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Optimal Left Ventricular Lead Position Predicts Reverse Remodeling and Survival After Cardiac Resynchronization Therapy

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Objectives The aim of the current study was to evaluate echocardiographic parameters after 6 months of cardiac resynchronization therapy (CRT) as well as long-term outcome in patients with the left ventricular (LV) lead positioned at the site of latest activation (concordant LV lead position) as compared with that seen in patients with a discordant LV lead position.

Background A nonoptimal LV pacing lead position may be a potential cause for nonresponse to CRT.

Methods The site of latest mechanical activation was determined by speckle tracking radial strain analysis and related to the LV lead position on chest X-ray in 244 CRT candidates. Echocardiographic evaluation was performed after 6 months. Long-term follow-up included all-cause mortality and hospitalizations for heart failure.

Results Significant LV reverse remodeling (reduction in LV end-systolic volume from 189 ± 83 ml to 134 ± 71 ml, $p < 0.001$) was noted in the group of patients with a concordant LV lead position (n = 153, 63%), whereas patients with a discordant lead position showed no significant improvements. In addition, during long-term follow-up (32 ± 16 months), less events (combined for heart failure hospitalizations and death) were reported in patients with a concordant LV lead position. Moreover, a concordant LV lead position appeared to be an independent predictor of hospitalization-free survival after long-term CRT (hazard ratio: 0.22, p = 0.004).

Conclusions Pacing at the site of latest mechanical activation, as determined by speckle tracking radial strain analysis, resulted in superior echocardiographic response after 6 months of CRT and better prognosis during long-term follow-up. (J Am Coll Cardiol 2008;52:1402–9) © 2008 by the American College of Cardiology Foundation

The rationale for cardiac resynchronization therapy (CRT) for the treatment of severe congestive heart failure is to coordinate the contraction of the dyssynchronous dilated heart, thereby improving left ventricular (LV) systolic function. Several large randomized studies demonstrated that CRT not only improves clinical status but also reverses LV remodeling (1–5). However, a significant percentage of patients do not show benefit from CRT (2,6). Different factors may influence the likelihood of response to CRT, such as lack of baseline mechanical dyssynchrony, insufficient device programming, and suboptimal LV lead position (7,8).

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Currently, the LV pacing lead is positioned preferably in a lateral or posterolateral branch of the coronary sinus. This approach is based on initial studies, which demonstrated that a (postero)lateral position of the LV pacing lead yielded greater acute hemodynamic benefit as compared with an anterior LV lead position (9). However, a few studies show no difference in long-term follow-up between patients with a lead in the anterior versus a posterolateral position (10–12). In addition, it has been shown that the region of maximal mechanical delay varies significantly between patients and may involve other sites remote of these branches (13). It has been suggested that positioning of the LV lead at the site of latest mechanical activation may result in maximum benefit of CRT (13–17).

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The aim of the current study was to evaluate clinical and echocardiographic 6-month outcome as well as long-term prognosis in a large cohort of patients by comparing patients with the LV lead positioned in the region of latest mechanical activation with patients with the LV positioned outside the site of latest mechanical activation. Two-dimensional (2D) speckle tracking radial strain analysis was used to determine the presence of LV dyssynchrony and the region of latest mechanical activation.

Methods

Patients and study protocol. Two-hundred fifty-seven consecutive patients with advanced heart failure (New York Heart Association [NYHA] functional class III or IV), depressed left ventricular ejection fraction (LVEF) (35%), and wide QRS complex (>120 ms) were prospectively included for implantation of a CRT device (18). Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in 1 or more of the major epicardial coronary arteries) and/or a history of myocardial infarction or prior revascularization.

The study protocol was as follows: before implantation, resting transthoracic echocardiography was performed to measure LVEF and LV volumes. Next, 2D speckle tracking radial strain analysis was performed to determine the extent of LV dyssynchrony as well as the site of latest mechanical activation. Clinical status was assessed at baseline and after 6 months of CRT, including assessment of NYHA functional class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire) (19), and evaluation of exercise capacity using the 6-min walking test (20). At the 6-month follow-up, LV volumes and LVEF were reassessed. Hospitalization for decompensated heart failure and survival and cardiac transplantation were assessed during follow-up after CRT device implantation.

Echocardiography and data acquisition/analysis. Echocardiographic images were obtained with a 3.5-MHz transducer in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cine-loop format for off-line analysis (EchoPac 6.06, GE Medical Systems, Horten, Norway).

Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were derived, and LVEF was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (21). The severity of mitral regurgitation was graded semiquantitatively from color-flow Doppler images using the apical 4-chamber views. Mitral regurgitation was graded on a 3-point scale: mild (jet area/left atrial area <20%), moderate (jet area/left atrial area 20% to 45%), and severe (jet area/left atrial area >45%) (22).

LV dyssynchrony was assessed using 2D speckle tracking radial strain analysis on baseline midventricular short-axis images (23,24). All the images were recorded with a frame rate of at least 30 frames/s to allow for reliable operation of the software (EchoPac 6.1, GE Medical Systems). Time-strain curves for the 6 segments (septal, anteroseptal, anterior, posterior, lateral, and inferior) were constructed (Fig. 1). Times from QRS onset to peak radial strain were obtained for all 6 segments, and reliable curves were obtained in 92% of 1,542 attempted segments. Consequently, the location of the earliest and latest activated segments and the heterogeneity in time-to-peak radial strain for the 6 segments were determined (25). LV dyssynchrony was defined as the maximal time difference between the earliest and latest activated segments. The site of latest mechanical activation was also noted. Inter- and intraobserver variability for the assessment of the site of latest activation showed a good agreement, with, respectively, 80% and 83% of the segments scored identically ($\kappa = 0.71$ and $\kappa = 0.76$).

Abbreviations and Acronyms

CI = confidence interval
CRT = cardiac resynchronization therapy
HR = hazard ratio
LV = left ventricle/ventricular
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
NYHA = New York Heart Association
PH = proportional hazards
2D = two-dimensional

Response to CRT and long-term follow-up. Echocardiographic and clinical improvement was assessed after 6 months of CRT. Patients were classified as responders to CRT ('responders') if they showed a decrease of >15% in LVESV (26,27). The remaining patients, including those who died during the 6-month follow-up period, were classified as 'non-responders.'

Long-term follow-up was performed by chart review, device interrogation, and telephone contact. Events were defined as follows: death from any cause or cardiac transplantation and heart failure requiring hospitalization. The primary end point was the composite of death, cardiac transplantation, and hospitalization for decompensated heart failure.

CRT implantation and LV lead position. A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or posterolateral vein (28). Of note, the electrophysiologist was blinded for all echocardiographic data, so LV lead positioning was not guided by the echocardiographic information on latest mechanical activation.

The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual-chamber

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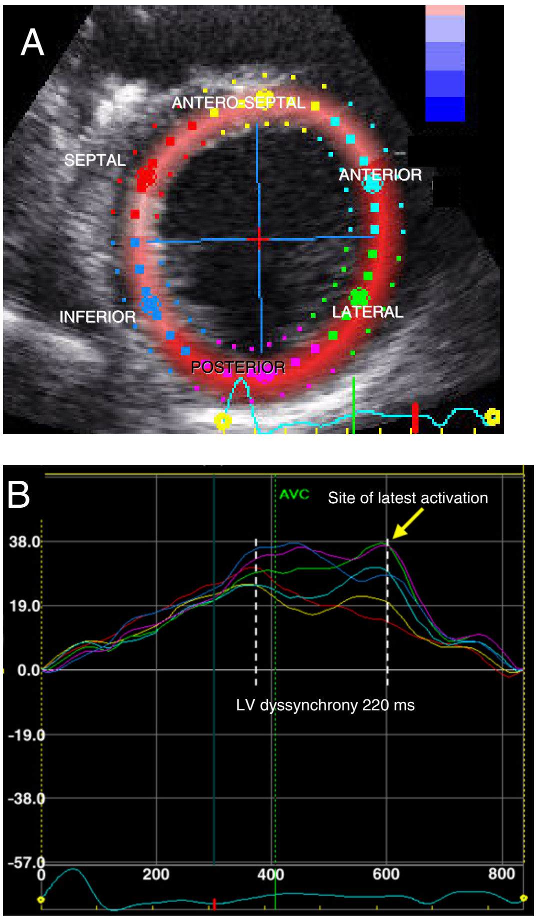

Figure 1 **Speckle Tracking Radial Strain Analysis**

(A) Short-axis of the left ventricle (LV) at the level of the papillary muscles, with reconstruction of the 6 LV segments. **(B)** Demonstrates the separate strain-time curves for each individual segment. In this patient example, severe baseline LV dyssynchrony was present; a maximum delay of 220 ms was calculated between the septum **(red)** and the posterior wall **(purple)**. Site of latest activation was the posterior LV segment **(purple)** AVC = aortic valve closure.

biventricular implantable cardioverter-defibrillator (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).

One day after implantation, the LV lead position was assessed from a chest X-ray (29). The LV lead positions were scored anterior, lateral, posterior, or inferior using the lateral views. Only LV lead positions that were located in the basal and midregion of the LV (frontal views) were related to the site of latest mechanical activation model (midventricular short-axis view); LV lead positions that were located in the apical regions were excluded from further analysis. LV lead positions were classified as 'concordant' when the lead was positioned at the latest activated segment; in case of differences between the LV lead position and site of latest mechanical activation, these positions were classified as 'discordant.' Interobserver and intraobserver agreement for the assessment of LV lead position was excellent with both 91% LV lead positions scored identically ($\kappa = 0.88$).

Statistical analysis. Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between patients with concordant and discordant LV lead positions were analyzed using unpaired Student *t* tests (continuous variables) and chi-square or Fisher exact tests (dichotomous variables) as appropriate. The paired Student *t* test was used to compare continuous data within the subgroups during follow-up. Interobserver and intraobserver agreement for assessment of the site of latest activation and LV lead position were calculated, and κ values were determined (<0.40 poor agreement, 0.40 to 0.75 fair to good, and >0.75 excellent).

Event and survival curves were determined according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test. To adjust for (potential) confounding factors for LV lead position such as age, gender, etiology, NYHA functional class, QRS duration, left bundle branch block configuration, cardiac rhythm, LV volumes, and LV dyssynchrony, univariable and multivariable Cox proportional hazards (PH) analysis was performed. All variables entered the multivariable stage, irrespective of the results of the univariable analyses. Multivariable regression was then performed according to the principle of backward deletion. All variables with a p value of <0.15 remained in the final model. Adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs) are reported. For all tests, a p value <0.05 was considered statistically significant.

To check the PH assumption, log(−log[survival probability]) was plotted against time for patients with concordant versus discordant LV lead position. Similar plots were created for (different categories of) potential confounders. The curves were reasonably parallel for all variables studied, indicating that the proportionality assumptions were not violated. However, there were 2 exceptions: there was evidence that the PH assumption was violated for the relation between LV lead position and the single end point hospitalization for heart failure, and the composite end point of all-cause death, cardiac transplant, or hospitalization for heart failure. Since the event curves representing the latter end point diverged at 24-month follow-up (see the Results section), we decided to report separate HRs for the first 24 months and the subsequent period.

Results

Patients. Baseline characteristics of the 257 consecutive patients (211 men, mean age 66 ± 10 years) included in this study are summarized in Table 1. Patients had severely depressed LV function, with a mean LVEF of 24 ± 7%. Mean LVEDV was 232 ± 86 ml, and mean LVESV was 180 ± 76 ml. Severe LV dyssynchrony was present, as indicated by a maximal delay of 177 ± 117 ms. The site of

Table 1 Patient Characteristics

	All Patients (n = 257)
Age (yrs)	66 ± 10
Gender (male/female)	211/46
NYHA functional class (III/IV)	232/25
Ischemic etiology	148 (58%)
QRS duration (ms)	161 ± 33
LBBB	181 (70%)
SR/atrial fibrillation/paced	208/29/30
LVEF (%)	24 ± 7
LVEDV (ml)	235 ± 86
LVESV (ml)	182 ± 76
MR (moderate-to-severe)	46 (18%)
LV dyssynchrony (ms)	177 ± 117
Medication	
Anticoagulants	225 (88%)
Diuretics	219 (85%)
ACE inhibitors	232 (90%)
Beta-blockers	176 (68%)
Spironolactone	114 (44%)

ACE = angiotensin-converting enzyme; LBBB = left bundle branch block; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association; SR = sinus rhythm.

latest mechanical activation was most frequently located in the lateral (84 patients, 33%) and posterior segments (93 patients, 36%) (Fig. 2).

Device implantation was successful in all patients, and no procedure-related complications were reported. Most LV pacing leads were positioned in the basal-midventricular region, including the lateral region in 111 patients (45%), the posterior region in 119 patients (49%), and the anterior region in 14 patients (5%); no patients received an LV lead in the inferior region. Thirteen patients had an apical LV lead position and were excluded from further analysis.

Concordant versus discordant LV lead position. One-hundred fifty-three patients (63%) had an LV lead position located in the latest activated region, whereas 91 patients (37%) had a discordant LV lead position. Baseline characteristics were comparable between the 2 groups, except for a significantly shorter QRS duration and more often ischemic etiology in patients with discordant LV lead positions (Table 2).

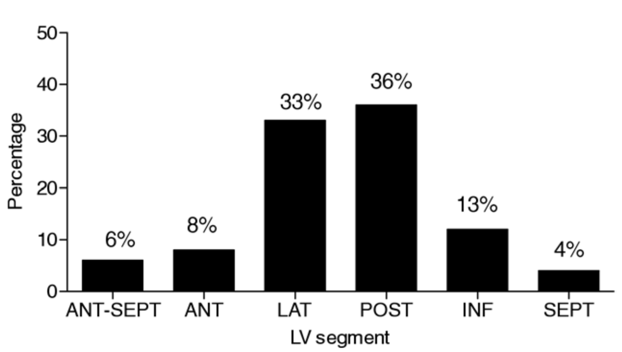

Figure 2 Distribution of Site of Latest Activation

ANT = anterior left ventricular segment; ANT-SEPT = anteroseptal left ventricular segment; INF = inferior left ventricular segment; LAT = lateral left ventricular segment; LV = left ventricular; POST = posterior left ventricular segment; SEPT = septal left ventricular segment.

Table 2 Baseline Characteristics Between Patients With Concordant and Discordant LV Lead Positions

Variable	Concordant LV Lead Position (n = 153)	Discordant LV Lead Position (n = 91)	p Value
Age (yrs)	67 ± 10	65 ± 10	0.3
Gender (male/female)	120/33	79/12	0.1
NYHA functional class (III/IV)	140/13	81/10	0.5
Ischemic etiology	75 (49%)	67 (74%)	<0.001
QRS duration (ms)	164 ± 31	154 ± 34	0.02
LBBB	114 (75%)	66 (73%)	0.4
SR/atrial fibrillation/paced	121/10/22	87/11/19	0.6
LVEF (%)	23 ± 7	24 ± 7	0.3
LVEDV (ml)	242 ± 92	225 ± 71	0.1
LVESV (ml)	189 ± 83	172 ± 61	0.1
MR (moderate-to-severe)	24 (16%)	17 (19%)	0.6
LV dyssynchrony (ms)	189 ± 118	160 ± 119	0.1

Abbreviations as in Table 1.

6-month clinical follow-up after CRT. After 6 months of CRT, 152 patients (62%) showed an improvement of at least 1 NYHA functional class (106 patients showed an improvement of 1 NYHA class, 46 patients showed an improvement of 2 NYHA classes, $p < 0.001$ vs. baseline). The quality-of-life score improved from 39 ± 18 to 23 ± 18, and exercise capacity improved as indicated by an increase in 6-min walking distance from 292 ± 120 m to 388 ± 131 m (both $p < 0.001$). In addition, LVEF improved from 23 ± 7% to 31 ± 9% ($p < 0.001$), with a reduction in LVEDV (236 ± 85 ml to 204 ± 80 ml, $p < 0.001$) and LVESV (183 ± 75 ml to 144 ± 70 ml, $p < 0.001$).

6-month CRT response versus LV lead position. After 6 months of CRT, patients with a concordant LV lead position demonstrated significant improvements in echocardiographic parameters; LVEDV decreased from 242 ± 92 ml to 194 ± 83 ml, LVESV from 189 ± 83 ml to 134 ± 71 ml, and, consequently, LVEF increased from 23 ± 7% to 33 ± 9% (all $p < 0.001$). However, patients with a discordant LV lead position showed no significant reduction in LV volumes (LVEDV from 225 ± 71 ml to 220 ± 70 ml and LVESV from 172 ± 61 ml to 162 ± 63 ml, both p = NS) and no improvement in LVEF (from 24 ± 7% to 27 ± 8%, p = NS) (Fig. 3).

Long-term prognosis versus LV lead position. Mean duration of follow-up was 32 ± 16 months (range 3 to 92 months). There were 55 hospitalizations for decompensated heart failure in 25 patients (10%). Patients were hospitalized

24 ± 15 months (range 1 to 55 months) after CRT implantation. Furthermore, 56 patients died (23%) after a mean follow-up of 20 ± 14 months (range 2 to 55 months), and 1 patient underwent heart transplantation.

Hospitalization rates for decompensated heart failure in the 2 groups are shown in Figure 4A. During follow-up, patients with a discordant LV lead position experienced more hospitalizations for decompensated heart failure as compared with patients with a concordant LV lead position

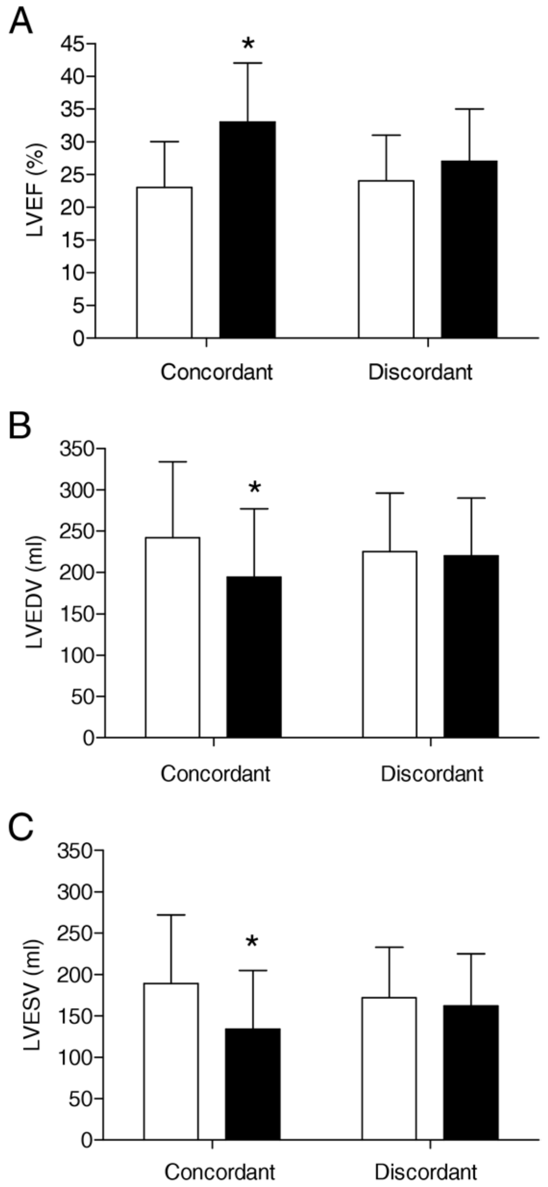

Figure 3 **Echocardiographic Response After CRT in Patients With Concordant LV Lead Positions (n = 153) and Patients With Discordant LV Lead Positions (n = 91)**

Open bars = baseline; **solid bars** = follow-up. *p < 0.001. CRT = cardiac resynchronization therapy; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

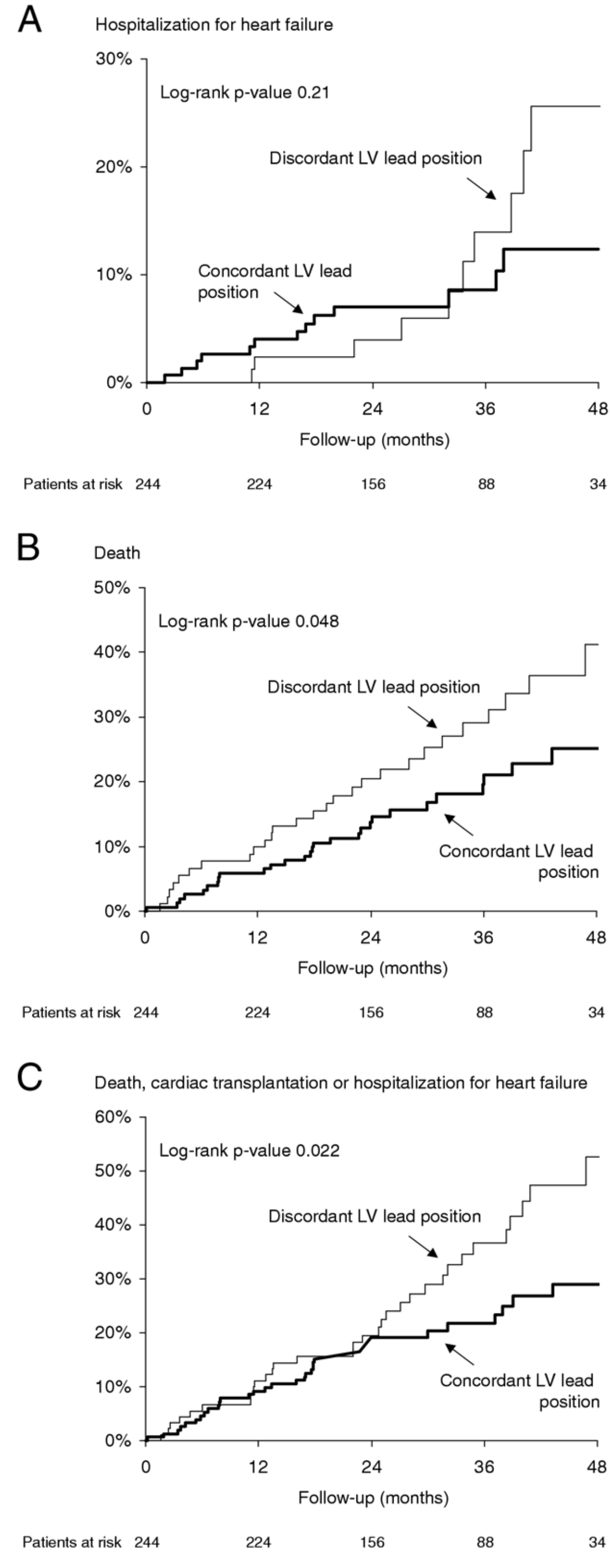

Figure 4 **Survival and Event Curves After CRT According to LV Lead Position**

(A) Hospitalizations for heart failure, **(B)** survival, and **(C)** event-free survival including death, heart transplantation, and hospitalization for heart failure. Abbreviations as in Figure 3.

(20 vs. 35 hospitalizations, $p = 0.04$). However, the number of patients who were hospitalized was not significantly different among both groups as demonstrated by Figure 4A. At 24 months of follow-up, hospitalization rates were, respectively, 4% and 7%. However, during long-term follow-up, a trend for more hospital admissions in the discordant group was noted (at 48 months, respectively, 12% vs. 26%) (Fig. 4A).

Mortality rates for the 2 groups are shown in Figure 4B. Importantly, 13 patients (14%) in the discordant patient group already died before the 6-month follow-up evaluation as compared with 1 patient (1%) in the concordant group ($p < 0.001$). Furthermore, 12- and 24-month survival rates for patients with concordant LV lead positions were 94% and 85%, respectively; in patients with discordant LV lead positions, the 12- and 24-month survival rates were 90% and 79%, respectively (Fig. 4B).

The cumulative event rates of the primary end point (combined for death, hospitalization for heart failure, and heart transplantation) in both groups are shown in Figure 4C. The 12- and 24-month event-free survival rates were quite similar in patients with a concordant LV lead position as compared with those in the discordant group; respectively, 9% versus 11% at 12 months and both 19% at 24 months of follow-up. However, longer follow-up revealed a worse outcome in patients with a discordant LV lead position; 3-year event-free survival is 57% in the discordant patient group versus 78% in the concordant group.

Univariate analysis revealed that a concordant lead position was no predictor of primary outcome within the first 24 months of follow-up (HR: 0.96, 95% CI: 0.527 to 1.758, $p = 0.9$). After 24 months, however, both uni- and multivariate analysis revealed that concordant lead position was an independent predictor of hospitalization-free survival (HR: 0.22, 95% CI: 0.078 to 0.623, $p = 0.004$).

Discussion

The findings of the present study can be summarized as follows: 1) patients who are candidates for CRT exhibit varying sites of latest mechanical activation; 2) in one-third of patients undergoing CRT, the position of the LV lead did not match the site of latest mechanical activation on echocardiography; and 3) a match between LV lead position and site of latest mechanical activation resulted in a better echocardiographic response after 6 months of CRT, with a superior long-term outcome after CRT.

Importance of LV lead position in CRT. It has been suggested that 20% to 30% of patients do not respond to CRT when a clinical end point is used (e.g., improvement in NYHA functional class, quality-of-life score, and so on); however, when reverse LV remodeling is considered as an end point, the nonresponse rate may be as high as 40% to 50% (2,6,7). Several studies have demonstrated that the key mechanism of benefit from CRT is the presence of baseline mechanical LV dyssynchrony as assessed with echocardiography and its subsequent reduction after CRT implantation (5,27,30). In this perspective, the position of the LV pacing lead is important. A recent animal study using magnetic resonance imaging highlighted that regions with maximal resynchronization after CRT also exhibited maximum gain in systolic LV function; these regions were referred to as the "sweet spot" and may be the optimal regions for the LV lead (31).

With the more advanced echocardiographic techniques, adequate identification of the region of latest mechanical activation is possible, and recent data emphasized that the site of latest activation may vary significantly with 67% having the (postero)lateral wall as site of latest activation, but 33% having different regions of latest activation (32). Similarly in the current study, 2D speckle tracking radial strain analysis was used to assess the site of latest mechanical activation. In the majority of patients ($n = 177$), the posterolateral region was the site of latest mechanical activation, whereas one-third of the patients ($n = 80$) revealed another region of latest mechanical activation.

Recent studies in small patient groups have indeed shown that patients with a concordance between the LV lead position and the site of late mechanical activation responded significantly better to CRT, as compared with patients with discordance between LV lead position and the site of latest activation. Ansalone et al. (13) evaluated 31 patients undergoing CRT and demonstrated that patients (42%) who were paced at the site of latest activation (according to tissue Doppler echocardiography) showed significant improvements in LVESV, LVEF, and exercise tolerance after 1 week of CRT, whereas patients paced at any other site (58%) showed no improvement. Longer follow-up was obtained in 2 studies, both using 2D strain analysis to determine the site of latest mechanical activation. Suffoletto et al. (25) demonstrated that patients with a concordance between the LV lead position and the site of latest activation had a larger increase in LVEF at mid-term follow-up as compared with patients with a discordance ($10 \pm 5\%$ vs. $6 \pm 5\%$, $p < 0.05$). Becker at al. (16) confirmed these findings and reported that the distance between the site of latest mechanical activation and the actual pacing site was predictive of reverse LV remodeling at 10-month follow-up. Murphy et al. (15) used a more sophisticated approach with 3D tissue synchronization imaging; the patients were divided into 3 groups according to the relation between the LV lead position and the area of latest mechanical activation. The greatest hemodynamic and clinical benefit from CRT was observed in patients who were paced at the site of latest mechanical activation, whereas the response was less in patients with the LV lead adjacent to the site of latest mechanical activation and absent in patients with the LV lead placed remote from the site of latest mechanical activation.

The current study evaluated a large cohort of patients undergoing CRT ($n = 257$) and confirmed the aforementioned findings; a greater echocardiographic improvement (reverse LV remodeling and increase in LVEF) was noted in patients with a concordant LV lead position as compared with that in patients with a discordant LV lead position. Clinically more important, however, is whether concordance or discordance between LV lead position and the site of latest mechanical activation has prognostic value. Regarding hospitalizations for heart failure, a trend for more admissions in the discordant group was noted. Importantly, mortality was significantly lower in the patients with concordant LV lead position (15% vs. 21% at 24 months, log-rank p = 0.048). Moreover, a concordant LV lead position appeared to be an independent predictor of the combined end point of hospitalization and mortality after long-term CRT.

Clinical implications. The current study further supports the importance of the LV lead position in CRT. With sophisticated echocardiographic techniques, including tissue Doppler imaging and speckle tracking 2D radial strain imaging, it is possible to locate (before device implantation) the site of latest activation, which may even be further optimized by 3D echocardiogram techniques. Ideally, positioning of the LV pacing lead could thus be guided by echocardiography during the CRT implantation. However, it is important to realize that LV lead positioning may be limited by anatomical and technical factors including presence, accessibility, and lead stability within the appropriate region of the appropriate vein. Venous anatomy can be obtained during the procedure with retrograde venography but is also possible with noninvasive imaging using multislice computed tomography before CRT implantation (33). The precise incidence of suitable veins for CRT is not known and may differ between patients with ischemic and nonischemic cardiomyopathy (34). When the site of latest activation is not in the region of suitable veins, surgical LV lead positioning may be considered, using limited left-lateral thoracotomy with direct epicardial LV lead placement (35). Ideally, one could thus integrate the information from echocardiography (latest mechanical activation) and multislice computed tomography (venous anatomy) to determine the approach. In addition, the presence of posterolateral scar tissue appeared to be an important factor for nonresponse after CRT (36). However, assessment of scar tissue was not routinely performed in the current study population. Still, prospective large studies are needed comparing empiric and guided LV lead implantation (targeted at the site of latest activation).

Conclusions

Positioning of the LV pacing lead at the site of latest mechanical activation resulted in significant reverse LV remodeling and increase in LVEF after 6 months of CRT, whereas discordant LV lead position did not result in echocardiographic improvement. Moreover, long-term prognosis was significantly better in patients with a concordant LV lead position; a concordant LV lead position appeared to be an independent predictor of outcome (combined end point of hospitalization and death) after long-term CRT.

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