Electrocardiographic Alterations Produced by a Decrease in Plasma pH, Bicarbonate and Sodium as Compared with those Produced by an Increase in Potassium

By Kathleen E. Roberts, M.D., and Melville G. Magida, M.D. With the technical assistance of Mrs. Hilda Satran and Mrs. Sarah Ward

The effects of a decrease in plasma pH, bicarbonate and sodium on the electrocardiographic pattern are compared with those produced by elevation of serum potassium and lithium in the dog. The electrocardiographic alterations were found to be similar in form and progression. The alterations can be correlated with those found in isolated nerve and muscle preparations.

It has become apparent, in clinical situations accompanied by hyperkalemia, that the electrocardiographic abnormalities and clinical symptomatology cannot be closely correlated with the plasma potassium concentration. In many of these conditions, there occurs a coincident decrease in sodium, bicarbonate, and pH accompanied by variable disturbances in chloride, phosphate, and magnesium.

The effects of potassium, calcium, and magnesium on the electrocardiogram have been well defined experimentally. However, the effects of bicarbonate, pH, and sodium, which are known to influence the electric potentials in isolated nerve and muscle have not been delineated in the intact organism.

The present experiments in normal dogs were undertaken (1) to define the electrophysiologic changes which occur as a result of disturbances of those ions known to be altered in clinical situations associated with hyperkalemia, and (2) to correlate these changes with those previously ascribed solely to potassium.

Methods and Materials

Forty-two experiments were performed on 31 female mongrel dogs, anesthetized with sodium pentobarbital. Following a preliminary control period, the substance to be investigated was infused through polyethylene tubing into an antecubital vein, utilizing a calibrated constant infusion pump. Serial electrocardiograms and blood samples for the determination of carbon dioxide, pH, sodium, potassium and chloride were taken at intervals of 10 to 20 minutes.

Respiratory acidosis was produced by the administration of carbon dioxide-oxygen mixtures delivered by a Palmer pump through a closed tracheotomy site at rates of 7.5 to 10 liters per minute. The carbon dioxide-oxygen mixtures were increased in stepwise fashion beginning with 20 per cent and terminating with 80 per cent carbon dioxide.

Electrocardiograms, including the standard limb and augmented unipolar extremity leads, were taken with a Sanborn Viso-Cardiette. In order to avoid axis shifts, the animals were maintained in a fixed position and electrocardiograms were taken in the same phase of respiration. Electrodes were not shifted during the course of an experiment.

Arterial blood was obtained from an indwelling needle in the femoral artery. Blood was drawn into an oiled syringe containing potassium oxalate, and agitated with a small quantity of mercury. A part of this blood was transferred to a Van Slyke pipet for determination of pH; the remainder was introduced into a test tube under oil, sealed with paraffin, immediately centrifuged and refrigerated for 1 to 2 hours before determinations of carbon dioxide were made. Heparinized blood samples were analyzed.

From the Department of Physiology, Cornell University Medical College, New York, N. Y.

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Dr. Magida is a Post-Doctorate Research Fellow, National Heart Institute, United States Public Health Service, Bethesda, Md.

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for sodium and potassium with an internal standard flame photometer. Chloride was determined by Van Slyke and Hiller's modification of Sendroy's method and total carbon dioxide by the method of Van Slyke and Neill. Whole blood pH was determined with a Cambridge condensor type glass electrode surrounded by a constant temperature water jacket at 37 C. Bicarbonate was calculated from the total carbon dioxide and pH utilizing the Henderson-Hasselbach equation.

In order of appearance they consisted of an initial tachycardia, augmentation or peaking of the T wave, obliteration of the ST segment with the T wave arising from the S wave, bradycardia with loss of the P wave, development of a nodal rhythm or ventricular origin of the cardiac impulse with increased duration of QRS and T. With continuation of the infusion, bizarre ventricular complexes appeared.

**Infusion of Potassium Chloride.** Figure 1 illustrates the typical alterations in plasma electrolytes and the electrocardiogram which result from the infusion of potassium chloride at a rate of 0.6 mEq. per minute. Similar results were obtained in four additional experiments. The increase in potassium concentration was associated with decreases in plasma bicarbonate and pH, and a small, but definite, fall in sodium concentration. The electrocardiographic alterations followed the same general pattern described by others.1-8

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**Fig. 1.** Effect of the Infusion of Potassium Chloride. Each period represents an interval of 40 minutes. Duration of infusion 170 minutes.

**Infusion of Lithium Chloride.** Because of its similarity to potassium, both as to chemical properties and its influence upon the isolated nerve preparation, and because of its known clinical toxicity, the effect of lithium chloride was examined in relation to the electrocardiogram and electrolyte structure of the body fluids in four dogs. Figure 2 illustrates the similar effects of this ion and of potassium upon the electrocardiogram and the plasma electro-
lyte pattern. In these experiments lithium chloride was infused at the rate of 0.95 mEq. per minute. The plasma alterations in pH, bicarbonate, and sodium are similar to, but more profound than those produced by the infusion of potassium chloride. Especially striking is the appearance of electrocardiographic changes in the absence of significant alteration in the plasma concentration of potassium.

Infusion of Ammonium Chloride, Hydrochioric Acid and Sulfuric Acid. Common to the infusion of either potassium or lithium chloride is a fall in plasma pH and bicarbonate. For this reason, it seemed appropriate to produce an acidosis by the infusion of ammonium chloride, hydrochloric or sulfuric acid and to examine the effects of these agents upon the electrocardiogram. The typical alterations produced by the infusion of ammonium chloride at a rate of 1.25 mEq. per minute are illustrated in figure 3. Similar results were obtained in three additional experiments. As anticipated, there was a marked fall in plasma pH and bicarbonate concentration, accompanied by progressive electrocardiographic alterations similar to those seen in figures 1 and 2. We were unable to demonstrate, however, what specific influences the decreased pH and bicarbonate might have on the electrocardiogram, since there was a concomitant fall in plasma sodium and a rise in potassium.

The specific influence upon the electrocardiogram of a decrease in the pH and bicarbonate of the extracellular compartment is better illustrated by the infusion of hydrochloric acid at a rate of 1.3 mEq. per minute. Figure 4 illustrates the observation, as noted in 10 experiments, that the infusion of hydrochloric acid may produce electrocardiographic changes which are similar to those produced by the infusion of potassium chloride. It is worthy of note that these changes may be unassoci-
### Fig. 3. Effect of the Infusion of Ammonium Chloride. Each period represents an interval of 40 minutes. Duration of infusion 140 minutes.

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### Fig. 4. Effect of the Infusion of Hydrochloric Acid. Each period represents an interval of 20 minutes. Duration of infusion 110 minutes.

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EFFECT OF DECREASED pH, HCO₃, Na AND K ON ECG

ated with alterations in plasma potassium, and that the changes in sodium are of minor degree.

Since antecedent alterations were produced by the infusion of the chloride ion in combination with potassium, lithium, ammonium, or hydrogen, one might infer that this ion was responsible for the production of the plasma and electrocardiographic alterations. To eliminate this possibility, sulfuric acid was infused in two experiments at a rate of 0.95 mEq. per minute. Such an experiment is presented in figure 5. Examination of the data and records reveals that the same plasma and electrocardiographic alterations may be produced without the infusion of exogenous chloride.

Respiratory Acidosis. In order to determine whether the electrocardiographic changes, described above, result from alterations in plasma pH alone, a severe respiratory acidosis was induced in two dogs. The inhalation of 20 to 60 per cent carbon dioxide produced more striking decrements in pH than were produced by any of the aforementioned techniques. Yet, as is evident in figure 6, only minor alterations in the electrocardiogram developed, and little by way of a sequential pattern of change was noted, despite the marked fall in plasma pH to 6.58.

The Influence of the Rate of Injection. Of major importance is the rate at which the various substances are infused. The administration of small total amounts of these solutions at rapid rates was sufficient to produce immediate death in the animal. Under these circumstances the animals frequently developed a terminal electrocardiographic picture without concomitant alteration in plasma electrolytes or the sequential development of electrocardiographic abnormalities, as have

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**Fig. 5.** Effect of the Infusion of Sulfuric Acid. Each period represents an interval of 30 minutes. Duration of infusion 105 minutes.
been described. Only with infusion rates such that the infused substances did not reach the heart in amounts greater than 1.3 mEq per minute were we able to demonstrate progressive alterations in plasma electrolytes and the electrocardiogram.

Further, the action potential as well as the conduction of nervous impulses is dependent upon the maintenance of an adequate sodium concentration in the extracellular fluid. Evidence for similar alterations in myocardial units of the intact organism may be deduced from the finding that potassium and lithium produce similar changes in the electrocardiogram. Studies on the distribution of these ions following their infusion into dogs have shown that both enter the intracellular compartment. In the case of potassium, extracellular bicarbonate accompanies the intracellular shift, resulting in an increase in the intracellular pH. Results presented in figure 2 suggest that a like transfer of bicarbonate ions occurs with the infusion of lithium chloride. It has been pointed out that the infusion

\[
\begin{array}{|l|l|l|l|l|l|}
\hline
 & \text{CONTROL} & \text{20\% CO}_2 & \text{40\% CO}_2 \\
\hline
\text{pH} & 7.41 & 7.04 & 6.94 & 6.82 & 6.81 & 6.73 \\
\text{H}_2\text{CO}_3 & 1.10 & 3.60 & 3.50 & 6.00 & 5.30 & 6.80 \\
\text{Na} & 14.7 & 14.8 & 14.7 & 151 & 146 & 146 \\
\text{K} & 3.75 & 3.55 & 3.55 & 4.40 & 4.30 & - \\
\hline
\end{array}
\]

\text{FIG. 6. Effect of Respiratory Acidosis.}

\text{DISCUSSION}

From the data presented it may be seen that electrocardiographic abnormalities similar to those ascribed to hyperkalemia may be produced by alterations in the plasma concentration of sodium, bicarbonate and hydrogen ion, with or without a concomitant change in the concentration of potassium. It is well established that the concentration gradients of potassium and sodium which exist across the cell membrane are of paramount importance in the maintenance of cellular activity. Potassium, is implicated in the maintenance of the resting potential; an elevation of the external concentration of this ion or of the lithium ion results in depolarization of the cell. Further, the action potential as well as the conduction of nervous impulses is dependent upon the maintenance of an adequate sodium concentration in the extracellular...
of either lithium or potassium is accompanied by a fall in plasma sodium concentration. That this alteration in plasma sodium may be responsible, in part, for the alterations in cellular function cannot be refuted.

Although little is known concerning the influence of hydrogen ion concentration on the bio-electric properties of the cell, certain deductions may be made. It has been established that the intracellular pH is maintained close to a value of 6.8; in the extracellular compartment the concentration of bicarbonate and carbonic acid are such that the pH of this compartment is maintained at the normal of 7.4.13 Thus, a hydrogen ion gradient is established across the cell membrane. A change in the extracellular pH from 7.4 to 7.0 approaches the maximum compatible with life. From this it would appear that alterations in the hydrogen ion gradient may influence the electric potentials upon which the fundamental properties of nerve and muscle depend.

The infusion of ammonium chloride, hydrochloric acid or sulfuric acid causes a decrease of pH and bicarbonate which evokes an alteration of the hydrogen ion gradient between the extra- and intracellular compartments. No alteration in extracellular concentration of potassium need be implicated as seen from the finding that electrocardiographic aberrations may be produced, as in the case of hydrochloric acid infusion, without concomitant alteration in the concentration of potassium.

Although the absence of electrocardiographic abnormalities in the presence of respiratory acidosis would seem incompatible with the thesis that alterations in pH influence cardiac function, this need not be the case. Carbon dioxide permeates all cells of the body and rapid equilibrium is achieved between the extra- and intracellular compartments. Since no change occurred in those other ions which were measured, it is conceivable that little alteration in ionic gradient occurred across the cell membrane under the conditions of these experiments. Since carbon dioxide has been reported to repolarize a nerve previously depolarized with potassium,9 it would be illogical to presume that similar alterations would be produced by carbon dioxide and potassium in the myocardium of the intact animal.

The defect in myocardial function which can be implicated in sodium loss is a dual one. As has been pointed out, the action potential in an isolated nerve is dependent upon the concentration of sodium in the extracellular fluid; a decrease in the concentration of this ion is accompanied by a progressive change in action potential, with eventual loss of excitability of the cell. In addition, this ion represents available base in the bicarbonate buffer system. The drainage of this cation which is responsible for the maintenance of pH stability in the extracellular compartment leads to a profound acidosis.

Clinical Implications

The electrolyte and electrocardiographic abnormalities which were experimentally induced have counterparts in the clinical conditions of diabetic acidosis, adrenal and renal insufficiency and in cases of salt depletion or deprivation. Although the alterations in the acid-base picture in these clinical situations are infinitely more complex than the experimentally induced alterations by which each component has been studied, it is conceivable that certain similarities and interrelationships may be mutually shared. In all situations, experimental or clinical, there is evidence to indicate an alteration in the concentration gradient across the myocardial cell which involves sodium, potassium, bicarbonate, and hydrogen ion and perhaps other components which were not measured by us. Since myocardial function is ultimately dependent upon processes by which depolarization and repolarization occur in sequence with systole and diastole, severe alterations in electric potential must eventuate in cardiac failure. Although it is not possible in these experiments to indict any single alteration in ionic concentration, we infer that the alteration in plasma potassium is not alone responsible for the electrocardiographic alterations which have been described in conjunction with those clinical states in which hyperkalemia is a prominent finding.
Conclusions

1. Similar electrocardiographic alterations can be produced by the infusion of potassium chloride, lithium chloride, ammonium chloride, hydrochloric and sulfuric acid.

2. These electrocardiographic alterations are similar in form and development to those previously ascribed to hyperkalemia, but may be produced with or without an elevation of plasma potassium.

Acknowledgment

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References


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