Left ventricular paced activation in cardiac resynchronization therapy patients with left bundle branch block and relationship to its electrical substrate

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BACKGROUND Cardiac resynchronization therapy (CRT) uses left ventricular (LV) pacing to restore rapid synchronized LV activation when it is delayed in patients with myocardial disease.

OBJECTIVE Although intrinsic LV activation delays are understood, little is known about reactions to LV stimulation and whether they are affected by QRS duration (QRSd), morphology, LV substrate, or choice of electrode pair. The purpose of this study was to test these interactions.

METHODS In 120 heart failure patients with left bundle branch block (LBBB) and QRS >120 ms receiving CRT with quadripolar LV leads, device-based measurements of intrinsic activation delay (qLV) and paced inter- (and intra-) LV conduction times were evaluated at the proximal and distal LV bipoles.

RESULTS During intrinsic conduction, qLV varied little between the proximal and distal pairs in patients with LBBB (n = 120; age 68 ± 11 years; 63% male; ejection fraction 25% ± 7%; 33% ischemic cardiomyopathy; QRSd 162 ± 19 ms). A minority (30%) had conduction barriers (ie, gradients) (ΔqLV 29 ± 8 ms vs 9 ± 5 ms in patients without gradients; P <.01), which occurred equally in ischemic and nonischemic patients. A majority were functional (and not scar-mediated), as they resolved with pacing in most patients (75%). Importantly, LV-paced conduction times were unrelated to baseline QRS morphology (LBBB 166 ± 30 ms vs RBBB control 172 ± 30 ms; P = NS), longer than intrinsic conduction (166 ± 30 ms vs 129 ± 28 ms; P <.01), and varied significantly by electrode pair (ie, small distances) and etiology. Correlation between intrinsic activation delay (qLV) and LV-paced conduction time was poor (R^2 = 0.278; P <.05).

CONCLUSION LV-paced effect, which is core to CRT, is unpredictable based on conventionally used measures and should be considered during CRT optimization.

KEYWORDS Cardiac resynchronization therapy; Electrical dyssynchrony; Left bundle branch block; Pacing; qLV

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Introduction

Left ventricular (LV) pacing is the essential component of atrio–biventricular pacing during cardiac resynchronization therapy (CRT), which improves survival of heart failure (HF) patients with prolonged QRS duration (QRSd).[1] However, its effect on LV depolarization has been little characterized since its original description by Wiggers.[2] Potentially, intrinsic or right ventricular (RV) paced wavefronts, pattern, and extent of intrinsic conduction delay, and the presence or development of myocardial conduction barriers (scar or functional), each can affect LV activation and thereby CRT effect. Additionally, others have shown that QRS morphology and duration,[3] LV activation relative to lead position (qLV),[4] and biventricular vs LV pacing[5] may affect CRT response. Whether these factors affect LV pacing effect is unknown. The purpose of this study was to test these interactions.

Methods

This single-center retrospective study sought to characterize intrinsic conduction and effects of ventricular pacing (RV and LV) on electrical parameters among CRT patients with quadripolar LV leads (electrode spacing 20 mm [D1-M2], 10 mm [M2-M3], 17 mm [M3-P4]). The study protocol was approved by the local ethics committee, and the requirement for patient consent was waived by the committee. Study enrollment criteria included patients with New York Heart Association (NYHA) functional class II to IV HF symptoms, LV ejection fraction (EF) <35%, and QRS duration >140 ms (males) and 130 ms (females) while receiving optimal medical therapy. Data

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KEY FINDINGS

- The area of latest left ventricular (LV) activation spanned by a multipolar lead is large; however, conduction barriers exist in a significant minority of patients (equally among ischemic and nonischemic cardiomyopathy patients) but are mostly functional as they are resolved by pacing.
- Although intrinsic LV electrical delay (qLV) usually varied little between the distal and proximal electrode pairs of quadripolar leads, the response to LV pacing could vary significantly.
- LV pacing exerted a range of effects that were unrelated to baseline QRS morphology or qLV, and remained unpredictable based on LV stimulation site. These effects should be considered during CRT optimization.

on demographics were collected from patient records. Left bundle branch block (LBBB) was defined as intrinsic QRSd $\geq$120 ms with a broad notched or slurred R wave in leads I, aVL, V_5, and V_6 and occasional RS pattern in leads V_5 and V_6. In addition, Q waves were absent in leads I, V_5, and V_6, and R-wave peak time was >60 ms in leads V_5 and V_6 but normal in leads V_1–V_3. Right bundle branch block (RBBB) was defined as intrinsic QRS duration $\geq$120 ms with rsR′ in leads V_1–V_3 and prolonged S waves in I, aVL, and V_5–V_6.[6]

The right ventricular (RV) lead was placed in the RV apical septum. LV leads were positioned through the coronary sinus on the free wall of the lateral or posterolateral LV. The orientation ensured that the distal electrode pair (D1-M2) was closer to the apex and the proximal electrode pair (M3-P4) remained more basal. In leads oriented in the opposite orientation, the distal and proximal electrode pair measurements were reversed to maintain anatomic consistency. The final LV lead position was chosen based on (1) lead stability; (2) capture threshold; and (3) lack of diaphragmatic stimulation. Operators were encouraged to select final lead position based on the longest qLV (interval from QRS onset to local LV lead activation).

Testing was performed intraprocedurally after CRT implant. The following conduction intervals were measured using the implanted device: interval from QRS onset to (1) RV lead activation (qRV: a surrogate measure of right bundle branch [RBB] conduction time); (2) latest LV electrode activation (qLV: a measure of LV activation delay at LV lead site); the time interval from (3) the RV-paced to LV-sensed intracardiac electrograms (EGMs) (RVp–LVs: a measure of RV-paced wavefront propagation), (4) the LV-paced to RV-sensed intracardiac EGMs (LVp–RVs: a measure of LV-paced wavefront propagation), and (5) the pacing artifact on one LV bipole to the sensed intracardiac EGM on the opposite LV bipole (LVp–LVs: a measure of intra-LV-paced wavefront propagation) (Figure 1).

Intrinsic conduction

qLV was determined in distal (D1-M2) and proximal (M3-P4) LV bipoles of all patients analyzed and was taken as the average of 3 measurements. Measurements were made with a device-based EGM using electronic calipers. qRV and qLV were measured as the interval between QRS onset (as determined by device-based far-field RV tip to can EGM) to the intrinsicoid of the local bipolar EGM. (Correlation between device-based and electrophysiology lab recording system measurements had been validated previously: qRV [r = 0.859; n = 39; P <.001] and qLV [r = 0.915; n = 40; P <.001] [Supplemental Figure 1]). In addition to qLV, the automatic device-based time interval from the RV-sensed to the LV-sensed intracardiac EGM (iEGM) (RVs–LVs) was evaluated at both the distal and proximal electrodes and presented as the average of 8 measurements.

Interventricular pacing

Pacing was performed from the RV bipole to the distal (LV electrode cathode of D1 or M2) and then the proximal (LV electrode cathode of M3 or P4) LV bipole. For paced measurements, the time delay between the RV-paced complex to the LV distal (and then LV proximal) electrode pair sensed iEGM was measured (RVp–LVs). Pacing was reversed, and the time from LV distal (and also LV proximal) pacing to RV-sensed iEGM was measured (LVp–RVs). For automated measurements, the average of 8 measurements (collected by the algorithm) was taken for each interval. Measurements were performed during ventricular pacing at a rate 10–20 bpm above that of the patient's intrinsic rate in either VVI or DDD mode with short (<50 ms) atrioventricular delays. A gradient was defined as >20-ms difference between 2 measured values (sensed or paced). This cutoff was chosen based on 2 SD of the mean of the difference between the proximal and distal qLV during intrinsic conduction.

Intraventricular (intra-LV) conduction

One confounding factor is that the paced measurements described represent biventricular activation (ie, RV to LV or vice versa) during which propagating wavefronts must transit the interventricular septum, which itself is a site of conduction delay in LBBB.[7–10] To better define conduction (time and velocity) as well as conduction barriers (scar or functional lines of block), we assessed intra-LV activation in a subset of LBBB patients. Paced intra-LV conduction times were measured as the interval between pacing artifact on the LV distal bipole (D1-M2) and sensed iEGM on the LV proximal LV bipole (M3-P4). Pacing was then reversed, and the paced conduction time was measured between LV pacing at the proximal bipole to the iEGM inscription on the distal LV bipole. In addition, the intrinsic intra-LV conduction time (in the absence of pacing) was measured as the difference in qLV between the proximal and distal bipoles.

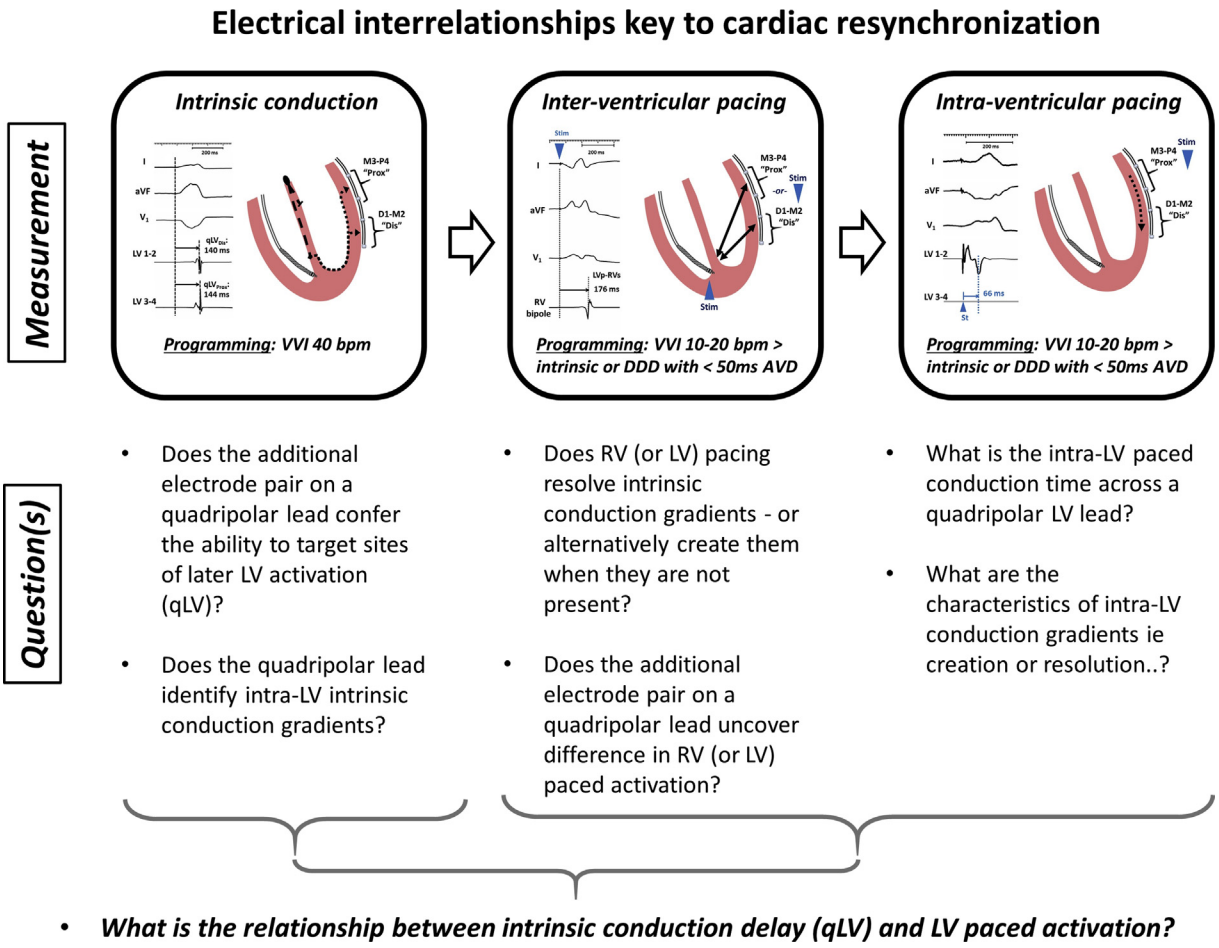

Figure 1 Electrical relationships key to cardiac resynchronization: analytical plan. AVD = atrioventricular delay; LV = left ventricle; RV = right ventricle.

Statistical analysis

Categorical variables are expressed as number (percentage). Continuous variables are mean with standard deviation, or median with interquartile range. Continuous variables were compared using the Wilcoxon test and included intrinsic and paced conduction times, QRS duration, LVEF, and age. Categorical variables were compared using the χ^2 test or Fisher exact test. $P < .05$ was considered significant.

Results

Baseline

A total of 152 patients receiving a *de novo* CRT implant were evaluated between April 2012 and June 2019. Pacemaker-dependent patients were excluded. Baseline clinical characteristics are listed in Table 1. The primary study group comprised patients with LBBB at baseline (n = 120; age 68 ± 11 years; 63% male; EF 25% ± 7%; 33% ischemic cardiomyopathy; QRSd 162 ± 19 ms [range 120–212 ms]; PR interval 207 ± 39 ms [range 109–318 ms]). qRV was 23 ± 11 ms (range 4–56 ms). qLV_{Max}/QRSd ratio was 0.79 ± 0.14 (range 0.35–1.13). At testing, 9 patients were in atrial fibrillation, 1 did not have an atrial lead, and 5 underwent analysis during atrial pacing. A secondary group with RBBB was included for comparison of paced measurements (n = 32; age 65 ± 14 years; 88% male; EF 27% ± 8%; 62% ischemic cardiomyopathy; QRSd 156 ± 19 ms [range 124–200 ms]; PR interval 240 ± 26 ms [range 191–277 ms]). qRV was 54 ± 18 ms (range 5–91 ms). qLV_{Max}/QRSd ratio was 0.46 ± 0.15 (range 0.01–0.75). (Results are reported for LBBB patients unless otherwise stated.)

Intrinsic conduction

LV activation delay

Overall, during intrinsic conduction in LBBB, qLV was 121 ± 28 ms (range 40–203 ms). qLV did not differ significantly between distal (D1-M2) and proximal (M3-P4) bipoles. This condition was preserved among patients with ischemic cardiomyopathy. In contrast, among nonischemic patients, qLV was slightly longer in proximal compared to distal bipoles (123 ± 28 ms vs 117 ± 28 ms; $P < .05$) (Figure 2A). No significant differences were observed when qLV was normalized to intrinsic QRS duration (qLV/QRSd).

Because relative interventricular delay has been associated with a substrate that may be treated effectively by

Table 1 Baseline patient demographics

	LBBB	RBBB	*P* value
No. of patients	120	32	—
Male/female	63%/37%	88%/12%	.68
Nonischemic	67%	38%	<.01
Age (y)	68 ± 11	65 ± 14	.22
LVEF (%)	25 ± 7	27 ± 8	.50
Intrinsic QRSd (ms)	162 ± 19	156 ± 19	.10
qRV (ms)	23 ± 11	54 ± 18	<.001
qRV/QRSd (%)	14 ± 7	35 ± 12	<.001
qLV_{Max} (ms)	129 ± 28	70 ± 21	<.001
qLV_{Max}/QRSd (%)	79 ± 14	46 ± 15	<.001
qLV >95 ms	90%	6%	<.001

	LBBB			RBBB		
	Nonischemic	Ischemic	*P* value	Nonischemic	Ischemic	*P* value
No. of patients	80	40	—	12	20	—
Male/female	58%/42%	75%/25%	.7	83%/17%	90%/10%	.62
Age (y)	65 ± 12	74 ± 8	<.05	64 ± 16	69 ± 13	.88
LVEF (%)	26 ± 8	25 ± 7	.64	30 ± 11	25 ± 7	.21
Intrinsic QRSd (ms)	159 ± 19	168 ± 19	<.05	160 ± 23	154 ± 17	.25
qRV (ms)	22 ± 11	25 ± 11	.26	55 ± 20	54 ± 17	.30
qRV/QRSd (%)	14 ± 7	15 ± 6	.88	38 ± 12	35 ± 11	.50
qLV_{Max} (ms)	127 ± 29	132 ± 26	.40	73 ± 21	68 ± 24	.61
qLV_{Max}/QRSd (%)	80 ± 15	78 ± 12	.58	47 ± 14	45 ± 17	.92
qLV_{Max} >95 ms	89%	93%	.75	8%	5%	1

Values are given as mean ± SD unless otherwise indicated.

LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; qLV = QRS onset to left ventricular lead activation; QRSd = intrinsic QRS duration; qRV = QRS onset to right ventricular lead activation; RBBB = right bundle branch block.

CRT, we assessed the interval between RV-sensed and LV-sensed iEGM (RVs–LVs). Overall, the interval was 83 ± 29 ms, with no difference between ischemic and nonischemic patients. Notably, no differences were observed between the proximal and distal bipoles of the LV lead for either etiology (Figure 2B). The correlation of RVs–LVs with qLV was 0.857.

Intra-LV conduction

qLV was greater in the proximal than distal poles in of 71 of 120 patients (59%). The overall magnitude of the difference between proximal and distal bipoles was 14 ± 11 ms and did not differ between etiologies. Significant intrinsic conduction gradients were seen in 35 of 120 patients (29%): 13 of 40 ischemic patients (33%; maximum 53 ms) and 22 of 80 nonischemic patients (28%; maximum 47 ms) (Figures 3A and 3B).

To explore whether functional or permanent conduction barriers were responsible for intra-LV gradients when observed, we assessed responses to altered direction of LV activation by ventricular pacing, reasoning that functional barriers would resolve. During RV pacing, intrinsic gradients resolved in 10 of 13 ischemic patients (77%) and in 13 of 22 nonischemic patients (59%). During LV pacing, resolution occurred in 8 of 13 ischemic patients (62%) and 16 of 22 nonischemic patients (73%) (Figure 3C). Exacerbation of existing gradients occurred rarely (17%) with either pacing mode (Figure 3D).

An important consideration is that RV (or LV) pacing in itself may create functional gradients where they did not exist previously (or unmask fixed barriers by altering the direction of wavefront activation). In our series, 85 patients without pre-existing intrinsic LV conduction gradients (ΔqLV 9 ± 5 ms) were identified. New pacing-induced gradients were created in 36% patients (31/85). RV pacing was more likely to create gradients where they did not exist previously compared to LV pacing (31% [26/85] vs 15% [13/85]; *P* <.05). Nonischemic patients were nearly twice as likely as ischemic patients to experience pacing-induced gradients (52% [30/58] vs 33% [9/27], respectively).

Ventricular pacing

During RV pacing in LBBB patients, LV activation was delayed compared to intrinsic conduction (ie, RBB-mediated conduction). Overall, the RV-paced to LV-sensed time (RVp–LVs) was 160 ± 30 ms compared to qLV of 121 ± 28 ms (*P* <.05). This was most prominent in the proximal LV bipole. RVp–LVs proximal vs distal LV bipole in nonischemic patients was 160 ± 29 ms vs 151 ± 28 ms (*P* <.05), and in ischemic patients was 174 ± 31 ms vs 165 ± 29 ms (*P* <.05) (Figure 4A). RVp–LVs times were 9% greater in ischemic than nonischemic patients in both the proximal and distal bipoles.

We measured the reciprocal interval, that is, LVp–RVs conduction times during LV pacing. Overall, LVp–RVs was 166 ± 30 ms, which is 4.4% longer compared to RVp–LVs (*P* <.05). LVp–RVs time was 11% greater in ischemic than nonischemic patients in both bipoles (Figure 4B). Altering the site of LV pacing affected this

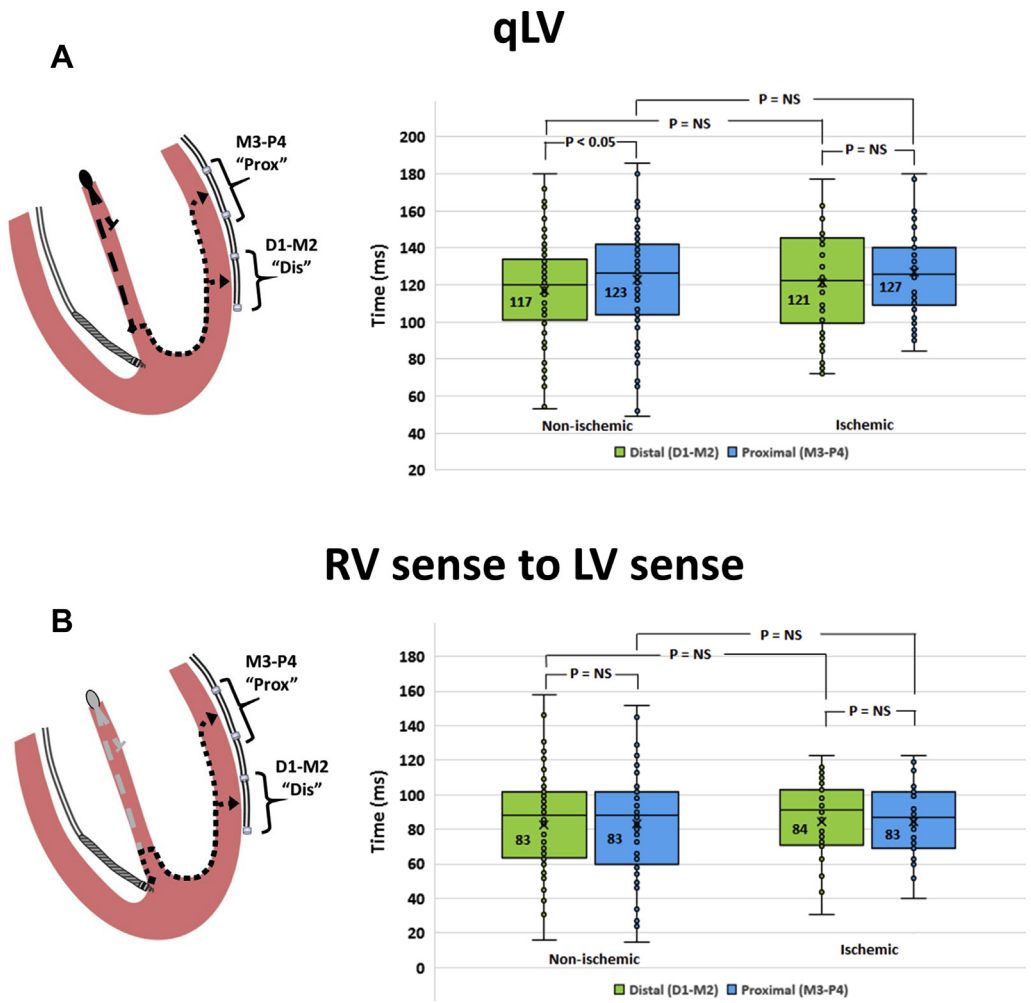

Figure 2 Intrinsic conduction in left bundle branch block. **A:** Intrinsic left ventricular electrical delay (qLV) varies little between the distal and proximal bipoles of quadripolar leads in both ischemic and nonischemic patients. **B:** A similar trend is seen in RV sense to LV sense time (RVs–LVs), an automated device-based surrogate of intrinsic LV electrical delay. However, this measurement is significantly less than qLV (32% ± 15%). LV = left ventricle; RV = right ventricle.

finding. LVp–RVs was significantly longer during pacing from the proximal vs distal LV bipole in both nonischemic patients (162 ± 28 ms vs 158 ± 25 ms; $P < .05$) and ischemic patients (181 ± 32 ms vs 175 ± 30 ms; $P < .05$).

We assessed conduction anisotropy observed between RV and LV pacing. Overall, left-to-right paced conduction times (LVp–RVs) were longer than right-to-left (RVp–LVs) conduction times in 75% of patients, with no difference between etiologies (Figure 4C). Anisotropy (ie, difference between right-to-left and left-to-right conduction times >20 ms) occurred in a significant minority of patients (23%), with an average gradient of 31 ± 11 ms and no difference between etiologies.

To evaluate whether LV transit time depended on underlying LV activation pattern or alternatively was simply a reflection of myocardial conduction properties in HF, we contrasted the findings in LBBB patients to a secondary group with RBBB (n = 32) (Supplemental Table 1). There were no significant differences between groups for (RVp–LVs) or (LVp–RVs) during pacing from either bipole (Supplemental Table 1A). Overall there was no difference when comparing RBBB and LBBB patients of either etiology (Supplemental Table 1B).

LV activation during LV pacing compared to intrinsic activation

We tested for the presence of any relationship between LV activation delay in LBBB (qLV) and responses to LV pacing (LV-paced to RV-sensed time). Overall correlation was poor ($R^2 = 0.278$). When addressed by etiology, for nonischemic cardiomyopathy, qLV exhibited poor correlation with LV-paced activation in both the distal ($R^2 = 0.364$) and proximal ($R^2 = 0.283$) electrode pairs. For ischemic cardiomyopathy, correlation was even poorer ($R^2 = 0.249$ and 0.183, respectively) (Figure 5).

Intra-LV conduction time

Interbipolar intervals along the quadripolar LV lead were evaluated in a subset of patients with LBBB (n = 42; age 70 ± 11 years; EF 27% ± 8%; 71% male; 32% ischemic; QRSd 165 ± 17 ms; qLV/QRSd = 0.78 ± 0.14). During intrinsic conduction, the intra-LV conduction time (ΔqLV [proximal – distal])

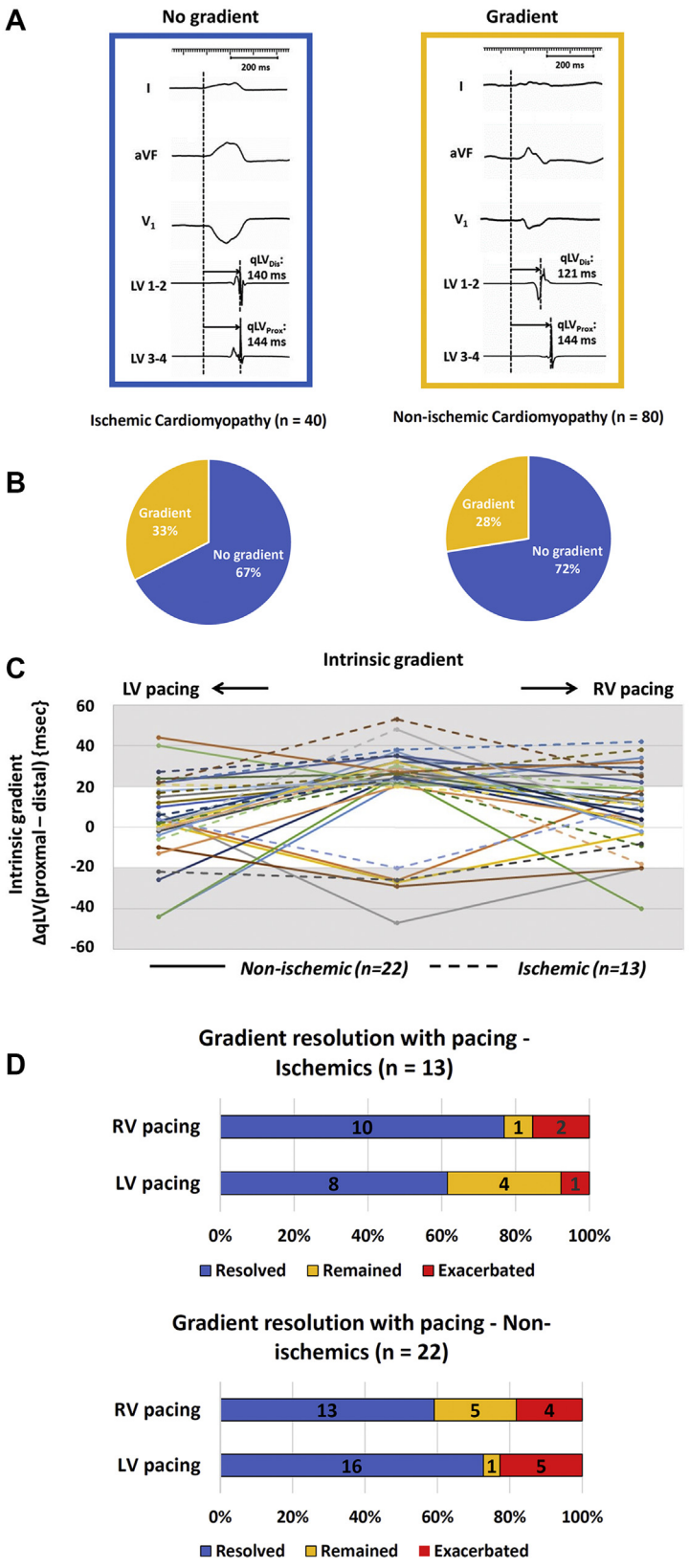

Figure 3 Characteristics of intrinsic conduction gradients: effect of pacing. **A:** Representative tracings of RV and LV intrinsic electrical delay (qLV) from the electrophysiology lab recording system. Intervals were measured from the onset of the surface QRS to the RV (qRV), LV distal (D1-M2), and LV proximal (M3-P4) bipoles. **B:** Gradients, defined as ≥20 ms difference between qLV at the distal and proximal LV bipoles, are thought to be confined to patients with ischemic disease yet are present in a similar proportion in nonischemic patients. **C:** Resolution (or exacerbation) of intrinsic conduction gradients during LV (**left**) or RV (**right**) pacing. Each line represents 1 patient with nonischemic (*solid*) or ischemic (*dashed*) etiology. Gradients are highlighted in *gray*. **D:** In both ischemic and nonischemic patients, a majority of gradients are functional, as they are resolved by changing the direction of ventricular activation with RV or LV pacing. Exacerbation of existing gradients was rare. LV = left ventricle; RV = right ventricle.

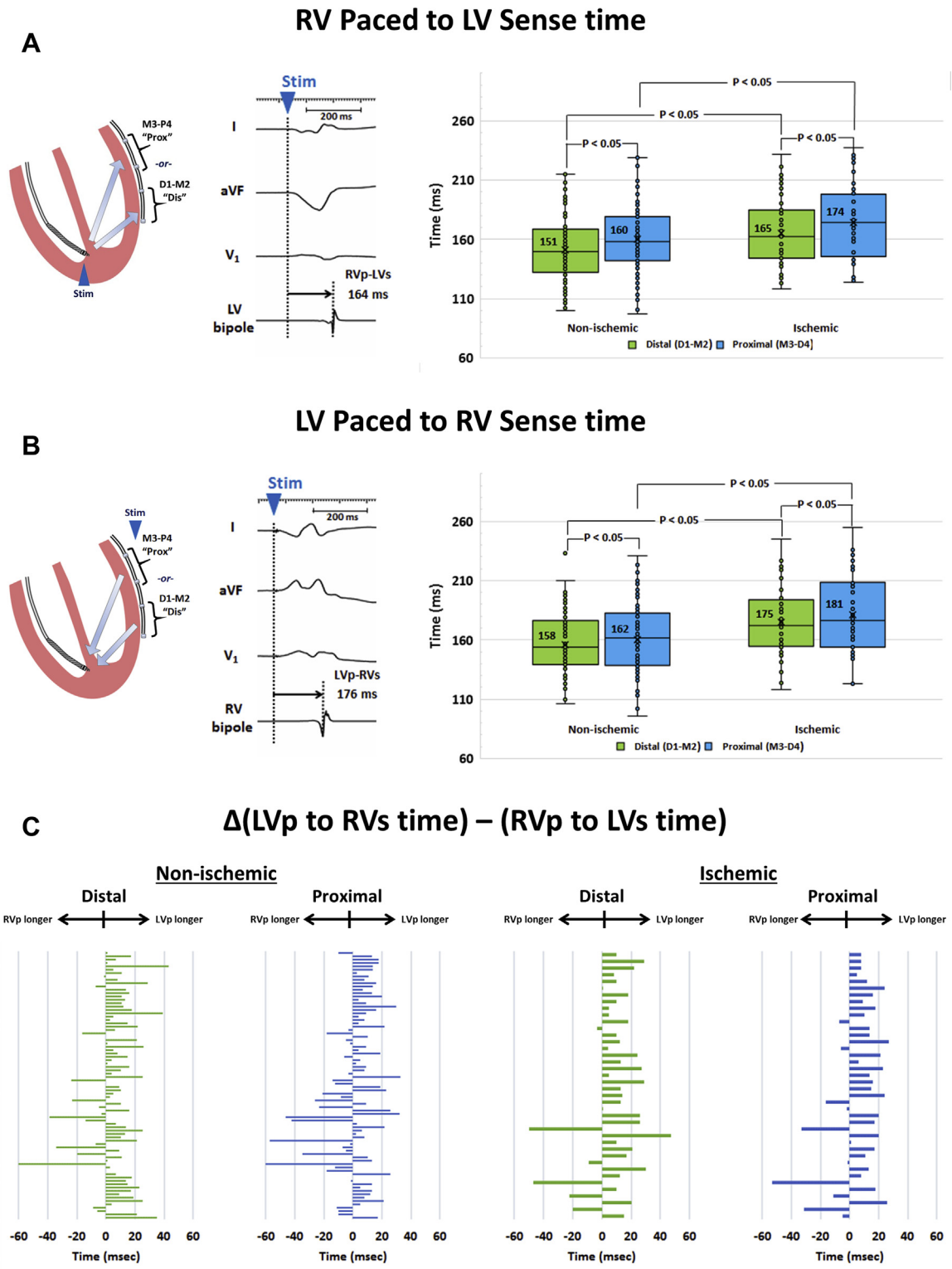

Figure 4 Characteristics of right ventricular and left ventricular pacing in left bundle branch block. **A:** RV paced to LV sense time: schematic representation of the pacing protocol (**left**) and representative tracings from the electrophysiology lab recording system of time from the pacing artifact of the surface QRS during RV pacing (**middle**). LV electrical activation times during RV pacing (**right**) are significantly longer when measured at the proximal vs distal LV bipole regardless of etiology and 9% longer in patients with ischemic cardiomyopathy. **B:** LV paced to RV sense time: schematic representation of the pacing protocol (**left**) and representative tracings from the electrophysiology lab recording system of time from the pacing artifact of the surface QRS during LV pacing (**middle**). LV electrical activation times during LV pacing (**right**) with similar differences in conduction time are observed during distal (or proximal) LV pacing measured to the RV bipole. LV paced to RV sense times were significantly longer than the RV paced to LV sense times in all but the proximal bipole of nonischemic patients. **C:** Difference in paced conduction time [(LV pace to RV sense) – (RV pace to LV sense)] in the individual patients. LV = left ventricle; RV = right ventricle.

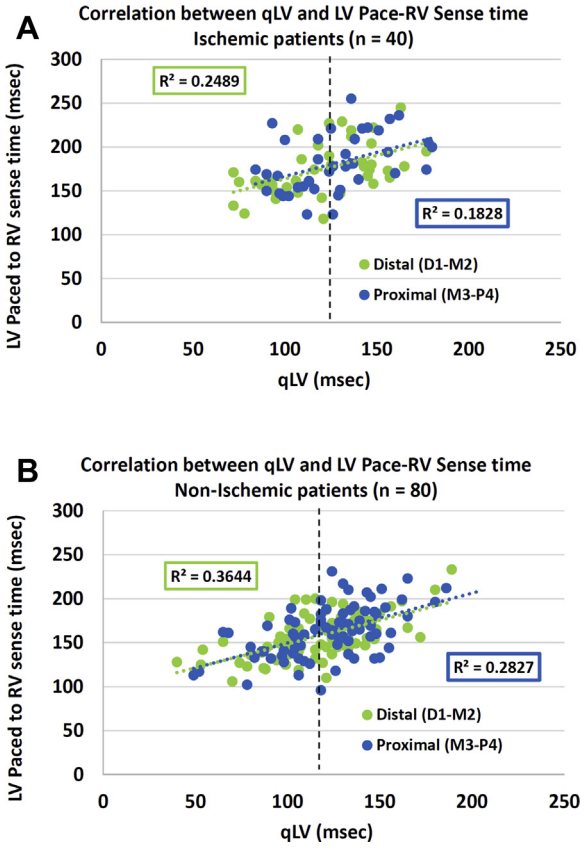

Figure 5 Relationship between intrinsic LV electrical delay (qLV) and LV paced conduction in patients with left bundle branch block (LBBB). There is poor corelation between maximum intrinsic electrical delay (qLV) and LV pace to RV sense time (LVp–RVs) from the same bipole in both ischemic **(A)** ad nonischemic patients **(B)** with LBBB. This suggests that LV-paced conduction is largely independent of intrinsic electrical delay and electrical substrate and should be evaluated independently of qLV. LV = left ventricle; RV = right ventricle.

was 14 ± 13 ms. This was compared to intervals recorded during LV pacing. During LV distal bipole (D1-M2) pacing, time to depolarization of the basal LV reported by the proximal (M3-P4) LV bipole was 70 ± 21 ms. Reversing the pacing direction (from bipole D1-M2 to M3-P4) resulted in similar timing (68 ± 18 ms; both $P < .001$ vs intrinsic but P = NS to each other) (Figure 6). Nonischemic (n = 28) and ischemic (n = 14) patients did not differ. In 21% of patients (17/84 measurements), intra-LV paced conduction time (LV-paced to RV-sensed) was ≥95 ms. The correlation between intrinsic and paced intra-LV conduction was poor ($R^2 = 0.00007$).

Discussion

This study showed that the area of latest LV activation spanned by a multipolar lead is large and that conduction barriers exist in a significant minority (equally among ischemic and nonischemic cardiomyopathy) but are mostly functional. Key findings were that LV pacing exerted a range of effects that were unrelated to baseline QRS morphology, or qLV, and remained unpredictable based on LV stimulation site. Although intrinsic LV electrical delay (qLV) usually varied little between the distal and proximal electrode pairs of quadripolar leads, the response to LV pacing could vary significantly. Conceivably, unpredictable LV-paced effects may contribute to the range of responses to CRT despite best patient selection by current criteria and should be considered during CRT optimization.

Intrinsic conduction

CRT aims to correct LV depolarization delay. In LBBB, delay may occur at the septum and/or free wall. Terminal activation occurs basally in the posterolateral LV. Current practice favors positioning LV leads in this region, as in our series (depolarization in the final 25% of QRSd). We discovered important characteristics of terminal LV activation. Overall, the activation time from distal to proximal pair was rapid. This is consistent with invasive mapping studies that showed LV free-wall activation remained normal in HF pts with LBBB,[11] and the septum was the point of delay.[12] The electrode span of 47 mm suggests that the "sweet spot" of terminal activation is large, contradicting a widely held notion that the zone of late activation is a point. Thus, a quadripolar lead tends to cover the target area and only rarely needs to be redeployed simply to improve qLV.

Nevertheless, proximal to distal electrode gradients were observed in a minority. This phenomenon has been observed in mapping studies and attributed to scar, especially in ischemic disease.[13] Here, we were surprised to detect these gradients in equal proportions (~30%) in patients with either ischemic or nonischemic disease and to observe their tendency to resolve with pacing maneuvers (pacing rarely exacerbated gradients) (Figure 3). This finding suggests that these conduction barriers were functional and dependent on the interaction of the direction of wavefront propagation with fiber orientation.[14]

Ventricular pacing

Biventricular pacing forms the basis of CRT, although the individual effects of RV and LV pacing in this patient population have been little studied. In this study, RV pacing significantly prolonged LV activation time, to a greater extent in ischemic than nonischemic patients. Basal LV marked by the proximal pole was activated last. This is consistent with previous mapping studies showing that RV pacing introduced additional LV conduction barriers, prolonged free-wall activation, and exaggerated the load of late activated myocardium, worse than LBBB.[15] Notably, in our series, pacing-induced new gradients (where they did not exist previously) were twice as likely to occur in patients with nonischemic cardiomyopathy than in those with ischemic disease.

LV pacing is the essence of CRT. Wiggers[2] showed that pacing the posterolateral LV epicardium (ie, the zone favored for LV pacing in CRT) was associated with slow conduction in normal LV. The effect may be exaggerated in patients with HF. This is important: CRT assumes LV pacing causes homogeneous global LV activation, but the presence of LV disease and conduction

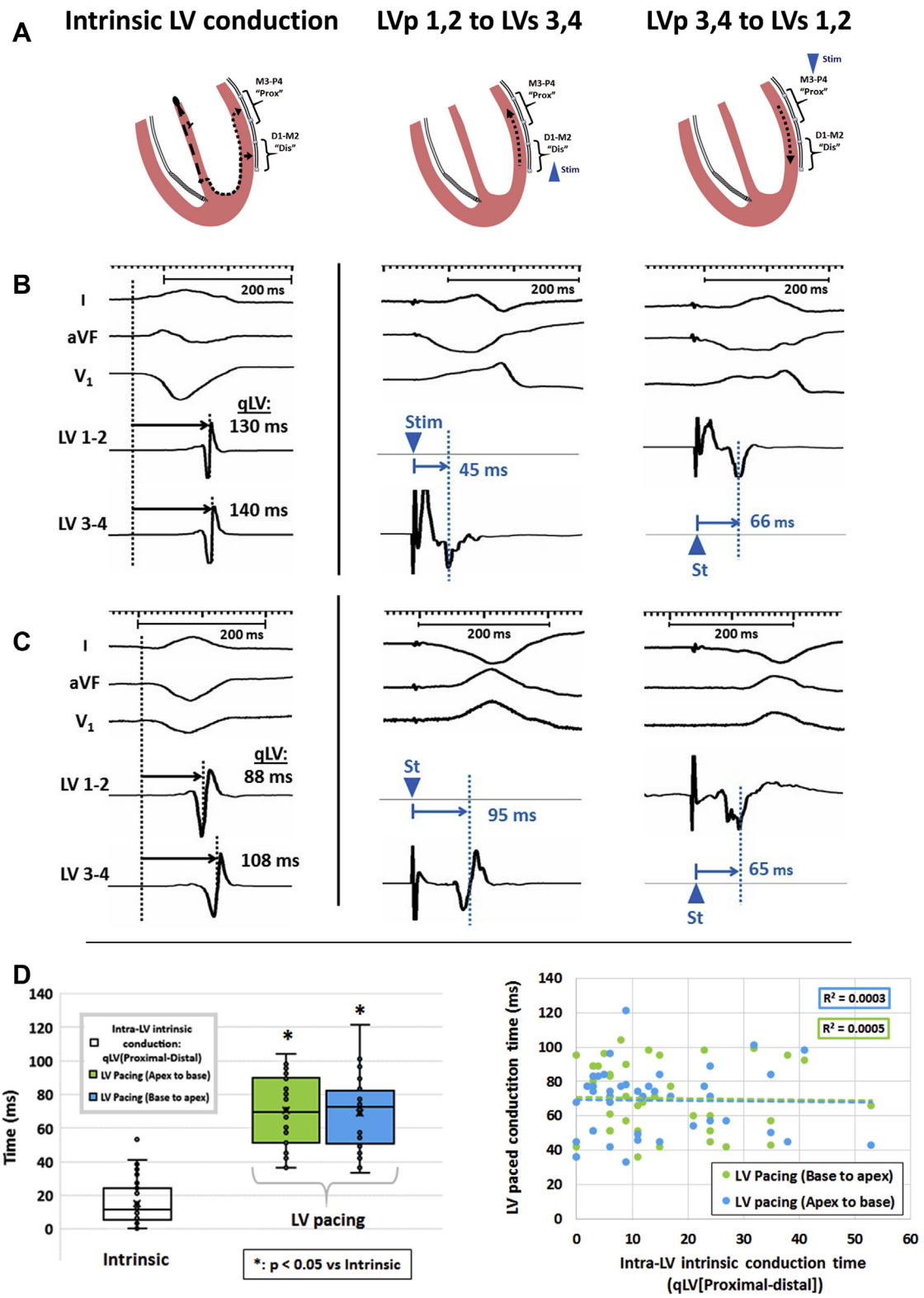

Figure 6 Left ventricular intraventricular conduction time: intrinsic and paced. **A:** Schematic representation of conduction time measurements during intrinsic conduction (**left**) and pacing from the distal LV bipole (**middle**) and the proximal LV bipole (**right**). **B, C:** Representative tracings from the electrophysiology lab recording system showing the intraventricular conduction time during intrinsic conduction (**left**) between the proximal and distal LV bipoles (ΔqLV), and paced conduction time measured from the pacing artifact on the surface QRS during LV-only pacing from the distal bipole to the local intracardiac electrogram on the proximal LV bipole (**middle**). Pacing was then reversed, and the interval between the proximal and distal LV bipoles was measured (**left**). Two different patients show variability in intraventricular paced conduction times: one short (45 ms) (**B**) and one long (95 ms) (**C**). **D:** LV epicardial paced conduction times are significantly longer than during intrinsic conduction (**left**) and are unrelated to pre-existing intrinsic conduction gradients (**right**). LV = left ventricle.

barriers from scar and fibrosis may modulate propagation and may render it ineffective. Mapping data in small series of patients support this notion.[13,16] However, determinants of LV-paced activation and any relation to current CRT selection criteria (eg, LBBB, qLV) have been little studied. In our series, LV-paced wavefront propagation was slow, with LVp–RVs conduction time twice that of intrinsic conduction (Figure 4). Regional intra-LV paced conduction was significantly slower compared to intrinsic conduction (Figure 6). Neither of these measures was related to qLV, pre-existing conduction gradients, or ischemic disease (ie, baseline characteristics do not predict LV-paced responses). Moreover, LV-paced time was similar in patients with LBBB compared to RBBB, indicating that the response to LV pacing results from intramyocardial conduction and is unrelated to the type or location of a His-Purkinje system lesion.[17] Importantly, in some individuals LV-paced time varied from one electrode pair to another, indicating that small changes in the site of LV stimulation with similar qLV can significantly change LV propagation characteristics (as suggested by electrocardiographic imaging).[18] Thus, none of the elements of current CRT practice (LBBB, qLV, LV lead position) predict LV-paced effect.

Study implications

The predictive value of current class 1 indications for CRT response is modest and little improved by machine learning, with area under the curve (AUC) of 0.65 and 0.70, respectively.[19] This is similar for qLV >95 ms or RVs/LVs, which correlates with qLV.[20] However, these criteria omit measures of successful delivery. Logically, CRT efficacy may be improved by optimizing LV pacing—its core component. LV-paced propagation is slow but rarely induces conduction barriers (in which cases multipoint or multisite LV pacing may be useful). Importantly, it is independent of standard patient selection criteria and needs to be measured. Using the surface electrocardiogram as a surrogate, shorter QRS duration (<200 ms) during LV-only pacing predicted NYHA functional class improvement.[21] LV- and RV-paced QRS duration difference was found to be a stronger predictor (AUC 0.74)[22] of clinical response compared with qLV (AUC 0.63)[4] and QRS narrowing (AUC 0.63).[23] Device-based intervals (ie, to minimize LVp–RVs time) as measured here may provide similar predictive value and facilitate attempts at CRT optimization. The importance of paced effects was highlighted by studies showing that the difference in paced interlead electrical delay [(RVp to LVs) – (LVp to RVs)] was a stronger predictor of LV remodeling than paced QRS duration (AUC 0.86).[24] These differences may not be related solely to conduction time. In 1 report, latency between the LV pacing stimulus and the onset of the paced QRS strongly predicted LV remodeling (AUC 0.91).[25] Evaluation of these differences, and the utility of optimizing programming configurations and/or inclusion of additional electrodes with quadripolar LV leads to enable more effective LV-paced effect, remain largely undescribed but represent an opportunity to enhance CRT response.[26]

LV-paced wavefronts may interface with RBB and/or RV-paced wavefronts.[27] For "fusion pacing," we showed that RBB conduction (qRV) is consistently intact, but inconsistency of LV conduction or paced effect/capture may limit the efficacy of this mode.[28] The role of RV pacing has been debated. When committed to RV pacing, LV conduction delays that already are present in LBBB are aggravated. However, transseptal and/or anterior LV delay (the source of delay in most LBBB) may be functional conduction barriers and resolved by RV pacing.[15,29] Capturing this initial effect may be useful in some patients, especially if incorporating RBB effect as in "triple fusion."[30] This effect is more likely at longer paced atrioventricular delay.[31] Our results support the finding that LV preactivation through LV-first programming is often needed to produce optimal electrical synchronization. Furthermore, these data may explain the puzzling observation that RV first is sometimes best.[30,32] Therefore, altering the timing of RV pacing (relative to LV pacing) during CRT merits individualized prescription according to its electrical action.[33] This may be facilitated by quadripolar leads.

Study limitations

Although intuitive, whether optimization of LV-paced effect affects clinical outcomes needs to be prospectively determined. The response of fixed or functional conduction barriers to pacing in any individual patient is complex. Patterns of paced wavefront propagation may be homogeneous (ie, arriving nearly simultaneously at the separate bipoles and appearing as resolution of functional gradients) or heterogeneous (ie, resulting in actual resolution or, alternatively, creation of new gradients). However, these exact mechanisms cannot be confirmed without endocardial/epicardial mapping and deciphering intramural activation patterns. Furthermore, correlation of the size and location of scar on magnetic resonance imaging with electrical findings may confirm the basis of conduction barriers (ie, functional or scar related). In the current study, our analysis was limited to the span of electrodes available: local conduction barriers during LV pacing may not predict whole LV activation. Even in the presence of LV conduction barriers, RV pacing and/or RBB activation may facilitate LV activation and permit successful biventricular resynchronization.[31]

Conclusion

In patients with LBBB, the area of latest LV activation is large and spanned by a multipolar lead, although functional conduction barriers exist in a minority. Intrinsic LV electrical delay (qLV) is similar between the distal and proximal electrode pairs of quadripolar leads, but is unrelated to responses to LV pacing which vary widely and are unpredictable from baseline QRS morphology or LV stimulation site. Evaluation of these parameters should be considered during CRT optimization.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2020.04.002.

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