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

Bijl, P. van der

Author: Bijl, P. van der
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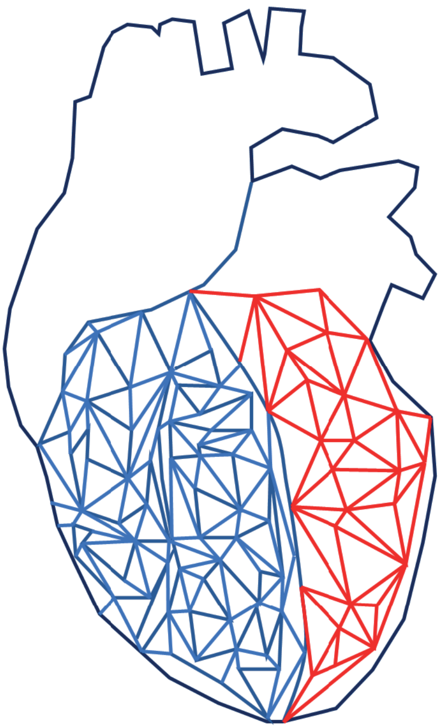
Part I:

The role of echocardiography in predicting outcome after CRT



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

Van der Bijl P
Khidir M
Leung M
Mertens B
Ajmone Marsan N
Delgado V
Bax JJ

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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 ≥150 ms and 814 (55%) showed LBBB. The group with QRS ≥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 (≥120 ms) and reduced left ventricular ejection fraction (LVEF ≤35%).[1] The benefits of CRT may differ, based on QRS complex duration and morphology. Recent registries, meta-analyses and sub-studies of randomized controlled trials have shown that patients with left bundle branch block (LBBB) morphology and QRS duration ≥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. ≥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 ≥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

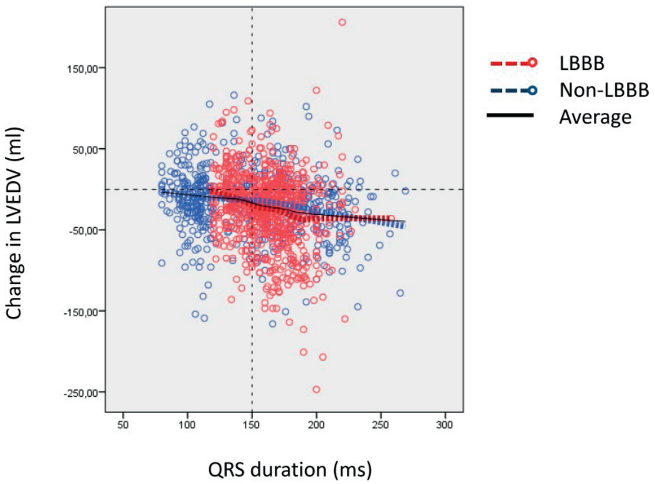

Figure 1: Influence of QRS duration as a continuous variable on left ventricular end-diastolic volume (LVEDV) reduction after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation 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.

Table 1: Baseline characteristics.

	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
Male gender, n (%)	598 (73.5)	528 (80.9)	0.001	668 (75.6)	458 (78.6)	0.206
Ischemic etiology, n (%)	439 (53.9)	427 (65.4)	<0.001	466 (52.7)	400 (68.6)	<0.001
Heart rhythm, n (%)						
- Sinus rhythm	693 (85.1)	362 (55.4)	<0.001	591 (66.9)	464 (79.6)	<0.001
- Atrial fibrillation	118 (14.5)	148 (22.7)	<0.001	158 (17.9)	108 (18.5)	0.804
- Paced	3 (<0.1)	143 (21.9)	<0.001	135 (15.3)	11 (<0.1)	<0.001
NYHA functional class, n (%)						
- I	28 (3.4)	34 (5.2)	0.114	29 (3.3)	33 (5.7)	0.033
- II	195 (24.0)	168 (25.7)	0.409	210 (23.8)	153 (26.2)	0.252
- III	519 (63.8)	379 (58.0)	0.045	557 (63.0)	341 (58.5)	0.148
- IV	57 (7.0)	52 (8.0)	0.517	70 (7.9)	39 (6.7)	0.473
6 MWT (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
Diabetes, n (%)	170 (20.9)	146 (22.4)	0.54	176 (19.9)	140 (24.0)	0.071
eGFR <60 ml/min/1.73 m^2, n (%)	326 (40.0)	262 (40.1)	0.956	381 (43.1)	207 (35.5)	0.006
LVEF (%)	25.7±7.9	28.3±8.3	<0.001	26.2±8.3	27.9±7.9	<0.001
LVEDV (ml)	219.0±80.3	192.9±71.4	<0.001	220.0±81.3	188.4±67.2	<0.001
LVESV (ml)	165.5±71.2	140.7±60.8	<0.001	165.7±72.8	137.6±55.7	<0.001
Medication, 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
- Mineralocorticoid antagonist	365 (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

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.

Table 2: Changes in LV volumes and ejection fraction, according to QRS morphology and duration.

	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, -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, 7.50	+3.7	2.6, 4.9	<0.001	+6.8	6.1, 7.4	+5.2	4.1, 6.1	<0.001

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.

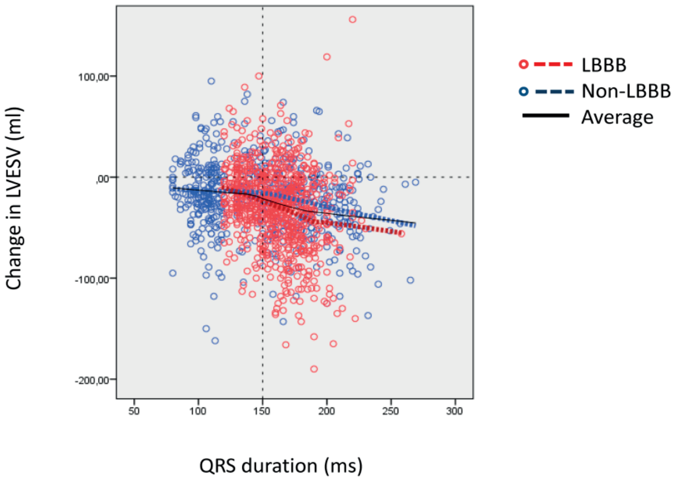

Figure 2: Influence of QRS duration as a continuous variable on left ventricular end-systolic volume (LVESV) reduction after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation 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 ≥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 ≥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 ≥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]

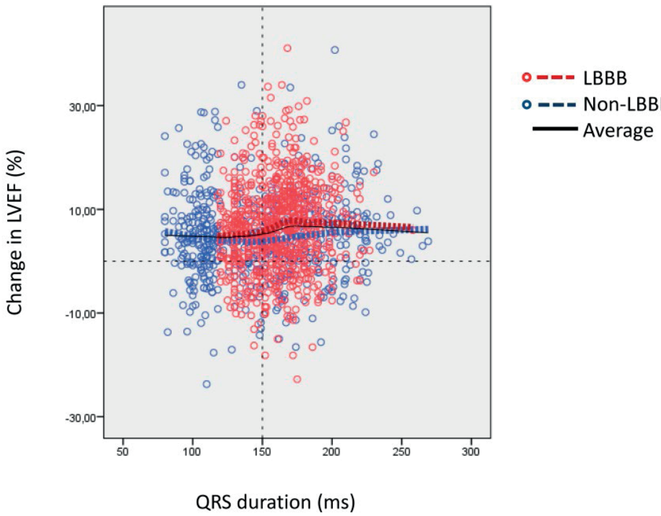

Figure 3: Influence of QRS duration as a continuous variable on left ventricular ejection fraction (LVEF) change after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation curve 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 ≥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±5.1% in the LBBB group, vs. 8.8±4.9% 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/m^2 mean reduction in LVESV index (P<0.0001), whereas non-LBBB patients had smaller reductions in LVESV (6.7 ml/m^2; 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 ≥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 ≥150 ms) who received CRT. These findings are supportive of contemporary guidelines for CRT placement.

REFERENCES

1. Brignole M, Auricchio A, Baron-Esquivias G et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;34:2281-329.
2. Birnie DH, Ha A, Higginson L et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail* 2013;6:1190-8.
3. Cleland JG, Abraham WT, Linde C et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013;34:3547-56.
4. Peterson PN, Greiner MA, Qualls LG et al. QRS duration, bundle-branch block morphology, and outcomes among older patients with heart failure receiving cardiac resynchronization therapy. *JAMA* 2013;310:617-26.
5. Ruschitzka F, Abraham WT, Singh JP et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;369:1395-405.
6. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-70.
7. Surawicz B, Childers R, Deal BJ et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2009;53:976-81.
8. Moss AJ, Hall WJ, Cannom DS et al. Cardiac resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-38.
9. Linde C, Abraham WT, Gold MR et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;52:1834-43.
10. Zareba W, Klein H, Cygankiewicz I et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the multicenter automatic defibrillator implantation trial - cardiac resynchronization therapy (MADIT-CRT). *Circulation* 2011;123:1061-72.
11. Tang AS, Wells GA, Talajic M et al. Cardiac resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;363:2385-95.
12. Sipahi I, Carrigan TP, Rowland DY et al. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Arch Intern Med* 2011;171:1454-62.
13. Sipahi I, Chou JC, Hyden M et al. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Am Heart J* 2012;163:260-7.

14. Bertini M, Hoke U, van Bommel RJ et al. Impact of clinical and echocardiographic response to cardiac resynchronization therapy on long-term survival. *Eur Heart J Cardiovasc Imaging* 2013;14:774-81.
15. Gold MR, Daubert C, Abraham WT et al. The effect of reverse remodeling on long-term survival in mildly symptomatic patients with heart failure receiving cardiac resynchronization therapy: results of the REVERSE study. *Heart Rhythm* 2015;12:524-30.
16. Ypenburg C, van Bommel RJ, Borleffs CJ et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009;53:483-90.
17. Gold MR, Thebault C, Linde C et al. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the resynchronization reverses remodeling in systolic left ventricular dysfunction (REVERSE) study. *Circulation* 2012;126:822-9.
18. Abraham WT, Young JB, Leon AR et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004;110:2864-8.
19. Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
20. Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.
21. Rickard J, Bassiouny M, Tedford RJ et al. Long-term outcomes in patients with ambulatory New York Heart Association class III and IV heart failure undergoing cardiac resynchronization therapy. *Am J Cardiol* 2015;115:82-5.
22. Van Bommel RJ, van Rijnsoever E, Borleffs CJ et al. Effect of cardiac resynchronization therapy in patients with New York Heart Association functional class IV heart failure. *Am J Cardiol* 2010;106:1146-51.
23. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891-975.
24. Higgins SL, Hummel JD, Niazi IK et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;42:1454-9.
25. Young JB, Abraham WT, Smith AL et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003;289:2685-94.
26. St John Sutton MG, Plappert T, Abraham WT et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003;107:1985-90.
27. Auricchio A, Stellbrink C, Butter C et al. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 2003;42:2109-16.