Statistical Investigation of Correlations Between Serum Potassium Levels and Electrocardiographic Findings in Patients on Intermittent Hemodialysis Therapy

By Peter P. Frohnert, M.D., Emilio R. Giuliani, M.D., Mordecai Friedberg, M.S., William J. Johnson, M.D., and W. Newlon Taufe, M.D.

SUMMARY
Simultaneous determinations of serum potassium and sodium, blood pH, blood pressure, and 12-lead electrocardiograms were obtained in hyperkalemic patients with chronic renal failure. Statistical investigation of the data showed a high correlation between serum potassium levels and ventricular repolarization abnormalities. “Mean intracellular potassium concentration” derived from total body potassium and total body water values was not accurate enough to show significant correlations to ECG changes and did not improve on the already significant correlations with serum potassium levels. Equations are presented which would permit the estimation of serum potassium levels (in a narrow range) from electrocardiographic findings in patients with chronic renal failure and suspected hyperkalemia.

Additional Indexing Words:
Electrolytes
Hyperkalemia
Dialysis requirements
Heart

The number of patients with chronic renal failure who are maintained by intermittent hemodialysis therapy is increasing. Frequency and duration of this treatment are usually determined on clinical grounds and on the basis of serum creatinine and potassium levels. The physician responsible for this type of patient is forced to compromise between the need for frequent blood tests to ensure the safety of the procedure and the considerable expense and inconvenience these tests cause the patient.

In animal experiments, potassium infusion or dialysis against potassium-free dialysate has caused the gradual development of certain electrocardiographic patterns with progressive deviation of the potassium level from normal. However, there have been no similar studies on man and no attempts have been made to evaluate these alleged correlations by statistical means in a prospective study.

Recent investigations of potassium metabolism in patients with chronic renal disease offered the opportunity to obtain a large number of electrocardiographic tracings on patients with normal and with increased serum potassium levels. The results of analysis of these tracings are the subject of this paper.
Methods

Patients

Electrocardiograms were obtained from patients with oliguric renal failure who were being maintained by intermittent hemodialysis and who were undergoing one of two different types of study. The first of these groups (group A) comprised patients under the rigidly controlled conditions of a metabolic unit; the second (group B) comprised outpatients who were on relatively unrestricted diets and who returned to the dialysis center twice weekly for hemodialysis. No patient of either group was receiving treatment with cardiac glycosides or antihypertensive or antidysrhythmic drugs during the course of this study. All had been hypertensive during the course of their disease.

Metabolic Balance Study (Group A)

Three patients underwent four metabolic balance studies consisting of at least three 4-day periods each during which balances of potassium, sodium, and nitrogen were determined. Twelve-lead ECG tracings and blood pressure measurements were obtained daily in conjunction with simultaneous determinations of the serum potassium and sodium levels.

Long-Term Follow-up Study (Group B)

The following procedures were carried out before and after hemodialysis on 13 patients: estimations of serum sodium, potassium, calcium, magnesium, phosphate, and arterial blood pH (Astrup and associates3); measurement of blood pressure; and estimation of total body water by the deuterium oxide method4 and of total body potassium by means of 40K counting in a whole-body counter.5 Twelve-lead ECG tracings were recorded simultaneously. This study was repeated, when feasible, every 6 to 8 weeks during a 15-month period.

Electrocardiographic Data

Only those ECG data which were obtained within 30 minutes of the blood sampling for biochemical determinations were considered for further evaluation. Because serum potassium levels changed rapidly during the period immediately after dialysis, data from this period were not used.

ECG tracings were written at a paper speed of 50 mm/sec by either a six-channel direct-writer electrocardiograph* or by a portable single channel machine (Sanborn 100 Viso). All tracings were equilibrated to show a 1-mv amplitude as a 10-mm deviation. The original tracings were processed by a standard technic for mounting, microfilming, and filing.8 Because the resulting disposable copy was only two thirds the size of the original, suitable R-R complexes from extremity leads II and chest leads V2 and V3 were enlarged by a scale of approximately 1:1.3 with a

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*Medtronic Inc., Minneapolis, Minnesota.
Polaroid MP-3 Land Camera with fixed focus. The following parameters were measured on the ECG (fig. 1) and recorded on punch cards:

1. R-R interval.
2. Lead II: P-wave amplitude and duration; PQ segment and QRS durations; amplitudes of R, T, and U waves; Q-U time (time between onset of Q wave and onset of U wave); Q-T time (time between onset of Q wave and onset of T wave); T maximum time (time between onset of T wave and time of maximal T-wave amplitude); T % time (time between onset of T wave and time of % of maximal T-wave amplitude); and S-T depression.
3. Lead V_2: P-R interval; QRS duration; amplitudes of S, T, and U waves; Q-U and Q-T times; T-wave duration; T maximum and T % times; and S-T elevation.
4. Lead V_3: Q-U and Q-T times; amplitudes of T and U waves; T-wave duration; and T maximum and T % times.

Exact and uniform definition of the onset of the T wave was essential for our measurements of Q-T time, T-wave duration, T maximum time, and

CL(T) = \bar{y} + b(x_i - \bar{x}) \pm t_{\alpha/2} \cdot S_{y|x} \sqrt{\frac{1}{n} + \frac{(x_i - \bar{x})^2}{\sum (x_i - \bar{x})^2}}

T % time. The T % time was introduced as a concept to determine the degree of tenting of the T wave as seen in hyperkalemic states. This variable represents that period from the onset of the T wave, point x on figure 1, to point y on figure 1, which is the projection of point v on fig. 1 on the ascending limb of the T wave having three fourths the height of the maximal T-wave amplitude. The more closely point y approaches point x (representing the time of maximal T-wave amplitude), the more tenting is present. Elevations of the S-T segment frequently masked the onset of the T wave (that is, the wave did not originate from the isoelectric line). Therefore, the following procedure was used in all instances: Tangential lines were drawn along the straight portion of each limb of the T wave resulting in a triangle with the isoelectric axis as its base. The isoelectric line itself was defined by the connection of two neighboring P-R segments. The intersection of the base and the tangential line along the ascending limb of the T wave was designated as the onset of the T wave (point x on fig. 1).

Chemical Analysis

Serum sodium and potassium were determined by standard flame photometric technics; the hydrogen-ion concentration was measured by the Astrup technic.* A semiautomated technic was used for determinations of serum calcium and magnesium levels,† and a fully automatic analysis was used for serum inorganic phosphorus as described by Frings and co-workers." for the AutoAnalyzer.‡ These and the data from determinations of total body potassium (TBK) and water (TBW) were also transferred to punch cards. Proper identification permitted association of corresponding ECG tracings and chemical data for computation of correlation coefficients.

Statistical Evaluation

Correlations were calculated by a digital computer according to standard statistical equations.°

1. Estimated regression equation:

\[ \hat{y}_i = a + bx_i + e_i \]

2. Analysis of variance to test \( H_0: \beta = 0 \)

\[ F_{(n-2, P)} = \frac{\left[ \sum (y_i - \bar{y}) (x_i - \bar{x}) \right]^2}{\sum (y_i - \bar{y})^2} \frac{n - 2}{\sum (x_i - \bar{x})^2} \]

3. Confidence limits around the regression line:

\[ CL(\hat{y}) = \bar{y} + b(x_i - \bar{x}) \pm t_{\alpha/2} \cdot S_{y|x} \sqrt{\frac{1}{n} + \frac{(x_i - \bar{x})^2}{\sum (x_i - \bar{x})^2}} \]

in which \( i \) = the ith observation; \( b \) = the sample estimate of the regression coefficient \( (\beta) \); \( \hat{y} \) = the sample estimate of the ith point of the regression line; \( \bar{y} \) and \( \bar{x} \) = the sampled population means for the dependent and independent means, respectively, and

\[ S_{y|x} = \frac{\sum (y_i - \bar{y}_i)^2}{n - 2} \]

The F test was utilized to test the null hypothesis of no regression \( (\beta = 0) \). \( P \) = the probability of rejecting the null hypothesis based on sample information when it is true for the population being sampled.

All ECG data were correlated to the following parameters: serum potassium concentration \( (K_0) \), serum sodium concentration \( (Na_0) \), \( Na_0 + K_0 \), systolic blood pressure, diastolic blood pressure, and hydrogen-ion concentration \( (H^+) \).

Initially, these correlations were calculated for each of the patients of group A separately. Highly significant combinations \( (P < 0.01) \) in at least two of the three patients were evaluated further by pooling the data of all three patients and calculating regression equations and F values. If these pooled data showed significant correlations,

*Astrup Microequipment, Radiometer, Copenhagen, Denmark.
†Technicon Corporation, Ardsley, New York.
then the pooled data of group B were examined in the same way. Finally, ECG changes which showed a high association to serum potassium levels were combined in an effort to increase further the correlations and to achieve a narrow fit of the confidence region around the regression line.

Results

Sixty-five simultaneous determinations of serum potassium, other biochemical data, blood pressure, and 12-lead ECG tracings were obtained from the three patients of group A. Serum potassium levels ranged from 3.3 to 8.7 mEq/L while serum sodium concentrations were between 123 and 140 mEq/L. The blood pressure was in general less than 160 mm Hg systolic and 100 diastolic. All three patients had been hypertensive in the past but did not require antihypertensive drugs at the time of the study.

Thirty-nine suitable studies were made on the 13 patients of group B. Serum potassium levels ranged from 3.4 to 8.6 mEq/L. Serum sodium levels were in general slightly higher (131 to 148 mEq/L) than those in group A, and there was a higher incidence of higher blood pressures. Concentrations of calcium and magnesium and blood pH were not significantly different between the two groups and usually were slightly below the normal range before dialysis.

None of the ECG tracings showed evidence of transmural myocardial infarction or cardiac dysrhythmias.

Table 1

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Dependent variable</th>
<th>ECG lead</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K</td>
<td>R-R interval</td>
<td>II</td>
<td>10.4*</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>T amplitude</td>
<td>II</td>
<td>24.2*</td>
<td>24.7*</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>12.8*</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>28.1*</td>
<td>8.7*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T maximum time</td>
<td>II</td>
<td>39.1*</td>
<td>19.5*</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>31.0*</td>
<td>12.6*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q-T time</td>
<td>V2</td>
<td>41.8*</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>57.3*</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T-wave duration</td>
<td>V2</td>
<td>45.7*</td>
<td>17.6*</td>
</tr>
<tr>
<td></td>
<td>R-wave amplitude</td>
<td>II</td>
<td>7.0†</td>
<td>0.1</td>
</tr>
<tr>
<td>Serum Na</td>
<td>T-wave amplitude</td>
<td>V2</td>
<td>12.0*</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>S-wave amplitude</td>
<td>V2</td>
<td>5.5†</td>
<td>0.4</td>
</tr>
<tr>
<td>Sum of K and Na</td>
<td>T-wave amplitude</td>
<td>V2</td>
<td>10.3*</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>S-wave amplitude</td>
<td>V2</td>
<td>6.3†</td>
<td>0.1</td>
</tr>
<tr>
<td>Arterial pH†</td>
<td>R-R interval</td>
<td>II</td>
<td>0.1</td>
<td>17.0*</td>
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<td></td>
<td>T-wave amplitude</td>
<td>II</td>
<td>1.9</td>
<td>11.2*</td>
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<tr>
<td>Systolic blood</td>
<td>Q-T time</td>
<td>V2</td>
<td>12.5*</td>
<td>1.1</td>
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<tr>
<td>pressure</td>
<td>V3</td>
<td>6.4*</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T-wave duration</td>
<td>V2</td>
<td>7.8*</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>R-wave amplitude</td>
<td>II</td>
<td>12.9*</td>
<td>0.0</td>
</tr>
<tr>
<td>Diastolic blood</td>
<td>R-R interval</td>
<td>II</td>
<td>5.7†</td>
<td>7.0†</td>
</tr>
<tr>
<td>pressure</td>
<td>T-wave amplitude</td>
<td>II</td>
<td>3.8</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>4.3†</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q-T time</td>
<td>V2</td>
<td>9.8*</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>5.3†</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

*†For F values: * = P < 0.01; † = P < 0.05.
Table 2

Regression Equations for Serum Potassium Levels and Combinations of Electrocardiographic Variables

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>ECG lead</th>
<th>Group A Regression equation</th>
<th>F value*</th>
<th>Group B Regression equation</th>
<th>F value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-T time + T maximum time‡</td>
<td>II</td>
<td>0.46 - 0.02 K s§</td>
<td>11.3*</td>
<td>0.44 - 0.01 K s</td>
<td>1.9</td>
</tr>
<tr>
<td>RR interval</td>
<td>V2</td>
<td>0.57 - 0.03 K s</td>
<td>49.2*</td>
<td>0.57 - 0.02 K s</td>
<td>5.4†</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>0.57 - 0.02 K s</td>
<td>33.2*</td>
<td>0.56 - 0.02 K s</td>
<td>6.1†</td>
</tr>
<tr>
<td>T amplitude**</td>
<td>II</td>
<td>- 0.19 + 0.12 K s</td>
<td>47.6*</td>
<td>- 0.32 + 0.15 K s</td>
<td>42.7*</td>
</tr>
<tr>
<td>T maximum time</td>
<td>V2</td>
<td>- 0.16 + 0.16 K s</td>
<td>40.2*</td>
<td>0.60 + 0.12 K s</td>
<td>6.7†</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>- 0.50 + 0.24 K s</td>
<td>37.5*</td>
<td>- 0.28 + 0.21 K s</td>
<td>17.5*</td>
</tr>
<tr>
<td>T amplitude × (Q-T time + T maximum)</td>
<td>II</td>
<td>18.15 + 20.96 K s</td>
<td>23.1*</td>
<td>- 12.68 + 24.02 K s</td>
<td>21.4*</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>95.63 + 31.46 K s</td>
<td>12.9*</td>
<td>51.73 + 29.48 K s</td>
<td>5.3†</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>7.31 + 52.61 K s</td>
<td>29.8*</td>
<td>36.04 + 40.37 K s</td>
<td>8.0*</td>
</tr>
<tr>
<td>T amplitude × (Q-T time + T maximum)</td>
<td>II</td>
<td>- 5.68 + 3.71 K s</td>
<td>50.0*</td>
<td>- 10.20 + 4.68 K s</td>
<td>43.2*</td>
</tr>
<tr>
<td>T maximum time</td>
<td>V2</td>
<td>- 5.30 + 4.92 K s</td>
<td>44.7*</td>
<td>- 0.84 + 3.76 K s</td>
<td>9.9*</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>- 17.37 + 7.69 K s</td>
<td>40.8*</td>
<td>- 8.16 + 6.23 K s</td>
<td>17.2*</td>
</tr>
</tbody>
</table>

*†For F values: * = P < 0.01; † = P < 0.05.
‡Times and intervals measured in 10⁻² sec.
§K s in mEq/L.
**Amplitudes measured in mm.
Figure 2
Correlation of serum potassium levels and T maximum time of standard lead II (in 10^{-2} sec). T maximum time = 12.15 - 0.75 K. Dashed lines = 99% confidence limits; dotted lines = 90% confidence limits.

All significant correlations for pooled data are compiled in table 1. Table 2 shows the correlations of serum potassium levels with combinations of ECG data. Figures 2 through 4 show three correlations and the confidence limits around the regression line as derived from data from group B.

Figure 3
Correlation of serum potassium levels and combination of electrocardiographic variables of standard lead II (amplitude in mm, time in 10^{-2} sec). 

T amplitude × (Q-T time + T maximum time) = T maximum time − 10.29 + 4.68 K. Dashed lines = 99% confidence limits; dotted lines = 90% confidence limits.

Figure 4
Correlation of serum potassium levels and combination of electrocardiographic variables of standard lead II (amplitudes in mm, time in 10^{-2} sec). T amplitude = −0.32 + 0.15 K. Dashed lines = 99% confidence limits; dotted lines = 90% confidence limits.

Discussion
The metabolic balance studies (group A) provided excellent sequences of gradually increasing serum potassium levels and associated ECG changes. Statistical evaluation of the data for each patient resulted in a multitude of statistically significant correlations. However, meaningful statements about associations of serum potassium levels with certain ECG variables for an entire population of hyperkalemic patients could be made only by pooling these data or, even better, by pooling nonsequential data of a larger group of patients (group B), a truly random sample. Therefore, the great number of possible correlations between ECG changes and serum potassium values as well as other variables with potential influence on ECG patterns was examined first with our sequential data, and only those correlations which seemed promising were evaluated further by pooling data and, finally, by investigating the true random sample of group B.
Because this study was limited to patients with chronic renal failure who were maintained by intermittent hemodialysis therapy, many complicating biochemical alterations of renal failure were avoided or at least minimized. For instance, acidosis was never of any clinical importance (pH of arterial blood was always greater than 7.30).

Hyperkalemia slows conduction velocity and increases the rate of repolarization due to increased membrane permeability for potassium.\textsuperscript{10-12} Thus, changes in repolarization are early signs of hyperkalemia.\textsuperscript{10,13} Our findings agree very well with this, showing excellent correlation of T-wave amplitude and duration to serum potassium levels. No significant relationship was noted between hyperkalemia in the observed range and widening of the QRS complex or reduction of P and R-wave amplitudes.\textsuperscript{14,15} However, a serial tracing obtained by cardiac monitoring during hemodialysis (fig. 5) demonstrated clearly that these relationships can exist in an individual case even without being significant when

**Figure 5**

Electrocardiographic tracings during and after dialysis (K-free dialysate; 12-hour dialysis; blood pressure 182/104 mm Hg initially, 138/82 mm Hg at termination of dialysis). Leads: Over apex, over sternum at level of second intercostal space, and on right midclavicular line over fifth intercostal space. Paper speed: 25 mm/sec; 10 mm = 1 mv. (A) Predialysis, K = 7.5 mEq/L. (B) After 30 min of dialysis, K = 6.6 mEq/L. (C) After 1 hour of dialysis, K = 6.2 mEq/L. (D) After 2 hours of dialysis, K = 4.6 mEq/L. (E) After 4 hours of dialysis, K = 3.4 mEq/L. (F) After 12 hours of dialysis, K = 2.7 mEq/L. (G) At 15 minutes postdialysis, K = 3.0 mEq/L. (H) At 30 minutes postdialysis, K = 3.1 mEq/L. (I) At 1 hour postdialysis, K = 3.4 mEq/L.
evaluated for a population. This stresses the point, made by Del Greco and Grumer,\textsuperscript{15} that no ECG suspected of showing hyperkalemic changes should be judged without having been compared to a control tracing taken prior to development of this disorder. Other factors such as left ventricular hypertrophy with strain pattern, bundle-branch block, infarction, pericarditis, and digitalis intoxication may obscure the picture of hyperkalemia.\textsuperscript{12} It should also be noted that changes of P-wave amplitude are extremely difficult to measure exactly and thus are less suitable for statistical evaluation.

No practical mathematical expression was detected for the definition of the tenting of the T wave seen in hyperkalemia. The T 3/4 time proved to be unsatisfactory, giving no better correlation with serum potassium levels than T maximum time or even T-wave duration. Probably the best result in this regard was obtained from the ratio of T-wave amplitude to T maximum time (table 2). This ratio together with the symmetric (peaked) T-wave appearance should be sufficient to characterize this phenomenon. However, it should be noted that bradycardia, left ventricular overload, or one of a number of different electrolyte disorders may produce a similar picture.\textsuperscript{12}

Combinations of T-wave changes and alterations of Q-T time and T maximum time were closely correlated to alterations of the serum potassium level in the normal to hyperkalemic range. The 90\% and 99\% confidence limits around the regression line and the high correlation coefficient permitted a rather exact prediction of these electrocardiographic changes on the basis of a measured serum potassium level. Under certain circumstances, a reversal of this relationship may be permissible—that is, prediction of the serum potassium level on the basis of ECG changes. Our data indicate that these conditions are met when the patient is oliguric and being maintained by chronic intermittent hemodialysis and when his ECG pattern suggests hyperkalemia (similar to the patients in this study). Thus, a reasonably accurate estimate of the serum potassium level in patients undergoing dialysis intermittently can be obtained by (1) measuring T-wave amplitude (in mm) and T maximum time (in seconds × 10\textsuperscript{2})* on lead II, (2) dividing the former variable by the latter, and (3) reading off the serum potassium estimate in mEq/L from figure 3 or by calculation using an appropriate transformation of the regression equation (table 2):

\[
K_\text{s} = \frac{T \text{ amplitude}}{T \text{ maximum time}} + 0.32 \times 0.15
\]

or

\[
K_\text{s} = 6.7 \times \left( \frac{0.32 + T \text{ amplitude}}{T \text{ maximum time}} \right)
\]

This application makes the portable ECG machine a valuable and inexpensive tool for the monitoring and adjustment of home dialysis therapy. Future application of these equations to ECG tracings of other patients with hyperkalemia will show whether they will be valid for hyperkalemia in general.

Although more than 90\% of total body potassium is intracellular potassium, the total potassium value tells little about the ratio between intracellular and extracellular potassium with its potentially decisive influence on myocardial action. Small shifts between these compartments have great effects on this ratio. Calculation of a “mean intracellular potassium concentration” on the basis of TBK, TBW, and \(K_s\) as devised by Moore and associates\textsuperscript{16} suffers not only from inadequate knowledge of actual compartment sizes but results in a mean value for intracellular potassium which could be far different from the actual myocardial potassium concentration. Studies of potassium content of various parts of the human heart showed considerable differences\textsuperscript{17–22}; however, studies of the total heart revealed a rather uniform potassium concentration among myocardial cells.\textsuperscript{23} The validity

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*The actual measured time is multiplied by 100 to avoid excessive decimal places in the calculation; thus a measured T maximum of 0.08 sec would be used in the calculation as 8.
of estimates of intracellular potassium levels based on analysis of muscle biopsy samples was questioned by Flear and coworkers who demonstrated differences in the intracellular potassium concentration even in samples taken from different locations of the same muscle. It was therefore not surprising that we were unable to find significant correlations between ECG changes and calculated mean intracellular potassium values.

Crismon and associates noted in animal experiments that the correlation of ECG findings to high serum potassium values was definitely better than to measured intracellular potassium levels, a finding not confirmed by others. Although evidence has accumulated that hypokalemic ECG changes correlate better with the ratio of intracellular to extracellular potassium, hyperkalemic ECG patterns seem to be related well to serum potassium level alone.

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