NON-PHARMACOLOGICAL TREATMENT OF CHRONIC SYSTOLIC HEART FAILURE

OPTIMIZATION OF RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY FOR THE TREATMENT OF CHRONIC HEART FAILURE

Ph.D. thesis

Anett Behon, MD

Doctoral School of Theoretical and Translational Medicine
Semmelweis University

Supervisor: Béla Merkely, MD, D.Sc
Annamária Kosztin, MD, Ph.D

Official reviewers: Gergely Szabó, MD, Ph.D
Péter Ezer, MD, Ph.D

Head of the Complex Examination Committee:
István Karádi, MD, D.Sc

Members of the Final Examination Committee:
Henriette Farkas, MD, D.Sc
Hassan Charaf, MD, D.Sc

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1. Introduction

Heart failure (HF) is a complex clinical syndrome, which affects approximately 1-2% of the adult population, reaching up to 10% among people above 70 years of age in developed countries. HF patients with left ventricular (LV) systolic dysfunction often experience atrioventricular, intra-, and interventricular mechanical dyssynchrony. Through the implantation of an additional left LV lead into a side branch of the coronary sinus, it becomes possible to pace both ventricles simultaneously, resolving primarily the intraventricular, and the interventricular delay to improve the cardiac function, which is called cardiac resynchronization therapy (CRT). CRT has been shown to reduce morbidity and mortality in a well-selected patient population - primarily in left bundle branch block (LBBB) patients with a QRS width ≥ 150 ms -, and to improve cardiac function in symptomatic HF patients. However, approximately 30-40% of CRT patients fail to show clinical improvement or reverse remodeling and are considered as non-responders. The high number of non-responders highlights the importance of careful patient selection, optimal device implantation, and device programming. LV lead position has been proposed to play a significant role in the response to CRT, especially in LBBB patients. Moreover, previous smaller studies have indicated that the duration between the electrical signals of the left and right ventricular leads (interlead electrical delay – IED) can predict both echocardiographic improvement and clinical outcomes.

2. Objectives

Our aim was to investigate important parameters in patient selection (age), implantation (LV lead position and IED), and long-term outcome with the reclassification of response.

In order to optimize patient selection, we aimed to assess whether age may negatively affect the CRT response. We evaluated the age-related differences in the effectiveness of CRT, peri- and postprocedural complications, and long-term outcomes after the implantation.

Moreover, we examined the impact of implantation parameters, such as LV lead position and IED on long-term outcomes. Our hypothesis was that non-lateral LV lead locations are associated with worse clinical outcomes.

We also focused on the question of reclassification of response to CRT. We used the recently changed criteria by response to evaluate the long-term outcome of CRT patients by their echocardiographic response. We aimed to sort out those with unchanged parameters to compare them with those in whom the progression could not be modified.

3. Methods

For better interpretation, we show our Methods and Results separately by the investigated parameters. In Part 1, data on our study of age differences are shown. In Part 2, we present our study of LV lead position and IED. While in Part 3, the question of reclassification of CRT response is shown.

3.1. Patient population

In Part 1, we included all of our patients who underwent successful CRT implantation between October 2000 and September 2020 following current guidelines at the Heart and Vascular Center, Semmelweis University in Budapest, Hungary. To investigate the association between age and the effectiveness of CRT, peri- and postprocedural complications, and long-term outcome, we divided our patients into 3 groups according to their age at the time of the implantation: Group I: < 65, Group II: 65-75, and Group III: > 75 years.

In part 2, we excluded patients with the need of transseptal or epicardial LV lead implantation and those who had no available data about the LV lead position. During classifying LV lead positions, three categories were established: anterior (anterior + anterolateral), lateral, and posterior (posterior + posterolateral).

In Part 3, we excluded patients with no available data about their baseline and/or post-implantation left ventricular ejection fraction (LVEF) within 12 months. To assess the correlation between the response to CRT and long-term outcomes, patients were categorized into 4 groups based on their response status. This classification was determined by analysing the change in LVEF up to 12 months following CRT implantation, resulting in the following groups: Group I: super-responders ≥ 20%, Group II: 6-19%, Group III: 0-5%, and Group IV: < 0%.

3.2. Device implantation

Implantations of devices were performed according to current standards and were carried out using either a transvenous approach or a transseptal method. The assessment of LV and right ventricular (RV) lead positions were conducted through antero-posterior (AP), right anterior oblique (RAO), and left anterior oblique (LAO) views, with the implanting physician providing the reported details. Intraoperative IED measurements were carried out following the placement of both ventricular leads. IED was quantified by determining the time delay between the peak activations of the right and left ventricular sensed signals, expressed in milliseconds (RV sensed - LV sensed IED). In pacemaker-dependent patients, measurements were taken during right ventricular pacing (RV paced – LV sensed IED).

3.3. Follow-up

The status of our patients was updated in September 2019 for Part 2, and in December 2021 for Part 1 and 3 from the National Health Insurance of Hungary Database, which provided us the precise 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.

3.4. Endpoints

In Part 1, The primary endpoint was echocardiographic response. Reverse remodeling was defined as a relative increase of LVEF $\geq$ 15% within 6 months after the implantation. Secondary composite endpoint was all-cause mortality or heart transplantation (HTX) or implantation of a left ventricular assist device (LVAD) during long-term follow-up. Tertiary endpoints were peri- and postprocedural complications. We also assessed time-trend effects on age, device types, and response rate.

In Part 2, the primary endpoint was the composite of all-cause mortality or HTX or a LVAD implantation during long-term follow-up investigated by lead locations as a categorical variable. Those patients who were found to have the most beneficial LV lead position were further investigated by IED length as a continuous variable. After ROC analysis the optimal cut-off value of IED was evaluated and its association with the greatest echocardiographic response was also investigated by logistic regression.

In Part 3, the primary composite endpoint was all-cause mortality, HTX, or LVAD implantation.

4. Results

4.1. Part 1 - Long-term outcome of cardiac resynchronization therapy patients in the elderly

4.1.1. Baseline clinical characteristics

A total of 2656 patients underwent successful CRT implantation and were included in the analysis for Part 1. Our patient cohort was categorized into three age groups: Group I: 1028 (39%) patients [median age 59, (IQR 53/62) years], Group II: 1004 (38%) patients [median age 70 (IQR 68/72) years], and Group III: 624 (23%) patients [median age 79 (IQR 77/82) years] (Table 1). Older patients were more commonly female (Group III: 28% vs. Group II: 26% vs. Group I: 22%; p<0.01), with an ischemic aetiology (Group III: 58% vs. Group II: 52% vs. Group I: 40%; p<0.01). Elderly had more comorbidities, such as atrial fibrillation (Group III: 45% vs. Group II: 41% vs. Group I: 31%; p<0.01), diabetes (Group III: 35% vs. Group II: 40% vs. Group I: 34%; p=0.01) or prior myocardial infarction (Group III: 43%

vs. Group II: 40% vs. Group I: 33%; p<0.01). Older patients more frequently received a CRT-P implantation (Group III: 56% vs. Group II: 44% vs. Group I: 40%; p<0.01).

4.1.2. Primary endpoint – Echocardiographic response by age

After the implantation LVEF showed a significant improvement in the total cohort [median 28 (IQR 24/33) % at baseline vs. median 35 (IQR 28/40) % at 6 months; p<0.01] as well as in each age group [Group I: median 27 (IQR 22/32) % vs. median 34 (IQR 28/40) %; p<0.01; Group II: median 29 (IQR 25/33) % vs. median 35 (IQR 29/40) %; p<0.01; Group III: median 30 (IQR 25/35) % vs. median 35 (IQR 29/43) %; p<0.01. The rate of responders was comparable among the three subgroups, 64% in Group I, 61% in Group II, and 56% in Group III (p=0.41)

4.1.3. Secondary endpoint – Long-term all-cause mortality by age

During the median follow-up time of 4.1 years (IQR 2.3/6.9), 1574 (57%) patients reached the secondary composite endpoint, 511 (50%) in Group I, 637 (63%) in Group II, and 426 (68%) in Group III. Kaplan-Meier curves showed a significantly lower survival rate in the older groups compared to the younger ones (log-rank p<0.001), which was also confirmed by multivariate analysis. Restricted cubic spline based on Cox regression was used to flexibly model the association between age and all-cause mortality risk. The lowest inflection point was found around 43 years.

4.1.4. Tertiary endpoint – Peri- and postprocedural complications by age

Peri- and postprocedural complications were observed in 710 (27%) patients of the total cohort. The most frequent complications were lead dislodgement (7%) and phrenic nerve stimulation (5%). We found no statistical difference in any complications among the three subgroups. Numerically pocket infection/decubitus (Group III: 1% vs. Group II: 2% vs. Group I: 3%; p=0.04) was observed less commonly in older patients but in a very low incidence in the total cohort.

4.2. Part 2 - Lateral left ventricular lead position is superior to posterior position in long-term outcome of patients underwent CRT implantation

4.2.1. Baseline clinical characteristics

After applying exclusion criteria, 2087 patients formed the study cohort for the analysis of Part 2. The anterior group comprised 108 (5.2%) patients, including 7 (0.3%) with a true anterior and 101 (4.8%) with an antero-lateral LV lead position. A true lateral LV lead location was identified in 1336 (64%) participants and a posterior position in 643 (30.8%) patients, which included 50 (2.4%) with a true posterior and 593 (28.4%) with a postero-lateral location along the short axis. No significant differences were observed in baseline clinical variables such as CRT device type, age, sex, LBBB morphology, or aetiology of heart failure among the three subgroups. IED measurements varied significantly between groups, ranging from 42 to 220 ms. The median IED value was 106 (IQR 89/123) ms in the study cohort, 83 (IQR 60/100) ms in the anterior, 110 (IQR 90/128) ms in the lateral, and 100 (IQR 85/120) ms in the posterior group, respectively. Notably, IED was significantly longer in the lateral group compared to the other groups (p<0.001).

4.2.2. Primary endpoint - Long-term all-cause mortality by LV lead position

Over the median follow-up time of 3.7 years, 1150 (55.1%) patients reached the primary composite endpoint. 78 (72.2%) with anterior, 710 (53.1%) with lateral, and 362 (56.3%) with posterior LV lead locations. Analysing the risk of all-cause mortality, patients with a lateral LV lead location exhibited a significantly lower rate of death compared to those with anterior (p<0.01) or posterior (p<0.01) positions, which was also confirmed by multivariate analysis.

4.2.3. Echocardiographic response

When assessing the echocardiographic response within the lateral group, there was a mean increase in EF of 7.3 (±9.7) %, and 65.5% of the lateral group were identified as echocardiographic responders to CRT based on our reverse remodelling definition. Our aim was to identify additional factors to further improve the clinical outcome of CRT patients and discovered a significant association between IED and echocardiographic response (ROC AUC 0.63; 95% CI: 0.53-0.73; p=0.012) within the lateral group. The optimal cut off value for IED, determined through ROC analysis, was 110 ms.

Upon logistic regression analysis, individuals with an IED longer than 110 ms showed 2.1 times higher odds of improvement in echocardiographic response 6 months after the implantation (OR 2.1; 95% CI: 0.99-4.24; p=0.05). However, no such association was observed between IED and echocardiographic response in patients with anterior or posterior LV lead positions (AUC 0.30 and 0.57). For further analysis, an IED threshold of 110 ms was used. Patients with a lateral position and an IED ≥ 110 ms demonstrated a more significant improvement in absolute percent change of LVEF 6 months after the implantation (baseline LVEF 27.4±6.0% vs. 6 months LVEF 36.4±9.2%) compared to patients with a lateral position but an IED < 110 ms (baseline LVEF 27.7±7.1% vs. 6 months LVEF 33.1 ±9.2%) (p=0.02).

4.3. Part 3 - Non-progressors to cardiac resynchronization therapy show long-term mortality benefit compared to progressors

4.3.1. Baseline clinical characteristics

After applying exclusion criteria, 1019 patients formed the study cohort for the analysis of Part 3. This cohort was categorized into four groups based on their response status: 113 (11%) were super-responders, 448 (44%) were responders, 244 (24%) were non-progressors, and 214 (21%) were progressors. The mean change in LVEF varied as follows: super-responders 24.5% ± 4.1%, responders 11.5% ± 3.8%, non-progressors 2.8% ± 1.8%, and progressors -6.6% ± 4.5% (p<0.0001). Regarding baseline clinical characteristics, non-progressors and progressors were more commonly male (Group IV: 80% vs. Group III: 75% vs. Group II: 75% vs. Group I: 61%; p<0.01), with an ischemic aetiology (Group IV: 63% vs. Group III: 58% vs. Group II: 47% vs. Group I: 35%; p<0.0001). They had a worse functional status (Group IV: 56% vs. Group III: 58% vs. Group II: 46% vs. Group

I: 43%; p<0.01) with worse renal function [Group IV: 61.9 (IQR 43.9/79.1) ml/min/1.73m^2 vs. Group III: 60.2 (IQR 45.3/79.9) ml/min/1.73m^2 vs. Group II: 64.1 (IQR 48.7/83.0) ml/min/1.73m^2 vs. Group I: 75.3 (IQR 51.7/92.3) ml/min/1.73m^2; p<0.01], and they less frequently had a lateral left ventricular lead position (Group IV: 53% vs. Group III: 55% vs. Group II: 85% vs. Group I: 60%; p<0.0001).

4.3.2. Primary endpoint - Long-term all-cause mortality by echocardiographic response

During the median follow-up time of 4.7 years 547 (54%) patients reached the primary composite endpoint, 35 (31%) among super-responders, 223 (50%) among responders, 133 (55%) among non-progressors, and 156 (73%) among progressors. Univariate Cox regression analysis demonstrated that non-progressors had a comparable long-term outcome to responders (HR 1.17; 95%CI 0.94-1.45; p=0.15) and a superior outcome compared to progressors (HR 0.60; 95%CI 0.48-0.76; p<0.0001), which was also confirmed by multivariate analysis after adjusting for age, gender, ischemic aetiology, LVEF, and serum creatinine levels: non-progressors vs. responders (HR 1.25; 95%CI 0.98-1.58; p=0.07) and non-progressors vs. progressors (HR 0.62; 95%CI 0.47-0.80; p<0.0001).

5. Conclusions

Cardiac resynchronization therapy is an effective device therapy option to improve cardiac function, and reduce symptoms, the risk of hospitalization for heart failure, and all-cause mortality in mild to severe heart failure patients with reduced ejection fraction and prolonged QRS. However, there is still a relatively high number of patients who do not show beneficial response after the implantation.

In our retrospective, large-scale single-center study which was implemented from Heart and Vascular Center, Semmelweis University, we investigated potential parameters that could influence the response to CRT and also analysed the reclassification of response to CRT and its impact on managing heart failure in everyday clinical practice.

In our real-world patient cohort, our findings demonstrate that CRT is as effective in improving left ventricular ejection fraction and as safe in the elderly as in younger ones. These findings suggest that patients with appropriate indications benefit from CRT, regardless of their age. Time-trend analyses showed an increase in the mean age of CRT-P and CRT-D recipients with a significant difference between the two groups, and in the percentage of CRT-D implantations. Moreover, response rate increased in each subgroup as a result of adding new effective pharmacological therapies.

Our results showed that after CRT implantation only the lateral left ventricular lead position was associated with long-term all-cause mortality benefit and it is superior to both anterior and posterior locations. Furthermore, higher odds for improving echocardiographic reverse remodeling can be detected when interlead electrical delay was longer than 110 ms in this patient group.

Analysing the new criteria by response, non-progressors to CRT had a comparable long-term outcome to responders and a superior outcome to progressors. Our findings support the concept that non-progressors are a separate phenotype, probably requiring different treatment strategies. These data suggest that non-progressor patients would have continued to adversely remodel without CRT. Moreover, these findings support the reclassification of our patients as super-responders, responders, non-progressors, and progressors. Selecting non-progressor and progressor patients will certainly influence our clinical decisions.

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