QT Duration and Plasma Electrolytes (Ca, Na, and K) in Uremic Patients

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Summary

On 79 ECG tracings obtained from 31 uremic patients, the influence of serum Ca, Na, and K concentrations on the QT duration in ECG was analyzed by multiple regression technique. It was found that Ca and K had negative and Na had a positive effect on QT duration, although only the effect of Ca was reaching the statistically significant level. Since serum electrolytes had correlations with each other, they were orthogonally and tested for significance once again. Still Na and K did not reveal significant influences by this procedure. However, the effects of Na and K on QT duration were in the same direction and magnitude as reported in earlier literatures.

In the course of orthogonalization it was found that Ca and Na had negative influences on K. It seems that this fact presents a sound basis for the therapeutic use of Ca and Na salts in hyperpotassemia.

Additional Indexing Words:

QT ratio  Ca therapy in hyperpotassemia  Na therapy in hyperpotassemia  Multiple regression analysis  Orthogonalization

QT duration has as its components, the propagation of depolarization wave, membrane action potential duration, and propagation of repolarization wave. Each of these components is influenced by the heart rate and also by the electrolyte concentrations in the surrounding medium. So, it is natural that, beside the influence of the heart rate on QT duration in ECG,¹ the effect of alterations in plasma Ca concentration on it has been one of the earliest findings in clinical electrocardiography.² In 1948 Nadler et al. reported that QT duration was inversely correlated with the serum K concentration in patients with diabetic acidosis.³ This observation was not confirmed by several authors, and some also noticed that QT duration in cases of hypopotassemia

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was much difficult to determine since T-U complex would obscure the true end of QT segment. Succeeding these discussions, Weaver and Burchell concluded that, after all, in hypopotassemia there might be some prolongation of QT interval. In 1961 Hanaoka made an extensive study on the effect of plasma electrolytes on ECG, and found in an experiment on dogs that QT ratio increased significantly during extreme elevations of plasma Na concentration.

In clinical studies it is always not easy to differentiate the effects of various electrolytes on ECG since they would change in many cases simultaneously. Uremia is a disease in which there may arise profound alterations in milieu intérieur, and plasma electrolytes move greatly in all directions. So, it was decided here to study the effects of Ca, Na, and K on QT duration in these patients using the statistical technique of multiple regression analysis.

**Material and Methods**

Seventy-nine ECG tracings were taken from 31 uremic patients hospitalized during 1962 and 1969 at our clinic of the First Department of Medicine. The patients were of various original diseases, most of them were chronic glomerulonephritis. Some of them were under dialytic therapy, and a few sent for renal transplantation. However, at the time of this study all were deceased already and many of them were autopsied.

ECGs were taken at the ward and the instruments were of ordinary heat-stylus type with a paper speed of 2.5 cm./sec. Blood samples were also taken at the ward and sent for analysis at the central laboratory of the hospital. There, Na and K were measured by flame photometry, and Ca by gravimetric method. Na and K were expressed in mEq./L. and Ca in mg./100 ml. Selection of ECGs and blood analyses was such that the time interval between the two was one day at the longest and no dialysis should be done during this period. RR and QT durations of ECG were measured on II lead only, and no comparison with other leads was made. As mentioned before, the measurement of QT duration includes some uncertainty on the recognition of the end of T wave. However, in our patients hyperpotassemia was the rule and prominent U waves were generally speaking infrequent.

The measured values for QT duration were then changed into QT ratio using the empirical graph of Lepeschkin. This QT ratio was brought in a multiple regression equation in terms of serum Ca, Na, and K concentrations as variables:

\[
\text{QT ratio} = \beta_0 + \beta_1 \text{Ca} + \beta_2 \text{Na} + \beta_3 \text{K} + e.
\]

Then all values were changed into their logarithms and the resulting equation would yield:

\[
\log \text{QT ratio} = \log \beta_0 + \beta_1 \log \text{Ca} + \beta_2 \log \text{Na} + \beta_3 \log \text{K} + \log e.
\]

Both were computed by the least squares method at the Data Processing Center of the University of Tokyo. Following these computations, the variables were orthogonalized by the method of Schmidt. The new variables were as follows:

\[
\text{Ca} = \text{Ca},
\]
\[
\text{Na} = \text{Na}(//\text{Ca}) + \text{Na}(\perp\text{Ca}),
\]
\[
\text{K} = \text{K}(//\text{Ca}) + \text{K}(//\text{Na}(\perp\text{Ca})) + \text{K}(\perp\text{Ca}, \perp\text{Na}),
\]
and the two regression equations as above were computed once again for the new variables.

RESULTS

As the results of computation of 2 regression equations, 2 sets of regression coefficients were obtained, and the final forms of equations would become as follows:

\[
\begin{align*}
 QT \text{ ratio} &= \beta_0 + \beta_1 \text{Ca} + \beta_2 \text{Na} + \beta_3 \text{K} \pm e, \quad \text{and} \\
 QT \text{ ratio} &= \beta_0 \cdot \text{Ca}^\beta \cdot \text{Na}^\gamma \cdot \text{K}^\alpha \times \div e.
\end{align*}
\]

QT ratio was expressed as a sum or as a product, respectively. The latter arguments, K and Na, were then deleted from the equations successively, and the new coefficients for the reduced equations were similarly computed again and again. All coefficients thus obtained were tabulated in Table I. As expected, Ca and K had negative influences on QT ratio, and Na had a positive one in both sets. After the computations were completed, the significance of each variables could be weighed in 3 ways. First, the correlation coefficients between QT ratio and serum electrolyte concentrations were calculated and tested for significance by Student’s t. Secondly, confidential range of each coefficient was determined, and if zero was included within the range its contribution would be negligible. Finally, the variances or the sum of square products of residuals, e, were compared between the original and the reduced equations. Following these tests, only Ca was inferred as contributing significantly to the variations of QT ratio, and other electrolytes, Na and K, were discarded as factors determining the value of QT ratio.

Table I. Coefficients of Multiple Regression Equations for QT Ratio

1. QT-Ratio = \(\beta_0 + \beta_1 \text{Ca} + \beta_2 \text{Na} + \beta_3 \text{K} \pm e\)

<table>
<thead>
<tr>
<th>(\beta_0)</th>
<th>(\beta_1)</th>
<th>(\beta_2)</th>
<th>(\beta_3)</th>
<th>(e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.223</td>
<td>-0.0429±0.0193</td>
<td>0.00276±0.00400</td>
<td>-0.0149±0.0199</td>
<td>±0.0983</td>
</tr>
<tr>
<td>1.053</td>
<td>-0.0402±0.0191</td>
<td>0.00325±0.00398</td>
<td>—</td>
<td>±0.0990</td>
</tr>
<tr>
<td>1.470</td>
<td>-0.0365±0.0187</td>
<td>—</td>
<td>—</td>
<td>±0.1001</td>
</tr>
</tbody>
</table>

2. QT-Ratio = \(\beta_0 \cdot \text{Ca}^\beta \cdot \text{Na}^\gamma \cdot \text{K}^\alpha \times \div e\)

<table>
<thead>
<tr>
<th>(\beta_0)</th>
<th>(\beta_1)</th>
<th>(\beta_2)</th>
<th>(\beta_3)</th>
<th>(e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.579</td>
<td>-0.313±0.140</td>
<td>0.300±0.474</td>
<td>-0.0732±0.093</td>
<td>(\times 1.090)</td>
</tr>
<tr>
<td>0.370</td>
<td>-0.292±0.139</td>
<td>0.358±0.472</td>
<td>—</td>
<td>(\times 1.090)</td>
</tr>
<tr>
<td>2.050</td>
<td>-0.270±0.136</td>
<td>—</td>
<td>—</td>
<td>(\times 1.091)</td>
</tr>
</tbody>
</table>

Following \(\beta_1, \beta_2, \) and \(\beta_3\) 95% confidential range is shown. For further legends see text.
Although the alterations in serum electrolyte concentrations in uremic patients were large and in diverse directions, there were also small correlations within each other (an example between Na and Ca, Fig. 1). So, there remains a possibility that significant contribution is hidden behind the apparent indifference. To obviate the computational misleadings the variables were orthogonalized as described in Methods. The resultant new variables were as follows:

\[
\text{Ca} = \text{Ca}, \\
\text{Na} = 1.13\text{Ca} + (128.2 + e), \\
\text{K} = -0.220\text{Ca} - 0.033\text{Na}(-\text{Ca}) + (11.46 + e).
\]

Table II. Coefficients of Multiple Regression Equations for QT Ratio in Orthogonalized Serum Electrolyte Concentrations

1. QT-Ratio = \(\beta_0 + \beta_1\text{Ca} + \beta_2\text{Na} + \beta_3\text{K} + e\)

<table>
<thead>
<tr>
<th>(\beta_0)</th>
<th>(\beta_1)</th>
<th>(\beta_2)</th>
<th>(\beta_3)</th>
<th>(e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.227</td>
<td>-0.0965±0.0184</td>
<td>0.00325±0.00394</td>
<td>-0.0151±0.0198</td>
<td>0.0982</td>
</tr>
<tr>
<td>1.054</td>
<td>-0.0365±0.0186</td>
<td>0.00325±0.00397</td>
<td>-</td>
<td>0.0990</td>
</tr>
<tr>
<td>1.470</td>
<td>-0.0965±0.0188</td>
<td>-</td>
<td>-</td>
<td>0.1001</td>
</tr>
</tbody>
</table>

2. QT-Ratio = \(\beta_0\text{Ca}^\beta\text{Na}^\delta\text{K}^\gamma + e\)

<table>
<thead>
<tr>
<th>(\beta_0)</th>
<th>(\beta_1)</th>
<th>(\beta_2)</th>
<th>(\beta_3)</th>
<th>(e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.579</td>
<td>-0.270±0.134</td>
<td>0.357±0.468</td>
<td>-0.0732±0.095</td>
<td>1.090</td>
</tr>
<tr>
<td>0.370</td>
<td>-0.270±0.135</td>
<td>0.358±0.472</td>
<td>-</td>
<td>1.091</td>
</tr>
<tr>
<td>2.050</td>
<td>-0.270±0.136</td>
<td>-</td>
<td>-</td>
<td>1.092</td>
</tr>
</tbody>
</table>

Legends are as same as in Table I.
The sets of regression coefficients for these new variables were computed again in all combinations as before, and the values of these sets were shown in Table II. The significance of contribution was tested also for these new equations, and it was concluded that Ca was the only factor and Na and K were nonetheless insignificant.

As the byproduct of above calculation it was revealed that Ca and Na had negative influences upon K and without their influences K would have much higher value than the actual concentration. Here, a reasonable ground was established for the infusion therapy of Ca and Na salts in hyperpotassemia, unless digitalis toxicity or edema accumulation would hamper their mitigating use.

**Discussion**

Bazett had first noticed that the duration of cardiac systole (QT duration) was proportional to the square root of cycle length with a proportionality constant, K.\(^1\) Since then, Carter and Andrus found that the QT duration lengthened relatively in patients with hypocalcemia,\(^2\) and Kellog and Kerr observed that in hypercalcemia it was shortened conversely.\(^3\) Barker et al. summarized the above findings and noted that the constants, K's, of Bazett varied with the changes in serum Ca concentration,\(^4\) and Hegglin and Holzmann also confirmed that the calculated QT duration was less than the actual one in hypocalcemia of various origin.\(^5\) Both authors noted that the configuration of T wave was not so much deformed in hypocalcemia. However, no attempts were made by these authors to correlate the changes in serum Ca concentration and the constant of Bazett quantitatively. The findings were also described in the precordial leads of ECG,\(^6\) and in the cardiac monophasic action potentials of experimental animal.\(^7\) Our present quantitative analysis clearly demonstrated that Ca had a negative influence on the QT duration separating aside the effects of Na and K.

As for the influence of K, not alike as the case of Ca, the observations were rather controversial in the literature. Thomson first reported that the QT interval was prolonged in hypopotassemia seen in the patients with Addison’s disease over-treated by DOCA.\(^8\) Stewart et al. found the similar prolongation in patients with familial periodic paralysis.\(^9\) They also observed that the configuration of RS-T segments and T waves was deformed in hypopotassemia whereas in hypocalcemia no such alterations occurred. Later, Martin and his colleagues,\(^10\),\(^11\) Tarail,\(^12\) and Lans et al. confirmed repeatedly these findings.\(^13\) Bellet and his group emphasized that the QT duration and the serum K concentration were inversely correlated,\(^14\),\(^15\)\(^–\)\(^21\) and Reynolds et al. also reported a
similar correlation in patients with various diseases.\textsuperscript{16} However, Ljunggren et al. could not find such a consistent relationship in patients with rheumatoid arthritis treated with ACTH, cortisone and DOCA.\textsuperscript{22} Schwartz et al. concluded that neither the total K deficit nor the serum K concentration was consistently related to the ECG changes.\textsuperscript{23} Herndon et al. also could not find a significant correlation between $Q$-$T_c$ and serum K concentration.\textsuperscript{24}

In another line of evidences, Jung and Jantz observed that U wave became prominent in hypopotassemia found in the patients with paroxysmal paralysis,\textsuperscript{25} and Ernstene and Proudfit first claimed that the apparent QT prolongation in hypopotassemia might be the result of a T-U fusion.\textsuperscript{26} After their publication, McAllen reported the same opinion,\textsuperscript{27} and Bellet also agreed the existence of such a fusion.\textsuperscript{28} On the other hand, Surawicz and his colleagues made much efforts to discriminate T and U waves, and stated implicitly and explicitly that the QT duration might in fact shortened in hypopotassemia.\textsuperscript{15,25–30} Considering all these discussions, Weaver and Burchell concluded that QT duration increased slightly in hypopotassemia.\textsuperscript{4} In hyperpotassemia due to K loading, Dietrich and Wolff could not observe a significant correlation between QT duration and serum K concentration.\textsuperscript{36} However, in recent experiment of similar nature on human controls and patients, Schwarzbach concluded that QT duration was shortened by elevation of serum K.\textsuperscript{37} Our present computation confirmed the finding of Nadler et al. that K had small negative effects on QT duration, although it did not reach the statistically significant level.

In the case of Na, older observations were scanty. Reynolds et al. at first believed that Na had no discernible influence on the QT duration. However, Hanaoka and his group increased the serum Na concentration up to 250 mEq./L. in dogs, and at this unphysiological condition found that the QT duration increased.\textsuperscript{5,6} According to our present formulae, both equations could reasonably predict quantitatively this prolongation, logarithmic (product) form being slightly more advantageous. It is interesting to note that the regression analysis technique is sound enough to elicit the concealed information buried within the ocean of noises as is in this example. Although the actual range of variation of serum Na concentration was narrow and the coefficient for Na failed to be statistically significant, it was capable to coincide with the result of animal experiment.

After sizing the influences of serum electrolytes on QT duration in this study, the residual error was still large ranging some 10%. So, it must be considered that there remained other factors than the serum electrolytes as with Martin and Wertman.\textsuperscript{15} Since in the present computation Ca was the only electrolyte influencing indispensably on QT duration, it became now possible to re-examine the Bazett's relationship taking into account both RR duration and
Table III. Coefficients of Multiple Regression Equations for QT Duration

<table>
<thead>
<tr>
<th></th>
<th>$\beta_0$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$e$</th>
<th>$p &lt; 0.01$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. $QT = \beta_0 + \beta_1RR + \beta_2Ca + e$</td>
<td>0.275</td>
<td>$0.270 \pm 0.054$</td>
<td>$-0.0106 \pm 0.0066$</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.172</td>
<td>$0.2925 \pm 0.0550$</td>
<td>$-0.033$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. $QT = \beta_0RR + \beta_2Ca$ ($\times e$)</td>
<td>0.742</td>
<td>$0.4806 \pm 0.1057$</td>
<td>$-0.2418 \pm 0.1530$</td>
<td>1.098</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.454</td>
<td>$0.5230 \pm 0.1075$</td>
<td>$-0.114$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Following $\beta_1$ and $\beta_2$ 95% confidential range is shown. For further legends see text.

serum Ca concentration simultaneously. The result demonstrated that the square root law of Bazett was still valid in the present small ECG specimens from uremic patients (Table III). However, it was interesting that the equation relating these 2 factors linearly in the sum gave slightly smaller mean residual error than the one in the product form. It was also noted that in the present series of ECGs the constant, K, of Bazett was a little larger than usually accepted for healthy people. If K was calculated for normal serum Ca concentration, it was 0.415 when Ca was 11, 0.425 when Ca was 10, and 0.436 when Ca was 9.

In due course orthogonalizing the serum electrolyte concentrations, it was found that Ca and Na had negative influences on K. This fact was empirically known and used for the therapy of K intoxication. Finch and Marchand was probably the first to report the therapeutic use of Ca and Na salts in this situation. Govan and Weiseth, Merrill et al. also advocated the use of Ca salts, and Braun et al. suggested that hypocalcemia increased susceptibility to the K intoxication. Merril at the same time argued that Na salts could reverse the deteriorating K effect on the heart, and that hyponatremia was an aggravating factor in those patients. It seemed that these therapeutic experiences had gained a sound theoretical ground by the present study, except when the patients’ condition would limit their usefulness.

REFERENCES

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