

Multimodality imaging in the characterization and risk-stratification of cardiac disease and CRT recipients

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Part I:

The role of echocardiography in predicting outcome after CRT





Impact of QRS complex duration and morphology on left ventricular reverse remodeling and left ventricular function improvement after cardiac resynchronization therapy

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ABSTRACT

Background: To evaluate the impact of the interaction of QRS duration and morphology on left ventricular (LV) reverse remodeling and LV functional improvement in heart failure (HF) patients treated with cardiac resynchronization therapy (CRT).

Methods: From an ongoing registry of HF patients treated with CRT according to contemporary guidelines, demographic, clinical, electrocardiographic (ECG) and echocardiographic characteristics were analyzed. Patients were divided according to QRS duration and morphology: <150 ms vs. ≥150 ms and left bundle branch block (LBBB) vs. non-LBBB, respectively. Echocardiographic measurements were performed at baseline and at 6 months of follow-up. The effect of the interaction between QRS duration and morphology on LV reverse remodeling and LV ejection fraction (LVEF) was analyzed using linear, mixed models.

Results: Of 1 467 patients (mean age 65±10 years, 77% male), 884 (60%) had a QRS \geq 150 ms and 814 (55%) showed LBBB. The group with QRS \geq 150 ms demonstrated larger LV reverse remodeling (mean reduction in LV end-systolic volume 34.3 ml vs. 14.8 ml; P<0.001) and improvement in LVEF (mean increase 6.8% vs. 5.2%; P<0.001) compared with their counterparts. Similarly, patients with an LBBB evidenced greater LV reverse remodeling (mean reduction in LV end-systolic volume 30.75 ml vs. 17.4 ml; P<0.001) and improvement in LVEF (mean increase 6.9% vs. 3.7%; P<0.001) than those with non-LBBB QRS morphology.

Conclusions: LV reverse remodeling and LV functional improvement are greater among HF patients with LBBB morphology and increasing QRS duration who receive CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure (HF) patients who remain symptomatic despite optimal medical therapy (New York Heart Association (NYHA) functional class II-III and ambulatory IV), with a wide QRS complex (\geq 120 ms) and reduced left ventricular ejection fraction (LVEF \leq 35%).¹ The benefits of CRT may differ, based on QRS complex duration and morphology. Recent registries, metaanalyses and sub-studies of randomized controlled trials have shown that patients with left bundle branch block (LBBB) morphology and QRS duration \geq 150 ms appear to benefit most from CRT in terms of improvement of clinical symptoms and survival,²⁻⁴ whereas in patients with non-LBBB morphology the benefit may be less, particularly when the QRS duration is <130 ms.⁵ However, little is known about the influence of QRS duration and morphology on the extent of LV reverse remodeling and improvement in LVEF. Accordingly, the present study evaluated the relation between baseline QRS duration and morphology, and LV reverse remodeling and LV systolic function improvement after CRT in a large population of HF patients (including NYHA class I-IV).

METHODS

Patient population

This retrospective, single-centre study included symptomatic HF patients who, despite receiving maximum-tolerated doses of optimal medical therapy, subsequently underwent CRT implantation according to contemporary guidelines.¹ Demographic, clinical, electrocardiographic (ECG) and echocardiographic characteristics were analyzed. QRS duration and morphology were dichotomized into groups <150 ms vs. \geq 150 ms and LBBB vs. non-LBBB, respectively. Echocardiographic measurements were performed at baseline (before CRT implantation) and at 6 months' follow-up, according to current guidelines on LV chamber quantification.⁶ Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and LVEF were compared at baseline and 6 months' follow-up between patients with and without LBBB, as well as between patients with QRS duration \geq 150 ms and <150 ms. The Dutch Central Committee on Human-related Research (CCMO) allows the use of anonymous data without prior approval of an institutional review board provided that the data are acquired for routine patient care. All data used for this study were acquired for clinical purposes and handled anonymously.

Analysis of QRS morphology and duration

QRS duration was determined by automated, digital algorithms from a 12-lead, surface ECG. Calibration of the ECG was set at 0.1 mV/mm and the paper speed was 25 mm/s. Previously

defined criteria were employed to define an LBBB, with the intrinsic complex being evaluated in the case of pre-existing pacing.⁷

Echocardiographic data acquisition and analysis

Prior to CRT implantation and at 6 months' follow-up, transthoracic echocardiography was performed in all patients in the left lateral decubitus position using a commercially available echocardiographic system (E9 or VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using 3.5 MHz or M5S transducers, while adjusting depth and gain settings. M-mode, 2-dimensional and Doppler data, triggered to the ECG, were acquired and digitally stored for off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee, USA). LVESV, LVEDV and LVEF were measured from the apical 2- and 4-chamber views, using the modified Simpson's biplane method.

Implantation of CRT

The right atrial and ventricular leads were positioned conventionally through a subclavian or cephalic vein. For implantation of the LV lead, a coronary sinus venogram was obtained using a balloon catheter and the LV pacing lead was inserted in the coronary sinus with the help of an 8 Fr guiding catheter and positioned, preferably, in a (postero-) lateral vein. All leads were connected to a dual-chamber biventricular CRT device. The majority of the patients (94%) received a CRT device with defibrillator function (ICD) and 6% received a CRT device without defibrillator capability. Evaluation of the device function was combined with the regular controls at the HF outpatient clinic. The atrioventricular and inter-ventricular delays were set empirically at 120-140 ms and 0 ms, respectively, and CRT optimization was performed at follow-up at the discretion of the treating physician.

Statistical analysis

Continuous variables are presented as mean and standard deviation when normally distributed. Dichotomous data are presented as numbers and percentages. Student t-tests were used to compare continuous variables, and χ^2 tests were used to compare dichotomous data. Changes in LVESV, LVEDV and LVEF at 6 months' follow-up were compared within and between groups using linear, mixed models corrected for gender and HF etiology. All analyses were performed with SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA). All statistical tests were two-sided. A P-value <0.05 was considered statistically significant.

RESULTS

A total of 1 467 patients (mean age 65±10 years, 77% male) were included in the analysis (Table 1). Ischemic cardiomyopathy was diagnosed in 59% of patients. LBBB was present in

55% of patients and the mean QRS duration was 156±33 ms, with 60% of patients having a QRS duration ≥150 ms. Compared to patients with LBBB QRS morphology, patients with non-LBBB QRS morphology were more frequently male, had more frequently ischemic cardiomyopathy and atrial fibrillation and showed significantly better LVEF and smaller LV volumes. Compared to patients with QRS duration ≥150 ms, patients with QRS duration <150 ms were significantly younger, had more frequently ischemic cardiomyopathy, less frequently chronic kidney disease, showed significantly better LVEF and smaller LV volumes and were more frequently treated with beta-blockers.

Influence of QRS duration and morphology on LV reverse remodeling and LVEF improvement

The mean changes in LV volumes and LVEF, according to QRS morphology and duration, are summarized in Table 2. Patients with LBBB configuration exhibited greater LV reverse remodeling, greater decrease of LVEDV and improvement in LVEF than patients with non-LBBB QRS morphology. Similarly, patients with QRS duration ≥150 ms demonstrated greater LV reverse remodeling, greater reduction of LVEDV and improvement in LVEF compared to those with QRS duration <150 ms.

Figure 1 illustrates the influence of QRS duration on the reduction of LVEDV after CRT in patients with LBBB vs. patients with non-LBBB. Regardless of the QRS morphology, the reduction in LVEDV was more pronounced with increasing width of the QRS, particularly with QRS duration ≥150 ms (inflection point). Beyond a QRS duration >190 ms, further decrease in LVEDV was not



QRS duration (ms)

Figure 1: Influence of QRS duration as a continuous variable on left ventricular end-diastolic volume (LVEDV) reduction after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation curve for each group (red = LBBB and blue = non-LBBB) and the solid line the overall population (black).

observed for patients with LBBB morphology, whereas patients with a non-LBBB QRS configuration showed progressive LVEDV reduction. Figure 2 illustrates the influence of QRS duration as a continuous variable (dichotomized into patients with LBBB and non-LBBB configuration) on changes in LVESV: progressive reduction in LVESV was observed with increasing duration of the QRS, particularly ≥140 ms for both LBBB and non-LBBB patients. Figure 3 illustrates the influence of QRS duration as a continuous variable (dichotomized into patients with LBBB vs. non-LBBB) on changes in LVEF. LVEF increased particularly in patients with QRS duration ≥150 ms and LBBB morphology and appeared to reach a plateau beyond 170 ms. LVEF improvement in patients with non-LBBB morphology was similar across the various QRS durations.

		LBBB (n=814)	Non-LBBB (n=653)	P-value	QRS ≥150 ms (n=884)	QRS <150 ms (n=583)	P-value
Age	(years)	65.7±10.2	65.1±11.1	0.3	66.5±10.4	63.9±10.8	<0.001
Ma	e gender, n (%)	598 (73.5)	528 (80.9)	0.001	668 (75.6)	458 (78.6)	0.206
Isch	emic etiology, n (%)	439 (53.9)	427 (65.4)	<0.001	466 (52.7)	400 (68.6)	<0.001
Hea - - -	rt rhythm, n (%) Sinus rhythm Atrial fibrillation Paced	693 (85.1) 118 (14.5) 3 (<0.1)	362 (55.4) 148 (22.7) 143 (21.9)	<0.001 <0.001 <0.001	591 (66.9) 158 (17.9) 135 (15.3)	464 (79.6) 108 (18.5) 11 (<0.1)	<0.001 0.804 <0.001
NY	A functional class, n (%)						
	 V	28 (3.4) 195 (24.0) 519 (63.8) 57 (7.0)	34 (5.2) 168 (25.7) 379 (58.0) 52 (8.0)	0.114 0.409 0.045 0.517	29 (3.3) 210 (23.8) 557 (63.0) 70 (7.9)	33 (5.7) 153 (26.2) 341 (58.5) 39 (6.7)	0.033 0.252 0.148 0.473
6 N	IWT (m)	326.2±122.5	319±121.5	0.305	321.0±124.0	326.0±119.1	0.504
Qol	score	32.6±19.0	33.6±19.7	0.385	33.0±18.4	33.0±20.1	0.952
Dia	betes, n (%)	170 (20.9)	146 (22.4)	0.54	176 (19.9)	140 (24.0)	0.071
eGł n (%	R <60 ml/min/1.73 m², %)	326 (40.0)	262 (40.1)	0.956	381 (43.1)	207 (35.5)	0.006
LVE	F (%)	25.7±7.9	28.3±8.3	<0.001	26.2±8.3	27.9±7.9	<0.001
LVE	DV (ml)	219.0±80.3	192.9±71.4	<0.001	220.0±81.3	188.4±67.2	<0.001
LVE	SV (ml)	165.5±71.2	140.7±60.8	< 0.001	165.7±72.8	137.6±55.7	<0.001
Me	dication, n (%)						
-	Diuretic	663 (81.4)	526 (80.6)	0.71	722 (81.7)	467 (80.1)	0.494
-	Digoxin	136 (16.7)	103 (15.8)	0.68	148 (16.7)	91 (15.6)	0.615
-	β-blocker	606 (74.4)	462 (70.8)	0.13	621 (70.2)	447 (76.7)	0.008
-	antagonist	305 (44.8)	292 (44.7)	1.0	380 (43.0)	277 (47.5)	0.098
-	ACE-inhibitor	722 (88.7)	563 (86.2)	0.18	781 (88.3)	504 (86.4)	0.318

Table 1: Baseline characteristics.

Values are mean ± standard deviation. ACE: angiotensin-converting enzyme, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, 6 MWT: 6-minute walk test, NYHA: New York Heart Association, QoL: quality of life.

	LBBB (n=814)		Non-LBBB (n=653)		P-value	QRS ≥150 ms (n=884)		QRS <150 ms (n=583)		P-value
	Mean change	95% CI	Mean change	95% CI		Mean change	95% CI	Mean change	95% CI	
LVEDV (ml)	-25.2	-28.6, -21.8	-14.5	-20.3, -8.8	0.005	-29.8	-33.5 <i>,</i> -26.0	-8.9	-13.3, -4.6	0.003
LVESV (ml)	-30.75	-33.8, -27.7	-17.4	-22.3, -12.4	<0.001	-34.3	-37.7, -30.9	-14.8	-18,7, -11.0	<0.001
LVEF (%)	+6.9	6.3 <i>,</i> 7.50	+3.7	2.6, 4.9	<0.001	+6.8	6.1 <i>,</i> 7.4	+5.2	4.1 <i>,</i> 6.1	<0.001

	Table 2:	Changes in L	/ volumes and	ejection fraction,	according to QR	S morphology and	I duration.
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LBBB: left bundle branch block, CI: confidence interval, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction. P-values based on linear, mixed model analysis.



QRS duration (ms)

Figure 2: Influence of QRS duration as a continuous variable on left ventricular end-systolic volume (LVESV) reduction after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation curve for each group (red = LBBB and blue = non-LBBB) and the solid line the overall population (black).

DISCUSSION

The main findings of the present study are the greater benefit of CRT (in terms of LV reverse remodeling (defined as reduction in LVESV) and improvement in LVEF) in HF patients with LBBB and a QRS duration ≥150 ms, compared to patients with non-LBBB QRS morphology or shorter QRS duration.

Influence of QRS morphology and duration on CRT efficacy

Several studies have demonstrated the influence of QRS morphology and duration on the outcome of HF patients treated with CRT.⁸⁻¹¹ In a large, retrospective cohort study, including

24 169 patients treated with CRT, Peterson et al. showed that patients with LBBB morphology and a QRS duration \geq 150 ms presented lower rates of all-cause mortality (20.9% at 3 years) compared to patients with LBBB and QRS <150 ms (26.5% at 3 years) or with non-LBBB morphology (30.7% for QRS \geq 150 ms and 32.3% for QRS <150 ms).⁴ These findings were also observed in a meta-analysis of 5 randomized trials including 5 813 CRT patients: QRS duration \geq 150 ms was significantly associated with a reduction of the risk of the composite clinical endpoint (risk ratio 0.60; 95% confidence interval (CI) 0.53-0.67; P<0.001) whereas a QRS duration between 120 and 149 ms was not (risk ratio 0.95; 95% CI 0.82-1.10; P=0.49).¹²



QRS duration (ms)

Figure 3: Influence of QRS duration as a continuous variable on left ventricular ejection fraction (LVEF) change after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation curve for each group (red = LBBB and blue = non-LBBB) and the solid line the overall population (black).

In the Resynchronization/defibrillation in Ambulatory Heart Failure Trial (RAFT), all-cause mortality and hospitalization for HF were reduced in patients with LBBB morphology, but not in those with non-LBBB morphology.² In a meta-analysis of 4 randomized controlled trials reported by Sipahi et al. (including 5 356 patients), composite clinical events (all-cause mortality and HF hospitalization) were reduced in patients with LBBB (relative risk (RR)=0.64, 95% CI 0.52-0.77, P=0.00001), but not in patients with a non-LBBB morphology (RR=0.97, 95% CI 0.82-1.15, P=0.75).¹³

Importantly, the prognosis of patients with CRT is also influenced by the response to CRT at mid-term follow-up, defined as LV reverse remodeling.¹⁴⁻¹⁶ In a study including 679 patients treated with CRT, LV reverse remodeling (reduction of \geq 15% in LVESV) at 6 months of follow-up was associated with better prognosis independently of improvement in clinical status.¹⁴ How QRS duration and morphology affect the extent of LV reverse remodeling and the degree of

improvement in LV systolic function after CRT has not been extensively studied, especially in patients with more advanced stages of HF (NYHA class III and IV).

QRS morphology and duration vs. LV reverse remodeling and improvement in LVEF after CRT

The effects of CRT on LV volumes and LVEF according to the QRS duration and morphology have been studied in few randomized trials, including only patients with HF NYHA class I and II symptoms.^{10,17} In the Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy (MADIT-CRT) trial, randomizing 1 820 patients (70% with LBBB morphology) with mild HF (NYHA class I and II) to CRT-D vs. ICD alone, patients with LBBB morphology had a greater decrease in LVEDV compared to those with non-LBBB (56.7±34.1 ml vs. 41.0±28.13 ml, respectively; P<0.001).¹⁰ Patients with LBBB also experienced a greater decrease in LVESV than patients with non-LBBB (62.1±31.5 ml vs. 45.7±28.13 ml, respectively; P<0.001).¹⁰ Lastly, LVEF improved by $11.9\pm5.1\%$ in the LBBB group, vs. $8.8\pm4.9\%$ in the non-LBBB group (P<0.001).¹⁰ Similarly, in the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial, 610 patients with mild HF (NYHA class I and II; 60% with LBBB morphology) randomized to CRT-ON vs. CRT-OFF, patients with LBBB experienced a 25.3 ml/m² mean reduction in LVESV index (P<0.0001), whereas non-LBBB patients had smaller reductions in LVESV (6.7 ml/m²; P=0.18).¹⁷ Moreover, baseline QRS duration was also a strong predictor of the change in LVESV index in the REVERSE trial. When patients were divided into quartiles according to baseline QRS duration, a progressively greater decrease in LVESV index was observed at 12 months of follow-up for longer QRS durations.¹⁷

Our results are consistent with the MADIT-CRT and REVERSE trials, 10,17 with LBBB and increasing QRS duration (especially \geq 150 ms) constituting the group of HF patients who benefit most from CRT in terms of LV reverse remodeling and LVEF improvement. In addition, similar to the REVERSE sub-study, the differences in LV reverse remodeling and improvement in LVEF remained significant after correcting for known confounders such as ischemic HF.¹⁷ More importantly, the present study expands the results of these randomized controlled trials by including a large number of patients with severe HF (NYHA class III and IV). This is highly relevant, since the majority of patients in previous randomized controlled trials and large registries had NYHA class III HF symptoms.^{4,18-20} However, the association between QRS morphology and duration and changes in LV volumes and LVEF after CRT in that group of patients has not been previously described. In addition, although the efficacy of CRT in NYHA functional class IV has been debated, our results show that this group of patients may also show significant reduction in LV volumes and improvement in LVEF, thus supporting CRT implantation in this group of patients as indicated in current guidelines.^{1,21-23} Current guidelines for the diagnosis and management of HF patients recommend CRT for HF patients with LBBB morphology and QRS duration ≥150 ms (class IA) or 130-149 ms (class IB).²³ For HF patients with non-LBBB morphology the recommendation level is II (IIa for patients with QRS duration ≥150 ms and IIb for patients with QRS

duration between 130-149 ms). The present results also support these recommendations since, for the first time, they demonstrate that the greatest benefit from CRT (in terms of LV reverse remodeling and LVEF improvement) was observed in a large population of NYHA class I-IV HF patients with LBBB morphology and QRS duration ≥150 ms.

Study limitations

This study was limited by its design: a retrospective, single-centre study, but an advantage is that it reflects experience from a large, real-world, referral centre. In this population, the number of patients receiving beta-blockers was still fairly low, although it was higher compared to many landmark trials which established the utility of CRT.^{18-20,24-27} This probably reflects that in daily practice, a significant percentage of severe HF patients do not tolerate beta-blockers. It is also known that other factors, such as the extent of scar tissue in the LV and the LV lead position may influence the response to CRT. These factors were not systematically available in the current population.

CONCLUSIONS

LV reverse remodeling and functional improvement are greater among HF patients with LBBB QRS morphology and increasing QRS duration (especially \geq 150 ms) who received CRT. These findings are supportive of contemporary guidelines for CRT placement.

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