QRS fusion complex analysis using wave interference to predict reverse remodeling during cardiac resynchronization therapy

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BACKGROUND Biventricular (BV) electrical wavefront fusion can induce improvement in left ventricular (LV) size and function during cardiac resynchronization therapy (CRT). Changes in BV wave propagation sequence and duration register in the QRS complex on the standard electrocardiogram. We developed a wave interference method for the characterization of BV fusion to predict LV reverse remodeling.

OBJECTIVE To develop a simple electrocardiographic method for predicting reverse remodeling during CRT.

METHODS QRS complexes during left bundle branch block (LBBB) and CRT were analyzed in 375 patients with ejection fraction $\leq$35% and New York Heart Association class III-IV (Leiden study: n = 226) as well as in patients with ejection fraction $\leq$40% and New York Heart Association class I-II (REVERSE trial: n = 149) for predictors of $\geq$10% reduction in left ventricular end-systolic volume at 6 months. CRT-induced changes in ventricular activation (QRS fusion contour), electrical asynchrony (QRS difference = BV-paced QRS − LBBB QRS, in milliseconds), and LBBB substrate (LV activation time and QRS score for LV scar) were quantified.

RESULTS Multivariable predictors of reverse remodeling were as follows: (1) either of 2 BV fusion patterns: QRS normalization in leads V_1 and V_2 (n = 66 [18%]; odds ratio [OR] 3.71; 95% confidence interval [CI] 1.26–10.94) or a new or an increased R wave in leads V_1-V_2 (n = 267 [71%]; OR 1.55; 95% CI 0.65–3.65); (2) QRS difference ≤ -25 ms (OR 2.35; 95% CI 1.12–4.91); and (3) good substrate (low to moderate QRS score and LV activation time $\geq$110 ms; OR 2.94; 95% CI 1.68–5.14). Remodeling rates were 40% for poor substrate and persistent LBBB QRS complex (absent BV fusion; QRS type 3: n = 42 [11%]) and 97% for the best BV QRS fusion pattern and greater reduction in electrical asynchrony (larger QRS difference).

CONCLUSION Easily determined QRS complex attributes before and after CRT predict LV reverse remodeling.

KEYWORDS Heart failure; Bundle branch block; Cardiac resynchronization therapy; Pacing; Waves

ABBREVIATIONS **BV** = biventricular; **CRT** = cardiac resynchronization therapy; **EAS** = electrical asynchrony; **ECG** = electrocardiogram/electrocardiographic; **HF** = heart failure; **LBBB** = left bundle branch block; **LV** = left ventricle/ventricular; **LVAT** = left ventricular activation time; **$LVAT_{max}$** = longest left ventricular activation time; **LVEF** = left ventricular ejection fraction; **LVESV** = left ventricular end-systolic volume; **QRS_{BV}** = biventricular-paced QRS; **QRSdiff** = QRS difference; **QRS_{LBBB}** = LBBB QRS duration (ms); **RV** = right ventricle/ventricular; **VAT** = ventricular activation time

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Introduction

Biventricular (BV) electrical wavefront fusion restores the normal electromechanical coupling of the heart with left bundle branch block (LBBB),[1,2] which improves pump function and induces left ventricular (LV) reverse remodeling. Ventricular activation changes during cardiac resynchronization therapy (CRT) are registered in the QRS complex.[3–5] We developed a wave interference method for QRS fusion complex analysis to predict reverse remodeling during CRT.

Methods

Overview and prior work

Exploratory work using QRS complex analysis established that one expression of BV fusion (new or increasing R wave in leads V_1-V_2) predicted increased probability of reverse remodeling after adjusting for substrate conditions.[3] The R-wave change was used as a proof-of-principle test case because it is an easily recognizable and quantifiable BV

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activation sequence change opposing LBBB electrical wave forces.[4,5] Reverse remodeling was chosen[3] because (1) experimental models link LV electromechanics and remodeling[1,2] and (2) it is nonsubjective and quantifiable and predicts better survival.[6]

Synchronous ventricular electrical activation generates a large number of opposing wavefronts, resulting in the normally narrow QRS complex owing to wave *cancellation* (destructive interference, wave forces substract). Asynchronous electrical activation during LBBB generates a large number of nonopposing wavefronts, resulting in a wide QRS complex owing to wave *summation* (constructive interference, wave forces add). Fusion during BV pacing restores synchronous electrical activation as a product of interference between 2 opposed, canceling wavefronts. A wave interference method was used to identify 3 QRS fusion types and a quantitative change measure for ventricular activation time (VAT) to estimate the effect of BV pacing on electrical asynchrony (EAS; see the Online Supplement).

This QRS fusion complex method was elaborated in a 46% larger, clinically diverse data set, including consideration of LV stimulation site (coronary vein, site within vein).

Study sample

QRS complexes during LBBB and CRT were analyzed in 375 consecutive patients with EF $\leq$35% and New York Heart Association class III-IV (Leiden study: n = 248)[3] as well as in patients with EF $\leq$40%, LV end-diastolic diameter $\geq$55 mm, and New York Heart Association class I-II (REVERSE trial: n = 149).[7] LBBB was QRS_{LBBB} $\geq$120 ms; delayed intrinsicoid deflection $\geq$50 ms and notched or broad slurred R waves in leads I, aVL,V_5, and V_6; rS or QS waves in leads V_1-V_2; ST-T-wave opposite major QRS vector.[3]

CRT programming

The atrioventricular delay was optimized by using echocardiography. The median value was 100 ms (range 100–120 ms); as proportion of PR interval, ms 57.0% (range, 49.0%–66.7%), which is consistent with experimental studies[8] and best clinical outcomes.[9] Simultaneous BV pacing was applied in 90.7% and sequential in 9.3%.

Echocardiography

Echocardiograms were obtained at baseline and 6 months post-CRT. Left ventricular end-systolic volume (LVESV) was measured by using apical 2- and 4-chamber views; left ventricular ejection fraction (LVEF) was calculated by using the Simpson method.[3]

QRS complex analysis

Standard electrocardiograms (ECGs) were obtained pre- and post-CRT (before hospital discharge). Measurements were made using digital calipers at 200% magnification.[3]

During LBBB

LBBB is characterized by sequential ventricular activation (right ventricle [RV] → LV)[1,10–12] registered as fragmented QRS complexes with RsR′ configuration ("notching"). QRS notching was $\geq$1 notch in the R or S wave in $\geq$2 adjacent anterior, lateral, or inferior leads.[3,13] *RV activation time* (in milliseconds) was defined as QRS onset to first notch in any of the 2 adjacent leads.[3] Left ventricular activation time (LVAT) was defined as QRS_{LBBB} – RV activation time (in milliseconds). For modeling, the longest LVAT ($LVAT_{max}$) recorded in any lead was used.[3] A numeric relationship between QRS_{LBBB} and $LVAT_{max}$ was derived,[3] permitting $LVAT_{max}$ estimation in the absence of notching. The QRS score for LBBB[3,13] quantified LV scar.

During CRT

The experimental models of LBBB demonstrate that the maximum improvement in LV pump function occurs when EAS is minimized by wavefront fusion.[1,11] Amplitudes, duration, directionality, and other aspects of LBBB and BV-paced QRS (QRS_{BV}) component waves (R, S, Q, QS, etc.) were used to quantify activation changes.[3] QRS complex analysis was conducted using leads V_1-V_2 (the most reliable inflection points for LBBB activation reversal)[3–5,14] for modeling purposes. Typical LBBB activation registers dominant negative (anterior → posterior) forces in leads V_1-V_2 (QRS contour: QS, rS, etc). Pacing from lateral/posterolateral LV registers dominant positive forces (posterior → anterior) and the largest opposition to LBBB forces in leads V_1-V_2 (QRS contour: R, Rs, etc).[4,5,14] BV fusion during CRT registers merging of anterior ↔ posterior forces (LBBB QS V_1-V_2 → BV-paced rS, RS, Rs, R, etc).[3,11] In this manner, the QRS contour morphology expresses the spread of BV activation.

The change in VAT to estimate EAS before and after CRT was quantified by QRS difference: QRSdiff (in milliseconds) = QRS_{BV} – QRS_{LBBB}. (−)QRSdiff indicates ↓VAT; neutral QRSdiff indicates no change in VAT; and (+)QRSdiff indicates ↑VAT.

QRS fusion types

Classical electrocardiographic principles of fusion resulting from the interaction between 2 independent electrical wavefronts specify a conformational change in the QRS complex, generating a hybrid possessing recognizable features of the patterns produced by each wavefront. The QRS fusion contour is intermediate in shape and duration between the QRS contours of the independent wavefronts. The exception occurs when the interacting wavefronts, each generating a uniquely abnormal QRS complex, fuse to create a normally narrow complex that bears no resemblance to either of the component complexes owing to wave cancellation.[15]

We identified 3 manifested BV QRS fusion types, numerically ordered by observed frequency (Figure 1). *From the viewpoint of leads V_1-V_2:* (1) QRS type 1: fusion QRS contour showing a conformational hybrid as a new or an