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Strong coherence between heart rate variability and intracardiac repolarization lability during biventricular pacing is associated with reverse electrical remodeling of the native conduction and improved outcome☆,☆☆

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Abstract

Background: Reverse electrical remodeling (RER) of the native conduction with cardiac resynchronization therapy (CRT) is associated with decreased mortality and antiarrhythmic effect of CRT. Still, mechanisms of RER are largely unknown. In this study, we explored repolarization lability during biventricular pacing.

Methods and Results: The width of native QRS was measured in lead II electrocardiogram before and at least 6 months after implantation of Cardiac Resynchronization Therapy Defibrillator (CRT-D) devices (Medtronic, Inc [Minneapolis, MN, USA] and Boston Scientific Corporate [Natick, MA, USA]) in 69 patients (mean age, 66.3 ± 13.9 years; 39 men [83%]) with either bundle-branch block (44 patients [64%]) or nonspecific intraventricular conduction delay (25 patients [36%]) and New York Heart Association class III and IV heart failure. Narrowing of the native QRS duration for at least 10 milliseconds was considered a marker of RER. Beat-to-beat QT variability and coherence was measured on surface electrocardiogram and intracardiac near-field electrogram during biventricular pacing. Reverse electrical remodeling was observed in 22 patients (32%) in whom coherence between heart rate variability and intracardiac repolarization lability was stronger (0.483 ± 0.243 vs 0.237 ± 0.146, *P* = .018) and normalized intracardiac QT variance was smaller (0.28 ± 0.0031 vs 0.46 ± 0.0048, *P* = .049), as compared with that in patients without RER. During a further 24 ± 13 months of follow-up, 21 patients (33%) died or experienced sustained ventricular tachycardia (VT)/ventricular fibrillation. Low intracardiac coherence (≤0.116) was associated with increased risk of death or sustained VT/VT (hazard ratio, 4.33; 95% confidence interval, 1.51-12.40; *P* = .006).

Conclusion: Strong coherence between heart rate variability and intracardiac repolarization lability during biventricular pacing is associated with RER of the native conduction with CRT. Low coherence is associated with increased risk of VT/ventricular fibrillation or death.

Keywords: CRT; Intracardiac electrograms; QT variability; Electrical remodeling; Cardiac memory

Ventricular conduction delay induces mechanical load heterogeneity and dyssynchronous contraction, which worsens congestive heart failure prognosis.[1,2] Cardiac resynchronization therapy (CRT) improves cardiac structure and function through reverse anatomical and mechanical left ventricular (LV) remodeling[3] in responders. However, at least a third of patients with indication for CRT does not respond to it fully.[4] Understanding the mechanisms of remodeling is crucial for selection of appropriate candidates and further advancement of CRT. Although substantial knowledge has been acquired during the past decade regarding mechanical response to CRT, the mechanisms of reverse electrical remodeling (RER) with CRT are less understood.

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[1] Tereshchenko: HRV-QTV coherence during pacing.

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For many years, electrical remodeling due to cardiac pacing was studied under the term *cardiac memory*. Methodologically, that approach implied a necessity to terminate pacing and restore normal activation to study cardiac memory. Recently, a distinct cardiac memory phenomenon was reliably shown during continuous ventricular pacing,[5] encouraging investigation of cardiac signals during ventricular pacing. Assessment of intracardiac lability of repolarization, although shown to be useful for prediction of ventricular tachyarrhythmias,[6] was not previously explored during ventricular pacing.

We recently showed that RER of the native conduction with the CRT is associated with an antiarrhythmic effect of CRT and lower mortality.[7] Decrease of native QRS duration after at least 6 months of CRT serves as the marker for overall recovery of the arrhythmogenic substrate. In this study, we investigate mechanisms of RER. We hypothesize that high concordance between the heart rate variability and intracardiac repolarization lability during biventricular pacing is associated with successful RER on CRT.

Methods

The study protocol was approved by the Johns Hopkins University and the Washington University Human Studies Committees, and all patients gave written, informed consent before entering the study.

Study population

The study population was previously described.[6,7] Briefly, adult patients with structural heart disease were eligible for the study if they had a Medtronic (Minneapolis, MN, USA) or Boston Scientific Corporate (Natick, MA, USA) Cardiac Resynchronization Therapy Defibrillator (CRT-D) device implanted for primary or secondary prevention of sudden cardiac death and standard indications for CRT. Exclusion criteria were pregnancy, inherited channelopathies, and concomitant conditions other than cardiac diseases that were associated with a high likelihood of death during 1 year after enrollment. Pacemaker-dependent patients, or those who had less than 85% ventricular pacing during at least 6 months after device implantation, were excluded from this analysis. Brady pacing mode was programmed DDD; lower rate, 60 ppm; and paced and sensed atrio-ventricular (AV) delay, 100 milliseconds. Rate-adaptive AV start rate was 80 beats per minute.

Intracardiac electrograms and surface electrocardiogram recording

Baseline 12-lead surface electrocardiogram (ECG) was recorded within 1 week before CRT-D implantation. At the 6-month office visit, lead II ECG was recorded simultaneously with atrial and near-field (NF) right ventricular intracardiac electrograms (EGMs) at rest via a programmer using the NI USB-9215A portable data acquisition system with customized LabVIEW (National Instruments, Austin, TX) software application (1000 Hz sampling frequency with 0.3 mV per bit amplitude resolution) during at least 5 minutes.

Assessment of the RER

The impact of CRT on native conduction was evaluated after at least 6 months of CRT as previously described.[7] Briefly, biventricular pacing was inhibited for 3 to 10 seconds to record native QRS in underlying sinus beats. Narrowing of the native QRS duration for at least 10 milliseconds was considered a marker of RER. Patients were categorized into 2 groups: those with and those without RER of native conduction after at least 6 months of CRT. QT interval duration was measured in the lead II ECG during sinus rhythm before and after at least 6 months of CRT. QT interval was corrected for heart rate by using the Bazett formula.[8]

Repolarization lability analysis during biventricular pacing

Temporal beat-to-beat QT variability during sinus rhythm on biventricular pacing was measured as previously described on surface ECG[9] and intracardiac NF right ventricular EGM[6] after at least 6 months of CRT. Custom software was written in MATLAB (MathWorks, Inc, Natick, MA). Recordings with more than 15% of ectopic or noise-distorted beats were excluded.

The heart rate mean (HRv) and variance (HRv) and QT interval mean (QTm) and variance (QTv) were calculated from the respective 3-minute time epochs. A normalized QT variability index (QTVI) was derived according to equation

$$\mathrm{QTVI} = \log_{10}\left[\left(\mathrm{QTv}/\mathrm{QTm}^2\right) / \left(\mathrm{HRv}/\mathrm{HRm}^2\right)\right]$$

In addition, QTv was normalized for the mean QT (QTVN) as follows:

$$\mathrm{QTVN} = \mathrm{QTv}/\mathrm{QTm}^2$$

For assessment of coherence between the heart rate variability and QT variability, spectral analysis of the RR′ and QT intervals was performed, and a cross spectrum was generated using the Blackman-Tukey method.[10] Coherence was calculated according to the equation[9]

$$\gamma(\mathrm{f}) = |\mathrm{P_{xy}}(\mathrm{f})|^2 / \left[\mathrm{P_{xx}}(\mathrm{f}) \times \mathrm{P_{yy}}(\mathrm{f})\right],$$

where γ(f) indicates coherence; *f*, frequency; Pxx(*f*), heart rate spectrum; Pyy(*f*), QT interval spectrum; and Pxy(*f*), cross spectrum. The mean coherence was obtained by averaging γ(f) over the 0 to 0.2 Hz frequency band.

End points

After assessment of RER, patients were followed up for at least 12 months as previously described.[7] Composite of all-cause death, cardiac transplantation, and sustained ventricular tachycardia (VT)/ventricular fibrillation (VF) with appropriate implantable cardioverter-defibrillator (ICD) therapies (ICD shock or antitachycharida pacing), whichever came first, occurring after the RER assessment served as the end point for survival analysis.

Statistical analysis

Results are presented as mean ± SD for normally distributed variables and as median and interquartile range (IQR) for nonnormally distributed variables. Continuous variables were compared using the independent samples *t* test if normally distributed and the Wilcoxon rank sum test if skewed. Kaplan-Meier survival analysis was performed to compare survival