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ORIGINAL RESEARCH ARTICLE

Lateral left ventricular lead position is superior to posterior position in long-term outcome of patients who underwent cardiac resynchronization therapy

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Abstract

Aims Preferring side branch of coronary sinus during cardiac resynchronization therapy (CRT) implantation has been empirical due to the limited data on the association of left ventricular (LV) lead position and long-term clinical outcome. We evaluated the long-term all-cause mortality by LV lead non-apical positions and further characterized them by interlead electrical delay (IED).

Methods and results In our retrospective database, 2087 patients who underwent CRT implantation were registered between 2000 and 2018. Those with non-apical LV lead locations were classified into anterior (n = 108), posterior (n = 643), and lateral (n = 1336) groups. All-cause mortality was assessed by Kaplan–Meier and Cox analyses. Echocardiographic response was measured 6 months after CRT implantation. During the median follow-up time of 3.7 years, 1150 (55.1%) patients died—710 (53.1%) with lateral, 78 (72.2%) with anterior, and 362 (56.3%) with posterior positions. When we investigated the risk of all-cause mortality, there was a significantly lower rate of death in patients with lateral LV lead location when compared with those with an anterior ($P < 0.01$) or posterior ($P < 0.01$) position. Multivariate analysis after adjustment for relevant clinical covariates such as age, sex, ischaemic aetiology, left bundle branch block morphology, atrial fibrillation, and device type revealed consistent results that lateral position is associated with a significant risk reduction of all-cause mortality when compared with anterior [hazard ratio 0.69; 95% confidence interval (CI) 0.55–0.87; $P < 0.01$] or posterior (hazard ratio 0.84; 95% CI 0.74–0.96; $P < 0.01$) position. When echocardiographic response was evaluated within the lateral group, patients with an IED longer than 110 ms (area under the receiver operating characteristic curve, 0.63; 95% CI 0.53–0.73; P = 0.012) showed 2.1 times higher odds of improvement in echocardiographic response 6 months after the implantation.

Conclusions In this study, we proved in a real-world patient population that after CRT implantation, lateral LV lead location was associated with long-term mortality benefit and is superior to both anterior and posterior positions. Moreover, patients with this position showed the greatest echocardiographic response over 110 ms IED.

Keywords Left ventricular lead position; Lateral left ventricular lead; CRT long-term outcome; Interlead electrical delay; RV-LV delay

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Introduction

Cardiac resynchronization therapy (CRT) has been shown to reduce heart failure (HF) symptoms, hospitalization events, and all-cause mortality in symptomatic patients with severely decreased left ventricular ejection fraction (LVEF) and a prolonged QRS.[1–9]

However, not all patients show symptomatic or remodelling response to CRT and approximately one-third of patients still have limited or unfavourable outcome after the device implantation.[10,11] There are several potential predictors of reverse remodelling such as optimal patient selection,[12,13] individual prognostication-based personalized treatment, and electrical parameters during the implantation, including left ventricular (LV) lead position[14–18] and interlead electrical delay (IED).[19–24]

It has been also proposed that LV lead placement is an important determinant of CRT response. Patients with lateral or posterior position showed a better long-term outcome in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial in the composite endpoint of HF or death from any cause and in all-cause mortality alone compared with implantable cardioverter defibrillator alone, while anterior location was associated with a significantly lower risk of the composite endpoint, but not in death from any cause.[18]

Besides LV lead placement, few smaller studies have indicated that the duration between the electrical signals of the LV and right ventricular (RV) leads predicted echocardiographic improvement and clinical outcome,[19–27] because IED does not only show the positions of the ventricular leads, but also contains the electrical dyssynchrony and prolonged activation pattern derived from the slow conduction due to, for example, scar tissue.[19–27] The IED is strongly associated with response in terms of reverse remodelling and HF hospitalization after CRT implantation and can be easily measured during lead placement.[21]

However, there have been no studies conducted to investigate the long-term effects of lateral LV lead position and longer IED in parallel so far.

Our hypothesis is that non-lateral LV lead positions are associated with worse clinical outcomes including long-term mortality, which confirms the everyday empirical practice, preferring the lateral LV lead position during CRT implantation. Therefore, the aim of our study was to evaluate the distribution of the length of IED by LV lead non-apical positions, to assess the long-term clinical outcome accordingly and further characterize the mid-term echocardiographic response by IED.

Methods

Patients and follow-up

Patients with symptomatic chronic systolic HF (New York Heart Associaton II–IVa), reduced LVEF [ejection fraction (EF) $\leq$ 35%], and a prolonged QRS (QRS $\geq$ 130 ms) undergoing successful CRT implantation at the Heart and Vascular Center, Semmelweis University, Budapest, Hungary, between October 2000 and September 2018 were registered in our database retrospectively. Candidates with ischaemic and non-ischaemic aetiology were implanted as per current guidelines.[28–31]

We excluded those with an unsuccessful procedure or the need of transseptal or epicardial CRT implantation and those who had no available data about LV lead position.

Baseline clinical characteristics such as demographic data, medical history, physical status, medical treatment, and electrocardiographic, echocardiographic, and laboratory parameters were collected from the medical record system at the time of implantation and up to 6 months after the procedure.

The status of our patients was updated in September 2019 from the National Health Insurance of Hungary Database, which provided us the exact date of death. The study protocol complies with the Declaration of Helsinki and the protocol was approved by the Medical Research Council (ETT TUKEB no. 161-0/2019).

Cardiac resynchronization therapy implantation procedure

Device implantations were performed according to the current standards by using a transvenous approach. During device implantation, coronary sinus venograms were performed routinely, and based on the discretion of the physicians, the optimal coronary sinus side branch was chosen. By RV lead positioning a septal location, during LV lead implantation, lateral or posterior location was preferred. LV and RV lead positions were assessed by anteroposterior, right and left anterior oblique views and reported by the implanting physician. In those with phrenic nerve stimulation or close to an apical position, LV leads were stabilized in a more proximal part by stent implantation. The final LV lead position was analysed by an expert cardiologist and was determined by where the lead tip was located, using the nomenclature of anterior, anterolateral, lateral, posterolateral, and posterior positions based on MADIT-CRT trial.[15]

After successful positioning of the leads, electrical parameters such as sensing, impedance values, and threshold were measured. During LV lead classification, three positions were grouped: anterior, lateral, and posterior. Due to the limited number of true anterior and true posterior patients, in the case of anterolateral positions, patients were grouped to anterior locations, while in the posterolateral positions, patients were grouped t to posterior locations. Thus, real lateral positions were not merged into any other category.

Interlead electrical delay measurement

Intraoperative IED measurements were performed regularly, after positioning both ventricular leads. IED was measured by the time delay of the peak activations of the right and LV sensed signals expressed in milliseconds (RV sensed − LV sensed IED). In pacemaker-dependent patients, values were measured during RV pacing (RV paced − LV sensed IED). In those cases, when patients were implanted with devices with an automatic IED measuring, the longest value was set and registered.

Study endpoint

The primary composite endpoint was all-cause mortality or heart transplantation (HTX) or an LV assist device implantation during long-term follow-up investigated by lead locations as a categorical variable. Those patients who proved to have the most beneficial LV lead position were further investigated by IED length as a continuous variable. Then, after receiver operating characteristic (ROC) analysis, the optimal cut-off value of IED was assessed and its association with the greatest echocardiographic response was also investigated by logistic regression. Echocardiographic response was also assessed as a continuous variable and reverse remodelling was defined as a relative increase of 15% or more in LVEF within 6 months after CRT implantation.

Statistical analysis

The statistical analysis was performed using the GraphPad Prism v8.0 software (GraphPad Inc., CA, USA) and the SPSS v21 software (IBM, NY, USA). Continuous variables with a normal distribution are expressed as mean ± standard deviation; those without a non-parametric distribution are shown as median and interquartile range. Categorical variables are presented as numbers and percentages (*n*, %). Unpaired *t*-tests were used for comparisons of normally distributed continuous variables, while not normally distributed variables were compared using the Mann–Whitney test. Kruskal–Wallis test was performed to compare three not normally distributed continuous variables. For categorical variables, Fisher's exact tests or χ^2 tests were performed. Time-to-event data were shown by Kaplan–Meier survival curves using the log–rank test. Cox proportional multivariate analysis was used to evaluate the impact of different LV lead locations (lateral vs. anterior, lateral vs. posterior, posterior vs. anterior) on the primary composite endpoint. Hazard ratios (HRs) with a 95% confidence interval (CI) were determined for clinical endpoints. ROC curves were performed to identify the optimal IED cut-off value to reach the greatest echocardiographic response. All statistical tests were two-sided, and a *P* value of less than 0.05 was considered statistically significant.

Results

Baseline clinical characteristics

Between October 2000 and September 2018, 2524 patients (total cohort) underwent successful CRT implantation of whom 2087 (study cohort) were enrolled in the current analysis after applying exclusion criteria. The study cohort did not differ significantly from the total cohort (*Table 1*). The baseline clinical characteristics of the patients were classified according to the position of the LV lead and are presented in *Table 2*. The anterior group contained 108 (5.2%) patients, of whom 7 (0.3%) were true anterior and 101 (4.8%) were anterolateral, and true lateral LV lead position was identified in 1336 (64%) and posterior position in 643 (30.8%) participants, with the latter including 50 (2.4%) true posterior and 593 (28.4%) posterolateral locations along the short axis. There was no significant difference between their baseline clinical variables such as CRT device type, age, sex, left bundle branch block (LBBB) morphology, or aetiology of HF (*Table 2*). A CRT with an implantable cardioverter defibrillator (CRT-D) was implanted in 1168 (56%) patients, while 919 (44%) had a CRT pacemaker (CRT-P) device. The median age of the study participants was 68 (61/75) years, with a median EF of 28% (24/33). Around 74.6% of the patients were men, 95.1% had typical LBBB morphology, and 49.5% had ischaemic aetiology. Supporting Information, *Table S1* shows the baseline clinical characteristics of the study cohort divided into 5-year periods by the time of implantation.

However, IED measurements were significantly differed by groups, ranging between 42 and 220 ms; the median value was 106 ms (89/123) in the entire patient cohort, 83 ms (60/100) in the anterior, 110 ms (90/128) in the lateral, and 100 ms (85/120) in the posterior group (*Figure 1*). IED was significantly longer in the lateral group than in others ($P < 0.001$).

All-cause mortality

During the median follow-up time of 3.7 years, 1150 (55.1%) patients reached the primary endpoint—78 (72.2%) with anterior, 710 (53.1%) with lateral, and 362 (56.3%) with posterior LV lead positions. When we investigated the risk of all-cause mortality, there was a significantly lower rate of death in patients with lateral LV lead location when compared with those with an anterior ($P < 0.01$) or posterior ($P < 0.01$) position (*Figure 2*).

Multivariate analysis after adjustment for relevant clinical covariates such as age, sex, ischaemic aetiology, LBBB morphology, atrial fibrillation, and device type revealed consistent results that lateral position is associated with a significant risk reduction of all-cause mortality when compared with anterior (HR 0.69; 95% CI 0.55–0.87; $P < 0.01$) or posterior (HR 0.84; 95% CI 0.74–0.96; $P < 0.01$) position (*Table 3*).

Echocardiographic response

When echocardiographic response was evaluated within the lateral group, the mean increase of EF was 7.3% (±9.7), and based on our definition of reverse remodelling, 65.5% of

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Table 1 Baseline clinical characteristics of total and study cohort

Baseline variables	Total cohort (n = 2524)	Study cohort (n = 2087)	P value
Age (years; median/IQR)	68 (60/74)	68 (61/75)	0.44
Gender (female; *n*, %)	637 (25.2%)	531 (25.4%)	0.87
NYHA III/IV (st; *n*, %)	1175 (46.6%)	973 (46.6%)	0.97
Ischaemic aetiology (*n*, %)	1234 (48.9%)	1034 (49.5%)	0.66
CRT-D (*n*, %)	1365 (54.1%)	1168 (56.0%)	0.20
RR systolic (mmHg; median/IQR)	125 (111/137)	125 (111/138)	0.92
RR diastolic (mmHg; median/IQR)	73 (65/80)	72 (65/80)	0.78
BMI (kg/m^2; median/IQR)	27.4 (24.6/30.8)	27.4 (24.6/30.7)	0.82
QRS (ms; median/IQR)	160 (140/180)	160 (140/180)	0.97
LBBB morphology (*n*, %)	1760 (96.1%)	1501 (95.1%)	0.10
Medical history			
Atrial fibrillation (*n*, %)	950 (37.6%)	786 (37.7%)	0.99
Diabetes mellitus (*n*, %)	927 (36.7%)	772 (37.0%)	0.85
Type 2 DM (*n*, %)	749 (29.7%)	623 (29.9%)	0.90
Hypertension (*n*, %)	1819 (72.1%)	1527 (73.2%)	0.41
Prior MI (*n*, %)	974 (38.6%)	814 (39.0%)	0.77
Prior PCI (*n*, %)	740 (29.3%)	637 (30.5%)	0.37
Prior CABG (*n*, %)	333 (13.2%)	276 (13.2%)	0.98
Prior COPD (*n*, %)	359 (14.2%)	303 (14.5%)	0.78
Laboratory parameters			
Serum urea (μmol/L; median/IQR)	8.3 (6.4/11.6)	8.3 (6.3/11.5)	0.71
Serum creatinine (μmol/L; median/IQR)	101 (81/131)	101 (82/130)	0.98
Serum cholesterol (mmol/L; median/IQR)	4.1 (3.4/5.1)	4.1 (3.4/5.1)	0.96
eGFR (mL/min/1.73 m^2; median/IQR)	60.0 (44.9/76.0)	59.8 (45.0/76.0)	0.93
NT-proBNP (pmol/L; median/IQR)	2829 (1453/4791)	2956 (1398/4807)	0.99
Echocardiographic parameters			
LVEF (%; median/IQR)	28 (24/33)	28 (24/33)	0.49
LVEDV (mL; median/IQR)	216 (164/278)	212 (164/274)	0.86
LVESV (mL; median/IQR)	159 (118/207)	154 (117/209)	0.87
LVEDD (mm; median/IQR)	63 (58/70)	63 (58/70)	0.74
LVESD (mm; mean/IQR)	53 (47/60)	53 (47/60)	0.93
Medical treatment			
Beta-blocker (*n*, %)	2043 (81.0%)	1724 (82.6%)	0.15
ACE-I/ARB (*n*, %)	2111 (83.6%)	1772 (84.9%)	0.24
MRA (*n*, %)	1557 (61.7%)	1303 (62.4%)	0.60
Furosemid (*n*, %)	1813 (71.8%)	1522 (72.9%)	0.41
Digoxin (*n*, %)	483 (19.1%)	373 (17.9%)	0.27
Amiodarone (*n*, %)	619 (24.5%)	513 (24.6%)	0.96
Oral anticoagulant therapy (*n*, %)	773 (30.6%)	668 (32.0%)	0.31

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

them were identified as echocardiographic responders to CRT. We aimed to find additional factors to further improve the clinical outcome of CRT patients and found a significant association between IED and echocardiographic response (area under the ROC curve, 0.63; 95% CI 0.53–0.73; P = 0.012) in the lateral group, with an optimal cut-off value of 110 ms based on the ROC analysis (*Figure 3*). Assessing by logistical regression, those with an IED longer than 110 ms showed 2.1 times higher odds of improvement in echocardiographic response 6 months after CRT implantation (odds ratio 2.1; 95% CI 0.99–4.24; P = 0.05). We did not find such association between IED and echocardiographic response in patients with an anterior or posterior LV lead locations (area under the ROC curve 0.30 and 0.57). We used an IED threshold of 110 ms for further analysis. Patients with lateral position and an IED $\geq$ 110 ms showed greater improvement in LVEF absolute percent change 6 months after the implantation (baseline LVEF 27.4 ± 6.0% vs. 6 months LVEF 36.4 ± 9.2%) compared with those with lateral position, but an IED $<$ 110 ms (baseline LVEF 27.7 ± 7.1% vs. 6 months LVEF 33.1 ± 9.2%) (P = 0.02).

Discussion

The main findings of our study can be summarized as follows.

1 Long-term clinical outcome of patients undergoing CRT implantation depends on the position of the LV lead. Lateral position was associated with a significantly lower risk of all-cause mortality compared with anterior and posterior positions, which was also confirmed by

Table 2 Baseline clinical characteristics of patients by left ventricular lead locations

Baseline variables	All patients (n = 2087)	Anterior (n = 108)	Lateral (n = 1336)	Posterior (n = 643)	P value
Age (years; median/IQR)	68 (61/75)	68 (60/76)	68 (61/75)	68 (61/74)	0.90
Gender (female; n, %)	531 (25.4%)	26 (24.1%)	333 (24.9%)	172 (26.7%)	0.65
NYHA III/IV (st; n, %)	973 (46.6%)	55 (50.9%)	617 (46.2%)	301 (46.8%)	0.63
Ischaemic aetiology (n, %)	1034 (49.5%)	48 (44.4%)	659 (49.3%)	327 (50.9%)	0.45
CRT-D (n, %)	1168 (56.0%)	57 (52.8%)	738 (55.2%)	373 (58.0%)	0.40
RR systolic (mmHg; median/IQR)	125 (111/138)	127 (110/144)	123 (110/136)	127 (111/139)	0.51
RR diastolic (mmHg; median/IQR)	72 (65/80)	75 (66/84)	72 (65/80)	72 (64/80)	0.71
BMI (kg/m^2; median/IQR)	27.4 (24.6/30.7)	27 (23.9/29.8)	27.6 (24.8/30.7)	26.9 (24.2/30.9)	0.29
QRS (ms; median/IQR)	160 (140/180)	163 (140/190)	160 (140/180)	160 (140/170)	0.10
LBBB morphology (n, %)	1501 (95.1%)	78 (98.7%)	962 (94.6%)	461 (95.6%)	0.99
Medical history					
Atrial fibrillation (n, %)	786 (37.7%)	40 (37.0%)	504 (37.7%)	242 (37.6%)	0.99
Diabetes mellitus (n, %)	772 (37.0%)	43 (39.8%)	491 (36.8%)	238 (37.0%)	0.82
Type 2 DM (n, %)	623 (29.9%)	33 (30.6%)	404 (30.2%)	186 (28.9%)	0.83
Hypertension (n, %)	1527 (73.2%)	74 (68.5%)	980 (73.4%)	473 (73.6%)	0.53
Prior MI (n, %)	814 (39.0%)	35 (32.4%)	530 (39.7%)	249 (38.7%)	0.33
Prior PCI (n, %)	637 (30.5%)	31 (28.7%)	395 (29.6%)	211 (32.8%)	0.31
Prior CABG (n, %)	276 (13.2%)	12 (11.1%)	178 (13.3%)	86 (13.4%)	0.80
Prior COPD (n, %)	303 (14.5%)	16 (14.8%)	188 (14.1%)	99 (15.4%)	0.73
Laboratory parameters					
Serum urea (μmol/L; median/IQR)	8.3 (6.3/11.5)	8.6 (6.2/10.8)	8.3 (6.3/11.5)	8.2 (6.4/11.7)	0.96
Serum creatinine (μmol/L; median/IQR)	101 (82/130)	96.5 (77/126)	102 (84/129)	100 (80/134.3)	0.40
Serum cholesterol (mmol/L; median/IQR)	4.1 (3.4/5.1)	4 (3.4/4.9)	4.2 (3.4/5.2)	4.1 (3.3/5.1)	0.49
eGFR (mL/min/1.73 m^2; median/IQR)	59.8 (45.0/76.0)	65.4 (47.2/79.9)	58.9 (45.3/74.9)	60.6 (43.7/76.5)	0.28
NT-proBNP (pmol/L; median/IQR)	2956 (1398/4807)	4390 (649/10777)	2579 (1287/4493)	3301 (1811/5628)	0.30
Echocardiographic parameters					
LVEF (%; median/IQR)	28 (24/33)	28 (21/33)	28 (24/33)	28 (24/33)	0.45
LVEDV (mL; median/IQR)	212 (164/274)	226 (150/260)	210 (168/260)	210 (152/306)	0.81
LVESV (mL; median/IQR)	154 (117/209)	157 (107/197)	154 (122/206)	154 (111/228)	0.99
LVEDD (mm; median/IQR)	63 (58/70)	65 (58/71)	63 (58/69)	63 (57/70)	0.73
LVESD (mm; mean/IQR)	53 (47/60)	54 (47/63)	53 (47/60)	53 (46/61)	0.73
Medical treatment					
Beta-blocker (n, %)	1724 (82.6%)	82 (75.9%)	1111 (83.2%)	531 (82.6%)	0.16
ACE-I/ARB (n, %)	1772 (84.9%)	86 (79.6%)	1148 (85.9%)	538 (83.7%)	0.12
MRA (n, %)	1303 (62.4%)	58 (53.7%)	850 (63.6%)	395 (61.4%)	<0.01
Furosemid (n, %)	1522 (72.9%)	74 (68.5%)	964 (72.2%)	484 (75.3%)	0.20
Digoxin (n, %)	373 (17.9%)	26 (24.1%)	226 (16.9%)	121 (18.8%)	0.13
Amiodarone (n, %)	513 (24.6%)	32 (29.6%)	326 (24.4%)	155 (24.1%)	0.45
Oral anticoagulant therapy (n, %)	668 (32.0%)	27 (25.0%)	415 (31.1%)	226 (35.1%)	0.05

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

multivariate analysis. To our knowledge, our current study is the first to demonstrate in a real-world patient population that lateral LV lead position is superior to posterior position when investigating long-term all-cause mortality.

2 Furthermore, we found that IED was significantly longer in the lateral group and associated with 2.1 times higher odds for echocardiographic response over 110 ms of IED.

Optimizing response continues to be an important goal for CRT and available data on the associations of LV lead locations with long-term clinical outcomes are scarce and controversial. Previous randomized, controlled trials demonstrated that the use of speckle-tracking echocardiography for assessing the latest activated part might help the LV lead placement. This method is associated with better subsequent outcome compared with routine approach.[32,33] However, this method could be limited by the anatomical location of coronary sinus side branches; thus, our method with evaluating the latest activated part by measuring the RV–LV interlead delay during CRT implantation seems to be superior.

The effect of left ventricular lead position on all-cause mortality

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy mid-term analysis found that LV apical lead position is associated with adverse clinical outcomes during mid-term follow-up in CRT-D patients, but in their analysis, lateral LV lead location did not emerge superior to anterior or posterior LV lead positions in

Figure 1 Interlead electrical delay (IED) length by left ventricular lead locations. IED was significantly longer in the lateral group than in others (lateral vs. anterior $P < 0.01$) (lateral vs. posterior $P < 0.01$). The boxes represent the 95% confidence interval, with the whiskers representing the minimum and maximum range. The central horizontal lines within the boxes represent the median levels for each group.

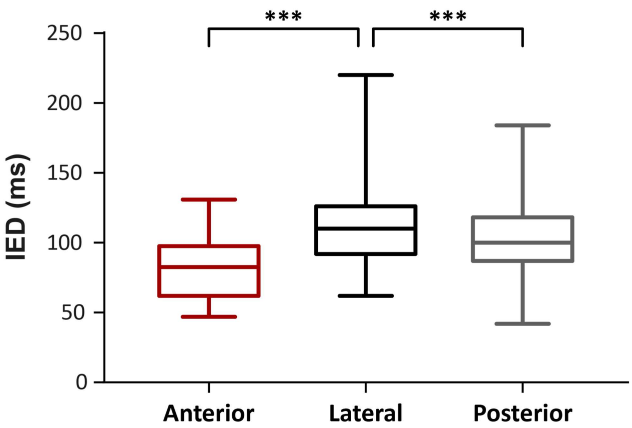


Table 3 The associations of LV lead location with the risk of all-cause mortality

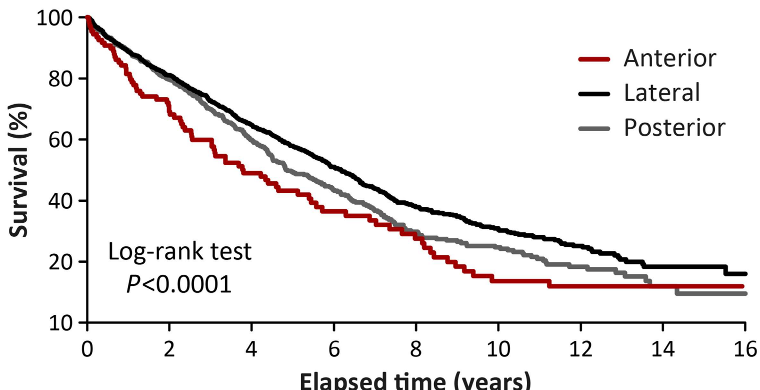
Comparison of different LV lead locations			
	All-cause mortality		
Endpoint	Hazard ratio	95% CI	*P* value
Lateral vs. anterior	0.69	0.55–0.87	<0.01**
Lateral vs. posterior	0.84	0.74–0.96	<0.01**
Posterior vs. anterior	0.77	0.60–0.99	0.04*

CI, confidence interval; LV, left ventricular.
All models were adjusted for age, gender, left bundle branch block morphology, device type, atrial fibrillation, and ischaemic aetiology.
* $p<0.05$, ** $p<0.01$

terms of reduction in HF or death, HF only, and death alone.[15] In the subgroup analysis of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, a mortality benefit was shown in CRT-D cohort regardless of LV lead position, while in CRT-P group, only patients with a lateral LV lead location experienced a lower all-cause mortality rate.[34] However, in this analysis, they compared patients with different LV lead locations with patients receiving only optimal pharmacological therapy, while in our current study, we assessed all-cause mortality by different LV lead positions and found that patients with lateral LV lead location had a significantly lower risk of all-cause mortality compared with anterior or posterior group.

Other studies reported inconsistent data on short-term clinical outcomes by LV lead locations in CRT patients. In the REsynchronization reVErses Remodelling in Systolic left vEntricular dysfunction (REVERSE) substudy, analysing 346 patients, Thebault *et al*. found that a lateral LV lead position was associated with a significantly lower risk of hospitalization for management of HF or of all-cause mortality than a non-lateral location.[14] Their results are in line with our findings that the lateral position is associated with a significantly lower risk of death from any cause or hospitalization for HF compared with non-lateral positions. However, in their study, lateral location was not associated with a significant risk reduction in death alone, whereas in our current analysis, lateral LV lead position was superior to the other locations in reducing the rate of all-cause mortality and was proved to be the only LV lead position to predict long-term mortality. These discordant results might be explained by the

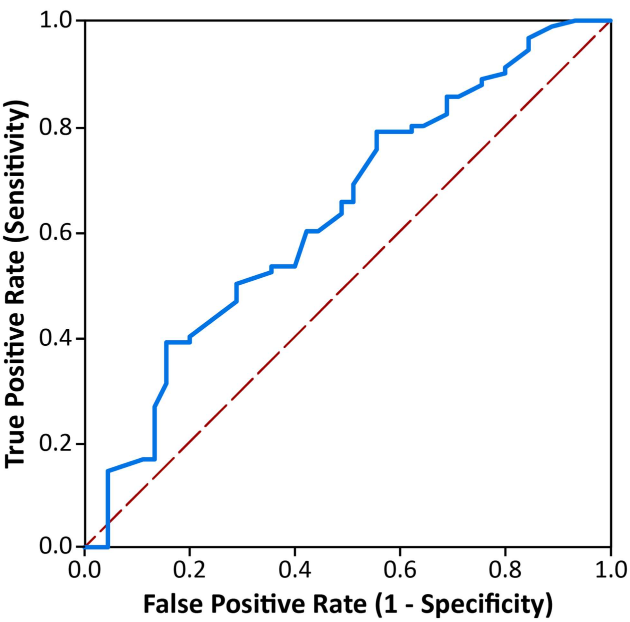
Figure 2 Kaplan–Meier estimates of the probability of survival by left ventricular (LV) lead locations. Patients with lateral LV lead position had significantly better outcome compared with other locations.



Patients at risk

Anterior	108	70	44	26	18	8	6	3	0
Lateral	1336	1004	654	387	228	123	58	15	6
Posterior	643	461	264	142	77	51	22	7	1

Figure 3 Receiver operating characteristic (ROC) curve of interlead electrical delay (IED) length to echocardiographic response in patients with lateral left ventricular lead location. There was a significant association between IED and echocardiographic response (area under the ROC curve, 0.63; 95% confidence interval 0.53–0.73; P = 0.012) in the lateral group, with an optimal cut-off value of 110 ms.



proportion of 'lateral' positions, including true lateral and posterolateral, which was 80.4% in REVERSE[14] compared with 59% in MADIT-CRT,[15] while in our database, 64.3% of the patients had true lateral LV lead position.

Regarding long-term follow-up data only, Kutyifa *et al*. reported that lateral or posterior LV lead locations are associated with long-term all-cause mortality reduction in mild HF patients with CRT-D and LBBB.[18] Furthermore, non-apical short axis positions were associated with reductions of the combined endpoint of HF or death, or HF alone compared with the implantable cardioverter defibrillator-only group.[18] But in this trial, posterior and lateral locations were combined because they found similar outcomes of HF or death in these two groups.[18] Thus, to our knowledge, our current study is the first to demonstrate in a real-world patient population that lateral LV lead position is superior to posterior position when investigating long-term all-cause mortality.

The effect of interlead electrical delay on echocardiographic response

Nevertheless, our present analysis provides further interesting insight into the long-term clinical outcome by IED in CRT patients. Our current analysis is in line with some smaller studies that the more beneficial response might be achieved in patients with longer IED.[19–27] In the SmartDelay Determined AV Optimization (SMART) study, Gold *et al*. found that all echocardiographic remodelling measures (including LV end-systolic volume, LV end-diastolic volume, EF) as well as quality of life were significantly improved by the length and increasing of RV–LV electrical delay.[21] Their best cut-off value for optimizing sensitivity and specificity was 80 ms, while in our present analysis, patients with IED longer than 110 ms showed 2.1 times higher risk of improvement in echocardiographic response 6 months after CRT implantation.

In a recent study, Sommer *et al*. also demonstrated an association between IED and LV reverse remodelling CRT response in patients with a presumed optimal LV lead position. They found that longer IED was associated with greater LV reverse remodelling, QRS shortening, and New York Heart Association class improvement, but patients with longer and shorter IED had comparable proportions of HF hospitalizations. Their best cut-off value for optimizing sensitivity and specificity was 101 ms, while ours was 110 ms.[25]

In our previous prospective study, LBBB patients with an IED of equal or greater than 86 ms showed the greatest improvement in LVEF 6 months after CRT implantation,[22] while in the current analysis, the greatest echocardiographic response was found when IED was longer than 110 ms.

Conclusions

In conclusion, to our knowledge, our study is the first to prove that after CRT implantation, only lateral LV lead location was associated with long-term all-cause mortality benefit and is superior to both anterior and posterior positions. Moreover, higher odds for improving echocardiographic reverse remodelling can be detected when IED was longer than 110 ms in this group.

Limitations

The present results should be interpreted in sight of certain limitations. First, this was a retrospective analysis of a single-centre registry and the results need to be interpreted in that light. Second, there was a limited number of patients with anterior position, which influenced the outcome data. Third, IED may have been influenced by the suitable vein distribution, which is a well-known bias for all CRT studies and is therefore to be acknowledged.

Conflict of interest

B.M. receives lecture fees from Biotronik, Medtronic, and Abbott. Other authors declare that they have no conflicts of interest regarding this manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline clinical characteristics of the study cohort divided into 5-year periods by the time of implantation.

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