Relationship Between Potassium and Vagal Action on Atrioventricular Transmission

By Kalman Greenspan, Ph.D., Charles M. Wunsch, M.D., and Charles Fisch, M.D.

Recent observations on the isolated rabbit heart\(^1\) and in the intact dog\(^2\) have indicated that potassium (K\(^+\)) is antagonistic to the action of acetylcholine (ACh) on atrioventricular (A-V) transmission. Both groups of investigators reported that A-V block induced by ACh was abolished by K\(^+\).

Furthermore, it has been demonstrated\(^3\) in human subjects with varying degrees of A-V block, that K\(^+\) infusion improved conduction to the extent of either decreasing the degree of block, or completely eliminating the block, at the node. In addition, it has been shown that administration of isotonic potassium chloride (KCl) to patients with atrial fibrillation may increase the ventricular rate presumably by improving A-V conduction.\(^4\) In the latter two studies\(^3,4\) many of the patients who responded to K\(^+\) were treated with digitalis prior to the KCl infusion and it is likely that the K\(^+\) effect was an expression of a direct antagonism to the vagal effect of digitalis.

The present investigation was undertaken to determine whether K\(^+\) would enhance A-V transmission in an intact animal manifesting A-V block induced by vagal activity. To produce an intermittent block at the A-V node we utilized the combination of: (1) the vagotonic action of morphine, (2) rapid cardiac pacing, and (3) direct electrical stimulation of the isolated left vagus. Based upon electrophysiological and other evidence it was assumed that the above manipulations resulted in a block restricted to the area of the A-V node.\(^5-9\)

Methods

Male mongrel dogs weighing 8 to 13 kg were anesthetized with morphine sulfate (2.5 mg/kg IM), and pentobarbital (30 mg/kg IV). Following endotracheal intubation, ventilation was controlled with a Harvard respirator set at a rate of 12 to 18 respirations/min and with a tidal volume of 300 to 500 cc of room air. Lead II of the electrocardiogram (ECG) was monitored on a Sanborn or Electronics for Medicine oscilloscope, and at appropriate intervals permanent records were obtained using a direct-writing Sanborn ECG polygraph. The animals were separated into three groups and studied as follows:

In group I, consisting of eight dogs, an electrode catheter was placed, via the external jugular vein, into the right atrium. The heart was then driven by a Grass stimulator at a rate between 110 and 190 beats/min. Pacing at this rate, in the presence of the vagal effect of morphine, caused many of the P waves to be blocked at the A-V junction. The vagi were then isolated, and while the heart was being electrically driven, the left vagus was stimulated. While the heart rate was maintained, constant stimulation of the vagus increased the number of blocked beats. After three control recordings, an isotonic solution of KCl (155 mEq/liter) was infused into a femoral vein at a rate of 1.2 mEq/min with a Harvard constant infusion pump. In a number of experiments the infusion rate was reduced to 0.3 mEq/min so as not to miss the point at which the dropped beats were eliminated by the cation. The effect of the infusion on
plasma K⁺ level and on A-V conduction was noted both with and without vagal stimulation. Venous plasma K⁺ levels were determined at frequent intervals.

In group II, consisting of five dogs, the direct vagal stimulation was omitted but otherwise the procedures were exactly the same as in group I. In group III, consisting of five dogs, the electrode catheter was again used to pace the heart at rates between 110 and 190 beats/min. In addition to the eec, the blood pressure (BP) was recorded through a catheter inserted into a femoral artery and connected to a Statham transducer. Epinephrine hydrochloride (Science Generic Drug Company) was infused into the opposite femoral vein at a rate of 0.23 µg/min and its effect on the BP and A-V conduction noted.

Results

The infusion of isotonic KCl consistently diminished the block induced by electrical stimulation of the vagus or that induced by enhancement of endogenous vagal tone by morphine. The plasma K⁺ level at which the inhibition of vagal effect occurred varied from animal to animal, the range being from 4.8 to 6.9 mEq/liter. At higher plasma levels stimulation of the vagus enhanced the A-V block. The range of plasma K⁺ levels at which this enhancement of A-V block was observed varied from 6.3 to 9.8 mEq/liter. Table 1 is a summary of the results obtained and shows the range and average control level of K⁺ prior to the KCl infusion and the plasma K⁺ levels at which the A-V block was eliminated and subsequently enhanced.

In animals belonging in group I the degree of A-V block induced by vagal stimulation prior to the infusion of KCl varied with each dog. As shown in figure 1, which is representative of this group of experiments, the cardiac pacing and simultaneous vagal stimulation produced in this dog a 2:1 A-V block (top strip). A stimulus artifact, at a rate of 187 beats/min, precedes each P wave but only every other atrial impulse causes ventricular excitation. The control plasma K⁺ level was 3.5 mEq/liter. On administration of K⁺ (middle strip) and when a plasma K⁺ level of 4.8 mEq/liter was attained, each paced P wave gave rise to a QRS complex. In order to demonstrate that the vagus was still functioning, pacing was terminated (bottom strip, between arrows) and the vagus stimulated. This maneuver reduced the heart rate to 79 beats/min; but the rate accelerated promptly to 100 beats/min when vagal stimulation was terminated. The vagally induced A-V block was relieved consistently by elevation of the plasma K⁺ level (table 1).

In animals belonging to group II the A-V block was not induced by direct electrical stimulation of the vagus, but resulted from the effects on vagal tone of the rate of pacing, of morphine, and of respiration. Figure 2 is an example of the results obtained in this group of dogs and shows again the diminution of A-V block by K⁺. In the top strip, prior to K⁺ infusion, the control plasma K⁺ level was 3.5 mEq/liter and each stimulus artifact was followed by a P wave. Due to changing vagal tone the ventricles responded intermittently to only every second or third P wave. After the plasma K⁺ level was raised to 4.8 mEq/liter by KCl infusion (bottom strip) all paced P waves were conducted to the ventricles. Figure 3 is another example of the results observed in group II. In this experiment the plasma K⁺ levels were permitted to return towards normal after the A-V block disappeared. Row A, recorded at a plasma K⁺ level of 3.0 mEq/liter, is the control eec in which the heart was paced at 177 beats/min with a varying 2:1 to 4:1

### Table 1

<table>
<thead>
<tr>
<th>Description</th>
<th>Plasma K⁺ Concentrations Affecting Atrioventricular (A-V) Conduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control plasma K⁺ prior to KCl infusion</td>
<td>Plasma K⁺ concentrations at which A-V block was eliminated</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td><strong>mEq/liter</strong></td>
</tr>
<tr>
<td>Average</td>
<td>2.5-4.0</td>
</tr>
<tr>
<td>SD</td>
<td>3.6</td>
</tr>
<tr>
<td>±</td>
<td>±0.43</td>
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block. In row B, at a $K^+$ concentration of 6.6 mEq/liter the A-V block disappeared. When the plasma $K^+$ level was allowed to decline to 4.0 mEq/liter (row C) the A-V block once again returned.

In a number of dogs of both groups I

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**FIGURE 1**

Top trace reveals 2:1 A-V block. Pacing artifact at 187 beats/min precedes each P wave. Plasma $K^+$ level is 3.5 mEq/liter. In the middle, recorded at plasma $K^+$ of 4.8 mEq/liter each paced P wave conducts to the ventricles. At this point pacing was stopped and the vagus stimulated (bottom strip, arrow up). Cardiac slowing ensues and heart returns to normal rate when vagal stimulation is stopped (arrow down).

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**FIGURE 2**

The heart is paced at a rate of 167 beats/min (upper trace). Note that a number of the paced P waves do not conduct to the ventricles. Following elevation of plasma $K^+$ to 4.8 mEq/liter, all paced P waves conduct to the ventricles (bottom strip).
Strip A shows again a number of paced P waves (177 beats/min), failing to cause QRS complexes. In strip B, when plasma K⁺ was 6.6 mEq/liter, each paced P wave evoked a QRS complex. When plasma K⁺ returned to 4.0 mEq/liter (C), 2:1 block reappeared.

and II, the KCl infusion was continued beyond the point at which the A-V block was eliminated. At higher plasma K⁺ levels, the antagonism between K⁺ and vagal activity was no longer demonstrable but instead the effect of K⁺ and vagal activity on A-V transmission became synergistic (table 1). Figure 4 is an example of this synergism. Column A tracings were taken prior to, and column B during, vagal stimulation. The pacing impulse at 187 beats/min is seen preceding each P wave and this rate, when coupled with vagal stimulation (plasma K⁺ level of 3.2 mEq/liter), produced 2:1 A-V block (top strip of column B). In the middle strip, the plasma K⁺ level was elevated to 6.3 mEq/liter and vagal stimulation produced 5:1 and 6:1 A-V block. As the plasma K⁺ level declined to 5.2 mEq/liter (bottom record) vagal stimulation again resulted in only 2:1 A-V block.

Animals in group III were studied in order to ascertain if the antagonism between the K⁺ and the vagally induced A-V block was due to release of endogenous catecholamines. Figure 5 was recorded during infusion of epinephrine at a rate of 0.23 μg/min. The atria were paced in a manner similar to that described in earlier experiments. The BP and ECG depicted in section A were recorded prior to the infusion of epinephrine. The ECG shows 2:1 A-V block. Following infusion of epinephrine (section B) the A-V block was not relieved and, in fact, increased from a predominant 2:1 to a predominant 3:1 A-V response. No significant change in plasma K⁺ level was observed during the epinephrine infusion. The control plasma K level was 3.8 mEq/liter and during the infusion of the catecholamines a level of 3.8 mEq/liter was recorded. The possible mechanism for the paradoxical increase in A-V block is discussed below.
Discussion

The results of the present study indicate that in the intact dog K+ may exert a dual action on A-V transmission. Whether K+ enhances or depresses A-V conduction in the presence of vagally induced A-V block depends on the plasma concentration of the cation. At levels between 4.8 to 6.9 mEq/liter, the cation abolishes A-V block produced by vagal stimulation. Similar observations were reported by Paes de Carvalho and Langan and Fisch et al. on the effect of K+ in relieving block induced by ACh. However, with increasing plasma K+ levels the degree of A-V block secondary to vagal stimulation becomes progressively more marked, a finding similar to that reported by Hoff. Finally, at plasma K+ levels greater than 8.2 mEq/liter, complete A-V block ensues. This block is independent of the vagus and cannot be inhibited by atropine.

It is interesting to consider the possible mechanisms by which K+ can counteract the effects of vagal stimulation on A-V conduction. Since the cation may cause a release of endogenous catecholamines, and the latter have been shown to speed A-V conduction it might be suspected that these amines were responsible for the improved A-V transmission observed in our experiments. However, under the conditions of our experiments, epinephrine sufficient to produce a rise in blood pressure failed to relieve the vagally induced A-V block. The "paradoxical" increase of A-V block during epinephrine infusion was probably vagally induced, representing a reflex response to rise of the blood pressure. Since the plasma K+ level did not change during epinephrine infusion, the enhanced block could not have been a result of endogenous release of K+. Paes de Carvalho and Langan, commenting on the failure of catecholamines to overcome an ACh-induced A-V block in the isolated rabbit heart despite the ability of these amines to enhance A-V conduction, suggest that the

![Figure 4](image-url)
catecholamines influence A-V conduction at a point along the A-V transmission system which is different from that acted upon by ACh. The amines may act by increasing the all-or-none conduction through the AN and NH layer of the A-V node while ACh exerts its action in the N region.

On the other hand, assuming that \( K^+ \) acts on the same area of the A-V node as does ACh, it may relieve the block by overcoming the decremental conduction induced by the vagus or ACh. Available evidence indicates that A-V block induced by ACh is a result of enhancement of decremental conduction.\(^8, 9, 14\) \( K^+ \) could override this enhanced decremental conduction initiated by vagal stimulation by reducing the resting potential and thus bring the latter closer to the threshold potential. This would result in more rapid transmission across the A-V system. It is also possible that \( K^+ \), by inhibiting the effect of ACh on the slow diastolic depolarization phase of the action potential, brings the depolarization more rapidly to the threshold potential and thus overcomes the depressing effect of ACh on A-V transmission.

**Summary**

The relationship between the effects of potassium and vagal stimulation on transmission through the atrioventricular transmission system was investigated. It was observed that infusion of isotonic potassium chloride alleviated atrioventricular block induced by vagal activity. This occurred at plasma potassium levels ranging from 4.8 to 6.9 mEq/liter. This antagonism does not appear to be mediated by catecholamine release since infusion of epinephrine (0.23 \( \mu \)g/min) did not relieve the block. At plasma levels higher than those capable of inhibiting vagal action, potassium enhances parasympathomimetic actions on A-V transmission and, at still higher levels, potassium is capable of inducing A-V block which is independent of the vagus.

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**References**

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