

EDITORIAL COMMENT

# Is Modest QT Interval Prolongation in Normal Adults Like the Canary in the Coal Mine?\*



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In the early 1900s, William Einthoven introduced the electrocardiogram (ECG) using a string galvanometer, and he named the P, QRS, and T deflections as we know them today (1). The initial clinical focus was on cardiac arrhythmias, with subsequent emphasis on associating altered ECG deflections with clinical disease. Early on, the QT interval was assumed to be a reflection of the duration of ventricular systole. In 1920, Bazett introduced the first formula for correcting the QT interval for heart rate ( $QT_b = QT/RR^{1/2}$ ) (2), and in the same year, Fridnerica introduced his correction formula:  $QT_f = QT/RR^{1/3}$  (3). Subsequently, the QT interval was appreciated as a measure of ventricular repolarization duration, and the more complex Framingham (4), Hodges (5), and other QT heart rate correction techniques were introduced. Over the years, the most frequent QT correction formula used in clinical practice has been the simple Bazett approach for heart rates in the 60 to 90 beats/min range, with the upper limit of the  $QT_b < 450$  to 460 ms. In 1957, Jervell and Lange-Nielsen (6) described the first reported family with inherited long QT syndrome; the members of this family had marked QT prolongation, complex ventricular arrhythmias, deafness, syncope, and sudden death (6). During the subsequent 50 years, the channelopathic genetics of this disorder have been elucidated and the arrhythmogenic risks associated with QT prolongation from

acquired cardiac disorders, electrolyte imbalance, and drugs have been appreciated. The distribution of the corrected QT interval in healthy subjects has been well documented in several epidemiological studies (7,8), but the cardiovascular risk of longer versus shorter corrected QT intervals in the normal range in healthy subjects has only recently been investigated (9,10).

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In this issue of the *Journal*, Beinart et al. (11) investigated the association of the corrected normal QT interval duration in more than 6,000 healthy adult subjects in the large MESA (Multi-Ethnic Study of Atherosclerosis) population for risk for cardiovascular events over a long-term follow-up averaging 8 years. In this elegant study, subjects were free of clinically apparent cardiovascular disease (CVD) at enrollment and standard 12-lead ECGs were digitally acquired and automatically processed, with the QT interval corrected using a linear regression equation with adjustment for relevant covariates (age, ethnicity, sex, and the RR interval). In addition, the RR interval was analyzed using restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles to allow a more flexible and nonlinear relationship between the QT and RR intervals. With this approach, the authors calculated a corrected QT interval ( $QT_{corr}$ ).

With a Cox model approach, each 10-ms increase in  $QT_{corr}$  was associated with a significant ( $p < 0.001$ ) increase in the risk for heart failure, CVD, and stroke during follow-up. Consistent results were observed using the spline regression models, in which the risk of these events progressively increased with increasing  $QT_{corr}$  intervals in a dose-response

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relationship. Similar findings were observed when the  $QT_b$  and  $QT_{\text{Framingham}}$  corrections were used.

The association of small increments of  $QT_{\text{corr}}$  in the normal range with subsequent cardiovascular events in overtly healthy, middle-aged subjects after adjustment for sex and ethnicity provides a new dimension to the cardiovascular risk associated with even small increases in ventricular repolarization. The unique features of this study are that the risk associations were strong and significant with appropriate statistical approaches that enhanced the validity of the findings.

The authors emphasized that their findings in this large study population highlight a strong association of modest QT interval lengthening with an increased risk for subsequent cardiovascular events.

These findings remind me of the “canary in the coal mine,” in which a canary is used to detect early evidence of dangerous carbon monoxide in the mine. The canary analogy is a little more specific because the risk mechanism is known: carbon monoxide is a fatal gas devoid of taste and smell and has been referred to as the silent killer. The presence of carbon monoxide can indicate a mine fire that puts miners at risk of death. Because the canary is more susceptible to the effects of low concentrations of carbon monoxide than the miners, it provides an early warning of a dangerous situation. Likewise, modest QT prolongation, even within the normal range, appears to be an early warning sign for subsequent problems. But what is the mechanism?

It is difficult to imagine that modest QT interval prolongation per se could produce heart failure, CVD,

and stroke. Thus, it is logical to think in terms of a basic mechanism that increases the risk for these events and modestly lengthens the QT interval. The investigators focused on the role of elevated sympathetic tone in adversely affecting the QT interval and increasing the propensity for CVD. This is a reasonable assumption in view of the very significant association of the frequency of baseline hypertension, use of antihypertensive medications, and increasing levels of blood pressure in the baseline characteristics of the study population with increasing length of the  $QT_{\text{corr}}$  as shown in Table 1 in the Beinart paper (11). Thus, the  $QT_{\text{corr}}$  interval may be the equivalent of the canary in the coal mine because it appears to be a risk marker for subsequent serious cardiovascular events.

Does modest prolongation of the  $QT_{\text{corr}}$  interval on an ECG in healthy adults have any clinical relevance for patient care? Subjects with  $QT_c$  intervals in the upper range of normal should be more carefully screened for subclinical CVD, and especially for hypertension. In such patients with modest QT prolongation and hypertension, one might consider using beta-blocker therapy in view of the benefit of beta-blockers in long QT syndrome (12), but this is only one of many considerations requiring further investigation.

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