Effects of Acute Removal of Potassium from Dogs
Changes in the Electrocardiogram

By John M. Weller, M.D., Bernard Lown, M.D., Rolf V. Hoigne, M.D.,
Norman F. Wyatt, M.D., Modesto Criscitiello, M.D.,
John P. Merrill, M.D., and Samuel A. Levine, M.D.

Potassium has been rapidly removed from the circulating blood of dogs in 22 experiments in which other extracellular electrolytes were maintained constant. In these experiments potassium extraction occurred in an acute phase accompanied by a reduction in serum level and a second phase of continued extraction with little change in the extracellular concentration. In the first phase the P wave increased markedly in amplitude and width. The A-V conduction time became prolonged. The QRS complex widened, the T wave became broadened and rounded, and the S-T segment depressed, the latter change occurring in the second phase of dialysis. In these experiments, acute depletion of potassium in dogs consistently reflects the electrocardiographic changes ascribed to hypokalemia.

Ringer clearly demonstrated by means of an isolated frog-heart preparation that the contraction of heart muscle was dependent on the electrolyte composition of the perfusing fluid.1 Numerous investigators have confirmed these findings in animals and have extended the observations to include the associated alterations in the electrocardiogram.2 However, until recently it has not been possible to remove a selected electrolyte quantitatively and rapidly from an intact animal and at the same time to maintain the relative constancy of other electrolytes. External hemodialysis permits such a procedure. This procedure has been applied to the removal of potassium from the circulating blood of dogs. This procedure permits the rapid removal of potassium from the extracellular fluid. In addition, our observations and those of Reinecke, Holland, and Stutzman3 have shown that an amount of potassium could be removed by hemodialysis that was equal to or greater than that calculated to be present in the extracellular fluid of dogs.

The present study had the following three objectives: (1) to assess the rapidity and extent of potassium removal by hemodialysis, (2) to delineate the alterations in the electrocardiographic pattern following such removal, and (3) to attempt to determine the role of both cellular and extracellular potassium in these changes.

METHODS

Rapid removal or addition of potassium was carried out in dogs by means of a Kolff-type hemodialyzer ("artificial kidney"). The technical aspects of dialysis were similar to those previously described4 except for the following modifications: (1) A flow of 100 to 300 ml. of blood per minute through the machine was obtained by cannulation of the femoral artery and vein. (2) The length of cellophane tubing was limited to 70 feet. (3) Prior to dialysis, the dead space in the machine was filled with 400 ml. of heparinized blood drawn from donor dogs. (4) The composition of the bath fluid, which approximated the electrolyte concentration of dog serum, was altered in these experiments only in respect to its potassium content. When potassium removal was begun, no potassium was present in the bath so that its concentration was nearly zero. When potassium addition was carried out, the concentration of...
potassium in the dialysate bath was raised to 8 mEq per liter.

Twenty-two hemodialyses were carried out on 14 mongrel dogs of both sexes ranging in weight from 10 to 14 Kg. The dogs were maintained under pentobarbital or morphine anesthesia or analgesia during dialysis. These drugs were administered intravenously. The dosage schedule of pentobarbital was 30 mg. per kilogram initially and approximately 3 mg. per kilogram at hourly intervals. The initial morphine dose was 3 mg. per kilogram followed by approximately 1 mg. per kilogram every hour. Heparin was administered intravenously in a dose of 20 mg. at the start and then 5 mg. hourly. Electrocardiograms were taken with a direct-writing, amplifier-type electrocardiograph. Limb, unipolar, and chest leads, maintained at a constant position, were recorded at frequent intervals during dialysis. Observations on the arterial blood pressure were made by means of an aneroid manometer attached by tubing to a side-arm of the arterial cannula. In the majority of experiments the arterial blood pressure was well maintained throughout dialysis.

The 22 dialyses consisted of three groups of experiments. In 13 dialyses, referred to as group I, the dogs were subjected to no other procedure except potassium extraction for an average duration of 4 hours and 8 minutes. Group II consisted of seven dialyses of shorter duration having approximately an average time of 1 hour and 23 minutes. In this group digitalization was carried out at the end of the period of potassium extraction to study the relation between digitalis toxicity and potassium. These studies will be reported later. In two dogs the extraction of potassium was begun after the serum potassium concentration had been raised to 8 mEq per liter. These dogs constitute group III. In dialyses in all groups after the completion of extraction, the serum potassium level was rapidly raised by dialyzing against a bath potassium of 8 mEq per liter.

The amount of potassium removed was determined by measuring the increment in the potassium concentration of the bath fluid. Sodium and potassium were determined with a Barclay flame photometer using lithium as an internal standard; chloride was determined by the method of Schales and Schales, and calcium by the method of Clark and Collip.

RESULTS

Rate of Potassium Transfer

During hemodialysis potassium is removed from the body if the concentration of potassium in the dialysate bath is lower than that in the plasma. In figure 1, the dotted line shows the rate of extraction of potassium when there is no potassium present in the bath. It can be seen that the removal of potassium from the body continues at a fairly constant rate throughout several hours of dialysis. The rate of potassium extraction averages nearly 10 mEq per hour, although there is some variation between experiments probably due to variations in the rate of flow of blood through the machine, the total amount extracted being less with a low rate of flow of blood and greater with a high flow rate.

The effect of this rapid removal of potassium upon the concentration of potassium in the extracellular compartment is shown in figure 1 by the solid line. During the first hour of dialysis there is a rapid fall in the plasma potassium concentration. However, following this initial period of rapid lowering, the level of potassium in the plasma tends to become stabilized at about one-half of its original value. In these experiments continuation of dialysis beyond two hours did not result in any further decrease in the plasma potassium concentration which averages about 2 mEq per liter. During this period potassium is continually being removed from the body. In a 10 Kg. dog with an assumed extracellular phase of 20 per cent of body weight (2 liters) a decrease in the extracellular potassium concentration from 4 to 2 mEq per liter represents an extraction of only 4 mEq. of potassium from this phase. More than two and
TABLE 1.—Data on 22 Hemodialyses on 14 Dogs. The Incidence of Electrocardiographic Changes Is Related to the Duration of Dialysis and the Alterations in Potassium

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Duration of Dialysis (minutes)</th>
<th>Serum K* (mEq./L.)</th>
<th>Amount K* Extracted (mEq.)</th>
<th>Rate (beats/min.)</th>
<th>Increase in P-wave Height (1 mm.)</th>
<th>Prolonged P-R Interval (0.02 sec.)</th>
<th>QRS Widening</th>
<th>Shift in Axis</th>
<th>Increase in T-wave Area</th>
<th>Depression of S.T segment (0.05 mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>248</td>
<td>3.8</td>
<td>3.1</td>
<td>6.2</td>
<td>150</td>
<td>12</td>
<td>3</td>
<td>9</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>83</td>
<td>4.0</td>
<td>2.2</td>
<td>1.8</td>
<td>154</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>115</td>
<td>8.0</td>
<td>2.3</td>
<td>5.7</td>
<td>155</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Data from 11 dialyses.

one-half times this amount is usually removed during the first hour of dialysis. The difference must be derived from some other source than the extracellular compartment as must be all potassium which is extracted during the period when the plasma potassium is being maintained at a constant level. Because the content of potassium in the cellular compartment is large, about 2 per cent of the total amount of potassium in the cellular phase is being removed hourly. Cellular potassium is apparently transferred into the extracellular compartment at a rate sufficient to maintain the concentration of potassium in the extracellular phase at a nearly constant level.

Extraction of body potassium by this method of hemodialysis may, therefore, be considered as occurring in two phases: (1) A phase of rapid lowering (during the first hour) of the extracellular potassium concentration to one half of its initial value, and (2) a phase of continuing extraction occurring beyond the first hour during which time the potassium concentration in the extracellular compartment remains nearly constant. The potassium extracted during this phase is presumably derived from the cellular compartment.

Electrocardiographic Changes

The removal of potassium from the body induced changes both in auricular and ventricular components of the electrocardiogram. The incidence and type of alterations, as related to the quantity of potassium extracted, are shown in table 1.

The earliest electrocardiographic effect was an increase in the height and width of the P wave. There occurred a doubling, or at times even a tripling, in its amplitude. These changes were best observed in leads II, III, and aV_1. The alterations in P wave were associated with a prolongation of auriculoventricular conduction time. With continued removal of potassium, the P-R interval lengthened, the P wave "migrated" and eventually fused with the T wave (figs. 2–4). In some instances it emerged before the inception of the T complex (fig. 3). Increases in the duration of A-V conduction were noted only in conjunction with changes in the P wave. These alterations were

FIG. 2. Increase in P-wave amplitude, prolongation of P-R interval with fusion between the P and T waves occurring during the early phase of dialysis.

In this and subsequent figures, the length of dialysis in hours and minutes is indicated under time; the serum potassium and sodium concentrations are expressed in milliequivalents per liter, and the amount of potassium removed in milliequivalents.
maximal during the first two hours of dialysis during the phase of rapid lowering of the extracellular potassium. In only one instance did the P wave continue to increase in size after the stabilization of the serum potassium level (fig. 6).

Significant augmentations of the heart rate resulted from the removal of body potassium. The increase in rate was a function of the duration of the extraction. In group I, rate accelerations of over 10 per cent occurred in 9 of the 13 hemodialyses, with an average increase of 27 beats per minute for the entire group. Similar degrees of acceleration were noted in only two of the seven hemodialyses in group II in which the increase averaged seven beats per minute (table 1). The increase in heart rate did not depend on changes in the P wave or P-R interval.

Widening of the QRS complex and shift in its axis were two common alterations in the ventricular component which attended the removal of potassium. Increase in the duration of the QRS was a notable feature only after the serum potassium level became fixed around 2.0 mEq. per liter. The so-called axis shift consisted of a diminution in the R wave in the standard leads and the emergence or increase in the amplitude of the S wave in leads II, III, aVF, and the precordial leads. The heart shifted in its electrical position with a counterclockwise rotation on the anteroposterior axis and clockwise rotation on the longitudinal axis (figs. 4 and 6). The vector projection of ventricular depolarization thus became directed toward the left upper limb and posteriorly. These changes began early and evolved throughout the entire dialysis.

T-wave changes were difficult to study because of the rapid heart rates and the superposition of the P wave on the T wave. This also prevented determination of changes in the Q-T interval. In those instances where P- and T-wave fusion did not occur, there was no alteration in the T-wave direction. Generally the T wave widened, increased in amplitude and assumed a rounded contour. Often it exhibited a small degree of notching at its apex. This may have been due to the incorporation of a U wave. Changes in the T wave began early in dialysis and were complete
FIG. 4. Acceleration of heart rate, fusion of P and T waves, shift in QRS axis, as well as depression of S-T segment occurring during extensive depletion of potassium.

FIG. 5. Increasing depression of the S-T segment during the continued removal of potassium while the serum level remains unaltered.
usually at the time the lowest serum potassium level was achieved.

Significant depression of the S-T segment occurred during the phase of slow removal of potassium, at a time when the serum level remained fixed. The degree of depression appeared to relate to the amount of potassium extracted from the body. When the serum potassium was restored to its predialysis level all electrocardiographic parameters, except for the S-T segment, rapidly reverted to normal. Even after the serum potassium level was rapidly raised to 11.2 mEq. per liter, the S-T segment depression persisted (fig. 6).

Ten of the 14 dogs in this study were subjected to additional dialyses during which the potassium ion concentration in the bath fluid was kept constant. These hemodialyses against normal baths were carried out for a minimum of eight hours. In no instance were any of the electrocardiographic effects of potassium removal noted. The sole results were occasional nonspecific alterations in the T wave.

Electrocardiographic changes resulting from potassium extraction can be classified into one of three groups: (1) Changes limited to the phase of rapid serum potassium decline, which consisted of increases in the amplitude of the P wave, widening and rounding of the T wave and prolongation of the P-R interval; (2) changes taking place throughout the process of potassium removal, which consisted of shifts in the QRS axis and acceleration of heart rate; (3) changes occurring during the phase of continuing extraction of potassium during which the serum level remains fixed; these consisted of depression of the S-T segment and widening of the QRS complex.

**DISCUSSION**

The rate of blood flow through the artificial kidney and the concentration of potassium in the bath fluid determine the rapidity with which this ion is removed from the body. Under the conditions of these experiments it was not possible to reduce the serum potassium concentration much below 2.0 mEq. per liter, with a blood flow through the apparatus ranging from 100 to 300 cc. per minute and with frequent changes of the bath fluid so as to maintain bath potassium close to zero. After this serum level was achieved, the extracellular space apparently served merely as a conduit for the transport and removal of body potassium. In those instances where technical factors caused temporary cessation of dialysis, there was a prompt rise in the serum concentration. It is of interest that patients who sustain massive potassium losses seldom exhibit serum potassium values of less than 2.0 mEq. per liter. When the organism is depleted of potassium, it appears that mechanisms are activated within the cellular compartments to defend the extracellular potassium concentration. The potassium level reached in these experiments represents an equilibrium between extracellular extraction and cellular restitution. What conditions equilibrate at about 50 per cent of the initial serum value is unknown. No doubt the rapidity of extraction as well as its duration are factors.

Extensive potassium depletion in human beings gives rise to distinctive electrocardiographic changes. The effects predominantly involve the process of ventricular repolarization. The S-T segment becomes depressed, the T wave becomes flattened and inverted with emergence and prominence of the U wave. The duration of the Q-T interval remains un-
altered.8 No similar T- or U-wave alterations were distinguishable in this study. This is attributable to the rapid heart rate, increased prominence of the P waves, and prolongation of the P-R interval which accompanied the removal of potassium. Attention has been drawn to the fact that similar alterations interfere with the electrocardiographic recognition of hypokalemia in patients.8

In advanced hyperkalemia, there is diminution of the P wave eventuating in auricular standstill. The converse changes in the auricular complex during potassium depletion have not been emphasized to date. Prominence of the P wave was noted in dog experiments in which the serum potassium concentration was lowered by the infusion of sodium bicarbonate.10

Peaked P waves have been observed in patients with hypokalemia due to diabetic acidosis.11, 12 Others have also commented upon the occurrence of A-V conduction disturbances13, 14 as well as ectopic auricular rhythms in association with hypokalemia.8, 15, 16 Surawicz and Lepeschkin found the P waves to be taller at the height of hypokalemia in all of their eight patients who experienced losses of potassium.8 Three of these patients demonstrated, in addition, prolongations of the P-R interval. These investigators believe that peaked P waves, A-V conduction impairments and ectopic rhythms are useful as corroborative evidence of hypokalemia when other electrocardiographic criteria are equivocal.8

These auricular changes shed light on the genesis of one of the arrhythmias encountered in patients with congestive heart failure. Lown and co-workers have demonstrated that, in the presence of potassium deficits, digitalis will precipitate ectopic auricular mechanisms. The prototype of these arrhythmias is paroxysmal auricular tachycardia with block.17, 18 When digitalis is administered in the presence of potassium depletion, there occurs an acceleration of pacemaker, changes in the P wave and varying degrees of A-V block. It has been demonstrated that digitalis in overdose induces loss of myocardial potassium.19, 20 These abnormal mechanisms may, therefore, be the result of accentuation by digitalis of existing potassium deficits within the myocardium.

In a recent study no correlation was found between the electrocardiogram and the serum potassium concentration or the cumulative potassium balance.21 These studies concerned for the most part moderate degrees of chronic potassium depletion produced experimentally in previously normal subjects. Such absence of correlation is not surprising. The electrocardiogram reflects directly only intracardiac events. It seems unlikely that all organs participate to the same degree when a deficit of potassium is chronically incurred. The varying metabolic activity of different tissues is known to effect the transfer of cations. The cellular compartment is not a homogeneous reservoir. "Factors governing the concentration of the bulk ions no doubt are differentiated to subserve specific tissue function and thus concentration will vary from tissue to tissue with changes in external and internal environment."21, 18 Thus, if the myocardium does not participate in the potassium loss, no changes will ensue in the electrocardiogram, irrespective of the extent of the depletion. It has been our experience that in many patients with severe heart disease, acute though minor shifts in body potassium resulted in full blown hypokalemie electrocardiogram. The critical difference appears to be the rate at which such deficits have occurred.

The present study suggests the participation of acute cellular potassium depletion in the effect upon the hypokalemic electrocardiogram. Sequential changes in the electrocardiogram continued during the extraction of body potassium at a time when the serum potassium concentration remained unaltered. This was especially evident in the changes of the S-T segment. Not only was there a delay in the depression of the S-T segment during dialysis, but its return to the base line was also delayed upon restoration of the serum potassium level to the predialysis concentration. Presumably there is a lag in the correction of cellular deficits, and this was reflected in the electrocardiogram.
Conclusions
1. The removal of potassium was accomplished by means of hemodialysis 22 times in 14 dogs. Other extracellular electrolytes were maintained at predialysis concentrations. Electrocardiograms were taken during the removal of potassium and following restoration of the serum level to its predialysis value.
2. Potassium extraction occurred in two phases: a phase of rapid reduction of the serum level to 2 mEq per liter, followed by a phase of continued extraction of body potassium with the extracellular concentration remaining fixed.
3. Striking changes were observed in the P wave, consisting of increases in amplitude and width. A-V conduction time became prolonged and the heart rate was accelerated. These alterations occurred in the first phase of dialysis during the period of rapidly developing hypokalemia.
4. Ventricular changes consisted of a widening in the QRS, a shift in its axis, broadening and rounding of the T wave and depression of the S-T segment. Changes in the S-T segment occurred in the second phase of dialysis during which time the serum potassium level remained stable.
5. This study suggests that acute depletion of potassium faithfully contributes to the electrocardiographic picture of hypokalemia.

Conclusiones in Interlingua
1. Per medio de hemodialyse le suppression de kalium esseva effectuate in 14 canes a 22 occasioes. Alte electrolytos extracellular esseva mantenite al concentrationes predialytics. Electrocardiogrammas esseva facite durante le suppression del kalium e post le restauration del nivello seral a su valores predialytics.
2. Le extraction de kalium occurriva in duo phases: un phase de rapide reduction del nivello seral a 2 mEq sequite per un phase de continuate extraction de kalium del corpore durante que le concentration extracellular remaneva constante.
3. Esseva observate frappante cambiamentos in le unda P. Istos consisteva de augmentos de amplitude e largor. Le tempore de conduction A-V esseva prolongate e le frequentia cardiac esseva accelerate. Iste cambiamentos occurriva intra le prime phase del dialyse durante le periodo del rapide disveloppamento de hypokalemia.
4. Cambiamentos ventricular consisteva in un allargamento de QRS, un transposition de su axe, un extension lateral e un rotendification de le unda T, e le depression del segmento S-T. Cambiamentos del segmento S-T occurriva in le curso del secunde phase dialytic, i.e. durante le tempore quando le nivello del kalium seral remaneva constante.
5. Iste studio suggere que un acute depletion de kalium contribue invariabilemente al configuracion electrocardiographic characteristica de hypokalemia.

References
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