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**ECG CHANGES BEFORE AND AFTER CARDIAC RESYNCHRONIZATION
THERAPY AS PREDICTORS OF A POSITIVE RESPONSE TO THERAPY**

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THE GENERAL STATE OF CURRENT KNOWLEDGE

Cardiovascular disease is the leading cause of morbidity and mortality and has historically been a major burden on both the health system and the health insurance system. In recent years, around 18 million deaths have been reported from cardiovascular disease, and by 2035 the death rate is expected to increase by at least 30%. Predisposing risk factors for cardiovascular disease include hypertension, hyperlipidemia, obesity, obesity, diabetes mellitus, smoking and physical inactivity(1,2).

Heart failure affects more than 23 million people worldwide, with the incidence gradually increasing at a rate of about 2 million new cases a year. It is a chronic, progressive and usually irreversible disease, which results in the heart muscle being unable to pump the heart muscle, eventually failing to provide adequate oxygen and nutrients to the body. Of all patients with heart failure, a relatively high percentage, about 30%, have electrocardiographic changes such as left bundle branch block. It is therefore assumed that there is an underlying electrical substrate underlying the heart failure and thus these patients may be candidates for cardiac resynchronization therapy under certain conditions.

Although the presence of left bundle branch block is a fundamental aspect in the selection of candidates for cardiac resynchronization therapy, it is important to keep in mind that this condition is complemented by a number of other criteria that will be discussed in the general part of this paper. Currently, cardiac resynchronization is one of the main therapies used for heart failure, aiming to increase the quality of life and decrease mortality in the medium term in more than one third of cases. In addition to medical therapy, implantation of cardiac resynchronization devices has come to be considered a standard therapy for heart failure refractory to other treatments and has been shown to improve symptoms, quality of life and survival, as well as cardiac remodeling. The efficacy of cardiac resynchronization has been demonstrated in patients with moderate and severe heart failure, not only in those with mild heart failure symptoms.

In medical practice, it has been observed over time that, despite rigorous patient selection based on strict criteria, a relatively high percentage of patients do not show improvement in heart failure or notable improvements in quality of life. Although clinical response to cardiac

resynchronization therapy is evident in the majority of cases, studies have, however, observed a lack of response in about one third of patients. This is one of the reasons why many experts in the field have tried to identify what other variables should be taken into account to predict the best possible response to resynchronization therapy. Understanding and identifying such predictors, as well as the correlations between them and their association with a positive final outcome, may guide future personalized treatment strategies as well as optimize patient selection for resynchronization therapy, ultimately improving outcomes in people with cardiovascular disease.

A multitude of studies have so far evaluated different parameters, both biohumoral, functional and electrocardiographic, with great international interest in the latter. Thus, the 12-lead electrocardiogram represents a gold standard in the overall management of the patient who is a candidate for or has received cardiac resynchronization therapy.

HYPOTHESIS

My aim in this PhD thesis was to discuss and analyze current data on electrocardiographic predictors in cardiac resynchronization therapy, as well as to conduct a prospective observational study, following which I will identify a series of predictive factors, as well as their correlations and association with different outcomes. I have chosen this topic because I consider it necessary to clarify some standardized pre- and post-implant EKG indications and criteria in order to determine the evolution and prognosis of recovery. I also believe that functional recovery and its impact on the individual's quality of life are key elements in my practice. To date, the publications on pre- and post-resynchronization EKG criteria are not so conclusive, even contradictory opinions are described in the literature.

MATERIALS AND METHODS

Documentation strategy and study organization

The data presented in this paper are based on an extensive bibliography, which includes renowned papers as well as publications by some of the leading experts in the field in high-impact international journals. This bibliography has been meticulously analyzed, and the data will be presented in a way that is as complete as possible, but also easy to follow. The main objective of the PhD thesis is to define electrocardiographic prognostic factors, both positive and negative, in

predicting the functional outcome of resynchronization therapy. I have chosen to organize the data obtained from my research in the form of three studies that I will present in the special part of this paper.

Therefore, the first study aimed to establish parameters with predictive value and to identify their associations with changes in ejection fraction following cardiac resynchronization therapy. We chose ejection fraction as the outcome of this therapy because changes in ejection fraction are the most important overall influence on the health status of patients with post resynchronization heart failure.

The second study presented will provide information on one of the most widely used functional tests, the 6-minute walk test. We have chosen this outcome as it provides a global assessment of the different systems involved during physical activity and has the advantage of being a simple, inexpensive and quick test that helps to determine the degree of functional impairment. Again, we considered a number of correlations with electrocardiographic, functional and demographic parameters.

The third study of the special part of my PhD thesis will be centered on the analysis of some associations between the above mentioned electrocardiographic, functional and demographic parameters and the variability of the results of the KCCQ - Kansas City Cardiomyopathy Questionnaire. This questionnaire is considered to be the most comprehensive and well-studied clinical tool for predicting quality of life and clinical outcomes of patients in daily life. We considered this tool to be particularly important because unlike functional or laboratory tests, it integrates the patient's perception of their own health status. It is also a reminder that beyond all therapeutic methods, laboratory tests and various indices and parameters, we are treating patients, not only pathologies, and this test provides us with data on aspects such as physical condition and social integration, perception of symptomatology, knowledge about one's own health, self-efficacy and the patient's overall quality of life.

I must emphasize the interdisciplinary nature of the approaches taken in the realization of this doctoral thesis. The study involved close collaboration with specialists from several fields, as the patients included in the research received the best medical care provided by the hospital unit where the study was carried out. This interdisciplinary collaboration was essential for an efficient integration of the patients' clinical data and played a crucial role in understanding the results

obtained. Thus, by involving specialists from different fields, we ensured a comprehensive approach and proper interpretation of our study results.

Patient sample and eligibility criteria for inclusion in the study

A total of 69 patients diagnosed with heart failure, left bundle-branch block (LBBB) and low left ventricular ejection fraction who underwent cardiac resynchronization therapy between 2017 and 2022 were enrolled in this prospective observational study. The study endpoints were related to improvement in patients' hemodynamic status, quantified by an improvement in ejection fraction, which was measured at four time points: pre-procedure, 6 months, 9 months and 12 months post-procedure. To be eligible for cardiac resynchronization therapy (CRT), patients had to have a left ventricular ejection fraction (LVEF) $\leq 35\%$ or moderate to severe left ventricular systolic dysfunction on the most recent echocardiography, SPECT analysis, contrast ventriculogram, or magnetic resonance imaging. When available, the most recent left ventricular ejection fraction measurement was used for multiple assessments(3). In line with previous studies, ejection fraction measurements older than 1 year were considered if they were still relevant and updating was not necessary if the documented dysfunction remained unchanged and the treatment was not modified(4).

Patients were excluded when they met the following criteria: those with unipolar or bipolar pacemakers or candidates for device replacement, people with psychiatric disorders that prevented return to medical management, those who did not demonstrate consistent adherence to medical treatment, and those with recent infections or considered to be at very high risk for device-related infections.

Technical aspects of the cardiac resynchronization procedure

Electrode placement is one of the fundamental steps in CRT procedures, and detailed information on the location and depth of the scar and its possible transmural extension allows the physician to choose an alternative stimulation site from postero-lateral, anterolateral and lateral areas(5). This is why we performed cardiac MRI in patients with documented ischemia to identify

myocardial scar tissue and quantify its extent and to prevent inappropriate placement of the left ventricular electrode in scar regions.

Cardiac ultrasound and ejection fraction measurement

The left ventricular ejection fraction (LVEF) is determined by numerous modalities such as echocardiography, CT, MRI, cardiac nuclear imaging, radionuclide angiography, single photon emission computed tomography, positron emission tomography technique and left ventricular contrast ventriculography during invasive catheterization. For this study, we used biplane echocardiography to assess left ventricular ejection fraction. It is a simple and easily reproducible technique and is recommended by almost all cardiology societies. The left ventricular ejection fraction was measured by tracing the endocardial border in the apical four-chamber window and in the two-chamber view at the end of systole and end of diastole, according to ECG(6). The end-systolic volume image was defined as the frame preceding 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(7).

The measurements were performed in a correct and uniform manner to overcome one of the biggest problems of the Simpsons Biplan method, namely the shortening of the left ventricular cavity(8). In accordance with anatomic relationships, measurements were performed with a basal plane perfectly perpendicular to the left ventricular apex.

Electrocardiographic data

Patients included in this study received electrocardiograms pre-procedurally, post-procedurally and at all time points of return to control. Electrocardiograms were performed in the 12 standard leads using electrocardiograms provided by the cardiology department of the hospital.

The more complicated part was the measurements of the various waves, intervals or complexes on the electrocardiogram. In most of the cases described in the literature we reviewed, both the initial and post-implantation electrocardiographic data of the resynchronization devices were obtained from digitally stored information. Unfortunately, the possibility of working with digitally stored electrocardiographic data is still a luxury in most medical facilities in our country, because not all hospitals have access to modern technique. For example, in studies of the QRS

complex area, electrocardiograms were converted almost automatically, their authors were able to easily extract the data from digital signals. This allowed them to convert the 12-lead electrocardiogram into a vectorcardiogram which was then used to calculate the three orthogonal vectorcardiogram leads X, Y, Z using an algorithm based on the Kors (9), and finally obtain the area of the QRS complex.(10)

In the present study, we had to stick to the usual paper-based electrocardiograms, and extracting data from paper-based electrocardiograms was a laborious process. Also, in our country, paper-recorded data as well as paper-recorded electrocardiograms are the most common source of data, as the healthcare system is currently undergoing a large digitization process, but it still has a long way to go. These are the reasons why we tried to see if there is any correlation between the area of the surface QRS complex on the paper electrocardiogram and the outcome after cardiac resynchronization therapy. Moreover, for most physicians, analyzing digital signals (be it ECG or EMG) using complex software or programming language would be a difficult task and this is also the reason why I tried to design a very simple method that could be accessible to almost everyone. Also, it is important to mention that in this research we used only freeware software, which makes this method cheap and can be applied by anyone.

Electrocardiograms on paper were scanned using a Canon PIXMA TR4650 multi-functional printer scanner at a resolution of 600dpi, and various parameters were measured using a free software called IC-Measure(11). The software gives the user the possibility to import the scanned images (Figure 1) and to perform a precise calibration using the built-in microscope. The distances were calibrated on the large 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 duration of 40 milliseconds or 0.04 seconds, and on the vertical axis 1 millimeter to 0.1 millivolts. (Figure 2)

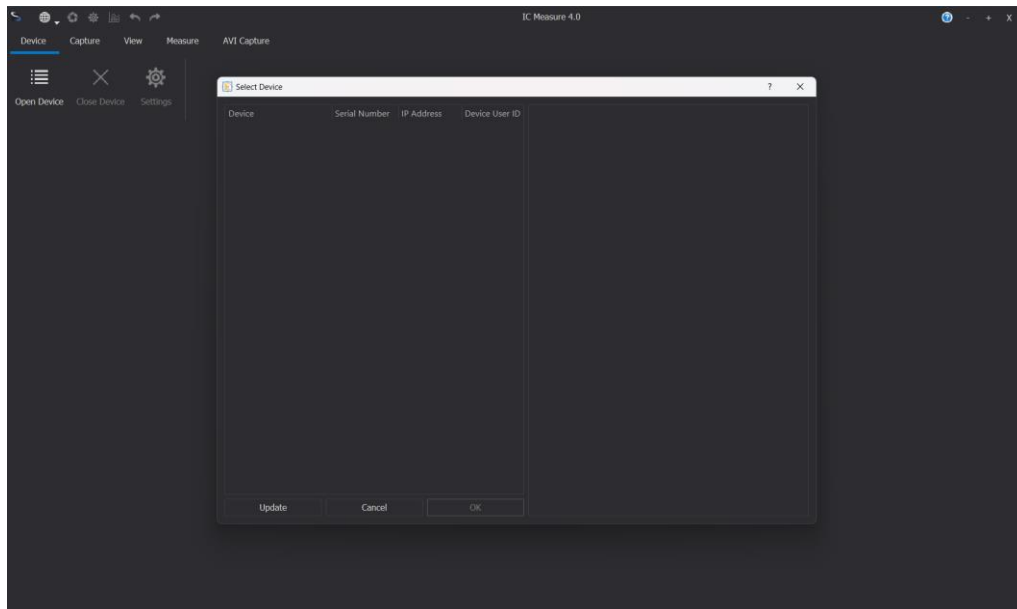


Figure 1: The IC Measure software allows the import of scanned images using the OPEN DEVICE option, which opens a sub-menu where the images to be analyzed can be searched. By then accessing the MEASURE menu on the top row, the necessary calibrations can be performed to take the measurements

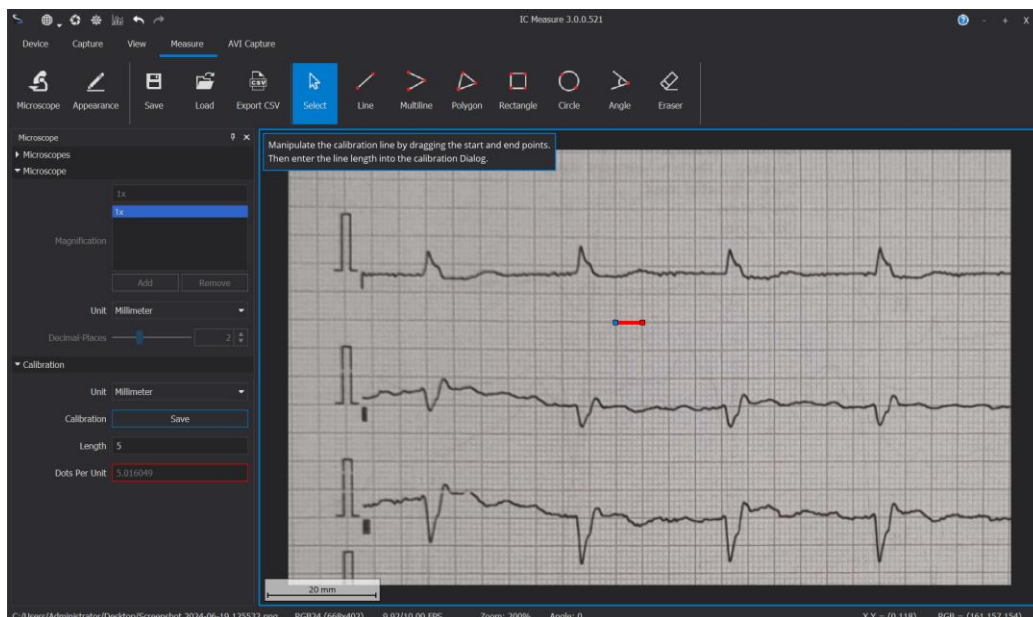


Figure 2: Calibrating instruments for electrocardiogram measurements

Finally, everything was recorded in our database and statistical analysis was performed using R. For this work, the outcome analyzed was the evolution of left ventricular ejection fraction (EF), which was measured before the procedure and then at three time points post-procedure: 6, 9 and 12 months, respectively.

I have been trying to discover an alternative method to obtain a vectorcardiogram to help me calculate the area of QRS complexes in the absence of digital data. The new method was, however, particularly complicated and I will only present it in this context for scientific interest.

Researchers at Beth Israel Deaconess Medical Center and Imperial College London have succeeded in creating an online tool that allows the user to select the corresponding image of a scanned electrocardiogram and the software to perform an artificial intelligence analysis. Thus, starting from a simple image, the program can translate the graph into a digital signal that will be recorded in a table with 13 columns: the first one corresponding to the time, expressed in milliseconds, and the others corresponding to the amplitudes recorded for each lead. The online program also reproduces this information graphically (Figure 3).

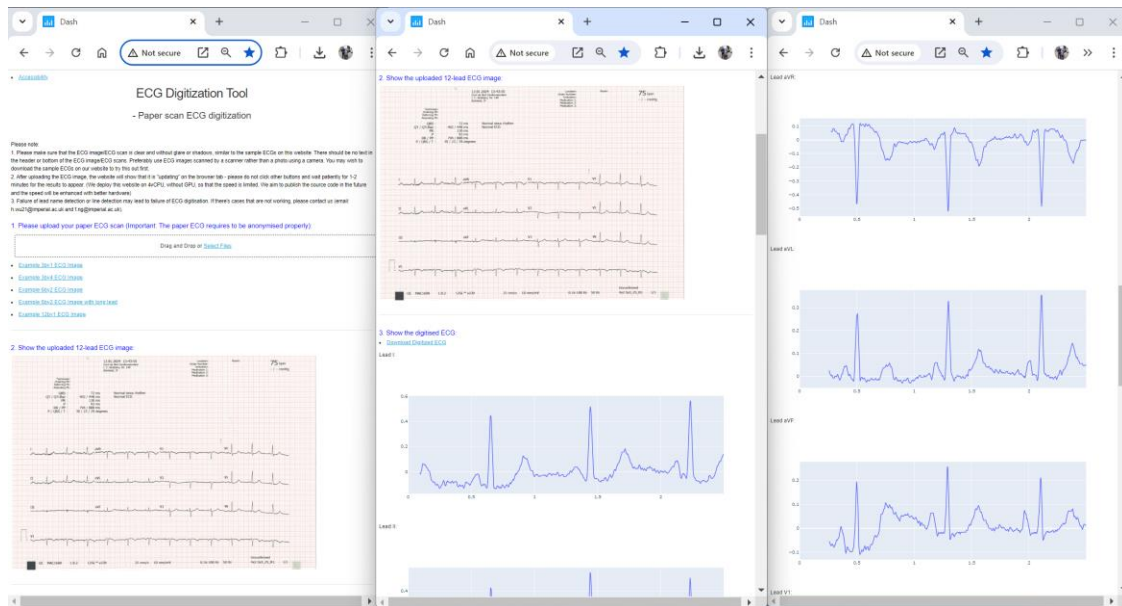


Figure 3: Online software provided free of charge by Beth Israel Deaconess Medical Center and Imperial College London that allows you to upload electrocardiogram scans to extract the appropriate signal for each lead.

As mentioned above, the obtained signals can be downloaded as an Excel table and further processed. In Figure 4, the first 13 columns are those obtained using the online software, while columns N, O, P represent the new orthogonal derivatives of the vectorcardiogram obtained using the Kors conversion matrix (Table 1). This algorithm allows obtaining the signals for the X, Y, Z derivatives based on mathematical calculations.

Lead	I	II	V1	V2	V3	V4	V5	V6
X	0,38	-0,07	-0,13	0,05	-0,01	0,14	0,06	0,54
Y	-0,07	0,93	0,06	-0,02	-0,05	0,06	-0,17	0,13
Z	0,11	-0,23	-0,43	-0,06	-0,14	-0,20	-0,11	0,31

Table 1: Derivations and their coefficient used to obtain vectorcardiographic derivations X, Y, Z.

The signal for each orthogonal derivative X, Y, Z is calculated as follows:

- $X = 0,38 \times DI - 0,07 \times DII - 0,13 \times V1 + 0,05 \times V2 - 0,01 \times V3 + 0,14 \times V4 + 0,06 \times V5 + 0,54 \times V6$
- $Y = -0,07 \times DI + 0,93 \times DII + 0,06 \times V1 - 0,02 \times V2 - 0,05 \times V3 + 0,06 \times V4 - 0,17 \times V5 + 0,13 \times V6$
- $Z = 0,11 \times DI - 0,23 \times DII - 0,43 \times V1 - 0,06 \times V2 - 0,14 \times V3 - 0,20 \times V4 - 0,11 \times V5 + 0,31 \times V6$

Using this algorithm, we computed in columns N, O, P the orthogonal derivatives X, Y, Z (Figure 4). These were plotted as graphs on the left of the image using the Plot Graph function.

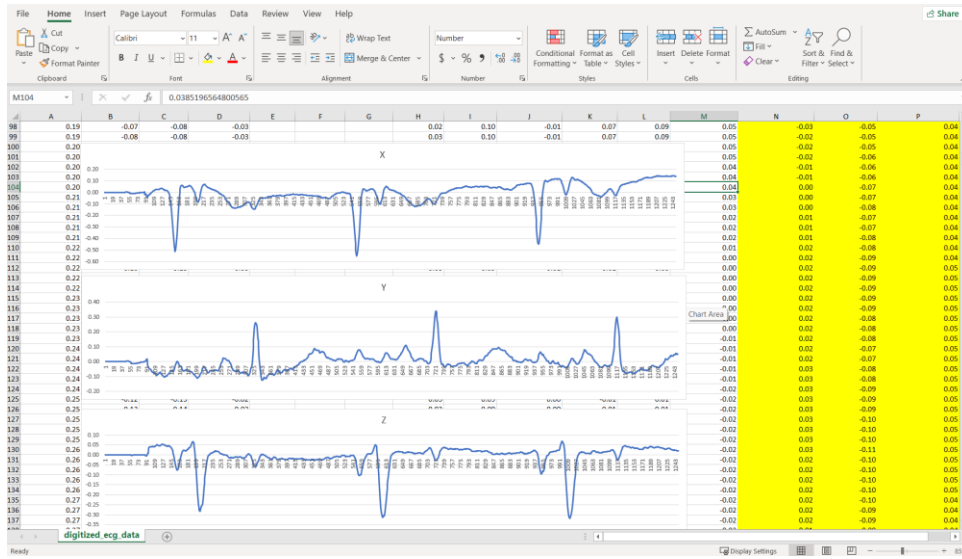


Figure 4: Table with the signals of the 12 leads processed online and the three vectorcardiographic leads, with yellow on the left side

The area of the QRS complex in each of the three leads was calculated using a formula for determining the area under the subgraph, which was based on the assumption that each curve, complex or deflection can be divided into numerous trapezoidal segments. Therefore, the area of each individual trapezoid was calculated and then summed. In short, the formula used was of the type Area of a trapezoid = $(N1+N2)/2 \times A1$, where N1 and N2 represented the amplitudes in the orthogonal derivative X at 2 different times, and for the formula used these were the two bases of the trapezoid, while A1 represented the time interval between the times corresponding to the two amplitudes and represented the height of the trapezoid in our formula. There is no direct way to calculate the area under a graph in excel, but this method can be extremely useful. Finally, the area of an entire QRS complex was calculated using the SUM function applied to a range of rows corresponding to the start and end of the QRS complex. The entire area of a vectorcardiographically determined QRS complex was finally determined using the formula **QRS Area** = $\sqrt{[X^2 \text{ area} + Y^2 \text{ area} + Z^2 \text{ area}]}$ (12).

This very complex method was used in this study only experimentally to test the veracity of the data. I limited myself to the calculation of a mean value of the areas on the surface electrocardiogram, as I wanted to obtain a quick and simple to apply method. Concerning the other electrocardiographic parameters measured and added to the database, their determination was

much simpler once I had calibrated the IC Measure software, as these were just simple linear measurements, which were transformed into microvolts or milliseconds after setting up some formulas in Excel spreadsheets.

Monitored parameters

Parameters such as QRS duration(13), ischemia and BiV pacing percentage(14) are well-documented topics in the literature, but we have also added in this study morphology elements such as QRS complex area (15)(10), The blood pressure monitored during the procedure(16) and the evolution of ejection fraction could be used as predictors, as these are recently proposed topics. After measuring these parameters on electrocardiograms, they were recorded in the database. Intraprocedural systolic blood pressure was also monitored by means of a 5French intra-arterial catheter mounted in the radial or femoral artery, and the variations were recorded.

To summarize, in this study, we considered the following clinical, biological and electrocardiographic parameters: age, gender, background (urban/rural), hemoglobin, creatinine, NT-proBNP level (reported per 100), presence of ischemic cardiac pathology, atrial fibrillation, diabetes mellitus, VSTD index value, systolic blood pressure response to the start of the resynchronization machine (>5 mmHg), QRS complex duration, QRS complex area, R-wave amplitude in the aVR lead, R-wave amplitude in the right precordial leads, biventricular pacing percentage, QS wave duration in the DI and aVL leads, R/S fraction, and the deviation resulting from the formula $(Sv1 + Rv6) - (Rv1 + Sv6)$. These parameters were included to assess potential predictors of response to cardiac resynchronization therapy.

Statistical analysis

R, version 4.2.3 Copyright (C) 2023 The R Foundation for Statistical Computing, R Core Team (2023) was used for statistical analysis.(17).

In the following, I will summarize the data that I have obtained from my work and present for each study the premises, main results and conclusion.

Study I: Contributions to the study of correlations between clinical, demographic parameters and electrocardiographic predictors and ejection fraction variability as outcome of cardiac resynchronization therapy

Premises

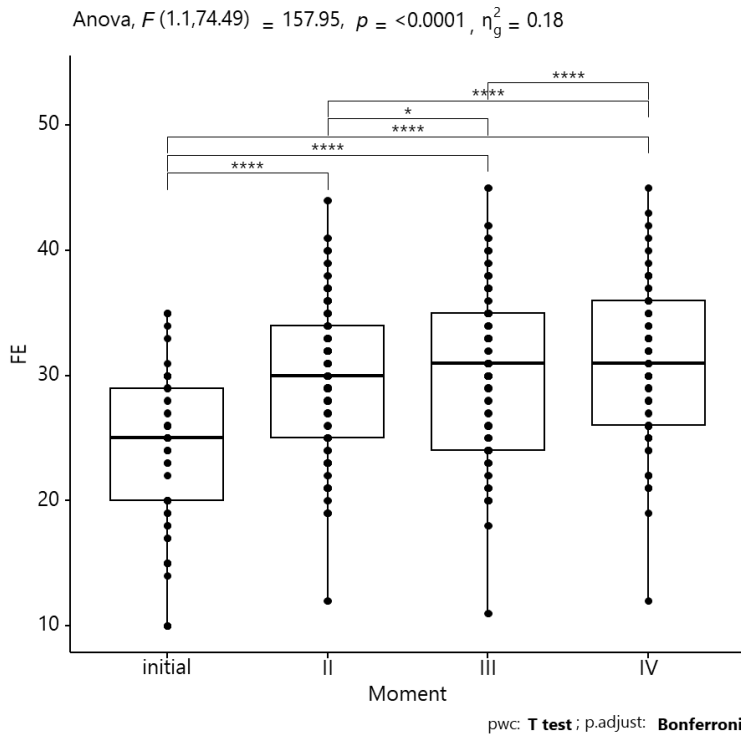
Cardiac resynchronization therapy (CRT) has revolutionized the management of heart failure associated with conduction abnormalities. Studies have shown that by synchronizing ventricular contraction (18) and cardiac remodeling (19), resynchronization therapy makes an important contribution to increasing ejection fraction in these patients and improving exercise tolerance and quality of life, as well as reducing mortality and the rate of heart failure-related events.

Following a review of the literature, we found that other authors have attempted to correlate various predictors with the evolution of ejection fraction, but to date there is relative uncertainty in this regard, some opinions are even contradictory. An interesting study by Vernooij and co-workers(10), aimed to correlate the QRS complex area and the pre- and post-procedural area difference with echocardiographic response (quantified by left ventricular ejection fraction) and long-term outcome of patients. They hypothesized that a greater difference between the QRS complex areas measured pre- and post-procedurally would correlate with better outcomes. I also set out to explore this in my research, in addition to other established predictors.

Results

After analyzing the variation in ejection fraction over a 12-month period for patients undergoing cardiac resynchronization therapy, it was possible to compare different measurements. The ejection fraction measurements were obtained at four key time points: the baseline assessment and subsequent assessments at 6, 9 and 12 months. The mean ejection fraction in this cohort showed a progressive trend, with the initial assessment revealing a mean ejection fraction of 23.30% with a standard deviation of 6.45%. At 6 months, the ejection fraction increased to 29.80% +/-6.29%. Assessment at 9 months showed a further improvement - 30.10% and a standard deviation of 6.51%, reaching a maximum of 30.90% (standard deviation: 6.38%) at the 12-month assessment

To determine whether the differences were statistically significant, an ANOVA test was used. The test result ($F(1.1, 74.49) = 157.95, p < 0.0001$) shows that there were statistically significant differences across all follow-up time points. A post-hoc procedure, using Bonferroni-adjusted paired T-tests, revealed that there were statistically significant differences in ejection fraction values at all follow-up moments; however, clinically important significance was observed mainly between the initial ejection fraction value and the ejection fraction values at the subsequent time points (Figure 1).



Predictors for which the associated p-value was less than 0.05 were included in a univariate multiple linear regression. Then, we applied a backward selection algorithm and built a model in which all predictors had statistically significant influences. We created a table containing the predictors that showed statistical significance (Table below).

Figure 5: ANOVA test to determine whether the differences between the ejection fraction values measured at different time points were statistically significant.

The analysis identified several significant predictors of ejection fraction improvement following cardiac resynchronization therapy. The left ventricular end-diastolic volume was negatively associated with the change in ejection fraction, with each 1 mL increase correlating with an average decrease of 0.02%. Similarly, both QRS duration and QRS area showed negative associations: a 1 ms decrease in QRS duration correlated with an average increase of 0.10% in ejection fraction, while a 1 mm² decrease in QRS area was associated with an average increase of 0.07%.

	FE		
Predictors	Estimates	CI	p
(Intercept)	54.55	48.86 – 60.23	<0.001
VSTD	-0.02	-0.04 – -0.00	0.017
QRS duration	-0.10	-0.12 – -0.08	<0.001
QRS area	-0.07	-0.08 – -0.06	<0.001
R amplitude in right precordial leads	1.44	0.35 – 2.53	0.010
Random Effects			
σ^2	3.72		
τ_{00} ID	29.68		
ICC	0.89		
N ID	69		
Observations	276		
Marginal R ² / Conditional R ²	0.517 / 0.946		

In contrast, the amplitude of the R wave in the right precordial leads (V1 and V2) emerged as a positive predictor, with a 1 mm increase being associated with an average increase of 1.44% in ejection fraction.

The statistical model used explained approximately 95% of the variation in ejection fraction, with 52% attributed to fixed effects and 43% to random effects.

Conclusion

The study confirms that the reduction in QRS area and duration following cardiac resynchronization therapy is significantly correlated with improvement in ejection fraction. Additionally, ejection fraction was directly proportional to systolic blood pressure and inversely proportional to left ventricular end-systolic volume. The identified correlations support the concept of effective cardiac remodeling and may contribute to more personalized treatment strategies and better selection of patients eligible for CRT.

Study II: Contributions to the Study of the Correlations Between Clinical, Demographic, and Electrocardiographic Predictors and the Outcomes of the 6-Minute Walk Test Used as an Endpoint for Cardiac Resynchronization Therapy

Premises

The six-minute walk test (6MWT) is a simple and accessible method for assessing functional capacity in patients with cardiopulmonary conditions. It involves covering the greatest possible distance within six minutes, along a marked course, under controlled conditions. Before, during, and after the test, parameters such as oxygen saturation, heart rate, blood pressure, and the degree of dyspnea and fatigue (using the Borg scale) are monitored. The test reflects the integrated response of multiple systems and is useful for evaluating disease severity and treatment response.

Cardiac resynchronization therapy (CRT) is an essential intervention for patients with heart failure, particularly in the presence of an electrical substrate characterized by delayed activation of the left ventricle. This dyssynchrony contributes to impaired systolic function and worsening of symptoms (3). Although cardiopulmonary exercise testing remains the gold standard for assessing exercise capacity, the six-minute walk test is increasingly used in clinical practice for monitoring and adjusting treatment(4) In this context, the present study aimed to analyze whether performance on the six-minute walk test correlates with changes in electrocardiographic and hemodynamic parameters after CRT, such as QRS complex area and duration, percentage of biventricular pacing, and intraprocedural systolic blood pressure, with the goal of anticipating postprocedural outcomes(20).

Results

After analyzing the six-minute walk test distances in patients undergoing cardiac resynchronization therapy, comparisons were made across different time points. The test was performed at four intervals: pre-procedurally, and at 6, 9, and 12 months post-procedure. Initially, the mean distance walked by the subjects was 240.6 meters, with a standard deviation of 63.5 meters. At 6 months, the distance increased to 286.7 meters (SD: 72.5 meters). At 9 months, a further improvement was observed, with a mean distance of 291 meters and a standard deviation of 75.2 meters, culminating in a peak of 297.2 meters (SD: 77.2 meters) at the 12-month follow-

up. An ANOVA test was used to determine whether the differences were statistically significant. The test result ($F(1.1, 74.36) = 82.10, p < 0.0001$) indicates that there were statistically significant differences across the follow-up time points. A post-hoc procedure, using Bonferroni-adjusted paired t-tests, showed that there were statistically significant differences in the six-minute walk distance at all follow-up points; however, clinically meaningful differences were observed between the baseline value and the values at the subsequent time points (Figure 3).

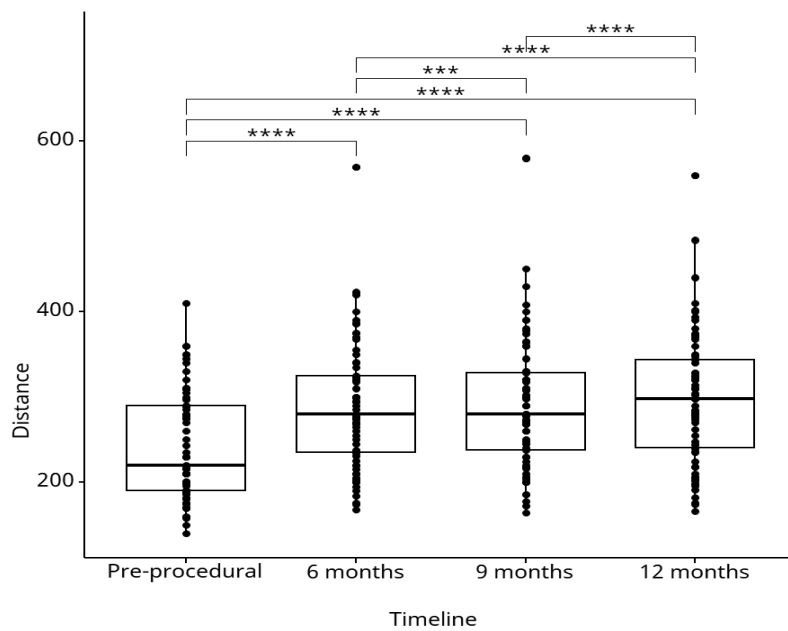


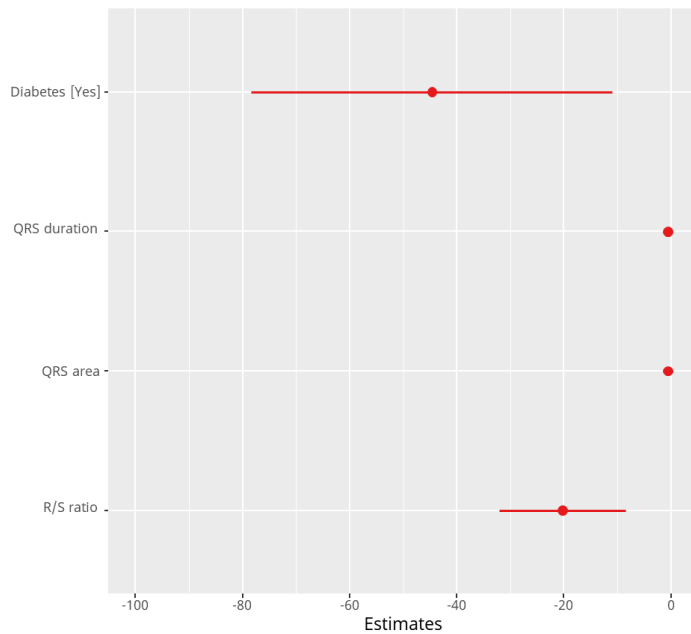
Figure 3: ANOVA Analysis of the Distance Walked at Key Follow-Up Time Points

The correlation analysis between clinical, biological, and electrocardiographic parameters and the distance walked during the six-minute walk test identified several statistically significant predictors. Among these, creatinine and NT-proBNP levels were negatively associated with physical performance, suggesting that renal function and the degree of cardiac decongestion influence exercise capacity. Additionally, the presence of diabetes mellitus and higher values of left ventricular end-systolic volume (LVESV) were negatively correlated with the distance walked, indicating further functional impairment in these patients. Intraprocedurally measured systolic blood pressure, particularly increases greater than 5 mmHg, showed a positive correlation,

reflecting a potentially favorable hemodynamic recovery. Regarding electrocardiographic parameters, QRS duration and area were strongly negatively associated with the walking distance, while a higher percentage of biventricular pacing (BIV pacing) was positively correlated. Finally, the R/S ratio showed a significant negative correlation, supporting its potential role as an additional electrocardiographic marker in evaluating functional response.

	6-minutes walk test		
Predictors	Estimates	CI	p
(Intercept)	474.88	441.15 – 508.61	<0.001
Diabetes – Yes	-44.65	-78.36 – -10.95	0.010
QRS duration	-0.62	-0.81 – -0.44	<0.001
QRS area	-0.61	-0.76 – -0.47	<0.001
R/S fraction	-20.29	-32.09 – -8.48	0.001
Random Effects			
σ^2	473.02		
τ_{00} ID	4758.94		
ICC	0.91		
N ID	69		
Observations	276		
Marginal R^2 / Conditional R^2	0.336 / 0.940		

Predictors with an associated p-value less than 0.05 were included in a univariate multiple linear regression. Then, using a backward selection algorithm, a model was built including all predictors that had statistically significant influences (see adjacent table). From the table, it can be observed that in patients with diabetes, the distance walked during the six-minute walk test decreased by 44.65 meters. QRS duration was negatively associated with test results, with a 1 ms decrease in QRS duration being associated with an average increase of 0.62 meters in the distance walked.



Additionally, QRS area was negatively associated with the distance walked, with a decrease of 1 mm² being associated with an increase of 0.61 meters. The R/S ratio was also negatively associated with the six-minute walk distance (6MWD); an increase of 1 unit in the R/S ratio was associated with an average decrease of 20 meters in the distance walked. The model explains 94% of the variation in the six-minute walk distance, with 34% explained by fixed effects and 60% by random effects (Figure 4).

Figure 4: Model explaining the variation in the six-minute walk distance, with 34% accounted for by fixed effects and 60% by random effects.

Conclusion

In summary, the six-minute walk test can provide an accurate reflection of a patient's daily activity level and short-term prognosis, especially in those with heart failure and reduced ejection fraction. It is inexpensive, easy to perform, and requires relatively less time compared to maximal exercise tests, such as cardiopulmonary exercise testing (CPET). Based on our results and the correlations with well-established predictors, we observed that the test can offer clinicians valuable insight into the prognosis of patients who have undergone cardiac resynchronization therapy. In my opinion, future research should focus on developing a standardized methodology for this test and providing more precise reference values to enable more accurate predictions after cardiac resynchronization therapy.

Study III: Contributions to the Study of the Correlations Between Clinical, Demographic, and Electrocardiographic Predictors and the Outcomes Measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) as an Endpoint for Cardiac Resynchronization Therapy

Premises

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a reliable tool used to quantify quality of life in patients who have undergone cardiac resynchronization therapy (21,22). It is considered the most comprehensive and well-studied clinical tool for predicting overall well-being and clinical outcomes in real-world settings(23). Research suggests that the KCCQ may be more accurate than the NYHA functional class in assessing outcomes for patients with cardiomyopathy and reduced ejection fraction(24). A study conducted by Stephen Greene and collaborators suggests that the NYHA class has low reproducibility, as it assesses the severity of a patient's heart failure based on the perceived difficulty in performing daily activities—a perception that can vary considerably between patients. This cohort study, which included 2,872 patients evaluated over 12 months, showed that the prognostic value of NYHA classification is also less relevant compared to the KCCQ: an improvement of 5 or more points in the KCCQ score was independently associated with reduced mortality, whereas improvement in NYHA class was not (24). According to M.B. Kronborg and J.C. Nielsen, approximately 30–50% of patients undergoing resynchronization therapy do not benefit from the treatment and are thus considered non-responders. Potential candidates for this procedure often have comorbidities such as ischemic cardiomyopathy, renal dysfunction, or diabetes. Despite its high success rate, the implantation of a resynchronization device carries a higher risk compared to other electronic implantable devices. Their study shows that the KCCQ could be very useful in identifying non-responders, and these patients might greatly benefit from closer post-procedural follow-up (25).

Results

After analyzing the variation in KCCQ scores over a 12-month period in patients undergoing cardiac resynchronization therapy, it was possible to compare different measurements. The KCCQ score was obtained at four key time points: the initial evaluation and follow-up evaluations at 6, 9, and 12 months. The mean KCCQ score in this cohort showed a progressive trend, with the initial assessment revealing an average score of 33.70 points with a standard

deviation of 11. By the 6-month mark, the score increased to 52.90 ± 15.7 points. The 9-month evaluation showed a further improvement to 53.40 points with a standard deviation of 16 points, culminating in a peak of 54.50 points (standard deviation: 16 points) at the 12-month follow-up (Figure 5).

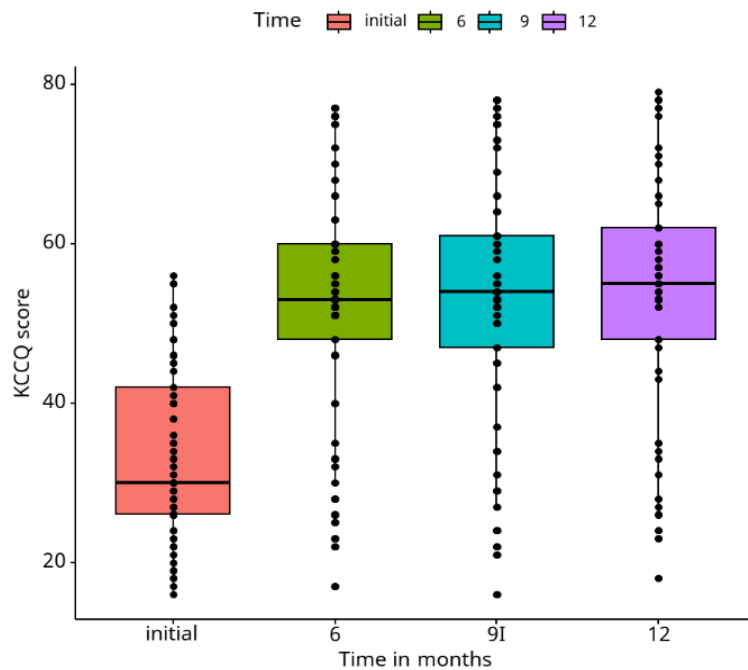


Figure 5. A repeated measures ANOVA test was used to determine whether the differences were statistically significant. The test result ($F(1, 70) = 179.42$, $p < 0.0001$) indicates that there were statistically significant differences between the follow-up time points. In my study, several parameters were identified as significantly correlated with the clinical outcome analyzed. The presence of ischemia was associated with a significant decrease in the clinical score ($\beta = -$

6.9, $p = 0.042$), while an increase of >5 mmHg in systolic blood pressure during the procedure was correlated with a significant improvement in the score ($\beta = 20$, $p < 0.001$). Electrocardiographic parameters, such as QRS complex duration and area, showed strong negative associations ($\beta = -0.43$ and $\beta = -0.33$, $p < 0.001$), suggesting that a greater degree of electrical dyssynchrony is linked to a less favorable clinical course. Additionally, the percentage of biventricular pacing was positively correlated with the clinical outcome ($\beta = 4.2$, $p = 0.013$), indicating the beneficial impact of effective resynchronization. Moreover, the duration of the QS wave in lead aVL showed a significant negative association ($\beta = -0.10$, $p = 0.029$), suggesting a potential additional predictive value in assessing treatment response.

	KCCQ		
Predictors	Estimates	CI	p
(Intercept)	101.23	92.61 – 109.85	<0.001
Increase of > 5mmHg of the intraprocedural blood pressure	10.80	3.17 – 18.42	0.006
QRS duration	-0.28	-0.32 – -0.23	<0.001
QRS area	-0.19	-0.22 – -0.15	<0.001
Random Effects			
σ^2	31.32		
τ_{00} ID	181.79		
ICC	0.85		
N ID	69		
Observations	276		
Marginal R^2 / Conditional R^2	0.562 / 0.936		

Predictors that showed statistically significant influences in the simple model were included in a multiple model, and then, using a regression algorithm, a table was constructed including all predictors that had statistically significant influences.

The following were observed:

- Independently of the other predictors, an intraprocedural increase of more than 5 mmHg in systolic blood pressure is positively associated with KCCQ evolution, leading to an average increase of nearly 12 points in the KCCQ score.
- Independently of the other predictors, QRS duration is negatively associated with the KCCQ score; a decrease of 1 ms in QRS duration is associated with an average increase of 0.28 points in the KCCQ score.
- Independently of the other predictors, QRS area is negatively associated with the KCCQ score; a decrease of 1 mm² is associated with an average increase of 0.19 points in the KCCQ score.

The model explains nearly 94% of the variance in the KCCQ score, with 56% explained by fixed effects and 38% by random effects (Figure 6).

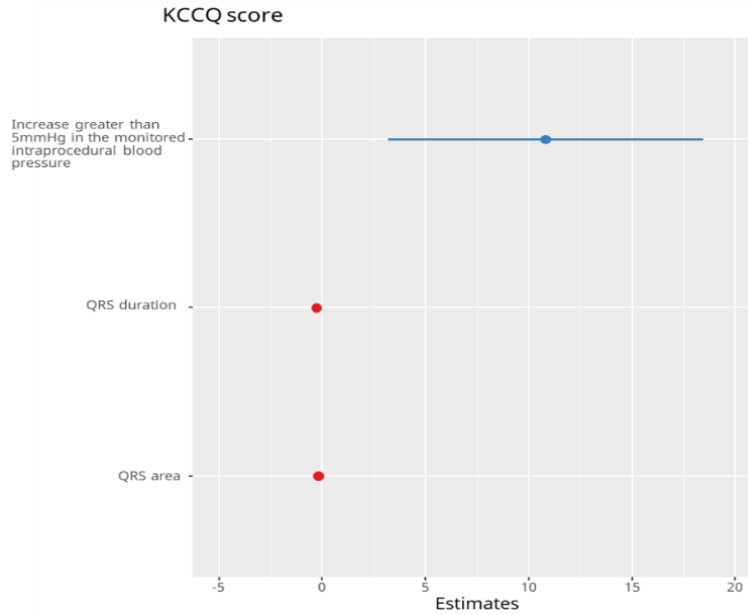


Figure 6: Explanation of the KCCQ Score Variance by Fixed and Random Effects

Conclusion

The reduction in QRS area and duration after CRT, along with an increase in intraprocedurally monitored systolic blood pressure, is associated with both an increase in the KCCQ score and improved outcomes in terms of quality of life, including reduced mortality and morbidity in patients with heart failure and a wide QRS, as well as the early identification of non-responders. We observed a correlation between QRS area and duration, reflecting the severity of ventricular dyssynchrony, and intraprocedural systolic blood pressure, indicating the hemodynamic impact of cardiac resynchronization. Moreover, our findings suggest a nuanced relationship between these electrocardiographic and hemodynamic parameters and patient-reported outcomes assessed through the KCCQ score. While QRS area and duration serve as objective measures of cardiac electrical activity and dyssynchrony, intraprocedural systolic blood pressure provides valuable insight into acute hemodynamic responses. The significant correlations observed with the KCCQ score illustrate how CRT influences quality of life, symptom burden, and functional status in patients. By further understanding these correlations, we can guide personalized treatment strategies, optimize patient selection for interventions, and ultimately improve outcomes for individuals with cardiovascular disease.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

For Study I – Contributions to the study of the correlations between clinical, demographic parameters and electrocardiographic predictors and the variability of ejection fraction as an outcome of cardiac resynchronization therapy (CRT)

Conclusions:

- Reduction of QRS complex area and duration after CRT was significantly associated with improvement in left ventricular ejection fraction (LVEF), highlighting the importance of these parameters as predictors of therapeutic response.
- Intraprocedural monitoring of systolic blood pressure proved to be a determinant factor in ventricular remodeling, indicating the necessity of close monitoring during CRT device implantation.
- Left ventricular end-systolic volume (LVESV) was inversely correlated with post-CRT LVEF, confirming that patients with severe ventricular dilation may have a poorer response to resynchronization therapy.
- Interindividual differences in response to CRT suggest that other electrophysiological and clinical factors also require further investigation for optimized patient selection.
- The study demonstrates that optimizing electrocardiographic parameters before and after the procedure can directly influence the success of resynchronization therapy and should be considered in the therapeutic strategy.

Personal contributions:

- I conducted a detailed analysis of the relationship between QRS area reduction and cardiac remodeling, offering a new interpretation angle for patient selection in CRT.
- I proposed integrating systolic blood pressure monitoring during CRT device implantation as a potential early response marker.
- I highlighted the important role of LVESV as a negative predictive factor, underlining the need for personalized strategies in patients with dilated ventricles.

- My study contributed to a better understanding of the mechanisms through which resynchronization therapy induces positive cardiac remodeling, offering insights into therapy optimization.
- The study contributed to the development of a more objective approach for assessing CRT efficacy, based on electrocardiographic and hemodynamic changes.
- Through this research, I provided new directions for future investigations, suggesting the correlation of electrocardiographic data with advanced imaging parameters for more precise patient selection.

For Study II – Contributions to the study of the correlations between clinical, demographic parameters and electrocardiographic predictors and the results obtained in the six-minute walk test (6MWT) used as an outcome of cardiac resynchronization therapy

Conclusions:

- The six-minute walk test (6MWT) proved to be a reliable predictor of CRT response, showing a significant correlation between increased walked distance and improvement in the clinical condition of patients.
- QRS complex duration was inversely correlated with 6MWT performance, with patients with prolonged QRS initially displaying lower functional capacity but showing significant improvement after CRT.
- Patients who showed significant improvement in the six-minute walk test generally had a more pronounced reduction in QRS duration post-CRT, confirming the impact of resynchronization on ventricular function.
- Reduction of QRS area post-CRT was associated with greater increases in 6MWT distance, suggesting a direct impact of cardiac resynchronization on exercise tolerance.
- NYHA score improved significantly in patients who achieved major increases in 6MWT distance, strengthening the value of this test as a post-CRT evaluation tool.
- Using the walk test as a monitoring method may guide clinical decisions regarding therapy adjustments in CRT patients, optimizing their treatment.

Personal contributions:

- I demonstrated the value of the 6MWT as a practical and accessible method for evaluating CRT efficacy, consolidating its role in clinical practice.
- I highlighted the link between QRS area reduction and increased walked distance in the 6MWT, offering a new perspective on the pathophysiological mechanisms involved in CRT response.
- I contributed to clarifying how different electrocardiographic parameters influence physical recovery of patients post-CRT, an essential aspect in heart failure management.
- The study provides a starting point for future research investigating the association of the 6MWT with other functional, imaging, and biochemical markers.
- My study made an important contribution to the integration of the 6MWT into medical practice for monitoring CRT patients, supporting its value as a non-invasive functional assessment method.
- I demonstrated that the six-minute walk test can be used not only as a post-CRT evaluation tool but also as a long-term prognostic marker in patients with heart failure.

For Study III – Contributions to the study of the correlations between clinical, demographic parameters and electrocardiographic predictors and the results obtained using the Kansas City Cardiomyopathy Questionnaire (KCCQ) as an outcome of cardiac resynchronization therapy**Conclusions:**

- The KCCQ score improved significantly post-CRT in patients who exhibited a marked reduction in QRS area and duration, demonstrating the impact of resynchronization on quality of life.
- Reduction in QRS duration and area was associated with an improvement in patients' perception of their own health status, underlining the importance of electrocardiographic parameters as indicators of therapy response.

- Monitoring systolic blood pressure during CRT device implantation proved to be a useful predictor of the KCCQ score, with patients showing significant increases having a better quality of life.
- A correlation was observed between objective functional improvement (evaluated by LVEF and 6MWT) and subjective health improvement measured by KCCQ.
- Results suggest that the KCCQ score should be used more frequently in clinical studies and practice to quantify the benefits of heart failure therapies.
- Patients who improved in NYHA classes also reported significant increases in KCCQ scores, suggesting that quality of life improvements are closely related to the optimization of heart functional parameters.

Personal contributions:

- I demonstrated that QRS area reduction is a predictor not only of functional improvement but also of increased patient quality of life.
- I emphasized the relevance of using the KCCQ score in the management of CRT patients, providing objective data that supports its clinical value.
- I highlighted the necessity of including KCCQ in clinical routine for monitoring CRT efficacy and adjusting the treatment of heart failure patients.
- I succeeded in contributing to the creation of a solid foundation for future research that could analyze factors influencing the KCCQ score in the long term.
- My study offers a model for the global evaluation of CRT patients, combining objective measurements (electrocardiographic, echocardiographic) with patient self-assessment for a more complete understanding of therapy benefits.

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Scientific Publications

1. **Rosu Andrei-Mihnea**, Luminita-Florentina Tomescu, Theodor-Georgian Badea, Emanuel-Stefan Radu, Andreea-Liana Rosu, Lavinia-Nicoleta Brezeanu, Maria-Daniela Tanasescu, Sebastian Isac, Teodora Isac, Oana-Andreea Popa, and et al. 2024. "The Relationship Between the Kansas City Cardiomyopathy Questionnaire and Electrocardiographic Parameters in Predicting Outcomes After Cardiac Resynchronization Therapy" *Life* 14, no. 12: 1564. <https://doi.org/10.3390/life14121564> - **ISI impact factor: 3.2**
2. **Rosu Andrei Mihnea**, Theodor Georgian Badea, Florentina Luminita Tomescu, Andreea Liana Rosu, Emanuel Stefan Radu, Oana Andreea Popa, Liliana Catalina Andrei, and Crina Julieta Sinescu. 2024. "Clinical and Electrocardiographic Predictors of Cardiac Resynchronization Therapy Response That Correlate with the 6 min Walking Test" *Journal of Clinical Medicine* 13, no. 20: 6287. <https://doi.org/10.3390/jcm13206287> - **ISI impact factor: 3.0**
3. **Andrei Mihnea Roșu**, Theodor Georgian Badea, Florentina Luminița Tomescu, Andreea Liana Roșu, Emanuel Ștefan Radu, Oana Andreea Popa, Maria-Daniela Tănăsescu, Liliana Cătălina Andrei and Crina Julieta Sinescu. "Electric and Clinical Predictors Related to the Outcomes of Cardiac Resynchronization Therapy and their Association with Changes in Left Ventricular Ejection Fraction over Time". *Internal Medicine Sciendo*, 21, no. 4 (2024): 19-43. <https://doi.org/10.2478/inmed-2024-0305> - **ISI impact factor: 1.6**