Determination of the Longest Intra-patient Left Ventricular Electrical Delay May Predict Acute Hemodynamic Improvement in Patients After Cardiac Resynchronization Therapy

Francesco Zanon, MD, FESC, FHRs; Enrico Baracca, MD; Gianni Pastore, MD; Chiara Fraccaro, MD, PhD; Loris Roncon, MD; Silvio Aggio, MD; Franco Noventa, MD; Alberto Mazza, MD, PhD; Frits Prinzen, PhD

Background—One of the reasons for patient nonresponse to cardiac resynchronization therapy is a suboptimal left ventricular (LV) pacing site. LV electric delay (Q-LV interval) has been indicated as a prognostic parameter of cardiac resynchronization therapy response. This study evaluates the LV delay for the optimization of the LV pacing site.

Methods and Results—Thirty-two consecutive patients (23 men; mean age, 71±11 years; LV ejection fraction, 30±6%; 18 with ischemic cardiomyopathy; QRS, 181±25 ms; all mean±SD) underwent cardiac resynchronization therapy device implantation. All available tributary veins of the coronary sinus were tested, and the Q-LV interval was measured at each pacing site. The hemodynamic effects of pacing at different sites were evaluated by invasive measurement of LV dP/dt max at baseline and during pacing. Overall, 2.9±0.8 different veins and 6.4±2.3 pacing sites were tested. In 31 of 32 (96.8%) patients, the highest LV dP/dt max coincided with the maximum Q-LV interval. Q-LV interval correlated with the increase in LV dP/dt max in all patients at each site (AR1 ρ=0.98; P<0.001). A Q-LV value >95 ms corresponded to a >10% in LV dP/dt max. An inverse correlation between paced QRS duration and improvement in LV dP/dt max was seen in 24 patients (75%).

Conclusions—Pacing the LV at the latest activated site is highly predictive of the maximum increase in contractility, expressed as LV dP/dt max. A positive correlation between Q-LV interval and hemodynamic improvement was found in all patients at every pacing site, a value of 95 ms corresponding to an increase in LV dP/dt max of ≥10%. (Circ Arrhythm Electrophysiol. 2014;7:377-383.)

Key Words: cardiac resynchronization therapy ■ cardiomyopathies ■ heart failure ■ hemodynamics

It has been proven that cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with heart failure (HF).1-3 Large clinical trials have demonstrated the benefit of CRT on HF symptoms, exercise capacity, and left ventricular (LV) remodeling.1,2,4-9 However, up to one third of patients with HF do not respond to CRT.10 Gorcsan and Prinzen11 proposed an algorithm to determine the probability of response to CRT. During left bundle branch block (LBBB), QRS duration >150 ms, nonischemic cardiomyopathy, presence of mechanical dyssynchrony, and female sex are pre-existing clinical conditions that cannot be influenced; the proper choice of the position of LV lead depends on the CRT implantation procedure.

Purely anatomically defined regions do not seem to predict CRT response. In the Pacing Therapies for Congestive Heart Failure (PATH-CHF) study, Auricchio et al12 proposed the midportion of the LV lateral wall as the most favorable pacing site. In contrast, recent papers from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) and the RESynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) suggested that the apical region was the worst area for pacing,13,14 but at the population level, no clear difference emerged between anterior, lateral, and posterior regions.

To find a more functional definition of the best pacing site, several authors have focused on the region that is activated latest owing to LV dyssynchrony and have tried to identify the best site by using various electrocardiographic and echocardiographic measurements.15 Some investigators have looked at the latest activated site as the target position for LV lead.16,17 In these studies, the relationship between LV electric delay (Q-LV
Methods
We analyzed the relationship between LV dP/dt\textsubscript{max} increase and LV electric delay in a CRT population. The study was approved by the local ethics board, and all patients provided written informed consent.

In accordance with our standard implantation procedure, the right ventricular and atrial leads were positioned in conventional sites in all patients. Specifically, the right ventricular leads were implanted in the midseptum. The coronary sinus was cannulated via a telescopic approach, as previously described\textsuperscript{12}; coronary sinus angiography was performed, and all suitable collateral veins were subcannulated and visualized selectively. For the purpose of the present article, we define available veins as all veins that were actually cannulated and used for measurement. We did not collect data on veins that were visualized but not cannulated. We collected data on the available pacing site; in some veins, for anatomic reasons, it was not possible to reach the apex.

In the right anterior oblique view, the long axis of the heart was divided into basal, mid, and apical ventricular segments. In the left anterior oblique view, the short axis of the heart was divided into anterior, anterolateral, lateral, posterolateral, and posterior segments. This classification system was used by Singh et al\textsuperscript{13} in the MADIT-CRT analysis.

A bipolar or quadripolar LV lead was positioned within each available collateral vein. The choice between a bipolar or quadripolar lead was based on the type of device used or the vein size; in the case of small veins, we used the thinner bipolar lead, which is only 4F. A bipolar lead was selected predominantly for pacemaker implantation and a quadripolar lead for implantable cardioverter-defibrillator implantation. Data were collected from the apical, mid, and basal portions of each vein: intrinsic Q-LV interval, biventricular-paced QRS complex, pacing threshold, phrenic nerve stimulation threshold, and LV dP/dt\textsubscript{max} during biventricular pacing were measured at each site.

We always mapped in the bipolar configuration, starting as apically as possible. The lead was then withdrawn, and we took further measurements to map the entire vessel in the bipolar configuration. We never used the unipolar configuration. The mapping dipole for the quadripolar or bipolar lead had an interdipole length of 20 mm.

Electrophysiology Laboratory Measurements
QRS duration and Q-LV interval were measured by means of a BARD Labsystem Pro EP V2.4a (C.R. Bard Inc, Lowell, MA) with high-resolution electronic calipers at a display speed of 100 mm/s.

The paced QRS duration was measured from the beginning of the ventricular pacing spike to the end of the QRS complex, using the maximum paced QRS duration in any of the 12 ECG leads.\textsuperscript{19}

The Q-LV interval was defined as the interval from the onset of the intrinsic QRS on the surface ECG to the first large positive or negative peak of the LV electrogram (Figure 1). The amplitude of the first large peak needed to be >50% of the amplitude of the largest peak in the same cardiac cycle.\textsuperscript{17}

In patients with sinus rhythm, biventricular pacing was performed in the VDD mode (with a fixed atrioventricular delay of 130 ms). The VV interval was always set to 0 ms. In patients with atrial fibrillation, VVI pacing was performed at a rate 5 to 10 beats above the intrinsic ventricular rate.\textsuperscript{20}

Pacing and phrenic nerve stimulation thresholds were measured by means of a Merlin EX3100 Pacing System Analyzer (St Jude Medical, Sylmar, CA).

Acute Hemodynamic Measurements
Measurements of LV dP/dt\textsubscript{max} were taken with a Certus Pressure Wire and PhysioMon software (St Jude Medical Systems AB, Uppsala, Sweden). The Certus Pressure Wire is a 0.014-inch-diameter guide equipped with a high-fidelity tip sensor. The guide was inserted through the femoral access site by means of a 4F multipurpose catheter. The tip of the pressure wire was placed in a stable LV position.

Baseline LV dP/dt\textsubscript{max} was calculated over an interval of 15 seconds; premature ventricular contractions were eliminated electronically. A period of ≥30 seconds was allowed to elapse after any change in pacing settings or lead position to allow hemodynamic stabilization.\textsuperscript{20}

During LV pacing at different sites, each value of LV dP/dt\textsubscript{max} was measured over an interval of 15 seconds, and premature ventricular contractions were eliminated electronically.

Statistical Analysis
A generalized linear mixed model\textsuperscript{21} was used to identify independent factors that influenced LV dP/dt\textsubscript{max} reached after stimulation. The maximum Q-LV interval was determined by repeated measurements at various sites in the LV wall; 15 anatomically identified sites (Figure 2) were investigated in each patient. The covariates baseline LV dP/dt\textsubscript{max} and Q-LV interval were considered to be random effects.
within this model. In the analyses, sex, presence of atrial fibrillation, LBBB, or ischemic cardiomyopathy (as fixed effects) were controlled for as potential confounders. If no evidence of the interaction term (P interaction > 0.10) was found, a model without the interaction term was fitted. The generalized linear mixed model allowed us to use the different numbers of observations in different subjects because of the different accessibility of the various anatomic sites.

To look for a rule of thumb to find the site providing the most effective stimulation, we counted the number of patients in whom the maximum value of Q-LV interval and maximum hemodynamic effectiveness (LV dP/dt max) coincided; we then estimated the proportion of this parameter with 95% confidence interval (Wilson method).

Values of 2-sided P < 0.05 were considered statistically significant. Intrapatient correlation was calculated through linear regression analysis by means of Pearson R coefficient. Statistical analysis was performed by SPSS statistical software, version 20.0 (IBM-SPSS, Inc, Chicago, IL).

**Results**

CRT devices were implanted in 32 consecutive patients with HF. The characteristics of our patient population are displayed in Table 1.

No complications related to the implantation procedure or to the femoral approach were reported. The mean procedural time was 148±32 minutes, and mean fluoroscopy time was 32±16 minutes.

Overall, 2.9±0.8 different veins and 6.4±2.3 pacing sites were tested. At least 2 veins were tested in 30 patients. Table 2 reports the total number of available veins and pacing sites tested. Details of the sites tested are displayed in Figure 2, which shows the anatomic classification and optimal pacing sites.

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population, n</th>
<th>ICM, n (%)</th>
<th>Age, y</th>
<th>Male sex, n (%)</th>
<th>NYHA class II, III, IV, n (%)</th>
<th>Sinus rhythm, n (%)</th>
<th>LVEF, %</th>
<th>QRS, ms</th>
<th>LBBB, n (%)</th>
<th>RBBB, n (%)</th>
<th>ICVD, n (%)</th>
<th>Pacemaker-dependent, n (%)</th>
<th>CRT—defibrillator, n (%)</th>
<th>CRT—pacemaker, n (%)</th>
<th>Quadrupolar LV lead, n (%)</th>
<th>Bipolar LV lead, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32</td>
<td>18 (56.2%)</td>
<td>71±11</td>
<td>23 (71.8%)</td>
<td>5 (15.6%); 26 (81.2%); 1 (3.1%)</td>
<td>21 (65.6%)</td>
<td>30±6</td>
<td>181±25</td>
<td>17 (53.1%)</td>
<td>6 (18.7%)</td>
<td>7 (21.9%)</td>
<td>2 (6.2%)</td>
<td>24 (75%)</td>
<td>8 (25%)</td>
<td>25 (78.1%)</td>
<td>7 (21.9%)</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SD. QRS morphology was classified according to American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society guidelines.25 CRT indicates cardiac resynchronization therapy; ICM, ischemic cardiomyopathy; ICVD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular (LV) ejection fraction; NYHA, New York Heart Association; and RBBB, right bundle branch block.

The mean Q-LV interval of all the pacing sites considered was 88±38 ms, whereas the average of the maximum delay was 126±29 ms. The mean baseline LV dP/dt max was 915±189 mm Hg per second.

In each patient, ≥1 biventricular pacing site resulted in hemodynamic improvement (increase in LV dP/dt max) compared with the baseline. When pacing was performed at the site of Q-LV max during biventricular pacing, the mean increase in LV dP/dt max from baseline was 27.8±16.5%.

Table 2 shows QRS duration, QRS morphology, QRS narrowing during biventricular pacing at the Q-LV max site, Q-LV max, and increase in LV dP/dt max during biventricular pacing from the site corresponding to Q-LV max in each patient.

In 31 of 32 patients, pacing at the latest activated site corresponded to the maximum increase in LV dP/dt max (96.8%; 95% confidence interval, 83.3–99.4%). An example is represented in Figure 3. The increase in LV dP/dt max was plotted as a function of Q-LV interval and of QRS reduction (Figure 3D and 3E). Figure 4 displays the individual regression lines. The per-patient median correlation coefficient was 0.88 (interquartile range, 0.84–0.95).

The generalized linear mixed model found a positive correlation (β-coefficient=1.26; AR1 P=0.985; P<0.001) between Q-LV interval and poststimulation LV dP/dt max after correction for baseline LV dP/dt max and for the presence of atrial fibrillation (coefficient=−21.5; P=0.038) and of LBBB (coefficient=37.4; P=0.002); no evidence of the significant interaction between considered terms was found. Figure 4 displays the individual regression lines to depict variability.

Figure 5 shows a dispersion points graph of measurements taken at the various sites in all subjects and the common regression line (estimated by generalized linear mixed model) between Q-LV interval and resulting relative increment in LV dP/dt max with their confidence intervals. A Q-LV value >95 ms resulted in an increase of ≥10% in LV dP/dt max; a value already reported as a highly sensitive and specific predictor of remodeling.17,20

In 24 of 32 patients (75%), pacing at the latest activated site resulted in the maximum narrowing of QRS duration. However, when data from all patients were pooled, a significant correlation did not emerge.

**Discussion**

Establishing clinical parameters or implantation procedures that can reduce the proportion of nonresponders to CRT is an important challenge to clinicians and device implanters.

In our study, a strong correlation between electric delay and acute hemodynamic improvement during biventricular pacing was found in each patient. In 31 of 32 patients (96.8%), pacing from the latest activated site produced the highest increase in LV dP/dt max. Moreover, in 24 of 32 patients (75%), pacing from the latest activated site resulted in the greatest narrowing of the QRS complex.

LV lead position is known to be a major determinant of CRT success. Many observers have pointed out that electric intraventricular dysynchrony strongly relates to LV impairment.17 Consequently, pacing at the site of the latest activation would best correct the mechanically uncoordinated contraction and improve global heart function. Our data are the first...
to demonstrate this at the individual level: in 31 of 32 patients, pacing at the latest activation site yielded the best improvement in LV $dP/dt_{max}$, a reliable expression of cardiac contractility.

Hemodynamic improvement occurred in all patients regardless of ischemic cause, presence of LBBB or RBBB, sex, and sinus rhythm or atrial fibrillation. However, as already reported in the literature, the greatest hemodynamic improvement was found in patients with LBBB and sinus rhythm. This probably reflects the true importance of pacing at the latest activation site as a major determinant of CRT success, and especially one that can be influenced by the implanting physician. Moreover, our data confirm the cut-off value of 95 ms as a predictor of successful CRT, as previously reported by other authors from population-based studies. Gold et al.\(^{10}\) reported a cut-off value of 95 ms in responders to CRT >6-month follow-up. Similarly, Kandala et al.\(^{23}\) found a correlation between LV electric delay and a composite clinical end-point of time to first HF hospitalization, and the composite outcome of all-cause mortality, HF hospitalization, LV assist device implantation, and cardiac transplantation at 3 years. Specifically, in 144 LBBB and non-LBBB patients, a long LV electric delay was associated with an improved outcome. Specifically, in non-LBBB

<table>
<thead>
<tr>
<th>Table 2.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>QRS Morphology</td>
</tr>
<tr>
<td>1</td>
<td>IVCD</td>
</tr>
<tr>
<td>2</td>
<td>LBBB</td>
</tr>
<tr>
<td>3</td>
<td>LBBB</td>
</tr>
<tr>
<td>4</td>
<td>IVCD</td>
</tr>
<tr>
<td>5</td>
<td>LBBB</td>
</tr>
<tr>
<td>6</td>
<td>IVCD</td>
</tr>
<tr>
<td>7</td>
<td>IVCD</td>
</tr>
<tr>
<td>8</td>
<td>RBBB</td>
</tr>
<tr>
<td>9</td>
<td>RBBB</td>
</tr>
<tr>
<td>10</td>
<td>LBBB</td>
</tr>
<tr>
<td>11</td>
<td>LBBB</td>
</tr>
<tr>
<td>12</td>
<td>LBBB</td>
</tr>
<tr>
<td>13</td>
<td>LBBB</td>
</tr>
<tr>
<td>14</td>
<td>PM DEP</td>
</tr>
<tr>
<td>15</td>
<td>LBBB</td>
</tr>
<tr>
<td>16</td>
<td>LBBB</td>
</tr>
<tr>
<td>17</td>
<td>RBBB</td>
</tr>
<tr>
<td>18</td>
<td>LBBB</td>
</tr>
<tr>
<td>19</td>
<td>IVCD</td>
</tr>
<tr>
<td>20</td>
<td>IVCD</td>
</tr>
<tr>
<td>21</td>
<td>LBBB</td>
</tr>
<tr>
<td>22</td>
<td>LBBB</td>
</tr>
<tr>
<td>23</td>
<td>LBBB</td>
</tr>
<tr>
<td>24</td>
<td>LBBB</td>
</tr>
<tr>
<td>25</td>
<td>LBBB</td>
</tr>
<tr>
<td>26</td>
<td>RBBB</td>
</tr>
<tr>
<td>27</td>
<td>RBBB</td>
</tr>
<tr>
<td>28</td>
<td>IVCD</td>
</tr>
<tr>
<td>29</td>
<td>PM DEP</td>
</tr>
<tr>
<td>30</td>
<td>LBBB</td>
</tr>
<tr>
<td>31</td>
<td>RBBB</td>
</tr>
<tr>
<td>32</td>
<td>LBBB</td>
</tr>
</tbody>
</table>

Avg 2.9±0.8 (total 93) 6.4±2.3 (total 206) 126±29 181±25 −6.3±17.2% 27.8±16.5% QRS morphology, AF, number of available veins and pacing sites, Q-LV$_{max}$, baseline QRS duration, QRS narrowing during BIV pacing at site with Q-LV$_{max}$, increase in LV $dP/dt_{max}$ during BIV pacing from the site corresponding to Q-LV$_{max}$, slope, intercept, and correlation coefficient of regression line for each patient are shown. AF indicates atrial fibrillation; Avg, average (mean±SD); BIV, biventricular; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; N, no; PM DEP, pacemaker-dependant; RBBB, right bundle branch block; and Y, yes.
patients, a long electric LV delay ≥50% was associated with improved event-free survival with respect to time to first HF hospitalization (hazard ratio, 0.34) and the composite outcome (hazard ratio, 0.41). Our data confirm the observation of Kandala et al\textsuperscript{23} especially in non-LBBB patients. This underscores the importance of determining intrapatient Q-LV interval, because CRT is becoming increasingly controversial in non-LBBB patients.

Moreover, the hemodynamic benefit was observed regardless of the anatomic position of the LV lead, thus strengthening the concept that the most important parameter is electric delay, regardless of QRS morphology, ischemic cause, or...
anatomic lead position. We systematically collected data from every single point that could be reached by selectively can-
nulating all the available collateral veins; at each pacing site, we measured the acute increase in LV \( \frac{dP}{dt_{\text{max}}} \), which is an expression of acute improvement in cardiac contractility and correlated this acute improvement with electric delay, which is a manifestation of electric dyssynchrony. To our knowledge, this is the first study to implement such an approach.

Our observation that the best pacing site varies from one patient to another is in agreement with the findings of Derval et al. On exploring LV endocardial pacing sites in 35 patients, these investigators found that acute hemodynamic improvement depends on the pacing site, but that study does not provide a clue as to why a certain site performs better than another. Our data indicate that LV delay could constitute a simple, feasible, and reliable means of guiding LV lead positioning.

We did not find a strong correlation between QRS narrowing and hemodynamic improvement. Q-LV interval may vary anatomically inside the LV and predicts contractility improvement better than QRS narrowing or a prespecified midlateral position.

Study Limitations
Because this was an acute study, no data are reported on clinical outcome (quality of life, New York Heart Association class) or remodeling results on medium- or long-term follow-up. Moreover, relatively few patients were recruited, and the sample was not homogeneous in terms of cause, QRS morphology, or presence of sinus rhythm. However, this lack of uniformity may strengthen the predictive value of the Q-LV interval.

The question of whether acute improvement in LV \( \frac{dP}{dt_{\text{max}}} \) predicts long-term clinical benefit is also controversial. For all measurements, we used a fixed AV and VV inter-
val, without optimization; this could be a limitation. However, because our intention was to analyze the different sites, we decided to limit these measurements to reduce the time of the procedure.

In the light of the above considerations, the data from the present study need to be confirmed in larger, prospective studies.

Conclusions
Pacing the LV at the site of the latest activation yielded the greatest increase in cardiac contractility in 31 of 32 patients. In all patients, a cut-off interval of 95 ms correlated with an increase of \( \geq 10\% \) in cardiac contractility. In 24 of 32 patients, the most delayed electric activation corresponded to the greatest narrowing of biventricular-paced QRS duration.

Acknowledgments
We thank Paola Rafagnato, Antonella Tiribello, Susanna Ferro, Graziano Boaretto (S. Maria Della Misericordia Hospital, Rovigo, Italy), and Domenico Pacetta (St Jude Medical, Italy) for their technical support in collecting data.

Disclosures
Dr Zanon has received speaker fees from Boston Scientific, Medtronic, St Jude Medical, and Sorin. Dr Prinzen receives research grants from Medtronic, MSD, EBR Systems, and Proteus Biomedical. The other authors report no conflict.

References
3. Holzmeister J, Hürlimann D, Stef
fel J, Ruschitzka F. Cardiac resynchro-
center study. Am J Cardiol. 1999;83:130D–135D.

**Clinical Perspective**

Cardiac resynchronization therapy is a well-accepted therapy for patients with heart failure and electric dysynchrony. Although it produces clear benefits, one third of patients do not benefit from the therapy. Reasons for nonresponse include clinical characteristics that are intrinsic to the patient and the left ventricular (LV) lead position. After 20 years of cardiac resynchronization therapy, no indices for best positioning of an LV lead exist. Previous studies demonstrated the predictive value of LV electric delay (Q-LV interval) on clinical outcome in patients with left and right bundle branch blocks. These data were, however, derived from a comparison of Q-LV and outcome between patients, which does not indicate whether the region with latest activation is also the best pacing site within each patient. In the present study, we related the values of Q-LV and LV dP/dt max (a measure of contractility) achieved during pacing at 5 to 8 different sites within each patient. Our data demonstrate a positive correlation between Q-LV and LV dP/dt max within each patient, independent of morphology of the QRS complex, indicating the importance of the parameter Q-LV interval. This correlation may be useful to implanters, because Q-LV is a single and easy index to guide the best placement of an LV lead.
Determination of the Longest Intrapatient Left Ventricular Electrical Delay May Predict Acute Hemodynamic Improvement in Patients After Cardiac Resynchronization Therapy
Francesco Zanon, Enrico Baracca, Gianni Pastore, Chiara Fraccaro, Loris Roncon, Silvio Aggio, Franco Noventa, Alberto Mazza and Frits Prinzen

_Circ Arrhythm Electrophysiol._ 2014;7:377-383; originally published online March 25, 2014; doi: 10.1161/CIRCEP.113.000850

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/7/3/377

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Arrhythmia and Electrophysiology_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Arrhythmia and Electrophysiology_ is online at:
http://circep.ahajournals.org//subscriptions/