

IMPACT OF QRS DURATION LIMITS ON CARDIAC RESYNCHRONIZATION THERAPY IN HEART FAILURE PATIENTS: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has proven effective in reducing clinical events among heart failure patients with prolonged QRS intervals. Previous research, utilizing surrogate measures and subgroup analyses from large trials, indicates that the benefits of CRT are more prominent in patients with severely prolonged QRS intervals. The objective of our study is to investigate the impact of QRS duration limits on cardiac resynchronization therapy in heart failure patients, along with an exploration of related factors.

Objective: The main purpose of this study was to evaluate the effect of QRS duration, etiology, type of bundle branch block and gender on the outcome of CRT-D implantation in patients with heart failure.

Methods: A retrospective cohort study involving 151 heart failure (HF) patients who underwent cardiac resynchronization therapy (CRT) from January 2019 to November 2023 was conducted at Kalsoom International Hospital. Statistical analysis utilized SPSS versions 18 and 20. The cohort comprised 62 patients with QRS duration (QRSd) between 130 and 149 milliseconds (46 male and 16 female) and 89 patients with QRS duration greater than 150 milliseconds (64 male and 25 female). Diagnostic criteria for non-ischemic heart disease included X-ray, electrocardiogram, and echocardiography results, with coronary interventions performed for ischemic heart disease. Primary inclusion criteria encompassed QRS duration, left bundle branch block (LBBB) and non-left bundle branch block (NLBBB), ischemic and non-ischemic heart diseases, New York Heart Association (NYHA) Class II-IV, and left ventricle ejection fraction (LVEF) less than or equal to 35%.

Results:

Our results showed both QRS groups (1: 130 <QRSd< 149, 2: >150) were compared. Subsequently, subgroups including ischemic heart disease (IHD) and non-ischemic heart disease (NIHD), left bundle branch block (LBBB) and non-LBBB, rural and urban groups, as well as gender, were assessed for differences and responses. In all patients, preoperative left ventricular ejection fraction (LVEF) in group 1

(28.50±5.90) and group 2 (28.38±5.54) significantly increased after CRT-D implantation, with a postoperative LVEF of (37.21±9.68) in group one and (37.37±10.46) in group two, with a p-value of <0.05. Most patients with CRT showed that preoperative left ventricular end-systolic volume (LVESV) (61.77±9.39 & 62.91±12.28) is higher compared to postoperative LVESV (56.00±11.15 & 56.57±12.93) ml, indicating a significantly lower postoperative LVESV (P < 0.05). Overall, both groups exhibited a good response, rather than a super-response, in terms of EF and LVESV.

Conclusion:

In conclusion, age correlates with an increased prevalence of ischemic heart disease (IHD), particularly observed in urban areas and among male patients. Following CRT implantation, nearly all patients showed a significant improvement in ejection fraction. Notably, non-ischemic heart disease (NIHD) patients displayed a superior response compared to IHD patients with QRS >150.

Keywords:

Cardiac Resynchronization Therapy; Heart Failure; cardiac rhythm

Abbreviations:

ACE	angiotensin converting enzyme	ICD	implantable cardioverter-defibrillator
ACEI	angiotensin converting enzyme inhibitor	ICM	ischemic cardiomyopathy
AF	atrial fibrillation	IVD	interventricular delay
AHF	acute heart failure	IVS	interventricular septum
AMI	acute myocardial infarction	LA	left atrium
ARB	angiotensin II receptor blockers	LAD	left axis deviation
AV	atrioventricular	LBBB	left bundle branch block
AVNRT	atrioventricular nodal tachycardia	LV	left ventricular
AVRT	atrioventricular re-entry tachycardia	LVEDD	left ventricular end-diastolic diameter
BNP	B-type natriuretic peptides	LVEF	left ventricular ejection fraction
BP	blood pressure	L VH	left ventricular hypertrophy
CABG	coronary artery bypasses graft	L V O T	left ventricular outflow tract
CHF	chronic heart failure	LVSD	left ventricular systolic dysfunction
CRT	cardiac resynchronization therapy	MR	mitral regurgitation
CRT-D	cardiac resynchronization therapy-defibrillator	NYHA	New York Heart Association
DCM	dilated cardiomyopathy	QRSd	QRS duration
DD	diastolic dysfunction	RA	right atrium
EAD	extreme axis deviation	RAD	right axis deviation
HCM	hypertrophic cardiomyopathy	RBBB	right bundle branch block
REF	reduced ejection fraction	RV	right ventricular

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INTRODUCTION

Approximately 6 million Americans and 6.5 million Europeans suffer from heart failure at the moment [1, 2]. Heart failure is linked to death and a low quality of life, but it also significantly increases resource consumption; in the United States, heart failure-related expenses were predicted to exceed \$39 billion in 2010 [1]. Over the last ten years, implanted device therapy has emerged as a major component of this disease's treatment regimen in addition to medicinal therapy. Biventricular pacing, commonly referred to as cardiac resynchronization treatment or CRT, has been demonstrated to enhance hemodynamics, encourage reverse remodeling, and lower clinical outcomes, such as mortality, in patients with extended QRS duration on the ECG[3-5]. Historically, CRT has been advised for patients with systolic heart failure, New York Heart Association (NYHA) class 3 or 4 symptoms, and a QRS duration of 120 milliseconds or longer, according to treatment guidelines supported by the American College of Cardiology, American Heart Association, Heart Rhythm Society, European Society of Cardiology (ESC), and Heart Failure Society of America (HFSA) [6-8]. Approximately one-third of systolic heart patients have a QRS duration longer than this 120 ms threshold [9-11]. It was discovered that between one-third and half of patients getting CRT in accordance with the guidelines did not react to this treatment shortly after it became a widely used treatment for heart failure [12, 13]. Based on the entry requirements of two significant trials, the QRS cutoff of 120 milliseconds or more was recommended for the implantation of CRT devices [14, 15]. Recently, the HFSA [16] and ESC [17] guidelines for management of heart failure were revised in response to the MADIT-CRT trial [18]. The updated recommendations included a new QRS threshold of more than 150 milliseconds for this population, along with a new recommendation for CRT in NYHA 1 and/or NYHA 2 systolic heart failure. The MADIT-CRT trial's subgroup analysis served as the foundation for the revised cutoff [18], study found that CRT did not reduce the number of heart failure events in individuals whose QRS interval was less than 150 milliseconds. According to these revised recommendations, individuals with heart

failure classified as NYHA 3 or 4 and with a QRS cutoff of 120 milliseconds or above are still advised to undergo CRT. Nonetheless, regardless of their NYHA functional class, research employing surrogate measures of response, such as hemodynamics or peak oxygen consumption, indicates that individuals with a QRS length between 120 and 150 milliseconds do not benefit from CRT [19]. To the best of our knowledge, no comprehensive analysis has yet been done on how the degree of QRS prolonging affects the effectiveness of CRT in lowering unfavorable clinical outcomes, such as hospitalization and mortality. Thus, our goal was to ascertain how cardiac resynchronization treatment in patients with heart failure and its associated parameters is affected by the QRS length restriction.

Materials and methods:

Study Population and Sample

In this retrospective cohort study spanning from January 2019 to November 2023, 151 Heart Failure (HF) patients undergoing cardiac resynchronization therapy (CRT) were examined. The study included 62 patients with QRS duration (QRSd) between 130 and 149 milliseconds (46 male and 16 female) and 89 patients with QRS duration greater than 150 milliseconds (64 male and 25 female) from Kalsoom International Hospital. Data, obtained with full patient consent and commission on clinical research approval, were sourced from the cardiovascular department's medical archives. Diagnostic criteria for Non-Ischemic Heart Disease included X-ray findings indicating an increased heart size, Electrocardiogram strips, and Echocardiography results. For ischemic heart disease, coronary interventions such as Cardiac Catheterization and/or Interventional therapy were performed. The primary inclusion criteria comprised QRS duration ≥ 130 ms, N.Y.H.A Class II-IV, left bundle branch block (LBBB) along with non-left bundle branch block (NLBBB), and left ventricle ejection fraction (LVEF) $\leq 35\%$.

Statistical Analysis

Analysis of statistics was executed operating SPSS for Microsoft Windows v. 18 and V20 (SPSS) for Microsoft windows 10. The data was compared using multiple categories of response markers for CRT which were collected one-year post-implant. Paired sample T test was exercised for the purpose of

evaluation. $P < 0.05$ was noted as statistically substantial.

Results:

The study included 62 patients with QRS duration (QRSd) between 130 and 149 milliseconds (46 male and 16 female) and 89 patients with QRS duration greater than 150 milliseconds (64 male and 25 female) with 7 females and 24 males, while 120 patients (79.5 percent) were diagnosed with non-ischemic heart disease (NIHD), comprising 34 females and 86 males. The data indicates a higher prevalence of males in both IHD and NIHD, with a graphical representation showing a higher percentage of females in NIHD (28.3%) compared to IHD (22.6%), and more males with IHD (77.4%) compared to NIHD (71.7%).

Table 1.1 Comparison of Age groups with IHD and NIHD.

Age Group	IHD (n)	NIHD (n)	P. value
40—50	1	16	.009
51—60	7	43	
61--70	10	42	
> 70	13	19	
Total	31	120	

In the above graph the percentage of Ischemic heart Disease is increasing as the age increases. There are 3.2% patients in group one (40-50) which is lesser than the patients 22.6% in group two (51-60) and the patients in group three 32.3% (61-70) are more than that of group two. The patients whose age is more than 70 showing more percentage (41.9%) of IHD than all other three groups. The percentage of NIHD is more in the second and third group.

A significant relationship found between Ischemic and Non ischemic heart disease with Rural and Urban area ($P < 0.05$). Patients with Ischemic Heart disease (31) were found more in Urban people (22) as compare to people who are living in Rural area (9) and there are more patients with NIHD (120) in

people who belongs to Rural area(70) than Urban area (50).

ECG findings of Pre and Post CRT/CRTD implantation are also mentioned, which includes mean and standard deviation of QRS duration pre and post CRT/CRTD implantation, which shows significant (P<0.05)decrease in QRS duration after CRT/CRTD in all groups. QRS morphology is LBBB and NLBBB in 79(52.31%) and 72(47.68%) patients, respectively. All of these patients received appropriate Heart Failure medications which were

Beta blockers, Diuretics, CCBs (Calcium Channel blockers) and ACEI or ARBs

In table 1.2, the preoperative and postoperative values are shown for comparison according to QRS Duration, i.e. 130 <QRSd< 149 & QRS>150. The variables compared are EF, LVEDV, LVESV and Mitral Regurgitation (MR). In this comparison, all parameters show significantly good response under all categories except Mitral Regurgitation which only showed significant improvement postoperatively in QRS >150 msec patients (P<0.05).

Table 1.2 Echocardiography Response in two main groups after CRT-D

ECHO	130 <QRSd< 149		p. value	QRSd>150		p. value
	Pre	Post		Pre	Post	
EF	28.50+5.90	37.21+9.68	.000	28.38+5.54	37.37+10.46	.000
LVEDV	72.23+9.10	67.62+10.78	.012	73.51+10.44	68.29+12.16	.002
LVESV	61.77+9.39	56.00+11.15	.003	62.91+12.28	56.57+12.93	.001
MR	8.867+10.28	6.006+4.48	.139	7.875+5.83	5.081+4.56	.004

Out of 151 patients who received CRT, 17 IHD and 45 NIHD patients in group1 (130 <QRSd< 149) and 14 IHD and 75 NIHD in group2 (QRS >150) have preoperative EF in group1 is 30.53±4.403 and 27.73±6.246 and in group2 is 31.14±4.622 and 27.86±5.573. While post-operative EF in group1 is

41.24±10.097 and 35.69±9.177 and in group2 is 37.07±7.447 and 37.43±10.973, it shows that significant changes were made in post-operative EF(P<0.001) except IHD group2 in which p valve is .018 and also MR which is much higher than others, it might be because of more scar burden table 1.2

Table 1.3 Comparison of ECHO parameters with IHD and NIHD in two major group

Diagnose	ECHO	130 <QRSd< 149		p.value	QRSd>150		p.value
		Pre	Post		Pre	Post	
IHD	EF	30.53+4.403	41.24+10.097	.000	31.14+4.622	37.07+7.447	.018
	LVEDV	69.18+7.994	62.94+8.842	.039	72.50+10.098	66.64+9.881	.133
	LVESV	58.53+7.125	50.35+9.868	.009	62.57+9.565	55.86+9.526	.074
	MR	5.59+3.442	3.58+3.277	.137	6.04+3.326	5.61+3.613	.798
NIHD	EF	27.73+6.246	35.69+9.177	.000	27.86+5.573	37.43+10.973	.000
	LVEDV	73.38+9.309	69.43+11.004	.071	73.69+10.560	68.60+12.575	.008
	LVESV	63.00+9.909	58.34+10.924	.041	62.97+12.777	56.71+13.522	.004
	MR	10.26+11.847	7.28+4.575	.272	8.14+6.082	4.99+4.738	.004

Patients in group 130 <QRSd< 149 responded well as the EF increased from an average of 30.53 to 41.24 while the other valves decreased significantly than group QRS >150 where the EF increased from 31.14 to 37.07 and Mitral regurgitation not improved significantly.

Patients in group QRS >150 responded well as the EF increased from an average of 27.86 to 37.43 while the other valves decreased significantly than group 130 <QRSd< 149 where the EF increased from 27.73 to 35.69.

Table 1.4 Comparison of ECHO parameters with LBBB and NLBBB in two major groups

Diagnose	ECHO	130 <QRSd< 149		p.value	QRSd>150		p.value
		Pre	Post		Pre	Post	
LBBB	EF	28.75+4.794	41.04+10.084	.000	27.57+5.134	37.69+11.912	.000
	LVEDV	72.21+8.293	66.38+11.934	.055	73.85+10.750	67.40+13.681	.007
	LVESV	61.25+8.588	53.92+12.261	.021	62.75+12.409	55.85+14.514	.009
	MR	9.82+15.518	3.56+2.423	.218	7.64+4.702	5.37+5.145	.036
NLBBB	EF	28.34+6.561	34.79+8.703	.000	29.68+5.999	36.85+7.699	.000
	LVEDV	72.24+9.685	68.43+10.051	.099	72.94+10.054	69.74+9.202	.175
	LVESV	62.11+9.962	57.47+10.243	.056	63.18+12.251	57.74+9.952	.049
	MR	8.27+4.952	7.12+4.804	.393	8.30+7.554	4.49+3.148	.049

All LBBB Patients in group 130 <QRSd< 149 responded well as the EF increased from an average of 28.75 to 41.04 while the other valves decreased significantly than group QRS >150 where the EF increased from 27.57 to 37.69.

All Patients in group QRS >150 responded well as the EF increased from an average of 29.68 to 36.85 while the other valves decreased significantly than group 130 <QRSd< 149 where the EF increased from 28.34 to 34.79.

Table 1.5 Comparison of ECHO parameters with Gender in two major groups.

Gender	ECHO	130 <QRSd< 149		p.value	QRSd>150		p.value
		Pre	Post		Pre	Post	
Male	EF	27.76+5.774	35.80+8.387	.000	28.21+5.833	37.14+11.337	.000
	LVEDV	73.98+8.681	69.36+10.218	.022	75.44+10.909	70.66+12.661	.024
	LVESV	63.41+9.205	58.17+10.248	.013	64.59+13.394	58.72+13.734	.016
	MR	9.13+11.856	5.83+4.711	.215	8.23+6.582	5.14+4.986	.017
Female	EF	30.62+5.920	41.25+12.108	.004	28.80+4.805	37.96+7.966	.000
	LVEDV	67.19+8.620	62.75+11.150	.218	68.56+7.206	62.24+8.278	.006
	LVESV	57.06+8.512	50.31+11.768	.073	58.60+7.427	51.08+8.626	.002
	MR	8.12+3.267	6.40+4.168	.260	7.05+3.557	4.96+3.613	.073

(1.5), shows that out of 151 patients who received CRT, 46 & 64 male patients in group one and two have preoperative EF 27.76±5.774 & 28.21±5.833 and post-operative EF 35.80±8.387 & 37.14±11.337, it shows that there was significant improvement in post-operative EF(P=.000 & .000). 16 & 25 female

patients in group one and two have Preoperative 30.62±5.920 & 28.80±4.805 and post-operative EF 41.25±12.108 & 37.96±7.966, it shows that there was significant improvement in post-operative EF(P=.004 & .000).

Table 1.6 Comparison of ECHO parameters with area in two major group

Area	ECHO	130 <QRSd<149		p.value	QRSd>150		p.value
		Pre	Post		Pre	Post	
Rural	EF	27.20+7.009	34.17+9.060	.002	28.73+6.087	37.10+10.471	.000
	LVEDV	73.20+10.199	70.52+10.891	.333	74.08+9.834	69.27+11.710	.030
	LVESV	63.03+10.858	59.93+10.103	.270	64.12+11.364	57.43+12.585	.007
	MR	11.37+13.850	8.03+4.598	.404	8.11+6.485	4.97+5.161	.032
Urban	EF	29.72+4.401	40.06+9.500	.000	27.95+4.835	37.70+10.576	.000
	LVEDV	71.31+7.994	65.00+10.144	.007	72.80+11.228	67.10+12.742	.037
	LVESV	60.59+7.762	52.58+11.054	.001	61.42+13.313	55.52+13.432	.052
	MR	6.45+3.774	4.62+3.952	.114	7.57+4.969	5.21+3.860	.052

Table 1.7 shows QRS Duration-specific response in group1 (130 <QRSd< 149) and group 2(QRS >150) respectively. Among the 110 males, 46 had 130 <QRSd< 149, and the preoperative QRSd value (140.83+5.934) increased significantly

Post operatively with QRSd value (122.83+8.24) and a P-value=.000; 64 male patients had QRS >150, and the preoperative QRSd value (171.64+13.38) increased significantly postoperatively with an QRSd value (147.53+14.69), (P=.000).

Table 1.7 Comparison of ECG'S in all subgroups with two major groups

Parameters	130 <QRSd< 149		p.value	QRSd>150		p.value
	Pre	Post		Pre	Post	
Male	140.83+5.934	122.83+8.24	.000	171.64+13.38	147.53+14.69	.000
Female	141.06+4.85	118.56+5.11	.000	171.44+13.07	139.80+14.20	.000
IHD	141.00+5.29	121.35+8.34	.000	169.93+12.51	143.07+11.05	.000
NIHD	140.84+5.81	121.87+7.61	.000	171.89+13.41	145.79+15.53	.000
LBBS	142.58+5.241	124.42+6.78	.000	172.65+13.14	146.00+14.15	.000
NLBS	139.82+5.68	120.03+7.93	.000	169.85+13.36	144.32+16.18	.000
RURAL	139.97+6.00	121.90+8.15	.000	171.22+11.20	146.08+14.52	.000
URBAN	141.75+5.21	121.56+7.48	.000	172.02+15.48	144.48+15.47	.000

Discussion

Our analysis includes 41.05% of patients with QRS duration between 130 and 149 milliseconds and 58.94% of patients with QRS duration greater than 150 milliseconds who underwent CRT-D implantation. Generally, I observed a favorable response to CRT, with a tendency to prioritize non-ischemic heart disease (NIHD), female, and left bundle branch block (LBBB) patients in my study. It's important to note that this prioritization is not universally accepted among physicians worldwide. Various factors can predict changes in morbidity and mortality rates, and the degree of reverse remodeling is one of the most significant mechanisms of CRT. However, it's crucial to recognize that in patients with ischemic pathology, the improvement of left-ventricular function may be limited due to the presence of cardiac scar tissue. Beneficial remodeling of myocardial scar tissue in these cases is challenging or impossible [20].

Post-CRT, if patients have improved heart functions then it is assumed that these subjects have improved prognosis [21]. However, this mechanism is a comparatively small fraction of the effect of CRT on long-term death rates at the same time as most studies showed some or close to no benefit of CRT in NLBBB subjects [22, 23]. Improvement of cardiac function is a welcome sign after implant of CRT devices, but an untrustworthy response marker for long-term responses [24]. In addition, in a randomized controlled study trial in subjects with HF and QRS < 130 ms, CRT also failed to benefit (QoL) quality of life and operative and echocardiographic parameters [25]. According to the Heart Failure Cardiac-Resynchronization (CARE-HF) study, different criteria were used to determine the improvement if there was a 5-6 percent improvement in the reduction of N.Y.H.A class or a 5-6 percent improvement in the quality of life, and then a positive response is considered [26]. Whilst other research concentrate on the result of echocardiography. A contrary association between QRS duration and LVEF endures [8]. The degree of QRS post CRT reduction projected a positive response [27].

In our study, in all subgroups 62 patients with 130 <QRSd< 149 and 89 patients with QRS>150ms had significantly increased LVEF. Difference in length of

QRS was indicator of improvement in the clinically fused ranking, in evaluation PROSPECT-ECG [28]. Iler et al have demonstrated increased mortality and increased cardiac transplantation in patients with a broader QRS post-implantation [29]. Rickard et al. demonstrated worst aggravation of Left ventricular activity with QRS extension brought by CRT [12]. LVESV Post-CRT implantation has also witnessed a major decline in several studies [20, 21, 24, 26, and 27]. This change becomes apparent as quickly as 1 month after implantation [27] and is sustained for up to 29 months [30] as predictor of good response. According to White H D et al, the LV (LVESV) sinks into the end-systolic volume as the most important gage of reverse LV remodeling.

In our analysis, a decrease in QRS duration post-cardiac resynchronization therapy (CRT) is associated with a more significant reduction in left ventricular end-systolic volume (LVESV) and a higher postoperative left ventricular ejection fraction (LVEF) compared to cases with an increase in QRS duration ($p=0.05$). These positive outcomes are particularly notable in patients with left bundle branch block (LBBB) morphology. Our findings align with a study by Auricchio et al., which discourages direct CRT implantation in subjects with non-left bundle branch block (NLBBB).

Among CRT patients, preoperative LVESV levels were generally higher than postoperative levels, indicating a significant decrease in LVESV after CRT ($P < 0.005$). In both LBBB and NLBBB patients, our study yielded improved results, with more noticeable benefits observed in LBBB cases. Notably, patients with LBBB morphology showed favorable outcomes in echocardiographic factors, such as LVEF and left ventricular end-diastolic volume (LVEDV). Similar to the findings by Auricchio et al., our research suggests caution against direct CRT implantation in patients with right bundle branch block (RBBB).

Specifically, among NLBBB patients, those with QRS duration between 130 and 149 milliseconds exhibited a significant increase in postoperative LVEF, as did NLBBB patients with QRS duration greater than 150 milliseconds. Both genders demonstrated improved responses, with females showing a slightly better response in our study.

Conclusion:

As age increases, the prevalence of ischemic heart disease (IHD) also rises, with IHD more commonly found in urban areas and among male patients. Patients who received cardiac resynchronization therapy (CRT) implantations generally demonstrated significant improvement in ejection fraction post-implantation. Notably, non-ischemic heart disease (NIHD) patients showed a better response than IHD patients in the QRS >150 group, and rural patients responded more favorably than urban patients. In the 130 <QRSd< 149 group, IHD patients exhibited a better response compared to NIHD patients. Female patients displayed a superior response in ejection fraction compared to male patients. Both left bundle branch block (LBBB) and non-LBBB (NLBBB) patients showed significant differences in post-CRTD outcomes. Both genders experienced a substantial reduction in left ventricular end-systolic volume (LVESV) post-CRT, with patients with LBBB showing a more significant reduction compared to NLBBB patients. In all subgroups of QRS duration, both group one and group two showed a significant decrease after CRT/CRTD (P value <0.05). Patients with NYHA class II, III and IV showed better response than that of class I.

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