in the dog in which 2% sodium lactate was infused (Fig. 1–A). It converted, after a while, spontaneously to atrial fibrillation (Fig. 1–B).

IKUTA\(^{41}\) observed that not only atrial flutter but also fibrillation were induced by the original ROSENBLUETH method. FUJIWARA\(^{30}\) found a number of dogs in which both atrial fibrillation and flutter were induced by topical application of acotinate to the atrium. And SCHERF et al.\(^{30}\) observed that atrial fibrillation with or

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Fig. 8. Procedure after intravenous infusion (40 cc/kg/75 min.) of 2% sodium bicarbonate.

A. atrial fibrillation occurred at the point shown by the arrow in the upper strip during vagal stimulation, 30 minutes after the infusion.

B. about 6 minutes and 30 seconds after the onset of atrial fibrillation. Note that atrial waves are relatively regular.
without short periods of flutter was obtained by subepicardial injection of hypertonic solution of sodium chloride over the area of the sinus node and faradic stimulation of the vagus.

As being suggested by these findings, the pathogeneses of atrial fibrillation and flutter of various origins are presumably much the same, although details are still obscure.

**SUMMARY**

1) Both vagal stimulation and epinephrine injection during vagal stimulation initiated atrial fibrillation in closed chest preparations, but the incidence was low.

2) After infusion of sodium lactate or sodium bicarbonate solution, atrial fibrillation was induced at a high percentage by epinephrine injection during vagal stimulation and also by mere vagal stimulation.

On the other hand, atrial fibrillation was not observed after the infusion of physiological sodium chloride solution or lactic acid solution.

3) The incidence of atrial arrhythmias induced after the infusion of sodium bicarbonate solution was higher than that of sodium lactate solution.

4) After the infusion of 2% sodium lactate with 0.2% of sodium bicarbonate asphyxia resulted in atrial fibrillation.

5) At the onset or at the end of atrial fibrillation fibrillo-flutter was often observed.

6) Atrial fibrillation mostly began shortly after a QRS complex with or without a P wave of the electrocardiograms.

7) The possible pathogeneses of the initiation of atrial fibrillation in this experiment were discussed.

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