Repolarization of the ventricular myocardium is a complex process that varies in duration from site to site and from beat to beat. The mechanisms that govern spatial heterogeneity in ventricular repolarization are well studied, and are largely related to variation in ion channel function and density from one myocardial region to another (1). The mechanisms responsible for temporal fluctuations in repolarization, however, are poorly understood.

Several clinical studies over the past decade have examined beat-to-beat variability in QT interval of the surface electrocardiogram (ECG) as a means for quantifying temporal repolarization lability. While measuring subtle variation in QT interval duration is technically challenging, new methodology (2) has enabled investigators to study the effect of disease states on ventricular repolarization variability, and the prognostic value of the QT interval variability measure. QT variability has been shown to be elevated in congestive heart failure (CHF) (2,3), ischemia (4), some types of hypertrophic cardiomyopathy (5,6) and long QT syndrome (7), and panic disorder (8). Increased QT variability was found to predict appropriate implantable cardioverter-defibrillator shocks in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II) study (9), as well as total mortality and sudden death in post-myocardial infarction patients without implantable cardioverter-defibrillators (10).

Only recently, however, have we seen efforts to establish which physiologic mechanisms give rise to or alter QT variability. Just as heart rate variability arises primarily from autonomic influence on the sinus node (11), it is tempting to think QT interval variability reflects autonomic modulation of ventricular electrical activity. Since QT variability is elevated in CHF (2), and sympathetic tone is also elevated in heart failure (12,13), one might hypothesize that QT variability is a measure of cardiac sympathetic tone. Indeed, QT variability has been shown to increase in healthy subjects with both postural change from supine to standing, and infusion of isoproterenol (14), interventions that clearly increase beta-adrenergic stimulation. However, Baumert et al. (15) recently found that QT variability measures did not correlate with norepinephrine levels in blood sampled from the coronary sinus in 17 subjects with depression and panic disorder, challenging the notion that beat-to-beat QT variability measurement provides an assessment of cardiac autonomic activity (16).

Further insight on this puzzle comes in an interesting report by Piccirillo et al. (17) in this issue of the Journal. These investigators analyzed data from 6 chronically instrumented dogs before and after induction of CHF by rapid pacing. Although the study is based on a rather small number of animals, it is elegant in its use of implanted data transmitters monitoring integrated left stellate ganglion nervous activity (iSGNA) and integrated vagus nerve activity (iVNA) as direct measures of cardiac sympathetic and parasympathetic tone, respectively. Beat-to-beat ventricular repolarization variability was quantified by the QT variability index (QTVI), and heart-rate-to-repolarization coupling was assessed by QT-RR coherence, metrics previously described and validated (2), based on the surface ECG.

The main findings of the study were that at baseline QTVI correlated inversely with iVNA but not at all with iSGNA, while after CHF induction, QTVI correlated directly with iSGNA but not at all with iVNA. To interpret these results, it is important to understand the definition of QTVI and recognize the component variables involved in the definition. QTVI is defined as: \(\log_{10} \left(\frac{(QT_v / QT_{m,v}^2)}{(RR_v / RR_{m,v}^2)}\right)\), where QT_v is the QT interval variance, QT_m is the mean QT interval, RR_v is the RR interval variance, and RR_m is the mean RR interval. The QTVI thus quantifies the magnitude of QT interval fluctuations, normalized by both the mean QT duration and the magnitude of heart rate fluctuations. Although there is rationale behind the use of such normalization techniques, it is important to realize that a rise in QTVI could be due to either an increase in QT variance or a fall in heart rate variance. In the present
study, the baseline dependence of QTVI on iVNA was due to vagal modulation of heart rate, since QTv was uncorrelated with both iVNA and iSGNA. However, during CHF, QTVI was directly related to sympathetic activity, evidenced by a strong correlation between QTv and iSGNA. RRv was uncorrelated with both iVNA and iSGNA during CHF.

These findings are reminiscent of early work on the mechanistic underpinnings of heart rate variability. In a landmark study, Akselrod et al. (18) showed that heart rate variability reflects vagal modulation when vagal activity is high, and mirrors fluctuations in sympathetic activity when the latter is high. Intuitively, it makes sense that when multiple factors influence a physiologic variable, the correlation between any one input and the output variable is highest when the strength of that input rises above all others, and fades when that input becomes overwhelmed by the others. The results of the Piccirillo et al. study (17) are therefore consistent with a framework in which sympathetic tone is one of several input signals that influence beat-to-beat fluctuations in ventricular repolarization, and becomes the dominant input during CHF. Other mechanisms affecting QT interval variability, competing or conspiring with sympathetic activity, include electrical restitution, which couples the action potential duration of one beat to the diastolic interval of prior beats, and membrane instability leading to early afterdepolarizations particularly in the setting of prolonged repolarization.

The new study results shed light on the previous work of Baumert et al. (15), who found no relationship between QTVI and cardiac norepinephrine levels, as mentioned in the preceding text. Since the subjects studied by Baumert et al. (15) had no history of CHF or heart disease, one would expect QT interval variability to behave similarly in these individuals as in the baseline state of the canine model studied by Piccirillo et al. (17), as indeed it did.

A surprising finding in the present study was a rather high coherence between QT and RR interval fluctuations both at baseline and during CHF in this animal model. Several clinical studies have reported substantially lower coherence values in both normal subjects and patients with CHF (2,19). It remains unclear whether this disparity relates to a species difference in RR-QT coupling or the elimination of extraneous noise in the ECG in the animal preparation, since noise reduces the measured coherence when present.

With the results of this report, we are a step closer to understanding the genesis of beat-to-beat fluctuations in ventricular repolarization. QT interval variability is not a direct measure of ventricular sympathetic activity, but is related to sympathetic tone as the latter becomes elevated in certain pathophysiologic states. This likely explains the progressive rise in QTVI with worsening functional status observed in patients with CHF (2), and may account for the enhanced arrhythmia risk associated with elevated QTVI (9,10). The insights gained from this work should stimulate further investigation of the mechanisms that underlie this recently recognized phenomenon and guide the development of clinical trials to further assess the clinical utility of QT interval variability measurement for arrhythmia prediction and risk stratification.

Reprint requests and correspondence: Dr. Ronald D. Berger, 600 North Wolfe Street, Carnegie 592, Baltimore, Maryland 21287. E-mail: rberger@jhmi.edu.

REFERENCES


Key Words: repolarization • sympathetic activity • electrocardiogram.