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ELECTRIC AND CLINICAL PREDICTORS RELATED TO THE OUTCOMES OF CARDIAC RESYNCHRONIZATION THERAPY AND THEIR ASSOCIATION WITH CHANGES IN LEFT VENTRICULAR EJECTION FRACTION OVER TIME

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Abstract

Background: *Cardiac resynchronization therapy represents a well established treatment for heart failure patients, recommended for those with severely depressed left ventricular systolic function and left bundle branch block. The aim of this study was to determine the correlation between electrocardiographic changes, clinical, functional, and demographic parameters with the improvement in left ventricular ejection fraction after resynchronization therapy. Another focus of this study was to identify which parameters have predictive value for better patient selection and proper resynchronization strategy.*

Methods: *The study included 69 patients who underwent cardiac resynchronization therapy in our center. The parameters were monitored at 4 different key moments: before the procedure and at 6, 9 and 12 months after procedure.*

Results: *There was a significant improvement in the ejection fraction, which reached a peak at the 12-month follow-up. The value of atrial natriuretic factor precursor was negatively associated with the evolution of ejection fraction. QRS duration and left ventricular end-diastolic volume correlate with improvement in ejection fraction. Newer variables, such as the QRS area, the R wave amplitude in the right precordial leads, the QS duration, the percentage of biventricular pacing, and the intraprocedural blood pressure, were examined for their potential association with cardiac resynchronization therapy outcomes. However, the presence or absence of significant correlations with ejection fraction improvement requires further analysis.*

Conclusion: *Cardiac resynchronization induces cardiac remodeling, leading to echocardiographic and quality of life improvements. It also provides electrical improvements and correct ventricular dyssynchrony. Patients with narrower QRS durations after CRT experienced a rise in the ejection fraction based on higher rates of reverse remodeling.*

Rezumat

Context: *Terapia de resincronizare cardiacă reprezintă un tratament bine stabilit pentru pacienții cu insuficiență cardiacă, fiind recomandată celor cu funcție sistolică sever deprimată a ventriculului stâng și bloc de ramură stângă. Scopul acestui studiu a fost să determine corelația dintre schimbările electrocardiografice, parametrii clinici, funcționali și demografici și îmbunătățirea fracției de ejecție a ventriculului stâng după terapia de resincronizare. Un alt obiectiv al acestui studiu a fost identificarea parametrilor cu valoare predictivă pentru o selecție mai bună a pacienților și o strategie corespunzătoare de resincronizare.*

Metode: *Studiul a inclus 69 de pacienți care au beneficiat de terapia de resincronizare cardiacă în centrul nostru. Parametrii au fost monitorizați în 4 momente cheie: înainte de procedură și la 6, 9 și 12 luni după procedură.*

Rezultate: *A existat o îmbunătățire semnificativă a fracției de ejecție, care a atins un vârf la urmărirea pacienților la 12 luni. Valoarea precursorului factorului natriuretic atrial a fost asociată negativ cu evoluția fracției de ejecție. Durata QRS și volumul final diastolic al ventriculului stâng se corelează cu îmbunătățirea fracției de ejecție. Variabile mai noi, precum aria QRS, amplitudinea undei R în derivațiile precordiale drepte, durata QS, procentajul de* *stimulare biventriculară și tensiunea arterială intraprocedurală, au fost examinate pentru posibila lor asociere cu rezultatele terapiei de resincronizare cardiacă. Cu toate acestea, prezența sau absența unor corelații semnificative cu îmbunătățirea fracției de ejecție necesită o analiză suplimentară.*

Concluzie: *Terapia de resincronizare cardiacă induce remodelare cardiacă, ceea ce duce la îmbunătățiri ale funcției ventriculului stang evaluate ecocardiografic și a calității vieții. De asemenea, aceasta oferă îmbunătățiri ale conducerii electrice și corectarea disincroniei ventriculare. Pacienții cu durate QRS mai înguste după CRT au experimentat o creștere a fracției de ejecție pe baza unor rate mai mari de remodelare inversă.*

Cuvinte cheie: *terapie de resincronizare cardiacă; ecocardiografie; insuficienţă cardiacă; zona QRS; durata QRS; tensiune arterială intraprocedurală; electrocardiografie; predictori pentru terapia de resincronizare cardiacă; rezultatele terapiei de resincronizare cardiacă*

Introduction

Cardiac resynchronization therapy (CRT) has revolutionized the management of heart failure with conduction abnormalities. Studies have demonstrated that by synchronizing the contractions of the heart's ventricles[1] and through reverse remodeling[2], CRT has an important contribution in increasing EF in patients with heart failure, improving exercise tolerance and quality of life, and reducing mortality and heart failure event rates. However, many patients continue to experience a lack of reverse remodeling and a markedly poor daily functional status.

The effectiveness of CRT seems to involve several factors: careful patient selection, precise positioning of pacing electrodes in both the right and left ventricles, and optimal timing of electrode stimulation. Still, predicting a favorable result has proven to be quite a challenge.

Numerous studies were conducted to determine which parameters and their respective changes could serve in predicting a favorable outcome in patients who have undergone a cardiac resynchro-nization procedure.

The aim of the present study was to elucidate aspects related to the impact of CRT on the hemodynamic status and left ventricular ejection fraction.

Materials and Methods

A series of parameters were monitored, like intraprocedural blood pressure, ejection fraction, clinical and electrocardiographic variables, with the aim of identifying possible correlations between them and post-procedural outcomes. The analyzed outcome consisted of the evolution of the left ventricular ejection fraction (EF), which was measured before the procedure and then at three post-procedural time points: 6, 9, and 12 months, respectively.

In order to achieve the research objectives, the present study included 69 consecutive patients diagnosed with heart failure, major left bundle branch block (LBBB) and low left ventricular ejection fraction (EF) that have undergone CRT between 2017 and 2022. It is important to mention that all the enrolled patients survived one year, fulfilling the first year follow-up period. The primary endpoints of the study were related to the improvement in the patient's hemodynamic status, quantified by an improvement of the EF, which was measured at four-time points: pre-procedure, 6 months, 9 months, and 12 months post-procedure.

Ethical Approval

The study was conducted according to the World Medical Association Declaration of Helsinki, using a protocol approved by the local Bioethics Committee (15037/05. 06.2017). The patients previously signed the informed written consent about hospitalization, treatment, and future data publication.

Inclusion Criteria

To be eligible for cardiac resynchronization therapy (CRT), patients were required to have a quantitative severe depressed left ventricular ejection fraction (LVEF) of ≤ 35% on the most recent echocardiogram, nuclear multiple-gated acquisition scan, contrast ventriculogram or magnetic resonance imaging. If available, the most recent LVEF measurement was utilized for multiple assessments. Consistent with previous studies, EF measurements older than 1 year were taken into consideration and updating was unnecessary, when documented dysfunction remained unchanged, and therapy modification was not planned[3]. At the time of enrollment, the indications for resynchronization therapy were in accordance with the international guidelines for heart failure treatment[4]. They were updated later to the newer 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy and ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, and the patients were both included and treated accordingly[5].

Exclusion Criteria

Patients were excluded if they met the following criteria: those with unipolar or bipolar pacemakers or candidates for device replacement, individuals with psychiatric disorders preventing attendance at follow-up appointments, those unable to demonstrate consistent adherence to medical therapy, severe chronic obstructive pulmonary disease, poor echographic window and those with recent infections or deemed to be at very high risk for device-related infections.

Electrocardiographic Data

In most cases described by the literature, the baseline and post-CRT implantation ECG data are obtained from digitally stored information. Unfortunately, having the ability to store ECG data digitally is still considered a luxury in some healthcare settings, as not all hospitals have access to this technology. In papers over topics related to the QRS area, data was converted almost automatically, their authors being able to easily extract the data from the digital 12-lead ECG signals to transform the ECG to a vectorcardiogram which would later be used to calculate the three orthogonal X, Y, Z vectorcardiographic leads via the Kors[6] conversion matrix, and finally, the area of the QRS complex will be calculated.[7]

Even more, for most physicians, having to analyze digital signals (whether it is ECG or EMG) by using complex software or programming language would be a difficult task, and this is also why we tried to use a straightforward method that could be accessible to almost everybody.

ECG data was obtained from paper ECGs as paper-recorded ECG is the most available data source, and aimed to see if there is any correlation between the surface area of the QRS complex on the paper ECG and the post-CRT outcome. It is also important to mention that only freeware-type software was used, making this method cheap to apply.

Paper electrocardiograms were scanned using normal scanners, and various parameters were measured with freeware software named IC-Measure[8]. The software allows the user to perform precise calibration by using the built-in microscope and caliper settings. The calipers were adjusted on the big squares of each ECG and set to a value of 5 mm. Various conversions were possible, knowing that each millimeter on the horizontal axis corresponds to a timeline of 40 milliseconds or 0.04 seconds and on the vertical axis to 0.1 millivolts. **(Figure 1)**

Monitored Parameters

Aspects such as QRS duration before and after CRT[9], ischemic background pathology, and the percentage of biventricular pacing[10] are well documented in the literature, but the present study also aimed to check if QRS morphology elements, QRS area[11,7], intraprocedural increases in blood pressure[12] and the evolution of the EF could be used as predictors, as they are newer researched topics. After measuring these parameters on the electrocardiograms, they were recorded in the database. The intraprocedural systolic blood pressure was also monitored via a 4 or 5 French intra-arterial catheter, and variations were recorded.

The left ventricular ejection fraction was assessed using the two-dimensional biplane method of disks echocardiography, a reproducible and simple technique recommended by all cardiology societies. LVEF was measured by tracing the endocardial border in the apical four-chamber window and two-chamber view in end-systole and end-diastole, gated by the ECG[14]. The end-systolic volume image was defined as the frame preceding the mitral valve opening at the end of the T wave. End-diastolic volume was measured at the onset of the QRS complex in the frame following mitral valve closure[15].

Measurements were performed in a correct and uniform manner to overcome one of the biggest problems with Simpson's Biplane method, the foreshortening of the LV cavity[16]. Following the anatomical relations, the measurements were executed with a perfectly perpendicular basal plane to the apex of the LV.

Lead Placement and CRT Device Implantation Procedure

CRT device implantation was performed under sterile conditions in the cardiac catheterization lab with patients in a supine position under local anesthesia or conscious sedation.

Venous access, typically via the subclavian or cephalic vein, allowed for lead insertion into the right atrium, right ventricle, and coronary sinus for left ventricular pacing. Fluoroscopy guided lead placement to the right atrial appendage, right ventricular apex or septum, and the lateral or posterolateral coronary sinus vein. Pacing thresholds, lead impedance, and sensing were verified before securing the leads. The device was connected and implanted subcutaneously in a pre-formed pectoral pocket, followed by programming to ensure effective biventricular pacing and scheduled follow-ups to monitor performance.

Lead placement represents one of the fundamental steps in CRT procedures. Detailed knowledge of the scar location, its depth, and transmural extension allows the physician to select an alternative pacing site from the posterolateral, anterolateral, and lateral areas[17]. For this reason, cardiac MRI was performed in patients with documented ischemia in order to identify myocardial scar tissue and quantify its extent, preventing inappropriate placement of the left ventricular lead within scarred regions. It also helped identifying the most suitable vein for lead placement, as this method has demonstrated good results.

The longest Q-LV interval measured for each patient's electrode positions was taken into consideration when placing the left ventricular electrode in the lateral, anterolateral, or posterolateral vein of the left ventricle in order to maximize the likelihood of achieving better cardiac remodeling[18,19].

Statistical analysis

Data analysis was conducted using Python 3.7.4. The pandas library facilitated tasks such as variable selection, crosstabulation, patient group categorization, and extraction of descriptive statistics(19). Graphs were generated using the matplotlib library(20) and seaborn libraries(21).

Differences in categorical variable distributions across groups were assessed using contingency tables and chi-square tests, implemented with the SciPy library(22)Student's t-tests (SciPy) were used to compare numerical variables between two groups, while one-way ANOVA followed by Tukey's HSD test was applied for comparisons involving more than two groups. Multinomial logistic regression analysis, performed with the statsmodels package, was used to identify independent clinical factors predicting response to resynchronization therapy(23).

The Pearson correlation coefficient for variable pairs was calculated using SciPy, and the results were organized into a matrix. Columns and rows were grouped using the unweighted pair group method with arithmetic mean (UPGMA) to identify related parameters.

To assess the prognostic value of numerical parameters from EKG measurements before or after resynchronization therapy, a linear logistic regression model was applied and visualized with Receiver Operating Characteristic (ROC) curves using the sklearn package(24). Sensitivity and specificity were calculated for all possible threshold values, with the threshold yielding the highest

Youden J index reported alongside its corresponding sensitivity and specificity. A significance level of p = 0.05 was used for all statistical analyses. For this purpose, the formulas used were:

$$Sensitivity = \frac{TP}{TP + FN}$$

$$Specificity = \frac{TN}{TN + FP}$$

where TP is True Positives, TN – True Negatives, FP – False Positives, and FN – False negatives; and

$$\text{Youden J} = \text{Sensitivity} + \text{Specificity} - 1$$

In all statistical analyses a significance threshold of p=0.05 was used and the strength of statistical significance was indicated in figures, tables and text as *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

Results

After performing statistical analysis, we categorized the study cohort (n = 69) based on the evolution of their ejection fraction (EF) following cardiac resynchronization therapy (CRT) into two groups: stable EF (n = 16) and responsive EF (n = 53). Table S1 from the supplemental files presents the demographic, clinical, and paraclinical characteristics of these groups.

The analysis revealed notable differences between the groups. Patients with stable EF were slightly older on average and predominantly male. They were also more likely to have ischemia and to reside in urban areas. In contrast, patients with responsive EF had a higher proportion presenting with NYHA Class III symptoms. Despite these distinctions, paraclinical parameters such as hemoglobin, creatinine, and Nt-Pro BNP levels were comparable between groups.

EF evolution

The evolution of ejection fraction (EF) after cardiac resynchronization therapy (CRT) is depicted in Figure 2, showing a progressive improvement over time. At baseline, patients had a mean EF of approximately 25%, reflecting significant cardiac dysfunction. By 6 months, there was a marked increase to around 30%, indicating an early positive response to therapy. This improvement was sustained at 9 months and 1 year, with the mean EF stabilizing between 30% and 35%, highlighting the long-term benefits of CRT on cardiac function. The shaded area around the mean represents the variability among patients, with most showing improvement while a small subset exhibited little or no change.

Individual EF trajectories demonstrate this variability, as reflected in the upward trends for most patients and the flat or declining lines for a few. These findings emphasize both the overall efficacy of CRT and the heterogeneity of patient responses. The mean EF deviation from baseline at different time points is shown in figure S2 from the supplemental files.

Pairwise comparisons of ejection fraction (EF) at different time points reveal a statistically significant improvement from baseline to both 6 months and 12 months post-CRT (Table S2 in the supplemental files). The mean EF increased by 7.55% at 12 months and 6.41% at 6 months compared to baseline (p=0.001 for both). These results underscore the early and sustained impact of CRT on cardiac function. However, no significant differences were observed when comparing EF between 6 months, 9 months, and 12 months, suggesting that the majority of EF improvement occurred within the first 6 months post-CRT. This plateau in EF highlights the importance of early follow-up to evaluate CRT effectiveness. Confidence intervals further support these findings, demonstrating significant improvements from baseline but no significant changes during later follow-ups.

A progressive and statistically significant improvement in ejection fraction (EF) following cardiac resynchronization therapy (CRT) is demonstrated in Figure 3. At baseline, patients presented with a median EF of approximately 25%, reflecting significant cardiac dysfunction. By 6 months, there was a notable increase in median EF to around 30%, which remained stable at 9 months and 1 year. The interquartile ranges indicate variability in patient responses, with some patients experiencing greater EF improvements than others. The statistically significant increases (**$p < 0.01$**) at all follow-up points underscore the overall effectiveness of CRT in enhancing cardiac function over time.

Figure 4 illustrates the distribution of changes in ejection fraction (Delta EF) after cardiac resynchronization therapy (CRT) for patients categorized as stable EF and responsive EF. The histogram and kernel density estimate (KDE) curves provide a visual representation of the variability within each group. The **responsive EF group** shows a broad distribution of Delta EF values, with most patients achieving substantial improvements in EF, clustering around a mean Delta EF of approximately 9 to 10%. In contrast, the **stable EF group** demonstrates a much narrower distribution, with Delta EF values primarily concentrated between 0 and 3%, indicating minimal or no improvement.

The clear separation between the two groups highlights the distinct differences in therapeutic response to CRT. While the majority of patients in the responsive EF group experienced significant enhancements in cardiac function, those in the stable EF group showed little to no change. This finding underscores the heterogeneous nature of patient outcomes following CRT and emphasizes the need for further investigation into the clinical and paraclinical factors that influence response. Identifying these predictors could help refine patient selection and optimize the effectiveness of CRT.

Correlation between the EF and clinical parameters

This following table summarizes the baseline demographic, clinical, and paraclinical characteristics of the study population, categorized into two groups based on their response to cardiac resynchronization therapy (CRT): stable EF (n = 16) and responsive EF (n = 53). The total cohort comprised 69 patients with a mean age of 67.94±9.57 years. Patients in the stable EF group were slightly older, with a mean age of 70.75±7.41 years, compared to 67.09±10.03 years in the responsive EF

Figure 1. *Calibrating the measurement tool using the calipers provided by the software.*

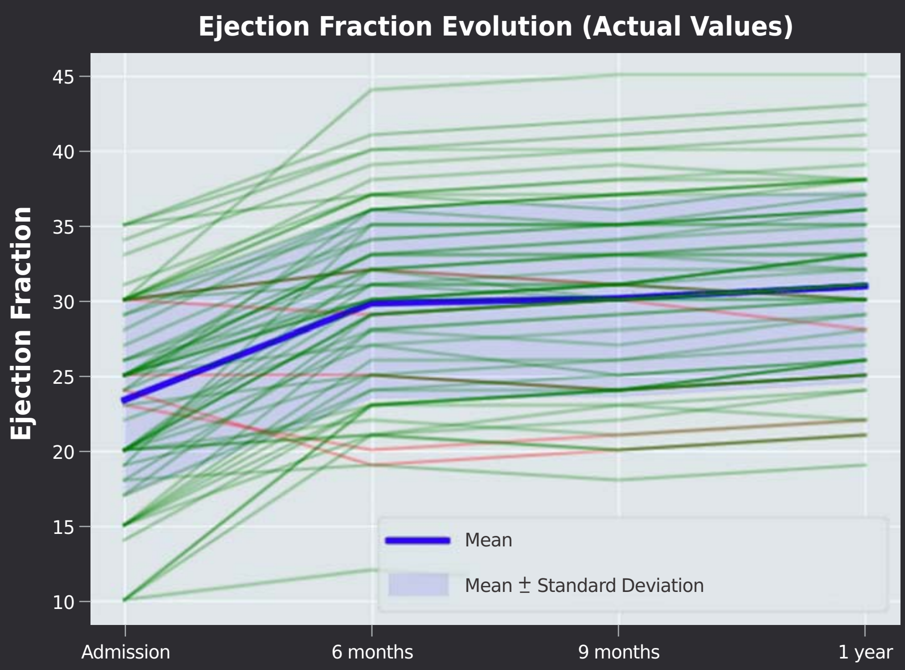

Figure 2. *Evolution of ejection fraction (EF) after cardiac resynchronization therapy (CRT), showing a progressive increase in mean EF from baseline (~25%) to 6 months (~30%), with stabilization between 30% and 35% at 9 months and 1 year.*

group. Notably, men accounted for the majority of the population (84.06%), with the proportion being higher in the stable EF group (93.75%) compared to the responsive EF group (81.13%).

At admission, most patients presented with advanced heart failure symptoms, with 65.22% classified as NYHA Class III. In the stable EF group, an equal proportion of patients were in NYHA Class II and III (50%), whereas 69.81% of the responsive EF group were in Class III, reflecting a potentially more severe baseline functional status. Additionally, the living environment differed between groups, with a greater proportion of stable EF patients residing in urban areas (75%) compared to responsive EF patients (54.72%).

Comorbidities, such as ischemia, atrial fibrillation, and diabetes mellitus, were prevalent in the cohort. Ischemia was notably more common in the stable EF group (56.25%) compared to the responsive EF group (33.96%), which may have influenced their limited response to CRT. Atrial fibrillation and diabetes mellitus were similarly distributed between the groups, with nearly half of the patients affected.

Paraclinical parameters revealed that hemoglobin levels were comparable across both groups (13.46±1.41 overall), as were Nt-Pro BNP levels, with a mean of 3303.26±1911.92. Creatinine levels were slightly higher in the stable EF group (1.19±0.42) than in the responsive EF group (1.12±0.51).

Correlation between the EF and electrocardiographic parameters

Further on, key clinical and electrocardiographic parameters between patients with stable outcomes and those classified as responsive in terms of EF improvement were compared using the t-test. The t-test results are presented in table 2. The supplemental section (Supplemental Figures S2) contains the visual representations of the t-tests performed for all the parameters and the ROC curves for the parameters with the highest prognosis value.

Several parameters demonstrated significant differences between the stable EF and responsive EF groups, highlighting key factors associated with CRT response. The Q-LV interval was significantly longer in the responsive EF group (mean: 108.4 ms, SD: 6.05) compared to the stable EF group (mean: 71.75 ms, SD: 13.12; $p < 0.0001$), indicating greater potential for synchronization improvement. Similarly, the immediate post-implant systolic blood pressure increase was markedly higher in the responsive group (mean: 9.26 mmHg, SD: 1.36) than in the stable group (mean: 2.69 mmHg, SD: 1.2; $p < 0.0001$), reflecting improved hemodynamics shortly after CRT.

Electrocardiographic parameters also showed notable differences. The QRS area

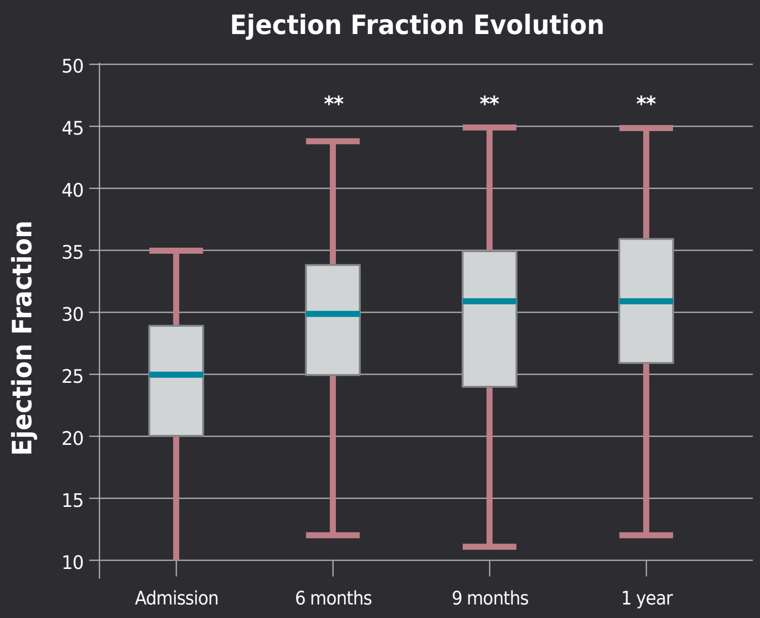

Figure 3. *Repeated measures ANOVA showing the evolution of ejection fraction (EF) at admission, 6 months, 9 months, and 1 year post-CRT. The analysis revealed significant improvements in EF at 6 months, 9 months, and 1 year compared to admission ($p < 0.01$). No significant differences were observed between the follow-up intervals, indicating that the majority of EF improvement occurred within the first 6 months, with stabilization thereafter. The boxplot illustrates the median, interquartile range (IQR), and variability in EF across time points. Asterisks (**) denote statistically significant differences ($p < 0.01$) compared to baseline, as determined by the ANOVA test (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$).*

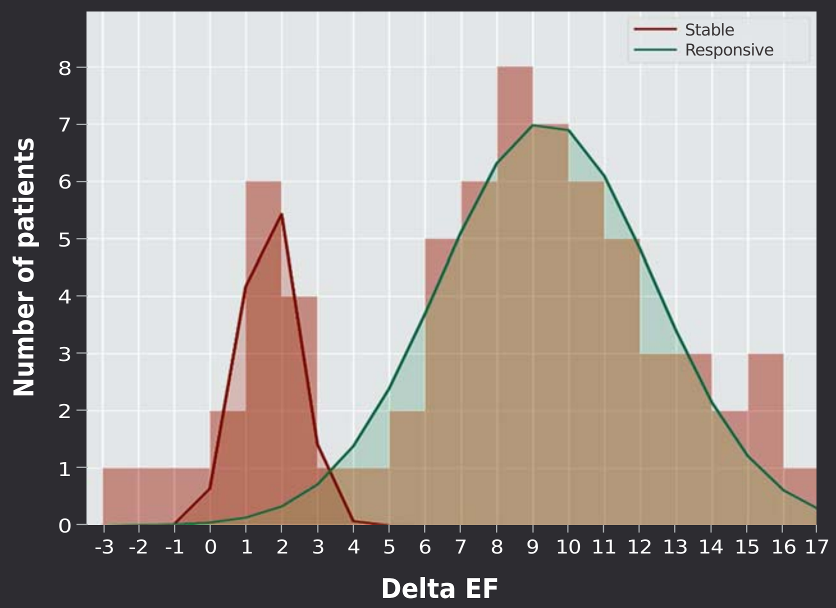

Figure 4. *The histogram showing the post-implant improvement in the Ejection Fraction presented two different populations which could be fitted with a two gaussian model with high R-squared value (0.867). Delta EF represents EF at 12 months – EF baseline. To Differentiate between patients with Stable EF and patients Responsive to therapy, the value at the intersection of the two curves was chosen, so an improvement of more than 3% in the Ejection Fraction was considered response to therapy. According to this criterion, 53 patients (76.8%) responded to therapy, while 16 (23,2%) did not.*

difference was significantly larger in the responsive group (mean: 48.06 µV·s, SD: 26.7) compared to the stable group (mean: -19.2 µV·s, SD: 28.63; $p < 0.0001$), suggesting better ventricular synchrony in responsive patients. A similar trend was observed in QRS duration differences, with greater reductions in the responsive group (mean: 40.8 ms, SD: 21.55) versus the stable group (mean: 10.84 ms, SD: 22.53; $p = 0.0001$). Moreover, the R-wave amplitude in leads V1/V2 was significantly higher in the responsive group (mean: 1.75 mm, SD: 1.24) compared to the stable group (mean: 0.9 mm, SD: 0.88; $p = 0.0047$).

Post-CRT QRS characteristics further underscored differences between the groups. The QRS area after CRT was significantly smaller in the responsive group (mean: 83.57 µV·s, SD: 41.77) than in the stable group (mean: 130.43 µV·s, SD: 57.47; $p = 0.0066$), indicating improved synchronization. Additionally, the QS wave duration in leads aVL and I, as well as QRS duration after CRT, were significantly shorter in the responsive group (lead aVL: mean: 81.69 ms, SD: 30.1 vs. 114.69 ms, SD: 45.89; $p = 0.014$; lead I: mean: 108 ms, SD: 30.79 vs. 134.61 ms, SD: 37.71; $p = 0.0175$; QRS duration: mean: 134.75 ms, SD: 17.96 vs. 155 ms, SD: 28.88; $p = 0.0158$), reflecting enhanced electrical activation and synchronization in these patients.

The predictive value of various EKG parameters for EF improvement following CRT was evaluated, identifying the optimal thresholds for each parameter, their corresponding Youden index, as well as their sensitivity and specificity in predicting a positive response (Table 3).

This table evaluates the diagnostic performance of various parameters in distinguishing between stable and responsive EF groups after cardiac resynchronization therapy (CRT). The most highly discriminative parameters were Q-LV (ms), immediate post-implant systolic blood pressure (BP) increase, and QRS area difference, each achieving outstanding sensitivity and specificity. Q-LV, with a threshold of 98 ms, had a perfect Youden's J index of 1.0, 100% sensitivity, and 100% specificity, making it a highly reliable marker for CRT response. Similarly, an immediate systolic BP increase of at least 7 mmHg provided near-perfect diagnostic accuracy, with a Youden's J of 0.981, sensitivity of 98.11%, and specificity of 100%. The QRS area difference, using a threshold of 16.33 µV·s, also demonstrated excellent diagnostic performance (Youden's J: 0.924, sensitivity: 92.45%, specificity: 100%), highlighting its role in capturing ventricular synchrony improvements post-CRT.

Moderately discriminative parameters included the QRS duration difference, QS wave duration in Lead aVL after CRT, and R-

	All	Stable EF	Responsive EF
Number	69	16	53
Age (mean ± stdev)	67.94 ± 9.57	70.75 ± 7.41	67.09 ± 10.03
Sex			
F	11 (15.94%)	1 (6.25%)	10 (18.87%)
M	58 (84.06%)	15 (93.75%)	43 (81.13%)
NYHA Class at Admission			
II	24 (34.78%)	8 (50.00%)	16 (30.19%)
III	45 (65.22%)	8 (50.00%)	37 (69.81%)
Living Environment			
Urban	41 (59.42%)	12 (75.00%)	29 (54.72%)
Rural	28 (40.58%)	4 (25.00%)	24 (45.28%)
Ischemia	27 (39.13%)	9 (56.25%)	18 (33.96%)
Atrial Fibrillation	33 (47.83%)	8 (50.00%)	25 (47.17%)
Diabetes Mellitus	31 (44.93%)	6 (37.50%)	25 (47.17%)
Paraclinical			
Hemoglobin (mean ± stdev)	13.46 ± 1.41	13.50 ± 1.41	13.45 ± 1.42
Creatinine (mean ± stdev)	1.13 ± 0.49	1.19 ± 0.42	1.12 ± 0.51
Nt-Pro BNP (mean ± stdev)	3303.26 ± 1911.92	3177.44 ± 1618.19	3341.25 ± 2004.62

Table 1. *This table highlights important baseline differences between the stable and responsive EF groups. Patients in the stable EF group were slightly older, more likely to live in urban areas, and had a higher prevalence of ischemia, which may contribute to the lack of EF improvement.*

wave amplitude in V1/V2 after CRT. The QRS duration difference, with a threshold of 24 ms, achieved good sensitivity (88.68%) and specificity (87.5%), supported by a Youden's J index of 0.762. Similarly, the QS wave duration in Lead aVL after CRT showed a threshold of 119.6 ms, with a sensitivity of 88.68% and specificity of 56.25% (Youden's J: 0.449), indicating moderate utility in assessing changes in ventricular depolarization. The R-wave amplitude in V1/V2 after CRT demonstrated moderate sensitivity (81.13%) and specificity (62.5%) with a threshold of 0.55 mm (Youden's J: 0.436), making it a partial but noteworthy contributor to CRT response evaluation.

Other parameters, such as QRS area after CRT and QS wave duration in Lead I, displayed limited diagnostic utility, with Youden's J indices below 0.5.

Meanwhile, parameters like the percentage of biventricular pacing, QRS area before CRT, and PR interval before and after CRT exhibited low discriminative power (Youden's J < 0.3).

These findings suggest that although some parameters have limited individual utility, they might still provide complementary insights when combined with more robust markers. Overall, the results emphasize the diagnostic strength of Q-LV, systolic BP increase, and QRS area difference in identifying CRT responders, while other parameters may serve as secondary markers in clinical assessments.

The ROC curves for the predictors of EF improvement are included in the supplementary section to visually demonstrate the predictive accuracy of these EKG parameters in identifying patients likely to experience significant improvements in EF following CRT (Supplemental figures S3).

Analysis of the independent demographic and clinical factors before resynchronization predisposing therapy response

To identify clinical parameters that independently of other parameters led to therapy response, multinomial logistic regression analyses were performed for each of the three outcome variables, using the statsmodels package in Python3 (Figure 5). Multinomial logistic regression is a statistical method used to estimate the probability of a patient responding to CRT based on various clinical and demographic parameters. Since patients may exhibit overlapping or distinct patterns in these parameters, this analysis helps model the contribution of each factor to the outcome. It reveals how the outcome is expected to change with a one-unit increase in a predictor while holding all other variables constant. The results are presented as odds ratios (OR), which indicate the strength of each parameter in influencing the odds of responding to CRT. OR values greater than 1

Parameter	Mean Stable	Std Stable	Mean Respon-sive	Std Respon-sive	T Statis-tic	P Value	P Value Sum-mary
Q-LV (ms)	71.75	13.12	108.4	6.05	-10.8322	< 0.0001	****
Immediate Post-Implant Systolic BP Increase (mmHg)	2.69	1.2	9.26	1.36	-18.6565	< 0.0001	****
QRS Area Difference	-19.2	28.63	48.06	26.7	-8.3639	< 0.0001	****
QRS Duration Difference	10.84	22.53	40.8	21.55	-4.7093	0.0001	****
R-wave Amplitude in V1/V2 after (mm)	0.9	0.88	1.75	1.24	-3.0248	0.0047	**
QRS Area after (microV*sec)	130.43	57.47	83.57	41.77	3.0289	0.0066	**
(S1+R6) - (S6+R1) after	2.15	1.54	3.69	2.89	-2.7997	0.0073	**
QS Wave Duration in Lead aVL after (ms)	114.69	45.89	81.69	30.1	2.7056	0.014	*
QRS Duration after (ms)	155	28.88	134.75	17.96	2.6539	0.0158	*
QS Wave Duration in Lead I after (ms)	134.61	37.71	108	30.79	2.5756	0.0175	*
Percentage of Biventricular Pacing (%)	98.38	0.89	98.83	0.99	-1.7503	0.0912	n.s.
Age	70.75	7.41	67.09	10.03	1.5837	0.1227	n.s.
QRS Duration before (ms)	165.84	26.28	175.55	24.87	-1.3123	0.202	n.s.
QRS Area before (microV*sec)	111.23	58.11	131.63	58.15	-1.2306	0.23	n.s.
R-wave Amplitude in aVR after (mm)	1.44	2.17	2.14	2.13	-1.1352	0.2674	n.s.
R6/S6 Ratio after	1.42	2.33	0.89	1.02	0.8851	0.3886	n.s.
Creatinine	1.19	0.42	1.12	0.51	0.5697	0.5731	n.s.
Nt-Pro BNP	3177.44	1618.19	3341.25	2004.62	-0.3347	0.7401	n.s.
PR Interval before	200.64	37.55	204.87	41.05	-0.2873	0.7779	n.s.
Hemoglobin (Hgb)	13.5	1.41	13.45	1.42	0.1359	0.893	n.s.
LVEDV (ml)	251.06	68.69	252.94	67.22	-0.0965	0.9239	n.s.
PR Interval after	100	0	100	0			n.s.

Table 2. *Comparison of clinical, electrocardiographic, and hemodynamic parameters between stable and responsive EF groups. Significant differences were observed in Q-LV, immediate post-implant systolic blood pressure increase, QRS area and duration differences, and other electrocardiographic markers (p < 0.05). Non-significant differences (n.s.) are noted for parameters such as age, creatinine, Nt-Pro BNP, hemoglobin, and left ventricular end-diastolic volume (LVEDV).*

Parameter	Threshold	Youden_j	Sensitivity (%)	Specificity (%)
Q-LV (ms)	98	1	100	100
Immediate Post-Implant Systolic BP Increase (mmHg)	7	0.981	98.11	100
QRS Area Difference	16.33	0.924	92.45	100
QRS Duration Difference	24	0.762	88.68	87.5
QS Wave Duration in Lead aVL after (ms)	119.6	0.449	88.68	56.25
R-wave Amplitude in V1/V2 after (mm)	0.55	0.436	81.13	62.5
QRS Area after (microV*sec)	131	0.412	84.91	56.25
QRS Duration after (ms)	130.4	0.409	47.17	93.75
QRS Duration before (ms)	159.2	0.399	77.36	62.5
R-wave Amplitude in aVR after (mm)	0.9	0.392	64.15	75
QS Wave Duration in Lead I after (ms)	118	0.379	56.6	81.25
(S1+R6) - (S6+R1) after	1.13	0.318	94.34	37.5
Percentage of Biventricular Pacing (%)	100	0.283	28.3	100
QRS Area before (microV*sec)	61.89	0.275	96.23	31.25
PR Interval before	202	0.198	64.29	55.56
LVEDV (ml)	294	0.158	28.3	87.5
R6/S6 Ratio after	2.58	0.15	96.23	18.75
PR Interval after	100	0	100	0

Table 3. *Ejection Fraction prediction value of the EKG parameters*

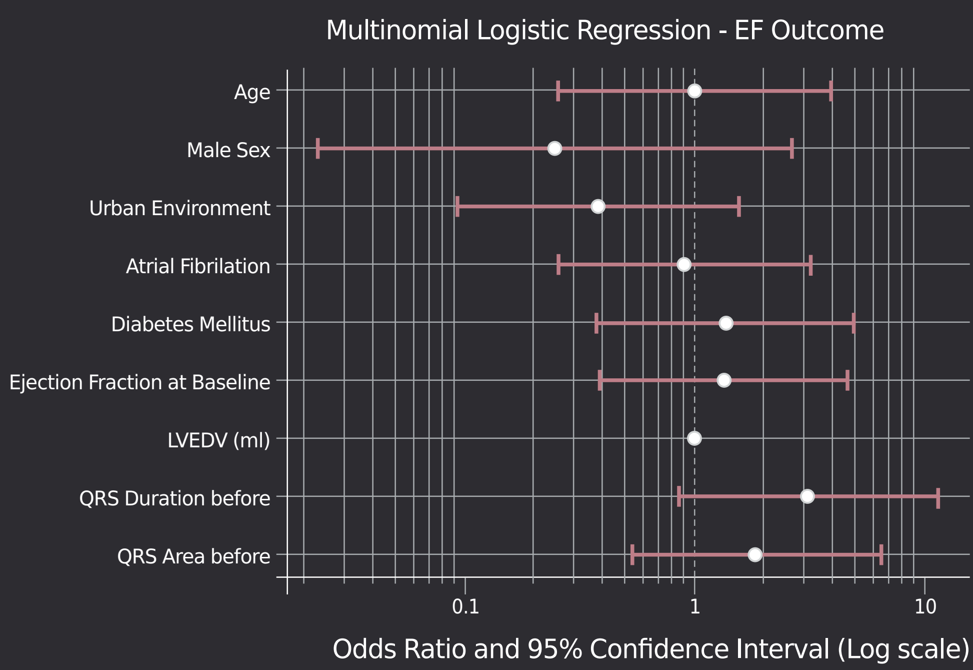

Figure 5. *Forest plot showing the Odds Ratio for the response to therapy in terms of Ejection Fraction improvement at 12 months. The error bars represent the 95% confidence interval (from 2.5% to 97.5%) of the odds ratio for each parameter tested. Statistically significant results were represented in red, and parameters without statistical significance in gray. No clinical or paraclinical parameter tested predisposes patients to better or worse outcomes in term of ejection fraction increase at 12 months post resynchronization.*

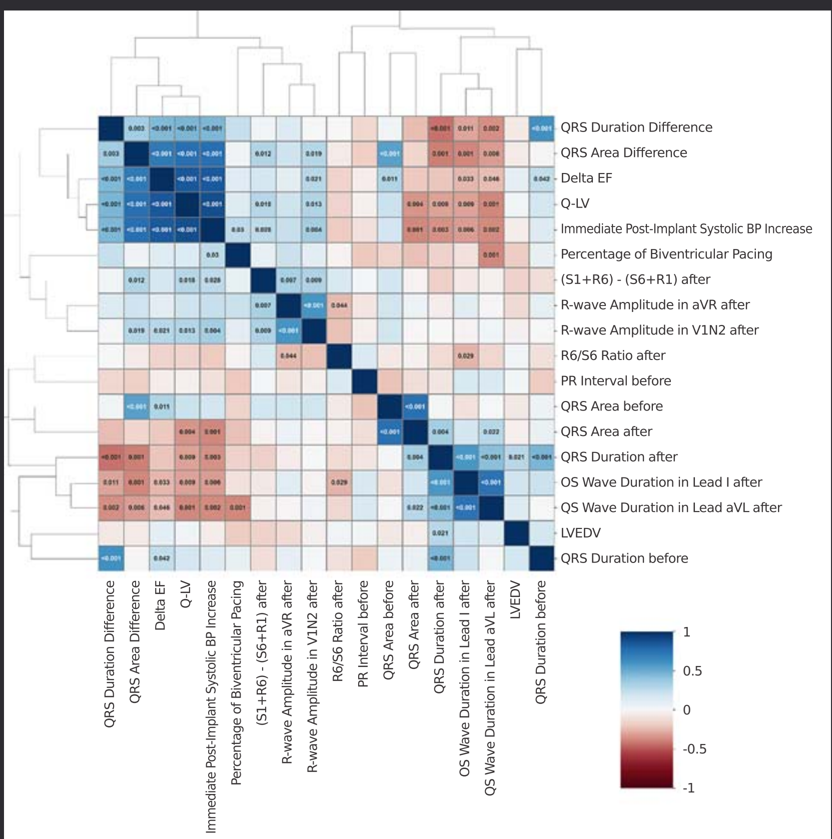

Figure 6. *Correlation matrix that illustrates the relationships between various clinical and electrocardiographic parameters and their association with ejection fraction (EF) outcomes following cardiac resynchronization therapy (CRT). Each cell represents the strength and direction of the correlation, with darker blue indicating stronger positive correlations and darker red indicating stronger negative correlations.*

suggest an increased likelihood, while values less than 1 suggest a decreased likelihood. Forest plots effectively visualize these results, offering a clear summary of the ORs for each variable along with their 95% confidence intervals (CI), enabling easy comparison of the relative importance of the predictors.

The plot above illustrates the results of a multinomial logistic regression analysis, which evaluates the relationship between baseline clinical and demographic factors and ejection fraction (EF) outcomes following cardiac resynchronization therapy (CRT). Each factor is represented by an odds ratio (OR) and its corresponding 95% confidence interval (CI), displayed on a logarithmic scale. The OR quantifies how a one-unit change in the predictor variable affects the odds of responding to CRT, with OR > 1 indicating a positive association and OR < 1 indicating a negative association. The vertical dashed line at OR = 1 represents no effect.

Key findings from the analysis indicate that none of the evaluated baseline factors demonstrated statistically significant associations with EF outcomes, as all confidence intervals crossed the OR = 1 line. For example, factors such as age, male sex, urban environment, atrial fibrillation, and diabetes mellitus had ORs close to 1 with wide confidence intervals, suggesting no strong or significant influence on CRT response. Similarly, baseline EF, left ventricular end-diastolic volume (LVEDV), QRS duration before CRT, and QRS area before CRT also showed confidence intervals that crossed 1, indicating no significant predictive value.

These results suggest that the baseline clinical and demographic parameters included in the model are not sufficient to predict CRT outcomes independently. This highlights the potential importance of other factors, such as post-CRT measurements, procedural parameters, or individual patient characteristics, in determining the effectiveness of CRT.

Correlation of EKG parameters with EF improvement (Figure 6)

Notable strong correlations were observed between QRS Duration Difference, QRS Area Difference, and Delta EF, emphasizing the importance of changes in electrical activity in predicting EF improvement. For instance, QRS Area Difference demonstrated significant positive correlations with both Delta EF and other electrical parameters, suggesting that enhanced ventricular synchrony, as reflected in these differences, plays a pivotal role in EF improvement.

In addition, parameters such as Immediate Post-Implant Systolic BP Increase and Q-LV were significantly correlated with Delta EF, reinforcing the role of immediate hemodynamic changes and pre-CRT electrical timing in predicting CRT success. These findings highlight the interconnected nature of electrical and hemodynamic improvements in driving EF outcomes.

On the other hand, weaker or non-significant correlations were observed for parameters like R6/S6 Ratio and PR Interval Before, suggesting that these variables are less reliable predictors of EF improvement. These weaker associations allow clinicians to focus on parameters with stronger predictive value, streamlining the assessment of CRT efficacy. (The scatterplots for the corelations can be viewed in the supplemental Figures S4).

Discussion

Current knowledge about CRT shows that cardiac resynchronization induces cardiac remodeling, leading to echocardiographic improvements. It also provides electrical improvements by correcting ventricular dyssynchrony, which is the main benefit of CRT. This study is an attempt to correlate the EF score with various electrocardiographic parameters, based on the fact that the EF has proven to be a reliable indicator for both cardiac functionality and quality of life. Some authors state that normalization of LVEF by CRT brings the survival rate close to the general population[20]. There were no significant differences observed between patients with defibrillator support (CRT-D) and those without defibrillator support in this study. The only notable finding during the one-year follow-up was the occurrence of two arrhythmic events in two different patients, both successfully treated with internal electrical shocks, without loss of consciousness.

Many studies based on QRS changes and patterns have been published, making QRS duration one of the most studied parameters as well as including it in the fundamental CRT criteria[5]. These studies also emphasize its predictive value after CRT and the current research demonstrates a link between the QRS duration after CRT and EF. Consequently, patients with narrower QRS durations after CRT experienced a rise in the ejection fraction based on higher rates of reverse remodeling. At the same time, for those with a greater QRS duration, there was less improvement as they continued to experience various degrees of heart failure symptoms, lower effort tolerance, and lower quality of life. In the present study, a significant reduction in QRS duration after CRT ($p = 0.0001$) confirmed the electrical optimization achieved in responders. Although less pronounced than QRS duration difference, the absolute QRS duration after CRT ($p = 0.0158$) remained an important parameter, reaffirming the relevance of ventricular conduction times in assessing response. Therefore, it is important to aim for the shortest QRS duration with CRT pacing by properly programming AV delays and VV timing to promote fusion with intrinsic septal activation.

Better ventricular synchrony and proper myocardial contraction also translate into a higher cardiac output, which was assessed by monitoring the intraprocedural blood pressure. Studies suggest using a 5mmHg threshold[12], but in this research, all the recorded values were filled in the database. Variation in the monitored systolic blood pressure can be influenced by autonomic tone, underlying cardiovascular physiology, medication effects, and individual patient characteristics. In this study, the substantial increase in systolic blood pressure immediately post-implantation ($p < 0.0001$) indicates an acute hemodynamic benefit of CRT. This parameter may serve as a straightforward and practical clinical marker to assess the immediate effectiveness of therapy.

In the Markers and Response to CRT (MARC)[21], research that included 240 patients, vectorcardiography-derived QRS area was shown to be more predictive of echocardiographic response to CRT than QRS morphology and duration. Some other studies link the delayed activation of the left ventricle to a larger QRS area and also suggest that the area better depicts the electrical substrate of the disease.(11) The current study emphasizes that **QRS Area after CRT** was significantly lower in responders compared to stable patients ($p = 0.0066$) and that the change in QRS area before and after CRT ($p < 0.0001$) also reflects improvements in electrical activation efficiency. These findings suggests that responders exhibit more efficient and synchronized ventricular depolarization post-CRT, reflected by a reduction in the overall QRS area. This contrasts with non-responders, who retain a higher QRS area, potentially indicating less effective electrical remodeling.

According to some studies, the presence of a positive vector in V1 and/or a negative vector in lead I on the initial postprocedural electrocardiogram (ECG), a sign of posterolateral capture from cardiac resynchronization therapy, correlates with enhancement in left ventricular ejection fraction. In the present study, an increase in R-wave amplitude in leads V1/V2 ($p = 0.0047$) reflects enhanced electrical activity in the anterior and right-sided regions of the heart, suggesting improved electrical conduction following CRT.

In the present study, the Q-LV interval, which reflects the time delay between the onset of QRS and the activation of the left ventricle, emerged as a critical determinant of CRT effectiveness. A longer Q-LV interval post-CRT was associated with better electrical synchronization and improved hemodynamics. The Q-LV interval demonstrated the strongest statistical significance ($p < 0.0001$) and substantial differences between responders and non-responders. The significantly longer Q-LV interval in responders supports its role as a determinant of CRT success.

This study also evaluated the immediate systolic blood pressure (BP) variation during the procedure and its relationship with CRT outcomes and observed an increase in systolic BP immediately post-implantation ($p < 0.0001$) in patients where CRT had success. This hemodynamic improvement likely reflects enhanced cardiac output and more efficient ventricular contraction, aligning with the core therapeutic goals of CRT. The simplicity of monitoring systolic BP variation make it an accessible clinical tool for assessing the immediate effectiveness of therapy and its predictive value emphasizes the importance of acute physiological responses in forecasting long-term patient outcomes.

In the present study, prolonged QS wave durations in leads I ($p = 0.0175$) and aVL ($p = 0.014$) emerged as significant markers of CRT response, reflecting regional activation delays in key myocardial segments. These leads represent the electrical activity in the lateral and high-lateral walls of the left ventricle-regions often associated with electrical dyssynchrony in heart failure patients. The observed prolongation of QS wave duration after CRT suggests that therapy successfully engages these delayed segments, correcting the regional dyssynchrony that underlies impaired ventricular contraction.

Lead aVL primarily reflects the high-lateral segments of the left ventricle, while lead I provides insight into activation along the lateral wall. The consistent findings across both leads emphasize the role of lateral and high-lateral regions in CRT-mediated resynchronization.

Prolonged QS wave durations in these leads may signify improved electrical conduction in previously delayed areas, which translates into more effective mechanical contraction and enhanced hemodynamic performance. This regional improvement aligns with the goals of CRT, aiming to optimize both electrical and mechanical synchrony for better cardiac output and clinical outcomes. The integration of findings from leads I and aVL highlights the value of regional electrophysiological markers in assessing CRT effectiveness. These waveforms not only reflect the underlying electrical remodeling induced by CRT but also provide a non-invasive method to evaluate therapy success. By targeting the lateral and high-lateral walls, which are often regions of delayed activation, CRT can restore coordinated ventricular contraction, resulting in better clinical responses.

The derived parameter *(S1+R6) - (S6+R1)*, which reflects the balance of ventricular electrical forces across multiple myocardial regions, was significantly higher in responders ($p = 0.0073$), indicating its potential utility as a novel marker of CRT effectiveness. This parameter integrates amplitudes from leads that represent opposing regions of the heart, offering a more comprehensive view of the electrical remodeling induced by CRT. A higher value likely signifies improved activation of previously delayed myocardial regions, coupled with a reduction in electrical dyssynchrony between the septal and lateral walls. By capturing these shifts, this metric provides unique insights into the redistribution of ventricular electrical forces, which correlates with mechanical improvements and favorable clinical outcomes. Its significance suggests that *(S1+R6) - (S6+R1)* could serve as a complementary tool to established parameters in evaluating CRT success, particularly in patients where traditional markers provide ambiguous results.

Clinical Perspective

More accurate patient selection is needed to improve CRT efficacy and limit implantation in patient groups with poor outcomes. A study performed by Sylvian Ploux et al suggests that QRS duration or the presence of LBBB might be outperformed by electrocardiographic mapping[25].

Improvement can be done by better lead placement and device programming. Different left ventricular pacing sites can be analyzed by performing a body surface mapping with an ECG belt during cardiac resynchronization and can upgrade CRT outcomes with the existing technology[26]. Even though patients have benefited from all lead positions, authors agree that placing the left lead in the AL and PL positions is better for achieving optimal CRT benefit than leads placed in the anterior position[27]. Click or tap here to enter text. New pacing approaches are required for better ventricular synchronization. In the future, ultra-high-frequency electrocardiography (UHF-ECG) holds promise for benefiting these patients. With its rapid dyssynchrony analysis and real-time visualization, UHF-ECG can potentially optimize cardiac resynchronization therapy. This advancement will enable clinicians to tailor therapy to each patient's unique characteristics more effectively[28].

Accurate determination of predictive parameters is both necessary and important as cardiac physiologic pacing is an innovative method, with promising results, which seems to be a perspective in the coming years, including in patients with indication for cardiac resynchronization. It may be a definite alternative for patients with great difficulty in cannulating the coronary sinus or who do not have a suitable vein for implantation of the LV lead, those with unacceptably high pacing threshold or phrenic nerve entrapment. However, physiologic pacing has the disadvantage of lacking the option of defibrillation, and studies who explore the use of defibrillation lead for left ventricular pacing with Hisian or IBBAP (Interventricular Bundle Branch Area Pacing) pacing are still limited. As research evolves, further evaluation of the efficacy and safety of physiologic pacing compared with CRT is needed, particularly in terms of ventricular arrhythmia prevention and long-term benefits(28).

Limitations

In the present study, all the electrocardiographic data was acquired manually, making this method still user-dependent despite having precise software measurement tools (i.e., IC Measure[8]) and well-trained physicians. Perhaps digitizing the process would make data recording more exact and less time-consuming. Also, determining EF echocardiographically is a user-dependent method. Next, it is known that optimization occurs within a few hours to a few days after CRT device implantation. Still, a small study emphasizes that the QRS duration can remain the same in the first 6 postprocedural months(29) and aspects regarding the QRS area are yet to be researched.

Another limitation of this study is the relatively small sample size of 69 patients enrolled over a 6-year period. While the findings offer valuable insights into the relationship between electrocardiographic parameters and changes in ejection fraction following cardiac resynchronization therapy (CRT), the limited cohort size restricts the generalizability of these results. Although statistically significant for this analysis, the study population may not fully reflect the broader spectrum of heart failure patients undergoing CRT. To enhance the applicability of these findings, future studies should include larger and more diverse patient cohorts. Expanding the sample size would not only validate the correlations observed here but also refine predictive models for CRT outcomes, ensuring their relevance across various patient demographics and clinical contexts.

Conclusions

This study provides insights into the relationship between electrocardiographic parameters and the evolution of left ventricular ejection fraction (LVEF) following cardiac resynchronization therapy (CRT). Key findings highlight the importance of parameters such as Q-LV interval, QRS area difference, QS wave duration, and immediate post-implant systolic blood pressure variation in predicting CRT effectiveness. Among these, the Q-LV interval emerged as a critical determinant, with a longer post-CRT interval significantly associated with better electrical synchronization and hemodynamic improvements.

Similarly, the reduction in QRS area and duration reflects enhanced ventricular depolarization efficiency, indicating effective electrical remodeling in responders. The rise in systolic blood pressure immediately after CRT underscores its role as a straightforward and practical clinical marker for assessing acute therapeutic success. Together, these parameters align with the core goals of CRT: optimizing electrical synchrony, improving cardiac output, and enhancing clinical outcomes.

Additionally, this study emphasizes the value of regional markers such as QS wave durations in leads I and aVL, which reflect delayed activation in lateral and high-lateral myocardial segments—key regions targeted by CRT. These findings, along with the derived parameter (S1+R6) - (S6+R1), provide unique insights into ventricular electrical force redistribution and its correlation with mechanical and clinical improvements. The ability to monitor and integrate these electrocardiographic parameters into clinical practice could refine patient selection, optimize therapy programming, and enhance predictive models for CRT success. Future research should validate these findings in larger, more diverse cohorts to ensure broader applicability and to further strengthen the predictive utility of these markers in CRT.

Author Contributions

Conceptualization, A.-M.R., A.-L.R., O.-A.P, C.-J.S.; Methodology, E.-S.R., F.-L.T., T.-G.B, C.-J.S.; Software, T.-G.B., M.-D.T., A.-L.R.; Validation, A.-L.R., A.-M.R., L.-C.A., E-S.R.; Formal analysis, E.-S.R., M.-D.T., L.-C.A., C.-J.S.; Investigation:, A.-.M.R., O.-A.P.; Resources, T.-G.B., L.-C.A.; Data curation, T.-G.B., E-S.R., C.-J.S.; Writing- original draft preparation, A.-M.R., T.-G.B., C.-J.S.; Writing—review and editing, T.-G.B., E.-S.R.; Visualization, A.-L.R., T.-G.B., O.-A.P., L.-C.A.; Supervision, A.-M.R., E.-S.R., M.-D.T., F.-L.T.; Project administration, T.-G.B, O.-A.P., A.-M.R.; Funding acquisition, A.-M.R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Carol Davila University of Medicine and Pharmacy (15037/05.06.2017).

Informed Consent Statement

Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement

Data are contained within the article.

Conflicts of Interest

Andreea-Liana Roșu is employed by the company BBraun, but they were not part in our study. The authors declare no conflicts of interest.

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