Simple electrophysiological predictor of QRS change induced by cardiac resynchronization therapy: A novel marker of complete left bundle branch block

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BACKGROUND QRS complex shortening by cardiac resynchronization therapy (CRT) has been associated with improved outcomes.

OBJECTIVE We hypothesized that the absence of QRS duration (QRSd) prolongation by right ventricular mid-septal pacing (RVP) may indicate complete left bundle branch block (cLBBB).

METHODS We prospectively collected 12-lead surface electrocardiograms (ECGs) and intracardiac electrograms during CRT implant procedures. Digital recordings were edited and manually measured. The outcome measure was a change in QRSd induced by CRT (delta CRT). Several outcome predictors were investigated: native QRSd, cLBBB (by using Strauss criteria), interval between the onset of the QRS complex and the local left ventricular electrogram (Q-LV), and a newly proposed index defined by the difference between RVP and native QRSd (delta RVP).

RESULTS One hundred thirty-three consecutive patients were included in the study. Delta RVP was 27 ± 25 ms, and delta CRT was −14 ± 28 ms. Delta CRT correlated with native QRSd ($r = -0.65$), with the presence of ECG-based cLBBB ($r = -0.40$), with Q-LV ($r = -0.68$), and with delta RVP ($r = 0.72$) ($P < .00001$ for all correlations). In multivariable analysis, delta CRT was most strongly associated with delta RVP ($P < .00001$), followed by native QRSd and Q-LV, while ECG-based cLBBB became a nonsignificant factor.

CONCLUSION Baseline QRSd, delta RVP, and LV electrical lead position (Q-LV) represent strong independent predictors of ECG response to CRT. The absence of QRSd prolongation by RVP may serve as an alternative and more specific marker of cLBBB. Delta RVP correlates strongly with the CRT effect on QRSd and outperforms the predictive value of ECG-based cLBBB.

KEYWORDS Cardiac resynchronization therapy; Heart failure; Left bundle branch block; Electrocardiography; Outcome predictors

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Introduction

Cardiac resynchronization therapy (CRT) improves heart failure symptoms, exercise capacity, morbidity, and mortality in a symptomatic patient with left ventricular (LV) systolic dysfunction and wide QRS complex.[1–3] Despite its effectiveness as measured in clinical trials by various surrogate and clinical end points, ∼30% of patients have reduced or no benefit from this therapy.[4]

Multiple factors modify the CRT response during the patient selection phase, intraoperatively, and during follow-up.[4] Among them, electrocardiographic (ECG) markers such as baseline QRS width and QRS morphology play a key role in patients' selection and influence CRT outcomes. Secondary analyses of major CRT studies have shown that both QRS width and QRS morphology predict the outcome of CRT recipients. Specifically, QRS duration (QRSd) below 150 ms and QRS morphologies other than left bundle branch block (LBBB) were associated with reduced or no benefit from CRT.[5,6] Since the LBBB morphology on ECG may represent a heterogeneous group of conduction and myocardial abnormalities, Strauss et al[7] proposed criteria to diagnose

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complete LBBB (cLBBB) to improve the selection of CRT candidates and understanding of the underlying LV activation abnormalities. Compared with other conduction abnormalities, cLBBB is associated with better CRT outcomes.[8–10] The interval between the QRS complex onset and the local LV electrogram (Q-LV) is yet another electrophysiological parameter used in LV lead placement optimization and has been shown to improve outcomes in patients treated with CRT.[11,12] However, its predictive value for future echocardiographic CRT response is modest (area under the curve 0.63) and it may be artificially prolonged in areas of scar and/or slow conduction and may not reflect LV lead pacing effects during biventricular pacing.[11,13]

The narrowing of the QRS complex with CRT has been documented since the advent of the therapy as a readily available noninvasive marker of electrical resynchronization.[14] Lack of electrical resynchronization defined as unchanged or prolonged QRS complex with CRT is associated with increased mortality risk during follow-up.[15–17] Patients with LBBB and QRS narrowing with CRT have a lower mortality risk than do those with prolonged QRS complex with the therapy.[18]

We studied the predictive role of baseline QRSd, Q-LV, and presence of cLBBB by using Strauss criteria in QRSd change induced by CRT. We also hypothesized that QRS prolongation by right ventricular (RV) mid-septal pacing (RVP) is associated with a loss of residual left bundle branch (LBB) conduction and that the absence of such prolongation may be a marker of cLBBB and predict more pronounced QRSd shortening by CRT.

Methods

Patients

Consecutive patients undergoing CRT first system implantation were included in the study. Local human research ethics committees approved the study protocol, and all patients signed informed consent. The study complied with the Declaration of Helsinki. The indication for CRT therapy was based on the European Society of Cardiology recommendations for CRT device implantation valid at the time of study initiation: patients with persistent heart failure symptoms despite optimal medical therapy, LV ejection fraction $\leq$35%, and QRSd $\geq$120 ms.[19] We excluded patients with right bundle branch block, absent spontaneous rhythm (atrioventricular block), nonanalyzable ECG and/or intracardiac electrograms, and patients undergoing a system revision or upgrade to minimize bias introduced by previous RV lead implantation not matching our standards or not matching the newly implanted LV lead.

CRT device implantation

CRT device implantation was performed using commercially available CRT devices manufactured by St. Jude Medical, Medtronic, Biotronik, and Boston Scientific using the left subclavian transvenous approach. Both bipolar or quadripolar LV leads were positioned in one of the available posterolateral, lateral, or anterolateral tributaries of the coronary sinus or great cardiac vein. Lead positions were verified using biplane right and left anterior –30° oblique views (Online Supplemental Figure 1). Q-LV was used to optimize the LV lead position as described previously.[11] Whenever the LV lead electrogram was not recorded within the terminal part of the QRS complex (specifically, Q-LV/QRSd ratio $\leq$ 0.7 was considered suboptimal), other available veins and lead positions were explored. RV leads were placed in the RV mid-septal region within the target anatomical area in the proximity of the septomarginal trabecula septal insertion (Online Supplemental Figures 1 and 2). No interventricular delay (VV) and atrioventricular delay (AV) optimization was performed before study measurements.

Data processing

The baseline conduction block pattern was classified as cLBBB when the QRS morphology matched the Strauss criteria.[7] ECG and electrogram recordings (a duration of 20 seconds and a sampling rate of 1000 Hz) were obtained by the electrophysiological system CardioLab (GE Medical Systems Information Technologies, Milwaukee, WI) at the end of the CRT implant procedure during spontaneous rhythm, RV mid-septal, and biventricular pacing. Purpose-made software in the Microsoft Excel environment was used for data processing. Digitized recordings were exported and edited to exclude rhythm and morphological abnormalities and artifacts. After signal-averaging and magnification, intervals of interest were manually measured by electronic calipers with the step of 1 ms. Particularly, we measured QRSd and Q-LV during native conduction and QRSd during RVP and biventricular pacing (Figure 1; Online Supplemental Figure 3).

Statistical analysis

Clinical and electrophysiological characteristics of the total population, as well as subgroups of the dichotomized population according to the selected factors, are presented as mean $\pm$ SD or numbers (percentages) and compared using the t test for independent samples or χ^2 test, as appropriate. A P value of $<.05$ was considered significant. The outcome measure of the study was QRSd shortening induced by CRT (delta CRT), specifically QRSd during biventricular pacing minus native QRSd. We predefined several factors that potentially influence delta CRT as follows: native QRSd, presence of cLBBB, Q-LV, and a newly proposed index defined by the difference between RVP and native QRSd (delta RVP). The anatomical site of the implanted LV lead was also considered. Specifically, the location was categorized in 2 planes as anterolateral-lateral-posterolateral and basal-midventricular-apical. For subsequent analysis, the optimum dichotomies appeared either anterolateral location vs other locations or basal location vs other locations. Associations of individual baseline factors that potentially influence delta CRT were assessed by univariable linear regression. Pearson and Spearman coefficients, as appropriate, were

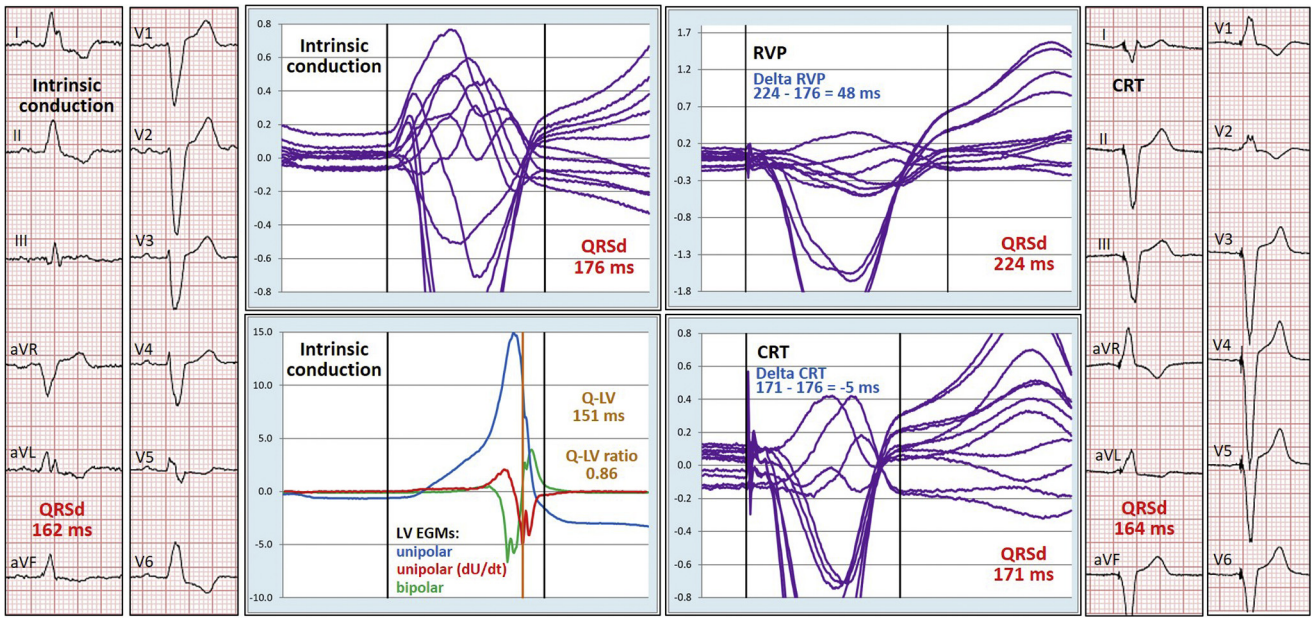

Figure 1 Electrophysiological measurements using signal-averaged surface ECG with superimposed leads and intracardiac electrograms. Note that CRT did not shorten QRSd substantially (−5 ms) even when the baseline QRS complex fulfilled the criteria of cLBBB by using Strauss criteria and the position of the LV lead was reasonable according to the Q-LV ratio (0.86). The absence of the CRT effect agrees with considerable prolongation of native QRSd by right ventricular pacing (+48 ms). cLBBB = complete left bundle branch block; CRT = cardiac resynchronization therapy; delta CRT = QRS duration difference (cardiac resynchronization therapy – native); delta RVP = QRS duration difference (right ventricular pacing – native); dU/dt = first derivative of the unipolar electrogram voltage (its minimum defines the local activation time); ECG = electrocardiography; LV = left ventricular; LV EGM = left ventricular electrogram; Q-LV = interval between the onset of the QRS complex and the local left ventricular electrogram; QRSd = QRS duration; RVP = right ventricular pacing.

used for simple correlation analysis. The predictors from univariable analysis ($P < .2$) were then evaluated in a multivariable model by a forward stepwise selection method with entry ($P < .05$) and removal ($P > .10$) criteria. All analyses were performed using STATISTICA version 12 (StatSoft, GmbH, Hamburg, Germany).

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their interpretation.

Results

A total of 133 consecutive patients were included in the study. The baseline demographic characteristics of the study population are summarized in Table 1. Native QRSd was 180 ± 21 ms, and it fulfilled the diagnostic criteria for cLBBB in 81% of cases. The LV pacing lead was implanted at the position with a Q-LV/QRSd ratio of 0.73 ± 0.11 (median 0.75; interquartile range [IQR] 0.65–0.81).

Pacing-derived effects

Native QRSd prolonged during RVP with a delta RVP of 27 ± 25 ms (median 24 ms; IQR 6–41 ms) and shortened during biventricular pacing with a delta CRT of −14 ± 28 ms (median −19 ms; IQR −30 to −2 ms). Table 2 compares subgroups of patients when the population was dichotomized according to selected predictors of outcome: cLBBB and delta RVP.

Univariable and multivariable associations

Delta CRT correlated with delta RVP ($R = 0.72$), native QRSd ($R = -0.65$), Q-LV ($R = -0.68$), and presence of cLBBB ($R = -0.40$) ($P < .00001$ for all correlations)

Table 1 Baseline characteristics of the study population (N = 133)

Characteristic	Value
Age (y)	67 ± 10
Male sex	96 (72)
Coronary artery disease	59 (44)
NYHA class	2.5 ± 0.6
LV ejection fraction (%)	26 ± 5
LV end-diastolic diameter (mm)	66 ± 8
Native QRS duration (ms)	180 ± 21
cLBBB	108 (81)
LV lead – anterolateral location	45 (34)
LV lead – basal location	39 (29)
RV lead – mid-septal location	113 (85)
RV lead – RVOT location	15 (11)
RV lead – low septal location	5 (4)
Q-LV ratio	0.73 ± 0.11
ICD	110 (83)

Values are presented as mean ± SD or as n (%).

For RV septal pacing anatomy definitions, see the Online Supplement.

cLBBB = complete left bundle branch block; ICD = implantable cardioverter-defibrillator; LV = left ventricular; NYHA = New York Heart Association; Q-LV = interval between the onset of the QRS complex and the local left ventricular electrogram; RV = right ventricular; RVOT = right ventricular outflow tract

Table 2 Baseline and electrophysiological variables in dichotomized population by the median of delta RVP and cLBBB

	Delta RVP			Presence of cLBBB		
	≤23 ms (n = 66)	≥24 ms (n = 67)	*P*	Yes (n = 108)	No (n = 25)	*P*
Age	65 ± 11	67 ± 9	.20	66 ± 10	66 ± 8	.95
Male sex	39 (59)	57 (85)	.001	76 (70)	21 (84)	.15
CAD	21 (32)	37 (55)	.01	42 (39)	16 (64)	.02
NYHA class	2.4 ± 0.7	2.6 ± 0.5	.10	2.5 ± 0.6	2.7 ± 0.6	.09
LV ejection fraction	27 ± 5	26 ± 5	.24	26 ± 5	26 ± 5	.96
LV end-diastolic diameter (mm)	66 ± 8	67 ± 7	.48	66 ± 8	66 ± 8	.77
Native QRSd	190 ± 17	170 ± 20	<.00001	184 ± 19	161 ± 19	<.00001
cLBBB	62 (94)	46 (69)	.0001	108 (100)	0 (0)	NA
Q-LV	146 ± 22	117 ± 28	<.00001	136 ± 28	110 ± 23	<.00001
LV lead anterolateral location	23 (35)	22 (33)	.81	37 (34)	8 (32)	.83
LV lead basal location	21 (32)	17 (25)	.41	32 (30)	6 (24)	.58
Q-LV ratio	0.77 ± 0.09	0.68 ± 0.12	<.00001	0.74 ± 0.11	0.68 ± 0.10	.03
QRSd with RVP	196 ± 17	217 ± 23	<.00001	206 ± 23	207 ± 24	.90
Delta RVP	6.3 ± 8.1	47 ± 19	NA	23 ± 24	47 ± 21	<.00001
QRSd with CRT	160 ± 15	171 ± 26	.002	165 ± 19	170 ± 31	.30
Delta CRT	−30 ± 15	1 ± 29	<.00001	−20 ± 25	9 ± 31	<.00001
QRSd prolongation with CRT	2 (3)	28 (42)	<.00001	18 (17)	12 (48)	.0006

Values are presented as mean ± SD or as n (%).

CAD = coronary artery disease; cLBBB = complete left bundle branch block; CRT = cardiac resynchronization therapy; delta CRT = QRS duration difference (cardiac resynchronization therapy – native); delta RVP = QRS duration difference (right ventricular pacing – native); LV = left ventricular; NA = not applicable; NYHA = New York Heart Association; Q-LV = interval between the onset of the QRS complex and the local left ventricular electrogram; QRSd = QRS duration; RVP = right ventricular pacing.

(Figure 2). In multivariable analysis, delta RVP was most strongly associated with delta CRT ($P < .00001$), followed by native QRSd and Q-LV, while ECG-based cLBBB became a nonsignificant factor (Table 3). The percentage of explained delta CRT variance was 32% for delta RVP, 17% for Q-LV, and 16% for native QRSd. Figures 3 and 4 illustrate the role of delta RVP in the prediction of CRT-induced electrical effects.

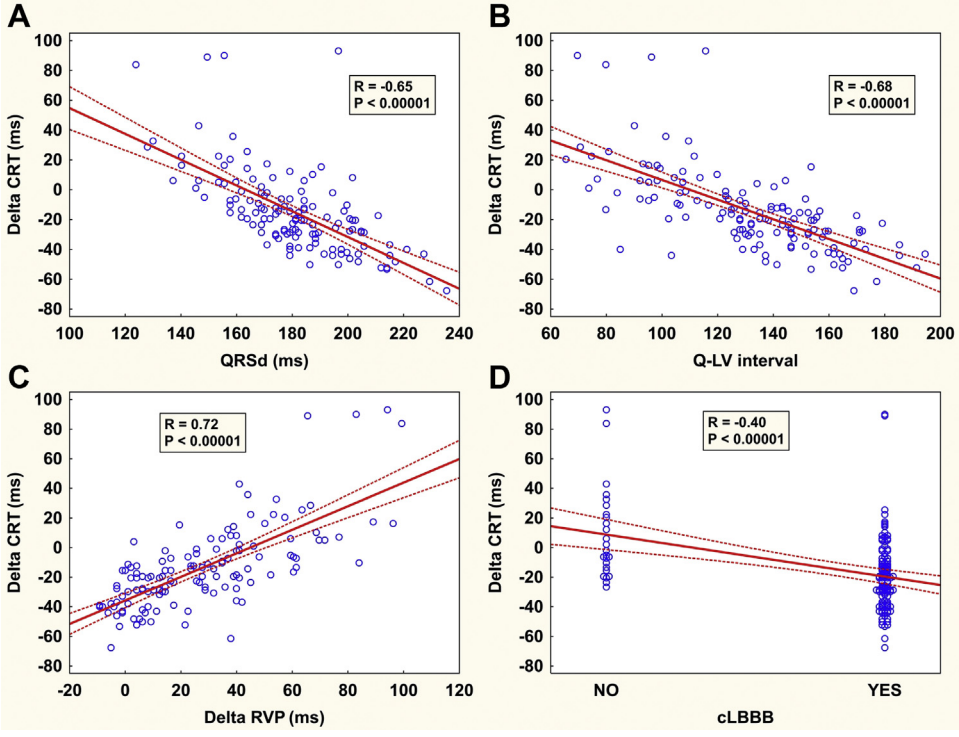

Figure 2 Correlations between native QRSd (**A**), Q-LV (**B**), RVP-paced QRSd change, that is, delta RVP (**C**), and presence of cLBBB (**D**) and CRT-induced QRSd change, that is, delta CRT. cLBBB = complete left bundle branch block; CRT = cardiac resynchronization therapy; delta CRT = QRS duration difference (cardiac resynchronization therapy – native); delta RVP = QRS duration difference (right ventricular pacing – native); Q-LV = interval between the onset of the QRS complex and the local left ventricular electrogram; QRSd = QRS duration; RVP = right ventricular pacing.

Table 3 Univariable and multivariable linear regression analysis of factors associated with CRT electrical response

	Univariable				Multivariable		
					$R = 0.80$; Intercept $= 57 \pm 16$; $P <$ .00001		
Factor	Regression slope	SEM	R	P	Regression slope	SEM	P
Male (1/0 = yes/no)	15.2	5.3	0.24	.005	NA	NA	.40
CAD (1/0 = yes/no)	10.0	4.8	0.18	.04	NA	NA	.09
NYHA class	8.6	4.1	0.18	.04	NA	NA	.30
Native QRSd (ms)	−0.86	0.09	−0.65	<.00001	−0.30	0.11	.006
cLBBB (1/0 = yes/no)	−28.4	5.7	−0.40	<.00001	NA	NA	.39
LV lead – anterolateral location (%)	−7.1	5.1	−0.12	.17	NA	NA	.16
LV lead – basal location (%)	−9.7	5.3	−0.16	.07	NA	NA	.14
Q-LV (ms)	−0.66	0.06	−0.68	<.00001	−0.24	0.08	.004
Delta RVP (ms)	0.80	0.07	0.72	<.00001	0.50	0.07	<.00001

Delta CRT was the dependent variable. Only factors from univariable analysis with $P < .2$ are shown.
NA = not applicable; R = correlation coefficient; SEM = standard error of the mean for the regression slope; other abbreviations as in Table 2.

Discussion

The principal finding of this study is that absence of QRS prolongation by RVP is a novel marker of cLBBB. Consequently, this parameter proved to be the best quantitative predictor of CRT-based shortening of depolarization, stronger than, and independent of, several established predictors of the ECG CRT effect, such as baseline QRS width and morphology, and electrical position of the LV lead.

Rationale for the use of electrophysiological predictors and end points in CRT

The primary mechanism of CRT and its therapeutic effect is electrical atrioventricular, interventricular, and LV resynchronization with a varying contribution of each component in individuals.[20] On the ventricular level, QRS complex narrowing assessed by conventional 12-lead ECG has been used as a readily available measure of electrical resynchronization. Nevertheless, its role was a subject of controversy for many years. Only recently, studies in patients with LBBB have confirmed that QRSd change is a robust biomarker and end point of CRT device implantation[12,18] and that postoperative QRS prolongation is associated with increased mortality risk during follow-up.[17] Mechanical effects, that is, improved contraction coordination, are secondary to modified electrical activation.

Numerous predictors and outcome measures related to CRT have been studied. Whereas clinical response predictors

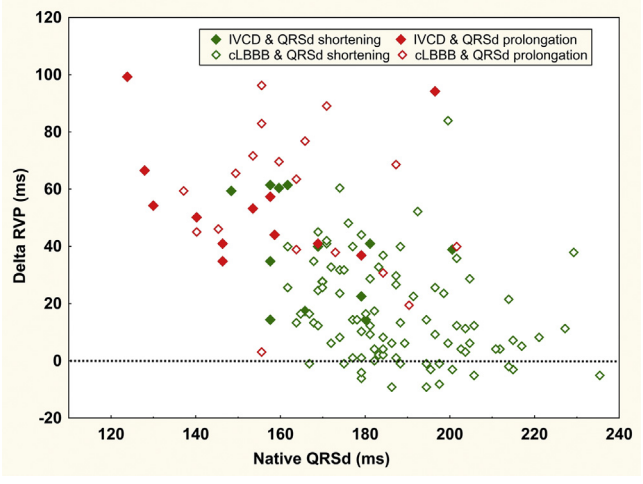

Figure 3 Scatterplot of delta RVP vs native QRSd categorized by 2 binary factors: cLBBB (yes/no) and delta CRT dichotomized at ≤0 ms (indicating CRT-induced QRSd shortening or prolongation). Note the cases (*red open diamonds*) in whom CRT resulted in QRSd prolongation despite the presence of cLBBB. This is in agreement with their considerable QRSd prolongation by RVP (delta RVP 0). cLBBB = complete left bundle branch block; CRT = cardiac resynchronization therapy; delta CRT = QRS duration difference (cardiac resynchronization therapy – native); delta RVP = QRS duration difference (right ventricular pacing – native); IVCD = intraventricular conduction delay (or apparent left bundle branch block); QRSd = QRS duration; RVP = right ventricular pacing.

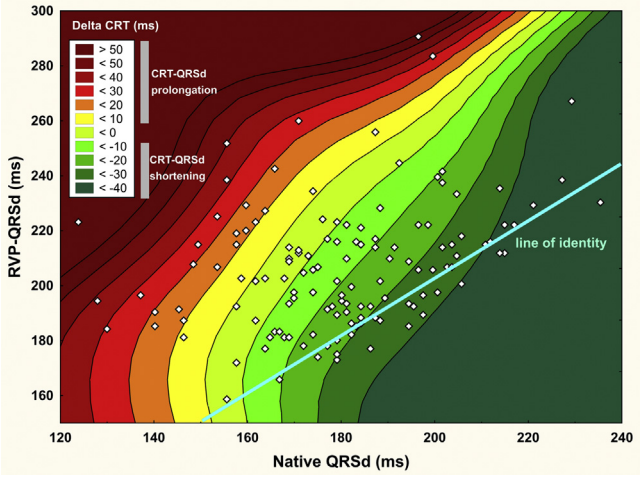

Figure 4 Contour plot of delta CRT stratified by native QRSd and RV-paced QRSd. Cases (*white diamonds*) close to the line of identity are those with absent prolongation of QRSd by RVP (ie, likely cLBBB] and maximum effect of CRT. cLBBB = complete left bundle branch block; CRT = cardiac resynchronization therapy; CRT-QRSd = QRS duration during biventricular pacing; delta CRT = QRS duration difference (cardiac resynchronization therapy – native); RVP-QRSd = QRS duration during right ventricular pacing; QRSd = QRS duration; RV = right ventricular; RVP = right ventricular pacing.

are mostly comorbidity outcome confounders, echocardiographic predictors are associated with the likelihood of reverse remodeling but are impractically biased, imprecise, and prone to intra- and interindividual variability even in expert hands.[21,22] In contrast, electrical predictors and outcome parameters such as baseline QRSd, baseline QRS morphology, Q-LV, or QRSd change with CRT are directly related to the electrophysiology of CRT and can be measured with a high degree of accuracy and precision.

Secondary analyses of major CRT studies have shown that both QRS width and QRS morphology predict the outcome of CRT recipients. Specifically, QRSd below 150 ms and morphologies other than LBBB were associated with absent benefit from CRT.[5,6] Q-LV (and Q-LV ratio) is yet another electrophysiological parameter that predicts outcomes in patients treated with CRT.[11,12] Since the LBBB morphology on ECG represents a heterogeneous group of conduction and myocardial abnormalities, Strauss et al[7] proposed stricter ECG criteria to diagnose cLBBB to improve the selection of CRT candidates and understanding of the underlying LV activation pathologies. Compared with other LBBB conduction abnormalities, cLBBB has been associated with better CRT outcomes.[8–10]

All the above indices have been previously demonstrated to be associated with CRT outcomes, but their contribution has been subject to debate.[23] This study confirms that they represent robust independent predictors of QRSd narrowing with CRT. This implies their interaction, in which the QRSd change with CRT is a final common pathway of their additive effects. Given the results of this study, the effect size of CRT on the ventricular function is likely to be the sum of particular effects on levels of the electrical correctable substrate (cLBBB), the magnitude of possible QRSd shortening (baseline QRSd), and quality of the LV lead positioning (Q-LV).

RV pacing to diagnose cLBBB

There is currently no clinically useful method to diagnose cLBBB, apart from direct mapping of the LBB and the myocardial activation sequence at the interventricular septum,[24] which is not feasible in routine clinical practice. The presence of cLBBB is usually suggested by the ECG criteria proposed by Strauss et al.[7]

We postulated the hypothesis that RVP imitates the right bundle branch–only activation sequence and might reproduce the cLBBB-like QRS complex.[25] It has been supported by a study showing that in patients with LBBB, RV septal pacing does not prolong total LV activation, does not result in left-to-right electrical dyssynchrony, and does not change LV activation dispersion in the LV or localization of the late activated areas.[26] QRS prolongation by RVP indicates loss of residual LBB conduction compared with intrinsic depolarization, and consequently, the absence of such prolongation would suggest cLBBB. The present study shows that the lack of QRSd prolongation by RVP is strongly associated with QRSd shortening by CRT to the extent that it eliminates the ECG-based cLBBB definition from the multivariable prediction model.

Scholz et al[27] recently described another method of discrimination between apparent LBBB and cLBBB by comparing Q-LV/QRSd ratios during intrinsic activation and RV apical pacing. They used a coronary sinus catheter to map LV activation (Q-LV) as part of the electrophysiology study and to obtain Q-LV ratios that are close to those measured with the use of the LV lead electrogram during the CRT implant procedure. Given the results of our study, it appears that the predictive power of their quotient of 2 ratios is driven more by the difference in QRSd between the native and the RV-paced complex than by the difference in activation time at the most delayed LV segment. They also used suboptimal RV apical pacing instead of RVP as in our study. It was shown that RV apical pacing produces an activation pattern that differs from the intrinsic LBBB activation with shorter transseptal activation time, prolonged RV activation, more pronounced apical to basal activation, and different latest activated areas.[28,29] Finally, their study included only 25 patients with LBB conduction abnormalities (18 with cLBBB), so validation of their results in a larger cohort of CRT candidates is warranted.

Clinical implications

Our method provides continuous instead of binary results by Strauss' classification. Since CRT response is also a continuous variable ranging from super-response to nonresponse, or even to harm, a quantitative description of electrophysiological properties of the LV conduction system may capture the benefit from CRT more properly than a dichotomous variable.

Our results support the concept of electrophysiological CRT optimization. The combination of baseline electrical parameters (QRSd and cLBBB), intraoperative electrical system optimization (Q-LV), and degree of therapeutic benefit (QRSd change) provides the operator with a powerful toolset to fine-tune the therapy. Furthermore, patients with a significant RVP-induced QRSd prolongation require specific attention, since it may not only be a harbinger of residual LBB conduction but have a deleterious effect on electrical resynchronization with biventricular pacing. Future research should focus on several aspects. The relation between RVP effects and LBB conduction properties needs to be confirmed by direct LBB mapping. We hypothesize that RV-paced QRS prolongation defines CRT candidates who may benefit from fusion-optimized LV pacing (eg, adaptive CRT). Such patients with incomplete LBBB may also benefit from physiological (His bundle or LBB) pacing.

Limitations

A limitation of this study is the absence of ultimate electrophysiological assessment of the LBB conduction properties. Electroanatomic mapping was not part of the study design because of costs and associated risks of left-sided heart catheterization. Another limitation of this study is the use of a

surrogate ECG end point instead of an acute change in hemodynamics or reverse LV remodeling as assessed by echocardiography. The study was designed as a mechanistic electrophysiological experiment. The results obtained herein should be reproduced in subsequent studies with relevant clinical end points. Finally, the study protocol complied with routine clinical and guideline-supported practice, so AV and VV optimization or fusion-based LV pacing was not performed. Although one cannot exclude minor changes in the measured variables by AV and/or VV optimization, the complexity of AV and VV manipulations might as well introduce variability in study outcome measure.

Conclusion

Baseline QRSd, delta RVP, and LV electrical lead position (Q-LV) represent strong independent predictors of ECG response to CRT, and their additive effect can be used in maximizing the overall benefit of the therapy. RVP induces variable QRSd prolongation that reflects a loss of residual left bundle conduction. The absence of such prolongation may serve as an alternative and more specific marker of cLBBB. The corresponding index correlates more tightly with the electrophysiological effect of CRT and outperforms the predictive value of ECG-based cLBBB.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.05.033.

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