The relationship between ventricular electrical delay and left ventricular remodelling with cardiac resynchronization therapy

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Aims
The aim of the present study was to evaluate the relationship between left ventricular (LV) electrical delay, as measured by the QLV interval, and outcomes in a prospectively designed substudy of the SMART-AV Trial.

Methods and results
This was a multicentre study of patients with advanced heart failure undergoing cardiac resynchronization therapy (CRT) defibrillator implantation. In 426 subjects, QLV was measured as the interval from the onset of the QRS from the surface ECG to the first large peak of the LV electrogram. Left ventricular volumes were measured by echocardiography at baseline and after 6 months of CRT by a blinded core laboratory. Quality of life (QOL) was assessed by a standardized questionnaire. When separated by quartiles based on QLV duration, reverse remodelling response rates (>15% reduction in LV end systolic volume) increased progressively from 38.7 to 68.4% and QOL response rate (>10 points reduction) increased from 50 to 72%. Patients in the highest quartile of QLV had a 3.21-fold increase (1.58–6.50, P = 0.001) in their odds of a reverse remodelling response after correcting for QRS duration, bundle branch block type, and clinical characteristics by multivariate logistic regression analysis.

Conclusion
Electrical dyssynchrony, as measured by QLV, was strongly and independently associated with reverse remodelling and QOL with CRT. Acute measurements of QLV may be useful to guide LV lead placement.

Keywords
Cardiac resynchronization therapy • Heart failure • Electrical dyssynchrony • Left ventricular reverse remodelling • Outcomes

Introduction
Cardiac resynchronization therapy (CRT) is a well accepted therapy for patients with heart failure (HF), left ventricular (LV) systolic dysfunction and QRS prolongation. Previously, prospective, randomized trials demonstrated that CRT improves quality of life (QOL), exercise capacity, LV systolic function, and decreases hospitalizations for HF.1–8 With longer follow-up, large randomized studies have now shown a reduction in mortality with CRT in both mild and advanced HF.3,4,7 Subgroup analyses of these trials have frequently identified QRS duration and morphology as independent predictors of outcomes. Specifically, patients with left bundle branch block (LBBB) and more prolonged QRS duration (≥150 ms) tend to have better response rates, whether measured by acute haemodynamics, reverse remodelling, or clinical outcomes.7–9 This has reinforced the concept that LV electrical delay or electrical...
dyssynchrony is an important factor for predicting benefit from CRT.\textsuperscript{10–12} To investigate this further, we evaluated the relationship between such electrical delay defined by time interval from the first deflection on a surface ECG to local intrinsic activation at the LV stimulation site (QLV) and reverse remodelling in a prospectively designed substudy of the SMART-AV Trial.\textsuperscript{13,14}

**Methods**

Details of the design and primary results of the SMART-AV study have been published previously.\textsuperscript{13,14} Briefly, this was a multicentre, randomized trial of atrioventricular (AV) optimization techniques among patients with advanced HF undergoing CRT defibrillator implantation. A subset of 426 (50.4\%) of the 846 patients in SMART-AV was included in the QLV substudy. At the final lead positions, surface Lead II, right ventricular (RV) and LV EGM were recorded simultaneously on paper strips at a sweep speed of 100 mm/s. QLV was measured by a blinded core lab with no knowledge of lead position or clinical outcomes. The QLV interval was measured in sinus rhythm and in the absence of pacing as the interval from the onset of QRS from the surface ECG to the first large positive or negative peak of the LV EGM during a cardiac cycle with the resolution of 5 ms (Figure 1A). The amplitude of the first large peak needed to be \( >50\% \) of the amplitude of the largest peak in the same cardiac cycle. The QLV interval measured for every patient was reduced by 30 ms to account for the average variable latency (or noise) between the alignment of surface ECG and the EGM channels in device programmers. Core lab measurements were performed independently by two reviewers, and a sample of 15 EGMs were reviewed by both to assess reproducibility of the results.

The primary endpoint of the SMART-AV trial was left ventricular end-systolic volume (LVESV). Secondary endpoints included left ventricular end-diastolic volume (LVEDV), LV ejection fraction (EF), QOL score, as measured by the Minnesota Living With Heart Failure Questionnaire, New York Heart Association (NYHA) functional class and 6-min hall walk distance. All deaths, HF-related hospitalizations and emergency room visits were collected as defined previously.\textsuperscript{13,14} The echocardiographic endpoints were analysed blindly by a single echocardiography core laboratory unaware of group assignment. Off-line software (Pro-Solv version 3.0 or GE Echo Pac version 6.0) was used for measurements. Two-dimensional-derived LV volumes were determined in the apical four and two chamber views by the biplane method of discs. In 94\% of images, the apical two chamber view image quality was deemed excellent or good with respect to visualization of the anterior wall. Intra- and inter-observer core lab reliability for LV volumes was evaluated in a sample of 20 images using Lin's concordance correlation coefficient (Lin's CCC). For both LVEDV and LVESV, excellent reliability was observed [EDV intraobserver: CCC = 0.981 95\% CI: (0.956–0.992), EDV interobserver: CCC = 0.981 95\% CI: (0.956–0.992), ESV intraobserver: CCC = 0.986 95\% CI: (0.966–0.994), ESV interobserver: CCC = 0.986 95\% CI: (0.964–0.994)]. In addition to LV volumetric measurements, mechanical dyssynchrony was measured as the delay between the time of peak systolic velocity was achieved at basal septal and basal lateral segments. All echocardiographic measures were performed at baseline and following 6 months of CRT. Quality of life was self-assessed by patients blinded to their QLV. Lifetime \% biventricular (BiV) pacing was determined from the device interrogation disc data collected from the 6-month visit, and was available for 375 (88\%) of the 426 patients in the substudy.

**Statistical analysis**

Since no difference was shown in primary or secondary outcomes between randomized treatment groups in the main study,\textsuperscript{13,14} data were pooled for the present analyses. QLV and echo measurement reliability was assessed using Lin’s CCC. The CRT responses were compared by QLV median values or quartiles. The effect of QLV on CRT response was evaluated using univariate and multivariate logistic regression models. Stratified models and inclusion of QLV by subgroup interactions in multivariate analysis were utilized to assess for heterogeneity of effect. Prespecified response metrics to CRT included a \( >15\% \) reduction in LVESV,\textsuperscript{15,16} \( b \) and \( a \), a \( >10 \) points reduction in QOL response from implant to 6 months. Continuous variables were compared with Kruskal–Wallis and Wilcoxon tests. Discrete variables were compared with Fisher exact and Pearson chi\(^2\) tests. All the tests were two-sided. A \( P \leq 0.05 \) was considered statistically significant. Data are presented as median and inter-quartile range unless noted otherwise. R\textsuperscript{\textregistered} version 2.12.2 was used for statistical analysis.

**Results**

**Patient population**

The 426 patients included in the QLV substudy were typical of those undergoing CRT for advanced HF, including predominately late middle aged males with a reduced EF and advanced HF. A summary of baseline clinical data is presented in Table 1. Of note, none of these values differs from the larger full cohort included in the SMART-AV trial, other than a slightly shorter mean QRS duration in the substudy population (151 ± 19 ms vs. 154 ± 21 ms, \( P < 0.05 \)).

**QLV response**

Examples of QLV measurements are shown in Figure 1. The QLV measurement was reproducible, as evidenced by a strong concordance among QLV reviewers in the sample of duplicate reviews evaluated. (Lin's CCC, 95\% CI: 0.93, 0.82–0.98). The median value for QLV in this population was 95 ms with inter-quartile range of 70–120 ms.
Biventricular pacing

All patients were programmed to a lower pacing rate of 60 b.p.m. The programmed AV delay varied depending on whether nominal (120 ms), SmartDelay™ electrogram optimization or echocardiographic optimization was used. Overall, the median sensed AV delay was 120 ms with inter-quartile range of 120–140 ms. These programmed parameters resulted in a very high rate of lifetime BiV pacing during this study with a median of 98.4% (95.1–99.6%), which is higher than the 92% threshold often used to insure a maximal CRT response. When separated at the median QLV, patients with longer QLV intervals had shorter programmed AV delays [median (Q1–Q3): 120 (110–130) vs. 120 (120–140), \( P = 0.016 \)] and slightly higher percentages of BiV pacing [median (Q1–Q3): 98.8% (94.8–99.7%) vs. 97.9% (95.2–99.3%), \( P = 0.014 \)].

CRT responses

When separated by the QLV median value (95 ms), LVESV, LVEDV, EF, and QOL responses all were significantly larger for patients with long vs. short QLV (Figure 2). The responses for LVESV, LVEDV, EF, and QOL from baseline to 6 months all significantly increased with the increase in the QLV from the shortest quartile (<70 ms) to the longest quartile (>120 ms) (Figure 3). The relationships between QLV and other secondary endpoints are presented in Table 2. Specifically, changes in NYHA class, 6-min Hall walk distance and HF events are shown for each QLV quartile. Although these relationships were only statistically

| Table 1 | Patient characteristics \((n = 426)\) |
|---------|----------------------------------|
| Age, years | 66 ± 11 |
| Gender (male, %) | 66 |
| Ischaemic heart disease (%) | 59 |
| NYHA functional class (%) |  |
| I | 0 |
| II | 3 |
| III | 94 |
| IV | 3 |
| LV ejection fraction (%) | 26 ± 7 |
| Cardiac medications (%) |  |
| ACE/ARB | 84 |
| Beta-blocker | 92 |
| Diuretic | 82 |
| Digoxin | 22 |
| ECG characteristics |  |
| QRS duration (ms) | 151 ± 19 |
| LBBB (%) | 75 |
| RBBB (%) | 13 |
| IVCD (%) | 12 |
| Baseline LVESV (mL) | 128 ± 62 |
| QOL | 46 ± 26 |

Values expressed as mean ± SD. ACE/ARB, angiotensin-converting enzyme inhibitor/receptor blocker.

**Figure 2** Comparisons of the changes in left ventricular end-systolic volume, left ventricular end-diastolic volume, ejection fraction, and quality of life from implant baseline to 6 months for the two QLV groups separated by the median value. The data were presented as median ± inter-quartile range.
significant for NYHA, the largest response was consistently observed in the fourth quartile.

**CRT response rate**

The overall response rates were 50% for LVESV and 60% for QOL in this population, which is typical for response rate for these parameters to CRT. The response rates for each QLV quartile are shown in Table 3. The response rates increased progressively from the shortest quartile to the longest quartile of QLV for both LVESV (38.7–68.4%) and QOL (50–72%) criteria. It is noteworthy that the median value (95 ms) was also the optimal cut-point for QLV based on ROC analysis using the point on the ROC curve as a measure of diagnostic accuracy.

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### Table 2 Relationship of QLV with clinical outcomes

| QLV quartiles | Patients with HF events | NYHA | Six minute walk delta |
|---------------|-------------------------|------|-----------------------|
|               | Q1: 0–70 ms (%)         | Improved | 89 (73.0) | 52 ± 118 |
|               | Q2: 70–95 ms (%)        | No change | 33 (27.1) | 68 ± 91 |
|               | Q3: 95–120 ms (%)       | Worsened | 0 (0.0) | 50 ± 104 |
|               | Q4: 120–195 ms (%)      | Overall | 35 (8.2) | 70 ± 93 |
|               |                         | Total | 321 (76.6) | 59 ± 103 |

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*Figure 3* Comparisons of the changes in left ventricular end-systolic volume, left ventricular end-diastolic volume, ejection fraction, and quality of life from implant baseline to 6 months for the QLV quartiles. The data were presented as median ± inter-quartile range (box).
Table 3 The left ventricular end-systolic volume and QOL response rates for the QLV quartiles

| QLV  | n  | LVESV response (%) | QOL response (%) |
|------|----|-------------------|-----------------|
| 0–70 ms | 124 | 38.7 | 50.0 |
| 70–95 ms | 98 | 39.8 | 54.6 |
| 95–120 ms | 109 | 57.8 | 65.1 |
| 120–195 ms | 95 | 68.4 | 72.0 |
| Pearson $\chi^2$ | $<0.001$ | 0.004 |

Relationship between baseline parameters and QLV

QLV is expected to be longer with increased QRS duration as well as LBBB. For QRS duration $>150$ ms, QLV was $113 \pm 33$ ms, compared with $78 \pm 30$ ms for QRS $<150$ ms ($P < 0.001$). However, QRS duration was not strongly correlated with QLV, as it accounted for only 35% of the variability observed ($r^2 = 0.35, P < 0.001$). Similarly, among LBBB patients QLV was $100 \pm 35$ ms compared with $73 \pm 30$ ms for non-LBBB patients ($P < 0.001$). Median mechanical dyssynchrony was $35$ ms with inter-quartile range from 13 to 68 ms. In contrast to the relationships between QLV and QRS duration and morphology, mechanical dyssynchrony did not vary by QLV quartile ($P = 0.55$, Kruskal–Wallis test).

In the multivariate regression models, QLV added significant predictive value for CRT responses, assessed by either reductions of LVESV or QOL, after accounting for baseline covariates (Table 4). Patients in the highest quartile of QLV had a greater than three-fold increase in their odds of LVESV response vs. the shortest quartile. The full multivariate results are also shown in Table 4. For the endpoint of a >15% reduction in LVESV, QLV, gender and aetiology of HF were the only independent variables that were significantly associated with the response. For the QOL endpoint, only QLV and gender were independently associated with the response. It is noteworthy that, as expected, both QRS and LBBB were univariately associated with both LVESV and QOL. It is noteworthy that, as expected, both QRS and LBBB were univariately associated with both LVESV and QOL. However, neither were independent predictors of the responses after adjusting for QLV.

The association between longer QLV and CRT response was assessed in several pre-specified subgroups. The univariate relationship between QLV and CRT response was consistent in all groups. This was the case for both LVESV (Figure 4A) and QOL (Figure 4B) response criteria. No significant interactions with QLV were observed in the logistic regression models for both endpoints.

Relationship between electrical intervals and anatomical locations

The location of the LV lead was not controlled in this study. However, as expected, most leads were placed in the anterolateral or posterolateral veins, as reported by the implanting physicians. In fact, only 46 of 426 patients had leads placed apically and only 13 had them placed in an anterior or septal location. These small numbers preclude any meaningful analysis of the impact of lead location on QLV or response rate. However, even in similar locations, there was marked variation in QLV. For instance, the QLV interval ranged from 10 to 195 ms in the midanterolateral location ($n = 89$), and from 15 to 195 ms in the mid-posterolateral location ($n = 230$). The majority of patients (76%) had bipolar leads, 19% patients had unipolar leads, and for 5% patients the lead type was not available. The sensing configuration was true bipolar in 68% of patients, extended bipolar in 28% of patients, while the remaining 4% used unipolar sensing.

Discussion

The present study is the first comprehensive evaluation of the relationship between electrical delay or dyssynchrony as measured by QLV and CRT outcomes in a large clinical trial. The results demonstrate that the QLV was strongly associated with reverse remodelling and QOL improvement. Longer QLV at the LV...
Figure 4 Univariate logistic regression results for left ventricular end-systolic volume (A) and quality of life (B) by subgroups.
stimulation site was associated with better CRT responses even after adjusting for baseline covariates, including QRS duration, bundle branch block, and aetiology of HF.

Previously, in small preliminary studies of QLV, this measure was shown to correlate directly with acute haemodynamic response as assessed by invasive measurement of LV dP/dt\text{max}. Subsequently, in a study of 71 patients, Singh et al. reported that the percentage of LV delay as a function of QRS duration predicted not only acute haemodynamic response but also chronic clinical outcomes after 12 months of follow-up. The present trial extends these findings by showing the QLV was strongly associated with chronic reverse remodelling and QOL in a much larger prospective, multicentre trial.

The role of pacing site to influence CRT outcomes is an area of active research. Early studies suggested that pacing the left lateral wall was optimal. However, analyses of multicentre trials have failed to support this strategy. In the COMPANION study, lead position had little effect on outcomes, whereas in MADIT CRT apical positions were associated with worse outcomes, rather than non-apical positions. Similarly, Merchant et al. showed that pacing in non-apical regions was better than apical regions. However, other studies have showed that ~30% of patients had optimal pacing site in the apical regions. These discrepant findings suggest that anatomic lead position alone is unlikely to be a sufficient guide for optimization of CRT. In support of this notion, studies of mechanical dyssynchrony to guide lead position showed that optimal pacing site varies from patient to patient. However, current measurement of mechanical dyssynchrony requires echocardiography or other imaging modalities that may be hard to correlate with fluoroscopic imaging at the time of device implantation and have shown to have a high degree of variability. In contrast, QLV can be easily and reliably measured during the implantation process. Further study will be needed to test the hypothesis that positioning LV leads at the site of maximal QLV rather than simply by anatomical location improves the response rate to CRT and clinical outcomes.

Electrical dyssynchrony measures and CRT responses

Most HF patients with wide QRS have left ventricular conduction delays (LBBB). One mechanism of the benefit of CRT is to restore electrical synchrony by pre-exciting the delayed LV area to achieve more synchronous electrical activation and thus contraction within the left ventricle. To identify patients with such conduction delays, QRS duration is commonly used. Yet the QRS duration reflects the conduction system condition of both ventricles. Thus, patients with right bundle branch block (RBBB) can also have a prolonged QRS duration, yet typically will have delayed right but not LV activation. Patients with RBBB show little or no response to CRT. To reduce the contribution of activation time from the RV, Sweeney et al. used left ventricular activation time (LVAT), which is the QRS width after subtracting the early part that corresponds to the RVAT. This estimate of LVAT, however, is applicable only to LBBB patients. Moreover, LVAT also reflects the overall left ventricular activation time, and does not identify regions with latest delay. Therefore, it identifies the potential for a good clinical response to CRT by measuring electrical dyssynchrony. To insure good CRT responses, it is desirable to have an indicator that reflects the degree of delayed LV activation at the pacing site. The QLV interval is such an index. The QRS onset is the earliest ventricular activation which usually starts in the septum. Thus QLV reflects the time that it takes for the ventricular depolarization wavefront to reach the LV electrode site, and thus the resynchronization that will occur with pacing. It is intriguing to speculate that this can be utilized during the implant procedure to determine an area of late activation by repositioning the LV electrode and examining the QLV value at different locations.

In contrast to the strong relationship between QLV and QRS and LBBB, no correlation was observed with mechanical dyssynchrony. This may be due to the fact that QLV reflects electrical dyssynchrony at the stimulation site which is not well correlated with global measures of mechanical dyssynchrony, which are weak predictors of CRT response at best.

Much attention has been focused recently on clinical predictors of CRT response. In this regard, QRS duration, morphology (i.e. LBBB), aetiology of HF and gender are consistently associated with outcomes. These variables were also strongly associated with outcomes in the present study. However, LBBB and QRS duration were no longer predictive of CRT response after adjusting for QLV. This suggests that QLV or ventricular electrical delay at the stimulation site is a fundamental mechanism for the enhanced CRT response in the presence of LBBB or more prolonged QRS duration.

Clinical implications

Non-responders continue to be a challenge for CRT therapy despite optimized device programming. Recent studies suggest that a purely anatomic approach to lead position will be of limited value. However, the QLV interval is strongly associated with response and helps identify good LV pacing sites. Thus, it seems reasonable to consider repositioning the pacing lead either within a vein or in a different vein towards a larger QLV value, particularly if an initial QLV value is 95 ms or less, which could be associated with poor outcome.

Limitations

This study should be interpreted in light of certain methodologic limitations. QLV was measured at the final lead position. Thus, there was only one QLV interval associated with each patient. The intra-patient data may not be the same as cross-patient data for guiding lead placement. In addition, the choice of lead position was not controlled with a marked preponderance on the lateral wall. This limits the ability to evaluate fully the relationship between QLV and lead position, as only ~11% of subjects had apical and only 3% had true anterior positions. Furthermore, since the QLV is currently measured from electrodes that are placed epicardially through a coronary vein branch, it may not be able to identify intramural or endocardial latest activated regions. Advancement in LV lead placement technology may improve this shortcoming when the lead is able to be placed via endocardial approach. Finally, an echocardiographic measure of reverse remodelling (LVESV) at 6 months was the primary endpoint of this study, whereas reverse remodelling is a good predictor of survival.
Association of QLV and remodeling with CRT

and clinical outcomes with CRT,\(^{10}\) ‘harder’ endpoints such as hospitalization and survival were not powered endpoints in the SMART-AV trial and the short follow-up precluded more complete assessment of HF events.

In summary, electrical dyssynchrony, as measured by QLV, was strongly and independently associated with chronic outcomes with CRT. The best outcomes were observed with a QLV >95 ms, so this target should be considered when selecting LV lead position at the time of CRT implantation. Further study is warranted to assess the value of using QLV rather than anatomic location to guide lead positioning to improve response rates with CRT.

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CARDIOVASCULAR FLASHLIGHT

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Double mechanical prosthesis, correct international normalized ratio, and giant atrial mass

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A 78-year-old man was referred to our hospital because of new onset weakness and distended jugular veins; as background, history of valvular rheumatic disease with mitral and tricuspid valve replacement by mechanical prostheses in 2002 (in revisions at outpatient department of cardiology the patient had remained stable and with correct levels of anticoagulation; Figure A). Chest radiography showed mild signs of heart failure and a correct international normalized ratio (INR 3.1). The first suspicion was pulmonary thrombo-embolism. Chest computerized tomography showed a giant heterogeneous mass at the left atrium without signs of pulmonary thrombo-embolism (Figure B, arrow). Transesophageal echocardiography revealed severe enlargement of the left atrium with a giant mass (Figure C, arrow) attached to the atrial septum, affecting mitral prostheses with reduced mobility anterior disk. Results from a colour-Doppler examination showed peak gradients across mitral prosthesis, assessed by continuous-wave Doppler, and indicated a severe obstruction (transmitral mean pressure gradient of 24 mmHg; Figure D). The patient was submitted to cardiac surgery, it was found a mass of 60 × 50 mm (Figure E) with its origin in the atrial septum and roof of the left atrium occluding right lower pulmonary veins and occupied 80% of the atrium, with partial blockage of mitral prosthesis. Tricuspid mechanical prosthesis was not affected. Pathological anatomy showed intra-atrial giant thrombus (Figure F). Thrombophilia screening was negative. We demonstrate such a case of giant thrombus despite a correct INR, without affecting tricuspid mechanical prosthesis (place with low velocity of blood).

LA, left atrium; RA, right atrium; TP, tricuspid prostheses; AV, aortic valve.