Programming Cardiac Resynchronization Therapy for Electrical Synchrony: Reaching Beyond Left Bundle Branch Block and Left Ventricular Activation Delay

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Background—QRS narrowing following cardiac resynchronization therapy with biventricular (BiV) or left ventricular (LV) pacing is likely affected by patient-specific conduction characteristics (PR, qLV, LV-paced propagation interval), making a universal programming strategy likely ineffective. We tested these factors using a novel, device-based algorithm (SyncAV) that automatically adjusts paced atrioventricular delay (default or programmable offset) according to intrinsic atrioventricular conduction.

Methods and Results—Seventy-five patients undergoing cardiac resynchronization therapy (age 66 ± 11 years; 65% male; 32% with ischemic cardiomyopathy; LV ejection fraction $28\pm8\%$; QRS duration 162 ± 16 ms) with intact atrioventricular conduction (PR interval 194 ± 34, range 128–300 ms), left bundle branch block, and optimized LV lead position were studied at implant. QRS duration (QRSd) reduction was compared for the following pacing configurations: nominal simultaneous BiV (Mode I: paced/sensed atrioventricular delay=140/110 ms), BiV+SyncAV with 50 ms offset (Mode II), BiV+SyncAV with offset that minimized QRSd (Mode III), or LV-only pacing+SyncAV with 50 ms offset (Mode IV). The intrinsic QRSd (162 ± 16 ms) was reduced to 142 ± 17 ms (-11.8%) by Mode I, 136 ± 14 ms (-15.6%) by Mode IV, and 132 ± 13 ms (-17.8%) by Mode II. Mode III yielded the shortest overall QRSd (123 ± 12 ms, -23.9% [$P<0.001$ versus all modes]) and was the only configuration without QRSd prolongation in any patient. QRS narrowing occurred regardless of QRSd, PR, or LV-paced intervals, or underlying ischemic disease.

Conclusions—Post-implant electrical optimization in already well-selected patients with left bundle branch block and optimized LV lead position is facilitated by patient-tailored BiV pacing adjusted to intrinsic atrioventricular timing using an automatic device–based algorithm. (*J Am Heart Assoc*. 2018;7:e007489. DOI: 10.1161/JAHA.117.007489.)

Key Words: cardiac resynchronization therapy • left bundle branch block • optimization

Cardiac resynchronization therapy (CRT) improves patient outcomes.[1] However, the effect varies widely, and approximately one third of patients fail to respond.[2] Even among "responders," those with greater degrees of structural remodeling demonstrate better long-term survival.[3] To improve CRT response rates, recommendations emphasize attention to electrical parameters both before implant (ie, left bundle branch block [LBBB] and QRS duration [QRSd] ≥150 ms) and at implant during left ventricular (LV) lead positioning to maximize qLV (ie interval from QRS onset to first large peak of the recorded LV electrogram).[4,5] Logically, post-implant electrical optimization should follow, but this has been scarcely investigated. A reason may be that, in general, echocardiography-guided programming or device-based algorithms have yielded inconclusive results, and guidelines offer no recommendations.[5,6] Hence, devices commonly are left at nominal settings, irrespective of intrinsic atrioventricular and/or interventricular intervals.[7]

As CRT aims to restore electrical synchrony in dyssynchronous ventricles with a prolonged QRS complex, programming to enhance this effect seems intuitive. Electrical mapping and hemodynamic techniques support this, but these are not applied readily outside investigational settings.[8–11] The surface ECG, in contrast, is widely available, simple, inexpensive, and commonly used among implanters for adjudicating CRT programming. Although the value of QRS narrowing as a metric of electrical resynchronization and

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Clinical Perspective

What Is New?

- There is increasing value attached to electrical optimization of cardiac resynchronization therapy by selection of patients with left bundle branch block and optimization of left ventricular (LV) lead delivery, but little directed to paced effects, which also affect clinical outcome.
- Nominal programmed settings may be suboptimal or even exacerbate electrical dyssynchrony.
- We showed that QRS abbreviation was possible in all patients tested, but maximal effect required biventricular pacing adjusted to individual intrinsic atrioventricular interval.
- This offset range was wide and unpredictable.
- Generally, best biventricular pacing was superior to LV fusion pacing.
- Achieving QRS abbreviation was independent of qLV and optimized LV lead position, and demanded patient-tailored programming.

What Are the Clinical Implications?

- Cardiac resynchronization therapy programming should be included as an additional step following selection of patients with left bundle branch block and optimization of LV lead delivery.
- Electrical optimization requires attention to paced effects.
- QRS abbreviation is not ubiquitous (or maximal) with nominal programming, but is facilitated by an automatic dynamic device–based algorithm to accommodate variability in intrinsic atrioventricular intervals and furthered by individualization.
- Attention to electrical results of cardiac resynchronization therapy pacing in otherwise electrically optimized cardiac resynchronization therapy candidates may enhance clinical outcomes.

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long-term CRT response is conflicting, the balance supports this notion.[12,13] This may be explained by the fact that surprisingly few studies have deliberately targeted QRS narrowing as a goal, but those to do so showed changes in acute hemodynamics or chronic ventricular reverse remodeling superior to echocardiographic optimization or nominal device settings.[14–18] What is lacking is knowledge of: (1) whether QRS narrowing may be achieved in already electrically optimized CRT recipients with LBBB and well-positioned LV leads; (2) the modulating influences (if any) of variable intrinsic atrioventricular conduction and individual electrical substrate; (3) the impact of pacing Mode (LV-only versus biventricular); and (4) the relative merits of automatic device–based algorithms versus manual programming. These complexities suggest that a universal programmed strategy (eg,

nominal, adaptive LV fusion[19]) may have limited value. A further challenge is that any set of "optimal" programmed parameters may be affected by ambulatory variations in intrinsic atrioventricular conduction in response to natural changes in physiologic and autonomic conditions.[20]

In this study, we hypothesized that electrical resynchronization manifested by QRSd abbreviation could be improved in patients with LBBB and optimized LV lead positions (qLV/QRSd >70%[21]), but that this would be best implemented by patient-specific programming, rather than any universal "out-of-the-box" settings. In particular, we explored the impact of automatically programmed paced atrioventricular delay (AVD) based on measured intrinsic atrioventricular intervals. Additionally, to understand better the influence of electrical substrate, we assessed the relationship between electrical resynchronization and underlying myocardial conduction characteristics (eg, qLV and LV-paced effects). We tested these using a novel device-based algorithm (SyncAV) that automatically adjusts to the intrinsic atrioventricular conduction timing, while still providing the ability to manually program interventricular intervals and upper and lower AVD limits.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, since this incorporated a proprietary algorithm (SyncAV).

This was a multicenter, prospective study that compared nominal CRT settings to CRT with SyncAV, using either default or individualized offsets. SyncAV was used for the following reasons. There are 2 commercially available algorithms that perform periodic repetitive adjustments of CRT pacing according to variations in intrinsic atrioventricular conduction (ie, "dynamic platforms") to maintain delivery of CRT pacing during ambulatory variation in atrioventricular conduction.[22] AdaptivCRT preferentially delivers LV fusion pacing, is restricted to patients with PR intervals <200 ms, and does not permit individual programming.[19] In contrast, SyncAV permits BiV or LV pacing (allowing simulation of AdaptivCRT function if required), and wide atrioventricular programmability, in patients with PR intervals <300 ms. Briefly, SyncAV functions as follows. Every 256 beats, the algorithm automatically extends the paced and sensed AVD for 3 beats, during which it measures the intrinsic atrioventricular interval. With the default SyncAV offset, 50 ms is subtracted from the measured intrinsic atrioventricular interval, and the result is applied as the paced atrioventricular interval for the following 255 beats (ie, SyncAV paced AVD=intrinsic atrioventricular interval−50 ms). The cycle repeats every 256 beats, thus permitting dynamic adjustment of the paced atrioventricular

interval. The offset value may be reprogrammed across a wide range of offsets (10–120 ms). Additionally, ventricular pacing configuration may be changed from simultaneous biventricular (default) to introduce interventricular timing delays or commit to LV only. Thus, any selected set of optimized settings (atrioventricular and interventricular) in any individual may be preserved during ambulatory variations in atrioventricular interval resulting from changes in heart rate or autonomic tone.

The study protocol was approved by the local ethics committee at each of 5 participating institutions: Cleveland Clinic (Cleveland, OH), Austin Health Cardiology (Melbourne, Australia), University Hospital of Bordeaux (Pessac, France), IRCCS Policlinico San Donato (San Donato Milanese, Italy), and Montreal Heart Institute (Montreal, Canada). The requirement for patient consent was waived by the committees of the first 2 institutions but in the remainder all patients provided informed consent before enrollment in the remainder. The study enrolled patients with New York Heart Association functional class II to IV heart failure symptoms, LV ejection fraction <35%, preserved atrioventricular conduction (resting 12-lead ECG PR interval ≤300 ms), and LBBB, while on optimal medical therapy and without permanent atrial tachyarrhythmia. Demographics were collected from the patient record. LBBB was defined as intrinsic QRSd ≥120 ms with a broad notched or slurred R wave in leads I, aVL, V5, and V6, and occasional RS pattern in V5 and V6. In addition, Q waves were absent in leads I, V5, and V6, and R-wave peak time was >60 ms in leads V5 and V6 but normal in leads V1 to V3. All patients received either a St. Jude Medical CRT defibrillator (models CD3357, CD3365, CD3367, CD3369, or CD3371) or CRT pacemaker (PM3222, PM3242, or PM3262) with either a bipolar (1258T) or quadripolar (Quartet 1458Q) LV lead. All implanted devices were equipped with the SyncAV algorithm.

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 left ventricle. The LV pacing configuration was selected based on latest LV electrode activation, or maximal qLV (interval from QRS onset to activation of local electrode electrogram[4]). Operators were encouraged to select optimal LV lead location with consideration of qLV, and these values were recorded in all patients. In biventricular pacing (BiV) modes, the right ventricle and left ventricle were paced simultaneously. Testing was performed intraprocedurally following CRT implant.

The goal of the study was to evaluate the relative changes in QRSd associated with prespecified test settings, each of which was programmed for a minimum of 60 seconds. In each patient, QRSd was measured during intrinsic conduction (no RV or LV pacing), along with 4 programmed BiV modes (Modes I–IV; Table 1). Mode I was defined as BiV with nominal settings (paced/sensed AVD of 140/110 ms); Mode II:

Table 1. Definitions of Device Programming Modes

Programming Parameter	Mode I	Mode II	Mode III	Mode IV
	BiV	BiV+SyncAV (50 ms)	BiV+SyncAV (Optimal)	LV Only+ SyncAV (50 ms)
Pacing Mode	BiV	BiV	BiV	LV only
AVD	Paced/ sensed AVD: 140/110 ms	SyncAV on (offset: 50 ms)	SyncAV on (optimal offset: 10–60 ms)	SyncAV on (offset: 50 ms)

AVD indicates atrioventricular delay; BiV, biventricular pacing (simultaneous left ventricular-right ventricular pacing; LV, left ventricular. Mode IV results in "LV Fusion" pacing in patients with LBBB.

BiV+SyncAV with a offset of 50 ms (ie the default interval with SyncAV activation); Mode III: BiV+SyncAV with the offset value (10, 20, 30, 40, or 60 ms) individualized for each patient to yield the narrowest QRSd (ie, optimal offset); and Mode IV: LV-only pacing+SyncAV with the nominal offset of 50 ms (simulating AdaptivCRT[19]). QRSd was measured manually with electronic calipers on the EP lab recording system (sweep speed 100 mm/s) using 8 to 12 simultaneously recorded surface ECG leads (I, II, III, aVL, aVR, aVF, V1, and V6; V2-5 optional) and displayed in vertical alignment on the screen. QRSd was measured from the earliest onset to the latest offset of the waveform in all leads, following standard recommendations[23] (Figure 1). During pacing, the stimulus artefact was considered to mark onset. Operators who measured QRSd were blinded to pacing Mode.

The following conduction intervals were measured using the implanted device: atrial sensing to RV lead activation (a device-based measure of atrioventricular conduction); interval from QRS onset to RV lead activation (qRV; a surrogate measure of right bundle branch [RBB] conduction time), interval from QRS onset to latest LV electrode activation (qLV; a measure of LV activation delay at LV lead site), and time interval from LV-paced to RV-sensed intracardiac electrograms (LVp-RVs: a measure of LV-paced wavefront propagation time). A strong correlation ($r=0.9$) between recording-system and device-based measurements was previously established.[24]

Statistical Analysis

Categorical variables were expressed as number and percentage of patients. Continuous variables were expressed as mean±SD. QRSd was expressed in absolute terms (ms) for all pacing Modes, and in relative terms (percentage of intrinsic QRSd) for Modes I to IV. Multiple comparison analysis was performed using 1-way ANOVA (Tukey-Kramer method) to
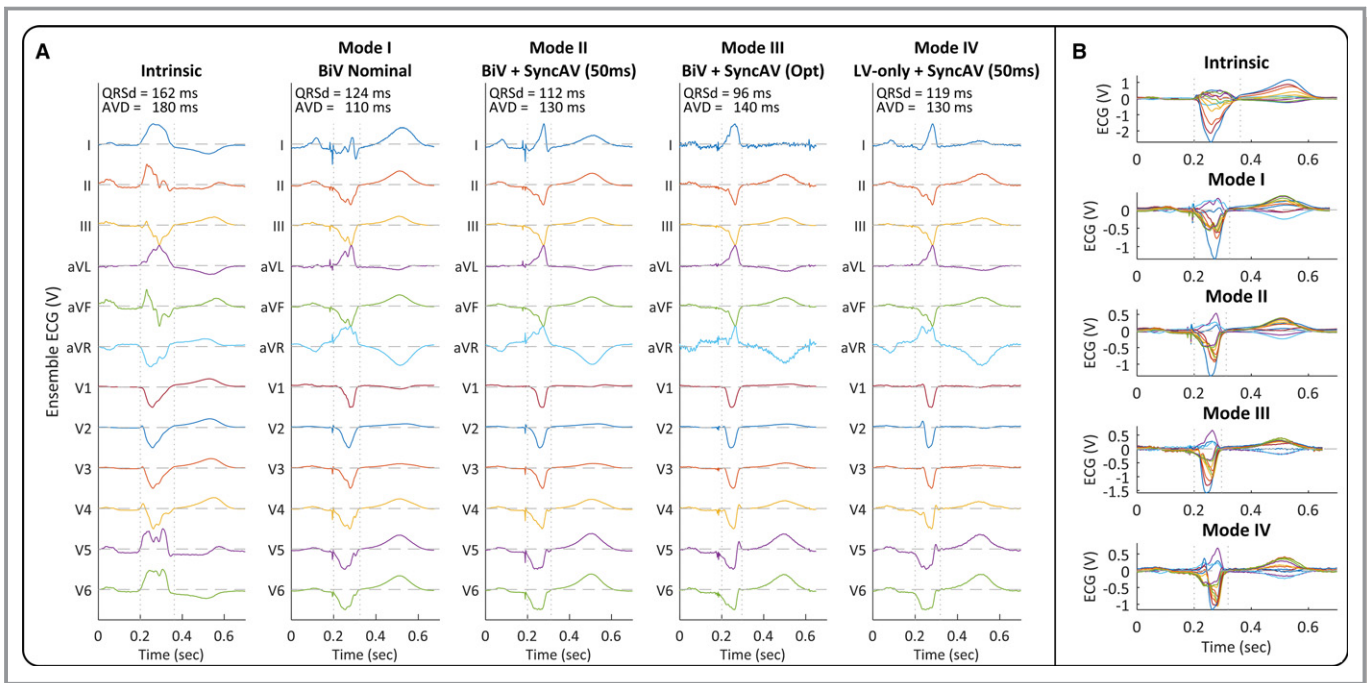
Figure 1. Representative 12-lead ECG for all pacing Modes. Simultaneous recordings of ECG leads in a single patient (A) displayed separately, for each Mode (left to right), and (B) depicted as a composite, for each pacing Mode (top to bottom). AVD indicates atrioventricular delay; BiV, biventricular pacing; QRSd, QRS duration.

assess the difference in QRSd among all 5 pacing Modes, as well as the difference in QRSd reduction (ΔQRSd) resulting from Modes I to IV, relative intrinsic QRSd. Ad hoc paired *t* tests were performed to confirm differences in QRSd and ΔQRSd across pairs of pacing Modes, with $P<0.05$ considered statistically significant. To test whether QRSd narrowing was influenced by underlying myocardial electrical properties, linear regression R^2 values were calculated for the correlation between QRSd reduction and qLV, qRV, and the time interval from LV-paced to RV-sensed intracardiac electrograms.

Results

Baseline Characteristics

Seventy-five patients (age: 66±11 years; 65% male; ejection fraction 28±8%; 32% with ischemic cardiomyopathy) receiving a de novo CRT implant were prospectively evaluated at 5 centers between December 2014 and March 2017. Baseline clinical characteristics are listed in Table 2. All patients were in sinus rhythm at the time of implant. The mean baseline PR interval was 194±34 ms (range 128–300 ms) and exceeded 200 ms in 25 of 75 (33%) patients. The device-determined atrial (sensed or paced) to ventricular sensed time was 193±36 ms. Mean QRSd was 162±16 ms (range 124–215 ms) and qLV was 125±29 ms (range 61–195 ms). The qLV/QRSd ratio was 0.76±0.15 (range 0.35–1.07), indicating an overall LV lead location at terminally activated LV regions.

qRV was 12±11 ms (range −5 to 51 ms). Of the patients tested, 5 of 75 underwent analysis during atrial pacing, rather than sensing, because of sinus node dysfunction. A list of device programming modes is described in Table 1. All 75 patients were evaluated in each programming configuration. The SyncAV algorithm operated successfully in all tested patients. A representative case is shown in Figure 1. Individual results are depicted in Figure 2A through 2E and summary comparisons in 2E and 2F.

QRSd: BiV at Nominal Settings

In Mode I (BiV nominal), QRSd was reduced by 20±17 ms ($P<0.001$), representing a decrease of 11.8±10.3% from intrinsic conduction (range +18.7% to −44.3%).

QRSd: SyncAV at Default Setting

Mode II (BiV+SyncAV, 50 ms offset) significantly reduced QRSd by 30 ms (17.8±8.4%, range +9.6% to −37.7%) compared with intrinsic conduction. This represented a further QRSd reduction of 6.0% relative to BIV at nominal settings (132±13 ms versus 142±17 ms; $P<0.001$).

QRSd: SyncAV Individualized

Mode III (BiV+SyncAV, optimal offset) significantly reduced QRSd by 39 ms (−23.9±7.9%, range −4.8 to −43.1%)

Table 2. Baseline Patient Demographics

Characteristic	No. (%) or Mean±SD
Patients, No.	75
Age, y	66±11
Male	49 (65)
Nonischemic etiology	50 (68)
NYHA class	
I	3 (4)
II	37 (49)
III	33 (44)
IV	2 (3)
LVEF, %	28±8
PR, ms	194±34
QRSd, ms	162±16
A-VS, ms	193±36
qRV, ms	12±11
qLV, ms	125±29
qLV/QRSd	0.76±0.15
RV paced—LV sensed, ms	162±28
LV paced—RV sensed, ms	160±29
Comorbidities	
Hypertension	42 (56)
Diabetes mellitus	23 (31)
Renal disease	8 (11)
History of smoking	14 (19)
COPD	6 (8)
Medications	
ACEIs/ARBs	61 (82)
β-Blockers	65 (87)
Calcium channel blockers	3 (4)
Diuretics	58 (77)
Nitrates	9 (12)
Cardiac glycosides	7 (9)
Antiplatelets	43 (58)
Anticoagulants	16 (22)
Antiarrhythmic (class I)	1 (1)
Antiarrhythmic (class III)	7 (9)

ACEIs indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular; QRSd, QRS duration; qLV, QRS onset to left ventricular lead activation; qRV, QRS onset to right ventricular lead activation.

compared with intrinsic conduction. This represented an absolute QRSd reduction of 12% (ie, 2-fold greater effect) compared with BiV at nominal settings, and an absolute QRSd reduction of 6.1% compared with SyncAV used with the default offset of 50 ms (123±12 ms versus 133±13 ms; $P<0.001$).

QRSd: LV Only+SyncAV

Mode IV (LV only+SyncAV, 50 ms offset) reduced QRSd to 136±14 ms (15.6±8.7%, range +10.7 to −32.1%) compared with intrinsic conduction. Although an improvement compared with Mode I (with SyncAV off), Mode IV offered similar QRSd narrowing to Mode II (BiV pacing+SyncAV, 50 ms offset). However, the effect associated with Mode IV was substantially less than with Mode III (8.3% less QRSd narrowing, $P<0.001$) (Figure 3).

Pacing Mode Comparison of QRSd

Multiple comparison analysis demonstrated that all 4 pacing Modes (I–IV) resulted in significantly different absolute QRSd values to each other, with the exception of Mode IV when compared with Modes I or II ($P<0.001$ for Mode I–II, I–III, II–III, and III–IV; $P=0.07$ for Mode I–IV; and $P=0.55$ for Mode II–IV) (Figure 2E). Similarly, the same analysis on ΔQRSd% (relative to intrinsic) demonstrated that all 4 pacing Modes (I–IV) resulted in significantly different relative ΔQRSd%, with the exception of Mode IV when compared with Mode II ($P<0.0001$ for Mode I–II, I–III, II–III, and III–IV; $P<0.03$ for Mode I–IV; and $P=0.43$ for Mode II–IV) (Figure 2F).

As expected from the aforementioned mean QRSd and ΔQRSd values presented for each pacing Mode, Mode III resulted in the narrowest QRSd in most patients (64/75, 85%), as shown in Figure 4A. Modes I, II, and IV resulted in the narrowest QRSd in 5 of 75 (7%), 12 of 75 (16%), and 11 of 75 (15%) patients, respectively. Note that the total percentage exceeds 100% because a shortest QRSd could be achieved by >1 pacing Mode in some individual patients.

Although each pacing Mode resulted in a mean QRSd that is narrower than that of intrinsic conduction, patient-specific changes in QRSd are also important. As shown in Figure 4B, Mode I reduced QRSd in the majority of patients (66/75, 88%) but actually prolonged QRSd in a small number of patients (8/75, 11%). Mode II and IV also reduced QRSd in most patients but prolonged QRSd in 2 of 75 patients (3%). The only pacing Mode that resulted in QRSd narrowing in every patient was Mode III (BiV+SyncAV, optimized offset). The SyncAV offsets most frequently associated with the narrowest QRSd (ie, offsets used for Mode III) were between 30 and 50 ms, as shown by the distribution in Figure 5.

The magnitude of reduction in QRSd did not differ between ischemic and nonischemic patients. In addition, Mode III narrowed the QRSd in all patients irrespective of intrinsic atrioventricular conduction (<200 ms versus >200 ms) and QRSd (<150 ms versus >150 ms).
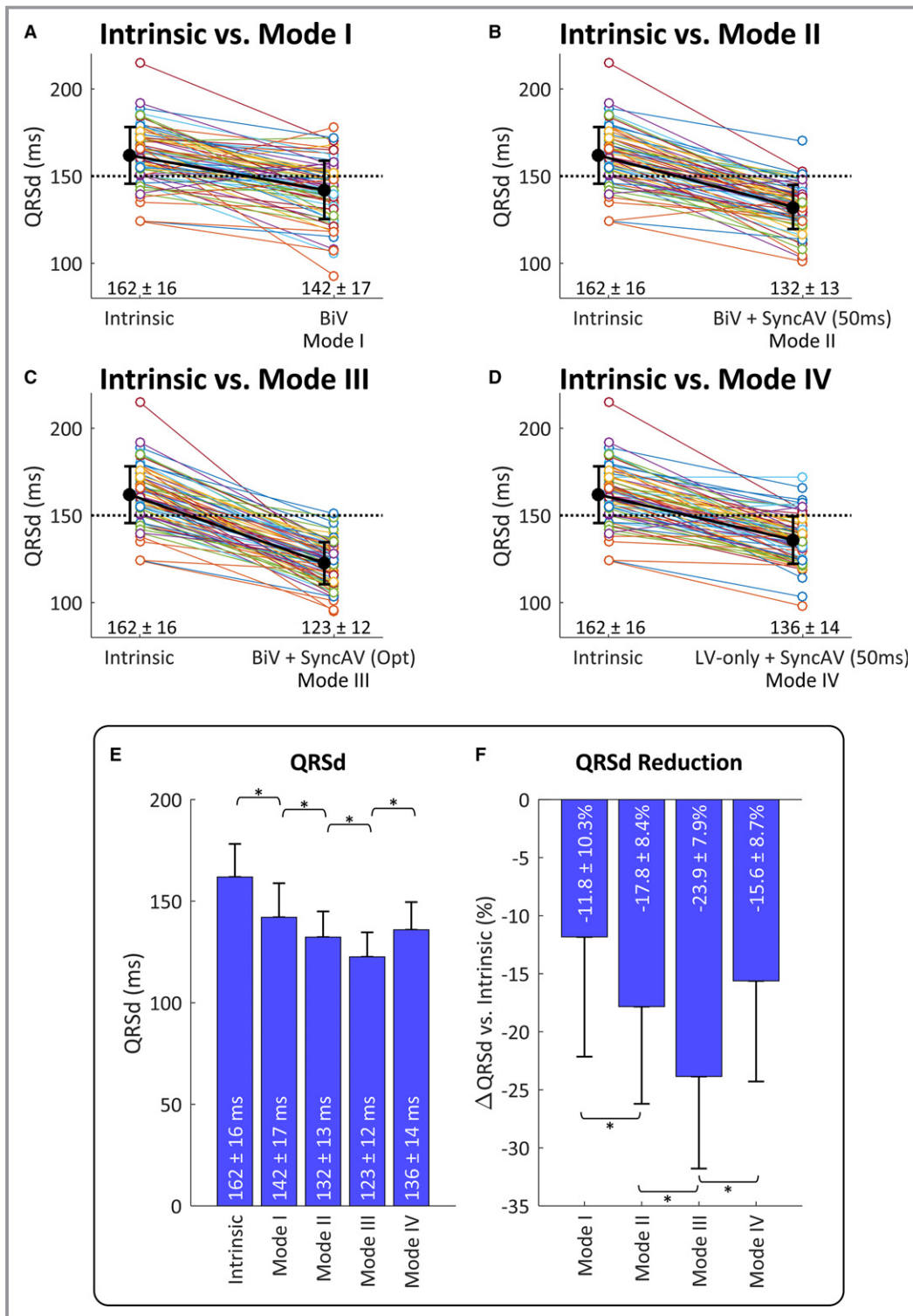
Figure 2. Distribution of QRS duration (QRSd) according to device programming. Individual comparisons: (A) Intrinsic QRS vs biventricular pacing (BiV) (Mode I). B, Intrinsic QRS vs BiV+SyncAV (50 ms) (Mode II). C, Intrinsic QRS vs BiV+SyncAV (optimal) (Mode III). D, Intrinsic QRS vs LV only+SyncAV (50 ms) (Mode IV). Summary results: (E) QRS duration for intrinsic conduction and all 4 pacing Modes. F, Reduction in QRSd for all 4 pacing Modes, relative to intrinsic. Mode I: BiV; Mode II: BiV+SyncAV (50 ms); Mode III: BiV+SyncAV (optimal); Mode IV: left ventricular (LV) only+SyncAV (50 ms). Asterisk indicates $P<0.05$.
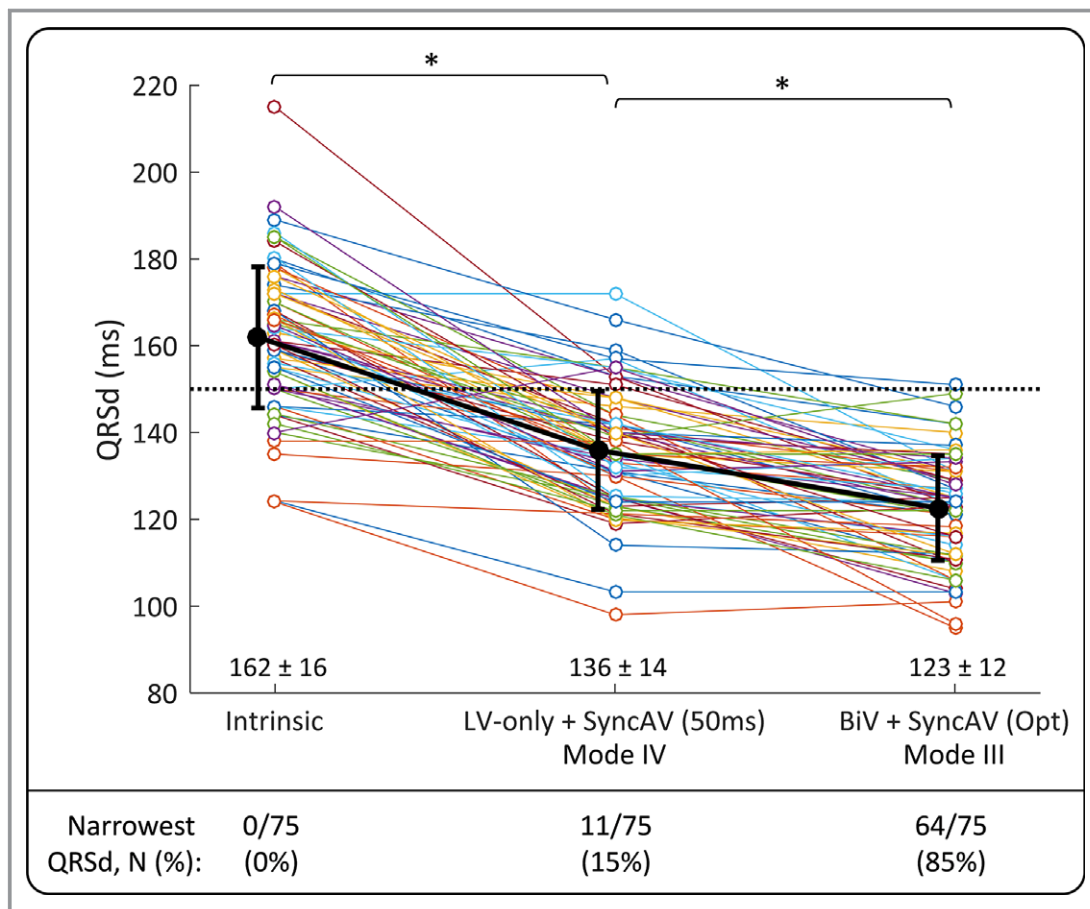
Figure 3. Left ventricular (LV)–only fusion pacing (Mode IV) reduced QRS duration (QRSd) by 15.6% relative to intrinsic, but individualized biventricular pacing (BiV) fusion pacing (Mode III) produced a greater effect (23.9% reduction, *P*<0.001 vs LV fusion pacing). **P*<0.001.

The AVDs associated with the greatest QRSd reduction, relative to the intrinsic PR interval, are shown in Table 3 for each pacing category. The baseline PR interval during intrinsic conduction was 194±34 ms (range 128–300 ms). In Mode II, the SyncAV-determined paced AVD was significantly greater than during Mode I (ie, fixed paced AVD) (143±36 ms versus 114±9 ms; *P*<0.05), representing a ratio relative to intrinsic of 73% versus 61%, respectively. Individualized SyncAV offset selection (Mode III) was associated with a further increase in paced AVD (158±39 ms versus 147±34 ms; *P*<0.05), equivalent to 81% of the intrinsic PR value. The etiology of cardiomyopathy did not affect the results.

The ability to reduce QRSd did not correlate with qRV, qLV, or LV-paced to RV-sensed times (Figure 6A through 6C). Correlation between qLV and LV-paced to RV-sensed intervals was weak (Figure 6D).

Discussion

The principal findings of this study were that post-implant ECG optimization could be significantly improved in otherwise electrically well-selected patients (LBBB and LV lead position) and was best achieved with patient-tailored programming facilitated with the SyncAV dynamic algorithm. Narrowing occurred irrespective of widely variable baseline myocardial conduction properties (including the intrinsic atrioventricular, qLV or LV-paced propagation intervals). Among default settings, nominal BiV settings using fixed atrioventricular intervals (Mode I) was least effective and produced mixed effects (QRSd narrowing in some individuals but widening in others). This was little changed by LV-only pacing (Mode IV). Better results were obtained with SyncAV default settings (Mode II), but best with individualized offsets (Mode III), which yielded an almost 2-fold greater QRSd reduction compared with static out-of-the-box settings. The results point to the importance of the atrioventricular interval and intramyocardial conduction characteristics for electrical optimization.

Currently, efforts to improve CRT effect are directed to patient selection (LBBB and QRSd >150 ms[5]) and lead position.[4,21] Despite this, nonresponse rates of >25% persist even in patients with nonischemic cardiomyopathy.[25] There has been prior interest in post-implant programming to
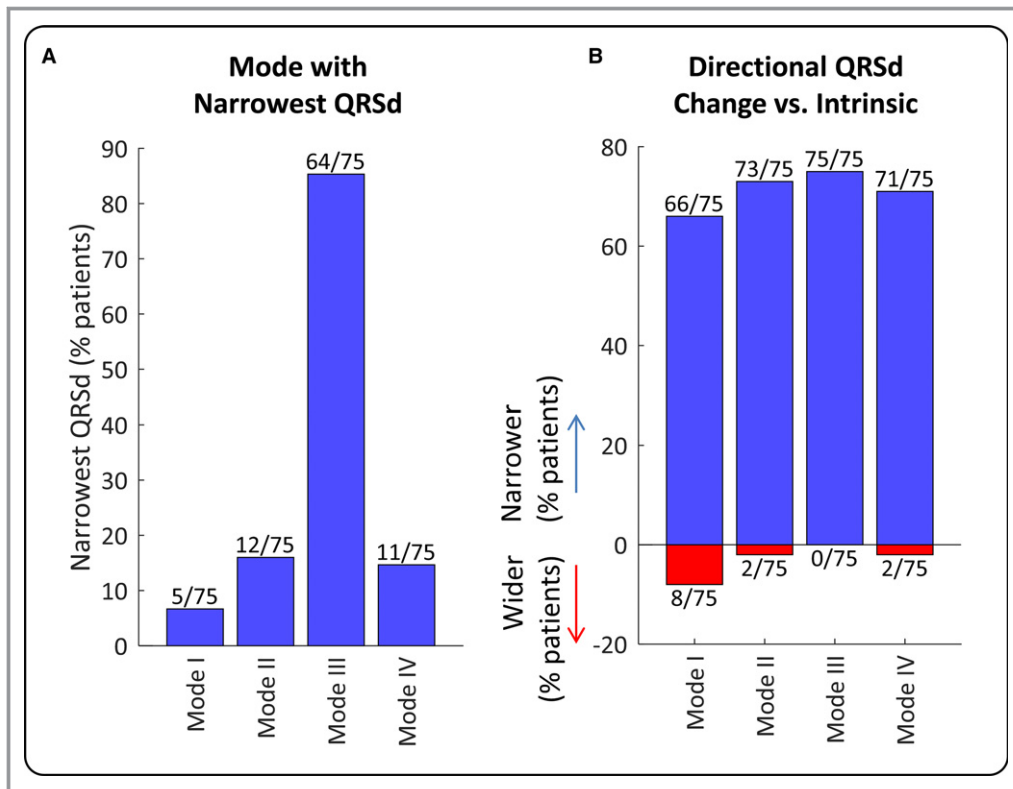
Figure 4. A, Distribution of pacing Modes associated with the narrowest QRS duration (QRSd). Note: Total percentage exceeds 100% because the narrowest QRSd can be achieved by multiple pacing Modes. B, Distribution in directional QRSd change among patients, relative to intrinsic conduction (narrower in blue, wider in red).

address this issue. Generally, results with echocardiography–guided or automated (but static) device–based algorithms have been inconclusive.[5] Importantly, none reported any electrical end results (ie, effects on QRS complex configuration or duration), which may have varied. Although superior clinical outcome in some patients in the AdaptivCRT trial[26] was attributed to QRS narrowing, post-implant ECGs were not evaluated formally. Hence, evaluation of programming required to achieve QRS optimization was a specific goal of the current study. The importance of achieving electrical resynchronization to CRT benefit is supported by biventricular mapping and hemodynamic studies.[8–11] However, these methods remain inaccessible in general clinical practice. In contrast, the surface ECG is widely available and reproducible, and CRT programming for maximal QRS narrowing is an intuitive surrogate for electrical resynchronization, though controversial. Most studies examining QRS narrowing are significantly limited by being mostly post hoc comparisons, ie, electrical optimization was not prospectively attempted as a primary therapeutic goal (a critical limitation), nor was the measured QRSd precisely quantified (ie, % reduction relative to baseline). However, the few to do so in randomized trials demonstrated improved acute hemodynamics and long-term

structural remodeling in comparison to nominal settings or to echocardiographic optimization.[14–18] This strategy reduced the incidence of negative responders to CRT and simultaneously increased the proportion of "super responders." In addition, the power of post-implant QRS narrowing to predict CRT response is comparable to that of qLV (area under the curve=0.63 for both[4,27]). Conversely, QRS widening by CRT among echocardiographically optimized patients correlated with poorer outcomes.[28] Collectively, these data point to the potential benefit of achieving electrical resynchronization manifested by ECG optimization. However, fundamental questions persist: in how many patients can this goal be achieved and to what extent, and is it modulated by other electrical characteristics such as atrioventricular conduction, baseline QRSd, and intraventricular conduction intervals?

To the authors' knowledge, this is the first study to investigate the role of post-implant programming in otherwise well-selected patients (LBBB) and optimized LV lead position.[21] QRSd optimization could be achieved in all patients, despite significant interindividual variations in PR and QRS intervals, qRV, qLV, or LV-paced to RV-sensed interval. Although CRT at nominal settings resulted in QRS narrowing (baseline 162 ms to paced 142 ms), in a range consistent with
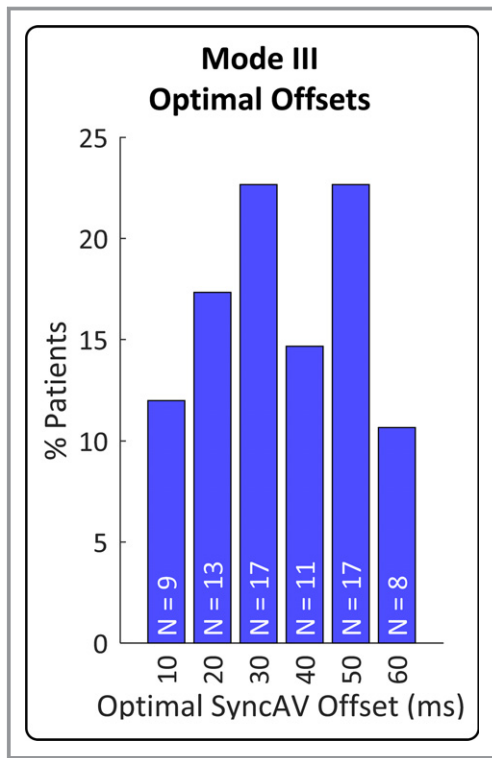
Figure 5. Distribution of optimal SyncAV offsets associated with Mode III.

results from randomized trials,[12] these summary results concealed the occurrence of QRS widening in a minority of patients (8/75, 11%) (Figure 4B). Importantly, out-of-the-box static settings do not account for intrinsic PR intervals, which vary widely among CRT candidates (range 128–300 ms in the current series). The significance of this is illustrated by the longer paced atrioventricular intervals implemented with default SyncAV (50 ms offset, Mode II) (Table 3), which more consistently produced QRS narrowing and to a greater degree (Figure 2) compared with static settings. Although paced QRS morphology and duration were not described with the dynamic algorithm used in the AdaptivCRT trial,[19] we confirmed that this form of dynamic LV-only pacing (Mode

IV) was superior to nominal settings: overall QRSd narrowed by 15.6% from baseline. However, QRSd widened in some patients, and when directly compared, this pacing Mode (which results in LV "fusion" pacing in patients with LBBB) was ultimately "best" of all tested modes in only 15% of patients. In comparison, individualized programming on the SyncAV platform (Mode III) performed superiorly to all other tested CRT modes. Overall QRSd was reduced by 39 ms from baseline, representing a 23.9% abbreviation, and importantly QRSd did not widen in any patient. This was observed among patients irrespective of QRS >150 ms or <150 ms, or PR interval >200 ms or <200 ms, indicating a consistent effect.

Our results point to a distinct electrical parameter that should be considered beyond LBBB and LV activation delay. This is implied by the relatively modest sensitivity/specificity (0.63/0.61 [area under the curve=0.63]) of the widely practiced cut point of qLV >95 ms for prediction of positive CRT effect.[4] The wide range of pacing parameters required for QRS optimization (Figure 5), despite conformity of electrical substrate (LBBB) and LV lead positions, point to significant variability in the electrical effects of LV pacing among individual CRT recipients. Although wider QRSd and longer LV activation delay (qLV) (ie, descriptors of electrical substrate) indicate greater likelihood of CRT response, in our study there was no correlation between qLV and ability to narrow the QRSd (R^2=0.07, Figure 6B), implying that the paced response to CRT is an independent factor. Mapping studies also indicated that patterns of wavefront propagation during LV pacing may differ from those during intrinsic conduction[8,10,29] and may be modulated by conduction barriers, which affect CRT efficacy. The presence of MRI-adjudicated scar adjacent to site of LV pacing was shown to compromise CRT effect, but no attempt was made to program around this barrier in that study.[30] Notably, in our series, ischemic cardiomyopathy did not prevent electrical resynchronization when customizing programming. Functional conduction barriers to LV-paced wavefronts may develop *without* underlying scar and limit electrical resynchronization

Table 3. Intrinsic and Paced AVDs

Population	Intrinsic AV Conduction Time, ms	AVD, ms (% Intrinsic)			
		Mode I	Mode II	Mode III	Mode IV
		BiV	BiV+SyncAV (50 ms)	BiV+SyncAV (Optimal)	LV Only+SyncAV (50 ms)
All patients (N=75)	193±36	114±9 61%	143±36 73%	158±39 81%	143±36 73%
Ischemic (n=25)	197±33	114±10 60%	147±33 74%	164±34 83%	147±33 74%
Nonischemic (n=50)	190±38	114±9 62%	140±38 73%	154±42 80%	140±38 73%

AV indicates atrioventricular; AVD, atrioventricular delay; BiV, biventricular pacing; LV, left ventricular.
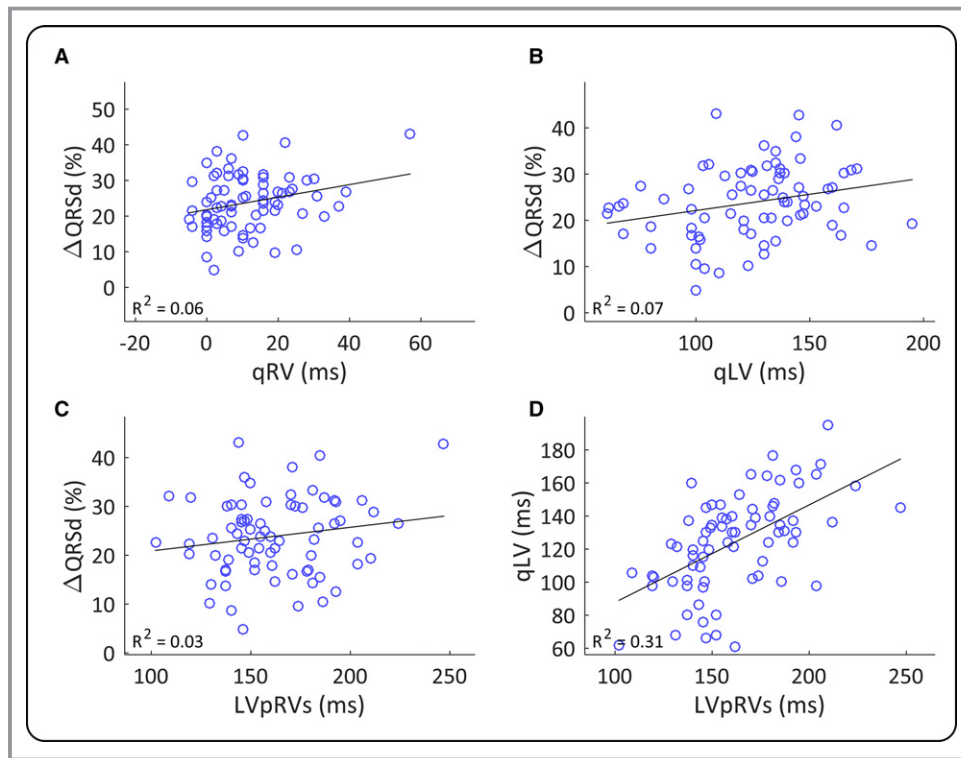
Figure 6. Scatter plots demonstrating the lack of correlation between the reduction in QRS duration (QRSd) and (A) QRS onset to right ventricular (RV) lead activation (qRV), (B) QRS onset to left ventricular (LV) lead activation (qLV), (C) LV-paced to RV-sensed time (LVpRVs), and (D) the lack of correlation between qLV and LVpRVs.

unless there is careful programming.[10,29] These mechanisms were assumed to underlie the association between nonresponse in CRT recipients with wide LV-paced QRSd (ie, a surrogate marker for induced LV conduction delay) despite echocardiographic optimization.[31,32] In contrast, during similar conditions in our study, QRS optimization could be accomplished even with long LV propagation times, when tailoring programmed parameters (Mode III). This has also been shown during ECG imaging mapping.[29] LV-paced QRSd, however, reflects biventricular activation. A more accurate measure of LV-paced activation may be the LV-paced to RV-sensed interval. Here, this measure was variable but importantly did not correlate with the ability to narrow the QRSd with individualized programming, and only modestly with qLV (R^2=0.31, Figure 6B and 6D). Direct imaging indicates that propagating wavefronts during LV pacing from relatively adjacent LV-pacing sites may differ significantly, although qLV at those sites remain similar,[33] indicating that LV substrate and LV-paced responses may be unrelated. Notably, in a prospective evaluation of ECG parameters in CRT, a shorter LV-paced QRSd was shown to be a strong predictor of clinical response following logistic regression analysis (area under the curve=0.74).[32] Hence, LV-paced propagation should be considered as a separate entity and an independent modulator of successful electrical resynchronization in CRT.

Our results indicate that BiV with customized attention to atrioventricular intervals more effectively restores ventricular electrical synchrony compared with LV fusion pacing (notably RBB conduction assessed by qRV intervals was preserved in our patients with LBBB[34]). Other investigators using different methods also found that this LV fusion mode to be best in fewer than 10% of patients with CRT.[14,16,18,35] This contradicts the notion that LV pacing fused to intrinsic RBB conduction always provides more "physiological" resynchronization in the pathology of LBBB and heart failure. LV epicardial free-wall pacing does not reproduce normal apex-to-base LV depolarization.[36] Longer QRSd (eg, QRSd >150 ms) in LBBB signifies larger transseptal conduction barriers, which sometimes may be resolved by RV apical pacing and not intrinsic RBB conduction.[37] Under these conditions, BiV (rather than LV only) pacing by activating both apex and base may more closely approximate physiological LV activation, and may explain our results. In support, long-term clinical response was *not* improved with LV fusion pacing in patients with QRSd >150 ms, and dynamic BiV was *superior* to LV-only pacing in preventing AF in the Adaptive Cardiac Resynchronization Therapy trial.[38,39] Nevertheless, optimized BiV pacing may retain some level of intrinsic RBB activation, as interaction between intrinsic RBB conduction and RV- and LV-paced wavefronts (ie, "triple fusion") appears to be important to electrical resynchronization.[11,18,40]

Limitations

We assessed patients with LBBB only and results with non-LBBB configurations were untested. Optimal lead position was assessed by electrical parameters and not echocardiographically by regions of latest contraction (a method that has also shown better outcome compared with conventional deployment, although limited by accuracy, reproducibility, and increased procedural time and radiation dose[41,42]). Recent work indicates that sites of latest mechanical and electrical activation coincide, in which case qLV represents an easier method to employ during implant.[43] We tested a range of paced settings that may be quickly applied intraprocedurally and compared with available algorithms. Possibly, additional permutations of atrioventricular/interventricular intervals may produce further QRS abbreviation. Other important QRS features (eg, morphology, vectorcardiography, and signal content[44–48]) with prognostic value additive to QRSd abbreviation may be integrated in the future. This was an acute study. The longer-term effects of CRT programming for electrical resynchronization coupled with a dynamic device-based platform are undergoing prospective evaluation in a randomized trial (Clinicaltrials.gov: NCT02903940).

Conclusions

Our results have several significant clinical implications. Although out-of-the-box settings are attractive to facilitate clinical workflow, nominal static settings (Mode I) have modest effect (and may be sometimes detrimental), but default settings with the SyncAV platform (Mode II) performed superiorly. This was further enhanced by individualization with relatively few adjustments to the SyncAV offset (more often using BiV rather than LV-only pacing) and this eliminated the potential risk of QRS widening. This illustrates the need to accommodate individual variations in myocardial conduction characteristics to gain maximal electrical resynchronization. We show a simple solution for delivery of properly timed and maintained CRT pacing.

Disclosures

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