Longer Left Ventricular Electric Delay Reduces Mitral Regurgitation After Cardiac Resynchronization Therapy

Mechanistic Insights From the SMART-AV Study (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy)

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Background—Mitral regurgitation (MR) is associated with worse survival in those undergoing cardiac resynchronization therapy (CRT). Left ventricular (LV) lead position in CRT may ameliorate mechanisms of MR. We examine the association between a longer LV electric delay (QLV) at the LV stimulation site and MR reduction after CRT.

Methods and Results—QLV was assessed retrospectively in 426 patients enrolled in the SMART-AV study (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in CRT). QLV was defined as the time from QRS onset to the first large peak of the LV electrogram. Linear regression and logistic regression were used to assess the association between baseline QLV and MR reduction at 6 months (absolute change in vena contracta width and odds of ≥1 grade reduction in MR). At baseline, there was no difference in MR grade, LV dyssynchrony, or LV volumes in those with QLV above versus below the median (95 ms). After multivariable adjustment, increasing QLV was an independent predictor of MR reduction at 6 months as reflected by an increased odds of MR response (odds ratio: 1.13 [1.03–1.25]/10 ms increase QLV; P=0.02) and a decrease in vena contracta width (P<0.001). At 3 months, longer QLV (≥median) was associated with significant decrease in LV end-systolic volume (ΔLV end-systolic volume −28.2±38.9 versus −4.9±33.8 mL, P<0.001). Adjustment for 3-month ΔLV end-systolic volume attenuated the association between QLV and 6-month MR reduction.

Conclusions—In patients undergoing CRT, longer QLV was an independent predictor of MR reduction at 6 months and associated with interval 3-month LV reverse remodeling. These findings provide a mechanistic basis for using an electric-targeting LV lead strategy at the time of CRT implant. **(*Circ Arrhythm Electrophysiol*. 2016;9:e004346. DOI: 10.1161/CIRCEP.116.004346.)**

Key Words: cardiac resynchronization therapy ■ echocardiography ■ logistic models ■ papillary muscles ■ ventricular remodeling

Cardiac resynchronization therapy (CRT) is associated with favorable ventricular remodeling and improved clinical outcomes in appropriately selected patients with left ventricular (LV) systolic dysfunction and electric dyssynchrony.[1] Given that a significant minority of patients do not derive clinical or echocardiographic benefit after CRT, there has been substantial interest in identifying determinants of response for this effective but nonetheless costly therapy.[2] Of these determinants, reduction in mitral regurgitation (MR) after CRT has emerged as a significant predictor of improved survival and has been linked to papillary muscle resynchronization and LV reverse remodeling (LVRR).[3–5]

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LV lead location at the time of CRT implant may influence these proposed mechanisms of MR reduction. For example, LV pacing at the site of the latest electric delay (ie, QLV) is associated with acute hemodynamic improvement and LVRR.[6–10] However, the optimal strategy of LV lead targeting in CRT (ie, anatomic versus electric) remains an open question,[11,12] and whether such targeting impacts changes in MR after CRT remains unknown. The expanding implementation of multisite pacing in CRT and the related capacity to deploy multiple pacing vectors reinforces the clinical importance of

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WHAT IS KNOWN

- MR is associated with worse outcomes in patients with heart failure, including those undergoing CRT.
- LV lead location may influence MR reduction during CRT and mechanical resynchronization and LVRR.

WHAT THE STUDY ADDS

- The degree of delay at the LV lead site (QLV) is an independent predictor of 6-month MR reduction after CRT, even after accounting for baseline MR and other established predictors of LVRR.
- The association between QLV and MR reduction was related—in part—to the LVRR.
- The findings suggest that an electrogram-based LV lead placement strategy, and pacing site optimization for nonresponders to CRT and those with persistent MR, warrants prospective investigation.

identifying a mechanistic basis for an electric-targeting strategy in CRT.[13]

Therefore, in this study, we examine the association between baseline QLV and reduction in MR after CRT in patients enrolled in the SMART-AV study (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in CRT).[14] We hypothesized that a longer QLV would be associated with more significant reduction in MR after CRT. We additionally assess potential mechanisms of QLV-mediated MR reduction, including interval mechanical resynchronization and LVRR.

Methods

Study Sample

The study cohort comprised patients enrolled in the SMART-AV study (NCT00677014), a multicenter randomized controlled trial comparing atrioventricular (AV) optimization strategies in patients undergoing CRT-defibrillator implantation for standard guideline indications.[15] After randomization, patients underwent baseline echocardiographic imaging and serial evaluation at 3 and 6 months after the implantation. In this substudy, patients who had interpretable baseline QLV measurement and who had serial echocardiograms were included (n=426; 50% of the original study cohort). QLV measurement was not mandated in the trial protocol. Reasons for inability to measure QLV included the presence of heart rate irregularity (atrial fibrillation and premature ventricular contractions) or the absence of available electric data (electrogram or surface ECG). Exclusion criteria included those enrolled who did not undergo CRT, did not complete 6-month follow-up (died or withdrew), or were missing echocardiography data (baseline or follow-up; Figure 1). The SMART-AV trial was conducted in accordance with the Helsinki Declaration and the ethics or regulatory committee of each individual institution. All patients provided written, informed consent to participate in the trial.

QLV Assessment

Details on QLV assessment for patients within the SMART-AV study have been previously reported in detail.[6,9] QLV assessment was performed retrospectively by 2 independent core laboratory reviewers blinded to lead position, patient characteristics, and clinical outcome. In brief, at the final lead positions, surface lead II, right ventricular (RV), and LV electrograms were recorded simultaneously on paper strips at a sweep speed of 100 mm/s. For participants in sinus rhythm and in the absence of ventricular pacing, the QLV interval was measured from the onset of surface electrocardiographic QRS to the first major peak (positive or negative) of the LV electrogram during a cardiac cycle at a resolution of 5 ms (Figure 2). The amplitude of the first major peak was required to be >50% of the amplitude of the largest peak in a given cardiac cycle. Using a sample of 15 electrograms to assess reproducibility of QLV assessment, the concordance correlation coefficient between reviewers was 0.93 (95% confidence interval, 0.82–0.98).[9]

Echocardiographic Assessment of MR and Dyssynchrony

The primary end point of this substudy was reduction in MR from baseline to 6 months after CRT implant. Echocardiography was analyzed at a single core laboratory blinded to group assignment. The severity of MR was assessed using a multiparametric approach according to the consensus guidelines using vena contracta (VC) width (narrowest component of the MR color Doppler jet in a parasternal long-axis view) and the ratio of the MR jet area/left atrial area (measured by planimetry in the 4-chamber view; Figure 2).[17,18] Severity was graded mild with VC <0.3 cm and jet

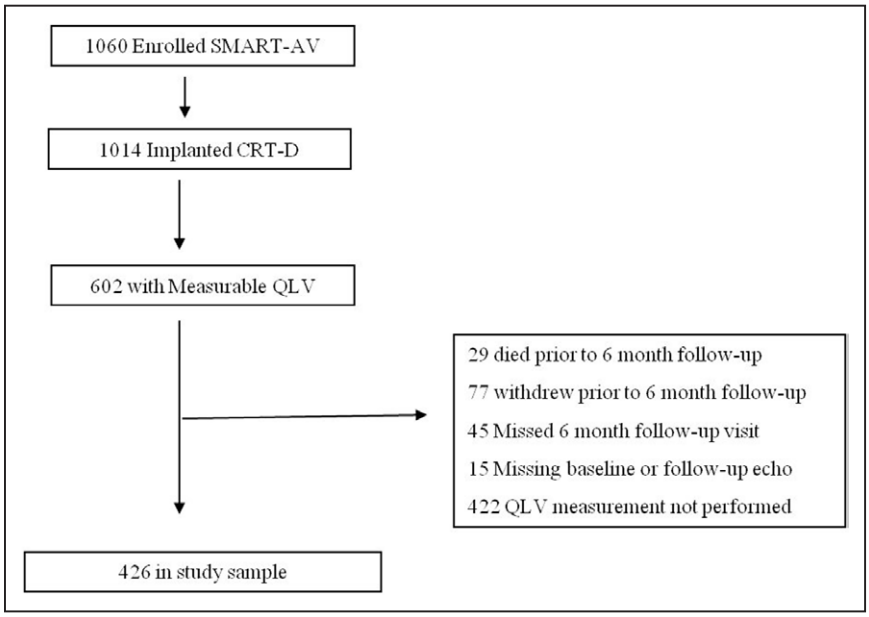

Figure 1. Study sample. Shown are patients enrolled in the SMART-AV study (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in CRT) and reasons for exclusion for this substudy. QLV indicates LV electric delay.

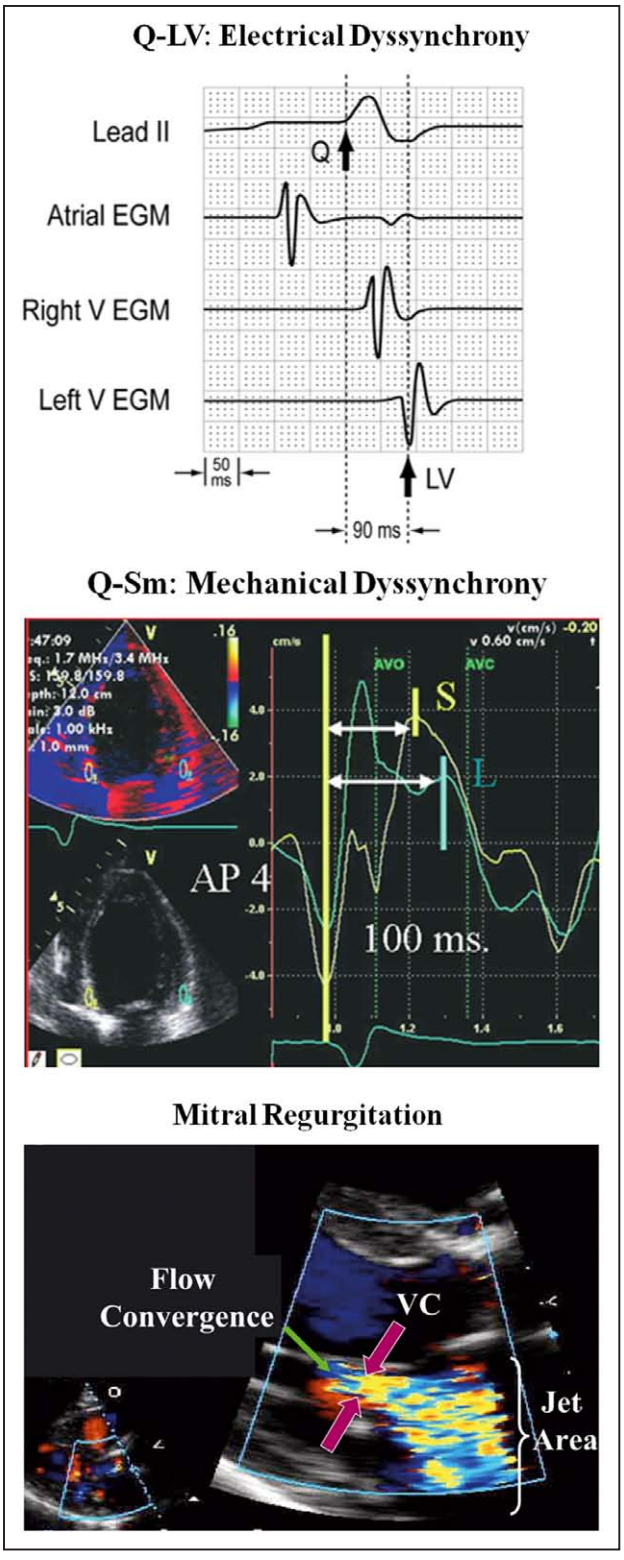

Figure 2. Representative measures of electric dyssynchrony, mechanical dyssynchrony, and mitral regurgitation. **Top**, Shown is an example of left ventricular lead electric delay (QLV) measurement. Calipers are aligned with the onset of QRS using surface ECG (denoted Q) and first major peak (positive or negative) of the left ventricular electrogram (denoted LV). The QLV was calculated as 90 ms for this patient. Reproduced with permission from Gold et al.[9] **Middle**, Shown is an example of LV intraventricular dyssynchrony measurement at the LV base using tissue Doppler imaging and quantified as the time from (*Continued*)

area <20%, moderate with VC 0.3 to 0.7 cm and jet area 20% to 40%, and severe with VC >0.7 cm and jet area >40%. The VC width held primacy if jet area values were discordant as previously described.[3] Pulsed Doppler mitral inflow E-wave velocity and the tissue Doppler early diastolic velocity (E′) at the lateral and septal positions were obtained in the apical 4-chamber view to determine E/E′ as an estimation of LV filling pressure. LV volumes were determined in the apical 4- and 2-chamber views by the biplane method of discs. Intraventricular dyssynchrony was quantified using pulsed Doppler tissue imaging in the apical 2-, 3-, and 4-chamber views (GE Echo Pac version 6.0) as suggested by expert guidelines.[16,19] LV dyssynchrony was quantified as the time from QRS onset to peak systolic velocity (ΔQ-Sm) and measured adjacent to the annulus at the LV base in 6 myocardial segments (anterior, anteroseptal, posterior, inferior, septal, and lateral; Figure 2). Global intraventricular dyssynchrony was then calculated as the maximal difference across the basal segments. Alternative definitions of dyssynchrony reflecting specific LV segments adjacent to papillary muscles (ie, lateral–inferior and lateral–septal) were additionally assessed. As these were not related to MR reduction at 6 months, we prioritized the use of global intraventricular dyssynchrony.

Statistical Analysis

Given no difference in the primary LV end-systolic volume (ΔLVESV) or secondary (Δquality of life score, 6-minute walk distance, LV ejection fraction, and LV end-diastolic volume) end points in randomized assignment groups of the SMART-AV study, data were pooled for this analysis. Continuous variables were expressed as mean±SD or median (interquartile range) and compared using 2-tailed *t* test or Wilcoxon test as appropriate. Categorical variables were expressed as percentages and compared using the χ^2 test. The association between QLV and change in MR after CRT was assessed using several complementary approaches. First, the distribution of MR grade (none/mild, moderate, and severe) was compared between QLV groups (≥ versus < median value) at baseline and 6 months. Stratification at the median QLV was performed given the previously demonstrated association between QLV ≥median and both echocardiographic (ie, LVRR) and clinical (ie, improved quality of life scores) outcomes in SMART-AV.[9] Second, logistic regression was performed to examine the relationship between QLV (assessed continuously) and MR response (defined as ≥1 grade reduction in MR at 6 months post CRT). As patients without MR at baseline can by definition never be MR responders, logistic models assessing MR response included patients with ≥1+ MR at baseline. To assess for a potential nonlinear relationship between QLV and log odds of MR response, we used a restricted cubic spline model with median QLV as the reference.[20] Third, linear regression was performed assessing the relationship between QLV (assessed continuously) and change in VC width from baseline to 6 months post CRT implant (ΔVC). Linear, spline, and logistic regression models were adjusted for prespecified covariates known to influence LVRR and clinical outcome after CRT: age, sex, New York Heart Association class (I-III versus IV), QRS duration (≥ versus < 150 ms), left bundle branch block (LBBB versus no LBBB), cause of cardiomyopathy (ischemic versus nonischemic), baseline LV ejection fraction, and baseline LV end-systolic volume (LVESV). As there was no association between QLV and anatomic lead location, the

Figure 2 Continued. the onset of QRS to peak systolic velocity (ΔQ-Sm). In the apical (AP) 4-chamber view, dyssynchrony was measured in the septal and lateral segments. The maximal Q-Sm in this view was noted for the lateral wall (100 ms). Reproduced with permission from Agler et al.[16] **Bottom**, Shown is a parasternal long-axis view with color flow Doppler demonstrating the components of the mitral regurgitant jet—flow convergence, vena contracta (VC), and jet area as measured in the left atrium. The VC is measured as the narrowest component of the regurgitant jet as indicated by arrows (pink). Reproduced with permission from Zoghbi et al.[17] EGM indicates electrogram.

Table 1. Baseline Characteristics of Study Sample

	All Patients, N=426	QLV<95 ms, N=209	QLV≥95 ms, N=217
Age, y	66±11	66±11	66±11
Female sex, n (%)	144 (34%)	59 (28)*	85 (39)
NYHA class, n (%)			
II	12 (3)	7 (3)	5 (2)
III	401 (95)	192 (93)	209 (96)
IV	11 (2)	8 (4)	3 (2)
QRS duration, ms	151±19	137±22*	162±22
Body mass index, kg/m^2	29.6±6.0	29.5±6.2	29.6±5.9
LBBB, n (%)	320 (75%)	130 (62)*	190 (88)
Ischemic cause, n (%)	251 (59%)	139 (67)*	112 (52)
LV lead location			
Short axis			
Apical, n (%)	46 (11)	19 (10)	27 (13)
Midventricular, n (%)	338 (82)	168 (85)	170 (80)
Basal, n (%)	27 (7)	11 (5)	16 (8)
Long axis			
Anterior, n (%)	13 (3)	9 (5)	4 (2)
Anterolateral/lateral, n (%)	106 (26)	59 (30)	47 (22)
Posterolateral, n (%)	269 (65)	122 (61)	147 (69)
Posterior, n (%)	24 (6)	9 (4)	15 (7)
Randomization group, n (%)†			
Echocardiographic	146 (34)	72 (34)	74 (34)
Fixed	137 (32)	67 (32)	70 (32)
SmartDelay	143 (34)	70 (34)	73 (34)
Pacing mode, n (%)			
DDD	319 (77)	151 (74)	168 (80)
DDDR	96 (23)	53 (26)	43 (20)
VVI	1 (<1)	1 (<1)	0 (0)

AV indicates atrioventricular; LBBB, left bundle branch block; LV, left ventricular; and NYHA, New York Heart Association class.

*P<0.05 for comparison of QLV ≥ vs < 95 ms.

†Randomization in the SMART-AV trial (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in CRT) was to AV delay using iterative technique (Echocardiographic), Fixed (120 ms), or the SmartDelay algorithm.

latter was not included in multivariable adjusted models. Final, to assess mechanisms of potential QLV-related reduction in MR at 6 months, we examined the association between QLV (≥ versus < median) and 3-month ΔLVESV and ΔQ-Sm. To assess if either of these mechanisms mediated the relationship between QLV and 6-month change in MR, the described multivariable logistic and linear regression models were then adjusted separately for each proposed mediator (ie, 3-month ΔLVESV and 3-month ΔQ-Sm). A 2-sided P value <0.05 was considered statistically significant. R version 2.12.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.3 (SAS Institute, Cary, NC) were used for statistical analysis.

Results

Study Sample

Baseline characteristics of the study sample are shown in Table 1. In keeping with a contemporary population undergoing CRT, patients were older (aged 66±11 years), predominantly male (64%) with advanced heart failure (>97% New York Heart Association class III/IV), electric dyssynchrony (QRS 153±25 ms), and LV systolic dysfunction (LV ejection fraction 28±9%). The majority of patients had an ischemic cause of cardiomyopathy (59%) and a baseline LBBB (75%). When stratified by median QLV, patients with longer baseline QLV were more likely to be women, have a longer baseline QRS duration, and were less likely to have an ischemic cause of cardiomyopathy. There were no significant differences in anatomic lead location, pacing mode, SMART-AV randomization assignment, or New York Heart Association functional class in patients with a longer compared with shorter QLV.

When compared with patients included in the final study cohort, those excluded (N=634; Figure 1) showed no significant difference in baseline demographics, LV dyssynchrony, or MR grade with clinically insignificant differences in QRS duration (151±19 versus 154±21 ms, P=0.03) and LV function (LV ejection fraction: 28±9 versus 27±9%, P=0.04; Table I in the Data Supplement). Only a minority of patients were excluded on the basis of death during the trial follow-up (N=29; 2.7% of the original SMART-AV cohort). As expected, those who died were older (71±11 versus 66±11 years, P=0.01) and had a lower body mass index (25.9±5.5 versus 29.6±6.0 kg/m^2, P=0.002) but otherwise showed no significant differences in demographics, electric, or echocardiographic measures (Table II in the Data Supplement).

Longer QLV Is Associated With Reduction in MR at 6 Months After CRT

At baseline, there were no significant differences in LV function or volumes, LV dyssynchrony, or MR severity in patients with a longer versus shorter QLV (Table 2; Figure 3). Given the modulation of the atrioventricular interval in SMART-AV and its potential influence on MR, pacing mode, PR interval, and % pacing (RV and LV) were compared across QLV groups (Table II in the Data Supplement). When stratified by median QLV (≥ versus < 95 ms), there was no significant difference in pacing mode distribution (P=0.09) or PR interval (199±53 versus 199±44 ms, P=0.95) at 6 months. The median % of RV and LV pacing was >97% in both groups and nominally higher in those with a longer QLV (P<0.01 for both RV and LV pacing comparisons).

In unadjusted analysis stratified by median QLV, longer QLV was associated with less severe MR (grade, VC width) at 6 months with parallel significant reductions in left atrial volume and LV filling pressures as reflected by a lower E/E′ ratio (Table 2; Figure 3). After multivariable adjustment for multiple covariates known to influence LVRR—including sex, ischemic cause, LBBB, QRS duration, baseline LVESV, and baseline MR—increasing QLV remained a significant predictor of decreased MR at 6 months (Table 3; Tables IIIA and IVA in the Data Supplement). For every 10 ms increase in QLV, VC width decreased significantly

Table 2. MR at Baseline and 6 Months After Cardiac Resynchronization Therapy, Stratified by Median QLV

	QLV<95 ms, N=209	QLV≥95 ms, N=217	*P* Value
Baseline			
LVESV, mL	122±54	134±69	0.05
LV ejection fraction, %	29±9	27±9	0.10
LV dyssynchrony (Q-Sm), ms	91±71	105±85	0.07
MR			
Grade, n (%)			
None/mild	100 (48)	101 (47)	0.93
Moderate	73 (35)	76 (35)	
Severe	36 (17)	40 (18)	
Semiquantitative measures			
Vena contracta, cm	0.35±0.37	0.36±0.38	0.64
MR jet area/LA area, %	11±13	12±14	0.48
Left atrial volume, mL	78±35	79±35	0.61
E/E′			
Lateral	7.2±3.1	7.0±3.4	0.48
Septal	7.4±3.1	7.1±3.4	0.43
6 mo			
MR			
Grade, n (%)			
None/Mild	100 (48)	126 (58)	0.03
Moderate	76 (36)	73 (34)	
Severe	33 (16)	18 (8)	
Semiquantitative measure			
ΔVena contracta vs baseline, cm	−0.01±0.41	−0.11±0.35	0.006
ΔLeft atrial volume, mL	1±33	−8±29	0.002
E/E′			
Lateral	6.9±2.8	6.3±2.8	0.01
Septal	7.1±2.9	6.3±2.8	0.006

Q-Sm denotes left ventricular mechanical dyssynchrony as assessed by tissue Doppler. CRT-D indicates cardiac resynchronization therapy with implantable cardioverter-defibrillator; DDD, dual chamber pacing; DDDR, dual chamber rate responsive; ESV, end-systolic volume; LA, left atrium; LV, left ventricular; MR, mitral regurgitation; NHLBI, National Heart, Lung, and Blood Institute; QLV, LV electric delay; Q-Sm, time from QRS onset to peak systolic velocity; and VVI, ventricular demand pacing.

(−0.02 [−0.03, −0.008] cm; *P*<0.001) and the odds of MR reduction ≥1 grade increased significantly (odds ratio: 1.13 [1.03, 1.25]; *P*=0.02). When assessed continuously, there was a significant linear relationship between QLV and MR response (*P* for linear trend =0.01; Figure 4). Of note, in fully adjusted models inclusive of QLV, the only other significant predictors of MR change were baseline MR grade and age; baseline LBBB was associated with a trend to greater VC width reduction (Tables IIIA and IVA in the Data Supplement).

Mechanisms of QLV-Mediated MR Reduction

We next examined potential mechanisms of QLV-mediated MR reduction at 6 months, including interval LV resynchronization and LVRR. When assessed at 3 months, longer QLV (≥ versus < median) was associated with greater reduction in LV dyssynchrony (ΔQ-Sm: −9±103 versus 10±90 ms; *P*=0.04) and greater LVRR (ΔLVESV: −29±39 versus −5±34 mL; *P*<0.001). When added to multivariable models, 3-month change in LVESV was significantly associated with 6-month MR reduction (odds of MR grade reduction and reduction in VC width; *P*<0.001 for both) and modestly attenuated the relationship between QLV and MR reduction (Table 3; Tables IIIB and IVB in the Data Supplement). In contrast, 3-month change in mechanical dyssynchrony was not associated with 6-month MR reduction (*P*>0.50 for both linear and logistic models) and furthermore did not attenuate the relationship between QLV and 6-month MR reduction (Table 3; Tables IIIC and IVC in the Data Supplement).

Discussion

In this substudy of 426 participants in the SMART-AV trial, longer QLV was a significant predictor of decreased MR at 6 months after CRT. Longer QLV was also associated with interval LVRR and mechanical resynchronization at 3 months. The mechanism of QLV-associated MR reduction was mediated, in part, by interval LVRR. These data provide a mechanistic basis for using an electric-based LV pacing strategy and provide insight into the role of LV pacing as therapeutic strategy for MR in advanced heart failure patients undergoing CRT.

MR is a well-established predictor of mortality in systolic heart failure,[21] and its reduction after CRT has been correlated with LVRR and improved clinical outcomes.[3–5] The mechanisms of MR reduction after CRT have been variably attributed to acute improvements in LV contractility and papillary muscle resynchronization and subacute improvements in LV sphericity and tethering forces related to LVRR.[22] For example, in 63 patients undergoing CRT, Ypenburg et al[23] demonstrated immediate improvement in MR associated with acute reductions in mechanical dyssynchrony. However, at 6 months and despite significant LVRR, temporary cessation of CRT was associated with recurrent MR and increased mechanical dyssynchrony—thus implicating LV resynchronization as the primary mechanism of MR reduction after CRT. Others have similarly identified immediate reductions in MR post CRT[5] and identified baseline mechanical dyssynchrony as a significant predictor of MR reduction.[3] In contrast, Madaric et al[24] identified 3-month LVRR as a more important predictor of MR reduction (rest and exercise) when compared with immediate reduction in mechanical dyssynchrony after CRT. To date, analyses of CRT and MR have been limited by the retrospective, post hoc evaluation of MR at varying time points after implant,[4,5] the absence of serial echocardiography at intermediate time points (eg, 3 months post implant),[3] or significant limitation in sample size (<100 patients).[3,24]

Strengths of this study include its size and related power to detect significant mechanistic associations, the prospective availability of serial echocardiography with dyssynchrony assessment nested within a randomized controlled trial, and complementary multimodal analysis of MR reduction (linear

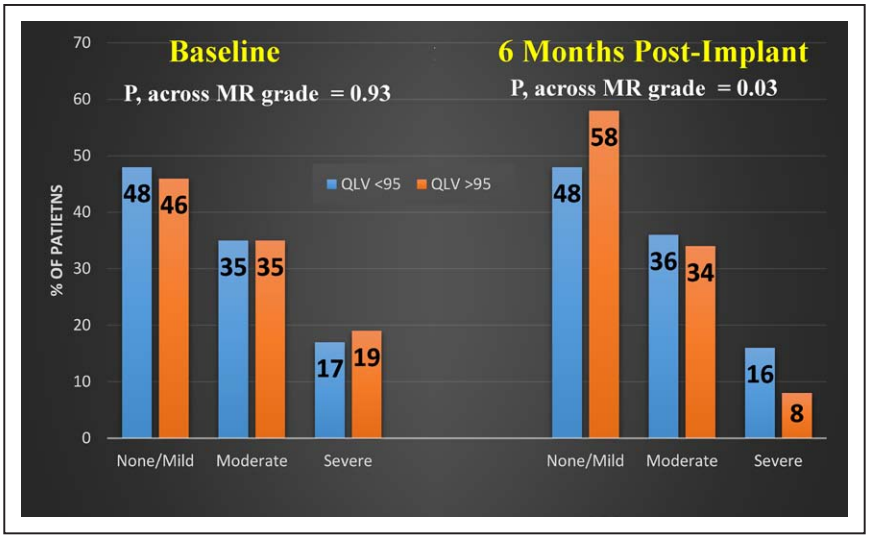

Figure 3. QLV and MR reduction after CRT. Shown is the distribution of MR area change (decreased, unchanged, or increased) from baseline to 6 months after CRT implant stratified by median left ventricular lead electric delay (QLV; ≥ vs < 95 ms). CRT indicates cardiac resynchronization therapy; MR, mitral regurgitation; and QLV, LV electric delay.

and logistic models) accounting for regression to the mean with adjustment for baseline MR. We also uniquely assessed the impact of a clinically relevant intervention (ie, QLV-based pacing strategy) associated with both proposed mediators of MR reduction (ie, LVRR and mechanical resynchronization). Although a longer QLV has been associated with acute hemodynamic benefits[10] and long-term improvements in quality of life and clinical outcomes,[8,9] our findings provide a mechanistic basis for a QLV-based pacing strategy, which was associated with interval LV resynchronization and LVRR with subsequent reduction in MR. In contrast to previous studies[3,23] but consistent with others,[25] reduction in mechanical dyssynchrony at 3 months was not a significant predictor of MR reduction. It is possible that our selected measure of mechanical dyssynchrony was an insensitive marker of dyssynchrony, although sensitivity analyses using alternative definitions of LV dyssynchrony (eg, difference across LV segments adjacent to papillary muscles) were similarly null. Nonetheless, alternative mechanisms of resynchronization not captured by tissue Doppler (Q-Sm) could still remain an important mechanism of MR reduction and may warrant future investigation. Others have proposed a multistaged process in which initial papillary resynchronization leads to reduction in MR, which then facilitates LVRR and further reductions in MR.[26] Although we were not able to assess resynchronization immediately after CRT, even in this multistaged model, dyssynchrony is still an upstream mediator of MR reduction and we would have still expected the relationship between QLV and MR reduction to have attenuated after adjustment for change in dyssynchrony.

In patients undergoing CRT, the optimal site of LV pacing remains an open question of significant clinical relevance.[1] Our study has several clinical implications. First, conflicting findings about the benefits of anatomic-based lead targeting strategies[11,12] have refocused interest in electric-targeting strategies, such as LV electric delay (ie, QLV) or RV-LV electric delay.[27] Longer QLV has been associated with acute hemodynamic benefits,[10] 6-month reverse remodeling,[9] and clinical outcomes 12-month postimplant.[8] With the expanding use of multisite LV

Table 3. QLV and 6-Month Reduction in MR: Multivariable and Mediator-Adjusted Estimates

	Multivariable-Adjusted ΔVC Width*		Multivariable-Adjusted Odds Ratio for MR Reduction ≥1 Grade†	
	β-Estimate	*P* Value	Odds Ratio [95% Confidence Interval]	*P* Value
Multivariable-adjusted model				
QLV, per 10 ms	−0.02 [−0.03 to −0.008]	<0.001	1.13 [1.03 to 1.25]	0.02
Multivariable-adjusted model+Potential mediators				
ΔLVESV (3 mo)				
QLV, per 10 ms	−0.01 [−0.02 to −0.004]	0.008	1.10 [0.99 to 1.23]	0.06
ΔLVESV at 3 mo, per 10 mL	0.002 [0.001 to 0.003]	<0.001	0.98 [0.97 to 0.99]	<0.001
ΔLV dyssynchrony (3 mo)				
QLV, per 10 ms	−0.02 [−0.03 to −0.007]	0.001	1.12 [1.01 to 1.24]	0.03
ΔQ-Sm at 3 mo, ms	0.001 [−0.003 to 0.004]	0.77	0.99 [0.96 to 1.02]	0.50

Q-Sm denotes left ventricular mechanical dyssynchrony as assessed by tissue Doppler. EF indicates ejection fraction; ESV, end-systolic-volume; LV, left ventricle; MR, mitral regurgitation; NYHA, New York Heart Association; QLV, left ventricular electric delay; and VC, vena contracta.

*Adjustment for age, sex, NYHA class, QRS duration, left bundle branch block, ischemic cause of cardiomyopathy, LVESV, LVEF, and baseline MR. Effect estimates for full model are shown in Table III in the Data Supplement.

†MR response was assessed in patients with >mild MR (N=225).

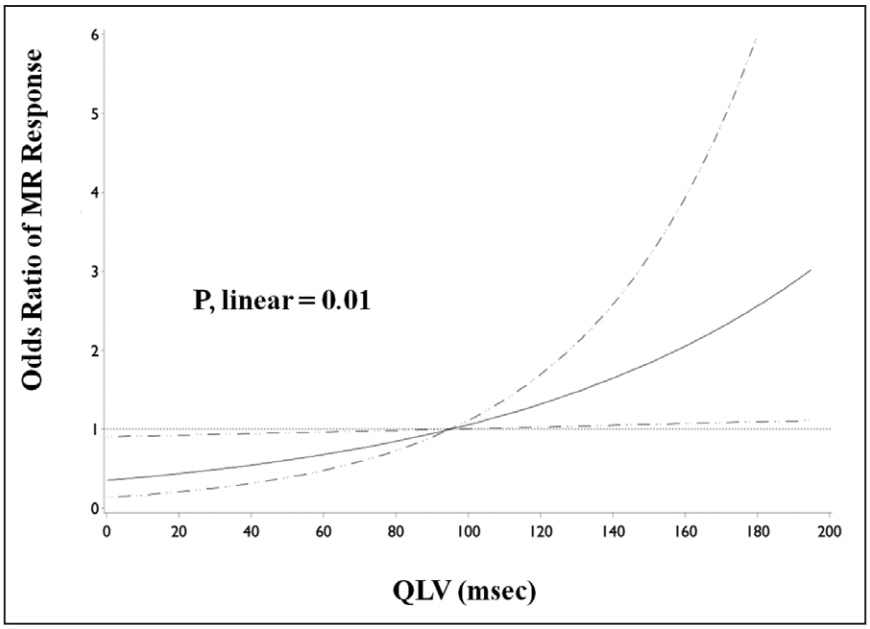

Figure 4. Relationship between QLV and odds ratio of mitral regurgitation (MR) reduction ≥1 MR Grade. Shown is the multivariable-adjusted association between left ventricular electric delay (QLV) and odds ratio of MR response (defined as ≥1 grade improvement in MR at 6 months after cardiac resynchronization therapy). The dotted lines represent the 95% confidence intervals. Adjustment is for age, sex, New York Heart Association class, QRS duration, left bundle branch block, ischemic cause of cardiomyopathy, LV end-systolic volume, LV ejection fraction, and baseline MR. The reference for the hazard ratio was taken as the median QLV of the study cohort (95 ms).

lead technology capable of multiple pacing vectors, the role and benefit of an electric-based pacing strategy will be of increasing significance.[13] Second, with the recent feasibility demonstration of leadless endocardial LV pacing,[28] important questions remain about the optimal strategy of targeting this novel technology. Of note, there was no correlation between anatomic lead location and QLV in our study, suggesting that a uniform anatomic pacing strategy may not be the optimal choice for either endocardial or epicardial LV pacing. Third, recent work has highlighted the potential survival benefit associated with electric-based LV lead implantation strategies in CRT.[27] Given the association between persistent MR and decreased survival in CRT,[3,4] our findings suggest a potential role for an electric-based optimization strategy post implant (eg, RV-LV electric distance and paced QRS width) particularly in those with nonresponse (clinical and echocardiographic) or persistent MR after CRT. Final, the impact of CRT on MR remains a point of active investigation with an emerging recognition of novel applications of LV pacing for the treatment of MR in heart failure.[29,30] A more refined understanding of the association between LV lead targeting with both acute and subacute changes in mitral valve functionality—including influence on tethering and closing forces—would offer important insight into the impact of LV pacing on MR reduction in those undergoing CRT.[29]

Limitations

The findings of this study should be interpreted within the limitations of the study design. First, QLV was measurable in a subset of the study sample and comparisons were made only for those survived to 6 months. Although QLV assessment was not mandated in the SMART-AV protocol, the similarities between those included versus excluded from this substudy (Tables I and II in the Data Supplement) support the generalizability of these findings to patients undergoing CRT. The association between longer QLV and certain baseline characteristics (eg, gender) may warrant further investigation though should be interpreted as hypothesis generating in the context of nonrandomized assessment of QLV. Second, echocardiography was performed only at rest. Dynamic mechanisms of MR during exercise and their relationship to QLV were not assessed and may warrant future investigation. Third, although MR assessment was performed using contemporary guideline criteria,[17] additional measures assessing complementary echocardiographic parameters (eg, mitral valve deformation indices)[23,31] were not assessed. The impact of longer QLV on specific indices of mitral valve function may warrant additional investigation. Fourth, the SMART-AV study was designed with short-term follow-up (ie, 6 months), and we were unable to assess longer-term clinical outcomes. Although the primary focus of this study was mechanistic, we would highlight that the association between MR reduction with improved outcomes in CRT has been demonstrated previously in several cohorts.[3,4] Final, the optimal assessment of echocardiographic dyssynchrony remains a point of active investigation.[19] Strain imaging was not used in the study protocol as its availability across study sites at the time of study design and enrollment was limited.

Conclusions

In summary, in patients undergoing CRT, LV pacing site at longer QLV was associated with a significant reduction in MR at 6 months. QLV-associated MR reduction was mediated, in part, by interval LVRR. An electric-based LV pacing strategy in CRT likely warrants prospective investigation.

Appendix

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Longer Left Ventricular Electric Delay Reduces Mitral Regurgitation After Cardiac Resynchronization Therapy: Mechanistic Insights From the SMART-AV Study (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy)

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SUPPLEMENTAL MATERIAL

Supplementary Table 1: Baseline characteristics of patients included versus excluded from study cohort

	Study Cohort (N=426)	**Excluded (N=634)**	**P-value**
Age, years	66 ± 11	66±12	0.67
Female Gender, n (%)	144 (33.8%)	189 (30)	0.18
NYHA Class, n (%) II III IV	 12 (3) 401 (95) 11 (2)	 14 (2) 593 (94) 21 (4)	0.80
QRS duration, msec	151 ± 19	154±21	0.03
Body Mass Index, kg/m^2	29.6 ± 6.0	29.5±6.5	0.84
MR Grade, n (%) None/Mild Moderate Severe	 201 (47) 149 (35) 76 (18)	 275 (50) 172 (32) 97 (18)	0.58
Q-Sm, msec	99±78	103±80	0.40
LVEF, %	28±9	27±9	0.04
LVESV, ml	128±62	131±66	0.53

NYHA, New York Heart Association class, MR, mitral regurgitation; LV, left ventricular; EF, ejection fraction; ESV, end-systolic volume.

Supplementary Table 2: Baseline characteristics of patients included versus those excluded secondary to death during study follow-up

	Study Cohort (N=426)	**Excluded (N=29)**	**P-value**
Age, years	66 ± 11	77±11	0.01
Female Gender, n (%)	144 (33.8%)	5 (17)	0.07
NYHA Class, n (%) II III IV	 12 (3) 401 (95) 11 (2)	 1 (3) 28 (97) 0 (0)	0.80
QRS duration, msec	151 ± 19	150±20	0.86
Body Mass Index, kg/m^2	29.6 ± 6.0	25.9±5.5	0.002
MR Grade, n (%) None/Mild Moderate Severe	 201 (47) 149 (35) 76 (18)	 9 (33) 10 (37) 8 (30)	0.22
Q-Sm, msec	99±78	84±63	0.33
LVEF, %	28±9	29±10	0.58
LVESV, ml	128±62	121±51	0.53

NYHA, New York Heart Association class, MR, mitral regurgitation; LV, left ventricular; EF, ejection fraction; ESV, end-systolic volume.

Supplementary Table 3: Multivariable-adjusted linear regression model of absolute change in vena contracta width

3A: Multivariable-adjusted model

	β-Estimate	**Lower 95% CI**	**Upper 95% CI**	**P-value**
QLV (per 10 msec)	-0.019	-0.029	-0.008	< 0.001
Age (per 5 years)	0.022	0.007	0.037	0.003
Gender (Male vs. Female)	-0.046	-0.117	0.025	0.205
NYHA (Class IV vs. II/III)	-0.083	-0.281	0.116	0.413
QRS (> 150 vs. ≤ 150 msec)	-0.020	-0.090	0.051	0.584
LBBB vs. Non-LBBB	-0.070	-0.146	0.007	0.075
Ischemic vs. Non-Ischemic etiology	-0.023	-0.091	0.044	0.498
LVESV (per 10 ml)	0.002	-0.006	0.009	0.686
LVEF (per 1%)	0.020	-0.496	0.536	0.939
Baseline MR (Moderate vs. None/Mild)	-0.319	-0.388	-0.251	< 0.001
Baseline MR (Severe vs. None/Mild)	-0.532	-0.619	-0.444	< 0.001

NYHA, New York Heart Association functional class; LBBB, left bundle branch block; LV, left ventricular; ESV, end-systolic volume; EF, ejection fraction; MR, mitral regurgitation

3B. Multivariable-adjusted model + 3-month change in LV end-systolic volume

	β-Estimate	Lower 95% CI	Upper 95% CI	P-value
Change in LVESV from Baseline to 3 Months (per ml)	0.002	0.001	0.003	< 0.001
QLV (per 10 msec)	-0.014	-0.024	-0.004	0.008
Age (per 5 years)	0.026	0.011	0.040	< 0.001
Gender (Male vs. Female)	-0.059	-0.130	0.012	0.103
NYHA (Class IV vs. II/III)	-0.090	-0.284	0.104	0.364
QRS (> 150 vs. ≤ 150 msec)	-0.023	-0.093	0.047	0.521
LBBB vs. Non-LBBB	-0.078	-0.153	-0.003	0.043
Ischemic vs. Non-Ischemic etiology	-0.033	-0.099	0.034	0.335
LVESV (per 10 ml)	0.005	-0.003	0.012	0.228
LVEF (per 1%)	-0.022	-0.529	0.485	0.931
Baseline MR (Moderate vs. None/Mild)	-0.538	-0.624	-0.452	< 0.001
Baseline MR (Severe vs. None/Mild)	-0.334	-0.402	-0.267	< 0.001

NYHA, New York Heart Association functional class; LBBB, left bundle branch block; LV, left ventricular; ESV, end-systolic volume; EF, ejection fraction; MR, mitral regurgitation

3C. Multivariable-adjusted model + 3-month change in LV dyssynchrony

Covariate	β-Estimate	Lower 95% CI	Upper 95% CI	P-value
Change in LV Dyssynchrony (Q-Sm) from Baseline to 3 Months (per 10 msec)	0.001	-0.003	0.004	0.770
QLV (per 10 msec)	-0.017	-0.028	-0.007	0.001
Age (per 5 years)	0.023	0.008	0.037	0.003
Gender (Male vs. Female)	-0.041	-0.112	0.031	0.263
NYHA (Class IV vs. II/III)	-0.084	-0.282	0.114	0.407
QRS (> 150 vs. ≤ 150 msec)	-0.026	-0.098	0.045	0.464
LBBB vs. Non-LBBB	-0.082	-0.159	-0.006	0.035
Ischemic vs. Non-Ischemic etiology	-0.021	-0.089	0.046	0.538
LVESV (per 10 ml)	0.002	-0.006	0.010	0.608
LVEF (per 1%)	0.064	-0.450	0.578	0.807
Baseline MR (Moderate vs. None/Mild)	-0.535	-0.623	-0.448	< 0.001
Baseline MR (Severe vs. None/Mild)	-0.323	-0.392	-0.255	< 0.001

NYHA, New York Heart Association functional class; LBBB, left bundle branch block; LV, left ventricular; ESV, end-systolic volume; EF, ejection fraction; MR, mitral regurgitation

Supplemental Table 4: Multivariable-adjusted logistic regression model of odds of mitral regurgitation response

A. Multivariable-adjusted model

	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
QLV (per 10 msec)	1.13	1.03	1.25	0.015
Age (per 5 year increase)	0.90	0.77	1.05	0.186
Gender (Male vs. Female)	1.10	0.56	2.18	0.776
NYHA (Class IV vs. II/III)	0.41	0.06	2.79	0.362
QRS (> 150 vs. ≤ 150 msec)	1.19	0.60	2.34	0.620
LBBB vs. Non-LBBB	1.45	0.69	3.03	0.326
Ischemic vs. Non-Ischemic etiology	0.99	0.51	1.92	0.984
LVESV (per 10 ml)	0.96	0.89	1.03	0.235
LVEF (per 1% increase)	1.32	0.01	159.88	0.910
Baseline MR (Severe vs. Moderate)	4.93	2.52	9.63	< 0.001

NYHA, New York Heart Association functional class; LBBB, left bundle branch block; LV, left ventricular; ESV, end-systolic volume; EF, ejection fraction; MR, mitral regurgitation.

4B. Multivariable-adjusted model + 3-month change in LV end-systolic volume

	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
Change in LVESV from Baseline to 3 Months (per ml)	0.98	0.97	0.99	< 0.001
QLV (per 10 msec)	1.10	0.99	1.23	0.061
Age (per 5 year increase)	0.84	0.71	0.99	0.040
Gender (Male vs. Female)	1.26	0.61	2.61	0.536
NYHA (Class IV vs. II/III)	0.30	0.04	2.15	0.231
QRS (> 150 vs. ≤ 150 msec)	1.17	0.56	2.43	0.681
LBBB vs. Non-LBBB	1.45	0.66	3.17	0.354
Ischemic vs. Non-Ischemic etiology	1.10	0.54	2.21	0.795
LVESV (per 10 ml)	0.93	0.86	1.01	0.078
LVEF (per 1% increase)	3.69	0.02	605.46	0.616
Baseline MR (Severe vs. Moderate)	5.32	2.58	10.95	< 0.001

NYHA, New York Heart Association functional class; LBBB, left bundle branch block; LV, left ventricular; ESV, end-systolic volume; EF, ejection fraction; MR, mitral regurgitation.

4C. Multivariable-adjusted model + 3-month change in LV dyssynchrony

Covariate	Odds Ratio	LCL	UCL	P-value
Change in LV Dyssynchrony from Baseline to 3 Months (per 10 msec)	0.99	0.96	1.02	0.499
QLV (per 10 msec)	1.12	1.01	1.24	0.033
Age (per 5 year increase)	0.88	0.75	1.03	0.120
Gender (Male vs. Female)	0.99	0.49	2.00	0.983
NYHA (Class IV vs. II/III)	0.42	0.06	2.93	0.384
QRS (> 150 vs. ≤ 150 msec)	1.27	0.63	2.55	0.507
LBBB vs. Non-LBBB	1.65	0.77	3.50	0.196
Ischemic vs. Non-Ischemic etiology	0.99	0.51	1.95	0.993
LVESV (per 10 ml)	0.96	0.89	1.03	0.213
LVEF (per 1% increase)	1.05	0.01	136.69	0.984
Baseline MR (Severe vs. Moderate)	5.20	2.61	10.34	< 0.001

NYHA, New York Heart Association functional class; LBBB, left bundle branch block; LV, left ventricular; ESV, end-systolic volume; EF, ejection fraction; MR, mitral regurgitation.