The effect of left ventricular electrical delay on AV optimization for cardiac resynchronization therapy

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BACKGROUND The role of atrioventricular optimization (AVO) for cardiac resynchronization therapy (CRT) is controversial. Identifying subgroups that benefit from optimization is important to improve CRT outcomes. Pacing at sites of late electrical activation, as assessed by the QLV interval, improves remodeling with CRT.

OBJECTIVE To evaluate whether pacing at sites of long left ventricular (LV) electrical delay increases the effectiveness of AVO.

METHODS This substudy of the SMART-AV trial included 280 subjects who were randomized to either an electrogram-based AVO (SmartDelay) or nominal atrioventricular delay (120 ms). The QLV interval was defined as the time from the onset of QRS to the LV electrogram peak. CRT response was defined prospectively as a $>15\%$ reduction in left ventricular end systolic volume from implant to 6 months.

RESULTS The cohort was 68% men, with a mean age of 66 $\pm$ 11 years and LV ejection fraction of 28% $\pm$ 8%. Longer QLV durations were significantly associated with CRT response ($P < .01$) for the entire cohort. Moreover, the benefit of AVO increased as QLV prolonged. At the longest QLV quartile, there was more than a 6-fold increase in the likelihood of a remodeling response compared with nominal atrioventricular delays.

CONCLUSIONS Baseline electrical dyssynchrony, as measured by the QLV interval, predicted CRT response. At long QLV intervals, AVO can increase the likelihood of structural response to CRT. AVO and QLV optimized that LV lead location may work synergistically to maximize CRT response.

KEYWORDS Cardiac resynchronization therapy; Heart failure; Electrical dyssynchrony; LV pacing site; Left ventricular reverse remodeling; Outcomes

ABBREVIATIONS **AV** = atrioventricular; **AVO** = atrioventricular optimization; **CRT** = cardiac resynchronization therapy; **EF** = ejection fraction; **EGM** = electrogram; **HF** = heart failure; **LBBB** = left bundle branch block; **LV** = left ventricular; **LVEDV** = left ventricular end diastolic volume; **LVESV** = left ventricular end systolic volume; **SD** = SmartDelay

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Introduction

Cardiac resynchronization therapy (CRT) is a well-established treatment for patients with symptomatic systolic heart failure (HF) and ventricular conduction delay. CRT results in structural and functional improvements as well as reductions in HF events and mortality.[1–5] Despite the consistently observed benefits of CRT in large multicenter randomized studies, many patients remain classified as nonresponders.[1,6] Typically, the nonresponder rate has been estimated at approximately 30% and this has not changed dramatically in the past decade. Several strategies have been tested in an attempt to identify and reduce the number of nonresponders. Such strategies include post hoc analyses of left ventricular (LV) lead placement, pacing at sites of maximal electrical or mechanical delay/dyssynchrony, and the use of atrioventricular optimization (AVO) for programming pacing intervals. The results of these studies have

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identified several factors that may impact response. For instance, LV pacing in apical regions is deleterious, whereas pacing at sites of late electrical or mechanical delay is associated with better outcomes.[7–15] The role of optimizing atrioventricular (AV) timing to improve responder rates has now been questioned on the basis of multicenter trial results.[16–19]

We hypothesized that AVO would be most effective when pacing is provided at sites of long electrical delay, which would provide maximal resynchronization. To test this hypothesis, we evaluated the impact of an electrogram (EGM)-based optimization algorithm on the relationship between LV electrical delay and the magnitude of echocardiographic changes with CRT.

Methods

The present analysis is a substudy of the SMART-AV trial. The SMART-AV trial was a multicenter randomized trial of AVO techniques among patients with advanced HF undergoing CRT defibrillator implantation.[17,20] Details of the QLV analysis of SMART-AV and the measurement of the QLV interval have been published previously.[10] There were 426 patients included in the QLV substudy. In the present analysis, patients randomized only to a nominal or SmartDelay (SD) AV delay (n = 280) were included. The sensed and paced AV delay was 120 ms in the nominal group, whereas the SD algorithm was used to program sensed and paced AV delays separately in the SD group. At the final lead positions, surface lead II, right ventricular, and LV EGMs were recorded simultaneously on paper strips at a sweep speed of 100 mm/s. QLV was measured by a blinded core laboratory 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 electrocardiographic lead II to the first major peak of the LV EGM during a cardiac cycle with the resolution of 5 ms (Figure 1). QLV measurements were performed independently by 2 core laboratory reviewers.

The primary end point of the SMART-AV trial was left ventricular end systolic volume (LVESV). Secondary end points included left ventricular end diastolic volume (LVEDV) and LV ejection fraction (LVEF). The echocardiographic end points were analyzed blindly by an echocardiography core laboratory and thus unaware of group assignment or QLV measurements. 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 4- and 2-chamber views by using the biplane method of discs. In 84% of the images, the apical 2-chamber view image quality was deemed excellent or good with respect to the visualization of the anterior wall. All echocardiographic measures were performed at baseline and following 6 months of CRT.

The CRT responses were compared by QLV median value or quartiles. The effect of QLV on CRT response was evaluated by using univariate and multivariate logistic regression models. Stratified models and inclusion of QLV by subgroup interactions in multivariate analysis were used to assess the heterogeneity of effect. A metric defining response to CRT was prespecified as a $>15\%$ reduction in LVESV.[21–23] Continuous variables were compared by using the 2-sided Wilcoxon tests, and categorical variables were compared by using the Fisher exact tests. An $\alpha = .05$ threshold was used to demonstrate statistical significance, with no adjustments made for multiple comparisons. Data are presented as mean ± SD unless noted otherwise. R version 2.12.2 was used for statistical analysis.

Results

Patient population

There were 280 patients included in this substudy, and they were representative of those included in the main SMART-AV study,[17] as reported in Table 1. The mean age was 66 ± 11 years, and 68% were men. The LVEF was 28% ± 8%, the baseline LVESV was 129 ± 61 mL, and 261 (93%) subjects had New York Heart Association class III functional status at enrollment. A left bundle branch block (LBBB) morphology was present in 76% of the subjects. There were no significant differences in any of these characteristics between the SD and nominal AV delay groups ($P > .35$ for all).

The electrocardiographic properties of the population were also typical for subjects receiving CRT. The baseline

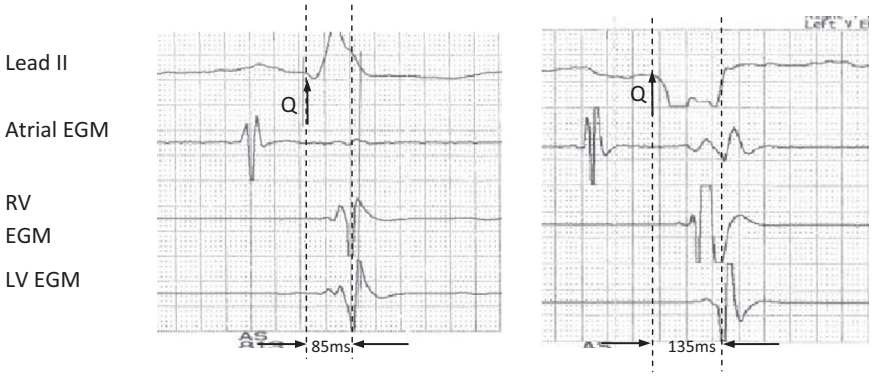

Figure 1 Two examples of QLV measurements in patients implanted with non-LBBB ECG morphology. The calipers are aligned with the onset of QRS and peak of the LV electrogram. The QLV was calculated as 85 ms for the patient in panel A and 135 ms for the patient in panel B. ECG = electrocardiographic; EGM = electrogram; LBBB = left bundle branch block; LV = left ventricular; RV = right ventricular.