The Spread of Sinus Activation During Potassium Administration

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In 1907, Keith and Flack described a direct muscular bundle connecting the sino-atrial and atrio-ventricular nodes and stated that it was "therefore possible for a non-arrhythmic rhythm to occur in the atrial region." Two years later Thorel published a short communication in which he described a direct path between the nodes leading to the cells constituting this bundle thought to be specialized fibers of the Purkinje type. Since then, although many studies have been devoted to the subject, the results obtained have failed to settle the question (see Discussion and Schütz).

A step forward was permitted by the introduction of the intracellular microelectrode. By use of this method, electrophysiologically specialized fibers were found to form a bundle along the margin of the caval region. These specialized cells, as well as those of the nodes, subsequently were shown to be particularly resistant to the depolarizing action of a high potassium concentration. As result of this property, the specialized fibers develop action potentials in the presence of an elevated extracellular [K⁺] when atrial muscle fibers are no longer excitable. The latter observation suggested that it might be possible to employ induced hyperkalemia as a means of investigate the spread of sinus impulses to and in the atria. If excitation followed specialized fibers, the sinus impulses would be expected to reach the ventricles in spite of the potassium-induced inexcitability of atrial muscle fibers. On the other hand, if sinus impulses propagate only through nonspecialized atrial muscle fibers, the inexcitability of these fibers would functionally isolate the sinus node from the rest of the heart. To test this hypothesis several electrodes were implanted on atria of intact dogs and local activity was recorded during administration of potassium. The results obtained show that during hyperkalemia sinus activity does propagate to the ventricles when atrial muscle fibers are no longer active.

Methods

Surgical preparation of animals was made under thiopental (Pentothal) anesthesia in ten mongrel dogs, weighing 18 to 27 kg. Electrodes were implanted on the epicardial surface of the sinus region and the ventricles; in nine of these animals an electrode was placed also in the coronary sinus area and/or over the His bundle. In seven of these same dogs other electrodes were attached on the muscular wall of either the left, right, or both atria. The technique of chronic implantation has been described in detail. Four days to several weeks after implantation of the electrodes, the animals were anesthetized with sodium pentobarbital (30 mg/kg, intravenously). Additional amounts of this anesthetic were administered during the experiment as required. The dogs were placed on the left flank and the trachea was cannulated. In some experiments,
arterial blood pressure was recorded through a catheter placed in either the femoral or carotid artery and connected to a Statham transducer. An unipolar catheter lead was introduced into the right external jugular vein and advanced toward the atrium until a monophasic and predominantly negative complex was recorded. A tie placed around the jugular vein prevented the catheter from slipping. At the autopsy, the tip of the catheter was found in the superior vena cava at or near its junction to the atrium. The standard electrocardiogram was recorded as L2 and L4. The right vagus was crushed in the neck and the distal end employed for stimulation. The duration of the stimulus was 0.5 to 1 msec and the frequency 20 impulses per second. The recording apparatus was an oscilloscope (Electronics for Medicine). Records were photographed on 7-inch paper moving at variable speed, usually 100 to 200 mm/sec.

Control tracings were recorded after an isotonic solution of potassium chloride in twice distilled, demineralized water was infused through a peripheral vein. The rate of infusion was 20 to 80 drops per minute and was varied during the experiment in order to obtain progressive electrocardiographic changes; in no case was it in excess of 98 drops per minute. At the end of the experiment, an autopsy was performed in six of the animals to verify the exact location of the electrodes on the heart. Some of the experimental animals had been employed on previous occasions for studies involving anesthesia and electrical stimulation through some of the electrodes.

In the course of these experiments, it was found that 2:1 block might develop within the atria. Namely, records from right and left atrial musculature showed an electrogram only after every second sinus beat. It was thought that the atrial fibers might be unable to follow the sinus rate. Therefore, to study the relationship between rate and the occurrence of block in the presence of an elevated extracellular [K+], experiments were conducted in vitro on pectinate muscles from the canine right atrium. The muscles were perfused with Tyrode solution in a tissue bath at 37°C. The composition of the solution, in millimoles/liter, was as follows: NaCl 137; KCl 2.7; MgCl2 0.5; NaHCO3 12.0; NaH2PO4 1.8; CaCl2 2.7; glucose 5.5. The solution was gassed with a mixture of 95% O2 and 5% CO2. Transmembrane potentials were recorded from single cells through an intracellular microelectrode filled with 3 M KCl. The control rate of stimulation was 60 per minute and was altered either by introducing an extra stimulus at different times during diastole or by varying the basal frequency. The maximum rate of rise of the action potential was determined by differentiating the transmembrane action potential through RC coupling. Records were displayed on a switched beam oscilloscope and photographed on moving paper. After control tracings had been made, the potassium content of the Tyrode solution was increased two to four times by adding solid KCl. The rate of stimulation was varied with each increase in [K+].

Results

IN VIVO EXPERIMENTS

As potassium chloride was infused intravenously, the bipolar electrograms recorded from several atrial sites underwent progressive enlargement. The ascending limb of the complexes became progressively slower and at the peak merged with an elevated "ST segment." These changes were at first noticeable in records from right atrial muscle and later in records from left atrium. Conduction within the atria was depressed at the same time, the interval between atrial complexes being lengthened in each case. An exact quantitative evaluation of the increase in conduction time was hindered by changes in the configuration of the electrograms. The atrial complexes not only became rounded, but also smaller components either disappeared or became low-voltage deflections which were difficult to identify. At this time the P wave in the standard limb leads was flattened and increased in duration. With further administration of potassium, a 2:1 intra-atrial block appeared in half of the animals; local atrial activity was present only with every alternate sinus beat. This block appeared most often in records from leads on right and left atrial muscle.

The next change was a transition to complete quiescence in the leads from right and left atrial muscle while the sinus node and the coronary sinus electrograms persisted. At the same time, the P wave no longer was apparent in standard limb leads; however, slowing of the rate, either spontaneous or provoked by means of graded vagal stimulation, very often caused the P wave to reappear temporarily. Later on, during the potassium infusion, the sinus node complex also became prolonged and a 2:1 or irregular sino-ventric-
ular block appeared. If the rate of the sinus node decreased appreciably and no other atrial pacemaker interfered, one-to-one conduction from the sinus to the ventricles was present even when the configuration of the QRS complex was markedly distorted. In one experiment, during progressive infusion of KCl the sinus node electrogram, which consisted only of small oscillations, became gradually smaller until it was difficult to identify. In another experiment, the rate of the sinus node was lower than that of the ventricles; however, in this experiment it could be shown that the sinus impulses propagated to the coronary sinus at a time when the right atrial musculature was inexcitable. In both the above experiments, the supraventricular location of the pacemaker driving the ventricles was demonstrated by the unaltered morphology of the electrogram recorded through the His electrode and by the induction of cardiac standstill during vagal stimulation.

Some of the results which have been described are illustrated in the following figures. A control tracing is shown in figure 1. The small notches which precede the main deflection on the sinus node electrogram (SA) are the earliest activity recorded during the cardiac cycle. The electrogram recorded from the coronary sinus and right and left atria follow the sinus activity in that order. Some of the changes produced by potassium infusion are apparent in figure 2. In this record only the atrial leads are displayed. In figure 2A, the right atrial electrogram follows only every second sinus beat, as indicated by the arrows, and it is so much delayed as to occur during the P-Q interval. Its shape is rounded with no sharp deflection. At this time the P wave, although flattened, still was present in L3. The earliest atrial activity now appears in lead EL. In figure 2B, no activity is evident in lead RA; the small deflections seen there are caused by ventricular activation. The 2:1 intra-atrial block now occurs in the LA lead, as indicated by the arrows. The sinus node

![Figure 1](http://circres.ahajournals.org/)

Control tracing. Lettering indicates the locations from which bipolar electrograms were recorded. SA: sinus node; CS: coronary sinus; RA: right atrial musculature; LA: left atrial musculature; RV: epicardial surface of the right ventricle. The unipolar record obtained through the catheter lead in the right atrium is marked EL; L2 and L3 are standard leads II and III. Paper speed 200 mm/sec; time lines at intervals of 40 msec.
Effect of potassium on atrial electrograms. Only the atrial traces are shown. A: activity in the RA lead appears after every second sinus impulse, as indicated by the arrows. One-to-one sino-ventricular conduction is present even in the absence of RA activation. B: after further progression of K-induced changes, no activity is recorded in the RA lead except for small deflections resulting from ventricular activation. In the LA lead, 2:1 sino-atrial block is indicated by the arrows. Sinus impulses are transmitted regularly to the coronary sinus, but irregularly to the ventricles. Paper speed 100 mm/sec; time lines at intervals of 100 msec.

Complex is enlarged and slightly irregular in its rate. The coronary sinus electrogram is diminished in amplitude and delayed; its rate changes synchronously with that of the sinus node. An atrial complex which precedes all other activity by a large interval is seen in EL. At this stage a P wave no longer was detectable in the standard leads. The temporal relationship between sinus activity and the QRS was not constant and remained so with further potassium administration. The potassium infusion then was discontinued and the changes associated with the recovery observed. When the relationship between sinus and ventricular activity still was variable, vagal stimulation repeatedly caused cardiac standstill. At the end of the period of vagal stimulation, on resumption of activity each sinus beat propagated to the ventricles (fig. 3) until the rate had returned to the prestimulation values. It should be noted that no signs of activity are present in RA and LA leads and also that the P waves are absent from the limb leads. Activity recorded from EL still precedes that in SA lead. After the end of vagal stimulation, the sinus accelerated and the last cycle in figure 3 is 23% shorter than the first; identical changes in cycle length are shown by the ventricles. The initial deflection in the coronary sinus lead is synchronous with the main deflection recorded from the sinus region, as in the control record. However, the small oscillations that initiated the control SA complex under control conditions are absent. The EL lead electrogram has maintained its control morphology and still is the first activity recorded in each cycle (see also fig. 2). The re-establishment of a regular 1:1 sino-ventricular rhythm is illustrated in figure 4. However, there are still no signs of atrial activity in RA, LA, L2 and L3 leads. At the arrow on the LA record, local activity is recorded once.

Some other aspects of the recovery of atrial...
activity after cessation of KCl infusion are presented in figure 5. In section 5A, the "ST segment" of CS complex is less elevated than in the previous figure. Also, the activity in lead LA reappears with the pattern of 2:1 intra-atrial block (see arrows). In section 5B, the restoration of a fast deflection is complete in CS and LA, although in the latter the

Vagal stimulation had been interrupted at the beginning of the record. Sinus node activity resumes and the rate accelerates; identical changes in cycle length are shown by the ventricles. No atrial activity is seen in the RA, LA, leads or in $L_2$ and $L_3$. This tracing was recorded after potassium administration had been discontinued. The SA trace has been retouched to show rapid deflections. Paper speed 100 mm/sec; time lines at intervals of 100 msec.

Sino-ventricular conduction. Sinus impulses propagate regularly to the coronary sinus and the ventricles in absence of activity in the other atrial leads and with complete absence of the $P$ wave. The arrow shows a single activation of the left appendage. SA trace retouched to show rapid deflections. Paper speed 100 mm/sec; time lines at intervals of 100 msec.

\[ \text{FIGURE 3} \]

\[ \text{FIGURE 4} \]
rapid deflection is inverted. At this time the P wave was barely visible in L₃. In section 5C, activity has returned in the RA lead and the LA complex now shows the control pattern. At this stage the P wave was visible in peripheral leads. In section 5D, further recovery is shown. However, initial activity still appears in the EL lead.

The location of the electrodes used in this experiment was confirmed at autopsy. The RA electrode was implanted on the epicardial surface of the right atrium, about a centimeter above the A-V groove, anteriorly. The LA electrode was sewn on the left appendage. The catheter lead tip was found in the superior vena cava in the immediate vicinity of the sinus node region. The SA lead was located midway along the sulcus terminalis.

The occurrence of 2:1 sino-ventricular block is illustrated in figure 6 which is taken from another experiment. The lettering of this figure is the same as in figure 1. During K administration, the P wave and RA electrogram are no longer recorded and the LA complex is reduced to a low voltage deflection. However, the sinus node complex (indicated by the arrow heads) and the CS electrogram (indicated by the dots) are present and every second sinus beat propagates to the ventricles with constant coupling. As in the previous experiment, after KCl infusion initial activity is recorded in lead EL. The location of the electrodes was checked at autopsy and was similar to that described above.

Figure 7 shows records obtained during potassium intoxication from another animal. The trace labeled V is lead V₄₅; other traces are as in previous figures. This figure is included to show two things. First, a regular relationship between sinus activity and ventricular activity is present after disappear-

Recovery of excitability by the atrial musculature after the end of the KCl infusion. "ST segment" of the CS electrogram is less elevated than in figure 4 and LA electrogram reappears with a pattern of 2:1 sino-atrial block. B: both CS and LA electrograms show sharp deflections. C: all the atrial leads present signs of activation. The P wave was clearly visible in the standard leads at this time. D: recovery is almost complete. Paper speed 100 mm/sec; time lines at intervals of 100 msec.
POTASSIUM AND SINO-VENTRICULAR RHYTHM

ance of P waves from body surface leads (see lead V). Second, as in the previous figures, under control conditions initial activity is recorded through the lead from the sinus region. After KCl administration, however, initial activity appears in lead EL (arrows).

IN VITRO EXPERIMENTS

Doubling the amount of KCl (from 2.7 to 5.4 mmoles/liter) resulted in a slight prolongation of the effective refractory period of isolated atrial muscle and a reduction in the rate at which the preparation could follow driving stimuli. More marked changes were obvious at three times the normal potassium concentration (8.1 mmoles/liter). In some experiments the stimulus duration and intensity had to be increased to obtain a response. Quite often, a stimulus introduced early in diastole provoked only a subthreshold de-

**FIGURE 6**

Example of 2:1 sino-ventricular block during potassium administration. On the left side of the picture the control tracing is shown. The lettering has the same meaning as in figure 1. Records on the right show effects of KCl administration. Arrow heads indicate the much enlarged sinus complexes and the dots show the low voltage coronary sinus electrogram. Note the constant relationship between these complexes in absence of activation in the RA lead. Also, the ventricles are activated after every second sinus beat with constant coupling. Paper speed 200 mm/sec; time lines at intervals of 40 msec.

**FIGURE 7**

Record obtained from another animal prior to and during K intoxication. Labels as in figure 1. V indicates precordial lead V1. Arrows indicate earliest activity recorded through the catheter electrode. Large, slow deflections are recorded from SA lead and show a fixed coupling with ventricular activity at a time when there is no indication of atrial activity in the body surface leads.
polarization or no effect at all, instead of the full response obtained in the control solution. If the premature stimulus was applied progressively later during diastole the size of the response and rate of rise of its upstroke increased progressively. However, as the extra stimulus was interpolated even later in diastole, the following action potential, due to a driving stimulus, might show a decreased rate of rise or fail to appear altogether. In some instances extrasystoles could not be elicited during most of diastole. In two experiments extracellular K concentration was increased to 10.8 mmoles/liter. The results are illustrated in figure 8. The first strip (A) is the control tracing; the following strips were recorded during perfusion with solution containing 10.8 mM K. In trace B, a step is visible on the upstroke of the action potential and the maximal rate of rise is obviously decreased. The extra stimulus, introduced progressively later during diastole, results in only a small response. Also, the step preceding the last three action potentials of this trace becomes gradually longer and eventually is not followed by full excitation. An increase in the rate of stimulation from 55/min to 84/min is sufficient to provoke a 2:1 block (strip C) and a further increase to a rate of 115/min leads to a more pronounced degree of block (strip

FIGURE 8

Relationship between rate of stimulation and electrical response of a single atrial muscle fiber in high [K]o. A: control tracing. Top horizontal trace indicates the zero potential in this and the following strips. Small vertical deflection on the bottom trace, synchronous with the upstroke of the action potential, is a measure of the maximum rate of rise of the action potential upstroke. Voltage calibration is shown at the end of the strip (100 mv); the time interval between the action potentials is one second. B: an extrasystole, interpolated at different times during diastole, fails to elicit an action potential. Basal rate of stimulation 55/min. C: an increase in the driving rate to 84/min provokes 2:1 block. Action potentials show a greater rate of rise than in the preceding strip. D: as the driving rate is brought to 115/min, the degree of block increases (4:1). E: rate of stimulation is increased from 60 to a maximum of about 550 and again decreased to 60. The last strip is a continuation of strip E.
D). In trace D, local responses become progressively bigger until, with every fourth stimulus, threshold is attained. With a sudden acceleration, at first the subthreshold responses increase in size and then decrease (strip E). It is only when the rate of stimulation is slowed (bottom strip) that the subthreshold responses once more grow bigger until an action potential is elicited.

**Discussion**

The results described in the present communication show that sinus impulses propagate to the coronary sinus region and the ventricles at a time when the atrial musculature has been rendered inexcitable by a high extracellular potassium concentration. These experiments thus provide support for 1) the existence of specialized paths within the atria; 2) the ability of these paths to conduct sinus impulses; 3) the continuity of the specialized paths between the sinus region and atrio-ventricular node. In fact, this is a demonstration of a sino-ventricular rhythm postulated by Keith and Flack. The results of this work, and one other study must be due to the lower sensitivity of the S-A and A-V nodes and the specialized fibers of the crista terminalis to the depolarizing action of potassium, as compared with the atrial muscle fibers. The reason for a differing sensitivity of the atrial structures to potassium ions has not been demonstrated. The results described in this study rule out the possibility that the K resistance observed in vitro was due to the dense connective tissue surrounding the specialized structures, since in our case the excess potassium arrived at the tissues through the normal capillary circulation. The high resistance to potassium of the specialized atrial fibers is clearly important for the maintenance of the activity of the ventricles; for idioventricular automaticity is depressed at an early stage of potassium administration. In the absence of specialized K-resistant paths in the atria, sinus impulses would fail to propagate through depolarized atrial muscle fibers and ventricular arrest or a very slow idioventricular rhythm would follow. However, these considerations do not help us understand the function of the specialized atrial paths under normal conditions. A reasonable suggestion is that a better coordination of the atrial contraction may be insured by these paths.

The findings described in this study provide a functional correlate to the anatomical description of specialized connections between the sinus node and the coronary sinus, where these fibers are joined by the expansions from the A-V node. Several investigators have stated that the specialized atrial bundles contain Purkinje fibers. However, in certain species, these specialized fibers have been described as forming a subendocardial net without collecting in circumscribed paths. Although the presence of specialized cells in the atrium is generally accepted, their organization in a conducting system is denied by many (see Schütz). The results of Eyster and Meek are somewhat similar to ours; they assumed that there were special connections between the nodes on the basis of measurement of conduction velocity and the changes which followed cuts and ligations made around the sinus node area. A similar view was shared by Rothberger and Scherf who, on the basis of their ligation experiments, considered the paths described by Thorel and Bachmann as preferential paths for the spread of sinus impulses.

In relation to the Bachmann bundle, it is interesting to note that, in those of our experiments in which activity was recorded from both right and left atria, during hyperkalemia, the right atrium consistently became quiescent before the left. One might wonder how the sinus impulses reach the left atrium through an inexcitable right atrium. A possible answer is that sinus impulses propagate to the left atrium through specialized fibers in Bachmann's bundle.

Lewis, on the basis of measurements of conduction time, concluded that the excitatory process spreads in all directions within the atria with the same speed, and that there was no evidence for specialized atrial paths or fibers. This finding was confirmed by Brendel et al. Before more is known about
the normal function of specialized paths in the atria, it is difficult to evaluate these conclusions.

The failure of the sinus impulses to propagate to the atrial musculature in high \([K]_0\) can be explained on the basis of decremental conduction. Decremental conduction has been defined by Hoffman and Cranefield \(^{20}\) as a condition in which the propagation of the stimulus is conditioned by the changes of membrane properties along the length of the fiber. As extracellular potassium increases, the resting potential of the atrial muscle fibers decreases to a larger extent than the resting potential of the specialized structures. It then may be expected that the rate of rise and the amplitude of the action potential (and the cell space constant) will decrease as the action potential propagates from the specialized to the ordinary muscle fibers. The effectiveness of the action potential as a physiological stimulus will decrease until block ensues. The fall in the resting potential of the atrial muscle fibers in high \([K]_0\) leads to a diminution in the availability of the “sodium-carrying system.” \(^{21}\) That such is the case also is shown by the fall in maximal rate of rise of the action potential in K-rich solution (fig. 8). A decrease in available “Na carriers” can account for the inexcitability of muscle fibers but not for the occurrence of a 2:1 intra-atrial block. The experiments conducted in vitro show that partial block is due to a marked increase in the effective refractory period and therefore is frequency-dependent. The prolongation of the effective refractory period may indicate that the partial block in high \([K]_0\) results from a marked reduction in the rate of reactivation of the “sodium-carrying system” during repolarization. Several facts appear to support such a suggestion. Thus, in vivo, atrial activity reappeared during slowing of the rate which was either spontaneous or induced by graded vagal stimulation. In vitro, the maximal rate of rise of the extrasystoles increased as they were elicited later during diastole. The action potential following an extrasystole might show a decreased rate of rise, but the rate of rise was “normal” if the extrasystole was omitted. Also, the maximal rate of rise increased with the occurrence of 2:1 block (fig. 8C). The lack of response at high frequency of stimulation may be interpreted in the same manner: with each local response, the membrane potential was prevented from returning to its resting value by the next stimulation. The result was a further depolarization. It was only when sufficient time was allowed for the potential to return to its resting level, and thus for the “sodium carrier” to be reactivated, that the local response grew in size and eventually reached the threshold.

The modification of the effective refractory period by potassium is of interest in relation to the anti-arrhythmic action of this ion. It has been shown that when idioventricular automaticity has been enhanced by ouabain, potassium administration depresses automaticity to less than the control level. \(^{22}\) However, in that communication, no data were available to account for the manner in which “re-entry” beats were abolished by potassium. It may be suggested now that this effect of potassium on re-entrant beats due to digitalis toxicity is due to a prolongation of the effective refractory period.

One additional point should be mentioned. In most experiments the first clearly defined atrial deflection shifted from the SA lead to the EL lead during hyperkalemia. The interpretation of this finding is difficult because of the uncertain meaning of the rounded wave of low voltage and long duration which often preceded and smoothly merged with the main deflection in the SA lead (figs. 6 and 7). If this long wave indicates the initiation of activity in the sinus node, the shift in pacemaker site is only apparent and the spread of propagation within the node is markedly reduced. Thus an alternative explanation of the shift in the initial atrial activity is that there is a gradation in potassium sensitivity of specialized cells in and around the sinus region and that fibers in the great veins retain a higher degree of automaticity in the presence of an elevated extracellular potassium concentration. The latter interpretation offers also...
POTASSIUM AND SINO-VENTRICULAR RHYTHM

some degree of uncertainty, since it cannot be proved that the tip of the catheter remained exactly in the same position during the whole experiment.

Summary

Electrodes were chronically implanted in intact dogs at several locations on the atria and ventricles, and studies made of the effect of an elevated extracellular K+ concentration on the spread of the sinus impulse throughout the atria. It was found that sinus activity propagates to the coronary sinus and ventricles at a time when the atrial muscle fibers have been rendered inexcitable. The finding of such a sino-ventricular rhythm supports the existence of a specialized conducting path between the sinus and the atrio-ventricular node; this path is particularly resistant to depolarization by potassium. Potassium-induced 2:1 sino-atrial block was described. In vitro experiments provided a demonstration that such block is frequency-dependent and due to marked prolongation of the refractory period provoked by high [K]o. It appears that the lengthened refractory period may be due to a marked reduction of the reactivation rate of the "sodium carrying system."

References

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