The Effect of KCl on Atrial Fibrillation Caused by Acetylcholine


Atrial fibrillation can be produced in the heart-lung preparation of the dog by the slow infusion of acetylcholine and the application of electric stimuli to the auricle. The fibrillation can then be maintained indefinitely, after stimulation ceases, by continuing the infusion of acetylcholine. The fibrillation can be restored to normal rhythm by the infusion of KCl. This throws light on the action of acetylcholine in maintaining atrial fibrillation.

In the course of previous work on the Starling heart-lung preparation of the dog, a means was discovered of producing atrial fibrillation, of maintaining it for long periods and of arresting it at will. The method consisted in infusing acetylcholine (ACh) at constant rate into the blood going to the heart and then applying electric stimulation to the tip of the right atrium. The stimulation caused atrial flutter or fibrillation and once this had begun the stimulation was stopped. The fibrillation was then maintained as long as ACh was infused; the fibrillation reverted to normal rhythm only when the infusion was discontinued or atropine was injected. Fibrillation was observed in different experiments for periods up to one and one-half hours. When fibrillation had stopped, it could always be started again by the same method.

The present paper describes the effect of potassium chloride on atrial fibrillation produced in this way.

METHODS

The heart-lung preparation of the dog was made as described by Knowlton and Starling, the blood being rendered incoagulable by heparin. The dog which was used to supply blood was anesthetized with ether, and the preparation in the second dog was made under chloralose. Since the blood in the heart-lung circuit was mainly that of the first dog, there was only a small proportion of chloralose present during the actual experiment. A pair of electrodes was held in position on the upper surface of the tip of the right atrium by a spring clip. These electrodes did not pierce the atrium and caused minimal trauma. Stimuli were square wave pulses of 1 mA strength and of 0.9 msec. duration. Mean aortic pressure was recorded and an electrocardiogram was taken using a Cessor machine (model 1314), the needle writing on teledeltos paper. ACh was infused at a constant rate from a burette into the blood entering the cannula tied in the superior vena cava. The infusion was maintained by pressure at a rate which could be as slow as 0.1 or as fast as 2.0 ml. per min. To ensure that the rate was constant, readings were taken every minute. KCl was infused from a second burette in the same way.

RESULTS

Effect of KCl infusion on atrial fibrillation. The effect of an infusion of KCl is illustrated (fig. 1) by a kymograph record of the aortic pressure. ACh was infused at a rate of 1.6 mg./min., and stimulation was applied to the right atrium at a rate of 628/min. When fibrillation began, the stimulation was stopped. Figure 1a begins at this point. The fibrillation (as shown by the electrocardiogram) continued for 9 minutes and the ACh infusion was stopped. The rhythm returned to normal, as shown by the change in the blood pressure record. The ACh infusion then began again and fibrillation was again produced by a second period of stimulating the atrium. The stimulation was then stopped, and figure 1b begins at this point. When the fibrillation had continued for 9.5 minutes an infusion of KCl was given in addition to the infusion of ACh. The fibrillation stopped in 30 seconds after 50 mg. KCl had entered the vein. The KCl infusion was stopped.

Fibrillation was started for the third time by stimulation during ACh infusion. When the stimulation was stopped (fig. 1c) fibrillation...
was allowed to continue for 4.5 minutes and the infusion of KCl was started again. After 4 minutes the fibrillation stopped, and the KCl infusion was soon discontinued, 125 mg. having entered the blood. After this, in spite of continued infusion of ACh, stimulation failed to cause fibrillation except while it was applied during the period marked "St"; fibrillation stopped as soon as stimulation stopped. A further attempt was made by stimulating for a longer period ("Stim" in fig. 1c), but fibrillation continued for less than 2 minutes after stimulation stopped. It was evident that the rise of potassium in the blood prevented the continuance of the fibrillation which was normally seen during the infusion of ACh.

Figure 2 shows the electrocardiogram record in another experiment. Figure 2a is fibrillation produced by the infusion of 2.8 mg. ACh/min. and stimulation at 760/min. The stimulation had stopped 20 minutes before the record was taken. KCl was then infused. Figure 2b shows the large upright T waves which were commonly seen during KCl infusion, and figure 2c shows the restored normal rhythm when 410 mg. KCl had been infused. The details of five experiments are summarised in table 1. The second column shows the rate at which ACh was infused, and the third column the rate of stimulation applied to the right atrium. The fourth column shows the period for which fibrillation was allowed to continue after stopping stimulation, before the infusion of KCl was begun. The infusion was made at the rate of about 50 mg./min., and the time which elapsed before the normal rhythm returned is recorded in the fifth column. In the sixth column is the total amount of KCl infused into the preparation in which there was usually 1 litre of blood.

After infusion of KCl, not only was normal rhythm restored, but it also became difficult to re-establish fibrillation and, if it was re-established, it persisted only for a short time. In 4 out of the 5 experiments, the fibrillation did not outlast the cessation of stimulation by more than 2 minutes, in the fifth it outlasted it only by 5 minutes.

**Experiments using an anticholinesterase.** In three other experiments eserine was added to the blood in the reservoir. In its presence the infusion of much smaller amounts of ACh was
EFFECT OF KCl ON ATRIAL FIBRILLATION

TABLE 1.—The Effect of KCl on Fibrillation Produced by Electric Stimulation in the Presence of ACh

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Rate of ACh infusion mg/min.</th>
<th>Rate of stimulation per min.</th>
<th>Duration of fibrillation before infusion of KCl in min.</th>
<th>Period of infusion of KCl before normal rhythm returned, in min.</th>
<th>Mg. KCl infused</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.6</td>
<td>628</td>
<td>10</td>
<td>0.5</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>768</td>
<td>15</td>
<td>5.0</td>
<td>270</td>
</tr>
<tr>
<td>3</td>
<td>0.92</td>
<td>526</td>
<td>16</td>
<td>1.5</td>
<td>130</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>1000</td>
<td>10</td>
<td>6.0</td>
<td>300</td>
</tr>
<tr>
<td>5</td>
<td>2.8</td>
<td>760</td>
<td>20</td>
<td>3.0</td>
<td>410</td>
</tr>
</tbody>
</table>

TABLE 2.—The Effect of KCl on Fibrillation Produced by Electric Stimulation in the Presence of an Anticholinesterase

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Concentration of eserine</th>
<th>Rate of ACh infusion pg/min.</th>
<th>Rate of stimulation per min.</th>
<th>Duration of fibrillation before infusion of KCl in min.</th>
<th>Mg. KCl infused</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>$3 \times 10^{-8}$ molar</td>
<td>6</td>
<td>748</td>
<td>14</td>
<td>159</td>
</tr>
<tr>
<td>7</td>
<td>$1.5 \times 10^{-4}$ molar</td>
<td>40</td>
<td>576</td>
<td>16</td>
<td>415</td>
</tr>
<tr>
<td>8</td>
<td>$3 \times 10^{-8}$ molar</td>
<td>8</td>
<td>1100</td>
<td>20</td>
<td>100</td>
</tr>
</tbody>
</table>

dogs in which the fibrillation was produced by a powerful electric shock. Wiggers injected 1 ml. of 5 per cent KCl per Kg. into each ventricle, arresting the fibrillation. The injection of a similar quantity of CaCl₂ then restored a co-ordinated beat. Piccione and Scherf produced extrasystolic arrhythmias by the application of 10 per cent NaCl to a small area on the right ventricle and abolished them by subsequent application of KCl to the same area. We have found no references to the effect of KCl on fibrillation of the atria.

Atrial fibrillation, produced in the heart-lung preparation of the dog by the method described, clearly depends on the action of ACh, since it continues for as long as ACh enters the blood, reverting to normal rhythm when the stream of ACh is stopped. Thus the fibrillation is no transitory phenomenon as when ACh is applied locally to the pacemaker, but is a condition which can be maintained indefinitely. The fibrillation must therefore be a manifestation of part of the action of ACh on the heart. We have to inquire whether there is any way
of explaining it and of explaining the action of KCl in stopping it.

Burgen and Terroux and Hoffman and Suckling have shown that the action potential in the cat's atrium is changed by ACh so that the falling phase becomes much steeper. Instead of the action potential having a duration of 150 to 300 msec, Burgen and Terroux observed that with higher concentrations of ACh it became a narrow spike looking not unlike a nerve action potential. Since the falling phase or phase of repolarization is regarded as being caused by the exit of K⁺, the change produced by ACh may be, partly at least, an increased permeability of the cell membrane to K⁺ as Burgen and Terroux suggested. If this conclusion is correct, an increased permeability to K⁺ must exist during atrial fibrillation maintained by the constant infusion of ACh. If the concentration of K⁺ in the blood is raised, the concentration gradient between the cells and the blood will become less steep, and the effect of the increased permeability of the cell membrane on the efflux of K⁺ will be neutralized. Our observations show that when the concentration of K⁺ in the blood is raised, the atrial fibrillation stops. Thus there are grounds for attributing the maintenance of the atrial fibrillation, once it has been started, to the maintenance by ACh of an increased permeability of the cell membrane to K⁺ ions.

Such a change of permeability is not an obvious feature of the ordinary action of ACh. When it is infused into the heart-lung preparation of ACh, the result of the perforation of the pacemaker and there may be some degree of A-V block. But if the effect on the pacemaker is sidestepped by applying electrical stimuli at a fast rate to the atrium, the result of the increased permeability to K⁺ ions may be seen, and the atria fibrillate. What is of great interest is that, provided the amount of ACh is sufficient, this fibrillation persists indefinitely after cessation of the electrical stimulation. The effect of ACh on the pacemaker is no longer the controlling influence.

SUMMARY

Atrial fibrillation can be produced in the heart-lung preparation of the dog by infusing a solution of ACh into the blood going to the heart and applying electric stimulation to the atrium. When fibrillation has begun, it continues after stimulation is stopped, so long as the infusion of ACh continues. The fibrillation maintained in this way has been shown to revert to normal rhythm when KCl is added to the blood. This observation affords a clue to the mechanism of atrial fibrillation maintained by ACh.

ACKNOWLEDGMENT

We wish to record our thanks to Mr. H. W. Ling for his valuable assistance.

SUMMARIO IN INTERLINGUA

Fibrillation atrial pote esser produite in le preparato cardiaco-pulmonar del can per infunder un solution de acetylcholina in le sanguine fluenta verso le corde e applicar stimulation electric al atrium. Le fibrillation assi inducide continua post le cessation del stimulatio providite que le infusion de acetylcholina es manteute. Nos ha demonstrate que iste typo de fibrillation retorna a un rhythmio normal si chlorido de kalium es addite al sanguine. Iste observation contribua al explication del mecanismo de fibrillation atrial mantenite per acetylcholina.

REFERENCES

The Mesencephalon and the Vasomotor System

It is quite generally assumed that the vascular reactions of cortical and hypothalamic origin are mediated by way of the medullary vasomotor centers.

By recording changes in venous blood flow from skeletal muscles, skin and intestines, Swedish investigators found that stimulation of the mesencephalic tectum causes vasodilation as well as vasoconstriction and adrenomedullary activation over separate unilateral pathways not connected with the medullary vasoconstrictor center or depressor area.

Vascular reactions are obtainable from mesencephalic stimulation after destruction of the bulbar regions. The vascular responses following mesencephalic stimulation differ qualitatively from those elicited by baroreceptor excitation; the former induce vascular relaxation through cholinergic sympathetic vasodilators whereas the latter merely inhibit sympathetic constrictor discharges.

The mesencephalon is apparently not concerned with maintenance of vascular tone, but represents the most caudal intracerebral relay station in the vasodilator pathway from cortex to preganglionic neurons. While the two systems have separate spinal pathways, the efferent vasoconstrictor fibers utilize the same final common pathway to blood vessels.

The two systems are believed to have different main functions and are regarded as both anatomically and functionally separate.

For comprehensive review of previous and personal work see P. Lindgren, Acta physiol. Scandinav. 35: suppl. 121, 1953.
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