Beat-to-beat QT variability and cardiac autonomic regulation

Marek Malik
Division of Cardiac and Vascular Sciences, St. George’s, University of London and St. Paul’s Cardiac Electrophysiology, London, United Kingdom

MODERN ELECTROCARDIOGRAPHIC (ECG) equipment allows easy collection of large volumes of digital signals. Their computer processing facilitates a number of ECG measurements that were previously unobtainable. Among such measurements, beat-to-beat QT interval variability has attracted some popularity and has been investigated in a variety of physiological and clinical conditions (3, 9, 11, 15–17, 21). Different numerical quantifiers of the beat-to-beat QT variability have been proposed, but perhaps most frequently the so-called QT variability index (QTVI) has been used. Together with QT/RR variability coherence, QTVI was initially proposed by Berger et al. (3). Since the initial publication, it has been assumed that QTVI is an indirect measure of autonomic regulation of cardiac ventricular electrophysiology. The well-established capabilities of investigation of cardiac autonomic regulation by heart rate variability are restricted to the autonomic influence on sinus nodal periodicity (4, 5). Thus the possibility of assessing the autonomic influence at the ventricular level has an obvious appeal. Ventricular abnormalities rather than anomalies of sinus periodicity are responsible for ventricular arrhythmias. Also, diagnosis of the early stages of impaired ventricular regulation might help in identifying hearts at risk of failure. Thus any test, and in particular an easily applicable noninvasive test, assessing ventricular autonomic regulation would cover presently unmet diagnostic needs.

Unfortunately, the hypothesis that the QTVI is an indirect measure of ventricular autonomic regulation has never been tested directly. It is therefore pleasing that Baumert et al. (2) report in the American Journal of Physiology-Heart and Circulatory Physiology on a direct investigation of the relationship between QT beat-to-beat variability and cardiac norepinephrine spillover in a group of patients in whom dynamicity in the cardiac autonomic regulation might be expected. It is disappointing that Baumert et al. were unable to find any relationship between norepinephrine spillover, i.e., the direct “gold standard” measure of cardiac sympathetic activity, and the beat-to-beat QT variability. As usual in such circumstances, a variety of questions might be asked about fine details of the study by Baumert et al. Still, despite the limitations listed in the article, their experimental settings appear credible and the conclusions valid. Hence, the expectations that we might have had for indirect assessment of ventricular autonomic regulation by beat-to-beat QT variability now appear to be on a less firmly established basis.

Assuming that the findings by Baumert et al. will be independently confirmed, it is appropriate to ask what is wrong with the QTVI. Well, several facets of the concept of QTVI (and likewise of QT/RR coherence) are potentially problematic. First, both QTVI and QT/RR coherence relate QT interval measurements to simultaneously assessed R-R interval durations. This neglects the effects of QT/RR hysteresis (7, 12) and introduces clear inaccuracy. While the QT interval duration is dependent on heart rate, the full heart rate history of up to several minutes influences the QT interval duration (18). In the presence of respiratory arrhythmia and other fast sinus nodal modulations, heart rate history is only poorly represented by a single R-R interval (and the same applies to frequency variations). Indeed, it has been shown repeatedly that during respiratory arrhythmia the QT interval remains constant (6).

Second, the exact duration of QT interval in any selected ECG lead is not a particularly consistent measure of the overall duration of ventricular repolarization (14). Each ECG lead
represents a certain projection of the vectorcardiographic T-wave loop (10) [as well as tiny non-dipolar T-wave residua (13)]. This projection depends on the orientation of the T-wave loop in relation to the given ECG lead, which is in turn influenced by the cardiac electrical axis. Since the axis is not absolutely constant because of the chest movements due to respiration and other physiological processes, a variability is introduced into the serial QT measurements that has nothing to do with ventricular autonomic regulation.

Moreover, the beat-to-beat QT interval variability is usually assessed by the template stretching algorithm as proposed by Berger et al. (3). While this algorithm is clearly more systematic than any attempt of visual classification and manual measurements, it is sensitive to noise. Even in the best possible circumstances, clinical ECGs are always polluted by some noise, and once we are interested in the tiny millisecond variability of QT duration, even low-level noise becomes a very serious problem and the necessary signal-to-noise ratio is possibly unachievable. These are the likely reasons for the different extent of QT variability seen in different ECG leads. Variability patterns are lead specific, with unimpressive interlead coherence (Fig. 1).

These methodological problems appear valid despite some physiological and clinical studies of QT variability reaching plausible statistical significance. For instance (considering just noise influence) ECG noise is substantially greater in standing compared with the supine position. It is thus not surprising that greater variability is found in standing subjects (21). Although sympathetic cardiac modulations are also increased in standing, the increased QT variability may have little to do with them. Similarly, in clinical outcome studies, the quality of an ECG recording appears to be a risk factor in its own right (without any formal study, however). Hence, even the risk prediction based on QT variability (16) might be influenced by technological artifacts.

These methodological problems might also have influenced the study by Baumert et al. Despite their findings, it is still possible that there is a direct correlate between autonomic ventricular regulation and beat-to-beat QT variability, which needs to be assessed with much greater and so far technically unachievable precision. Unfortunately, if this is the case, there is little practical value in a test that cannot be successful if performed under commonly feasible conditions.

Having said all this, it is clearly too early to dismiss the notion of beat-to-beat QT variability entirely. Nevertheless, the previous experiences with the concept of the so-called QT dispersion should not be forgotten. That concept also initially appeared to be fully plausible and was very popular while being later found merely a methodological absurdity (13, 19). Thus, before further applications of beat-to-beat QT variability are attempted, the credibility of the technology needs to be established. Methodology should be standardized. Reproducibility and stability studies are needed (8). Reproducible normality limits should be found, if they truly exist. Likewise, reproducible sensitivity and specificity values should be verified for any proposed diagnostic and risk prediction purposes. Visibly variable T-wave patterns are known in cases of both congenital and acquired (e.g., drug induced) long QT syndrome. Even in those cases, however, the morphological variability of the T-wave patterns is visibly larger than that of the overall QT duration. Thus, even if the QT beat-to-beat variability proves to be just misconception of the QT dispersion type, it is still possible that the surface ECG contains information on autonomic ventricular regulation. Instead of investigating QT interval duration, the beat-to-beat variability of T-wave morphological descriptors might be the suitable way forward. The assessment of some of these descriptors is much less noise dependent than the QT interval duration (1). Selected morphological indexes are also less heart rate dependent than the QT interval duration (20), which might help to avoid the problems of heart rate and hysteresis correction. Morphologies of the T-wave loop do not suffer from the ECG lead dependence, and many were found to be more reproducible than the QT interval duration (1).

Thus the findings by Baumert et al. might have brought us back to square one. Nevertheless, we clearly should not stay there. The prize of finding an ECG-based assessment of autonomic ventricular regulation is too high to be missed.

REFERENCES


