Repositioning and optimization of left ventricular lead position in nonresponders to cardiac resynchronization therapy is associated with improved ejection fraction, lower NT-proBNP values, and fewer heart failure symptoms

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BACKGROUND Observational data suggest that an anterior or apical left ventricular (LV) position in cardiac resynchronization therapy (CRT) is associated with worse outcome and higher likelihood of “nonresponse.” It is not known whether the benefits of optimizing LV lead position in a second procedure outweighs the procedural risks.

OBJECTIVE To evaluate the clinical effects of LV lead repositioning.

METHODS During the period 2015–2020, we identified all patients in whom the indication for the procedure was LV lead repositioning owing to “nonresponse” in combination with suboptimal LV lead position. All patients were followed with a structured visit 6 months post LV lead revision. Heart failure hospitalization and mortality data were gathered from the medical records and cross-checked with the population registry.

RESULTS A total of 25 patients were identified who fulfilled the inclusion criteria. All procedures were successful in establishing LV lead pacing in a lateral mid or basal location. Median follow-up was 2.5 years [1.1–3.7]. There were improvements in NYHA class (mean -0.5 ± 0.5 class, P < .001), LV ejection fraction (+5 [interquartile range 2–11] absolute %, P = .01), QRS duration (-36 [-44 to -8], P < .001) and N-terminal pro–brain natriuretic peptide (NT-proBNP) (-615 [-2837 to +121] ng/L, P = .03). Clinical outcome was similar to a reference population with CRT (P = ns).

CONCLUSION In nonresponders to CRT with either an anterior or inferior LV lead position, it was feasible to perform LV lead repositioning in all cases, with a low complication rate. Changing the LV lead position was associated with improved LV ejection fraction, larger QRS reduction, and larger NT-proBNP reduction.

KEYWORDS Cardiac resynchronization therapy; Heart failure; Left ventricular lead position; Clinical outcome; Reverse remodeling

Introduction
Cardiac resynchronization therapy (CRT) is well validated for the treatment of heart failure in presence of systolic dysfunction and widened QRS duration. Over the years, selection of patients has evolved based on accumulating evidence, and current guidelines allocate a class Ia recommendation for patients with left bundle branch block (LBBB) and QRS width >150 ms. For patients with non-LBBB morphology or QRS duration between 130 and 150 ms, a class IIa or IIb recommendation is given. The percentage of patients who experience clinical benefit and/or improved systolic function is higher in the LBBB group, but even in this group there remains a minority of patients who do not derive any measurable benefit from the CRT treatment. The reason for this can be multifactorial, and one modifiable factor may be suboptimal left ventricular (LV) electrode position. Several post hoc and observational analyses have indicated that an anterior or apical LV electrode position is associated with worse clinical outcome and less improvement of LV function. In studies with tailored LV lead placement (late mechanical or electrical activation), the optimal site is most commonly situated in the basal or mid inferolateral or anterolateral region of the left ventricle. However, it is not known whether the benefits of optimizing LV lead position for nonresponders in a second procedure outweighs the procedural risks, for patients with apical and/or anterior lead position after the first implant. We sought to investigate this in a cohort of patients

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Methods

From a larger cohort of 670 CRT-implemented patients at a tertiary referral center during the years 2015–2020, we identified all patients in whom the indication for the procedure was LV lead repositioning owing to “nonresponse” and suboptimal LV lead position. The initial CRT implant had been performed either at the same institution or at other referral institutions, and owing to either implanter inexperience or technical challenges, the LV lead had been implanted suboptimally, either anteriorly, inferiorly, or at the apex. During the initial implant, either a suitable vein was not visualized during the procedure (owing to lack of occlusive venogram or an overlooked early branch with retrograde filling), or the technique and tools selected did not permit implant in the most suitable vein. Five parameters were evaluated following each procedure: LV ejection fraction (EF) improvement ≥5% (absolute), NYHA class improvement (≥1 class), QRS duration reduction (≥20 ms), subjective physical improvement (“definitely yes” vs. “no definite improvement”), and reduction in N-terminal pro–brain natriuretic peptide (NT-proBNP) level (≥25% relative reduction). Patients with no subjective improvement and unchanged or worsened outcome on at least 3 of the other 4 criteria were defined as nonresponders and were offered a second procedure, if the LV electrode was in a nonlateral or apical position. Differential programming of the device settings by varying AV and VV delays were optimized by testing of multiple settings to produce as narrow QRS duration as possible. CRT devices from Abbott (Sylmar, CA) or Medtronic were used. If the device had an LV-only pacing algorithm and the patient had sinus rhythm with normal AV conduction, the algorithm was tested, and QRS duration was compared to the QRS duration with biventricular pacing. The study was approved by the Swedish Ethical Review Authority. The data collection was part of a large patient cohort where anonymized data were collected from all CRT-treated patients at our institution, and the requirement for written informed consent was waived by the review authority (No. 2020-05843).

Statistical methods

SPSS version 27 (IBM, Chicago, IL) was used for statistical analyses. Normally distributed data are presented as mean ± standard deviation; non-normally distributed data are presented as median [interquartile range]. McNemar’s test was used for paired comparisons between the first procedure and the LV repositioning procedure, for the prespecified categorical criteria such as LVEF response, and for the overall response score. Kaplan-Meier analysis with log-rank test
was used to compare survival between the intervention cohort and a reference cohort. For all analyses, a 2-sided P value < .05 was considered significant.

### Results

In all, 25 patients were identified who fulfilled the inclusion criteria. Baseline characteristics at the time of the primary implant are presented in Table 1. The median time between the primary implant and the LV lead repositioning was 1.6 [0.9–4.5] years and after the revision procedure they were followed for a median of 2.5 [1.1–3.7] years. Median procedure time and fluoroscopy time for the primary implant was 81 [IQR 62–115] minutes and 18 [10–41] minutes, respectively. LV lead location and LV paced segment was primarily anterior after the primary procedure, and primarily inferolateral after the second procedure (Figure 1). All LV lead revision procedures were successful in establishing LV lead pacing at another location than that from the primary procedure. A representative case including x-ray images of the lead positions is shown in Figure 2.

Programming was similar after both procedures; vendor-specific algorithms for AV and VV optimization were used. Four patients had atrial fibrillation; for the remainder the median AV time was 120 [IQR 100–130] ms vs 120 [105–140] ms, P = .62. The median LV preactivation was 15 [0–30] ms vs 0 [0–30] ms, P = .80. LV-only pacing was used in 2 patients after the first procedure and in 5 patients after the second procedure.

Median procedure and fluoroscopy time for the LV lead repositioning procedure was 78 [51–108] minutes and 12 [4–17] minutes, respectively. There were no early complications to the LV lead repositioning procedures, but there was 1 late local infection (n = 1 [4%]), which resulted in extraction of the system and replacement with a right-sided CRT implant (with the LV lead in the same position).

### CRT effect evaluation

Overall, there were significant positive effects of the lead revision procedures; a summary of this is shown in Table 2. In Figure 3 the sequential changes in NT-proBNP levels, QRS duration, and NYHA class symptoms are presented. The proportion of patients who had a significant positive effect according to the 5 evaluated criteria was higher in all categories except NT-proBNP after the LV repositioning procedure; 71% vs 29% improved LVEF (P = .016), 72% vs 28% improved QRS duration (P = .013), 64% vs 18% improved NT-proBNP (P = .13), 52% vs 0% improved NYHA class (P < .001), and 48% vs 0% had a definite subjective improvement of physical capacity (P < .001). The mean overall response score was 2.7 ± 1.5 vs 0.7 ± 0.8 (P < .001). Central illustration presents a representative case showing significant improvements on both EF, NT-proBNP levels, and QRS duration reduction.

During the period between the first implant and the LV lead repositioning, 4 of the patients were hospitalized for heart failure, on a total of 8 different occasions. During follow-up after the LV lead repositioning, 3 patients were hospitalized on a total of 6 different occasions, and 4 patients died: 1 from heart failure, 1 from Covid-19 infection, 1 from renal and multiorgan failure, and 1 from sepsis not related to the device. Since there was no formal control group, a reference material consisting of 550 consecutive CRT-treated patients at the same institution during the period 2015–2020 was used to compare the clinical outcome of the present cohort with the “expected” outcome. The results are presented in Kaplan-Meier analysis in Figure 4. In a capped analysis at 2 years, the patients with nonoptimal LV lead position (mostly prior to revision, which occurred after a median of 1.6 years) had higher risk of heart failure hospitalization (log-rank test P = .03), but this difference then disappeared during longer follow-up, ie, presumably after the beneficial LV repositioning effect.

Over the entire follow-up period, measuring from the primary implant, the overall survival in the LV lead repositioning cohort was significantly better compared to the reference
cohort in Kaplan–Meier analysis (log-rank $P = .01$), but in a landmark analysis starting from the second implant, this difference was not significant ($P = .43$).

**Discussion**

In this case series of 25 patients we show that repositioning of the LV lead from an anterior or apical position is feasible and can be done with low complication rate. Furthermore, there were significant improvements on several measures traditionally associated with beneficial CRT effect, such as QRS reduction, NT-proBNP reduction, and NYHA class improvement. Whether or not this translates into long-term clinical benefit with regard to mortality and risk of heart failure hospitalization cannot be determined owing to the limited sample size and the retrospective design of the study.

**The importance of LV lead location for successful CRT**

The objective of CRT is primarily to restore electrical synchrony of the left ventricle, with the assumption that this transforms into better mechanical synchrony, more effective

![Figure 1](image1.png)  
*Figure 1* Left ventricular (LV) lead position in the 17-segment bulls-eye model. The left panel shows lead position after the first procedure; the right panel shows lead position after the second procedure. The outermost segments are basal, followed by mid segments, apical segments, and apex (the innermost circle). Gray segments are septal and white segments are anterior, anterolateral, inferolateral, and inferior in clockwise order from 12 o’clock in the circle.

![Figure 2](image2.png)  
*Figure 2* An 80-year-old male patient with ischemic cardiomyopathy and cardiac resynchronization therapy–pacemaker. Initial left ventricular (LV) lead position was basal anterior, and after repositioning the position was mid inferolateral. Changes in lead position, electrocardiogram appearance, NT-proBNP, and New York Heart Association (NYHA) class are illustrated in the figure. LAO = left anterior oblique; RAO = right anterior oblique.
contraction, and, over time, reverse remodeling with reduced end-systolic volume and improved EF. Studies on electrical activation in patients with heart failure and LBBB have shown that the posterolateral basal and mid region is usually the latest activated part of the left ventricle. However, the electrically latest activated segment can vary, even in patients with classic LBBB, but more so in patients with atypical LBBB or nonspecific intraventricular conduction delay.10,11 Identification of the segment with latest mechanical activation has been evaluated by speckle-tracking echocardiography in several prospective trials. In the Imaging CRT trial, the optimal site was found in an anterior location in only 2 of 189 patients (1%) and inferior location in 1 patient (0.5%).12 In a similar study the percentage of anterior and inferior optimal locations were 7% and 8%, respectively.7 Early invasive studies showed that hemodynamic response varied significantly with LV lead position, and a lateral position resulted in significantly better acute hemodynamic performance, compared to an anterior position.13 Acute hemodynamic improvement was later linked to positive long-term remodeling effect.14 Indeed, results from the MADIT-CRT study showed that clinical outcome (risk of death or heart failure hospitalization) was worse for patients where the LV lead was in an apical position.5 Similarly, in a large cohort of more than 2000 patients, it was shown that an anterior LV lead position was associated with unfavorable outcome.6 The heterogeneity with regard to both electrical and mechanical activation patterns in CRT-eligible patients with wide QRS implies that some patients can actually have an optimal LV lead position in the anterior or apical segments and derive significant benefit from CRT with a lateral lead in this position. However, the patients in our cohort, the QRS appearance post-CRT had been either unchanged or significantly prolonged. In essence, there was a high a priori likelihood that repositioning of the lead could have a positive impact, and other influencing factors had been reasonably excluded. In such a cohort, we show that it is possible to obtain significant improvement on several measures by repositioning the LV lead.

Is improvement in surrogate measures good enough?

Reduction in QRS duration implies resynchronization of the ventricular activation, and larger reduction has consistently been associated with better outcomes.15–18 but only 1 prospective randomized trial has used QRS narrowing as the target for optimization.19 In this trial the rate of echocardiographic remodeling was 74%, in the patients where the LV lead was in an apical position.5 However, the clinically latest activated part of the left ventricular wall is usually the lateral LBBB segment, even in patients with classic LBBB, but more so in patients with atypical LBBB or nonspecific intraventricular conduction delay.10,11 Identification of the segment with latest mechanical activation has been evaluated by speckle-tracking echocardiography in several prospective trials. In a post hoc analysis of the MADIT-CRT trial, the optimal site was found in the anterior wall. In our cohort, the QRS appearance post-CRT had been either unchanged or significantly prolonged. In essence, there was a high a priori likelihood that repositioning of the lead could have a positive impact, and other influencing factors had been reasonably excluded. In such a cohort, we show that it is possible to obtain significant improvement on several measures by repositioning the LV lead.

| NYHA class (average) | Pre implant | After first implant | Change | Pre LV repositioning | After LV repositioning | Change | P value (for difference in delta) |
|---------------------|------------|------------------|--------|----------------------|----------------------|--------|----------------------------------|
| Class II            | 12 (48%)   | 8 (32%)          | +0.2 ± 0.4 | 4 (16%)              | 17 (68%)             | -0.5 ± 0.5 | <.001 |
| Class III           | 13 (52%)   | 17 (68%)         |         |                      |                      |        |                                  |

Patient-assessed response

- Deterioration
- No change
- Some positive effect
- Marked positive effect
- Not evaluated

LV EF (%) 28 [22–31] 28 [22–30] 0 [−2 to +7] 25 [22–30] 30 [25–35] +5 [±2 to +11] .01

QRS duration (ms) 168 [154–182] 176 [151–190] +2 [−23 to +22] 180 [170–196] 148 [136–163] −36 [−44 to −8] <.001

NT-proBNP (ng/L) 1104 [612–2007] 2192 [986–2708] +359 [−147 to +1628] 2448 [924–3884] 1977 [686–2688] −615 [−2837 to +121] .03

Biventricular pace (%) 97.5 [87–99] 97.5 [88–99] .9

Results are based on N = 25 patients; data are presented as n (%) or mean [interquartile range]. LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.
QRS-optimized group vs 53% for the control group. Reductions in NT-proBNP or BNP have been associated with both short-term response and favorable longer-term clinical outcome. Improvement in subjective functional capacity and in NYHA classification are subject to reporting bias both from the patient and from the physician. Nevertheless, these parameters have been incorporated in many studies regarding prediction of CRT response and have both been associated with better clinical outcome. Overall, there is good evidence to support that if CRT results in positive effects on the above parameters, these changes are likely to transform into improved clinical outcome for the patient.

Clinical implications
The clinical effect of CRT is highly dependent on patient selection. The a priori expected effect differs greatly between, for instance, a patient with high scar burden, EF <20%, atrial fibrillation, and nonspecific conduction delay, compared to a patient with dilated cardiomyopathy in sinus rhythm with a typical LBBB pattern. Our cohort was mixed, with 40% ischemic cardiomyopathy, 32% non-LBBB patients, and 36% with atrial fibrillation, and the beneficial effects were seen across all subgroups. The expected effect of CRT should always be evaluated on an individual basis, taking all the patient-specific factors into account, and a structured evaluation and correction of modifiable factors should be performed. This includes the use of device-integrated algorithms for AV and VV optimization. If, after this, there is a less-than-expected clinical effect of the CRT, and the patient has an LV lead position that is either apical or very close to the septum (anteriorly or inferiorly), then a repositioning should be attempted. The procedure should be performed by an experienced implanting physician, and care should be taken to minimize the risk of infection, including the use of local antibacterial envelope as appropriate.

Limitations
This was a single-center retrospective study, with all the inherent limitations of such a design. Evaluation of survival was subject to selection bias, since the patients survived until the second procedure, even though they did not have any measurable benefit from the first CRT implant. All procedures were performed by high-volume experienced operators familiar with interventional CRT techniques, in a tertiary care setting at a large university hospital, and the results may not be generalizable to all implanting centers.

Conclusion
In nonresponders to CRT with either an anterior, apical, or inferior LV lead position, it was feasible to perform LV lead repositioning in all cases, with a low complication rate. Changing LV lead position from apical/anterior/inferior to lateral was associated with improved LVEF, larger QRS reduction, and larger NT-proBNP reduction. Over time this may transform to better clinical outcome with regard to survival and heart failure hospitalizations, but larger prospective studies are needed to confirm these data.
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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: The data collection was part of a large patient cohort where anonymized data were collected from all CRT-treated patients at our institution, and the requirement for written informed consent was waived by the review authority (No. 2020-05843).

Ethics Statement: The research reported in this study was conducted according to the principles of the Declaration of Helsinki. The study was approved by the Swedish Ethical Review Authority.

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