The QT Interval in Clinical Practice

SECTION 3: The Effect of Heart Rate on QT - Rate-correction of QT (QTc)

The objective for Section 3 of The QT Interval in Clinical Practice is to describe the effect of differences in heart rate on the QT interval and how to correct for these differences by calculating the "rate-corrected" QT, or QTc; as well as discussing the normal range for QTc intervals and how the range is influenced by age and biologic sex.

QT Changes when Heart Rate Changes:

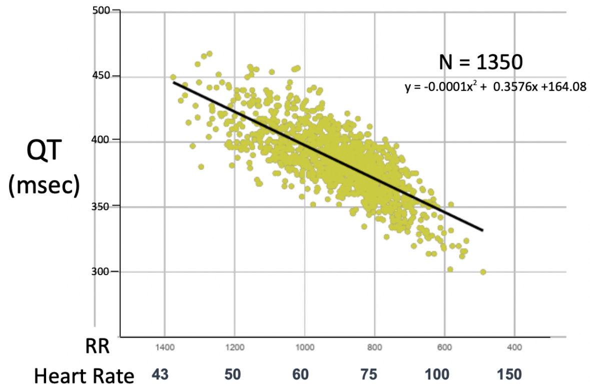
An important factor that complicates the interpretation of the QT interval is that the QT changes when the heart rate changes.

Basically, as the heart rate increases the QT interval naturally shortens. Therefore, any comparison of QT intervals at different heart rates requires a mathematical correction or adjustment of the value for the effects of a change in rate.

Because there are numerous mathematical corrections that have been proposed and reported in the medical literature, we will ask, "Is there a preferred method for heart rate correction of the QT interval?"

QT / RR Relationship:

First, this slide demonstrates the normal relationship between QT and RR interval - or heart rate - in ECGs recorded for 1,350 healthy subjects.



As you can see, at slower heart rates (i.e., higher RR values), the QT is longer and at faster heart rates (i.e., lower RR values), the QT is shorter. This difference complicates the comparison of two QT measurements if they are taken at times when the heart rates are not the same.

In 1920, two cardiologists independently published articles describing the effect of heart rate and each proposed a different formula to correct QT intervals to a standard heart rate of sixty bpm. One became the clinical standard but not a “gold standard.”

QT Rate Correction Methods:

The two rate correction formulae are referred to as the Bazett and Fridericia formulae. Bazett’s formula divides the QT interval by the square root of the RR interval whereas the Fridericia formula divides the QT by the cube root of the RR interval. In the last 100 years, the Bazett formula gained widespread use and, until recently, the Fridericia formula was virtually unknown, perhaps because of the inherent difficulty in calculating a cube root without a computer.

Although easier to calculate, the Bazett formula has long been known to perform poorly. Modern computing has created the opportunity for researchers to evaluate other approaches. More than a dozen rate-correction formulae have been described beginning in the 1980’s with the work by Hodges et al. The Hodges formula and the subsequently reported Framingham, Dmitrienko and Rautaharju formulae were based on regression analysis of data from groups of relatively healthy patients. Each of these approaches resulted in a formula that sought to convert the normally curvilinear relationship of RR vs. QT to a horizontal line with little, if any, slope. As will be shown, some perform better than others and some depend on the source of the ECG data.

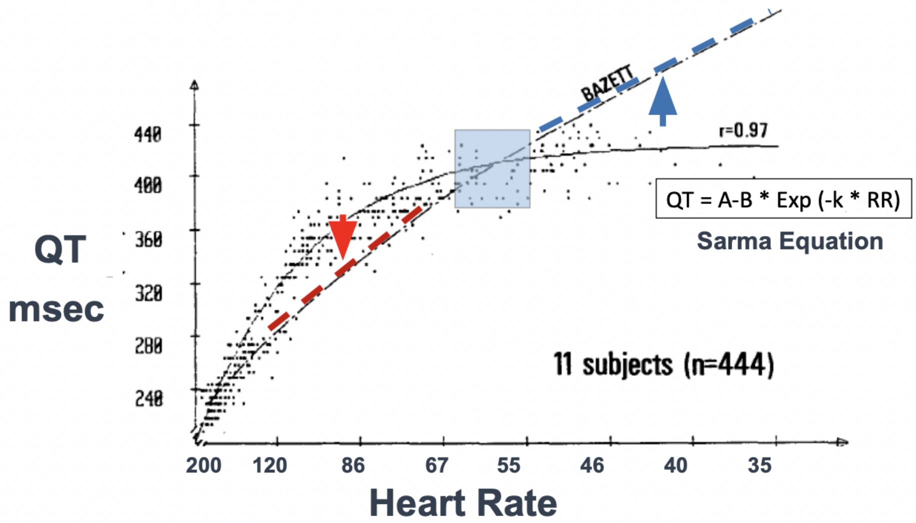
Karjalainen developed a nomogram that adjusted QT for bins of heart rate by simply adding or subtracting a number that would make the QT approximately what it would be at a heart rate of sixty.

These methods will be discussed further here - and all suffer from the limitation that one must assume the population from which the formula was derived accurately represents all other patients. This became an important consideration when Malik et al. described the RR/QT variability that exists in populations and proposed that each person should serve as their own control and have their own regression equation estimated and used for rate-correction.

We will see how each of these perform and consider which, if any, is preferred and under what circumstances.

Limitations of Bazett's Correction:

This slide is taken from a study supporting the use of the Sarma regression equation and demonstrates the inherent limitation of the Bazett correction.



Although the number of subjects in this study is small, the QT data span a large range of heart rates. The solid line is the best fit of the data to the Sarma formula and demonstrates the curvilinear relationship between QT and heart rate we saw in the earlier set of data. The authors reported that these data are best fit (r=0.97) by the mono-exponential formula on the right, developed and described by Sarma et al. in 1984.

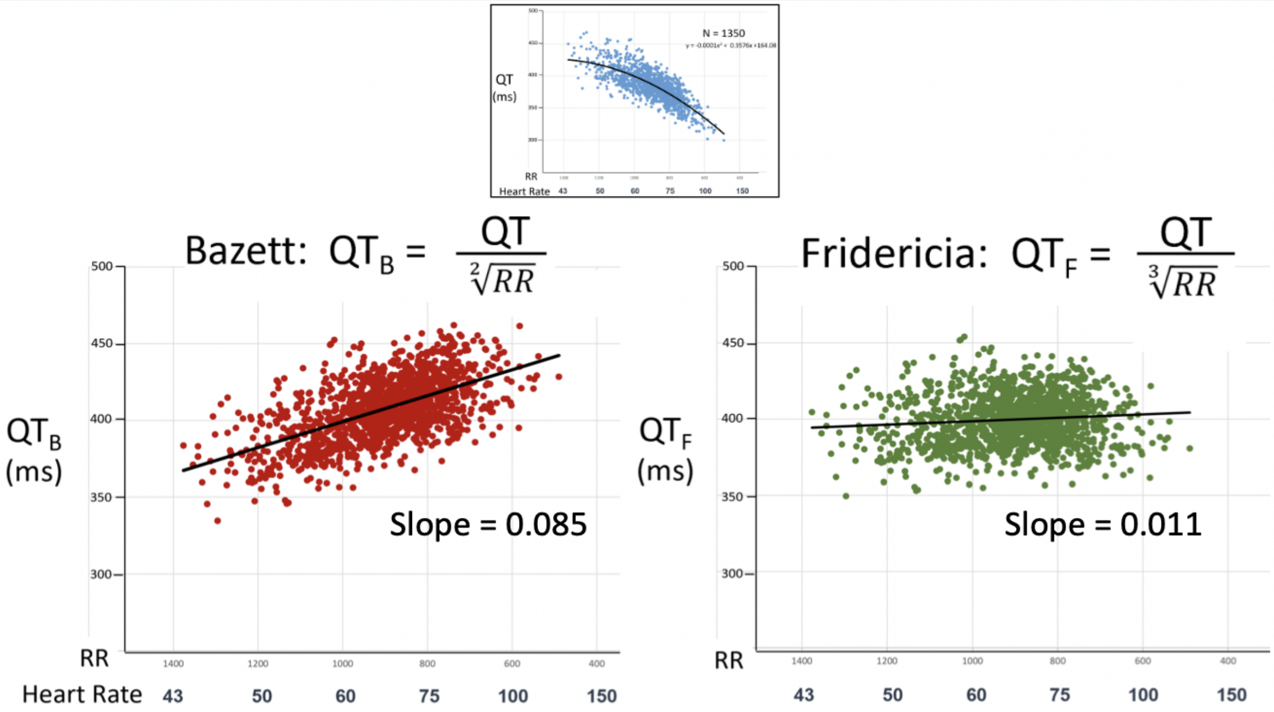
As can be seen, as the heart rate increases the QT shortens, but at rates below 60 the QT lengthens very little, if any. As can be seen by the red and blue dashed lines, applying the Bazett correction formula fails to fit most of the true RR/QT relationship for this group of subjects. It works fairly well for rates around 60 or those over 120.

For heart rates between approximately 70 and 120, the Bazett correction (red dashed line) over-corrects and gives much lower QT values than observed. Also, at rates below 50, Bazett gives far larger QTc values (blue dashed line) than actually occur.

Sarma JS, Sarma RJ, Bilitch M, Katz D, Song SL. An exponential formula for heart rate dependence of QT interval during exercise and cardiac pacing in humans: reevaluation of Bazett's formula. Am J Cardiol 1984;54:103-8.

Bazett vs. Fridericia:

The two most commonly used formulae in clinical practice today, Bazett and Fridericia, are shown in the two lower graphs. The upper graph is the data from the earlier slide to again show the curvilinear nature and negative slope of the uncorrected QT for these data.

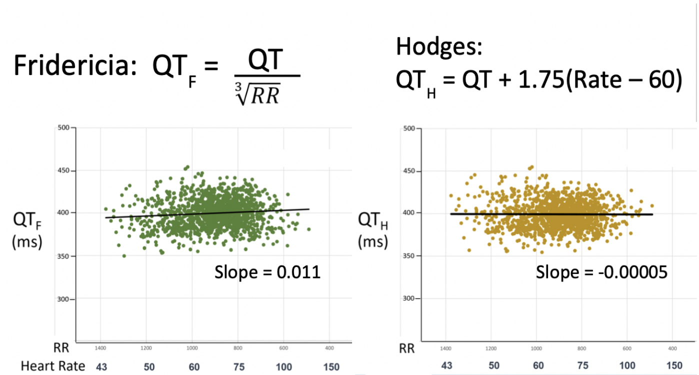


In the two lower graphs, you can compare how well each of these formulae perform with the same dataset. If the correction formulae were correcting perfectly for differences in heart rate, the corrected QT values would fall along a horizontal line with a zero slope.

However, as can be seen, the Bazett-corrected data now have a prominent positive slope indicating that it is over-correcting at high heart rates (low RR) and under-correcting at slow heart rates (high RR values). As has been shown in many other studies, the Fridericia correction, while not yielding a perfectly horizontal line, has a lower slope and produces far less over- or under-correction than Bazett. Because of Fridericia's overall better performance, the FDA has recommended that it be used during drug development research and it seems to be gaining greater clinical use in some centers.

Fridericia vs. Hodges:

This slide compares the results with Fridericia on the left to QT data corrected using the Hodges formula.

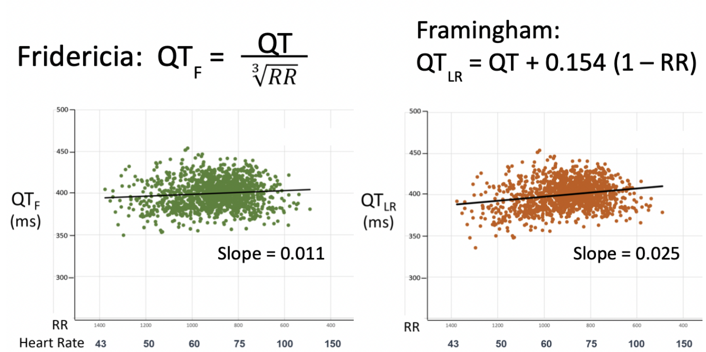


In this case, the Hodges correction formula yields a slightly lower slope; that is, it creates a slightly more horizontal line for the RR/QT relationship. Although the Hodges formula is sometimes used clinically, it has had limited acceptance, perhaps because the data were only published in abstract making it difficult to fully evaluate its merit.

(Hodges M, Salerno DM, Erlien D. Bazett's QT correction reviewed: evidence that a linear QT correction for heart rate is better. J Am Coll Cardiol 1983;1:694.)

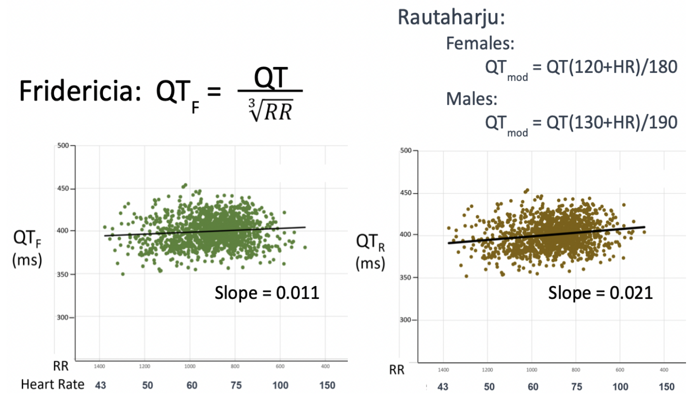
Fridericia vs. Framingham:

Another correction formula, the Framingham correction, was developed by Sagie et al. and was based on their analysis of ECG data from 5,018 patients in the Framingham Heart Study. These charts compare the Fridericia and Framingham correction formulae and, while the results are similar, the Fridericia correction performs better and has a slightly lower slope.



Fridericia vs. Rautaharju:

These charts compare the performance of the Fridericia formula and the Rautaharju formula.

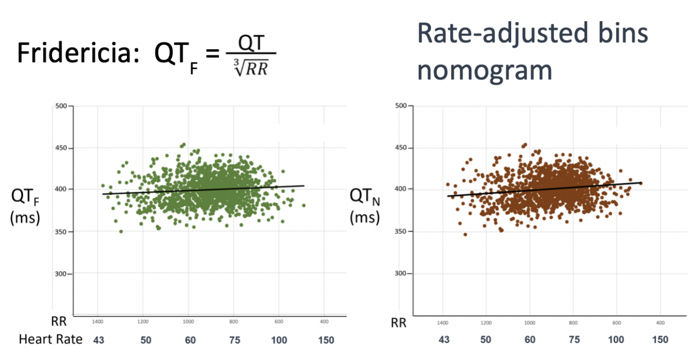


An important difference between these two is that Rautaharju et al. took into consideration biologic sex in their analysis and reported two equations, one for males and another for females. Despite this difference, Fridericia still has a lower slope.

Fridericia vs. Rate: Adjusted Bins Nomogram:

Karjalainen and co-investigators have recommended a very simple method to correct QT values by simply allocating the heart rate data to 5 beat bins and increasing or decreasing the QT to what it would be for a heart rate of 60. The amount of change for QT is determined by which "bin" the heart rate falls in. The rate-adjusted bins nomogram was applied for heart rates from 40 to 120. The QT is reduced by a negative number for heart rates less than 60 and increased by a positive number for heart rates above 60.

This graph shows that, for this set of ECGs, the Fridericia and the rate-adjusted nomogram performed about the same and neither produced a perfectly flat line for RR vs QT.



QT Rate-Correction Methods:

This slide compares the performance of seven of the most commonly used rate-correction methods on the same set of 1,350 ECGs. As a metric, the slope of the regression line for the RR/QT relationship was calculated using linear regression. The most effective correction formula should result in a perfectly horizontal line with a slope of zero.

Method Applied		Slope*
None	Uncorrected QT	+ 0.129
Bazett	Exponential	- 0.085
Dmitrienko	Exponential	- 0.046
Framingham	Large group regression	- 0.025
Rautaharju	Large group regression	- 0.0214
Karjalainen	Rate-adjusted bins nomogram	- 0.0183
Fridericia	Exponential	- 0.011
Hodges	Group regression	- 0.00005

As can be seen, on this set of data, the Hodges, Fridericia and Karjalainen methods have the lowest slopes and the Bazett formula again had the worst performance.

Impact of QT Rate-Correction Method Selection:

Clearly, some of the various rate-correction methods perform better than others when applied to a common set of ECGs. Seeking to quantify the potential impact of choosing one over another, Rosenblum et al asked the question, “How often do the Bazett and Fridericia formulae agree when diagnosing QTc prolongation?”

In 44,566 ECGs collected over a year period at a large tertiary hospital, they compared the results when the QT was corrected by the two methods and found that the mean QTc was 28 msec lower when corrected by the Fridericia formula.

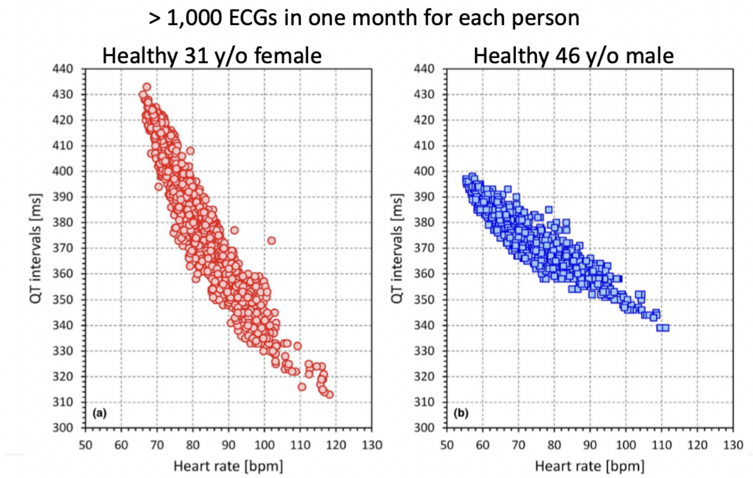
They found that utilizing QTcF in place of QTcB decreased the number of times prolonged QTc was diagnosed in their hospital by 21% - that is over 9,000 cases.

The authors concluded that rate-correction by Bazett potentially resulted in the misdiagnosis of prolonged QT in over 20% of patients. Without outcome data such as incidence of torsades, one cannot be sure that the 20% were really over-diagnosed.

Highly Variable QT/RR Profiles:

The use of a correction formula for QT rate-correction is based on the assumption that a mathematical formula derived for a representative relevant population reflects the RR/QT relationship for the rest of the population. However, Malik and his co-investigators have documented the extensive differences in the RR/QT relationship between individuals.

The charts show the RR/QT data for more than 1,000 ECGs taken for two healthy individuals and demonstrates their differences. The authors point out that a single regression equation is unlikely to be appropriate for all subjects in a study.



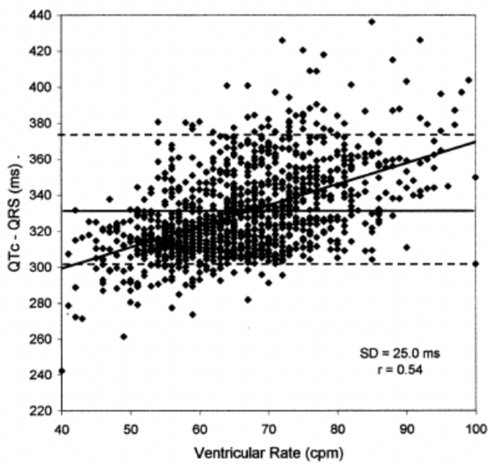
These authors have called attention to the value of establishing each patient's RR/QT relationship and using that for subsequent comparisons of QT. This approach, although ideal, is not practical for most clinical situations because of the large number of ECGs required to establish each patient's RR/QT relationship. However, it has been used in clinical research as will be described in Section 4 of this presentation.

JT Rate Correction when QRS↑

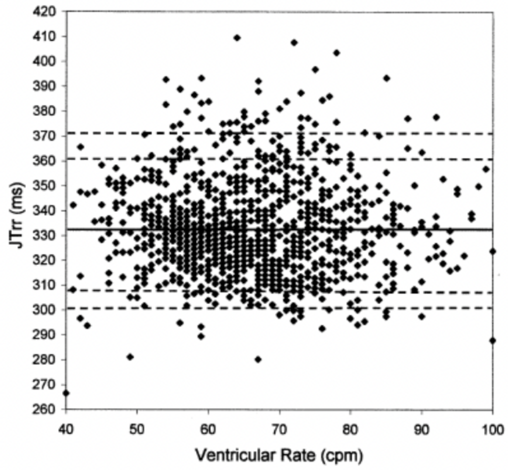
Because of the concern that intraventricular conduction delay (IVCD) could produce changes in QT that might confound its accuracy when patients have IVCD or bundle branch block, most authorities recommend measuring the JT interval.

The data in our chart are taken from a study designed to define a rate-correction formula for 1,251 patients with a prolonged QRS.

Bazett:



JT_c = QT - 155 X (60/HR – 1) -0.93 X (RR-139 + k)



As shown in the panel on the left, the Bazett formula fails to perform as well as the formula developed by Rautaharju et al. (right panel). This formula adjusts QT for the influence of ventricular rate, QRS duration and gender and gives a more consistent correction as shown by the more horizontal line for RR/QT, although the confidence intervals are very broad.

AHA/ACCF/HRS: 2009 QT Recommendations:

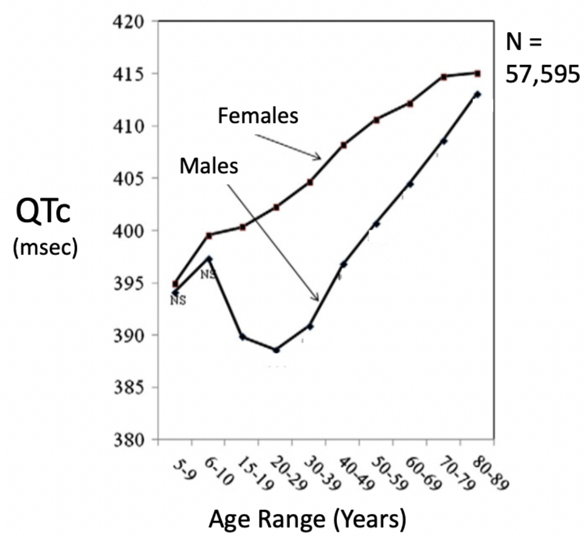
In 2009, the Practice Guidelines jointly approved by the American Heart Association, Heart Rhythm Society and the American College of Cardiology included a definition of the upper limit of normal QTc as ≥ 450 msec for men and ≥ 460 msec for women. The Guidelines also recommended that QT rate correction should consider the impact of age and biologic sex but the Guidelines didn’t specify how to make those adjustments. They recommended that the Bazett formula not be used, but instead use a method that is based on linear regression such as the Framingham Formula. They also cautioned that rate correction is not reliable if the heart rate is highly variable such as in conditions like atrial fibrillation.

Age/Sex and Normal QTc Interval:

In 2014, Rautaharju and colleagues proposed new upper limits for the normal QTc that are age and gender specific.

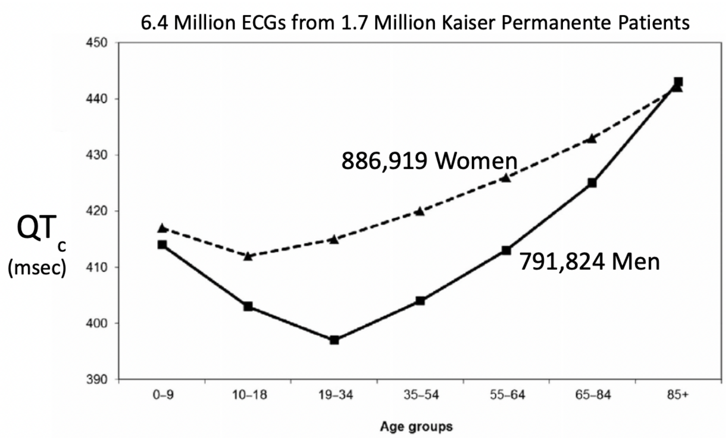
Age and QTc Interval:

This graph, adapted from the Rautaharju publication in 2014, shows the dramatic impact of age and how differences between men and women change over time.



The QTc of boys and girls age 5-9 are very similar but there is marked shortening of QT in boys during puberty that creates a difference that lessens during time as adults.

In that same year, a very large study from Kaiser Permanente confirmed the changing relationship between age and QTc in men and women. The authors used log-linear regression formulae with 98 strata for age, gender and ethnicity.



As can be seen, during puberty the QTc of males shortens and, with advancing age, QTc increases to match the QTc of women in their 80s.

This is the end of Section 3. Please continue to Section 4 where we will discuss when and why to measure the QTc interval, the Role of QTc risk assessment in Clinical Decision Support and QTc measurement in clinical research.