Editorial Comment

Bradycardia-Dependent Long QT Syndrome, Sudden Death and Late Potentials*

BORYS SURAWICZ, MD, FACC
Indianapolis, Indiana

The report by Tobé et al. (1) in this issue of the Journal about late potentials in patients with familial long QT syndrome offers a suggestion that the signal-averaged electrocardiogram (ECG) may be a useful diagnostic tool in the detection and risk stratification of patients with QT prolongation. The association between long QT syndrome and late potentials, a marker of structural substrate for reentrant ventricular tachyarrhythmias, is not as far fetched as it may seem. Although in several autopsy studies the mycardium of patients with congenital long QT syndrome was normal both grossly and microscopically, there are reports of neural degeneration and fibrosis within the conduction system that could explain the late potentials. But before pursuing further speculations along these lines it is necessary to take a closer look at the family reported on by Tobé et al. (1), the sudden death, the QT intervals and the signal-averaged ECG.

The reported family. Of 112 family members, 15 reportedly "died suddenly at young age during sleep." Figure 7 of the article (1) depicts only 8 of these persons, including 1 member who died at the age of 54 and another at the age of 70 years. Informed consent for examination was obtained in only 28 of the 97 presumably living consanguineous family members. Of these, two required pacemaker implantation for sinus arrhythmias and in one subject the QRS duration exceeded 120 ms. Table 2 (1) shows that among the 22 persons in the study group, 3 had a QRS duration of 110 ms, and 1 a QRS duration of 120 ms. It appears therefore that QT prolongation was not the sole cardiac abnormality in about 25% of the examined family members and that not all deaths in the family occurred at a young age.

Sudden death. A long QT interval with an abnormal T wave was recorded before death in one of the victims. No information about the ECG of the other 14 subjects who died suddenly is available, and no sudden death occurred during the follow-up of the studied cohort. Thus, except for one patient, sufficient information linking death with a long QT interval is not available.

QT lengthening. The reported QT lengthening in the nine subjects listed in Table 2 is not impressive at heart rates of 60 to 86/min. After correction for QRS duration >90 ms, the longest corrected QT (QTc) interval is only 463 ms in women and 479 ms in men. In the six subjects with late potentials the QTc interval corrected for QRS duration ranged from 430 to 453 ms. The three longest QTc values were recorded in the three oldest men, and no assurance is given that coronary artery disease and left ventricular hypertrophy were ruled out in these subjects.

Relation between QT and RR intervals. Figure 5 of Tobé et al. (1) explains that the QT interval (and presumably the QTc interval based on the Bazett formula) was prolonged only at slow heart rates. The use of the Lepeschkin oval (2), which incorporates most of the formulas used for QTc derivations, has enabled the authors to demonstrate the long cycle-dependent QT and QTc lengthening in several family members. The Lepeschkin oval defines the normal QT distribution within a wide range of RR intervals derived from 5,000 published QT values and 1,100 personal cases (2). It appears justifiable to refer to this material for identifying normal QTc values in persons without heart disease and with normal QRS duration. However, it is not known whether the oval is equally useful for defining the relation between the QT and RR intervals in persons with an abnormal ECG. Unfortunately, there are not many studies of this type. The shift of the QT interval toward longer values at long RR intervals found in the study of Tobé et al. (1) has its counterpart in the behavior of ventricular action potentials after application of potassium channel blocking drugs such as sotalol (3). A similar trend was found by Ahnve (4) in some patients with myocardial infarction whose QT values were outside (above) the oval at slower heart rates. Although patients with the brachycardia-dependent QT lengthening in the study of Tobé et al. (1) had no history of myocardial infarction and were not treated with antiarrhythmic drugs, the absence of information about the QT-RR relation at long cycles in other types of heart disease makes it uncertain whether the long cycle-dependent QT lengthening found in the study of Tobé et al. (1) is a specific marker of a familial long QT syndrome.

Abnormal signal-averaged electrocardiogram. Table 2 shows that the abnormalities were largely minor and to some extent related to longer QRS values. In four of six subjects with an abnormal signal-averaged ECG, the QRS duration of ≥110 ms identifies an intraventricular conduction disturbance. It has been shown (5) that in persons with intraventricular conduction disturbances without inducible ventricular tachycardia, the duration of the filtered QRS complex and the terminal QRS complex <40 μV is longer and the terminal QRS voltage is lower than in persons without such disturbances. Increased QRS duration could have contributed (5) to a 20 ms increase in filtered QRS value, a 10 ms increase in

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From the Krannert Institute of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana.

Address for reprints: Borys Surawicz, MD, Krannert Institute of Cardiology, 1111 West Tenth Street, Indianapolis, Indiana 46202-4800.
terminal QRS complex <40 μV, and an approximately 15 μV decrease in terminal QRS voltage. Application of these criteria would exclude Subjects 6, 7 and 8 and thereby reduce the number of persons with abnormal late potentials to 3, resulting in a much weaker statistical significance of the results. Moreover, one can see that the QTc values were not longer in Subjects 4, 5 and 9 with late potentials than in subjects who had a long QTc interval but no late potentials.

**Conclusions.** The purpose of such critical data dissection is not to undermine the substance of the study but to instill a measure of caution in interpreting the reported associations. It needs to be acknowledged that long cycle-dependent QT lengthening was present in several members of a large family with a high incidence of sudden and unexpected death during sleep. This nocturnal timing of sudden death differs from the circumstances of sudden death in patients with Jervell-Lange Nielsen and Ward-Romano familial long QT syndromes in whom sudden death is precipitated by exertion, emotional upset and increased sympathetic stimulation (6). Thus, this may indeed be a different type of congenital long QT syndrome.

The study of Tobé et al. (1) also points out the desirability of obtaining more data about the QT-RR relation within a wide range of RR intervals in patients with various types of heart disease with and without QT lengthening. Finally, the relation between long QT syndrome, various conduction disturbances and late potentials will require further scrutiny. The reported association, even if poorly understood and not perfectly documented, remains both provocative and stimulating, demonstrating that astute clinical observations can still be made in an era of emphasis on high technology and massive collaborative trials.

**References**