Long-term clinical outcome and left ventricular lead position in cardiac resynchronization therapy

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Aims
To identify the predictive value of a presumed optimal left ventricular lead positions (LV-Ps) on the long-term clinical outcome in patients with cardiac resynchronization therapy (CRT).

Methods and results
Clinical information was collected from patient files in consecutive patients treated with CRT from 1997 to 2007. A presumed optimal LV-Ps were defined as a position between 2 and 5 o’clock in the short-axis circumference and basal or mid-ventricular in the long axis. Symptomatic response was defined as improvement in NYHA class (≥1) and echocardiographic response as improvement in left ventricular ejection fraction of ≥5% absolute. We included 567 patients [median age 66 years, 453 (80%) male]. The LV-Ps were optimal in 334 (59%) patients. The hazard ratio for all-cause mortality with an optimal LV-Ps was unadjusted 0.79 (0.59–1.06) and adjusted 0.99 (0.71–1.40). The odds ratio (OR) for symptomatic response with an optimal LV-Ps was unadjusted 1.13 (0.79–1.64) and adjusted 1.05 (0.67–1.64), and the OR for echocardiographic response was unadjusted 1.60 (1.02–2.49) and adjusted 1.42 (0.88–2.31).

Conclusion
A presumed optimal LV-Ps between 2 and 5 o’clock in the short-axis circumference and basal or mid-ventricular in the long axis is not associated with a lower mortality or a better clinical response in patients treated with CRT.

Keywords
Cardiac resynchronization therapy • Biventricular pacing • Left ventricular leads • Mortality • Heart failure

Introduction
Cardiac resynchronization therapy (CRT) is a well-established treatment for patients with heart failure, low left ventricular ejection fraction (LVEF), and prolonged QRS duration.12 Randomized controlled trials have shown that CRT improves symptoms of heart failure, quality of life, exercise capacity, LVEF, and reduces all-cause mortality.3–7 Despite its convincing effect, the proportion of patients whose symptoms improve after CRT is only 50–70%.5,7 In most CRT candidates, the site of latest LV activation is typically lateral or posterior in the basal or mid-ventricular segments.8–11 Pacing at the site of latest activation has been suggested to give the optimal resynchronization.12 Previous studies have reported conflicting results with respect to the effects of different left ventricular lead positions (LV-Ps) on echocardiographic and clinical outcomes.13–16 The present study aims to identify the long-term clinical and echocardiographic outcome of a pre-defined presumed optimal vs. a non-optimal LV-Ps in consecutive patients treated with CRT.

Methods

Patients
To evaluate the effect of LV-Ps in patients with CRT or CRT-D, we included consecutive patients from the Danish Pacemaker Register17 treated at Aarhus University Hospital, Skejby from 1 January 1997 to 31 December 2007. Patients undergoing an upgrade of conventional devices to CRT in the period were also included. Survival data were obtained for the entire cohort from the National Board of Health. The study was approved by the Danish Data Protection Agency and the National Board of Health, and conforms with the principles outlined in the Declaration of Helsinki.

Implantation
Various transvenous delivery systems, LV leads, and CRT devices with or without ICD from different companies were used. In the period from 1997 to 1999, LV pacing was achieved through a Slimline® lead (Vitatron) positioned transvenously in a coronary sinus tributary...
using a coronary Amplatz catheter. A posterior/lateral and basilar/mid-ventricular LV-Ps were most often targeted; however, due to coronary sinus anatomy or technical difficulties, other stimulation sites were accepted in some of the patients. The right ventricular lead was in most cases placed on the septum. Two patients received a LV epicardial lead via thoracotomy early in the study period.

**Lead position**

Left ventricular lead positions were defined by fluoroscopy in two planes upon implantation, the left anterior oblique 30° and the right anterior oblique 60° view or chest radiographs in two planes after the implantation, anterior–posterior and lateral view. The coronary sinus encircles the mitral valve with its tributary radiating out like the hands of a watch, and the LV-Ps in the short-axis circumference were defined clockwise, as previously described by Mortensen et al. The longitudinal position was defined as the distance from the mitral plane to the tip of the pacing electrode and divided into three segments: basal, mid-ventricular, and apical (Figure 1). This method was used both in patients with fluoroscopy and in patients with chest radiographs.

In the present study, we expected a presumed optimal LV-Ps would be from 2 to 5 o’clock in the short-axis circumference combined with a longitudinal position basal or mid-ventricular. Other localizations were presumed to be non-optimal. All LV-Ps were interpreted retrospectively by the same experienced CRT implanter, who was blinded to the patient’s clinical and echocardiographic outcomes.

**Clinical data**

We collected clinical information from the entire patient group retrospectively. We included the New York Heart Association (NYHA) classification, heart failure aetiology, and LVEF before implantation and at the first follow-up after implantation, documented in patient files as a part of routine clinical care.

An improvement in NYHA class (≥1) after implantation was defined as a clinical response to CRT, and an improvement in absolute LVEF ≥5% after implantation was defined as an echocardiographic response to CRT.

**Statistics**

Normally distributed data are presented as mean ± SD, otherwise as median and 25th to 75th percentiles. Absolute frequency and percentages are reported for categorical data. The difference between groups was evaluated with t-tests for Gaussian variables, and Wilcoxon’s rank-sum tests for non-Gaussian variables. Pearson’s chi-squared test was used for all categorical data. Cox regression analysis was used for all-cause mortality and cardiac mortality. Logistic regression analysis was used for improvement in NYHA class and LVEF. Following variables known or suspected to be associated with outcome were included in the model: age, gender, QRS duration, heart failure aetiology, NYHA class, diabetes, atrial fibrillation, ICD, and LVEF at baseline. For LVEF and QRS at baseline, a median value was used to dichotomize the continuous variable. Hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Mortality rate was summarized by construction of Kaplan–Meier curves. All patients who underwent heart transplantation (HTX) were censored at the date of the operation. All P-values are two-sided and nominal. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using STATA software (STATA for Windows, version 10.0).

**Results**

**Patients**

Seven hundred and five patients received CRT or CRT-D in the study period. In 568 patients (81%), useful venograms (233 patients) or chest radiographs (335 patients) were obtained. One patient had moved abroad and was lost to follow-up so a total of 567 patients were included in the analysis. The median age at implantation was 66 (59–72) years, the median follow-up time for survival was 2.5 (1.2–4.2) years, and the median time from implantation to clinical and echocardiographic follow-up was 0.4 (0.2–1.0) years. Baseline data for all patients, patients with optimal LV-Ps, and patients with non-optimal LV-Ps including clinical parameters, pharmacologic therapy, and echocardiographic measurements are shown in Table 1.

![Figure 1](https://academic.oup.com/europace/article-abstract/11/9/1177/465448)
Left ventricular lead position

The LV-Ps in the short-axis circumference were before 2 o’clock in 81 patients (14%), between 2 and 5 o’clock in 456 patients (81%), and after 5 o’clock in 30 patients (5%). The longitudinal LV-Ps were basal in 59 patients (10%), mid-ventricular in 344 patients (61%), and apical in 164 patients (29%). The distribution of LV-Ps according to pre-defined criteria was optimal in 334 patients (59%) and non-optimal in 233 patients (41%). Left ventricular lead positions are illustrated in Figure 2.

Clinical outcome

Of the 567 patients in the study, 366 (66%) patients were alive, 23 (4%) patients underwent HTX, and 178 (34%) patients died, in 131 (74%) of these cardiac death were observed. In patients with optimal LV-Ps, 11 (3%) patients underwent HTX and 94 (30%) patients died, in 69 (73%) of these cardiac death were observed. In patients with a non-optimal LV-Ps, 12 (5%) patients underwent HTX and 84 (39%) patients died, in 62 (72%) of these cardiac death were observed. The HR for all-cause mortality was for an optimal vs. a non-optimal LV-Ps unadjusted 0.79 (95% CI 0.59–1.06; \( P = 0.12 \)) and adjusted 0.99 (95% CI 0.71–1.40; \( P = 0.97 \)).

The HR for cardiac mortality was for an optimal vs. a non-optimal LV-Ps unadjusted 0.83 (95% CI 0.59–1.17; \( P = 0.29 \)) and adjusted 1.09 (95% CI 0.74–1.61; \( P = 0.43 \)).

In 478 patients, we collected LVEF at baseline and at follow-up, and in 166 patients (52%) LVEF improved ≥5% absolute. The distribution of echocardiographic response was 107 patients (56%) in the optimal group and 59 patients (45%) in the non-optimal group. The OR for echocardiographic response for patients with an optimal vs. a non-optimal LV-Ps was unadjusted 1.60 (95% CI 1.02–2.49; \( P = 0.04 \)) and adjusted 1.42 (95% CI 0.88–2.31; \( P = 0.15 \)).

Hazard ratios and ORs are shown in Table 2.

Discussion

This study demonstrates no reduction during long-term follow-up in all-cause mortality or cardiac mortality and no significant

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Patients characteristics, ( n ) (%)</th>
<th>All (( n = 567 ))</th>
<th>Optimal LV-Ps (334)</th>
<th>Non-optimal LV-Ps (233)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (59–72)</td>
<td>66 (59–73)</td>
<td>67 (59–72)</td>
<td>0.70</td>
</tr>
<tr>
<td>Men</td>
<td>453 (80)</td>
<td>260 (78)</td>
<td>193 (83)</td>
<td>0.15</td>
</tr>
<tr>
<td>IHD</td>
<td>302 (53)</td>
<td>169 (51)</td>
<td>132 (57)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>94 (16)</td>
<td>51 (15)</td>
<td>43 (18)</td>
<td>0.31</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>143 (25)</td>
<td>79 (24)</td>
<td>64 (27)</td>
<td>0.29</td>
</tr>
<tr>
<td>ICD</td>
<td>229 (40)</td>
<td>127 (38)</td>
<td>102 (44)</td>
<td>0.16</td>
</tr>
<tr>
<td>Previous PM/ICD</td>
<td>132 (23)</td>
<td>83 (25)</td>
<td>49 (21)</td>
<td>0.29</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>162 ± 33.6</td>
<td>167 ± 36</td>
<td>159 ± 32</td>
<td>0.01</td>
</tr>
<tr>
<td>NYHA, ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (2)</td>
<td>8 (2)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>87 (16)</td>
<td>53 (16)</td>
<td>34 (16)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>378 (69)</td>
<td>229 (70)</td>
<td>149 (69)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>70 (13)</td>
<td>38 (12)</td>
<td>32 (15)</td>
<td>0.44</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>24 ± 8.1</td>
<td>24 ± 7.9</td>
<td>25 ± 8.5</td>
<td>0.41</td>
</tr>
<tr>
<td>LVEDD mm</td>
<td>70 ± 9.8</td>
<td>69 ± 9.7</td>
<td>70 ± 10</td>
<td>0.33</td>
</tr>
<tr>
<td>Medicine, ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>422 (75)</td>
<td>247 (75)</td>
<td>175 (75)</td>
<td>0.88</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>502 (89)</td>
<td>297 (90)</td>
<td>205 (88)</td>
<td>0.54</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>481 (86)</td>
<td>284 (86)</td>
<td>197 (85)</td>
<td>0.70</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>327 (58)</td>
<td>193 (58)</td>
<td>134 (58)</td>
<td>0.87</td>
</tr>
<tr>
<td>Digoxin</td>
<td>211 (38)</td>
<td>113 (34)</td>
<td>98 (42)</td>
<td>0.06</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>123 (22)</td>
<td>58 (18)</td>
<td>65 (28)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Baseline characteristics are presented as median and 25th to 75th percentiles or mean ± SD for continuous variables and as absolute frequency and percentages for categorical variables. The difference between groups was evaluated with \( t \)-tests for Gaussian variables, and Wilcoxon’s rank-sum tests for non-Gaussian variables. Pearson’s chi-squared test was used for all categorical data.
Patients Cardiac resynchronization therapy is indicated for patients with heart failure, NYHA class III and IV, reduced LVEF, and broad QRS. As a prophylactic measure or as a part of other clinical trials in this study period, CRT devices were also implanted in a small group of primarily younger patients in NYHA class I and II. However, even after excluding patients in NYHA class I or II at baseline from the analysis, the results were not significantly different. We also included patients with atrial fibrillation and previous mid-term improvement in LVEF or NYHA class among CRT patients with a presumed optimal LV-P.

Left ventricular lead position

Due to variability in coronary venous anatomy, it is important to have a useful classification system for LV-Ps. We used the clockwise method previously described by Mortensen et al. which gives a precise and reproducible position in the LV short and long axis, and can easily be correlated to wall motion abnormalities or dyssynchrony defined by echocardiography or other cardiac imaging.

In our study, the definition of an optimal LV-Ps was based on previous studies, which demonstrated that the posterior or lateral segments often are the site of latest mechanical activation and provides greater improvement in acute haemodynamic parameters in CRT candidates. Whether an apical position is inferior to a basal or mid-ventricular position is controversial. One small study has evaluated the haemodynamic effect of different LV-Ps sites within the same coronary vein and found no difference between a distal and proximal position and in an animal model for non-ischaemic hearts, a more apical position improved acute haemodynamic response. On the other hand, a study by Becker et al. showed that the site of latest activation most often was basal or mid-ventricular.

The distribution of LV-Ps in our study does not differ from other comparable studies.

Clinical outcome

The results of our study are in agreement with one previous study by Gasparini et al., where the LV-Ps were classified according to coronary sinus tributary. This study showed no differences in short-term clinical and echocardiographic outcome between any coronary sinus tributaries or between a lateral and a septal position.

Other studies on LV-Ps and outcome in patients with CRT show improvement in acute haemodynamic, echocardiographic, and clinical outcome in patients with a lateral/posterior LV-Ps compared with patients with an anterior LV-Ps. Two studies measured the distance between the LV and RV tip, and found that a large horizontal distance in the lateral view was correlated to improved acute haemodynamic and increased response to CRT.

This method was not used in our study and would be difficult to correlate to the latest site of mechanical contraction measured by echocardiography or other cardiac imaging before implantation.

In most of these follow-up studies, the numbers were too small to show any difference in mortality.

On study by Wilton et al. in 250 patients showed an increased all-cause mortality, cardiovascular mortality, and heart failure death or cardiac transplantation in patients with anterior LV-Ps compared with a non-anterior LV-Ps. This was not confirmed in a recent study on the influence of LV-P on outcome in the COMPANION study, where there was no difference in outcome between devices, which were excluded from most clinical trials in this period. Other baseline characteristic such as age, gender, heart failure aetiology, QRS duration, and LVEF were similar to that observed in other comparable studies. Except from a lower proportion of patients receiving amiodarone and a longer QRS duration before implantation in patients with an optimal LV-Ps, the baseline characteristics were similar in the two groups.

patients with an anterior, posterior, or lateral LV-Ps. The population in this study was larger, with a shorter follow-up and the study had a less-detailed classification of LV-Ps compared with our study.

Different classification of optimal and non-optimal LV-Ps might explain some of the differences in comparison with other studies. However, re-analysing the impact of LV-Ps in the present study mentioned with different cut-off values in the short and long axis, combined or alone, still reveals no significant differences in the outcomes measured.

All studies including detailed information on inter-ventricular activation patterns show that concurrence of the LV-Ps and the site of latest activation prior to CRT improve the clinical and echocardiographic outcome. These studies have also shown that approximately one-third of the patients had a LV-Ps discordant to the site of latest mechanical activation on echocardiography. In most studies, the site of latest activation has been measured during intrinsic conduction. Since both RV and LV pacing are used in CRT, it might be more correct to measure the site of latest activation during RV pacing.

The lack of correlation between an optimal LV-Ps and improved long-term clinical outcome in our study might be due to a high proportion of discordance between the LV lead and the site of latest activation. Whether an individual positioning of the LV lead improves outcome in CRT has not yet been validated in a randomised trial.

**Limitations**

This study presents the typical limitations of similar retrospective studies. The patients are more heterogeneous, there were different clinical and echocardiographic observers during the study period, and different follow-up periods. Furthermore, there was no blinding or control group in our study. Our study did not include other parameters usually considered of interest in modern CRT, especially intraventricular dyssynchrony and site of latest mechanical activation. We also lacked venograms/chest radiographs, echocardiographic measurements, and symptomatic evaluation in a minority of the patients. However, this is, to our knowledge, the largest study evaluating the effect of different LV-Ps on long-term clinical outcome in a single-centre cohort of consecutive patients treated with CRT. There may be a risk of missing a significant difference between the two groups, but considering the high number of events due to the large size and long follow-up period in the study, this is probably low.

**Conclusion**

In conclusion, the presumed optimal LV-P, defined as a position between 2 and 5 o’clock in the short-axis circumference combined with a longitudinal localization basal or mid-ventricular, is not associated with an increased improvement of survival, clinical, or echocardiographic outcome in patients treated with CRT.

**Conflict of interest:** none declared.

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**References**


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**Table 2 Clinical outcome**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th></th>
<th>Adjusted</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P-value</td>
<td>HR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>0.79</td>
<td>0.59–1.06</td>
<td>0.12</td>
<td>0.99</td>
<td>0.71–1.40</td>
<td>0.97</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.83</td>
<td>0.59–1.17</td>
<td>0.29</td>
<td>1.09</td>
<td>0.74–1.61</td>
<td>0.68</td>
</tr>
<tr>
<td>Response at follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class improvement ≥1</td>
<td>1.13</td>
<td>0.79–1.64</td>
<td>0.50</td>
<td>1.05</td>
<td>0.67–1.64</td>
<td>0.84</td>
</tr>
<tr>
<td>Improvement in LVEF ≥5% absolute</td>
<td>1.60</td>
<td>1.02–2.49</td>
<td>0.04</td>
<td>1.42</td>
<td>0.88–2.31</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Predictors of all-cause mortality, cardiac mortality, and response in patients with an optimal vs. a non-optimal LV-Ps. Reported as hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI).


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