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Relationship Between Repolarization Heterogeneity and Abnormal Myocardial Mechanics

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To the editor

Repolarization heterogeneity, the process of regional myocardial dispersion of action potential duration (APD) identified with QT-prolongation, has been shown to contribute significantly to proarrhythmia.¹ The heterogeneous endocardial to epicardial distribution of action potential duration (APD)² accompanied by transmural heterogeneity in calcium handling³ may partially explain the association between both a prolonged QT interval⁴ as well as a prolonged peak-to-end of T-wave interval (TpTe) and diastolic dysfunction.⁵ Abnormal myocardial mechanics have also been previously described among individuals with inherited long QT syndromes (LQTS) without structural heart disease.^{6–8} We postulated that heterogeneity of repolarization may contribute to or reflect abnormal myocardial mechanics due to heterogeneous myocardial contraction duration. Echocardiographic strain imaging can be used to demonstrate this phenomenon. We therefore hypothesized that longer TpTe is associated with increased heterogeneity of contraction duration (as measured by standard deviation [SD] of time to peak strain [tPks] across myocardial segments).

We performed a cross-sectional study of the association between TpTe interval and strain imaging markers of mechanical repolarization heterogeneity in 82 patients referred for echocardiography from June 30, 2008 to August 21, 2008 at the Bluhm Cardiovascular Institute of Northwestern Memorial Hospital (Chicago, Illinois). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, was approved by the institutional review board at Northwestern University Feinberg School of Medicine, and all study participants provided written informed consent.

We collected and analyzed demographics, comorbidities, medications, vital signs, body-mass index, and laboratory data (including serum potassium). All subjects underwent baseline 12-lead ECG recording (Marquette MAC 5000 Resting ECG System; GE Healthcare; Boston, MA) at the time of baseline echocardiogram. ECGs were analyzed by a

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DISCLOSURES

The authors have no conflicts of interest to disclose.

single trained reader blinded to the echocardiographic findings. There are no universally agreed-upon standards for measuring TpTe;⁹ therefore, we employed a modified tangent-threshold method suited for testing our hypothesis as previously described (Figure 1).⁵ In our laboratory there is good agreement in TpTe measurement among blinded investigators, as reported previously.⁵ All subjects underwent a comprehensive echocardiographic examination using a Sonos 7500 or iE33 system (Philips Medical Systems, Andover, MA). Echocardiograms were reviewed by a single trained reader blinded to the ECG and clinical data. Digitized cine loops were analyzed by 2 trained readers using 2D wall motion tracking software [2D Cardiac Performance Analysis (CPA), TomTec v4.5, Unterschleissheim, Germany]. For longitudinal, circumferential, and radial components of strain, the following measurements were recorded: regional and global strain values, time to peak strain (tPks, demonstrated in Figure 1), and the standard deviation of time to peak strain (SD-tPks). A validation of the speckle-tracking techniques employed in our laboratory have been reported elsewhere.¹⁰

We performed unadjusted linear regression analyses to determine whether TpTe (independent variable) was associated with strain, tPks, and SD-tPks (dependent variables) for each strain-imaging component (longitudinal, circumferential, and radial). We used a parsimonious model to avoid over-adjustment. For the above described strain imaging covariates noted to have a significant association with TpTe, we adjusted for age, sex, heart rate, QTc, and left ventricular mass index because these covariates had known confounding potential based on our previous study investigating the relationship between TpTe and diastolic dysfunction.⁵ All statistical analyses were performed using Stata v.10.1 (StataCorp, College Station, TX).

The mean±SD age was 52±14 years, and 44% were female. TpTe was 76±17 ms and ejection fraction was preserved (59±4%). QRS and QTc were 91±14 ms and 421±26 ms, respectively. Increased TpTe duration was associated with increased radial tPks (β -coefficient per 1-SD increase in TpTe = 23.8, 95% CI=10.2-37.4 ms; P=0.001) and increased heterogeneity of radial tPks as measured by SD-tPks (β -coefficient = 21.5, 95% CI=8.9-34.0 ms; P=0.001) on unadjusted analyses (Figure 2). The association between TpTe and radial contraction duration heterogeneity remained significant (β -coefficient = 17.8, 95% CI=1.3-34.5, P = 0.036) after controlling for age, sex, heart rate, QTc, and left ventricular mass index. The same held true for radial tPks (adjusted P = 0.041).

In a sample of 82 outpatients referred for echocardiography without known long QT syndrome, we found a significant linear association between TpTe and heterogeneity in contraction duration (SD-tPks) in the radial direction, as measured by strain imaging. This association persisted after adjustment for several important potential confounders—including age, sex, heart rate, QTc interval, and left ventricular mass. These findings are novel and relevant for at least two reasons. First, an observed independent relationship between TpTe (measuring electrical repolarization heterogeneity) and radial SD-tPks (measuring contraction duration heterogeneity) further supports the hypothesis that repolarization heterogeneity is electromechanically coupled, whereby heterogeneous contraction duration may contribute to both systolic and diastolic dysfunction. Second, the identification of subclinical markers of electromechanically coupled repolarization heterogeneity has not previously been demonstrated in patients without QT disorders and without significant cardiomyopathy.

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Figure 1. Examples of the relation between electrocardiographic T-peak to T-end interval and contraction duration heterogeneity

Subject A demonstrates a short TpTe interval of 55 ms while subject B demonstrates a prolonged TpTe interval of 110 ms. As shown for both ECG representations, the end of the T wave (a solid line) is defined as the intersection of the isoelectric line (dashed line) with the tangent to the terminal downslope of the T wave (dashed line). The images on the right represent subject A and subject B strain (%) and tPkS (ms, x-axis) for both the radial (top) and the circumferential (bottom) components in the mid-papillary parasternal short axis view. Each colored line represents one of the six myocardial segments and the colored dot on each line represents the peak strain and tPkS as follows: yellow = inferoseptal, magenta = anteroseptal, green = anterior, gray = anterolateral, light blue = inferolateral, dark blue = inferior. For both subjects, contraction duration heterogeneity is visually represented by the strain line configuration and also measured by SD-tPkS (standard deviation of time to peak strain).

Figure 2. Electrocardiographic T-peak to T-end interval and radial contraction duration heterogeneity

As TpTe interval (ms) increases (organized by tertiles for illustrative purposes), heterogeneity of radial component contraction duration also increases (as measured by the standard deviation of time to peak radial strain).