Could T-wave and Tpeak-end interval be new prognostic markers for patients after receiving cardiac resynchronization therapy?

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Abstract:

Aims: In this study, we investigated predictors of favourable responses to CRT using electrocardiography parameters in heart failure patients.

Methods : Seventy-two patients with heart failure, sinus rhythm, left bundle branch block and receiving CRT were included in the study. Patients were classified as "responders" with an improvement in ejection fraction of 10% and "non-responders" as any patient not meeting this definition. Electrocardiograms were evaluated before and after 6 months CRT implantation.

Results: There was no difference between responder and non-responder groups in terms of age, co-morbidities, medications, pre-implantation ECG parameters ($p>0.05$). A number of women CRT-responders higher than non-responder (25.4 % vs 6 %, $p=0.026$), and NYHA Class III patients dominantly in CRT-responder groups (36.9 % vs 29.2 %, $p=0.014$, respectively).Post–implantation QRS duration (143.3± 18.6 vs 160.1 ± 29.2 ms), cQT interval (474.8 ± 43.4 vs 502.7 ± 49.6 ms), T-wave (165.6 ± 25.7 vs 192.1 ± 25.0 ms) and T peak-end (82.9 ± 13.2 vs 98.1 ± 13.3 ms) values were very shorter in CRT responders group ($p<0.05$). In univariate regression analyses showed shortening of QRS, QT interval, T-wave, Tpeak-end interval associated with favourable response to CRT ($p<0.05$). The receiver operating characteristics curve analyses were showed the optimal cut-off T-wave <182 ms, with 76 % sensitivity, 75 % specificity, and Tpeak-end interval < 92 ms with 80 % sensitivity, for the favourable response CRT ($p<0.05$).

Conclusion: QRS duration and QT interval narrowing are known to be associated with favourable outcomes, although the T-wave duration and T peak-to-end interval may also be considered in heart failure patients to predict a favourable CRT response.

Keywords: Cardiac resynchronization therapy; heart failure; electrocardiography, Twave, Tpeak-end interval

What's Known: Heart failure (HF) is still a syndrome with high mortality and morbidity, despite current diagnosis and treatment methods. In addition to medications, in the current treatment of heart failure, sophisticated device treatments are also performed. Cardiac resynchronization therapy (CRT) is the preferred treatment method for patients with low ejection fraction, wide QRS and low functional capacity. After implantation of the CRT, the narrowing of the QRS duration and the QT interval are known good prognosis markers. However, researches on the association between post-implantation CRT response and T wave and T Peak-end interval are limited.

What's New: In this study, we newly found that T wave and T peak-end interval were associated with the favourable response after CRT implantation. T waves and Tpeak-end interval are markers that can be measured easily in electrocardiography, without the need for complex computer programs. By calculating the T wave and T peak-end interval only with ECG, it can easily provide information about whether the favourable response to the CRT during the patient's controls.

Introduction:

Heart failure (HF) is still a syndrome with high mortality and morbidity, despite current diagnosis and treatment methods (1). Mortality of patients admitted to the hospital approximately is 20%, whose over 75 age mortality arrives 40% despite the medical treatment. According to the Vi-Heft study, the average life expectancy in HF patients receiving pharmacological treatment was 3.5 years (3), while the addition of CRT implantation to this treatment (CARE-HF study) increased the average life expectancy by more than 8 years. (2,3,4)

CRT is improvement the symptoms of the heart failure patients by reduced the prolonged conduction time, acceleration myocardial contraction duration and decreasing mitral regurgitation (2). However, there is not observed favourable response to CRT in all HF patients, unfortunately, adverse clinical course may be experienced in some patients. The predictors of a favourable response after CRT implantation are still a matter of investigation. In this study, we investigated predictors of favourable responses to CRT using electrocardiography parameters in heart failure patients.

Methods

Study population

A total of 72 patients who were admitted to the hospital between January 2017 and February 2020, with New York Heart Association NYHA Class 2-3, ambulatory 4, normal sinus rhythm and complete left bundle branch block were included in the study. Five of these patients were excluded from the study because of the development of atrial fibrillation during their follow-up. From the medical records of the patients, demographic features, blood biochemical and haematological values were obtained. All patients have received their heart failure treatment optimal dosing (angiotensin-converting enzyme inhibitors or angiotensin

receptor blockers (ACEI/ARB), acetylsalicylic acid (ASA), ivabradine, B-blockers, mineralocorticoid antagonists and loop diuretics).

Patients were classified as "responders" and "non-responders" according to EF values. A "responder" was described as a patient with an absolute LVEF recovery ≥ 10 % on echocardiography six months after CRT implantation. "Non-responder" was classified as any patient who does not meet this definition. Patients were classified as above based on previously published study results (5,6).

The exclusion criteria were revascularization due to acute coronary syndrome in the last 6 months, severe mitral and aortic valve diseases, atrial fibrillation development, patients undergoing dialysis, cardiorenal syndrome, severe right heart failure and patients who developed ischemic hepatitis.

Ethics committee approval (decision no: 116.2017.178, date: 02.07.2020) was obtained from the Non-Interventional Clinical Research Ethics Committee of Istanbul Süreyyapasa Chest Disease and Chest Surgery Training and Research Hospital, before the initiation of the study. Written and verbal consents were obtained from all participants. Declaration of Helsinki's was followed in the application of the ethical rules of the study.

CRT device implantation

CRT devices (Boston Scientific [Natick, MA]) were placed in all patients by experienced electrophysiologists in accordance with current guidelines (1,2) The right atrial lead was inserted in the right atrium appendix, left ventricular lead was placed in basal lateral, posterolateral and anterolateral coronary sinus vein, and right ventricular lead was implanted in the apical and septal regions of the right ventricle.

Electrocardiograpy

All patients received a 12-lead ECG in the supine position after resting for at least 15 minutes (GE Marquette Mac 1200). Each ECG was taken at a paper rate of 25 mm/s, a gain of 10 mV, and paper format of 3x4. Before and after the CRT implantation ECG was interpreted by two different cardiologists independently. QRS duration was referred to the time interval from the onset to the end of the QRS complex. After CRT implantation, paced QRS duration was measured from the spike to the end of the QRS complex. QT interval was measured from the onset of the QRS complex to the end of the T-wave. The cQT interval was measured using the Bazett's formula. T wave duration was referred to the time interval from the onset to the end of the T wave. The interval from the peak of the T wave to the end of the T wave was defined as the Tpe interval. The QRS, T-wave and Tpeak-end interval were obtained from the precordial leads it was exactly seen on the ECG (7).

Echocardiography:

Echocardiography was performed all patients within one week before and six months after CRT implantation. In accordance with the recommendations of the American Society of Echocardiography, all patients underwent a transthoracic echocardiographic examination with a commercially available device using 4 MHz probes (Vivid 9 Pro, GE Vingmed, Milwaukee, Wisconsin, USA) in the left lateral decubitus position (8). All conventional measurements (LV end-diastolic and end-systolic diameters, LA end-systolic diameter etc.) were performed on the parasternal long-axis and apical four-chamber views. LV ejection fraction was calculated by Simpson’s method (8).

Chest Radiography:

Posteroanterior and lateral chest radiographs were taken for the location of the right and left ventricle leads after CRT implantation.

Follow-up :

All patients were followed by their cardiologists over the phone or during their hospital visits. During the follow-up, their heart rhythm, functional capacity and ECG samples were recorded. Patients who died during follow-up were questioned whether there was a death from cardiovascular cause and were added to the patient records.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Continuous variables are expressed as mean and SD or median interval interquartile (IQR), and categorical variables are expressed as proportions. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine whether the data conformed to normal distribution. The baseline characteristics of the CRT patients were compared using the Student's t-test for continuous variables and normal distribution and the $\chi 2$ Pearson's test used for categorical variables. Mann-Whitney U test was used to compare two independent groups when data is not normally distributed. Logistic regression analyses were performed for the association between CRT response and QRS duration, QT interval, T wave duration and T peak Tend interval. The receiver operating characteristics curve analysis (ROC) was used to evaluate the optimal cut-off the QRS, QT, T-wave and Peak prediction model for CRT responder

For all statistics, a 2 tailed p-value below 0.05 was considered significant.

Results:

The mean age of patients were 63.5±10.0 years, and most of the patients were men 44 (65.7 %) and have been non-ischemic cardiomyopathy (74.2 %). The average follow-up duration patients were 32 (9-41) months. The ejection fraction of pre-implantation was 28.2 ± 4.3, post-implantation was 38.9 ± 6.8. According to recently guidelines recommendations, patients

mostly used ACEI/ARB (98.5%), B-blockers (98.5 %), loop diuretics (78.1 %), aldosterone antagonist (23.4 %), ivabradine (30.6 %) and ASA (30.6 %). Majority of patients admitted to the hospital consisted of NYHA Class III (66.1 %), Class II (29.2 %) and Class IV (13.8 %) (Table 1).

There was no difference between responder and non-responder groups in terms of age 61.8 ± 10.4 vs 66.2 ± 8.9 years, p=0.060), Body Mass Index (28.2 ± 15.6 vs 29.8 ± 13.8 kg/m2, p=0.354), hypertension (57.7 % vs 42.3 %, p=0.787), diabetes mellitus (12.9 % vs 8.1 %, p=0.492), chronic obstructive pulmonary disease (4.7 % vs 1.6 %, p=0.412), chronic kidney failure (3.1 % vs 0 %, p=0.205). Medications [ACE/ARB (56.2 % vs 43.8 %, p=0.381), B-blockers 56.9 % vs 42.2 %, p=0.247), loop diuretics (43.8 % vs 43.4 %, p=0.939), aldesteron antagonist (14.1 % vs 9.4 %, p=0.738), ASA (23.0 % vs 21.3 %, p=0.678), Ivabradin (26.5 % vs 32.1 %, p=0.623)], follow –up duration 33 (7-45) vs 20 (7-44) months, p=0.157), the rate of ischemic cardiomyopaties (16.4 % vs 19.4 %, p=0.248) were similarly between in two groups (Table 1).

A number of women CRT-responders higher than non-responder (25.4 % vs 6 %, p=0.026), and NYHA Class III patients dominantly in CRT-responder groups (36.9 % vs 29.2 %, p=0.014, respectively) (Table 1).

Pre and post-implantation ECG parameters were not different in two groups concerning of heart rate (72.0 ±15.8 vs 75.3 ±13.8 bpm, p=0.450), p duration (93.8±17.3 vs 101.5± 11.9 ms, p=0.090), PR interval (177.4± 42.9 vs 181.5± 52.9 ms, p=0.755), QRS duration (150.5 ± 18.1 vs 153.6 ± 12.9 ms, p=0.510), QT interval (449.2± 52.8 vs 433.5± 43.7, p=0.076), cQT interval (482.7± 32.6 vs 478.5 ±35.7, p=0.140), T wave (197.9 ± 31.9 vs 185.1± 26.7, p=0.140), Tpeak-end interval (100.9 ±16.9 vs 93.3± 14.8, p=0.104) (Table 1).

Post–implantation QRS duration (143.3± 18.6 vs 160.1 ± 29.2 ms, p=0.010), cQT interval (474.8 ± 43.4 vs 502.7 ± 49.6 ms, p=0.005), T-wave (165.6 ± 25..7 vs 192.1 ± 25.0 ms, p<0.001) and T peak-end interval (82.9 ± 13.2 vs 98.1 ± 13.3 ms, p<0.001, respectively) values were very shorter in CRT responders group (Table 1).

In univariate regression analyses showed shortening of QRS duration (OR:0.976 95% CI (0.958-0.995), p<0.016), QT interval (OR:0.983 95% CI (0.971-0.996), p<0.010), T-wave duration (OR:0.952 95% CI (0.928-0.976), p<0.001) , T-peak-end interval (OR:0.905 95% CI (0.860-0.952), p<0.001) associated to response of CRT. In multivariate analysis, it was found that only reduced Tpe interval increased the favourable CRT-response (Table 2).

The receiver operating characteristics curve analysis (ROC) were showed the optimal cut-off value of predicting favourable response to CRT for the T-wave duration was < 182 ms with 76 % sensitivity, 75 % specificity, area under curve (AUC) 0.81 (95 % CI 0.709-0.916, p < 0.001), (Figure 1) the Tpeak-end interval was < 92 ms with 80 % sensitivity, 79 % specificity (AUC: 0.82, 95 % CI 0.725-0.926, p < 0.001) (Figure 2), the QRS duration was < 149 ms, with 64 % sensitivity, 63 % specificity (AUC: 0.68, 95 % CI 0.549 - 0.809, p < 0.012), the cQT interval < 483 ms, with 70 % sensitivity, 63 % specificity (AUC: 0.70, 95 % CI 0.565 - 0.820, p < 0.007) (Figure 3).

Discussion:

In our study, we found that in patients with significantly reduced QRS duration, cQT interval, T-wave duration and T Peak-end interval were associated with favourable response to CRT.

The objective of CRT is to reduced the cardiac conduction time, thus normalizing the depolarization and repolarization duration, and providing effective myocardial contractions. According to data from COMPANION and CARE-HF, CRT significantly reduced all-cause mortality or hospitalization in patients with a QRS duration of ≥ 150 ms (4,9). In parallel,

many studies have shown that after CRT implantation, reduced QT and cQT interval have associated improvement EF and decreased mortality and morbidity in patients with heart failure (4,10,11,12). Similarly, in our study, we found that the QRS duration was shortened in patients with a favourable CRT response, and especially in those with a QRS duration below 149 ms were better resulting. However, the shortened QRS duration is now almost an accepted view in determining the favourable CRT response (13).

The main intent of our study was to investigate whether repolarization shortening is as effective as shortening the depolarization. For this reason, the T wave and T peak wave which easily measurable in ECG parameters were considered. Although there is no certain evidence that the increased T wave duration demonstrated an unfavourable CRT response, publications are reported that the area and morphology of the T wave are associated with prognosis in patients with heart failure who underwent CRT (14). In addition, new measurements which can be calculated with automatic ECG programs such as absolute T-wave residuum, T-wave morphology dispersion and T-wave loop area, have been found to be effective in predicting the CRT response in recent years (15). However, these complex measurements are needed special computer programs and present struggling in daily practice when evaluating the CRT response at the bedside. Our aim in this study was to use a method that can be measured easily and does not take time, but whose correctness is as close as a shortening of QRS duration. As a matter of fact, we obtained significant results between easily measured T wave duration and Tpeak-end interval and CRT response. Actually, it is known that the longer the duration of the cQT and T wave, which indicates ventricular repolarization is related to the greater the risk of arrhythmia and sudden cardiac death (16). The Tpeak-end interval reflects the exact repolarization o the action potential of cardiac M cells, and it was more recently been shown to correlate with transmural as well as regional dispersion of repolarisation (17). Prolongation of the T peak-end interval is associated with adverse cardiovascular outcomes (18,19). In

previous studies, the Tpeak-end predicted SCD in the general population (20) as well as in patients with appropriate ICD therapies in patients undergoing ICD implantation for primary prevention of SCD (18). In our study, we found that the Tpeak-end interval was shorter in patients who had a CRT and showed a favourable prognosis than those with an unfavourable response. Since there was no exactly the same study before, it is could not be a comparison of Tpeak-end values for patients who received CRT.

Another study involving 318 patients with heart failure and implanted ICD / CRT were showed patients with high TpTe values measured after implantation, especially those above 110 ms, had more VT / VF episodes (45%) and all-cause mortality (25.2%) but those with Tpe value below 90 ms, VT / VF (11%) and mortality rate (11.3%), these rates are quite low (21). In our study, Tpeak interval below 92 ms was associated with a favourable CRT response. The VF was observed in the follow-up of two patients with unfavourable CRT responses. Patients with VF also had longer T duration and Tpeak interval after CRT than before CRT. Owing to the restricted number of our patients, we could not any interpretation regarding arrhythmia and unfavourable CRT response. However, comprehensive studies on this matter in the future will shed light on the topic.

One of the details of our study was about the female gender. The MADIT-CRT trial, shown that women have more non-ischemic aetiology, more LBBB patterns and have better outcomes than men after CRT implantation (22). It was even found that women with a typical LBBB and a QRS duration <150 ms benefitted better than CRT (23,24). In our study, all patients were with LBBB, but those of the majority female gender had a favourable CRT response. Therefore, our study results support previous studies. Besides, as shown in the MADIT, CARE-HF and COMPANION studies, the NYHA Class 3 patients were benefited most from CRT treatment that is similar to in our study (4,9,22).

As a result, it is not clear why some patients do not give favourable results after CRT implantation, for this reason, these patients should be evaluated in multiple aspects. Although it is known that QRS duration and QT interval narrowing is associated with favourable results, the ideally response cannot be provided in all patients. T-wave and T-peak intervals may also be considered in these patients to predicted the CRT response.

Limitation:

Our study was single-centred and it was retrospective. The number of our patients was limited owing to fact that only patients with normal sinus rhythm and LBBB were included in the study for obtaining homogenization. Our study results are not suitable to generalize to other patients with heart failure. When we decided the favourable CRT response, increased in EF values by performed echocardiography was considered. Another advanced technology could be considered to evaluate the CRT response than echocardiographic imaging. However, in our study, we have used echocardiography within the possibilities offered by our hospital.

Conclusion:

In our study, we found that the T wave duration < 186 ms and T-peak interval < 92 are significant predictors of a favourable CRT response in symptomatic patients with ischemic and nonischemic cardiomyopathy. We hope that using T-wave duration and Tpeak–end interval together with QRS duration and cQT interval will be useful in determining the favourable CRT response.

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Informed consent: All subjects gave informed consent for participation.

Table 1. Demographic, clinical and electrocardiographic features of patients receiving CRT with responder and non-responder group

Variables	Overall (67)	Responder (n=37)	Non-responder (n=30)	p-value
Age (years)	63.5 ± 10.0	61.8±10.4	66.2±8.9	0.060
Female gender, n (%)	23 (34.3)	17 (25.4)	6 (9.0)	**0.026**
BMI (kg/m^2)	29.5 ± 14.5	28.2±15.6	29.8±13.8	0.354
Hypertension, n (%)	26 (41.9)	15 (57.7)	11 (42.3)	0.787
Diabetes mellitus,n (%)	14 (21.9)	8 (12.9)	5 (8.1)	0.492
COPD,n (%)	3 (4.7)	1 (1.6)	2 (3.1)	0.412
Chronic kidney failure,n (%)	2 (3.1)	0 (0)	2(3.1)	0.205
İschemic CMP, n (%)	24 (35.8)	11 (16.4)	13 (19.4)	0.248
Follow-up (months)	32 (9-41)	33 (7-45)	20 (7-44)	0.062
Preimplantation EF (%)	28.2 ± 4.3	28.9 ± 4.1	27.4 ± 4.4	0.157
Post implantation EF (%)	38.9 ± 6.8	40.5 ± 5.1	28.0 ± 7.5	**<0.001**
Pharmacological therapy				
ACEI/ARB, n (%)	64 (98.5)	36 (56.2)	28 (43.8)	0.381
Beta-blockers, n (%)	64 (98.5)	37 (56.9)	27 (42.2)	0.247
Loop diüretics, n (%)	50 (78.1)	28 (43.8)	22 (34.4)	0.939
Aldesteron antagonist, n (%)	15 (23.4)	9 (14.1)	6 (9.4)	0.738
ASA, n (%)	39 (60.0)	15 (23.0)	14 (21.3)	0.678
Ivabradine, n (%)	19 (30.6)	5 (26.5)	14 (32.1)	0.623
NYHA Class, n(%)				
Class II	19 (29.2)	9 (13.8)	10 (15.3)	0.124
Class III	43 (66.1)	24 (36.9)	19 (29.2)	**0.014**
Class IV	9 (13.8)	4 (6.1)	5 (7.6)	0.246
Pre CRT ECG parameters				
Heart rate (bpm)	73.1 ± 15.1	72.0±15.8	75.3±13.8	0.450
P duration (ms)	96.4 ± 16.0	93.8±17.3	101.5±11.9	0.090
PR interval (ms)	178.3 ± 46.4	177.4 ±42.9	181.5 ±52.9	0.755
QRS duration (ms)	151.5 ± 18.81	150.5 ±18.1	153.6 ±12.9	0.510
QT interval (ms)	441 (378-598)	449.2±52.8	433.5±43.7	0.076
cQT interval (ms)	481.2 ± 33.4	482.7± 32.6	478.5 ±35.7	0.667
T wave (ms)	193.6 ± 30.6	197.9 ±31.9	185.1 ±26.7	0.140
Tpeak-end interval (ms)	96.5± 15.4	100.9 ±16.9	93.3 ±14.8	0.104
Post CRT ECG parameters				
Heart rate (bpm)	78.4±14.9	76.8±15.7	81.2±14.6	0.314
P duration (ms)	91.6±14.4	89.3±13.4	93.1±16.3	0.370
PR interval (ms)	138.6 ±28.2	141.0± 26.8	134.8 ±27.7	0.429
QRS duration (ms)	155.6 ±27.2	143.3 ±18.6	160.1 ±29.2	**0.010**
QT interval (ms)	438.6±48.21	432.7±47.2	448.7±49.4	0.181
cQT interval (ms)	488.4± 45.9	474.8 ±43.4	502.7 ±49.6	**0.005**
T wave (ms)	179.5±24.7	165.6 ±25.7	192.1 ±25.0	**<0.001**
Tpeak-end interval (ms)	88.9±13.1	82.9± 13.2	98.1 ±13.3	**<0.001**

Abbreviations: ASA: Acetilysalicylic acid, BMI: Body Mass Index, CMP: Cardiomyopathy, COPD: Chronic obstructive pulmonary disease.

Table 2. The association between responders and ECG parameters with logistic regression analysis

Variables	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
PC-QRS duration	0.976 (0.958-0.995)	**0.016**		
PC- cQT interval	0.983 (0.971-0.996)	**0.010**		
PC -T wide	0.952 (0.928-0.976)	**<0.001**		
PC -Tpeak-Tend	0.905 (0.860-0.952)	**<0.001**	0.905 (0.860-0.952)	**<0.000**

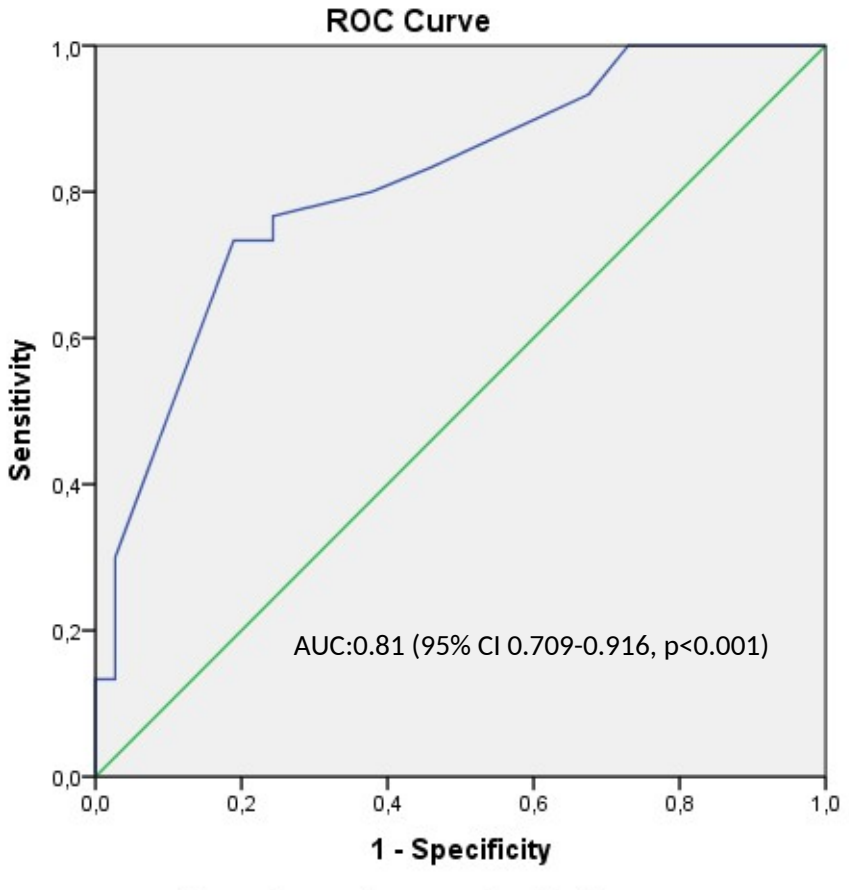

Figure 1. Receiver operating characteristic (ROC) curves for detecting patients with favourable responders to CRT, the optimal cut-off post-CRT T wave duration was < 182 ms with 76 % sensitivity, 75 % specificity and the area under the curve (AUC) of 0.81 (95 % CI 0.709-0.916, p < 0.001).

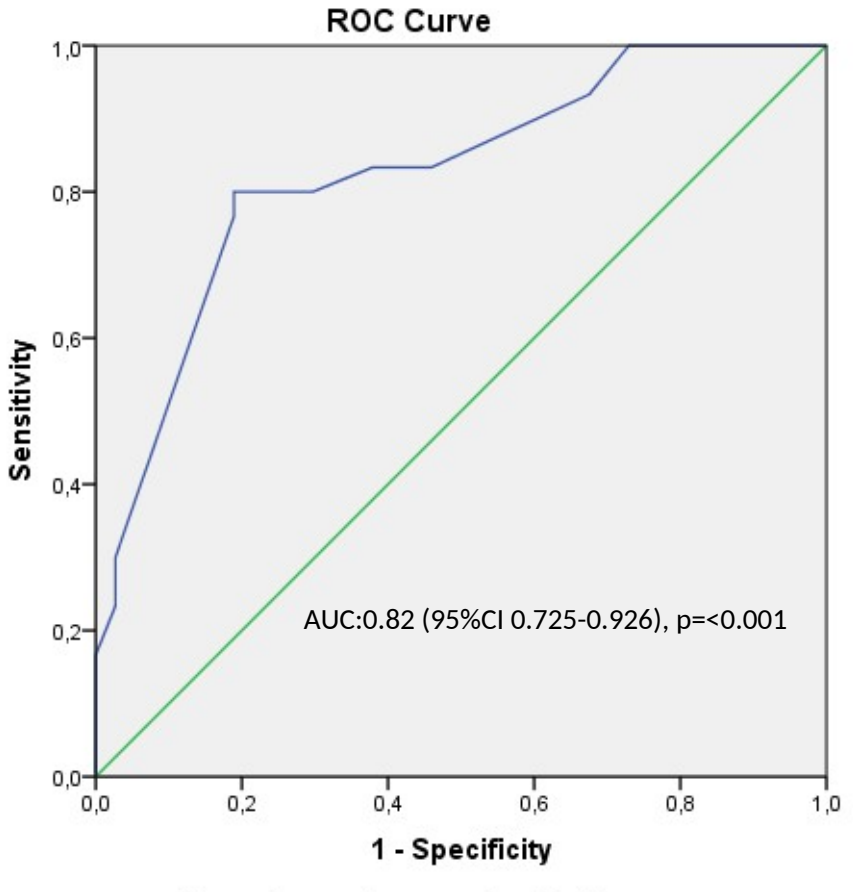

Figure 2. Receiver operating characteristic (ROC) curves for detecting patients with favourable responders to CRT, the optimal cut-off Tpeak-Tend was < 92 ms, with 80 % sensitivity, 79 % specificity and the area under the curve (AUC) of 0.82 (95 % CI 0.725-0.926, $p < 0.001$).

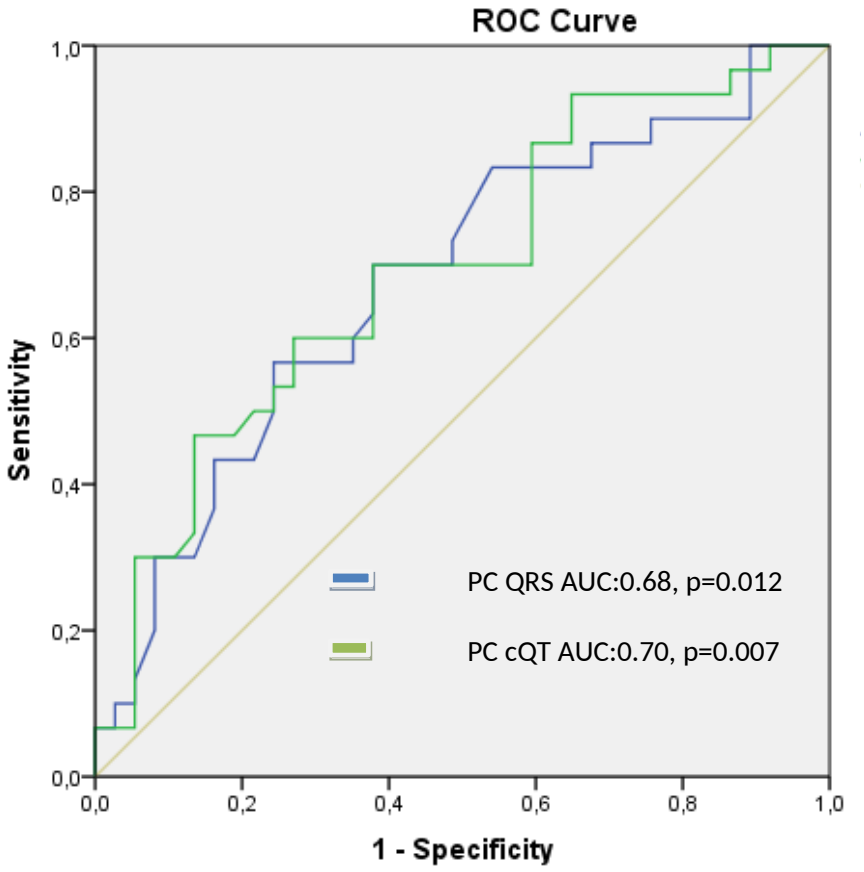

Figure3. Receiver operating characteristic (ROC) curves for detecting patients with favourable responders to CRT , the optimal cut-off post-CRT QRS duration was < 149 ms with 64 % sensitivity, 63 % specificity and the area under the curve (AUC) of 0.68, (95 % CI 0.549 - 0.809, p = 0.012).

The optimal cut-off post-CRT cQT interval was < 483 ms with 70 % sensitivity, 63 % specificity and the area under the curve of 0.70, (95 % CI 0.565 - 0.820, p = 0.007).

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