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

Anett Behon1++, Walter Richard Schwertner1++, Eperke Dóra Merkel1, Attila Kovács1, Bálint Károly Lakatos1, Endre Zima1, László Gellér1, Valentina Kutyifa1,2, Annamária Kosztin1+++ and Béla Merkely1++

1Heart and Vascular Center, Semmelweis University, Varosmajor 68, Budapest, H-1122, Hungary; 2Cardiology Division, University of Rochester Medical Center, Rochester, NY, USA

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

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

© 2020 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of the European Society of Cardiology
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
electrical parameters during the implantation, including left ventricular (LV) lead position\textsuperscript{14–18} and interlead electrical delay (IED).\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 Association II–IVa), reduced LVEF [ejection fraction (EF) ≤ 35%], and a prolonged QRS (QRS ≥ 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.\textsuperscript{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.\textsuperscript{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 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 tests were used for comparisons of normally distributed continuous variables, while not normally distributed variables were compared using the Mann–Whitney test. Kruskal–Wallis 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.

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
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)              | 72 (65/80)        | 72 (65/80)         | 72 (65/80)         | 0.71    |
| CRT, %                                 | 1168 (56.0%)            | 57 (52.8%)        | 738 (55.2%)        | 373 (58.0%)        | 0.40    |
| Ischaemic aetiology (n, %)             | 1034 (49.5%)            | 48 (44.4%)        | 659 (49.3%)        | 327 (50.9%)        | 0.45    |
| NYHA III/IV (st; n, %)                 | 973 (46.6%)             | 55 (50.9%)        | 617 (46.2%)        | 301 (46.8%)        | 0.63    |
| 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)              | 72 (65/80)        | 72 (65/80)         | 72 (65/80)         | 0.71    |
| CRT, %                                 | 1168 (56.0%)            | 57 (52.8%)        | 738 (55.2%)        | 373 (58.0%)        | 0.40    |
| Ischaemic aetiology (n, %)             | 1034 (49.5%)            | 48 (44.4%)        | 659 (49.3%)        | 327 (50.9%)        | 0.45    |
| NYHA III/IV (st; n, %)                 | 973 (46.6%)             | 55 (50.9%)        | 617 (46.2%)        | 301 (46.8%)        | 0.63    |
| 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)              | 72 (65/80)        | 72 (65/80)         | 72 (65/80)         | 0.71    |
| CRT, %                                 | 1168 (56.0%)            | 57 (52.8%)        | 738 (55.2%)        | 373 (58.0%)        | 0.40    |
| Ischaemic aetiology (n, %)             | 1034 (49.5%)            | 48 (44.4%)        | 659 (49.3%)        | 327 (50.9%)        | 0.45    |
| NYHA III/IV (st; n, %)                 | 973 (46.6%)             | 55 (50.9%)        | 617 (46.2%)        | 301 (46.8%)        | 0.63    |
| 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)              | 72 (65/80)        | 72 (65/80)         | 72 (65/80)         | 0.71    |
| CRT, %                                 | 1168 (56.0%)            | 57 (52.8%)        | 738 (55.2%)        | 373 (58.0%)        | 0.40    |

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 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.

ACE-1, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; CABB, 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.

ESC Heart Failure 2020; 7: 3374–3382
DOI: 10.1002/ehf2.13066
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.\textsuperscript{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 REscynchronization reVersed Remodelling in Systolic left vEntricular dysfunction (REVERSE) substudy, analysing 346 patients, Thebault\textit{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.\textsuperscript{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

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

LV lead location had a significantly lower risk of all-cause mortality compared with anterior or posterior group.

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.

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.

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

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 REscynchronization reVersed Remodelling in Systolic left vEntricular dysfunction (REVERSE) substudy, analysing 346 patients, Thebault\textit{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.\textsuperscript{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
proportion of ‘lateral’ positions, including true lateral and posterolateral, which was 80.4% in REVERSE, compared with 59% in MADIT-CRT, 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. 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. But in this trial, posterior and lateral locations were combined because they found similar outcomes of HF or death in these two groups. 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. 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. 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.

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, 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.
Funding

This work was supported by the New National Excellence Program of the Ministry for Innovation and Technology in Hungary (UNKP-19-3-I), the National Research, Development and Innovation Office of Hungary (NKFI; NVKP_16-1-2016-0017 National Heart Program), and the Higher Education Institutional Excellence Program of the Ministry for Innovation and Technology in Hungary, within the framework of the Therapeutic Development thematic program of the Semmelweis University. The research was also financed by the Thematic Excellence Programme (Tématerületi Kiválósági Program, 2020-4.1.1.-TKP2020) of the Ministry for Innovation and Technology in Hungary, within the framework of the Bioimaging thematic programme of the Semmelweis University.

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.

References

1. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350: 2140–2150.

2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352: 1539–1549.

3. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Kautzner J, Klemptner R, Qureshi M, Kleyberg M, Pfeiffer MA, Quesada A, Viskin S, McNitt S, Polonsky B, Ghamey A, Solomon SD, Wilber D, Zareba W, Moss AJ. Survival with cardiac-resynchronization therapy in mild heart failure. New England Journal of Medicine 2014; 370: 1694–1701.

4. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghiw S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008; 52: 1834–1843.

5. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J III, Gras D, Krum H, Sogaard P, Holzmeister J. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013; 369: 1395–1405.

6. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol 2006; 21: 20–26.

7. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 2003; 91: 684–688.

8. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichtenstein E, Pitschner H, Rashitian M, Solomon S, Viskin S, Wang P, Moss AJ, MADIT-CRT Investigators. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011; 123: 1061–1072.

9. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, Thibault B, Wells G, Tang A. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail 2013; 6: 1190–1198.

10. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. Circulation 2020; 142: 1198 – 1213.

11. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 2003; 91: 684–688.

12. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichtenstein E, Pitschner H, Rashitian M, Solomon S, Viskin S, Wang P, Moss AJ, MADIT-CRT Investigators. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011; 123: 1061–1072.

13. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, Thibault B, Wells G, Tang A. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail 2013; 6: 1190–1198.

14. Thebault C, Donal E, Meunier C, Gervais R, Gerrits B, Gold MR, Abraham WT, Linde C, Daubert JC, for the REVERSE study group. Sites of left and right ventricular lead implantation and response to cardiac resynchronization therapy observations from the REVERSE trial. Eur Heart J 2012; 33: 2662–2671.

15. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, Banshehet A, Cannom D, Goldberg I, McNitt S, Daubert JP, Zareba W, Moss AJ. Left ventricular lead position and clinical outcome in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial. Circulation 2011; 123: 1159–1166.

16. Dong YX, Powell BD, Asirvatham SJ, Friedman PA, Rea RF, Webster TL, Brooke KL, Hodge DO, Wiste HJ, Yang YZ, Hayes DL, Cha YM. Left ventricular lead position for cardiac resynchronization: a comprehensive cineangiographic, echocardiographic, clinical, and survival analysis. Europace 2012; 14: 1139–1147.

17. Jastrzebski M, Wilinski J, Fijorek K, Sondej T, Czarnecka D. Mortality and morbidity in cardiac resynchronization
patients: impact of lead position, paced left ventricular QRS morphology and other characteristics on long-term outcome. Europace 2013; 15: 258–265.

18. Kutyifa V, Kosztin A, Klein IU, Biton Y, Nagy VK, Solomon SD, McNitt S, Zareba W, Goldenberg I, Roka A, Moss AJ, Merkely B, Singh JP. Left ventricular lead location and long-term outcomes in cardiac resynchronization therapy patients. JACC Clin Electrophysiol 2018; 4: 1410–1420.

19. Kristiansen HM, Hovstad T, Vollan G, Keiligavlen H, Faerestrand S. Clinical implication of right ventricular to left ventricular interlead sensed electrical delay in cardiac resynchronization therapy. Europace 2012; 14: 986–993.

20. Gold MR, Yu Y, Wold N, Day JD. The role of interventricular conduction delay to predict clinical response with cardiac resynchronization therapy. Heart Rhythm 2017; 14: 1748–1755.

21. Gold MR, Singh JP, Ellenbogen KA, Yu Y, Wold N, Meyer TE, Birgersdotter-Green U. Interventricular electrical delay is predictive of response to cardiac resynchronization therapy. JACC Clin Electrophysiol. 2016; 2: 438–447.

22. Kosztin A, Kutyifa V, Nagy VK, Geller L, Zima E, Molnar L, Szlagay S, Ozcan EE, Szeplaki G, Merkely B. Longer right to left ventricular activation delay at cardiac resynchronization therapy implantation is associated with improved clinical outcome in left bundle branch block patients. Europace 2016; 18: 550–559.

23. D’Onofrio A, Botto G, Mantica M, La Rosa C, Occhetta E, Verlato R, Molon G, Ammendola E, Villani QG, Bongioni MG, Gelmini GP, Cardiello C, Dicandia CD. The interventricular conduction time is associated with response to cardiac resynchronization therapy: interventricular electrical delay. Int J Cardiol 2013; 168: 5067–5068.

24. D’Onofrio A, Botto G, Mantica M, La Rosa C, Occhetta E, Verlato R, Molon G, Ammendola E, Villani QG, Bongioni MG, Bianchi V. Incremental value of larger interventricular conduction time in improving cardiac resynchronization therapy outcome in patients with different QRS duration. J Cardiovasc Electrophysiol 2014; 25: 500–506.

25. Sommer A, Kronborg MB, Noregaard BL, Stephansen C, Poulsen SH, Kristensen J, Gerdes G, Nielsen JC. Longer interlead electrical delay is associated with response to cardiac resynchronization therapy in patients with presumed optimal left ventricular lead position. Europace 2018; 20: 1630–1637.

26. Singh JP, Fan D, Heist EK, Alabadi CR, Taub C, Reddy V, Mansour M, Picard MH, Ruskin JN, Mela T. Left ventricular lead electrical delay predicts response to cardiac resynchronization therapy. Heart Rhythm 2006; 3: 1285–1292.

27. Roubicek T, Wichterle D, Kucera P, Nedbal P, Kupec J, Sedlakova J, Cerny J, Stros J, Kautzner J, Polasek R. Left ventricular lead electrical delay is a predictor of mortality in patients with cardiac resynchronization therapy. Circ Arrhythm Electrophysiol 2015; 8: 1113–1121.

28. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.

29. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult 2014;Summary Article. Circulation 2005; 112: 1825–1852.

30. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Líncz C, McMurray J, Ponikowski P, Priori SG, Sutton R, Van Veldhuisen D, ESC Committee for Practice Guidelines (CPG). 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy developed with the special contribution of the Heart Failure Association and the European Heart Failure Association. Eur Heart J 2010; 31: 2677–2687.

31. Members ATR, Brignole M, Auricchio A, Barone-Esquivias G, Bordachar P, Boriani G Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti I, Sutton R, Vardas PE, ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach, S, Baumgartner H, Bax B, Dean V, Deaton C, Erol F, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knutti J, Kohn P, Lancetti P, Lindhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo J, Tendera M, Torbicki A, Wijns W, Windecker S, Document Reviewers, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev E, Bansch D, Baumgartner H, Batz W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Dr Heuzev JY, Mavrakis H, McDonagh T, Merino JI, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC) developed in collaboration with the European Heart Rhythm Association (EHRA). EP Europace 2013; 15: 1070–1118.

32. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O’Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study; a randomized, controlled trial. J Am Coll Cardiol 2012; 59: 1509–1518.

33. Saba S, Marek S, Schwartzman D, Jain S, Adelstein E, White P, Oyenuga OA, Onishi T, Soman P, Gorcsan J III. Echo-cardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. Circ Heart Fail 2013; 6: 427–434.

34. Saxon LA, Olsansky B, Volosin K, Steinberg JS, Lee BK, Tomassoni G, Guarnieri T, Rao A, Young P, Galle E, Leigh J. Influence of left ventricular lead location on outcomes in the COMPANION study. J Cardiovasc Electrophysiol 2009; 20: 764–768.