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Research Article

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THE INHIBITION OF ACETYLCHOLINE-INDUCED ATRIOVENTRICULAR BLOCK BY POTASSIUM *

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The exact relationship of potassium and digitalis is still an unsettled question despite intensive study by numerous investigators. There is evidence to indicate that in subjects with atrial fibrillation treated with digitalis, intravenous potassium results either in "improvement" of atrioventricular (AV) conduction, or in progression of the AV block (1–3). The possibility has been entertained that this paradoxical response to potassium depends on whether the digitalis-induced AV block is due to the vagal or to the direct effect of the glycoside on the conduction tissue (4).

The present study was thus designed to investigate the hypothesis that hyperkalemia acts by inhibiting the effect of acetylcholine on AV conduction.

METHOD

Eleven experiments were performed in seven mongrel dogs weighing 10 to 14 kg. The animals were anesthetized with either 30 mg per kg body weight of pentobarbital, or a combination of 2.5 mg per kg of im morphine followed by 15 mg per kg of iv pentobarbital. The dogs were then connected to a Harvard respirator, a bilateral cervical vagotomy was performed, and an arterial catheter was placed just above the aortic valve. Increasing amounts of acetylcholine were injected through this catheter for 15 seconds until an amount was reached that consistently induced second or third degree AV block. This amount was constant for any one experiment, but varied from 0.096 to 0.955 mg in the different experiments. With an electric interval-timer, this amount of acetylcholine was then given every 2 minutes without interruption throughout the experiment.

The control observations consisted of 4 to 8 consecutive injections of acetylcholine, each of which produced similar degrees of AV block. After a satisfactory number of control observations, an infusion of buffered, isotonic (155 mEq per L) solution of potassium phosphate in distilled water was administered at a rate of 0.5 to 1.0 mEq per minute. The effect of the gradually rising plasma K on the acetylcholine-induced AV block was recorded. In five instances, the observations were terminated when the block was inhibited by K (experiments 64–276, 67–278–2, 69–279–3, 70–280–2, and 73–283, Table I). In the other six studies (experiments 66–277, 67–278–1, 69–279–1, 69–279–2, 70–280–1, and 72–282, Table I), the injections of acetylcholine were continued after K was stopped, and the effect of acetylcholine on AV conduction during a declining blood cation level was recorded. The entire experiment was monitored with an oscilloscope, and when advisable, permanent records were obtained by a direct-writing electrocardiograph with standard lead II connections. Frequent determinations of arterial plasma K were made with a Beckman flame photometer. As a control study, identical experiments were carried out with the substitution of isotonic buffered sodium phosphate for the K solution.

RESULTS

The amount of acetylcholine that consistently induced AV block and altered the P wave and T_a segment averaged 0.292 mg per 15-second injection, with a range of 0.096 to 0.955 mg from experiment to experiment. This variation may have been due, among other factors, to the placement of the catheter in relation to the coronary ostia. The amount of K infused per kilogram of body weight averaged 0.49 mg with a range of 0.24 to 0.67 mg. During the control studies, the number of blocked atrial impulses averaged 22 per injection of acetylcholine with a range of 12 to 34. The consistency with which AV block can be reproduced with the same amount of acetylcholine is shown in Figure 1.

During its peak, infused K either markedly diminished or completely inhibited the ability of acetylcholine to induce AV block. In 6 of the 11

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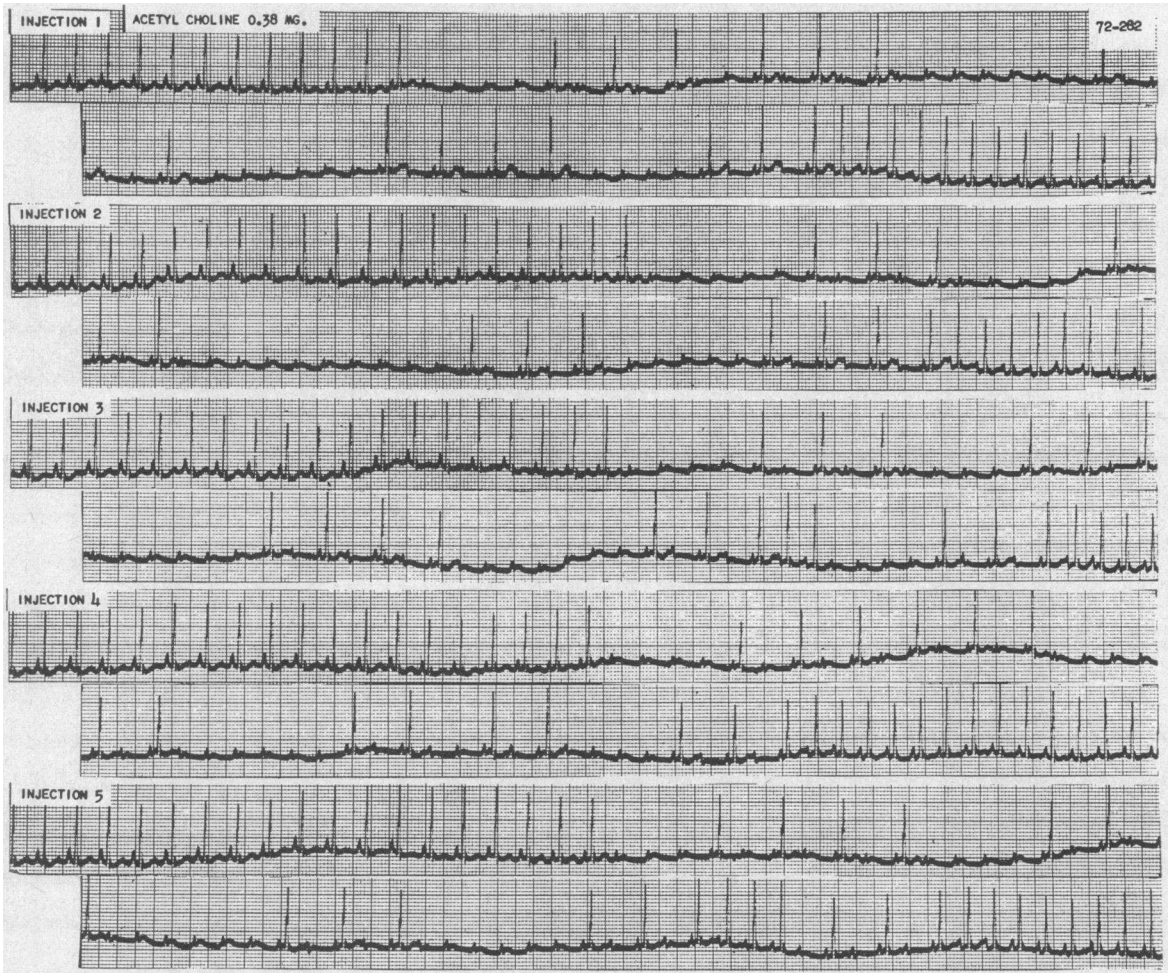

FIG. 1. EXPERIMENT 72–282, DEMONSTRATING THE CONSISTENCY WITH WHICH ATRIOVENTRICULAR BLOCK CAN BE REPRODUCED BY A PREDETERMINED AMOUNT OF ACETYLCHOLINE. Degree of block and effect of acetylcholine on P wave and T_a segment are identical in the 5 consecutive injections. Each injection consisted of 0.096 mg acetylcholine administered over 15 seconds and was repeated at 2-minute intervals.

experiments, rising K completely prevented acetylcholine from producing AV block (Figure 2). In experiments 67–278–2, 70–280–2, and 66–277, the number of blocked atrial impulses was reduced to only 1 per injection from a control level of 12, 20, and 32, respectively. In experiment 72–282, the number dropped from 34 to a mean of 2, and in the remaining experiment, 67–278–1, the number of blocked P waves was reduced from 25 to 8. Besides inhibiting the acetylcholine-induced AV block, the experimentally induced hyperkalemia abolished the effect of acetylcholine on the P wave and T_a segment (Figure 2). K infusion did not produce a consistent change of atrial rate. The average control rate for all of the experiments was 176 beats per minute with a range of 161 to 203, and at the time of peak effect of K, the average rate was 173 with a range of 131 to 200 beats per minute.

Control plasma K varied from 2.7 to 4.2 with an average of 3.4 mEq per L. When the maximal inhibitory effect of K was observed, the plasma level of the cation averaged 6.1 mEq per L with a range of 5.0 to 7.2 (Table I).

In the 6 experiments in which injections of acetylcholine were continued after K infusion was stopped and observations were made during a declining plasma K, acetylcholine was again noted to produce AV block. The plasma level at which the block recurred varied from 3.2 to 5.0

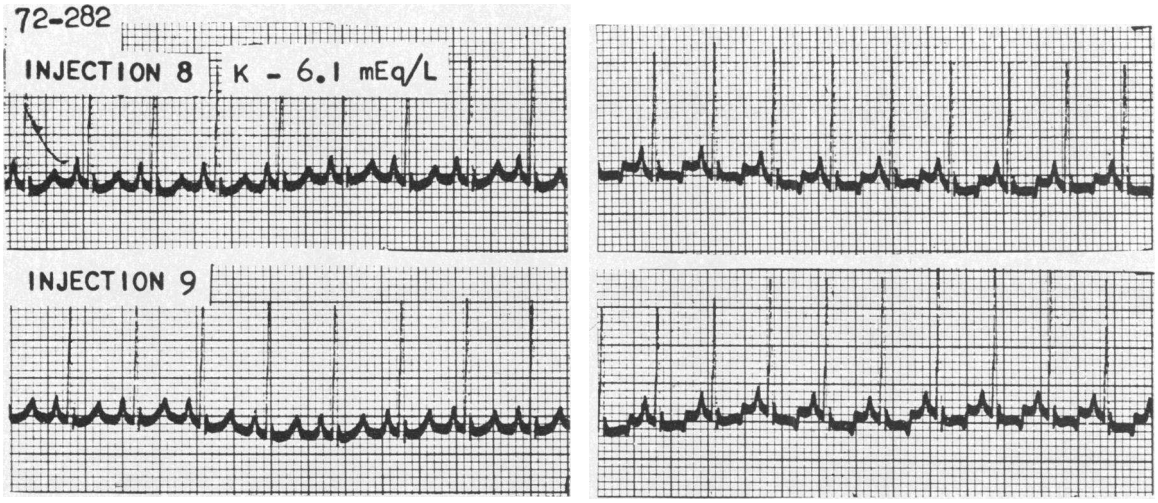

FIG. 2. MAGNIFICATION OF INITIAL AND TERMINAL PORTIONS OF INJECTIONS 8 AND 9 OF EXPERIMENT 72-282. A definite change of T wave and S-T segment indicates that acetylcholine was exerting a pharmacological action. At that point, however, owing to elevation of plasma K to 6.1 mEq per L, acetylcholine had no demonstrable effect on P wave, T_a segment, or atrioventricular conduction.

and averaged 3.9 mEq per L. The number of blocked atrial impulses varied from 16 to 37 with an average of 24 per injection. Figure 3 is representative of this group of 6 experiments in demonstrating the inhibition of acetylcholine-induced block and then its reappearance during the decline of plasma K.

The effect of acetylcholine on AV conduction during the control period, during K infusion, and when plasma K again declined is summarized in Figure 4. The detailed observations for each of the 11 experiments are presented in Table I.

When sodium phosphate was substituted for K, the acetylcholine-induced AV block was not inhibited.

DISCUSSION

The effect of acetylcholine on the various components of the electrocardiogram in the experimental animal was described in a series of observations reported by Burn, Williams, and Walker (5, 6), and Loomis and Krop (7). Our findings were similar to theirs, and for this reason a detailed description of electrocardiographic changes seemed unwarranted, except for AV block, which was pertinent to our study. We wish to stress the remarkable reproducibility of AV block by a standard amount of acetylcholine. Without this predictable response to acetylcholine, the effect of a rising plasma K on the acetylcholine-induced AV block would be difficult, if not impossible, to evaluate.

The results obtained in this study indicate that under the experimental conditions and within the range of plasma K considered in these studies, infused K can inhibit acetylcholine-induced AV block. Since acetylcholine mediates vagal action, it is reasonable to assume that a similar degree of hyperkalemia would also inhibit vagal stimulation. This is now being investigated in our laboratory.

The possibility that the observed inhibition of acetylcholine was a result of factors other than K has been considered. The failure of large amounts of sodium phosphate to inhibit the effect of acetylcholine on AV conduction rules out the possibility that either the volume of fluid or the phosphate contributed to the inhibition of acetylcholine-induced block. The possibility of increased cholinesterase activity with the increasing number of injections as an explanation of failure to induce AV block is ruled out by the demonstration that with a decreasing plasma K, the AV conduction system again becomes sensitive to the blocking action of acetylcholine. There was no consistent change in atrial rate during the experiments, so that a changing heart rate, with its possible effect on the AV conduction system, was not a factor in the results.

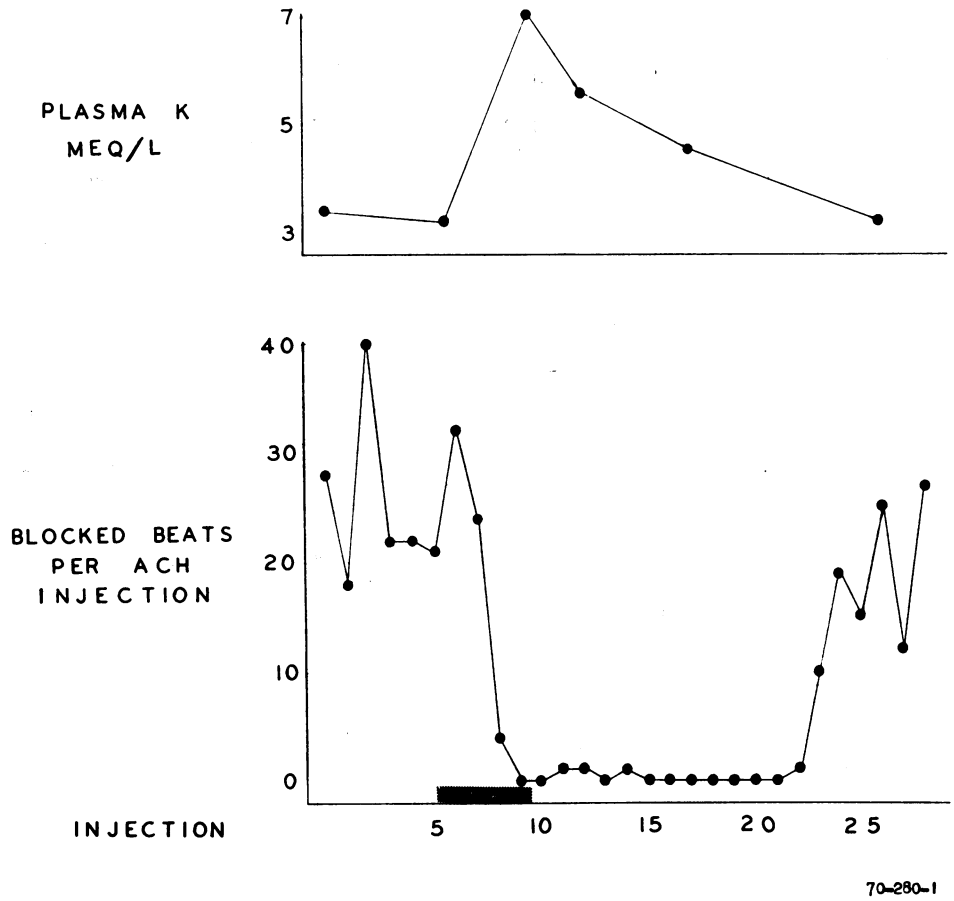

FIG. 3. EXPERIMENT 70–280–1, ONE OF SIX DEMONSTRATING INHIBITION OF ACETYLCHOLINE-INDUCED BLOCK AND ITS REAPPEARANCE DURING DECLINE OF PLASMA K. Injection number is indicated on the abscissa. The ordinate indicates the number of blocked P waves per injection of (acetylcholine) (lower graph) and the plasma level of K in milliequivalents per liter (upper graph). The dark bar along the abscissa indicates infusion of K. Before K infusion, the mean number of blocked P waves was 26 per injection; this number fell to zero during the maximal effect of K as plasma K rose to 7.0 mEq per L. With the drop of plasma K, acetylcholine was again able to block a mean of 19 P waves per injection.

The interrelationship of K, the vagus, and acetylcholine has been the subject of earlier studies, with conflicting results. One of the earliest investigators in this field, Bottazzi (8), was so impressed with the inhibitory effects of both K and the vagus that in 1896 he concluded that the two actions must be identical. In 1906, Howell (9), working with turtle and frog hearts, indicated that an increase in the concentration of K salts "within certain limits" increases the sensitivity of the heart to vagal stimulation. The increase of K in his experiments was stepwise rather than a gradual, continuous rise. Hoff, Humm, and Winkler (10), using the dog as an experimental animal, observed that K at plasma levels of 8.0 mEq per L or more potentiates the effect of the vagus.

The difference in the results of earlier workers and those reported in this paper might be explained by the fact that the inhibition of acetylcholine we observed was in a narrow plasma K range and at levels significantly lower than those considered by previous investigators. The antiacetylcholine effect could conceivably be missed unless the change in plasma K were gradual and continous. According to Hoffman and Cranefield (11), elevation of the extracellular K above the normal range necessitates the use of larger amounts of acetyl-

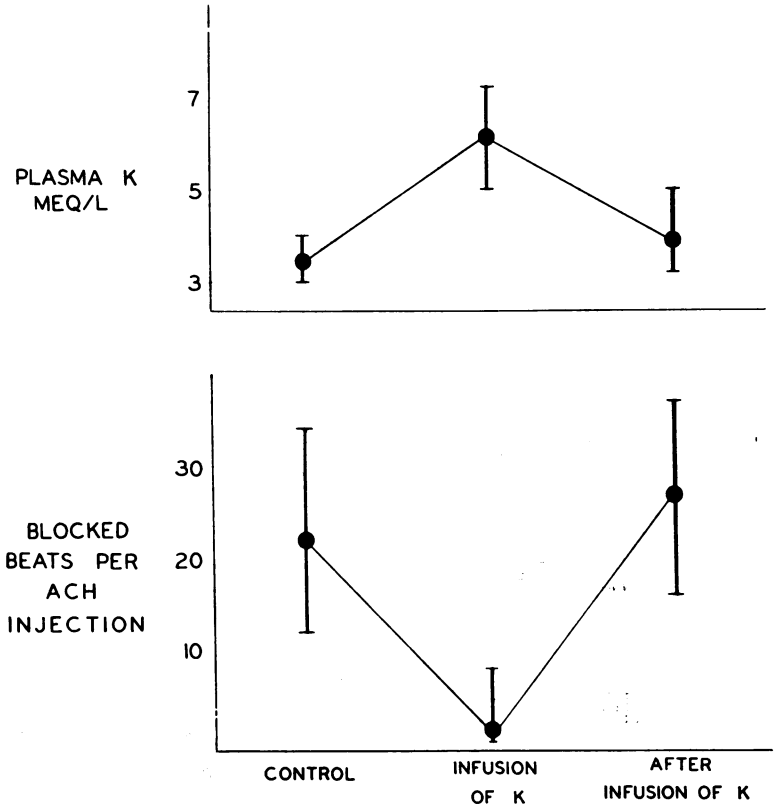

FIG. 4. COMPOSITE GRAPH OF ALL EXPERIMENTS. Means and ranges of blocked P waves during control study (11 experiments), during K infusion (11 experiments), and during decline of plasma K (6 experiments) are presented in the lower graph. Respective means and ranges of plasma K levels are shown in the upper graph.

choline in order to produce slowing or arrest of the sinoatrial node. Burn and Walker (12) observed that K inhibits acetylcholine-induced atrial fibrillation.

It is interesting to speculate on the possible mechanism of K action in our experiments. The antiacetylcholine action of K may stem simply from the opposing action of these agents on the resting membrane potential. The hyperkalemia in the presence of acetylcholine may enhance AV conduction by decreasing the resting membrane potential of the atrial fibers at the atrionodal junction, thus bringing the potential closer to its threshold level (11). On the other hand, the antagonism of acetylcholine and K may be at the level of cell membrane permeability, and there is evidence that acetylcholine increases the cell membrane's permeability to K (13–15). It is possible that the elevation of extracellular K within a certain range of the hyperkalemia may influence this action of acetylcholine. Burn and Walker (12) support this possibility and suggest that the inhibition by K of acetylcholine-induced atrial fibrillation may be due to the fact that the experimentally induced hyperkalemia prevents the increased efflux of K during administration of acetylcholine.

Atrioventricular conduction in digitalis-intoxicated dogs is very sensitive to K, and small doses of the cation promptly produce high degrees of AV block (16). In patients with atrial fibrillation treated with digitalis, however, where admittedly the exact degree of digitalis effect is not always clear, K either enhances or depresses AV conduction. This double effect may depend on whether digitalis exerts a largely vagal or a direct effect on conduction tissue (17). In digitalis intoxication, the depressing effect of the glycoside on the AV conduction is primarily direct and is

TABLE I

Effect of infused K on the plasma level, atrial rate, and acetylcholine-induced atrioventricular block

Experiment	Acetylcholine per injection	Infused K	Plasma K concentration			Atrial rate			No. of blocked P waves per injection of acetylcholine (mean and SD)		
			Control	During K infusion	After K infusion	Contro	During K infusion	After K infusion	Control	During K infusion	After K infusion
	mg	*mEq/kg body wt*	*mEq/L*	*mEq/L*	*mEq/L*						
64-276	0.955	0.50	4.1	6.6		191	179		12 ± 2.5	0 ± 0.0	
67-278-2	0.191	0.67	3.7	6.8		180	150		12 ± 2.1	1 ± 0.0	
69-279-3	0.124	0.52	3.2	5.7		170	172		16 ± 6.2	0 ± 0.0	
70-280-2	0.485	0.81	3.6	7.2		180	180		20 ± 6.4	1 ± 0.0	
73-283	0.191	0.45	3.2	5.8		203	200		16 ± 2.8	0 ± 0.0	
66-277	0.191	0.24	3.6	5.5	5.0	186	189	193	32 ± 5.8	1 ± 2.1	37 ± 5.8
67-278-1	0.242	0.73	2.7	6.5	3.7	161	131	173	25 ± 2.1	8 ± 0.0	14 ± 1.6
69-279-1	0.124	0.33	3.0	5.0	3.2	176	184	166	20 ± 5.9	0 ± 0.0	34 ± 11.2
69-279-2	0.124	0.34	3.2	5.3	3.2	166	176	171	34 ± 11.0	0 ± 0.0	22 ± 2.1
70-280-1	0.485	0.52	3.2	7.0	3.6	161	168	180	26 ± 7.7	0 ± 0.5	19 ± 6.5
72-282	0.096	0.26	4.2	6.1	4.5	165	168	163	34 ± 2.7	2 ± 3.0	15 ± 1.0
Mean and SD	0.292 ± 0.247	0.49 ± 0.17	3.4 ± 0.5	6.1 ± 0.8	3.9 ± 0.6	176 ± 14.5	173 ± 15.1	174 ± 12.5	22 ± 8.5	1 ± 2.2	24 ± 8.2

aggravated by relatively small doses of K (16, 18). On the other hand, it is reasonable to speculate, from observations reported here, that when the effect of digitalis is largely due to its vagal action, as seen with smaller doses of the glycoside, moderate hyperkalemia, via an antiacetylcholine effect, may result in accelerated AV conduction.

SUMMARY

1) In 11 experiments performed in dogs, an amount of acetylcholine found consistently to induce similar degrees of atrioventricular block and alteration of the P wave and T_a segment was injected at the base of the aorta.

2) Elevation of the plasma K from a control mean of 3.4 (range 2.7 to 4.2) mEq per L to a mean of 6.1 (range 5.0 to 7.2) mEq per L inhibited the acetylcholine-induced block and prevented changes of the P wave and T_a segment.

3) The observed antiacetylcholine effect of moderate hyperkalemia is discussed as a possible explanation of the paradoxical behavior of atrioventricular conduction in patients with atrial fibrillation treated with digitalis and with K.

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