Relation of Electrolyte Disturbances to Cardiac Arrhythmias

By CHARLES FISCH

SUMMARY
While a number of electrolytes play a role in the genesis of the transmembrane action potential (AP), the changes in the action potential most clearly related to arrhythmias are dependent to a large extent on K+. Potassium gradient is a major determinant of the magnitude of transmembrane resting potential (TRP), and secondarily the rate of rise (dV/dt) of phase 0, and consequently the speed of conduction. The cell membrane conductance for K+, or a decrease therein, is most likely the major determinant of spontaneous slow depolarization during phase 4. Thus K+ has a pronounced effect on both conduction and automaticity. Furthermore, these electrophysiologic properties are altered within levels of K+ encountered in clinical medicine, a situation which, with rare exceptions, is not seen with Ca++, Mg++, or Na-. These latter ions affect the action potential and induce experimental arrhythmias at concentrations which are unphysiologic and frequently incompatible with life. Consequently, of all the electrolytes, disturbed K+ metabolism accounts for the vast majority of clinical arrhythmias. For the same reasons, with the exception of the ability of Na+ and Ca++ to reverse the K+-induced depression of conduction, K+ is the only electrolyte with clinicians significant antiarrhythmic properties.

Additional Indexing Words:
Electrolytes
Arrhythmia
Electrocardiogram
Potassium

POTASSIUM (K+), calcium (Ca++), sodium (Na+), and magnesium (Mg++) play a role in the genesis of experimental arrhythmias.1 In the clinical setting, however, altered K+ concentration is responsible for the vast majority of such arrhythmias. This is true because within the ranges of levels of the various electrolytes encountered in clinical disorders, K+ is the electrolyte most likely to alter the electrophysiologic properties of the heart. Thus, our discussion will deal primarily with the effects of disordered K+ concentration and will touch briefly on the possible role of the remaining electrolytes.

The subject matter will be presented in general terms. Experimental designs and results of individual studies can be found in recent comprehensive and detailed reviews.1-5

Potassium
Potassium and the Transmembrane Action Potential
This section will deal briefly with the role of K+ in (1) maintaining the transmembrane action potential (AP), (2) impulse conduction, and (3) impulse formation.

During diastole (phase 4 of the AP) the membrane is largely permeable to K+ with a net loss of intracellular K+. Due to this selective permeability to K+, the magnitude of the transmembrane resting potential (TRP) is dependent largely on transmembrane concentration of K+. This relation of TRP to K+ is expressed in the Nernst equation which predicts that an increase in extracellular K+ decreases the TRP (becomes less negative) while a lowering of the extracellular K+ results in hyperpolarization, or an increase in TRP (becomes more negative).1,6

The rate of rise (dV/dt) of phase 0, a significant determinant of the speed of conduction, is to a great extent dependent on the magnitude of the TRP. The greater (more negative) the TRP at the onset of phase 0, the greater the dV/dt of phase 0 and the greater the speed of conduction. At any given state of the membrane, this relationship of the dV/dt of phase 0 to the TRP expresses membrane responsiveness.7 Since an increase in extracellular K+ lowers the TRP, the dV/dt of phase 0 will be reduced and conduction depressed (fig. 1).8

It should be noted at this juncture that reduction of the TRP will at the same time bring the TRP closer to the threshold potential (TP), and the

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Figure 1

(Bottom) Shows A-V block due to K⁺ in a digitalis-intoxicated dog. (Top) Illustrates the electrophysiological mechanism responsible for the block. The two control action potentials recorded about 1 mm apart and their expanded phase 0 is shown on the left. After infusion of KCl (right panel) the TRP (phase 4) is reduced from 90 to 70 mV; the dV/dt of phase 0 is reduced; the conduction between the two micro-electrodes is greatly delayed as indicated by an increase in distance between the two AP. (The ragged appearance of phase 0 is due to the fact that superimposed AP recorded at conventional speed were “erased”).

The strength of a given stimulus needed to reduce the TRP to TP (excitability) will thus be decreased. Consequently, conduction depression due to reduction of TRP may, within narrow ranges of hyperkalemia, be overcome to some extent by the increase in excitability. As a result, conduction alteration with changing K⁺ concentration may, at times, reflect the sum of altered dV/dt and excitability.

The slow depolarization during phase 4, which characterizes the automatic cells, is most likely due to a gradual influx of Na⁺ at a time when K⁺ efflux

Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>K⁺</th>
<th>Ca⁺⁺</th>
<th>Mg⁺⁺</th>
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<td>O</td>
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<td>I or 0</td>
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Abbreviations: RMP = resting membrane potential; dV/dt = rate of rise of phase 0; AP = action potential; TP = threshold potential; D = decreased; I = increased; ID = first increased, then decreased; O = unchanged; V = ventricular; P = Purkinje.

*Modified from Fisch C, Greenspan K.49

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is diminished or completely inhibited.9 The inhibition of diastolic depolarization by hyperkalemia is thought to be due to an increase in membrane conductance to K⁺, with an efflux of K⁺ and thus return of the TRP to a more negative level. Low K⁺, on the other hand, increases the rate of depolarization and may induce automaticity in latent automatic fiber.10,11 The myocardial cell of the rabbit, on the other hand, has been shown to be hyperpolarized by hypokalemia.12

Ordinarily, the ventricular myocardial cell is less sensitive to K⁺ than the atrial myocardial cell, and the specialized fibers of the SA node and the bundle of His are least sensitive.1 In addition, there are cells within the atria, other than the SA cells, such as the inter nodal tracts which show a selective resistance to K⁺ and may play a role in preferential intranodal and internodal conduction.13-17 The sensitivity of the cardiac tissues due to K⁺ may be modified by such factors as, for example, level of other electrolytes, pHi, O₂ saturation, and the rate of rise of plasma K⁺. All need to be included in any consideration of relative sensitivity of the various tissues to K⁺.

The rapidity with which changes of K⁺ level take place, not only the absolute level, is important in predicting the effect of K⁺ on impulse formation and conduction. A rapid increase of K⁺ level to normal in a preparation perfused with low K⁺ or in a K⁺-depleted animal or human may result in bradycardia, cardiac arrest, or depression of conduction.18 These changes are attributed to a sudden increase in negativity of the TRP due to increased K⁺ conductance secondary to rise of extracellular K⁺.

**Hyperkalemia and Conduction**

At plasma levels of 6.0-6.5 mEq/liter, representing "mild" hyperkalemia, A-V conduction is accelerated, and, at levels about 7.5 mEq/liter and higher conduction is depressed. Enhancement of A-V conduction has been confirmed in a Langendorff preparation of the rabbit heart, in the intact rabbit, and in vagotomized dog following intravenous and intracoronary injection of the cation.2,19,20 Conduction is most rapid at a K⁺ level of approximately 6.0-6.5 mEq/liter. In the clinical setting this accelerating effect of mild hyperkalemia may improve conduction in patients with sinus rhythm and A-V block21 (fig. 2), or enhance A-V conduction and thus ventricular rate in patients with atrial fibrillation.22 Because of the difficulty of maintaining the narrow therapeutic range, K⁺ is rarely, if ever, used to improve A-V conduction in patients with A-V block. The acceleration of conduction may be the result of interplay of a number of mechanisms, such as the antivagal effect of K⁺ and reduction of resting potential by the cation. In the dog, the antivagal effect of K⁺ can be demonstrated by infusion of the cation intravenously or directly into the coronary arteries. It has also been

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**Figure 2**

*Effect of mild hyperkalemia on A-V conduction. The control strip demonstrates a regular SA rhythm with a P-P interval of 0.66-0.68 sec and a 2:1 A-V block. Following administration of K⁺, SA rhythm with 1:1 A-V conduction was reestablished. Although it is possible that the mild hyperkalemia improved A-V conduction, the latter may be due to the considerably slower (and irregular) SA rhythm. The P-P varies from 1.06 to 1.50 sec which may be due to a direct or vagally mediated effect of K⁺ phase 4 of the SA nodal cells.*
shown that K⁺ inhibits the effect of exogenous acetylcholine on A-V conduction.\textsuperscript{23, 24} Increasing the excitability by bringing the TRP closer to threshold potential may also accelerate conduction.\textsuperscript{1, 21}

Depression of A-V conduction by K⁺, first reported by Mathison in 1911\textsuperscript{25} without the aid of the electrocardiograph, can be induced with ease in the laboratory. In dogs, an increase of plasma K⁺ on an average of 8.4 mEq/liter results, almost uniformly, in a variety of A-V conduction abnormalities.\textsuperscript{17} In some instances, complete A-V block is induced at a time when both P waves and QRS are recorded, suggesting that under conditions of a particular experimental design the A-V conduction system is less resistant to the depressing effects on K⁺ than either the atrial or ventricular tissue.\textsuperscript{6, 17} (fig. 3).

By recording directly from the His bundle it has been demonstrated that if K⁺ is infused at a rate varying from 0.96 to 1.6 mEq/min, the initial delay and/or block of A-V conduction is above the bundle of His, and only with further infusion of K⁺ does the block appear below the bundle of His. However, if the infusion of K⁺ is very rapid (2.5 mEq/min), the site of most marked depression of conduction may be demonstrated to be below the bundle of His at a time when the junction shows less marked depression.\textsuperscript{26} These results further suggest that any discussion of the effect of K⁺ on the different tissues of the heart should take into account the rate of infusion.

The uniformity with which one can produce A-V block in the dog is in striking contrast to the paucity of such observations in clinical hyperkalemia. In fact, to our knowledge, in “spontaneous” clinical hyperkalemia, that is, hyperkalemia due to the disease process per se and not to administration of K⁺, A-V block greater than a simple prolongation of the P-R is yet to be recorded. Scattered cases of high-degree A-V block have been documented following administration of large doses of K⁺ (130–200 mEq) for the treatment of arrhythmias\textsuperscript{22, 27} (fig. 4) or in the course of clinical investigation of the effects of K⁺ (fig. 5). This discrepancy between the experimental and “spontaneous” clinical hyperkalemia may be explained by the fact that experimental hyperkalemia is an expression of “pure” K⁺ effect, while in patients the hyperkalemia is ordinarily accompanied by disturbances of acid-base balance and electrolyte concentrations other than K⁺. Furthermore, the rate of rise of the K⁺ level plays an important role. In

![Figure 3](image)

**Figure 3**

Differential effect of K⁺ infused at a rate of 1.4 mEq/min on various cardiac tissues. Records were obtained from the SA region (SA), from the right atrium (RA), right ventricle (RV), and surface lead II (L-2). (A and B) The right atrial and ventricular activation is depressed at a time when the SA potential and surface P are clearly demonstrable. This indicates that the SA node and some parts of the atria (other than the area from which RA was recorded) are more resistant to K⁺ than the ventricular tissue. (C) Recorded after the K⁺ infusion was discontinued, the complete A-V dissociation indicates that the junctional tissue was less resistant to K⁺ than either the SA node, atria, or ventricles. Furthermore, the narrow QRS and the broad P wave suggests that the ventricles are more resistant to K⁺ than the atria.
Effect of $K^+$ on A-V and intraventricular conduction in a patient fully digitalized. The control tracing (leads V2 and L2) demonstrates atrial fibrillation with occasional escape (third, fourth QRS in lead V2). Following administration of 250 mEq of potassium over 15 hours and with a plasma $K^+$ level of 7.7 mEq/liter, there is a complete A-V block manifest by a slow and regular ventricular rate and depression of intraventricular conduction indicated by a change in morphology and prolongation of the QRS. The changes reversed when the plasma $K^+$ was reduced to 3.4 mEq/liter. Compared with figure 2, the rate of administration of $K^+$ was slower, but the plasma level attained was most likely greater.

In the experimental setting the plasma $K^+$ rises relatively rapidly, while in diseased states the plasma $K^+$ rises very slowly. The importance of the rate of rise of plasma $K^+$ is supported by the observation that in the occasional patient in whom second- or third-degree A-V block was induced by $K^+$ the cation was invariably administered rapidly or in large doses.

In the experimental preparation there is a transient phase of acceleration of intraventricular conduction as $K^+$ is elevated moderately, but with further rise of $K^+$ intraventricular conduction is depressed. In "spontaneous" clinical hyperkalemia only the depression is observed. In fact, in the face of a slowly rising plasma $K^+$, the mechanism of death is cardiac standstill due to diffuse depression of intraventricular conduction and only occasionally due to ventricular fibrillation.

In the surface ECG the depression of intraventricular conduction is manifest by a gradual prolongation of the QRS which often resembles right bundle-branch block (RBBB) and occasionally left bundle-branch block (LBBB). In comparison to bundle-branch block not due to $K^+$, intraventricular block due to high $K^+$ results from diffuse and fairly uniform depression of the entire intraventricular conduction system. Accordingly, the entire QRS, both initial and terminal parts, are prolonged. When the ECG of hyperkalemia simulates RBBB, the initial part of the QRS will also be prolonged, where in conventional RBBB it is unaffected. When the ECG simulates LBBB, the appearance of S waves over the left ventricular leads will indicate slowing of the terminal portion of the QRS, whereas in conventional LBBB only the initial and middle portions are prolonged.
With marked elevation of plasma $K^+$ intraatrial conduction is also depressed and the ECG characterized by prolongation and diminution of the $P$-wave amplitude and prolongation of the P-R interval, and finally disappearance of the P wave. It may be impossible from the surface ECG to diagnose the nature of the induced arrhythmia (fig. 6).

Potassium administered to an intact animal under light anesthesia with a slow control heart rate and sinus arrhythmia results in an initial sinus tachycardia (at $K^+$ levels of about 6.5 mEq/liter) followed by a gradual slowing of the sinus rate as the plasma $K^+$ rises to a level of 7.5–8.0 mEq/liter. Sinoatrial block either of the Wenckebach or Mobitz II variety is seen both in the experimental and clinical “spontaneous” hyperkalemia. This is probably due to the fact that SA fibers are much more resistant to the depressing action of $K^+$ than is the atrial myocardium. In other words, the SA impulse is generated but fails to propagate because of depression of intraatrial conduction. If, on the other hand, the SA node had been more sensitive than atrial myocardium, SA arrest would result.

In the clinical setting, the SA block results in passive or accelerated escape rhythms originating either in the junction or His-Purkinje system.

As with acceleration of conduction, the depression of conduction may be the result of interplay of a number of factors. These may include, for example, a reduction of TRP and potentiation of vagal action.

**Hypokalemia and Conduction**

In the experimental animal, hypokalemia may induce delay and block of A-V conduction. This has been documented in pigs fed low $K^+$ diet, in the isolated frog, and in turtle and rabbit heart exposed to low $K^+$ concentration. Depression of intraventricular conduction due to hypokalemia is less pronounced but has been described in the rabbit, turtle, and dog heart. The exact mechanism of conduction delay is not clear, but may perhaps be related to hyperpolarization of the myocardial cell. As a result, a stronger stimulus will be required to bring the TRP to TP. It may also be due to excitation of the cell before it repolarizes completely. In such a situation the takeoff potential is reduced with resultant depressed conduction. In contrast, with experimental hypokalemia, prolongation of P-R in the clinical setting is rare. Large numbers of ECGs in patients with low $K^+$ have been examined by numerous investigators, but no statistically significant prolongation of the P-R interval was noted. This is also true for the QRS.
Potassium and Automaticity

Slow administration of K⁺ to animals results in ventricular standstill due to depression of intraventricular conduction. On the other hand, rapid administration induces ectopy, junctional or ventricular in origin. The latter may terminate in ventricular fibrillation. Similarly, rapid administration of K⁺ to humans may result in ventricular ectopy. The ectopy is accompanied by evidence of K⁺-induced depression of conduction, suggesting that the mechanism of the ectopy is reentry rather than automaticity. Junctional tachycardia may be an exception in that it may well represent true enhanced automaticity. Ectopy is rare in "spontaneous" clinical hyperkalemia, except as a manifestation of a terminal event.

Hypokalemia induces ectopic rhythms under a variety of experimental and clinical situations. In the clinical setting, a wide spectrum of atrial, junctional, and ventricular arrhythmias appears. The ectopy may be due to enhanced automaticity of latent pacemaker fibers thought to be due to decreased K⁺ conductance, with consequent decreased efflux of K⁺ in face of influx of Na⁺, allowing for a more rapid loss in intracellular negativity. In addition, it has been shown that duration of recovery of AP may exceed the duration of the refractory period. Consequently a propagated impulse can be elicited before complete recovery of AP takes place, and at a time when the TRP is abnormally closer to TP, thus, requiring a "weaker" stimulus for excitation. Since hypokalemia may also depress conduction, it may also contribute to appearance of arrhythmias by enhancing reentry.

Figure 6

Effect of plasma K⁺ of 9.1 mEq/liter on rhythm and intraventricular conduction and reversal toward normal by 80 mEq of sodium bicarbonate. P waves are absent. The K⁺ etiology of prolongation of the QRS is suggested by prolongation of initial and terminal portions of the QRS best seen in leads L3 and V6, respectively. It is impossible to be certain about the nature of the arrhythmia. The possibilities are listed in order of probability: (1) SA rhythm without P waves identifiable in surface leads with 2:1 SA block in V1 and V6; (2) SA rhythm with 1:1 A-V conduction in L1 and L3 with 2:1 conduction in V1 and V6; (3) sinus slowing in V1 and V6; or (4) SA arrest or atrial fibrillation with a junctional tachycardia with 1:1 exit in L1 and L3, and 2:1 exit block in V1 and V6.
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Effect of Potassium on Arrythmias

Administration of K\(^+\) will frequently suppress ectopic arrhythmias in animals. This suppression is in large measure independent of the control plasma K\(^+\) level and most likely independent of the mechanism of the arrhythmia (automaticity or reentry). The antiarrhythmic effect is somewhat more predictable when the ectopy is due to digitalis. The reason, we believe, K\(^+\) is such a relatively reliable agent for suppression of arrhythmias is due to its effects on both automaticity and conduction. In the case of the former, K\(^+\) depresses spontaneous phase 4 depolarization by increasing K\(^+\) membrane conductance. If the arrhythmia is due to reentry, either acceleration or depression of conduction may interrupt the reentrant path and terminate the arrhythmia. Because the antiarrhythmic property of K\(^+\) is manifest at a level of 6.0-6.5 mEq/liter, a level at which K\(^+\) accelerates conduction, one may conjecture that in case of reentrant arrhythmias the elimination of the ectopy is due to improvement of conduction in the depressed limb of the reentrant pathway.

In patients with atrial fibrillation and ventricular ectopic activity, the latter may be depressed by another mechanism, namely enhancement of A-V conduction and increase in the ventricular rate, action somewhat analogous to atropine. This effect may well be due to the antivagal property of the cation.

Potassium and Excitability

Potassium, by lowering the resting potential, reduces the strength of stimulation necessary to bring the TRP to TP and consequently, within a narrow range of increased plasma K\(^+\), may restore responsiveness to external stimulation. It is difficult from the surface ECG to be certain whether the restoration of responsiveness is due to increased excitability, and failure to respond to pacemaker stimulation may result.

Potassium and Digitalis

The action of digitalis on electrophysiologic properties of the heart is frequently affected by alteration of K\(^+\) stores. This interrelationship may become manifest in the form of (1) depression of digitalis ectopy by elevated plasma K\(^+\), (2) enhanced ectopy with lowered K\(^+\) concentration, and (3) potentiation of digitalis-induced depression of conduction by elevated plasma K\(^+\).

As early as 1918, Loewi pointed out that K\(^+\) is capable of suppressing digitalis-induced ectopic rhythms in the experimental animal. This was confirmed for the human in a series of reports by Sampson and his associates, and subsequently by others. The mechanism of suppression of the automatic arrhythmias is probably related to activation of the ATPase pump by the K\(^+\), with increase of K\(^+\) efflux, depression of phase 4 depolarization, and thus a suppression of automaticity. In case of reentry, it is likely that K\(^+\), by altering conduction, eliminates ectopy.

Hypokalemia enhances digitalis-induced arrhythmias. This increased sensitivity to digitalis in the presence of hypokalemia has been demonstrated during renal dialysis, excessive diuresis, loss of K\(^+\) due to a variety of intestinal disorders, and administration of glucose and steroids. It may be that the loss of intracellular K\(^+\) due to heart failure may predispose to digitalis toxicity, and this may explain the increased sensitivity of the severely diseased heart to digitalis.

The observation that hyperkalemia, particularly if induced rapidly, enhances depression of conduction due to digitalis is not surprising. Both drugs depress conduction and, furthermore, digitalis by blocking K\(^+\) transport allows for a more rapid rise of the plasma K\(^+\). This enhancement has been noticed clinically, both with A-V and intraventricular conduction. A striking K\(^+\)-induced depression of conduction occurs in animals intoxicated with digitalis. The rapid and pronounced enhancement of digitalis-induced depression by K\(^+\) observed in the laboratory must be applied to clinical situations with serious reservations. The rather severe degree of digitalis intoxication and the rapid rate of rise of plasma K\(^+\) are less likely to be encountered in clinical medicine. Regardless of the difference between the experimental and clinical situation, the fact remains that K\(^+\) given at an inappropriately rapid rate to digitalis-intoxicated patients may result in rather striking depression of conduction, be it sinoatrial, intraatrial, atrioventricular, or intraventricular.

There exists a rather significant margin of safety between the ectopy and A-V conduction-depressing effects of K\(^+\). In a large number of animals studied, the plasma K\(^+\) at which acetylcholophantidin-induced ventricular arrhythmias were depressed averaged 6.2 mEq/liter, while the level necessary to induce A-V block averaged 8.4 mEq/liter. This is in keeping with the previously noted differential sensitivity of the Purkinje and A-V junctional
tissues.\textsuperscript{32} Thus, in the face of serious digitalis-induced arrhythmias, even in the presence of simple A-V conduction delay, the margin of safety between the antiectopic and conduction-depressing properties of K\textsuperscript+ permits judicious administration of K\textsuperscript+ (fig. 7).

**Calcium**

Calcium has an effect on the TP, hypercalcemia reducing (less negative) and hypocalcemia increasing (more negative) its magnitude, but does not significantly affect either the TRP, shape, or amplitude of the AP.\textsuperscript{3, 42} This is true with Ca\textsuperscript{++} concentrations varying from 1.2 to 20.8 mEq.\textsuperscript{43} Only at levels which are most likely incompatible with life does hypocalcemia reduce the TRP and increase the slope of phase 4 depolarization. Thus, within clinically encountered variations in Ca\textsuperscript{++} concentration, the ion is without any significant effect on either the magnitude of the TRP or phase 4 depolarization, two changes important in the genesis of arrhythmias.

In the intact experimental animal, marked elevation of the plasma Ca\textsuperscript{++} may induce depression of intraventricular conduction, ventricular premature systoles, and fibrillation.\textsuperscript{8} In patients with extreme elevation of Ca\textsuperscript{++}, prolongation of P-R, or higher degrees of A-V block and prolongation of the QRS have been reported\textsuperscript{44} (fig. 8). As a rule, however, the incidence of arrhythmias is not increased in disorder of Ca\textsuperscript{++} metabolism.

The suggestion that elevation of Ca\textsuperscript{++} levels enhances digitalis ectopy needs confirmation. The fact that lowering Ca\textsuperscript{++} with EDTA can reverse

\textbf{Figure 7}

This figure demonstrates digitalis-induced arrhythmias, suppression by K\textsuperscript+ administered uniformly at a rate of 1.2 mEq/min, and the margin of safety between the antiarrhythmic and A-V conduction depressing effects of K\textsuperscript+. The control tracing demonstrates sinus arrhythmia and, beginning with strip 2, induction of an ectopic arrhythmia with acetylstrophanthinidin. After 5 min of infusion and a plasma K\textsuperscript+ of 6.1 mEq/liter, the arrhythmia was suppressed, but returned promptly with discontinuation of K\textsuperscript+ infusion and a decline of K\textsuperscript+ level to 5.4 mEq/liter. After 9 min of infusion and a K\textsuperscript+ level of 8.2 mEq/liter, there was evidence of A-V block (bottom row).
Figure 8

This figure demonstrates a P-R interval which is within normal limits, but longer at the plasma Ca++ level of 16 mg% than when the Ca++ level is down to 9 mg%. The QRS appears minimally widened. Nonspecific T-wave changes simulating ischemic changes are also seen with the hypercalcemia. All the changes reverted to normal with decline of Ca++ level to normal.

Arrhythmias supports such a relationship but is far from conclusive, as this intervention affects both arrhythmias due to digitalis and those not related to digitalis.3, 45

By reducing the Ca+++ to 1/20 of its normal concentration, a situation not seen in clinical medicine, arrhythmias can be induced in animals. An interesting and potentially clinically useful relationship exists between K+ and Ca++. Potassium-induced depression of conduction and ectopy can be reversed by administration of Ca++. This effect of Ca++, in the presence of hyperkalemia, is probably related to an increase of the TRP by Ca++.

Sodium

Alteration of Na+ concentration affects the amplitude and rate of rise of the AP, but is without any significant influence on the TRP or phase 4 depolarization of pacemaker cells. Elevated Na+ concentration increases the amplitude of the AP, as well as the rate of rise of phase 0, while the opposite effect is noted with decreased Na+ concentrations. The Na+-induced changes are of little clinical significance because the levels necessary to alter the action potential are usually incompatible with life. Consequently, arrhythmias related to hyper- or hyponatremia are not seen in clinical medicine.
The interrelation of Na\(^+\) and K\(^+\) is of some therapeutic usefulness. The depression of conduction induced by K\(^+\) can be reversed by administration of Na\(^+\), and exaggerated by lowering the Na\(^+\) concentration. In the clinical setting, this is manifested most often by foreshortening of K\(^+\)-induced QRS prolongation by administration of Na\(^+\).\(^{46}\) The mechanism is probably related to reversal of the impaired Na\(^+\) conductance by administration of Na\(^+\) with a resultant increase in upstroke velocity of phase 0 and, thus, acceleration of conduction.

**Magnesium**

Elevation of extracellular Mg\(^+\) to 3–5 mEq/liter depresses A-V conduction.\(^{8}\) This may be due to slowing of the upstroke velocity of phase 0, a mechanism similar to or identical with that induced by hyperkalemia. Whether or not alteration of Mg\(^+\) concentration within clinical ranges induces arrhythmias remains to be seen. To date, however, there is very little evidence that “spontaneous” hypomagnesemia gives rise to arrhythmias. Study of children with protein-calorie malnutrition and depressed concentration of Mg\(^+\) failed to disclose any arrhythmias except for sinus tachycardia, and this was not felt to be due to low Mg\(^+\) levels.\(^{47}\)

The relationship of low Mg\(^+\) to digalism-induced arrhythmias is of potential interest. In one study, lowering the Mg\(^+\) level by means of dialysis with Mg\(^+\)-free solution reduced the amount of acetylstrophanthidin necessary to induce arrhythmia. The arrhythmia was promptly abolished in most, but not all, of the animals by administration of magnesium sulfate solution.\(^{48}\) The reduction of Mg\(^+\) was severe and occurred rapidly, and whether these results can be extrapolated to clinical situations remains to be seen. The question of the specificity of Mg\(^+\) for digitalis arrhythmias also needs further elucidation, for, as in the case of K\(^+\), Mg\(^+\) suppresses arrhythmias due to digitals, as well as those not due to the glycoside.

The advent of the electrocardiogram, microelectrode, and technics for the study of transmembrane ionic fluxes has contributed to our understanding of some of the complex relationships existing between altered electrolytes and arrhythmias. Simulation of the clinical states in which arrhythmias are recorded (e.g., simultaneous manipulation of a number of electrolytes with such variables as pH, oxygen saturation, metabolic wastes, histopathologic state of the tissue) both in intact animal and isolated tissue will further our understanding of the electrophysiologic mechanisms of arrhythmias. This is but one of many avenues for study of the genesis, maintenance, and control of arrhythmias open to us.

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