Serum Potassium and the Electrocardiogram in Hypokalemia

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The purpose of this study is to correlate changes observed in the electrocardiogram with varying concentrations of serum potassium in commonly encountered clinical conditions.

There has been much discussion and some disagreement in the literature concerning electrocardiographic criteria for hypokalemia. Many studies have dealt with the combination of 2 decidedly different aspects of hypokalemic states, namely the acute and the chronic. The electrocardiographic change may be related to the myocardial intracellular potassium, the myocardial extracellular potassium, the serum potassium, the transmembranous gradient of potassium, the rate of transmembranous diffusion of potassium, or the transmembranous gradient of hydrogen ion. It is not the purpose of this paper to present the merits or details of these various theories. Many of these phenomena would necessarily be affected by other factors such as the concentration of other electrolytes and the environmental pH. Until more is known of the physiologic and biochemical mechanisms of body potassium and their relationship to total acid-base and electrolyte balance it may be difficult to use patients with acute transient hypokalemia who have a rapid alteration of their internal and external environment for the enunciation of electrocardiographic criteria for hypokalemia.

Although of interest in cases of suspected or proved electrolyte imbalance, the electrocardiogram is often valuable in those clinical conditions in which hypokalemia often is not clinically apparent. Such states would include primary aldosteronism, familial periodic paralysis, chronic diarrhea, gastroileal anastomoses, potassium-losing nephritis, and hypokalemia secondary to diuretic therapy. The electrocardiogram is useful also when facilities for potassium determinations are not readily accessible or estimation of serum potassium is needed immediately.

Materials and Methods

A study was made of 1,800 patients who had concentrations of serum potassium of less than 4.0 mEq per liter. Of these 1,800 patients, 850 had had an electrocardiogram recorded near the time that blood was withdrawn for determination of potassium. In an attempt to minimize the number of variables in the study, the following types of cases were discarded from the study: (1) those in which unsteady clinical states, such as diabetic acidosis, hemodialysis, and postoperative periods were indicated; (2) those in which the electrocardiogram showed evidence of myocardial ischemia, ventricular rates in excess of 100, ventricular conduction defects, or rhythm disturbances; and (3) those of patients treated with digitalis or quinidine. Thus 130 patients who had one or more values for serum potassium of less than 4.0 mEq were selected. Several patients had serial determinations and in 152 instances the serum potassium was determined with nearly simultaneous recording of the electrocardiogram.

Other serum electrolytes also were determined in the majority of instances. Various observations were made on the electrocardiogram including rate, P-R interval, Q-T interval, amplitude of QRS complexes, deviations of S-T segment, amplitudes of T and U waves, and the incidence of ventricular and atrial premature contractions. Other abnormalities, such as left ventricular hyper-
Effect of intravenous administration of potassium. The tracing made at 9 p.m. shows the classic hypokalemic pattern with S-T depression, partial fusion of T and U waves, with U being of abnormal amplitude (2 mm.) and taller than T (T/U less than 1). Administration of potassium resulted in elevation of S-T segment, elevation of T waves, and lowering of U waves with restoration of normal T/U relationship. U is still abnormally tall but a later tracing (hyperkalemia) shows normal U waves as well as peaked T waves and elevation of the S-T segment. Lead V₃ of the tracing made at 10:45 p.m. shows that the measured Q-T interval (onset of QRS complex to T-U notch) would be shorter than the true Q-T interval, since the T wave is not isoelectric at this point. If the T wave slope were extrapolated, the true Q-T interval might be 0.04 to 0.06 second longer.

trophy, were also noted. The ratio of serum sodium to potassium was calculated in all instances in which the value for serum sodium was available. The Q-T index was calculated by means of the

Bazett formula

\[
\text{Q-T index} = \frac{\text{Q-T observed}}{\sqrt{\text{R-R interval}}}.
\]

The normal Q-T index with this formula is 35 to 44. The ratios of the T-wave amplitude to the U-wave amplitude and of the T-wave to the R-wave amplitude were calculated in all cases in leads II and V₃. The presence or absence of hypertension was noted, and the patients were divided into 3 groups—hypertensive patients alone, normotensive patients alone, and all patients. Each of the 3 groups was then subdivided on the basis of serum potassium concentration into 4 smaller groups.

Additional Electrocardiographic Observations

The Q-T interval was measured in all but 5 instances (in which there was fusion of T-U complexes). In several instances it was necessary to measure the Q-T interval from the onset of the QRS complex to the notch between the T and U waves as suggested by Lepeschkin and Surawicz. This maneuver would of course tend to make the measured Q-T interval shorter than the true Q-T interval (fig. 1). Q-T values corrected for rate and sex were obtained from Lepeschkin’s data. As a means of comparison, other normal values from Koch and Bazett’s formula also were used.

Measurement of amplitudes of T and U waves was frequently difficult due to lack of isoelectric (base-line) periods in the electrocardiogram. When this occurred the Ptₐ segment was used as a reference point.

Two sets of T/R values were calculated: one from the precordial lead where the highest T wave was commonly found (usually lead V₃) and the other from the left ventricular complexes which gave the largest T/R values as suggested by Reynolds and associates.

Results

Approximately half of the patients in the study were clinically hypertensive even though the initial selection was on the basis of a low concentration of serum potassium. After careful review of the records, it was noted that in all instances the abnormalities consistent with hypokalemia could be observed in standard lead II and precordial lead V₃.

Q-T Abnormalities

There is good evidence that the Q-T index is at the upper limits of normal (table 1). As
has been noted, the Q-T index contains a rate-correction factor. If observed Q-T intervals are to be compared to other normals it is readily seen that they must be evaluated individually or expressed as normal, greater than normal, or less than normal, as seen in table 2.

T-Wave Changes

The voltage of the T waves in leads II and V3 varied as shown in table 1. Inverted T waves were present in lead II in 13 per cent and in lead V3 in 11 per cent of our patients having hypokalemia (potassium less than 3.6 mEq.) (table 3). There was a paucity of chronically hypokalemic patients who had serial electrocardiograms with simultaneous determinations for serum potassium. However, in 2 cases an upright T wave became inverted as the concentration of potassium decreased, and in 3 cases an inverted T wave became upright as the concentration of potassium decreased (figs. 2, 3, and 4). The latter phenomenon also may occur as a result of fusion of the U wave with the inverted T wave (fig. 4).

U-Wave Changes

U waves were noted in 90 per cent of the electrocardiograms in this study. U-wave voltage in leads II and V3 increased as the concentration of serum potassium decreased (table 1; fig. 1).

T-U fusion of all degrees occurred with hypokalemia (figs. 1, 3 and 6). Some authors have devised methods for differentiating notched T waves from T-U fusion by means of comparisons between "QaT and QaU intervals." These measurements were performed in all cases in which they were applicable, but we found that this is not an infallible method of differentiating a T wave from a U wave. Both the intravenous administration of calcium and the simultaneous recording of heart sounds are especially helpful technics in delineating U waves but they are not available in retrospective studies such as this.

Relationship of T and U Waves

More important than the actual amplitude of the U wave is the relationship between the amplitudes of T and U waves. When the T/U
Table 2
Comparison of Methods Used to Determine Q-T Abnormality: Concentration of Serum Potassium, < 3.0 mEq. (38 Patients)

<table>
<thead>
<tr>
<th>Values* used for comparison</th>
<th>Per cent of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q-T &lt;normal</td>
</tr>
<tr>
<td>Bazett's†</td>
<td>3</td>
</tr>
<tr>
<td>Koch's‡</td>
<td>3</td>
</tr>
<tr>
<td>Lepeschkin's§</td>
<td>16</td>
</tr>
</tbody>
</table>

*The "normal" Q-T values stated by these authors were used for comparison.
†Bazett's formula, quoted in Winsor.§

Table 3
Incidence of Inverted T Waves in Hypokalemic Patients: Concentration of Serum Potassium, < 3.6 mEq.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Lead II</th>
<th>Lead V3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive (56)</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Hypertensive (51)</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>All</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 4
Incidence of Extrasystoles

<table>
<thead>
<tr>
<th>Premature contractions</th>
<th>Hypokalemic patients (value for potassium, &lt;3.6 mEq; no drugs)</th>
<th>Control (ambulant) of 1,001 cases</th>
<th>Normotensive, per cent of 51 cases</th>
<th>Hypertensive, per cent of 51 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular only</td>
<td></td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Atrial only</td>
<td></td>
<td>4</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Ventricular and atrial</td>
<td></td>
<td>1</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>13</td>
<td>24</td>
<td>30</td>
</tr>
</tbody>
</table>

value is 0.5 or less, hypokalemia usually has developed (fig. 7). When T waves are negative, the T/U value becomes negative, but even when these values are plotted they help to reinforce the contour of the initial portion of the curve; that is, a negative T/U value usually indicates an exceedingly low concentration of potassium in the serum.

S-T Segment

Depression of the S-T segment in lead II is a frequent finding in patients with a value for serum potassium of less than 2.6 mEq. (table 1). Isoelectric or depressed S-T segments in lead V1 to lead V3 were noted in several hypokalemic patients who had electrocardiographic evidence of left ventricular hypertrophy or left ventricular strain.

P-R Interval

P-R intervals remained in normal ranges for all groups (table 1). The P-R interval was consistently higher with hypokalemia, but this finding was not statistically significant. In isolated cases in which serial electrocardiograms were made the P-R interval was noted to increase slightly with decreased concentration of serum potassium.

P Waves

The P waves were not measured, but in several cases in which serial electrocardiograms were made the P-wave voltage was noted to increase slightly as the potassium decreased (fig. 3).

T-R Relationship

Our use of the method of Reynolds and associates showed only a minimal degree of correlation in the normotensive patients between the serum potassium and the T/R values. There was no correlation in the group of hypertensive patients.

Premature Contractions

A significant increase developed in atrial premature contractions as shown in table 4.

Ratio of Sodium to Potassium

The ratio of serum sodium to potassium showed an almost straight-line relationship to the concentration of serum potassium (fig. 8).

Index Hypertension

The influence of hypertension on the QTc in hypokalemia is shown in table 1. It has long been known that the Q-T interval is increased in the presence of hypertension. The T waves differed in the hypertensive group as would be expected, that is, they were lower in lead II and higher in lead V3 (table 1). Hypertension apparently did not affect amplitude of U waves, deviations of S-T segment, or P-R intervals (table 1).
Figure 3
The amplitude of the P wave was increased in lead II of patient with hypokalemia. There was progressive change of inverted T wave to upright T wave in lead II with increasing concentration of potassium. The U wave lowered progressively and the S-T segment returned toward normal. In leads V3 and V5 the T-wave inversion decreased progressively with a final upright T wave as potassium repletion occurred. The apparent increase of U-wave amplitude is due to gradual shift upward of the terminal portion of the T wave which is the U-wave take-off point. The actual amplitude of the U wave decreases with the increasing concentration of potassium. A third diastolic potential is present in lead V3 in tracing dated 8-14-57. This may be a notched T wave, notched U wave, or positive after-potential.

Acid-Base Abnormalities
There were 5 severely hypokalemic patients (potassium 2.9 mEq. or less) whose electrocardiograms were not typical of hypokalemia insofar as our established criteria for hypokalemia. In these patients the acid-base balance was disturbed, manifested either by low carbon dioxide combining power or low serum concentration of sodium (fig. 9). Another patient had an electrocardiogram that was typical of hypokalemia yet the value for serum potassium was 3.2 mEq. However, the value for carbon dioxide was 42.5 mEq. in this patient (fig. 5).

Discussion
Sidney Ringer11,12 in 1883 first emphasized the importance of potassium and other ions in maintenance of normal cardiac function. There are numerous reports13-20 of myocardial degeneration and of fibrosis as a result of potassium depletion. Whether the disturbed cellular function is dependent on relative (myocardial only) or absolute (total body) depletion of potassium is not clear. Other factors undoubtedly are involved. Similarly the electric manifestations of cellular function are disturbed with variations in the concentration of potassium.

Some investigators24, 25 have stated that the electrocardiogram cannot be relied on as a guide to potassium depletion. Others7, 26-28 have stated certain levels below which the electrocardiogram is a reliable guide. As has been implied, many factors determine the reliability of the electrocardiogram as an indicator of hypokalemia. Using dogs that were rendered acutely hypokalemic by dialysis, Nihopoulos and Hoffman29 found depression of the S-T segment and depression or inversion of the T waves to be the most consistent findings in the electrocardiogram. They did not note changes in the P-R interval and P waves, and U waves did not appear. Interestingly, they found an increase of 12 per cent
in myocardial potassium in hypokalemic dogs over that of dogs in the control group.

Weller and associates30 used dialysis to remove potassium from dogs and noted the first effect to be an increase in the height and width of the P wave. They noted increased A-V conduction time and eventually the P waves migrated and fused with the T and U waves. They also noted depression of the S-T segment which persisted for several hours after the serum potassium returned to normal levels. Bellet and co-workers31 described different electrocardiographic changes for various etiologic types of hypokalemia. The foregoing remarks serve to introduce the complexities involved in evaluation of the electrocardiographic signs of hypokalemia.

Q-T Interval

The relationship of Q-T interval to concentration of serum potassium has been studied frequently by many investigators. Originally the Q-T interval was thought to be prolonged by hypokalemia.7, 32-34 Ernstene and Proud-fit35 were the first to suggest that fusion of U waves with T waves causes an apparent lengthening of the Q-T interval. Some authors3, 26, 36 have suggested that the Q-T interval is actually normal or short. Another source of difficulty arises from not knowing the normal Q-T value and the effect of heart rate, blood pressure, sex, and other variables on it. The measurement of the Q-T interval is subject to some error. There may be isoelectric periods at both ends (QRS and T) of the interval in various leads.

Furbertha and co-workers37 pointed out the relatively large errors encountered even when simultaneous recording of heart tones is performed. Klakeg and associates38 emphasized that the Q-T interval may not be of the same duration as mechanical systole, particularly at slower rates. As previously stated, occasionally the measured Q-T interval (when minimal T-U fusion is present) will tend to be shorter than the true Q-T interval so that normal or prolonged Q-T intervals in our
study are even more meaningful. The use of available normal limits, however, makes it justifiable to conclude that the Q-T interval may be slightly prolonged in hypokalemia; the Q-T interval is either at or above the upper limits of normal in most cases (table 1).

**T Waves**

Inversion of the T waves has long been considered an electrocardiographic sign of hypokalemia. In the literature, the difference between the phrases ‘‘inverted T waves’’ and ‘‘inversion of the T waves’’ must be noted carefully. Inversion of T waves is by definition a phenomenon that requires more than one electrocardiogram for its recognition. We have mentioned that inverted T waves were present in some cases in this study (table 3) (figs. 2 to 6). It is obvious that the presence of an inverted T wave in a single electrocardiogram is not nearly so important as an inverted T wave that was upright in previous electrocardiograms. Although hyperkalemia has been shown to increase the amplitude of an inverted T wave, data are insufficient to give statistical support to the opposite phenomenon with hypokalemia, that is, a decrease in amplitude of an inverted T wave. The effect of potassium also may vary depending on the initial cause of the T-wave inversion. When dealing with the problems of T-wave inversion one must be certain to observe the T wave and not the T-U complex (fig. 3).

Another interesting T-wave phenomenon that we observed was a decrease in the slope of the descending limb of the T wave with hypokalemia. This is partly a function of loss of T-wave amplitude, but in figure 1 the so-called normal T wave has an opposite shape; the descending limb is steeper than the ascending limb. This decrease in slope occurred in cases with separate distinct U waves. It is probably what some authors refer to as a positive after-potential, which is usually seen as broad T-wave notching or slurring of the descending portion of the T-wave. Although the positive after-potential occurs commonly during hypokalemia according to Sjöstrand, changes in the U waves seem to be found more consistently in this study. Indeed we are of the opinion that in some cases of severe hypokalemia the bizarre undulations observed during repolarization are combinations of T waves,

\[ T/U \text{ ratio in } V_3 \]

Figure 7

*Relationship between T/U values in precordial lead V3 and the serum potassium concentration.*

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positive after-potentials, and U waves (figs. 3 and 6).

**U Waves**

The 4 main theories concerning the etiology of U waves are as follows: (1) caused by after-potentials which follow the action-potential proper, (2) caused by potentials elicited by the stretching of ventricular muscle during the stage of rapid filling, (3) caused by longer duration of action-potentials in some sections of the ventricles, and (4) caused by repolarization of the papillary muscles and interconnected structures.

Furbetta and associates\(^4\) are proponents of the last-mentioned theory and refer to abnormalities of the U wave and T-U segment as the "papillary muscle syndrome." Lepeschkin\(^4\) has favored the first theory and it seems the best available theory with good supportive experimental evidence. Certainly the factors mentioned in the other theories play some role in U-wave genesis.

Cannon and Sjöstrand\(^4\) suggested the presence of 2 separate diastolic potentials in the electrocardiogram — the positive after-potential and the U wave. Their positive after-potential is an electrocardiographic phenomenon and is not synonymous with the after-potentials of a monophasic action-potential. They described the positive after-potential as a slowly subsiding positive potential following the mechanical systole and appearing at the conclusion of the refractory period and T wave. They stated that hypokalemia causes appearance of the positive after-potential.

Sjöstrand\(^3\) later stated that whereas the positive after-potential varies inversely with the concentration of serum potassium, "the U wave varied apparently irrespective of the potassium concentration in the serum."

In a study of 100 electrocardiograms of normal patients Furbetta and associates\(^4\) found U waves in 99 per cent of electrocardiograms in lead V\(_3\) and 92 per cent in lead II. Electrocardiograms in 23 per cent of their cases showed U-wave amplitudes greater than 1 mm. and in 2 the U-wave amplitudes were greater than 2 mm. Lepeschkin\(^4\) stated that the U wave is seen in nearly 100 per cent of cases but noted amplitudes greater than 1 mm. in only 2 per cent of cases.

In addition to hypokalemia and related disturbances, U waves can be unusually high due to bradycardia, epinephrine, thyrotoxicosis, exercise, increased QRS amplitude, left ventricular hypertrophy, hypertension, and the therapeutic combination of digitalis and
quinedine. Changes in potassium may change the amplitude and polarity of T waves but only the amplitude of U waves.

Thompson in 1939 and Tarall in 1948 published the first articles dealing specifically with the relationship of the electrocardiogram to serum potassium concentration. Although not specifically mentioned, U waves were present in the published electrocardiograms. Also in 1948 Nadler and co-workers implied a relationship between U waves and the concentration of serum potassium. They noted the appearance of U waves when the potassium was low during treatment of diabetic acidosis and their disappearance when potassium was administered to the patient. There have been numerous isolated reports of electrocardiograms taken when a low concentration of serum potassium was known or suspected.

Stewart and associates referred to a case of familial periodic paralysis reported by Janota and Weber and noted, in a case of their own, prolongation of the P-R interval, the QRS interval, and the Q-T interval and a decrease in amplitude of T waves. U waves were present in their published records but were not recognized as such.

In 1944, Brown and associates reported cases of 3 patients who had muscular paralysis and electrocardiographic abnormalities with low concentrations of potassium. They noted the appearance of U waves but did not see any relationship to the low values for serum potassium. They said, “The prominence of the U waves is of interest but the explanation of this remains obscure.”

These and other reports point out changes in T waves and other changes with known low concentrations of serum potassium or conditions commonly associated with hypokalemia, and most of them show records with prominent U waves. Yet the relationship of the U wave to the concentration of serum potassium was not suggested until 1948. Since 1948 many investigators have noted and studied this relationship.

Bellet and co-workers in 1950 found U waves in 42 per cent of the electrocardiograms of patients with hypokalemia. Reynolds and associates in 1951 noted that 55 per cent of all patients with concentrations of serum potassium of less than 4.0 mEq. had U waves. Of their patients with a value for serum potassium of less than 3.0 mEq., 35 per cent had “large” U waves. Surawicz and Lepeschkin in 1953 noted an increase in amplitude of the precordial U waves with hypokalemia and also commented on T-U fusion and waves of differentiating the Q-T interval from the Q-U interval. Schwartz and co-workers first suggested the importance of the relationship of U-wave amplitude to T-wave amplitude. However, they concluded that “in potassium depletion of moderate severity the electrocardiogram cannot be relied upon as a guide to diagnosis or treatment.” Lepeschkin in 1955 suggested possible electrophysiologic explanations for the formation of the U wave in its relationship to the concentration of serum potassium. Bellet in 1955 commented on the increased amplitude of U waves with hypokalemia.
Table 5

Electrocardiographic Criteria for Hypokalemia

<table>
<thead>
<tr>
<th>Electrocardiographic signs</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/U 1 or less in lead II</td>
<td>1</td>
</tr>
<tr>
<td>T/U 1 or less in lead V3</td>
<td>1</td>
</tr>
<tr>
<td>U1 0.6-1.4 mm.</td>
<td>1</td>
</tr>
<tr>
<td>U1 1.5 or greater</td>
<td>2</td>
</tr>
<tr>
<td>U2 1.1-1.9 mm.</td>
<td>1</td>
</tr>
<tr>
<td>U3 2.0 or greater</td>
<td>2</td>
</tr>
<tr>
<td>S-T Depression of 0.5 mm.</td>
<td></td>
</tr>
<tr>
<td>in lead II or leads V1 to V3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Electrocardiographic score:
0-1, nondiagnostic
2, suggestive
3-7, characteristic

Hypokalemia and noted T-U and U-P fusion patterns. Surawicz and co-workers in 1957 related actual measured amplitudes of the U waves to varying levels of serum potassium. They also utilized the U/T amplitude relationship and correlated several electrocardiographic "signs" with serum potassium levels.

**Relationship of T and R Waves**

The relationship of T and R waves has not been studied extensively but Reynolds and associates found that the T-wave amplitude was consistently less than 15 per cent of the R-wave amplitude when the concentration of serum potassium was less than 3.0 mEq. We were not able to find a good correlation between the serum potassium concentration and the amplitudes of T and R waves in lead II, lead V3, or the precordial leads showing a left ventricular type of complex as suggested by Reynolds.

**Atrial Abnormalities**

The abnormalities occasionally associated with hypokalemia are increased amplitude of the P waves and increased P-R interval. The problem of atrial premature contractions will be discussed subsequently. There is a slight but statistically insignificant increase in P-R intervals in our study. Most of the few available serial electrocardiograms show an increased P-wave amplitude with hypokalemia (figs. 3 and 4). It should also be remembered that U-P fusion as well as T-U fusion can occur and the U-P fusion has occasionally been misinterpreted as P-wave increase and distortion with hypokalemia.

The appearance of atrial premature contractions with hypokalemia (figs. 4 and 6) has been commented on before in isolated cases. However, to our knowledge no incidence for a series of cases has been reported. The mechanism of production of ventricular premature beats and their relationship to U waves has been extensively discussed recently. The effect of potassium on conduction and ectopic rhythms also has been discussed recently. The U wave of the electrocardiogram corresponds to a supernormal phase of excitability and one notes that U-wave amplitude increases as the level of excitability increases, the effect of quinidine being an exception. It is difficult to ascertain which phenomenon comes first, that is, tall U waves or increased excitability.

**Deviations of S-T Segment**

Depression of the S-T segment has long been associated with hypokalemia. Depression of S-T segment is of particular value when it is present in leads V1 to V3 in a patient who shows evidence of left ventricular hypertrophy or strain. One would normally expect some elevation of S-T segment in these leads and the presence of an isoelectric or depressed S-T segment in leads V1 to V3 should cause one to suspect the presence of hypokalemia.

**Ratio of Serum Sodium to Potassium**

There has not been good agreement concerning the relationship of the electrocardiogram to the ratio of serum sodium to potassium. Rosen has suggested that the relationship of serum sodium to potassium is more important than the actual absolute concentration of potassium in the serum. Others, however, have found little or no correlation between the sodium-potassium ratio and electrocardiographic changes. Still others have suggested an indirect relationship between sodium, potassium, and electrocardiographic changes; for example, in those clinical states in which the serum pH is abnormal.
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There is often associated abnormality of either one or both of these ions.

If one uses the normal range of 25 to 40 for the sodium-potassium ratio, electrocardiographic changes would be expected if the ratio were greater than 40 (relative hypokalemia). As shown in figure 8 this would mean that the electrocardiographic changes of hypokalemia should be noted at values less than approximately 3.3 mEq. Certainly changes may be seen at this level and even above it but by no means with any degree of regularity. Thus, we feel that the sodium-potassium ratio is simply another factor in the production of electrocardiographic changes but certainly not the main one.

**Acid-Base Balance**

The discussion of this paper would not be complete without a consideration of the metabolic states of alkalosis and acidosis. It may be that the serum pH, with or without coexisting alterations of serum cations and anions, may be the main factor in the production of the electrocardiographic changes currently attributed to hypokalemia and hyperkalemia. As early as 1932 it was shown that an "excess of CO₂ increases the size of the T wave in all leads. . ." 66

In 1939 Barker and associates 67 reported that alkalosis (by hyperventilation or ingestion of sodium bicarbonate) is accompanied by a decreased amplitude of the T wave. Similarly acidosis was found to increase the T-wave amplitude. In a study of patients with diabetic acidosis, Nadler and associates 53 noted that T-wave amplitudes decreased as the serum pH increased and similarly as the carbon dioxide pressure (pCO₂) increased. In 1953 Magida and Roberts found that they could produce hypokalemic electrocardiographic changes.
changes in dogs by increasing the serum pH, bicarbonate, and sodium even though the serum potassium remained normal. No electrocardiograms of hypokalemia were shown and their only comment on the pattern was "sequential lowering and inversion of the T wave . . . ." They expressed the opinion that the transmembranous gradient of hydrogen ion is the important factor in the bioelectric phenomena of the heart. Bellet in 1955 pointed out that hypopotassemia is often associated with alkalosis. Alkalosis is associated with increased serum pH, increased serum sodium, decreased phosphate and increased carbon dioxide combining power; it also tends to affect the serum calcium by means of alteration of the solubility product, so that the result is a normal or low concentration of serum calcium which could also affect the electrocardiogram.

Scribner and associates have emphasized the importance of the ratio of extracellular potassium to intracellular potassium. They suggest that alkalosis causes a shift of potassium into the cell and consequently a decrease in the ratio of extracellular to intracellular potassium. Acidosis causes an opposite effect. It is in this way then, that acid-base imbalance profoundly affects the concentration of serum potassium. This may be one factor involved in the poor correlation between total body potassium and serum potassium. Thus hypokalemia in a patient with acidosis might indicate severer depletion of potassium than a similar degree of hypokalemia in a patient with alkalosis.

In 1953 it was pointed out that often in severe and chronic hypokalemic states, the
Electrocardiogram may not return to normal for more than a week, even though the repletion of potassium seems to have been well managed. At that time it was suggested that perhaps this was due to some organic change in the myocardial cells — perhaps similar to organic changes produced by experimental potassium deficiency.

In a report of a case of primary aldosteronism van Buchem noted that after removal of hyperplastic adrenal glands the serum potassium returned to normal in several days. However, the electrocardiogram showed typical hypokalemic changes for 5 weeks. It was then mentioned (without implying a relationship to the electrocardiogram) that acid-base balance and carbohydrate metabolism did not return to normal for "several weeks." In our own series the marked electrocardiographic effects of acid-base equilibrium are clearly shown in a few cases in which carbon dioxide determinations were available (figs. 5 and 9).

In the past it has not been clear why different patients with the same concentration level of serum potassium show different electrocardiographic changes. Bellet has suggested that because the normal concentration of serum potassium of patients varies from 3.6 to 5.6 mEq., a patient with a normal value for potassium of 5.5 mEq. would, in a relative sense, be more deficient at a level of 3.4 mEq. than would a patient with a normal value for serum potassium of 3.7 mEq. Such an explanation does not obtain, however, when one considers electrocardiograms and serial serum potassium changes solely in the hypokalemic ranges.

It has also been suggested that the rate of change of serum potassium is important, but, as was indicated in our method of procedure, this factor was minimized in our study. Ringer in 1883 showed similar effects of rubidium and potassium on the heart. Tarrail recently suggested the importance of this and other trace elements as possible additional factors in electrocardiographic changes seen with hypokalemia. Young and Daugherty, using hemodialysis to accomplish acute potassium depletion, showed that S-T depression

**Figure 12** Cumulative grouping of normotensive patients in relation to serum potassium concentration in milliequivalents. The electrocardiograms of the various groups were then evaluated with the criteria in table 5.

seemed more closely related to the quantity of potassium removed rather than to the concentration of potassium in the plasma. Exactly what the electrocardiogram reflects then is unclear. Certainly, the potassium metabolism and acid-base balance play major roles.

**Electrocardiographic Criteria for Hypokalemia**

With the understanding that the relationship between the electrocardiogram and the afore-mentioned factors is not clearly defined, the electrocardiographic criteria of hypokalemia shown in table 5 are proposed.

These criteria were obtained from data in this study. They pertain only to normotensive patients, since the presence of hypertension has been shown to obscure many of the electrocardiographic signs (fig. 10). It is to be emphasized that these criteria are to be used in a positive sense; that is, when the electrocardiogram scores 3 or more points the diagnosis of hypokalemia is almost certain. However, if the electrocardiogram scores less than 3 points, or even no points, this does not rule out the possibility of hypokalemia (figs. 10 and 11).

As shown in figure 12, the electrocardiographic diagnosis of hypokalemia in normotensive patients is fairly secure at the lower concentrations of serum potassium. In the literature much emphasis has been placed on
certain levels below which the electrocardiogram will be diagnostic of hypokalemia. It has been one of the purposes of this paper to show the multiple factors that affect the electrocardiogram in hypokalemic and normokalemic states.

Summary

A definite correlation can be established between the electrocardiogram and the serum potassium level at hypokalemic levels. A study was made at the Mayo Clinic of 130 hypokalemic patients with relatively stable clinical states. Variations in Q-T intervals, P-R intervals, atrial rhythm, P waves, T/R values, and T-wave and U-wave contour in hypokalemia were noted as were the relationships between the T-U complex, electrolyte repolarization phenomena and potassium metabolism. Since modifying factors such as drugs, certain disturbance of disturbances, variations in cardiac rate, conduction defects, and myocardial ischemia were eliminated by careful selection of patients, only the influence of acid-base imbalance, sodium-potassium ratio, and hypertension on the electrocardiogram was studied. Acid-base imbalance and hypertension often simulated or obscured electrocardiographic evidence of hypokalemia.

Electrocardiographic criteria of hypokalemic include various combinations of the following signs: (1) T/U value of 1 or less in lead II or V3, (2) U-wave amplitudes of greater than 0.5 mm. in lead II or greater than 1 mm. in V3, and (3) S-T depression of 0.5 mm. or more in lead II or leads V1, V2, and V3. It must be remembered that a normal electrocardiogram does not exclude hypokalemia and that an electrocardiogram which fulfills the established criteria does not necessarily indicate hypokalemia unless the factors discussed have been eliminated or minimized.

Summario in Interlingua

Un definite correlation pote esser establite inter le electrocardiogramma e le nivello serial de kalium quando le cifras pro isto representa valores hypokalemics. Esseva effectuate al Clinica Mayo un studio de 130 patientes hypokalemic in relativamente stabile status clinico. Variationes in le intervallas Q-T, in le intervallas P-R, in le rhythmio atrial, in le undas P, in le valores T/R, e in le contornos del undas T e U esseva note, si ben como etiam le relations inter le complexo T-U, le phenomenos de repolarisation electric, e le metabolismo de kalium. Le meticulose selection del patientes garantia le exclusion de factores modifieri como drogas, certe disturbaciones electrolytic, variations del frequenta cardiae, defectos de conduction, e ischemia myocardial, de maniera que solmente le influentia del imbalance de acido e base, del proportion de natrium a kalium, e de hypertension esseva includite in le studio del electrocardiogramma. Imbalance de acido a base e hypertension frequentemente simulava o obscureva le evidentia electrocardiographie de hypokalemia.

Le criterios electrocardiographie de hypokalemia include varie combinationes del sequente signos: (1) Valores pro T/U de 1 o minus in derivacion II o derivacion V3, (2) amplitudes del unda U de plus que 0.5 mm in derivacion II o de plus que 1 mm in derivacion V3 e (3) depression de S-T de 0.5 mm o plus in derivacion II o in le derivaciones V1, V2, o V3. On debe rememorar se que un electrocardiogramma normal non exclude hypokaliemnia e que un electrocardiogramma que satisfacce le establite criterios non indica necessarimente le presentia de hypokalemia, excepte si le supra-discutite factores ha essite eliminare, o si lor signification ha essite reducita a un minimo.

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Circulation, Volume XXI, April 1960


On Cardiac Murmurs
By Austin Flint, M.D.

The significance of organic murmurs is limited to the points of information already stated in the introductory remarks, viz., the existence of lesions, their localization, and the fact of valvular insufficiency or regurgitation. Whether the lesions involve immediate danger to life, or, on the contrary, are compatible with many years of comfortable health, the murmurs do not inform us, nor do they teach us how far existing symptoms are referable to the lesions, and how far to functional disorder induced by other morbid conditions. Neither the intensity nor the quality of sound in the murmurs furnish any criteria by which the gravity of the lesions or their innocuousness can be determined. A loud murmur is even more likely to be produced in connection with comparatively unimportant lesions than with those of a grave character, because in the former, rather than in the latter case, is the action of the heart likely to be strong, and the intensity of the murmur, other things being equal, will depend on the force with which the currents of blood are moved. Whether the murmur be soft, or rough, or musical, depends not on the amount of damage which the lesions have occasioned, but on physical circumstances alike consistent with trivial and grave affections.—Am. J. M. Sc. n.s. 44: 29, 1862.
Serum Potassium and the Electrocardiogram in Hypokalemia
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Circulation. 1960;21:505-521
doi: 10.1161/01.CIR.21.4.505
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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