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EFFECTS OF NORADRENALINE AND ADRENALINE ON THE ATRIAL RHYTHM IN THE HEART-LUNG PREPARATION

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Experiments have been carried out previously with the heart-lung preparation of the dog, in which the effects of infusing acetylcholine (ACh) at a constant rate were determined. These effects included slowing of the pacemaker, production of A–V block, and, when electrical stimuli were applied to the tip of the right atrium, atrial fibrillation (Burn, Vaughan Williams & Walker, 1955*a*). We describe in this paper the effect of infusing noradrenaline and adrenaline. We have determined their effect on the onset of A–V block when the right atrium was stimulated at increasing rates, and we have also investigated their effect on the rhythm after a period in which the atrium was stimulated at a high rate. Finally, we have explored their action on the production of atrial fibrillation by stimulating the atrium at a high rate during the infusion of ACh.

METHODS

The heart-lung preparation was set up as described by Knowlton & Starling (1912), using heparinized blood. ACh and adrenaline or noradrenaline were infused from burettes out of which the solution was displaced by liquid paraffin under constant air pressure. The solutions entered the tube carrying the blood from the venous reservoir to the superior vena cava, through a needle in the tube. The infusion could be maintained constant at any rate from 0·1 to 2·0 ml./min. Electrical stimulation was applied to the tip of the right atrium by electrodes held in contact with the upper surface by a spring clip; the electrodes caused a minimum of trauma. The stimuli were square wave pulses of 1 mA strength and 0·9 msec duration. To produce fibrillation during the infusion of ACh they were applied at a rate of 750/min and usually for a period of 1 or sometimes 2 min, though the duration was not important (Burn, Gunning & Walker, 1956).

RESULTS

Effect of adrenaline and noradrenaline on block. The right atrium was stimulated at increasing rates to determine the maximum rate at which all atrial beats were transmitted to the ventricles. Stimulation was then continued at progressively higher rates in order to record the course of the fall in the ventricular rate until it became half the atrial rate. The stimulation was

stopped, and after a minute or two was begun again at a low rate to see the effect of increasing rates for a second time; little difference was observed. Adrenaline or noradrenaline was then infused into the blood entering the cannula in the superior vena cava, the rate of infusion being kept constant by regulation of a fine-adjustment tap. Stimulation at increasing rates was then resumed, and it was found that the maximum rate to which the ventricles responded without missed beats was higher. Details of one experiment are given in Table 1, which shows that the infusion of 5 μg noradrenaline/min raised the maximum rate from 217 to 273/min, and raised the rate at which the ventricular rate fell to half the atrial rate from 257 to 334/min. This effect persisted for some time after the infusion of noradrenaline was stopped,

TABLE 1. Effect of adrenaline and noradrenaline on A-V block

	Maximum rate of driving at which ventricles followed every impulse (rate/min)	Minimum rate of driving at which the ventricular rate was half the atrial rate (rate/min)
1st control	227	270
2nd control	217	257
Noradrenaline, 5 μg/min	273	334
3rd control	240	278
Adrenaline, 5 μg/min	273	342

presumably because the noradrenaline was not immediately destroyed. Table 1 shows that when adrenaline was infused, also at 5 μg/min, it raised the maximum rate to exactly the same point. Very similar results were obtained in two other experiments. In one of these atropine was injected at the beginning; in this experiment also the maximum rate was raised by the infusion of adrenaline from 290 to 342/min.

Arrhythmias produced by adrenaline. Having observed that when the atria were stimulated during the infusion of ACh, the normal rhythm gave place to fibrillation, we wished to see what changes in the normal rhythm would occur when stimulation was applied during the infusion of noradrenaline or adrenaline. Adrenaline or noradrenaline was infused at rates varying from 10 to 100 μg/min, and the atria were stimulated at 750/min for 2 min during each infusion. In all, fifteen experiments were carried out. Whereas the effect of stimulation during the infusion of acetylcholine was to produce fibrillation in every experiment, its effect during the infusion of noradrenaline or adrenaline was unpredictable. In eight of the experiments stimulation had no persistent effect; when it ceased the rhythm was observed to be normal. In seven experiments, however, stimulation produced an arrhythmia which continued after the stimulation stopped, and sometimes continued after the infusion of adrenaline or noradrenaline was stopped. An example is shown in Fig. 1. In this experiment adrenaline was infused at 10 μg and then at 15 and 20 μg/min. Stimulation at a rate of 750/min was applied for 30 sec during the infusion

In each case the rhythm after stimulation remained as before. Adrenaline was then infused at the rate of 25 μg/min. The e.c.g. record in Fig. 1*a* shows a normal rhythm at the rate of 216/min. The T waves were large. Stimulation was applied to the atrium at the rate of 750/min for 30 sec. After the stimulation was stopped, the rhythm was irregular, as shown by the record of the blood pressure in the aorta, and the e.c.g. in Fig. 1*b* showed a tachycardia in which there appeared to be a nodal rhythm. The R waves were 326/min, and the P waves seemed to be 612/min though this was uncertain. The adrenaline infusion was continued for 4 min and was then stopped; 5 min later the arrhythmia ceased and a normal rhythm at the rate of 201/min returned.

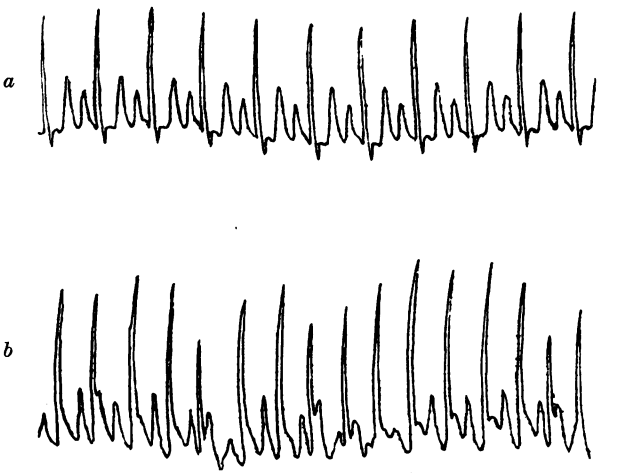

Fig. 1. Electrocardiograph records. *a*, normal rhythm during the infusion of adrenaline at 25 μg/min; heart rate 216/min. *b*, record after electrical stimulation of the atria for 30 sec at 750/min; the R waves were 326/min and the P waves appeared to be 612/min.

This was the one occasion in this experiment in which stimulation during the adrenaline infusion caused arrhythmia. For when subsequent infusions of adrenaline at the rates of 20, 25, 30, 40, 50, 68, 85 and 100 μg/min were given, and stimulation was applied during each infusion, there was no arrhythmia when the stimulation ceased.

Effect of acetylcholine on the tachycardia. In some experiments the arrhythmia appeared on the e.c.g. as a rapid succession of R waves with very few signs of P waves. In others the e.c.g. picture was difficult to distinguish from that of flutter. Thus Fig. 2 shows e.c.g. records in an experiment in which noradrenaline was infused at the rate of 5 μg/min. When stimulation was applied for 30 sec during this infusion it caused an arrhythmia which persisted after the infusion was stopped. It is seen in Fig. 2*c*, in which the P waves appear at 590/min and the R waves at 210/min. Although this e.c.g. resembled

that of flutter, such a condition never changed to fibrillation. This was in contrast to flutter seen after stimulation during the infusion of ACh, which always became fibrillation when the rate of infusion was increased.

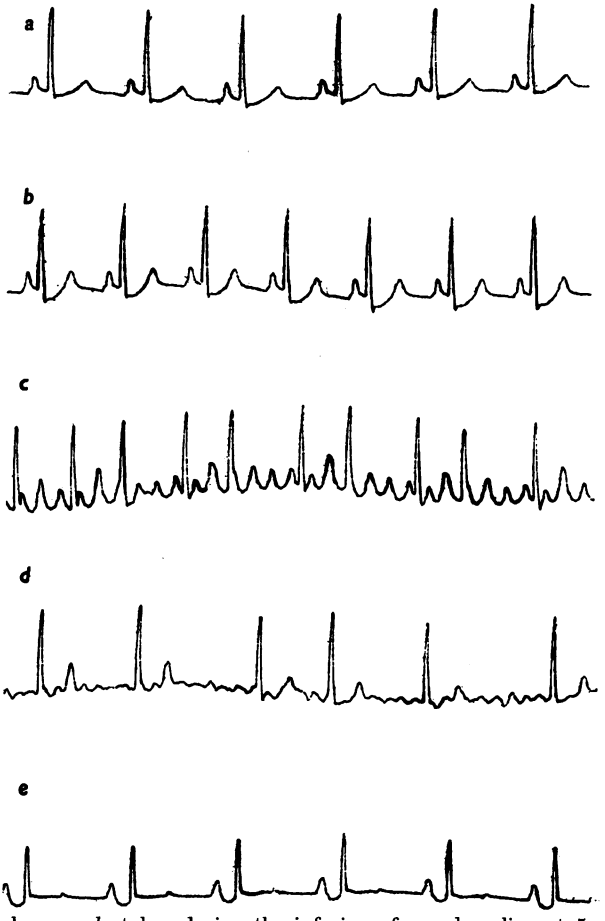

Fig. 2. *a*, normal e.c.g.; *b*, taken during the infusion of noradrenaline at 5 μg/min; *c*, after stimulation of the right atrium for 30 sec; P waves 590, R waves 210/min; *d*, during infusion of ACh at 0·75 mg/min; this caused fibrillation; *e*, after the infusion of ACh was reduced to 0·45 mg/min; the normal rhythm was restored.

The flutter-like condition could, however, be changed to fibrillation when ACh was infused. After the condition seen in Fig. 2*c* had continued for 10 min, ACh was infused at the rate of 0·75 mg/min. The arrhythmia became fibrillation, as shown in Fig. 2*d*. The rate of infusion of ACh was then reduced to 0·45 mg/min, and as a result a normal rhythm returned, as shown in Fig. 2*e*.

The kymograph record in another experiment is shown in Fig. 3. Arrhythmia resulted when the atria were stimulated for 2 min during the infusion of noradrenaline at the rate of 20 μg/min. The arrhythmia persisted after the

infusion was stopped, and Fig. 3 shows the blood pressure irregularity 16 min later. After 5 min an ACh infusion began at 0·6 mg/min and this caused the arrhythmia to become fibrillation. At ACh 2 (see Fig. 3) the infusion was reduced to 0·4 mg/min and after 1·5 min a normal rhythm returned.

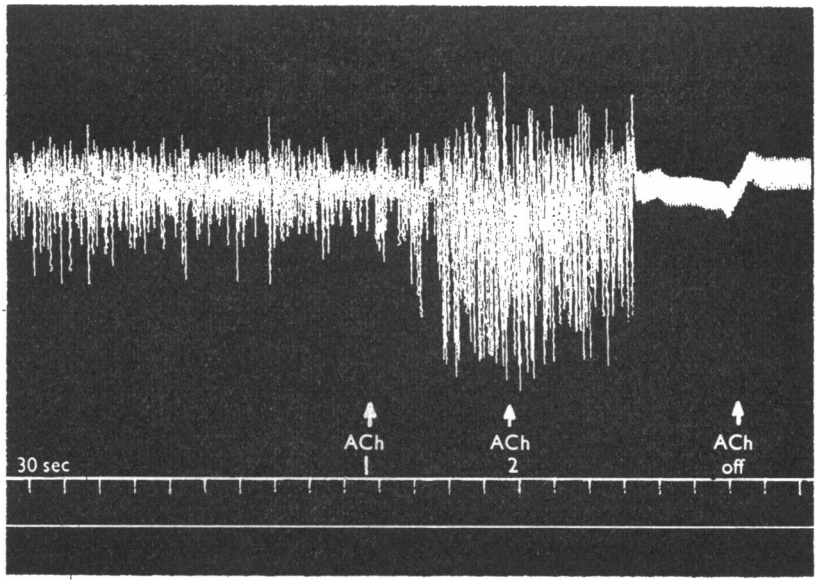

Fig. 3. The arrhythmia caused by atrial stimulation during the infusion of noradrenaline at 20 μg/min. This arrhythmia continued for 27 min until ACh was infused at 0·6 mg/min, which caused fibrillation. At 'ACh 2' the infusion of ACh was reduced to 0·45 mg/min when a normal rhythm returned in 1·5 min.

Effects of eserine and atropine. In four experiments observations were made after the addition of eserine to the reservoir, the concentration being 3×10^{-6} M. In one experiment this had no effect. Stimulation during the infusion of adrenaline at rates up to 50 μg/min did not cause arrhythmia either before or after eserine was added. In two experiments stimulation during the infusion of adrenaline and of noradrenaline respectively did not cause arrhythmia, but after the addition of eserine the stimulation caused flutter; in the adrenaline experiment the flutter lasted 1 min the first time stimulation was applied, and 5 min the second time it was applied. In the noradrenaline experiment the flutter lasted 23 min; atropine was then injected but the flutter persisted. The noradrenaline infusion was stopped, and 16 min later a slow infusion of KCl was given at 50 mg/min. This arrested the flutter when 400 mg KCl had entered the blood, and a normal rhythm was restored. In a fourth experiment stimulation during the infusion of noradrenaline at 60 μg/min caused a tachycardia lasting 6 min. After the addition of eserine

stimulation caused flutter, which peristed when the noradrenaline infusion was stopped 5 min later. Atropine was injected after a further 11 min, and the flutter changed to a rapid irregular rhythm. This reverted to a normal rhythm 7 min later.

These observations showed that the presence of eserine, which caused an accumulation of ACh, did not prevent the occurrence of rapid irregular rhythms when stimulation was applied during the infusion of adrenaline or noradrenaline, but made their occurrence more likely. As a counterpart to this, we observed in two experiments that in the presence of atropine stimulation during the infusion of adrenaline caused less arrhythmia than before.

TABLE 2
Stimulation was applied during infusion of ACh

Rate of ACh infusion (mg/min)	Duration of fibrillation after stimulation stopped (min)
0·4	0
0·6	0·58
0·8	1·16
1·0	4·0
1·1	6·0
1·2	10·0+

Effect of adrenaline on fibrillation. When fibrillation was produced by stimulation of the right atrium during the infusion of acetylcholine, as little as 0·1 mg/min might be sufficient or as much as 3·0 mg/min might be needed. The effect of increasing amounts is shown in Table 2, taken from an experiment in which infusions varied from 0·4 to 1·2 mg/min.

In observing the effect of adrenaline or noradrenaline on fibrillation produced by acetylcholine the one or the other was infused at the same time as acetycholine. In some experiments the infusion of adrenaline did not begin until atrial fibrillation had been established. In none of these did adrenaline arrest the fibrillation, no matter at what rate the infusion was made, nor did single injections up to 1·6 mg have any effect. Sixteen experiments were carried out in which adrenaline and ACh were infused together before stimulation was applied; in nine of these adrenaline or noradrenaline prevented fibrillation, in five they had no effect and in the remaining two they increased the fibrillating action of ACh.

Prevention of fibrillation. The effect of adrenaline or noradrenaline in those experiments in which it prevented fibrillation was beyond doubt, since the effect could be repeated. The experiment shown in Table 3 is given as an illustration; it was performed on an active and lively dog. Stimulation was applied to the right atrium during the infusion of ACh at rates up to 3·0 mg/min. At this rate fibrillation was maintained after the stimulation stopped until the ACh infusion was interrupted 7 min later. Stimulation was

then applied during the infusion of noradrenaline at rates of 10 μg/min and of 20 μg/min. No arrhythmia resulted. At 12.54 stimulation was applied during the infusion of ACh at 3·0 mg/min and of noradrenaline at 20 μg/min. No fibrillation resulted. At 1.02 the infusion of ACh was given alone, and stimulation then caused fibrillation which was once more maintained until the infusion was stopped 6·5 min later. Again at 1.21 the combination of ACh and noradrenaline was tested and again stimulation failed to cause fibrillation.

TABLE 3. Effect of noradrenaline in preventing fibrillation: stimulation applied at 750 /min for 2 min

Time	Rate of ACh infusion (mg/min)	Rate of noradrenaline infusion (μg/min)	Duration of fibrillation after stimulation
12.19	2·1	—	3·5 min
12.29	3·0	—	Until ACh was stopped
12.44	—	10	*
12.49	—	20	*
12.54	3·0	20	*
1.02	3·0	—	Until ACh was stopped
1.21	3·0	20	*
1.31	3·0	—	*
1.36	3·0	—	*
1.58	3·0	—	Until ACh was stopped

* No fibrillation

The noradrenaline infusion was stopped at 1.25, but its effect persisted for some time as was found in some other experiments. At 1.31 and at 1.36 stimulation during the infusion of ACh alone did not cause fibrillation; however, after an interval lasting to 1.58, stimulation during the infusion of ACh alone caused fibrillation which was watched for 20 min before the ACh infusion was stopped. Normal rhythm then returned in 1·5 min.

Similar results were obtained with adrenaline, and the e.c.g. records in another experiment taken immediately after the stimulation was stopped are shown in Fig. 4. The top record was taken during the infusion of adrenaline at the rate of 20 μg/min; the rhythm was normal, the rate having been raised by the adrenaline from 140 to 183/min. In record 2, taken during the infusion of adrenaline at 20 μg/min and of ACh at 0·9 mg/min, there was a 2:1 block, the atrial rate being 180 and the ventricular rate 90/min. The infusion of ACh was allowed to continue but the adrenaline infusion was stopped, and stimulation was again applied; in record 3, taken 7 min after record 2, there was atrial fibrillation which persisted until the ACh infusion was stopped 10 min later. In record 4 a second test was made of stimulating in the presence of both ACh and adrenaline infused at the same rates as in record 2. Again there was no fibrillation but only the 2:1 block seen before. Finally, in record 5 during the infusion of ACh alone there was fibrillation which continued until the infusion was stopped 12 min. later.

There were two further observations in this experiment which are not

illustrated in Fig. 4. Although fibrillation was prevented by infusing adrenaline, the fibrillation which was seen in records 3 and 5 was not arrested by infusing the same amount of adrenaline after fibrillation had begun. A further observation was also made of the effect of infusing twice the amount of ACh together with twice the amount of adrenaline. Again stimulation failed to cause fibrillation.

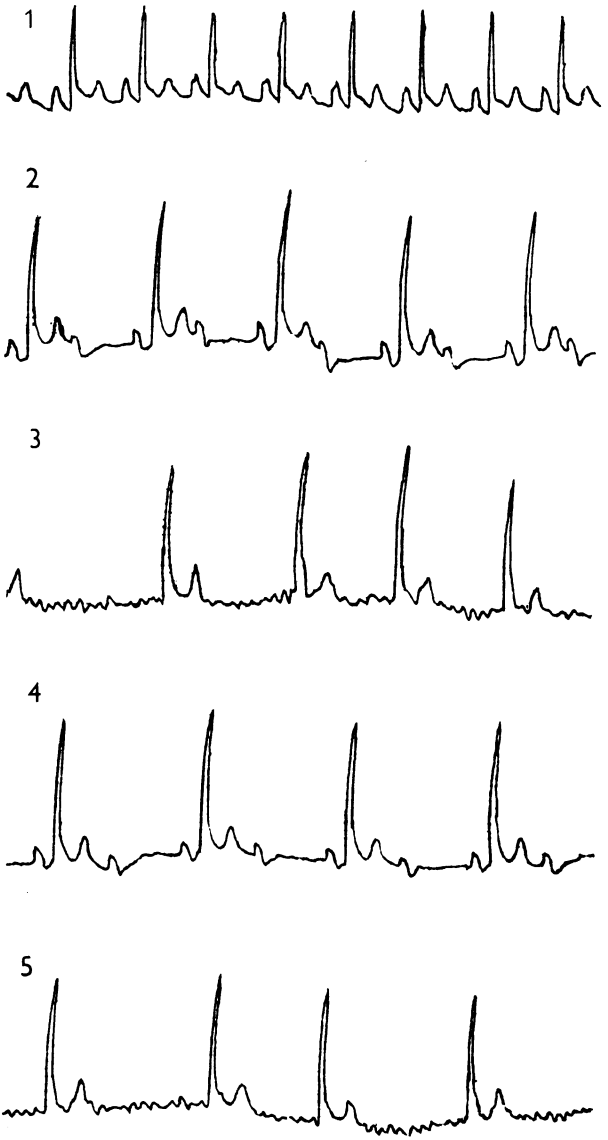

Fig. 4. (1) shows e.c.g. after stimulation for 2 min during the infusion of adrenaline 20 μg/min; (2) after stimulation during the infusion of ACh 0·9 mg/min as well as adrenaline; (3) after stimulation during infusion of ACh alone; (4) same as (2); (5) same as (3).

The effect of adrenaline in preventing fibrillation can also be seen from the kymograph tracing shown in Fig. 5 taken from a third experiment. In the top part of the figure is the blood-pressure record taken during the infusion of 1·2 mg ACh/min. The tip of the right atrium was stimulated at the signal and atrial fibrillation was caused. This lasted after the stimulation stopped until the infusion of ACh was turned off 4·5 min later, when normal rhythm returned. In the middle part of the figure is the blood-pressure record during the infusion of ACh at 1·2 mg/min, together with adrenaline at 35 μg/min. When stimulation was applied there was no disturbance of the blood-pressure record because there was no fibrillation. This observation was repeated during the infusion of ACh at 2·25 mg/min, together with adrenaline at 35 μg/min. Again there was no fibrillation. In the lower part of the figure is the blood-pressure record 30 min later when ACh was infused by itself at the rate of 1·29 mg/min. Stimulation again caused fibrillation, which persisted until the infusion of ACh was discontinued.

A summary of the results in six other experiments is given in Table 4. The times for the duration of fibrillation in the last column were the times until the infusion of ACh was stopped, except for Expt. 5 in which the rhythm became normal spontaneously after 4·75 min. In Expt. 4 adrenaline was not infused at a uniform rate but was injected into the blood during fibrillation to see if the injection would cause reversion to normal rhythm. A series of doses was given, 0·1, 0·2, 0·4, 0·8 and finally 1·6 mg. Fibrillation stopped only when the ACh infusion was stopped, but 4 min later fibrillation could not be re-established when the infusion of ACh was recommenced and stimulation was applied.

Enhancement of fibrillation. In two experiments, both with adrenaline, the opposite effect was seen. Both were carried out in the same way and differently from those already described. A rate of infusion of ACh was found which on stimulation of the atrium caused fibrillation of short duration only, the rhythm reverting to normal while the infusion continued. When this infusion was combined with the infusion of adrenaline, stimulation caused fibrillation which continued for a longer time. The essential details of these experiments are shown in Table 5.

There were finally five experiments in which the infusion of adrenaline or noradrenaline did not modify the action of ACh. In two of these the maximum rate of infusion of noradrenaline was 20 μg/min, and since in some other experiments the inhibition of fibrillation required the infusion of 50 μg/min, the failure may have been because too little was used.

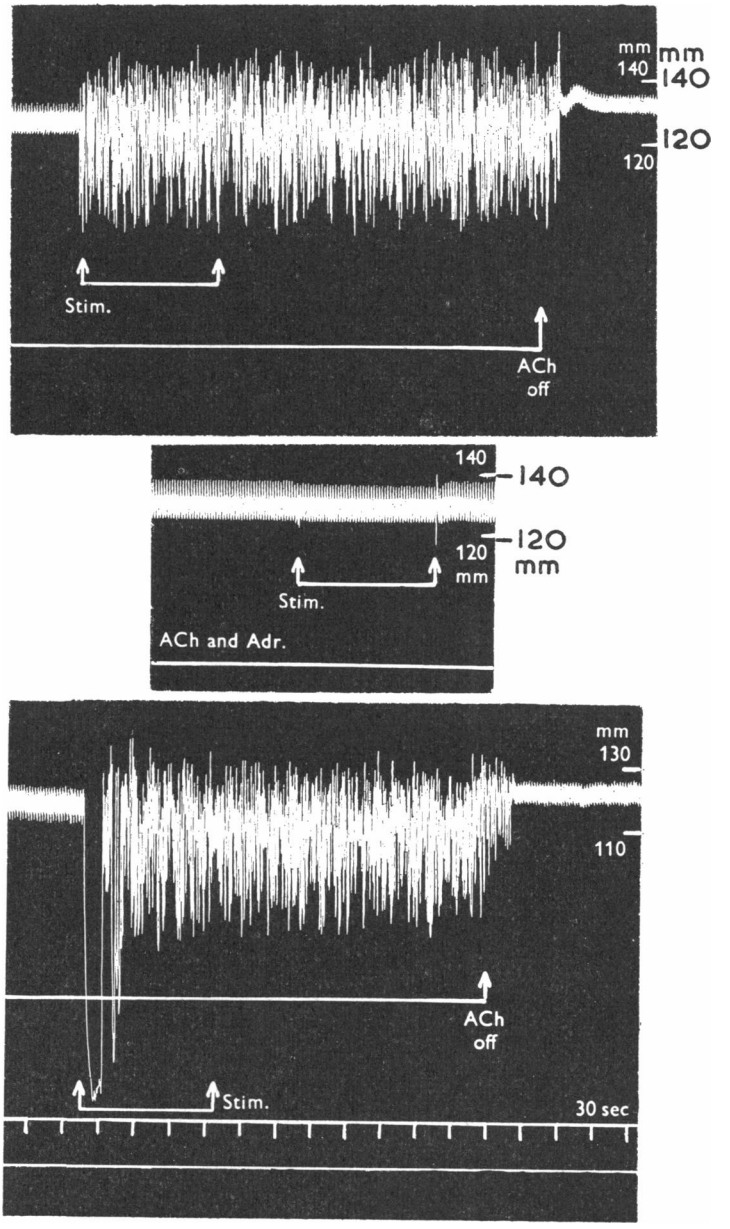

Fig. 5. Kymograph records during infusion of ACh at 1·2 mg/min showing at the top an arrhythmia produced by stimulation, which the e.c.g. revealed as fibrillation; the record in the middle shows that stimulation during the infusion of adrenaline at 35 μg/min as well as ACh at 1·2 mg/min did not cause arrhythmia. The record below shows a repetition of the observation at the top.

TABLE 4. Experiments not described in the text in which adrenaline or noradrenaline prevented fibrillation

Expt.	ACh (mg/min)	Adrenaline (μg/min)	Noradrenaline (μg min)	Duration of fibrillation after stimulation (min)
1	0·4	—	—	2
	0·4	40	—	*
2	1·65	—	—	14
	3·9	50	—	*
	1·56	—	—	6
3	0·9	—	—	5
	2·76	—	20	*
4	2·4	—	—	4
	2·3	(3·1 mg injected)	—	*
5	0·15	—	—	4·75
	0·15	100	—	*
6	0·9	—	—	8
	0·9	—	20	*

* No fibrillation.

TABLE 5. Experiments in which adrenaline prolonged fibrillation

Expt.	Rate of ACh infusion (mg/min)	Rate of adrenaline infusion (μg/min)	Duration of fibrillation after stimulation (min)
7	1·2	—	1
	1·2	—	0·5
	1·2	6·6	2·2
	1·2	10	>27
	1·2	—	8
	1·2	—	7·25
8	0·45	—	0·8
	0·45	20	>6
	0·45	—	2·5
	0·45	—	2·8
	0·45	10	>11

DISCUSSION

When the atria are driven at a rate which is increased in steps, a rate is reached at which the ventricles cease to follow each stimulus, and as the rate of stimulation rises beyond this point, the ventricular rate falls until it is half the atrial rate. Earlier work showed that when ACh was infused or when eserine or neostigmine was added to the blood in the heart-lung preparation, the atrial rate at which the ventricles first ceased to follow was much reduced (Burn, Vaughan Williams & Walker, 1955*a*, *b*). The present experiments show that the infusion of adrenaline or of noradrenaline has the opposite effect, and under their influence the ventricles follow a higher rate of stimulation.

When the atria were driven for a short period at 750/min during the infusion of ACh, flutter or fibrillation always occurred, and flutter could be converted to fibrillation by increasing the amount of ACh infused per minute. The present experiments show that atrial stimulation at 750/min during the infusion

of adrenaline or noradrenaline did not cause fibrillation. In some experiments there was no action of any kind. That is to say, when stimulation was stopped, the atrial rhythm returned to the normal rhythm which was present before it was applied. In other experiments the stimulation produced a tachycardia in which the ventricular rate was about 300/min but was irregular. The P waves were often difficult to count, but appeared to be about twice as fast (see Fig. 1). In some experiments the condition resembled flutter (Fig. 2). The arrhythmia sometimes reverted to normal rhythm when the infusion was discontinued but sometimes it persisted. If then ACh was infused, the atria fibrillated, and when the ACh infusion was slowed, the atrial rhythm became normal. The production of the tachycardia by stimulation during adrenaline infusion was, however, difficult to study, because it was rarely produced a second time in one preparation.

The main evidence presented in this paper concerns the action of adrenaline on atrial fibrillation produced by electrical stimulation in the presence of ACh. That the evidence is conflicting is no matter for surprise since there is no doubt that the action of adrenaline on the heart is complex. It might have been forecast that in some experiments adrenaline would intensify or prolong this fibrillation, for it has been known since the work Levy (1912) that during chloroform anaesthesia the injection of adrenaline causes ventricular fibrillation. Atrial fibrillation was, however, intensified by adrenaline in two experiments only, while in nine experiments out of sixteen the infusion of adrenaline or noradrenaline was found to prevent the onset of fibrillation.

To explain the onset of fibrillation during the infusion of ACh the observations of Burgen & Terroux (1953) and of Hoffman & Suckling (1953) may be relevant. These workers determined the action potential in the isolated atrium by using an intracellular electrode and found that while the rising phase in which depolarization occurred was almost vertical, the falling phase in which repolarization occurred was prolonged. In the presence of ACh, however, the falling phase became steeper so that repolarization occurred more quickly. They suggested that ACh increased the permeability of the cell membrane to K^+, and Harris & Hutter (1956) have recently demonstrated that this occurs in the frog sinus.

Recently Webb & Hollander (1956) have shown that adrenaline has the opposite effect to ACh on the action potential in the atrial cell. Whereas the duration of the action potential was reduced to 22·5% of its length by ACh, it was increased by 13% in the presence of adrenaline. Thus adrenaline caused a slowing of the rate of repolarization. How adrenaline produces this effect is not known. Our evidence that in the majority of experiments the infusion of adrenaline prevented the onset of fibrillation supports the view that the rate of repolarization of the cell membrane is decisive for the production and maintenance of atrial fibrillation. If the different cardiac muscle fibres, as a result

of brief stimulation at a high rate, get slightly out of phase, then when repolarization is rapid they may continuously re-excite one another. This re-excitation will be arrested by any means which prolongs the falling phase of the action potential.

SUMMARY

1. The atria were stimulated in the dog heart-lung preparation at rates which increased in steps, and the maximum rate at which all beats were transmitted to the ventricles was determined; the minimum rate at which a 2:1 rhythm was seen was also determined. When an infusion of adrenaline or of noradrenaline was given these maximum and minimum rates were increased. Adrenaline and noradrenaline were equal in effect.

2. When the atria were stimulated at a rate which would have produced fibrillation during the infusion of ACh, the stimulation did not produce fibrillation during the infusion of adrenaline or noradrenaline. Often stimulation was without action, but sometimes it produced an arrhythmia. The R waves were at an irregular rate near 300/min and the P waves, when they could be identified, were about 600/min; occasionally the e.c.g. resembled that in flutter. The arrhythmia could not be produced a second time.

3. Both adrenaline and noradrenaline were found to modify the occurrence of fibrillation due to stimulation during the infusion of ACh. In nine out of sixteen experiments it was found that when adrenaline was infused at a constant rate together with ACh electrical stimulation of the atrium did not precipitate fibrillation. This action may be due to the increase in the duration of the atrial action potential which adrenaline has been shown to cause. In two experiments the opposite result was obtained.

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