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Clinical Study

The Use of Epicardial Electrogram as a Simple Guide to Select the Optimal Site of Left Ventricular Pacing in Cardiac Resynchronization Therapy

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Cardiac resynchronization therapy (CRT) has been demonstrated to improve symptoms and survival in patients with left ventricular (LV) systolic dysfunction and dyssynchrony. To achieve this goal, the LV lead should be positioned in a region of delayed contraction. We hypothesized that pacing at the site of late electrical activation was also associated with long-term response to CRT. We conducted a retrospective study on 72 CRT patients. For each patient, we determined the electrical delay (ED) from the onset of QRS to the epicardial EGM and the ratio of ED to QRS duration (ED/QRS duration). After a followup of 30 ± 20 months, 47 patients responded to CRT. Responders had a significantly longer ED and greater ratio of ED/QRS duration than nonresponders. An ED/QRS duration ≥0.38 predicted a response to CRT with 89% specificity and 53% sensitivity.

1. Introduction

Cardiac resynchronization therapy (CRT) has been validated as an effective therapeutic approach for patients with drug-refractory heart failure associated with left ventricular (LV) dyssynchrony. In this population, CRT not only improves heart failure symptoms and quality of life [1, 2] but also leads to reverse remodeling [3] and reduces the risk of death [4]. Despite this unquestionable efficacy, 30% of patients do not appear to benefit from CRT, and substantial effort has been made to better identify potential responders [5, 6]. Several reports have indicated that LV lead placement at the site of latest mechanical contraction is a critical determinant of CRT outcome [7, 8]. The identification of these sites of greater dyssynchrony by echocardiography has been suggested by several authors to be associated with acute or long-term success of CRT. However, echo-guided lead positioning requires sophisticated techniques for assessment of LV dyssynchrony and selection of the site of latest mechanical activation [7, 9, 10]. The use of these techniques, during CRT, is challenging and may significantly prolong the procedure duration. Furthermore, data from the PROSPECT trial [11] illustrated the limited intra- and interobserver reproducibility of these measurements.

Another method of identifying sites of latest activation is the use of epicardial electrogram (EGM). Pacing at the site of maximal electrical delay (ED) determined electrophysiologically [12] or by electroanatomical mapping [13, 14] has been reported to result in greater acute hemodynamic response. However, data on the long-term value of this technique are very limited [12]. The goal of our study was to assess the value of the ED for the prediction of the long-term response and to determine the degree of conduction delay that was more likely to be associated with positive outcome.

2. Methods

We conducted a retrospective single-centre study on patients with a CRT device and in whom local epicardial EGM was available at the time of the procedure.

2.1. Patients' Selection. Patients were included in our study if they had successful implantation of a CRT device for drug-refractory congestive heart failure: NYHA functional class III

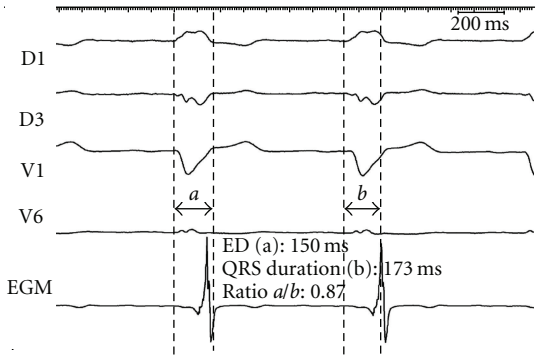


Figure 1: Recording of the epicardial EGM at the tip of the LV lead. a: QRS duration, b: electrical delay.

or IV, due to severe systolic LV dysfunction (LV ejection fraction (LVEF) ≤35% and long QRS duration (≥120 ms)) [15] and if epicardial EGMs were obtained during the procedure. Patients with severe ischemic heart disease and extensive myocardial scar (involving more than 4 LV segments) or history of lateral or posterolateral myocardial infarction who had a low likelihood of response were not considered for CRT and, therefore, were not included in our study.

2.2. Implantation Technique. Technical aspects of lead and device implantation were described in detail in previous publications [16, 17]. Efforts were made to place the LV lead in a lateral tributary of the coronary sinus. At the end of the procedure and before the LV lead was connected to the CRT device, simultaneous surface 12-lead ECG and epicardial EGMs were continuously acquired with a filter bandwidth of 0.05 to 40 Hz and 30 to 500 Hz, respectively, and displayed on a high-resolution video monitor at 100 mm/second paper speed for inspection and subsequent review (Prucka Engineering). The ED was measured from the onset of QRS to the peak of sharpest deflection of the EGM (Figure 1). We also determined the ratio of the ED to baseline QRS duration (ED/QRS duration). During the study period, the LV lead position was not modified on the basis of the ED. After the implant, each patient had a chest X-ray in the anteroposterior and left anterior oblique (LAO) views, and the final LV lead position was recorded in the latter view.

2.3. Patients' Followup. After implantation of the CRT device, patients were followed prospectively in our institution at 1, 6, and 12 months and every year thereafter. The following parameters were collected at baseline and each visit: functional status defined by NYHA class, 6-minute walked distance, and LV volumes by echocardiography: LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV). LVEF was determined by echocardiography or nuclear angiography. When LVEF was evaluated at baseline by one of the 2 techniques, the same method was used at long-term followup. Some parameters of LV dyssynchrony were also assessed at baseline and followup, but results of these parameters will not be reported in the present study, since their value in selection of patients for CRT has not been validated by the PROSPECT trial [11]. Response to CRT was defined by either improvement of functional status by at least 2 NYHA classes alone or by one NYHA class associated with increased LVEF by at least 5% [18].

Table 1: Comparison of clinical characteristics in responders and nonresponders.

	Responders $N = 47$	Nonresponders $N = 25$	P
Age (years)	70 ± 7	72 ± 8	.36
NIDCM (%)	72	60	.29
SR at implant (%)	89	92	.72
NYHA class	3.3 ± 0.5	3.1 ± 0.7	.37
NYHA class			
Class III (%)	69	73	.71
Class IV (%)	31	27	
Baseline treatment			
Beta-blocker (%)	67	65	.91
ACE inhibitor (%)	73	81	.48
ARA (%)	22	12	.35
Diuretics (%)	98	92	.55
Spironolactone	38	42	.71
Digoxin (%)	27	31	.71
Statin (%)	40	42	.85
Treatment at followup			
Beta-blocker (%)	80	65	.17
ACE inhibitor (%)	78	65	.26
ARA (%)	29	23	.59
Diuretics (%)	98	100	1
Spironolactone	27	42	.18
Digoxin (%)	24	42	.12
Statin (%)	49	46	.82
Change of treatment during followup (%)	89	89	1
6-minute walked distance (m)	354 ± 126	348 ± 119	.88
Follow-up duration (months)	32.1 ± 20.9	27.3 ± 19.1	.35
Δ NYHA class	−1.6 ± 0.7	−0.2 ± 0.9	<.001

Abbreviations used: SR: sinus rhythm, NIDCM: nonischemic dilated cardiomyopathy, NYHA class: New York Heart Association functional class, ACE inhibitors: angiotensin converting enzyme inhibitors, ARA: angiotensin receptor antagonist, Δ NYHA: difference of NYHA class between followup and baseline.

2.4. Statistical Analysis. Categorical data are expressed as incidence, and noncategorical data are expressed as mean ± standard deviation. A comparison of categorical data was performed using the Chi-square test, and noncategorical data were compared by Student's t-test. Linear regression analysis was performed using the Pearson correlation coefficients. Logistic regression analysis was used for identification of independent predictors of long-term response to CRT. A P value < .05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics. Our study population comprised 72 patients (47 men) who were implanted with a CRT device and in whom epicardial EGM was available at the time of the procedure. Mean age was 70 ± 8 years. Sixty-eight percent of patients had nonischemic dilated cardiomyopathy. Ninety percent were in sinus rhythm (SR) at the time of implant. Spontaneous baseline QRS duration was 178 ± 29 ms. Almost all patients had left bundle branch block (LBBB, $N = 69$). Only 3 patients had right bundle branch block (RBBB). Mean LVEF prior to CRT was 23 ± 8%. Six-minute walked distance was 351 ± 122 meters. Mean ED was 132 ± 36 ms, and the mean ratio of ED/QRS duration was 0.75 ± 0.17.

3.2. Long-Term Followup

3.2.1. Comparison of Baseline Characteristics between Responders and Nonresponders. After a mean followup of 30 ± 20 months, 47 patients were classified as responders and 25 as nonresponders. A comparison of patients' characteristics is summarized in Tables 1 and 2. No significant difference was observed between the 2 groups in baseline characteristics including age, nature of underlying heart disease, prevalence of SR at baseline, QRS duration, NYHA functional class, 6-minute walked distance, followup duration, and medications at baseline and followup. Optimization of medical therapy was equally frequent in both groups of patients. Baseline LVEF was higher in responders (25 ± 8% versus 20 ± 7%, $P = .01$). As expected, responders had significant improvement of their NYHA functional class and LVEF compared to baseline (Δ NYHA class = −1.6 ± 0.7, $P < .0001$, Δ LVEF = +19 ± 12%, $P < .0001$), whereas in nonresponders, there was no significant change of these same parameters at long-term followup (Δ NYHA class = −0.2 ± 0.9, $P = .63$, Δ LVEF = −0.6 ± 8%, $P = .60$). The difference between the 2 groups was statistically significant ($P < .001$). Nonresponders had significantly larger LVEDV and LVESV at baseline compared to responders (Table 2). At followup, responders exhibited significant reduction of their LV volumes (Δ LVEDV = −55 ± 72 mL, $P < .001$, Δ LVESV = −68 ± 66 mL, $P < .001$). In nonresponders, there was no significant change of LV volumes compared to baseline (Δ LVEDV = +5 ± 62 mL, $P = .73$, Δ LVESV = +5 ± 58 mL, $P = .69$). Again, the difference between the 2 groups was highly significant ($P = .002$ for Δ LVEDV and $P = .001$ for Δ LVESV).

ED was significantly longer in responders (139 ± 35 ms versus 119 ± 37 ms, $P = .03$). The ratio of ED/QRS duration was also significantly greater in responders (0.79 ± 0.16 versus 0.67 ± 0.18, $P = .005$).

3.2.2. Correlation between ED and Long-Term Outcome. Linear regression analysis showed a weak but significant positive correlation between ED and difference of LVEF from baseline to followup (Δ LVEF) ($r = +0.307$, $P = .009$) (Figure 2(a)) and also a weak but significant negative correlation with change of NYHA class from baseline to followup (Δ NYHA) (Figure 2(b)) ($r = −0.310$, $P = .008$). We also found a significant positive correlation between the ratio of ED/QRS duration and Δ LVEF ($r = +0.232$, $P = .05$) (Figure 3(a)) and a significant negative correlation with Δ NYHA ($r = −0.283$, $P = .016$) (Figure 3(b)).

Receiver operating characteristic analysis showed that an ED ≥ 150 ms predicted a response to CRT with 80% specificity and 47% sensitivity (odds ratio (OR): 3.5, confidence interval (CI): 1.1–11, $P = .025$). A ratio of ED/QRS duration ≥0.83 was associated with a response to CRT with 89% specificity and 53% sensitivity (OR: 8.3, CI: 2.2–31.7, $P = .001$).

Logistic regression analysis (Table 3) showed that, after adjustment for baseline rhythm and underlying heart disease, independent predictors of positive outcome were baseline LVEF and the ratio of ED/QRS duration.

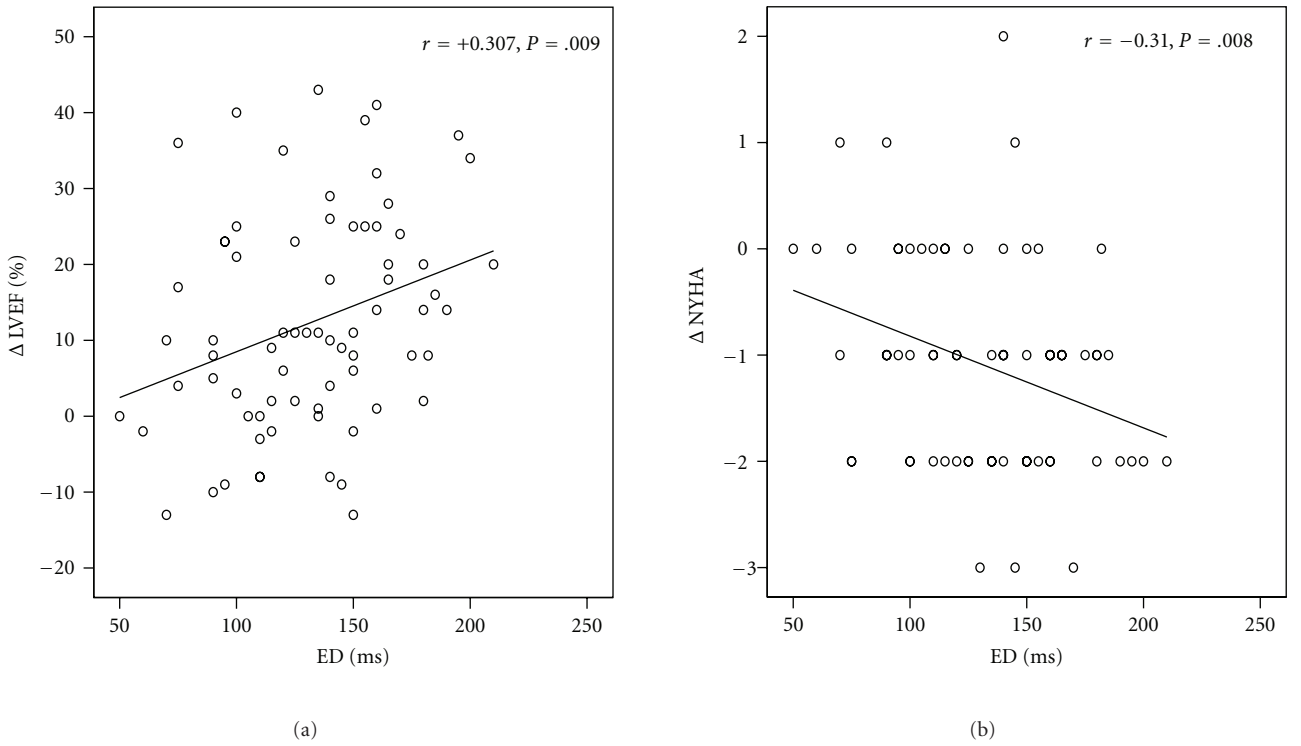
3.2.3. Comparison of Correlation between ED (or Ratio of ED/QRS Duration) and Response to CRT in Ischemic and Nonischemic Cardiomyopathy. The value of ED to predict response to CRT in patients with ischemic and nonischemic cardiomyopathy was analyzed separately (Table 4). We did not find a stronger correlation between ED and change of LVEF or NYHA class during long-term followup in patients with nonischemic dilated cardiomyopathy versus those with ischemic heart disease. The same result was observed when the correlation was examined with the ratio of ED/QRS duration.

3.2.4. Correlation between ED (or Ratio of ED/QRS Duration) and LV Lead Position in the LAO View. Figure 4 shows the distribution of ED (Figure 4(a)) and the ratio of ED/QRS duration (Figure 4(b)) based on the LV lead location in the LAO view. Almost all patients had their LV lead positioned between 1:30 and 5:00 o'clock. In 1 patient the LV lead was left in the great cardiac vein and in 2 patients, the final LV lead position was at 12:30. As shown in Figures 4(a) and 4(b), longer EDs and greater ratios ED/QRS duration were more likely to be located between 2:30 and 5:00 o'clock, but short EDs and small ratios were also observed in the same locations indicating that not all lateral sites were equal.

4. Discussion

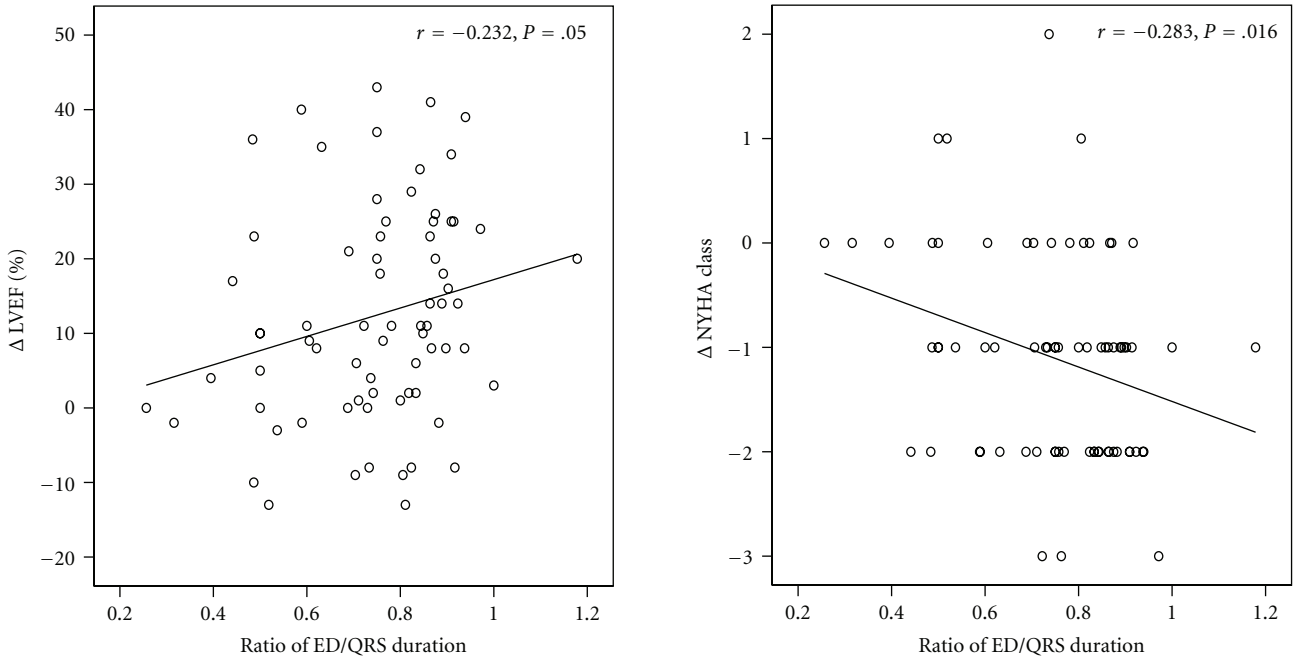
The present study demonstrates the value of intraprocedural epicardial EGM recording to direct placement of the LV lead in regions of long ED in order to increase the likelihood of long-term response to CRT. Although mechanical rather than electrical resynchronization has been suggested to be the primary determinant of hemodynamic benefit, we hypothesized that these two components are closely linked.

Controversial data from the literature raise the question whether positioning the LV lead should be guided by echocardiography to determine the site of latest mechanical contraction. Some of these reports indicate an enhanced response rate in patients in whom there is concordance between the position of the LV lead tip and the latest area of contraction [7, 9, 10, 19], whereas other investigators suggest that pacing at these sites is not always associated with



(a) (b)

Figure 2: Correlation between ED and Δ LVEF (a) and Δ NYHA class (b). Abbreviations: ED: electrical delay, Δ LVEF: difference of LVEF between long-term followup and baseline, Δ NYHA: difference of NYHA class between long-term followup and baseline.



(a) (b)

Figure 3: Correlation between ratio of ED/QRS duration and Δ LVEF (a) and Δ NYHA class (b). Abbreviations: ED: electrical delay, Δ LVEF: change in LVEF from baseline to long-term followup, Δ NYHA: change in NYHA class from baseline to long-term followup.

Table 2: Comparison of echocardiography and electrical parameters in responders and nonresponders.

	Responders	Nonresponders	*P*
Spontaneous QRS duration (ms)	177 ± 31	180 ± 26	.69
ED (ms)	139 ± 35	119 ± 37	.03
Ratio of ED/QRS duration	0.78 ± 0.15	0.68 ± 0.19	.02
LVEF (%)	25 ± 8	20 ± 7	.01
Baseline LVESV (mL)	182 ± 57	240 ± 63	<.001
Baseline LVEDV (mL)	269 ± 62	319 ± 75	.005
Δ LVEF (%)	+19.5 ± 11.9	−0.8 ± 7.7	<.001
Δ LVESV (mL)	−55 ± 72	+5 ± 62	.002
Δ LVESV (mL)	−68 ± 66	+5 ± 58	.001

Abbreviations: ED: electrical delay, LVEF: left ventricular ejection fraction, Δ LVEF: difference of LVEF between followup and baseline, LVESV: left ventricular end-systolic volume, LVEDV: left ventricular end-diastolic volume, Δ LVESV: difference of LVESV between followup and baseline, Δ LVESD: difference of LVESV between followup and baseline.

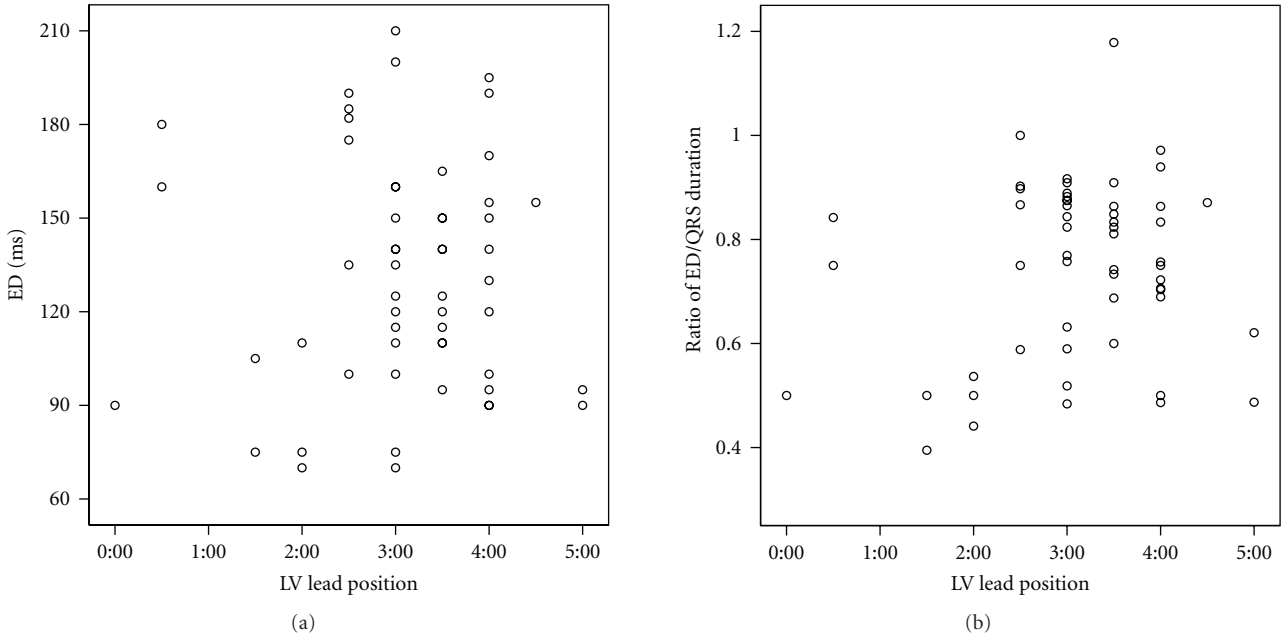


Figure 4: Distribution of ED (a) and ratios of ED/QRS duration (b) as a function of LV lead position in the LAO view. Abbreviations: ED: electrical delay, LAO: left anterior oblique.

Table 3: Multivariate predictors of response to CRT.

	OR	(95% CI)	*P*
SR at implant	1.3	0.2–10.1	.80
NIDCM	1.3	0.4–4.4	.69
LVEF	1.08	1.002–1.17	.045
Ratio of ED/QRS duration ≥0.83	6.8	1.7–27.5	.007

Abbreviations used: OR: odds ratio, CI: confidence interval, SR: sinus rhythm, NIDCM: nonischemic dilated cardiomyopathy, LVEF: left ventricular ejection fraction, ED: electrical delay.

acute or long-term response [20, 21]. On the other hand, adequate assessment of LV dyssynchrony and, more precisely, the site of latest mechanical activation requires sophisticated techniques that may prolong the implantation time, and their use is limited by high intra- and interobserver variability as illustrated by the results of the PROSPECT trial [11], whereas intraoperative assessment of ED is straightforward and can be used as a surrogate method for selection of optimal LV pacing sites.

Another method that can be used intraoperatively to select optimal sites of LV pacing is intracardiac mapping. In a human study conducted on 14 candidates for CRT, Tse et al. [13] showed the greater hemodynamic improvement by LV pacing in patients presenting with larger amount of LV area with late endocardial activation time and preserved LV myocardium measured by electroanatomical mapping.

Table 4: Comparison of the value of ED in patients with ischemic and nonischemic cardiomyopathy.

	IDCM		NIDCM	
	r	*P*	*r*	*P*
ED versus Δ LVEF	+0.39	.06	+0.20	.17
ED versus Δ NYHA	−0.44	.03	−0.26	.07
Ratio of ED/QRS duration versus Δ LVEF	+0.37	.08	+0.08	.57
Ratio of ED/QRS duration versus Δ NYHA	−0.41	.05	−0.23	.11

Abbreviations: IDCM: ischemic dilated cardiomyopathy, NIDCM: nonischemic dilated cardiomyopathy, ED: electrical delay, Δ LVEF: difference of LVEF between follow-up and baseline, Δ NYHA: difference of NYHA between follow-up and baseline, *r*: correlation coefficient determined by regression analysis, *P*: *P* value.

Previously, Singh et al. [12] reported the value of the ED to predict response to CRT defined by one-year mortality and hospitalizations for heart failure. They found that a reduced LV electrical delay less than 50% of the QRS duration was associated with worse clinical outcome within the entire patients' population as well as when stratified into ischemic and nonischemic subgroups. Our results confirm these data at longer follow-up durations using a different endpoint for response to CRT. As in the latter study, we purposely expressed, in our multivariate analysis, the ED as the percentage of the baseline QRS duration and not the absolute value, in order to eliminate a potential impact of the QRS duration on the predictive value of the local ED. Despite this adjustment, this parameter remained an independent predictor of positive outcome.

Our study population comprised patients with both ischemic and nonischemic heart disease. This could have influenced our results. Indeed, the presence of scar does not preclude electrical capture of the myocardium, but this may not translate into mechanical contraction and, therefore, may not result in effective correction of LV dyssynchrony in the presence of extensive myocardial infarction. This hypothesis has been verified by several studies using different imaging techniques of scar quantification: Bleeker et al. [22] defined LV scar burden using contrast-enhanced MRI and reported that patients who failed to respond to CRT were more likely to have transmural scar in the posterolateral region of the LV (an important target for lead placement). Ypenburg et al. [23] assessed the importance of transmural scar quantified by gated SPECT in the LV pacing target region and showed that pacing at these sites was negatively correlated to subsequent LV reverse remodeling. These observations confirm some study reports where CRT results in greater improvement of LVEF and reduction of LV end-diastolic volume in patients with nonischemic dilated cardiomyopathy compared to those with ischemic heart disease and extensive transmural scar [24].

In our series, we took every precaution not to implant CRT in patients with severe ischemic heart disease and extensive myocardial scar (involving more than 4 LV segments) or history of lateral or posterolateral myocardial infarction who had a low likelihood of response. That may explain the lack of significant difference in the prevalence of nonischemic cardiomyopathy between responders and nonresponders. Multivariate analysis of our results did not identify the nonischemic nature of the cardiomyopathy as an independent predictor of positive outcome. Furthermore, correlation between ED and long-term response was analyzed separately in patients with nonischemic cardiomyopathy and was not superior in this subgroup of patients. On the other hand, fibrosis might also be present in patients with nonischemic dilated cardiomyopathy and may also decrease the efficacy of LV pacing. MRI studies are required to quantify fibrosis in patients with nonischemic heart disease at the sites of latest mechanical contraction or greatest ED.

4.1. Lack of Correlation between ED and Sites of LV Pacing on Chest X-Ray. Our study results indicate that there is no correlation between ED and the location of the LV lead documented in the LAO view. A wide range of values of ED or ED/QRS duration are observed in the postero-lateral or lateral locations which are known as important targets for LV lead placement. This finding implies that not all LBBBs are created equal: the ventricular conduction abnormality in patients with LBBB and LV dysfunction is not a uniform conduction system lesion [25]. Both endocardial and epicardial electroanatomical mapping of LV activation disclose significant variations during intrinsic conduction in both ischemic and nonischemic cardiomyopathy [26–28]. In some patients, wavefronts from multiple directions contribute to overall LV activation. In others, activation spreads from the anterior to the inferior wall, or the reverse. Alternatively, LV epicardial activation starts from the septoapical region, spreading laterally and ending at the lateral or posterolateral base. Wavefront propagation is sometimes influenced by areas of slow conduction or lines of conduction block, some of which are fixed and correlate with areas of scar and others shift to other locations during pacing maneuvers due to their functional character. These variations, which occur with similar QRS configurations on surface ECG, may result from any combination of conduction tissue lesion, scar and fibrosis, and slow cell-to-cell conduction. Therefore, electroanatomical mapping or, more simply, local electrical delay may refine LV lead placement to achieve the best effect. Since the presumed mechanism for the efficacy of CRT is the correction of conduction delay, response is more likely when pacing is delivered at an area of greater LV conduction delay, as suggested in our study.

4.2. Study Limitations. Although we found a significant relationship between ED and long-term response to CRT, the correlation was weak. Based on our results, long ED recorded during spontaneous LBBB predicts reverse remodeling and positive clinical outcome, with good specificity but low sensitivity, which means that in the presence of ED $\geq$ 150 ms or ED/QRS duration $\geq$0.83, the likelihood of positive outcome is very high, but shorter EDs or lower ED/QRS durations do not necessarily preclude long-term improvement following

CRT. The mechanism of this finding is unclear and may result from our recording technique that was performed from the tip of the final LV lead position in a tributary of the CS indicating activation of the epicardial and not endocardial side of the left ventricle. Endocardial electroanatomical mapping might have elucidated the complex mechanism of positive response in some patients with short EDs measured from the epicardial EGM recording. It is also unknown if ED can vary at the same LV site with the level of patient's activity. On the other hand, in our study, we did not map the whole LV to determine the site of maximal electrical delay. With the use of electroanatomical mapping, we could have identified areas of latest electrical activation where LV pacing could have resulted in better outcome.

The definition of responders in our study was a pure clinical endpoint when improvement of functional status was important and a composite clinical and echocardiographic endpoint when improvement of functional status was more modest. The reason for this selection is that patients were followed at regular intervals in our institution and improvement of functional status by one NYHA class with no improvement of LVEF might have resulted from the optimization of medical therapy at each visit and not from CRT. A plethora of endpoints for response to CRT have emerged in the literature: some are merely clinical, defining response as improvement of functional status by at least one NYHA class [19, 29, 30] or including composite factors such as peak VO_2 [31, 32], quality of life score [33, 34], and 6-minute walked distance [19, 31, 33, 35], others are based on echocardiographic parameters including reduction of LV end-systolic volume by at least 15% [35–37] or improvement of LVEF by at least 5% [38, 39]. Even though our population was highly selected (mostly LBBB, nonischemic heart disease, long QRS duration), the proportion of responders in our series was in the range of that previously reported in the literature [5, 6]. With softer clinical endpoints (improvement of function status by one NYHA class), we would have expected a higher response rate. Another explanation for our result is our longer follow-up duration. On the other hand, in large CRT trials, although the cut-off value for QRS duration was usually 120–130 ms, the actual average mean QRS duration of included patients was in the range of values reported in our study (>150 ms) [18].

The small number of our patients might have been another limitation of the study. With larger number of patients, a stronger correlation might have been found between ED and response to CRT.

5. Conclusions

Selecting the LV lead position at the site of the delayed electrical activation may provide an important criterion for appropriate pacing site in patients with both ischemic and nonischemic cardiomyopathy, with high specificity but low sensitivity. Pacing at sites of increased ED is associated with long-term benefit. Gross anatomic lateral location of the LV lead is not always correlated with electrical delay and by itself is not enough to predict chronic response to CRT.

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