EDITORIAL COMMENT

QT Interval Prolongation and Prognosis: Further Validation of the Quantitative Approach to Electrocardiography*

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In the just over 100 years since the first body surface recording of the cardiac electrical signals by Einthoven (1), the 12-lead electrocardiogram (ECG) has evolved from a cumbersome analog recording technique available to only a few investigators into an portable, inexpensive, and widely available digital diagnostic tool. However, despite advances in computer processing that provide accurate amplitude and duration measurements on most ECG carts in use today, routine clinical interpretation of the ECG remains predominantly qualitative and descriptive in nature, limiting precision of the ECG for both diagnosis and prognosis.

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An aspect of ECG interpretation that has been routinely quantitative in nature is assessment of the QT interval, the body surface summation of ventricular depolarization and repolarization. As noted by Schweitzer (2), the QT interval was first measured in the frog heart by Burdo-Sanderson and Page in 1880 (3), with Einthoven introducing the term “QT interval.” Rate-dependence of the QT interval was recognized over 80 years ago by Bazett (4) with subsequent development of the commonly applied rule to adjust the QT interval for heart rate (corrected QT interval, or QTc) (5). Prolongation of the QTc interval has been associated with an increased risk of sudden death in the congenital long-QT syndromes (6) and with an increased risk of cardiovascular and all-cause mortality in a broad range of clinical populations as well as in healthy subjects in population-based studies (7–12). However, in his 1992 review of the value and limitations of the QT interval (2), Schweitzer further noted that clinical utility of the QT interval remained clouded by questions regarding the accuracy of QT interval measurement (13–19), the validity of the Bazett formula for correcting the QT over a wide-range of RR intervals (20–27), and by uncertainties regarding the upper limit of normal of QTc (22,27–30).

The past 10 years have seen a resurgence of investigation into application of the QTc for risk stratification, in part sparked by an evolving understanding of the genetic bases of the congenital long-QT syndromes and by the development of novel descriptors of repolarization based on vectorcardiographic quantification of the T-wave (6,8,11,26,27,29–38). Despite this resurgence of interest, the issues raised by Schweitzer (2) regarding measurement, rate-correction, and normal limits of the QT interval have persisted to this day. However, much of the controversy regarding rate-correction and measurement of the QT interval has been based on theoretic and methodologic studies that have not examined the impact of these varying approaches on performance of the QTc (15–25,27,29). Thankfully, the study by Dekker et al. (12) in this issue of the Journal goes a long way towards addressing some of these fundamental questions regarding QT interval use and highlights the importance of careful, quantitative assessment of the ECG in routine clinical application. Using incident coronary heart disease and cardiovascular disease mortality as the end point, this important study addressed the impact of computer versus manual QT interval measurement and of a number of different methods of rate correcting the QT on the predictive value of the QT interval in a large, biracial cohort of men and women from the Atherosclerosis Risk In Communities (ARIC) study.

How to best measure the QT interval has long been a major issue, with questions of how to identify T-wave offset, in which leads to measure the QT interval, and whether to use manual or computer measurements. Accurate manual identification of T-wave offset is difficult, particularly in the presence of low amplitude T-waves, T-U fusion, and at high heart rates when the P-wave may become superimposed on the T-wave (13–18). As a consequence, both intra- and inter-observer variability of manual QT interval measurements have been high (13), limiting the applicability of this approach when serial QT determinations are of relevance (26). Although the accuracy and reproducibility of computerized identification of T-wave offset has also been an issue (17,18,39,40), a computerized approach to QT interval measurement using a least-square fitting method to identify T-wave offset from the intersection of the maximal slope of the terminal T-wave with a threshold determined by the T-P segment has been demonstrated to have superior reproducibility to other automated methods of T-offset determination (17,18). Computer determination of the QT interval frequently involves measurement from the earliest onset of the QRS in any of 12 leads to the latest offset in any of the leads (17,18,41). This approach, used by Dekker et al. (12) in their study, would be predicted to result in longer QT intervals than when manual measurements of the longest QT interval in any ECG lead are used. Finally, the number and specific leads in which the QT intervals are determined will affect QT interval measurements, with interval duration increasing with the number of leads measured (19,29). Early studies recommended measure-
ment in limb lead II, but multiple and varying lead sets have been used over time (2,19), with implementation of computer measurements allowing routine determination of the QT interval in all 12 leads. Comparing careful manual measurements made in 3 leads with the aid of a digitizing tablet with computerized measurements in all 12 leads, Dekker et al. (12) found a high degree of correlation between manual and computer-measured QT intervals ($r = 0.81$) and that, as would be predicted, computer-measured QT intervals exceeded the manual measurement, by on average 10 ms (12). Most importantly, however, they found only minor differences in the predictive value of careful manual as compared with computer QT measurements and that these differences were negated by further adjusting for heart rate. These findings suggest that with careful QT measurement and adjustment of normal limits for the method used, either manual or computer QT interval measurements may be used for risk stratification.

The residual correlation of rate-corrected QT interval measurements with heart rate found by Dekker et al. (12) highlights the well-described imperfection of all methods of correcting the QT interval for its relationship to rate (20–27). The most commonly used formula for heart rate-correcting the QT interval is that of Bazett (4), in which measured QT is divided by the square root of the preceding RR interval measured in seconds. This nonlinear power correction has been widely examined and found to undercorrect the QT interval at low heart rates and to overcorrect at high rates (22,24). As a consequence, numerous QT rate-correction formulae have been developed using linear regression and other nonlinear power functions (20–27). However, many of these methods are computationally more complex, frequently also have residual correlations with heart rate, and have not been adequately tested for routine clinical use. Conclusions regarding the presence and degree of drug effects on the QT interval can vary significantly with the method of heart rate correction used, particularly when the agents have independent effects on heart rate (26). In addition, standard means of scaling the QT interval for heart rate produce rate-dependent distortion of the normal limits of the rate-adjusted QT interval (27), further clouding the applicability of standard rate-corrected QT intervals. Despite these intrinsic limitations, the Bazett equation remains in widespread clinical use today. Because the effect of differing rate-correction algorithms on prognostic value of the QT interval had not been adequately assessed, Dekker et al. (12) examined three different equations for rate-correcting the QT interval: Bazett (4), Hodges linear-regression equation (24), and the nonlinear QT index proposed by Rautaharju et al. (23). They found high degrees of correlation between the three methods and, most importantly, that there were only minor differences in the risk stratification provided by the three methods, with the Bazett correction appearing to provide slightly better separation, supporting the continued clinical use of this imperfect approach.

Finally, use of the QT interval depends heavily on the accurate delineation of normal ranges of QTc. In addition to the possible effects of measurement variability, lead selection and rate-correction already discussed, the QT interval has been noted to vary significantly with gender, race, and age in the general population (22,27–30). In addition, QTc distribution varies with genetic locus in the long-QT syndrome (6) and is significantly right-shifted compared with normal populations. Thus, Priori et al. (6) used a QTc of 500 ms$^{1/2}$ to stratify risk in patients with the long-QT syndrome, compared with values of 450 for men and 465 for women that identified the upper 10% of the ARIC study population (12). The study by Dekker et al. (12) found QTc to stratify risk in men and women and in whites and blacks, although there were racial differences in the prognostic value of the QTc that did not change when race-specific thresholds for QTc were used. Interestingly, there were no significant racial differences in mean QTc in their study (12), in contrast to the shorter QTc found in healthy black ARIC subjects without hypertension, diabetes, or history of cardiovascular disease (30). The known racial differences in QRS voltages (30,42) that exist independent of any potential influence of body mass index or left ventricular size (42) suggest that true racial differences in QT intervals may exist. The shorter QT intervals in men reflect gender differences in the dynamics of repolarization, with significantly greater dV/dT of the spacial vector in men than in women (43), suggesting possible gender differences in the behavior of the different ventricular transmural cell types that have an effect on the T-wave (43) and/or the possible effects of sex hormones on the behavior of channels that govern repolarization (44,45). These findings make it interesting to speculate on whether similar differences in the dynamics of repolarization and repolarizing currents may in part explain the potential racial differences in QT interval. Further study will be necessary to clarify this issue.

Detailed discussion of the possible mechanisms of prolongation of the QT interval in the general population is beyond the scope of this editorial. Some of these potential mechanisms are discussed by Dekker et al. (12), with particular emphasis on the relation between QTc prolongation and abnormalities of insulin and glucose metabolism that may be mediated via interactions with potassium channels (46,47). The potential relation of the QT interval to potassium channel behavior (46,47) and the established relation between mutations in potassium-channel and sodium-channel genes and the congenital long-QT syndrome (6) suggest that analysis of genetic variations in these channels may provide further insights into the acquired long QT found in the general population. Although additional study is required to clarify the meaning and mechanisms of a prolonged QTc, the findings of Dekker et al. (12) strongly support the value of careful, quantitative electrocardiography in the application of QTc prolongation for risk stratification in the general population. Hopefully, the next 10
years will see the routine application of additional ECG measurements of amplitude and duration (48, 49), as well as more complex measures of repolarization (32–38), in the serial assessment of the ECG in day-to-day practice.

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REFERENCES


