

The relationship of QRS morphology and mechanical dyssynchrony to long-term outcome following cardiac resynchronization therapy

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Received 8 September 2011; revised 16 December 2011; accepted 12 January 2012; online publish-ahead-of-print 19 February 2012

Aims

Because benefits of cardiac resynchronization therapy (CRT) appear to be less favourable in non-left bundle branch block (LBBB) patients, this prospective longitudinal study tested the hypothesis that QRS morphology and echocardiographic mechanical dyssynchrony were associated with long-term outcome after CRT.

Methods and results

Two-hundred and seventy-eight consecutive New York Heart Association class III and IV CRT patients with QRS ≥ 120 ms and ejection fraction $\leq 35\%$ were studied. The pre-specified primary endpoint was death, heart transplant, or left ventricular assist device over 4 years. Dyssynchrony assessed before CRT included interventricular mechanical delay (IVMD) and speckle-tracking radial strain using pre-specified cut-offs for each. Of 254 with baseline quantitative echocardiographic data available, 128 had LBBB, 81 had intraventricular conduction delay (IVCD), and 45 had right bundle branch block (RBBB). Radial dyssynchrony was observed in 85% of the patients with LBBB, 59% with IVCD*, and 40% with RBBB* (* $P < 0.01$ vs. LBBB). Of 248 (98%) with follow-up, LBBB patients had a significantly more favourable long-term survival than non-LBBB patients. However, non-LBBB patients with dyssynchrony had a more favourable event-free survival than those without dyssynchrony: radial dyssynchrony hazard ratio 2.6, 95% confidence interval (CI) 1.47–4.53 ($P = 0.0008$) and IVMD hazard ratio 4.9, 95% CI 2.60–9.16 ($P = 0.0007$). Right bundle branch block patients who lacked dyssynchrony had the least favourable outcome.

Conclusion

Non-LBBB patients with dyssynchrony had a more favourable long-term survival than non-LBBB patients who lacked dyssynchrony. Mechanical dyssynchrony and QRS morphology are associated with outcome following CRT.

Keywords

Cardiac resynchronization therapy • Heart failure • Conduction disturbance

Introduction

Cardiac resynchronization therapy (CRT) has been established as a useful therapy for heart failure patients with prolonged QRS duration and low ejection fraction (EF).^{1–4} However, clinical response rate to CRT remains at approximately two-thirds using routine guidelines and precise reasons for non-response are unclear. Although QRS widening ≥ 120 ms is currently one of the selection criteria for CRT, the specific QRS morphologies of left bundle branch block (LBBB), intraventricular conduction delay (IVCD), and right bundle branch block (RBBB) have been associated with

different outcomes following CRT.^{1,3,5,6} In particular, non-LBBB patients have benefited less from CRT than those with LBBB. Recent observations from the MADIT-CRT trial and others have resulted in an expanded indication for CRT in less symptomatic heart failure patients, but in those only with LBBB morphology.⁷ Mechanical dyssynchrony is widely believed to be the derangement treated by CRT with QRS width as its surrogate. However, the degree of mechanical dyssynchrony may not be reflected by QRS width or morphology, and there is evidence to support that response to CRT is related, at least in part, to the degree of mechanical dyssynchrony.^{8–13} Accordingly, the objective of this

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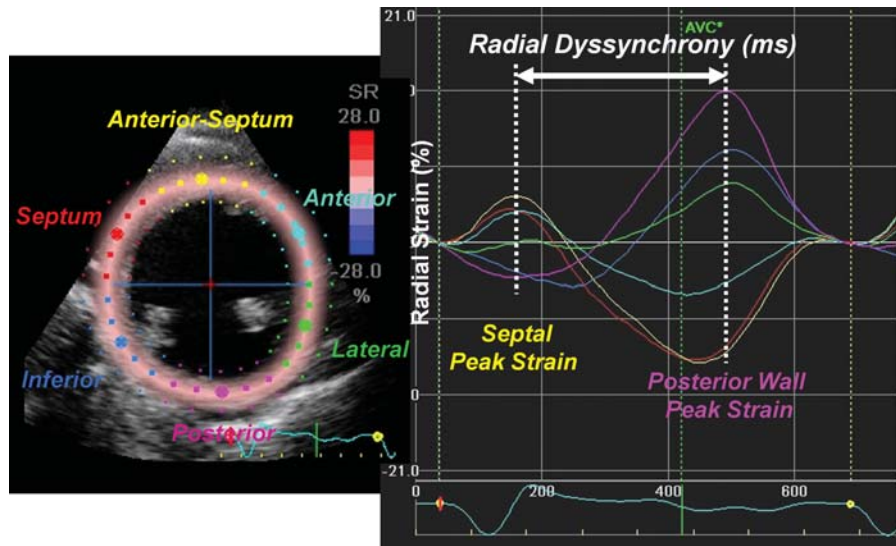


Figure 1 Representative speckle-tracking radial strain curves in a heart failure patient with left bundle branch block. Segmental strain curves in mid-left ventricular segments are shown in yellow (anterior septum), light blue (anterior), green (lateral), purple (posterior), dark blue (inferior), and red (septum). Time difference in peak strain in the anterior septum to the peak strain in the posterior wall was used to measure radial dyssynchrony.

study was to test the hypotheses that patient outcome following CRT is related to the degree of baseline mechanical dyssynchrony when considering QRS morphology.

Methods

We prospectively studied 278 consecutive patients referred for CRT with left ventricular (LV) EF $\leq 35\%$, QRS ≥ 120 ms, and symptomatic New York Heart Association (NYHA) class III or IV heart failure, despite the optimal pharmacological therapy. Patients with failed CRT implantation or who had right ventricular (RV) paced rhythm before CRT were not included. The protocol was approved by the Institutional Review Board on Biomedical Research, and patients were given informed consent consistent with this protocol. The mean age was 65 ± 12 years, EF was $24 \pm 6\%$, and QRS duration was 159 ± 27 ms. Eighty-one patients (29%) were female. One-hundred and fifty-eight patients (57%) had ischaemic cardiomyopathy, defined by coronary angiography. Cardiac resynchronization therapy was initiated with implantation of routine CRT pacing defibrillators in all with LV lead placement via the coronary sinus targeting the posterior or lateral wall using angiographic and fluoroscopic guidance.

Electrocardiograms

Baseline 12-lead electrocardiograms (ECG) were recorded at a paper speed of 25 mm/s. Left bundle branch block was defined as: (i) broad, notched R-wave in lateral precordial leads (V_5 and V_6) and usually leads I and aVL, (ii) smaller or absent initial r waves in right precordial leads (V_1 and V_2) followed by deep S-waves, and (iii) absent q waves in left-sided leads. Right bundle branch block was defined as: (i) broad, notched R waves (rsr', rsR', or rSR' patterns) in right precordial leads (V_1 and V_2) and (ii) wide and deep S waves in the left precordial leads (V_5 and V_6).¹⁴ Intraventricular conduction delay was defined as a conduction disturbance which does not meet the criteria of LBBB and

RBBB.¹⁵ Experienced observers who were blind to all other patient data interpreted QRS morphology.

Echocardiography

Echocardiograms were performed with a GE Vivid 7 system (GE-Vigmed, Horten, Norway), or Aplio 80 or Aplio Artida systems (Toshiba Medical Systems Tokyo, Japan) before and ~ 6 months after the CRT implantation. Routine digital grey-scale two-dimensional and tissue Doppler cine-loops were obtained from standard apical and mid-LV short-axis views.^{8,16,17} Quantitative analyses were performed using off-line software (EchoPac, version BT09, GE-Vingmed or Toshiba Medical Systems). Speckle-tracking radial dyssynchrony was evaluated using mid-short-axis images as previously described in detail.¹⁶ Briefly, a circular region of interest was traced on the endocardial and epicardial borders and manually adjusted for time-strain curves. Significant radial dyssynchrony was defined as the time difference between the peak strain in anterior-septum and posterior wall segments predefined as ≥ 130 ms (Figure 1).¹⁶ Left ventricular and RV pre-ejection delay (PED) was determined as the time from the QRS onset to the onset of pulsed Doppler flow in the LV and RV outflow tracts. Interventricular mechanical delay (IVMD) was calculated as the difference in LV and RV PED with a predefined cut-off of ≥ 40 ms.^{18,19} Tissue Doppler longitudinal dyssynchrony was defined as the maximum opposing wall time difference in peak systolic velocities with the predefined cut-off of ≥ 65 ms.^{11,17,20} The Yu index was calculated as the standard deviation (SD) of the 12 segments' time-to-peak velocities with the predefined cut-off of ≥ 32 ms.²¹ Left ventricular EF was assessed by biplane Simpson's rule.

Analysis of effects of cardiac resynchronization therapy on outcome

The pre-specified long-term outcome variable was the combined endpoint of death, cardiac transplant, or ventricular assist device (LVAD) implantation. This combined endpoint was pre-determined because

Table 1 Baseline patient characteristics

	LBBB (n = 128)	Non-LBBB (n = 126)	IVCD (n = 81)	RBBB (n = 45)	P-value
Age (years)	66 ± 12	65 ± 11	65 ± 11	63 ± 12	0.374
Male gender (n)	88 (69%)	92 (73%)	55 (68%)	37 (82%)	0.180
NYHA class III/IV (n)	113/15	114/12	73/8	41/4	0.839
Ischaemic cardiomyopathy (n)	63 (49%)	83 (66%)*	52 (64%)*	31 (69%)*	0.024
QRS duration (ms)	164 ± 26	153 ± 26*	148 ± 25*	163 ± 26 [†]	<0.0001
QRS >150 ms (n)	90 (70%)	58 (46%)*	27 (36%)*	29 (64%) [†]	<0.0001
Atrial fibrillation (n)	13 (10%)	17 (13%)	12 (15%)	5 (11%)	0.589
Mitral regurgitation (1 to 4+)	1.5 ± 1.2	1.7 ± 1.1	1.7 ± 1.1	1.6 ± 1.2	0.711

LBBB, left bundle branch block; IVCD, non-specific intraventricular conduction disturbance; RBBB, right bundle branch block; NS, not significant. P-value indicates comparison across LBBB, IVCD, and RBBB. Mitral regurgitation: 1+, mild; 2+, mild to moderate; 3+, moderate to severe; 4+, severe.

*P < 0.05 vs. LBBB.

[†]P < 0.05 vs. IVCD.

only patients with end-stage heart failure with a limited anticipated survival would undergo transplant or LVAD implantation in our institution. Follow-up was obtained from a combination of the patient's medical records, vital status registry, and when needed telephone contact with the patient's physicians. Analysis of effects of CRT on LV function and reverse remodeling was assessed at ~6 months in the subgroup of patients who had quantitative echocardiographic data available for EF and end-systolic volume (ESV).^{13,22,23}

Statistical analysis

Statistical analyses were conducted using SPSS (version 17.0, SPSS Inc., Chicago, IL, USA). Group data were presented as means ± SD. Data from all continuous variables were determined to have a normal distribution and were compared using the two-sided Student's *t*-test for paired and unpaired data, where appropriate. One-way ANOVA followed by the Tukey *post hoc* tests was used to compare parameters, including LV volume and EF among patients with LBBB, IVCD, and RBBB. Proportional differences were evaluated using Fisher's exact test and χ^2 was used for non-continuous variables. The Kaplan–Meier survival curves were plotted to measure outcome and the log-rank test used to compare survival between patients with or without dyssynchrony. A Cox proportional hazard model was used to assess for any potential influence of covariates. To test the appropriateness of the proportional hazards assumption in the Cox model, we determined that differences in QRS width and incidence of ischaemic aetiology at baseline were potential confounding covariates. Adjustments were made with the influence of these explanatory variables assumed to be constant over time. We verified the proportional hazards assumption using graphical methods and the log-rank test and observed the proportional hazards assumption to be appropriate. Data were reported as mean ± SD with a P-value of <0.05 considered as significant.

Results

Clinical characteristics

Of 278 consecutive patients referred for CRT, 24 (9%) had baseline echocardiographic images unsuitable for quantitative analysis and were eliminated from all further study. Accordingly, the study group consisted of 254 patients with the following QRS

morphologies: LBBB (n = 128), IVCD (n = 81), and RBBB (n = 45). There were no differences in age or gender among the groups. Ischaemic disease was more prevalent in patients with IVCD or RBBB compared with LBBB patients. Patients with IVCD also had significantly narrower QRS duration than those with either LBBB or RBBB (Table 1).

Baseline dyssynchrony analysis

Routine pulsed-Doppler, speckle-tracking radial strain, and tissue Doppler dyssynchrony results are shown in Table 2. Left bundle branch block patients overall had the most prevalent and significant degree of dyssynchrony by speckle-tracking radial strain compared with non-LBBB patients, and RBBB patients overall had the least. Left bundle branch block patients had time-to-peak radial strain occurred earlier in the anteroseptum and later in the posterior wall than non-LBBB patients (Figure 2). Left bundle branch block patients also had greater dyssynchrony by routine pulsed-Doppler methods than non-LBBB patients. Specifically, the LV PED and IVMD were greatest in LBBB patients and RV PED was greatest in RBBB patients, while the IVMD was usually minimal in patients with RBBB. However, there were no differences in the degree or prevalence of tissue Doppler longitudinal dyssynchrony between QRS morphology groups by opposing wall delay (at the pre-specified cut-off of 65 ms) or the Yu index among groups. *Post hoc* analysis of an opposing wall delay of ≥80 ms became statistically significant (P < 0.05). Of IVCD patients, the QRS width was 150 ± 26 (range 120–216 ms) in the 47 with radial dyssynchrony ≥130 ms and 142 ± 20 (range 120–200 ms) in the 33 patients without radial dyssynchrony (P = 0.117). Of 25 IVCD patients with IVMD ≥40 ms, QRS width was 162 ± 30 (range 120–216 ms) vs. 141 ± 19 (range 120–214 ms) in the 51 with no significant interventricular dyssynchrony (P = 0.0007). Of RBBB patients, the QRS width was 169 ± 32 (range 122–228 ms) in the 17 with radial dyssynchrony ≥130 ms vs. 160 ± 20 (range 120–200 ms) in the 26 without radial dyssynchrony (P = 0.240). Of the 6 RBBB patients with IVMD ≥40 ms, QRS width was 183 ± 31 (range 138–228 ms) vs. 159 ± 21 (range 120–212 ms) in the 30 with no significant IVMD (P = 0.027),

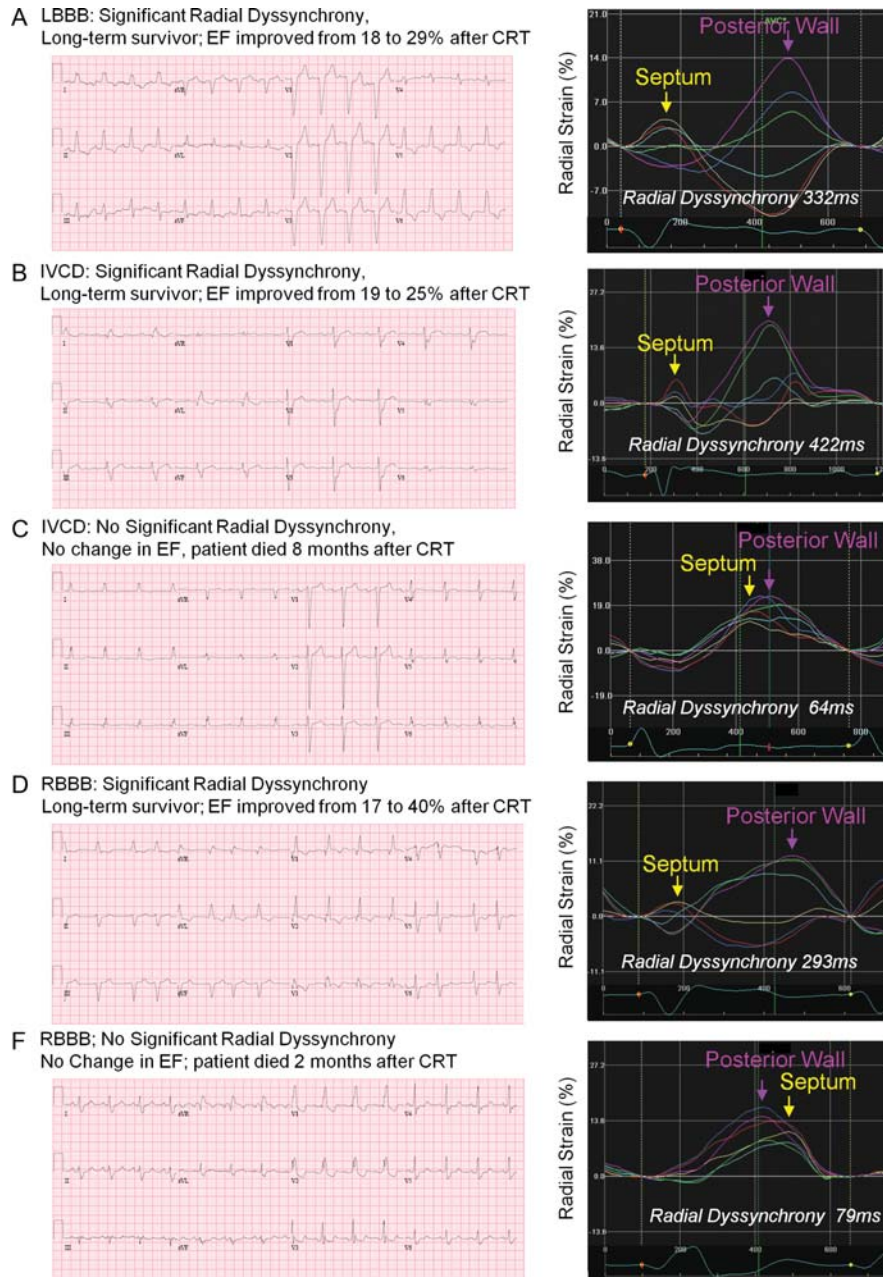


Figure 2 (A–E) Five patient examples of different QRS morphology and radial strain dyssynchrony, with ejection fraction (EF) response and long-term outcome following cardiac resynchronization therapy (CRT). LBBB, left bundle branch block; IVCD, interventricular conduction delay; RBBB, right bundle branch block.

supporting that significant IVMD occurred more often in non-LBBB patients with wider QRS.

Since ischaemic cardiomyopathy was represented in patients with non-LBBB more often than those with LBBB, the details related to dyssynchrony were as follows: in the 47 IVCD patients with radial dyssynchrony ≥ 130 ms, ischaemic aetiology was observed in 27 (57%) vs. 25 in 33 patients (76%) without radial dyssynchrony ($P = 0.146$). Of the 25 IVCD patients with IVMD ≥ 40 ms, ischaemic aetiology was observed in 12 (48%) vs. 38 in 51 patients (75%) without significant IVMD ($P = 0.042$). Of the

17 RBBB patients with radial dyssynchrony ≥ 130 ms, ischaemic aetiology was observed in 12 (71%) vs. 17 in 26 patients (65%) without significant radial dyssynchrony ($P = 0.982$). Of the 6 RBBB patients with IVMD ≥ 40 ms, ischaemic aetiology was observed in 3 (50%) vs. 20 in 50 patients (67%) without significant IVMD ($P = 0.756$).

Long-term clinical outcomes

Over a 4-year period, 75 outcome events occurred after CRT including 56 deaths, 12 transplants, and 7 LVAD implantations. Six

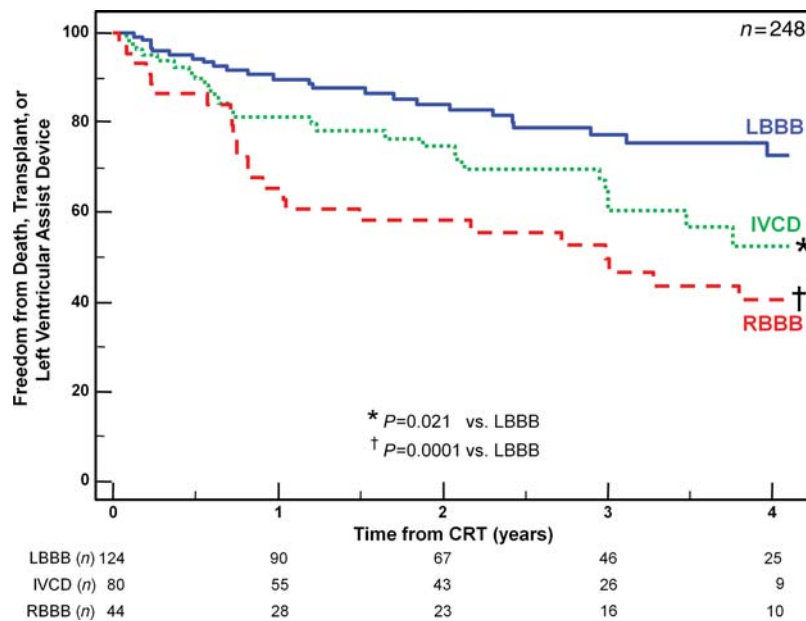


Figure 3 The Kaplan–Meier curves demonstrating the probability of freedom from death, transplant, or ventricular assist device after cardiac resynchronization therapy (CRT) comparing patients with left bundle branch block (LBBB), interventricular conduction delay (IVCD), and right bundle branch block (RBBB).

patients (2%) who were lost to follow-up could not be included in long-term analysis. Overall, patients with LBBB had the greatest freedom from death, transplant, or LVAD, compared with patients with IVCD with an intermediate outcome, and RBBB patients with the least favourable outcome (Figure 3). Non-LBBB patients with baseline dyssynchrony by radial strain or IVMD had significantly more favourable long-term outcome, which was similar to LBBB patients when compared with non-LBBB patients who lacked dyssynchrony (Figure 4). Specifically, in non-LBBB patients when associating dyssynchrony with survival, the hazard ratio of radial dyssynchrony was 2.58, with a 95% confidence interval (CI) of 1.47–4.53, $P = 0.0008$, and the hazard ratio of IVMD was 4.88, with a 95% CI of 2.60–9.16, $P = 0.0007$. When considered individually, both IVCD and RBBB patients who lacked radial dyssynchrony or IVMD had a significantly lower event-free survival following CRT than LBBB patients (Figures 5 and 6). Specifically when associating dyssynchrony with survival in IVCD patients, the hazard ratio of radial dyssynchrony was 2.25, with a 95% CI of 1.02–4.95, $P = 0.03$, and the hazard ratio of IVMD was 6.33, with a 95% CI of 2.76–14.52, $P = 0.004$. Finally when associating dyssynchrony with survival in RBBB patients, the hazard ratio of radial dyssynchrony was 2.75, with a 95% CI of 1.21–6.23, $P = 0.02$, although the hazard ratio of IVMD was not statistically significant. We then adjusted for the covariates of ischaemic disease and baseline QRS duration using a Cox proportional hazard model, and the presence of radial strain dyssynchrony remained independently associated with event-free survival in combined non-LBBB patients (adjusted hazard ratio: 2.50, $P = 0.002$) as well as IVCD (adjusted hazard ratio: 2.29, $P = 0.047$) and RBBB patients (adjusted hazard ratio: 2.78, $P = 0.033$). Interventricular

mechanical delay remained independently associated with event-free survival in grouped non-LBBB patients (adjusted hazard ratio: 5.34, $P = 0.002$) and IVCD patients (adjusted hazard ratio: 6.91, $P = 0.013$) individually. We then assessed the potential influence of a combination of interventricular and intraventricular dyssynchrony by examining IVMD and radial strain together (Figure 7). Patients with both IVMD and radial dyssynchrony appeared to have favourable outcome similar to LBBB after CRT, whereas patients who lacked significant IVMD and radial dyssynchrony had the least favourable outcome (Figure 7).

Subgroup results of ventricular volumes and ejection fractions

Of 248 possible patients for near-term echocardiographic follow-up, 24 reached a primary endpoint <7 months after CRT as follows: 8/124 (6%) in LBBB (5 deaths, 2 transplants, and 1 LVAD), 9/80 (11%) in IVCD (6 deaths, 1 transplant, and 2 LVAD), and 7/44 (16%) in RBBB (6 deaths and 1 transplant) (not significant across groups, $P = 0.170$). The sample for LV functional analysis consisted of 204 out of 224 remaining patients (91%) who returned for quantitative echocardiography 7 ± 5 months after CRT. Baseline LV volumes and EFs were similar when classified by QRS morphology (Table 3). After CRT, LBBB patients were observed to have a significantly greater absolute increase in EF and relative decrease in ESV than IVCD or RBBB patients, $P < 0.0001$. Left bundle branch block patients had greater improvements in EF (23 ± 6 – $34 \pm 12\%^*$, $P < 0.001$). However, non-LBBB patients with dyssynchrony improved their EFs (23 ± 6 – $31 \pm 10\%^*$, $P < 0.001$) compared with those without dyssynchrony (25 ± 6 – $27 \pm 8\%$, not significant $P =$

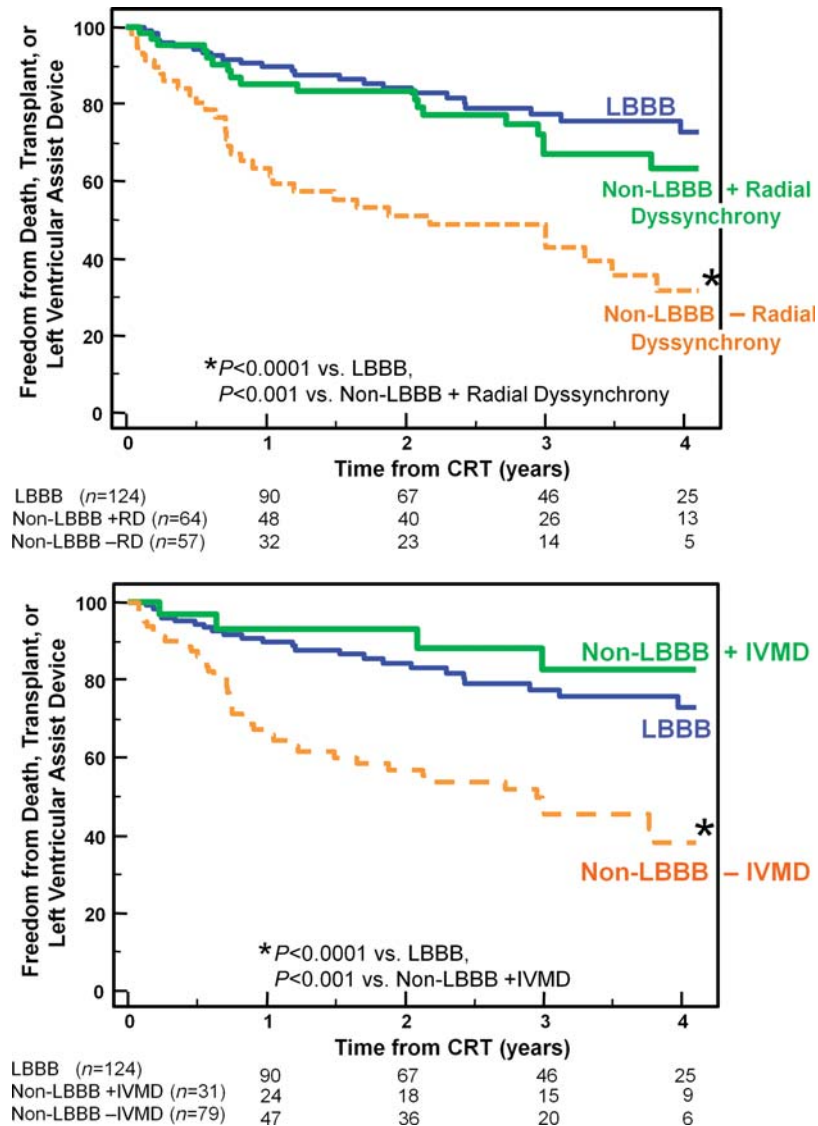


Figure 4 The Kaplan–Meier curves demonstrating the probability of freedom from death, transplant, or ventricular assist device after cardiac resynchronization therapy (CRT) comparing patients with left bundle branch block (LBBB), to those with non-LBBB with or without significant radial dyssynchrony (top panel) or with or without interventricular mechanical delay (IVMD) (bottom panel). Non-LBBB patients with dyssynchrony had similar outcome as those with LBBB, whereas Non-LBBB patients without dyssynchrony had a less favourable outcome.

0.151). Specifically, IVCD and RBBB patients with dyssynchrony had improvements in EF and ESV following CRT, whereas those who lacked dyssynchrony had no significant changes in EF or ESV (Figure 8). Right bundle branch block patients who lacked dyssynchrony had the least improvement in ESV or EF following CRT.

Discussion

This study of a large series of consecutive patients referred for CRT with routine indications demonstrated significant differences in long-term outcome when QRS morphology and mechanical dyssynchrony were considered. Overall, patients with LBBB had the most favourable outcome, patients with RBBB had the least

favourable outcome, and patients with IVCD and an intermediate outcome.⁶ Subgroup analysis of LV functional response was supportive in terms of EF increases and ESV decreases followed a similar association with QRS morphology as did long-term survival free from transplant or LVAD. Importantly, patients with non-LBBB QRS morphology who demonstrated evidence of mechanical dyssynchrony by speckle-tracking radial strain or IVMD appeared to have a significantly greater benefit from CRT. Conversely, patients with QRS morphologies of IVCD or RBBB who lacked mechanical dyssynchrony had a comparatively less favourable outcome following CRT.

Recent attention has focused on QRS morphology and outcome following CRT after the MADIT-CRT randomized trial.⁷ Zareba

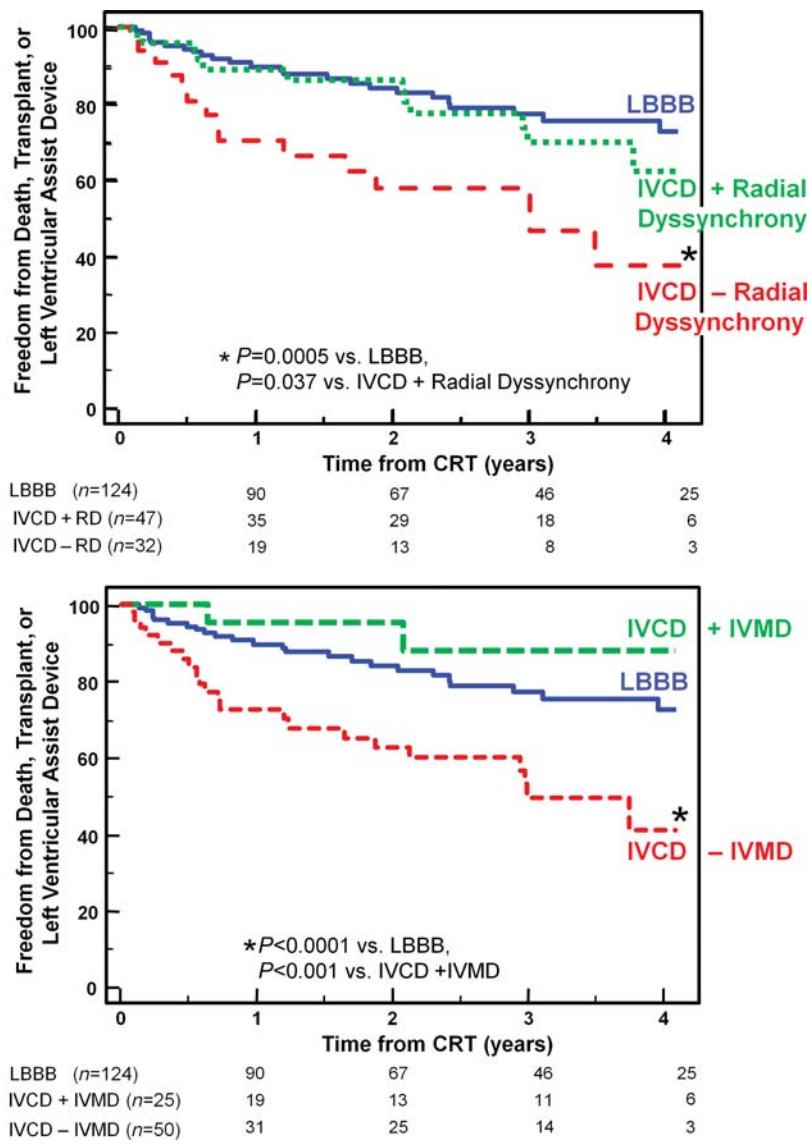


Figure 5 The Kaplan–Meier curves demonstrating the probability of freedom from death, transplant, or ventricular assist device after cardiac resynchronization therapy (CRT) comparing patients with left bundle branch block (LBBB), to those with interventricular conduction delay (IVCD) with or without significant radial dyssynchrony (top panel) or with or without interventricular mechanical delay (IVMD) (bottom panel). Interventricular conduction delay patients with dyssynchrony had similar outcome as those with LBBB, whereas interventricular conduction delay patients without dyssynchrony had a less favourable outcome.

et al.⁶ reported on 1817 patients with NYHA class I or II heart failure, EF $\leq 30\%$, and QRS ≥ 120 ms of whom 70% were LBBB and 30% were non-LBBB morphologies. The patients with LBBB derived substantial clinical benefits from CRT with reduction in heart failure hospitalizations, whereas patients with non-LBBB QRS morphology did not appear to benefit overall. The LBBB patients were more uniform in their favourable response to CRT, whereas subgroup analysis of the non-LBBB patients suggested a much wider variation in response as shown in their relative risk and hazard ratio analysis.⁶ Although we included only NYHA class III or IV patients, our data add a potential explanation for the variable response in non-LBBB patients in its association

with degree of dyssynchrony. Data from the RAFT trial suggested similar results with more favourable benefit in the LBBB patients vs. the non-LBBB patients.²⁴ Since LBBB patients had the greatest incidence and degree of dyssynchrony overall, our data suggest that dyssynchrony by imaging may be of less predictive value in these patients. However, patients with non-LBBB, including those with RBBB, appear to show the greatest association of mechanical dyssynchrony with LV functional improvements and overall survival. Previous observations in the COMPANION trial³ were that CRT benefited patients with LBBB the most by reducing death or hospitalization from any cause compared with pharmacology therapy. In the analysis of pooled data of RBBB patients in the

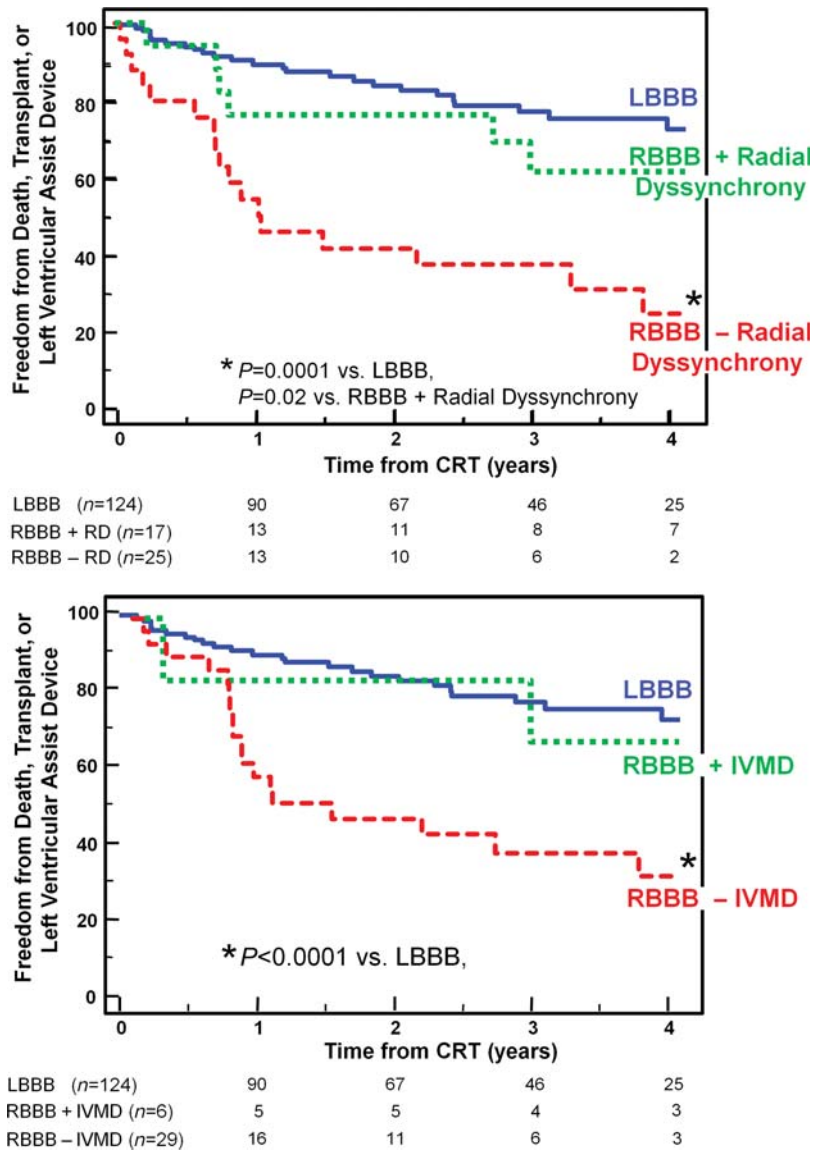


Figure 6 The Kaplan–Meier curves demonstrating the probability of freedom from death, transplant, or ventricular assist device after cardiac resynchronization therapy (CRT) comparing patients with left bundle branch block (LBBB), to those with right bundle branch block (RBBB) with or without significant radial dyssynchrony (top panel) or with or without interventricular mechanical delay (IVMD) (bottom panel). Right bundle branch block patients with dyssynchrony had similar outcome as those with left bundle branch block, whereas right bundle branch block patients without dyssynchrony had a less favourable outcome.

MIRACLE and CONTAK CD trials, there were no demonstrable benefits in any variables studied at follow-up, except NYHA functional class.^{1,25} Other large retrospective CRT studies of patients with different QRS morphologies also reported that improvements in symptoms, LV function, and survival were comparatively lower in patients with non-LBBB.^{5,26,27}

Ventricular contraction abnormalities in LBBB patients are typically characterized as early septal contraction and lateral stretch, followed by septum stretch and lateral contraction later in systole.^{27–32} We observed similar dyssynchrony patterns using radial strain where LBBB had an earlier anterior-septum peak radial strain and later posterior wall peak radial strain than those of the

non-LBBB patients. Interventricular mechanical delay was also greater in LBBB patients compared with IVCD or RBBB patients associated with larger LV PED. Non-LBBB patients in contrast showed later time-to-peak radial strain in the anterior-septal region and earlier time-to-peak strain in the posterior region, which resulted in lesser degrees of radial dyssynchrony, overall. However, non-LBBB patients had a wide range of dyssynchrony patterns associated with variable CRT response. Ventricular activation patterns in IVCD patients are more complex and heterogeneous than those of the LBBB patients.^{33–35} Less data are available on dyssynchrony in RBBB. An experimental study of right bundle ablation showed less intraventricular dyssynchrony

Table 2 Echocardiographic dyssynchrony

	LBBB (n = 128)	Non-LBBB (n = 126)	IVCD (n = 81)	RBBB (n = 45)	P-value
Speckle-tracking radial strain					
Time-to-peak strain					
Anterior septum (ms)	232 ± 115	310 ± 123*	302 ± 128*	325 ± 112*	<0.0001
Posterior wall (ms)	484 ± 84	449 ± 80*	468 ± 70	414 ± 87* [†]	<0.0001
Septal-posterior Wall (ms)	257 ± 112	160 ± 111*	176 ± 117*	130 ± 93*	<0.001
Septal-posterior Wall ≥ 130 ms (n)	105/124 (85%)	64/123 (52%)*	47/80 (59%)*	17/43 (40%)*	<0.0001
Pulsed Doppler					
LV PED (ms)	156 ± 32	134 ± 33*	137 ± 33*	131 ± 33*	<0.0001
LV PED ≥ 140 ms (n)	84/115 (73%)	49/119 (41%)*	33/76 (43%)*	16/43 (37%)*	<0.0001
RV PED (ms)	112 ± 22	118 ± 26	105 ± 22	135 ± 22* [†]	<0.0001
IVMD (ms)	46 ± 22	21 ± 35*	32 ± 24*	-3 ± 42* [†]	<0.0001
IVMD ≥ 40 ms (n)	73/109 (70%)	31/112 (28%)*	25/76 (33%)*	6/36 (17%)*	<0.0001
Tissue Doppler velocity					
Opposing wall delay (ms)	95 ± 36	86 ± 40	90 ± 39	77 ± 42	0.065
Opposing wall ≥ 65 ms (n)	95/123 (77%)	71/102 (70%)	55/74 (74%)	16/28 (57%)*	0.092
Opposing wall ≥ 80 ms (n)	87/123 (71%)	59/102 (58%)*	46/74 (62%)	13/28 (46%)*	0.043
Yu index (ms)	41 ± 17	38 ± 17	39 ± 17	34 ± 17	0.120
Yu index ≥ 32 ms (n)	88/123 (72%)	61/102 (60%)	44/74 (59%)	17/28 (61%)	0.178

LBBB, left bundle branch block; IVCD, non-specific intraventricular conduction disturbance; RBBB, right bundle branch block; LV PED, left ventricular pre-ejection delay; RV PED, right ventricular pre-ejection delay; IVMD, interventricular mechanical delay; NS, not significant. P-value indicates comparison across LBBB, IVCD, and RBBB.

*P < 0.05 vs. LBBB.

[†]P < 0.05 vs. IVCD.

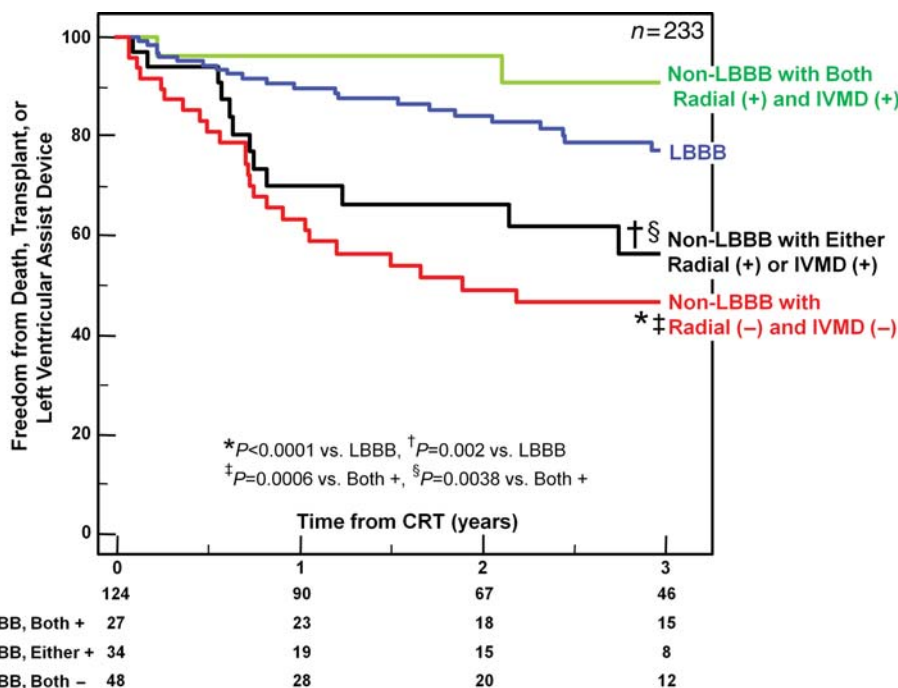


Figure 7 The Kaplan–Meier curves demonstrating the probability of freedom from death, transplant, or ventricular assist device after cardiac resynchronization therapy (CRT) comparing patients with left bundle branch block (LBBB), to those with non-LBBB with or without significant dyssynchrony by a combined approach of interventricular mechanical delay (IVMD) and radial dyssynchrony by speckle-tracking strain. More favourable outcome was observed in non-LBBB with both markers of dyssynchrony, and least favourable outcome in patients who lacked dyssynchrony by either method. +, positive; -, negative.

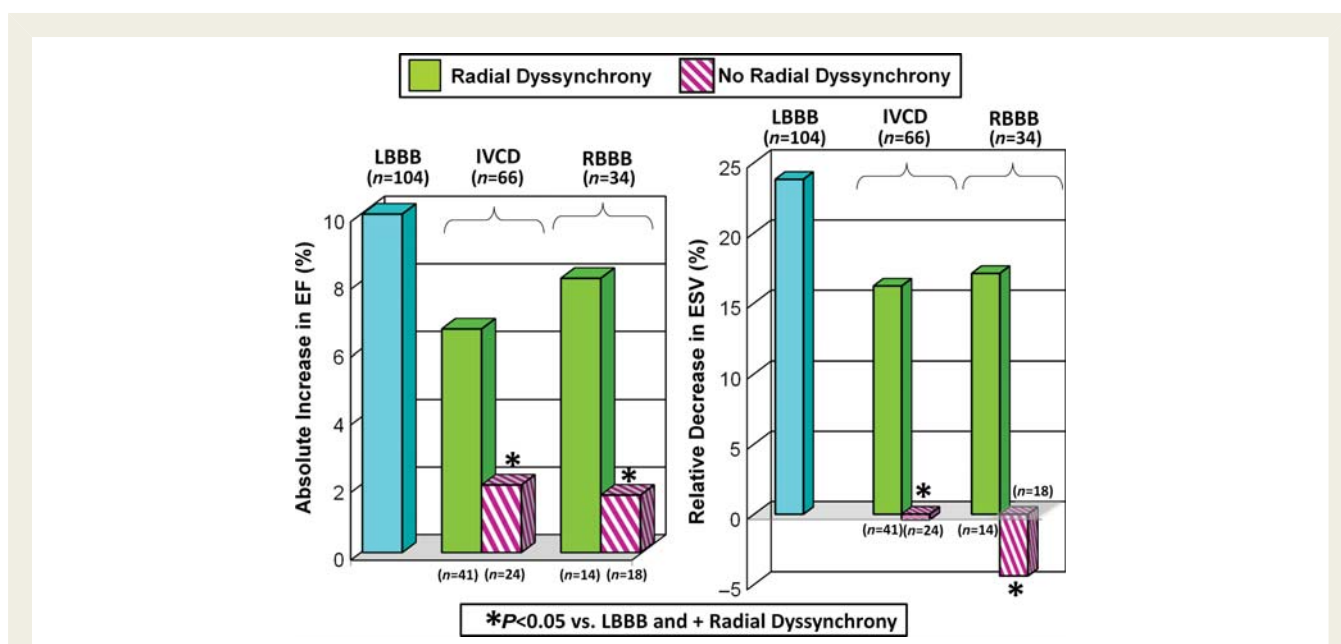


Figure 8 Bar graphs of subgroup analysis of absolute changes in ejection fraction (EF, %) and relative changes in end-systolic volume (ESV, %) after cardiac resynchronization therapy. Patients with left bundle branch block (LBBB) are shown in comparison to patients with interventricular conduction delay (IVCD) or right bundle branch block (RBBB) with or without significant radial dyssynchrony by speckle-tracking strain.

and less haemodynamic response to CRT than LBBB.²⁸ We observed variable mechanical activation patterns in patients with RBBB using radial strain analysis. Although RBBB patients had similar QRS duration compared with those of the LBBB patients (Table 1), the majority of the RBBB patients lacked significant dyssynchrony. On the other hand, a subgroup showed left-sided activation delay similar to those of the LBBB patients associated with a favourable response to CRT.^{33,35}

Several earlier echocardiographic studies reported on the potential utility of dyssynchrony as a means to predict response to CRT.^{8,11,17,21} The PROSPECT multicentre study with a 6-month follow-up suggested that dyssynchrony indices had an insufficient predictive value to alter the current selection criteria for CRT.³⁶ More recent data have demonstrated echocardiographic measures of dyssynchrony to be associated with patient outcome including heart failure hospitalization or long-term survival following CRT. In particular, speckle-tracking echocardiography, which was not studied in PROSPECT, is a promising newer method. The STAR study of 132 CRT patients showed that dyssynchrony by speckle-tracking radial or transverse strain was associated with EF response and long-term event-free survival.¹² Another study of 229 CRT patients with routine indications demonstrated that dyssynchrony measured by IVMD, tissue Doppler opposing wall delay, or Yu Index and speckle-tracking radial strain were all significantly associated with the long-term survival.¹⁰ Delgado *et al.*⁹ recently reported a study of 397 CRT patients with ischaemic heart disease that there was a significant association of radial strain dyssynchrony with survival and heart failure hospitalization over 3 years. Furthermore, the VALIANT study suggested that dyssynchrony may play a role in post-myocardial infarction prognosis of

death or heart failure using dyssynchrony by velocity vector speckle tracking in 381 myocardial infarction patients with LV dysfunction, heart failure, or both.³⁷ Most recently, dyssynchrony by SD of speckle-tracking transverse strain from apical views was associated with clinical outcomes in the MADIT-CRT trial.^{38,39} These previous studies along with our present study combine to support the association of echocardiographic dyssynchrony with patient outcome following CRT.

Study limitations

This study was not part of a randomized trial, and the relationship of echocardiographic dyssynchrony to survival in those who do not undergo CRT remains unknown. Although this study reports important associations of echocardiographic dyssynchrony with patient outcome in QRS morphology subgroups, a direct recommendation for patient selection for CRT would require further study by a randomized controlled trial. Another limitation was that dyssynchrony analysis could not be performed on ~10% of the patients and speckle tracking is operator-dependent and requires user experience.^{16,20,40} However, IVMD requires no specialized equipment or training and was shown to have the greatest feasibility and reproducibility in the PROSPECT study.³⁶ Dyssynchrony by the tissue Doppler longitudinal velocities was not associated with long-term outcome in QRS morphology groups. The reason for this observation is unclear, but longitudinal velocity appears to measure different mechanical phenomena than radial strain or IVMD and tissue Doppler velocities could not differentiate between active and passive motion like speckle-tracking strain imaging. Previous comparisons of tissue Doppler by QRS morphology have not been made. A limitation was that not all patients

Table 3 Left ventricular volumes and ejection fractions

	LBBB	Non-LBBB	IVCD	RBBB	P-value
Echo follow-up (n)	104/116 (90%)	100/108 (93%)	66/71 (93%)	34/37 (92%)	0.638
Follow-up (months)	7 ± 5	7 ± 4	7 ± 4	8 ± 5	0.735
LV end-diastolic volume					
Baseline (mL)	194 ± 81	192 ± 67	195 ± 69	185 ± 61	0.764
Follow-up (mL)	169 ± 80	179 ± 62	182 ± 68	173 ± 48	0.527
LV end-systolic volume					
Baseline (mL)	152 ± 73	147 ± 57	151 ± 61	139 ± 49	0.535
Follow-up (mL)	118 ± 74	131 ± 57	134 ± 62	123 ± 42	0.295
Relative decrease (%)	24 ± 21	8 ± 24*	10 ± 24*	5 ± 22*	<0.0001
Relative decrease ≥10% (n)	66/104 (63%)	38/100 (38%)	27/66 (41%)*	11/34 (32%)*	0.001
LV ejection fraction					
Baseline (%)	23 ± 6	24 ± 6	24 ± 6	25 ± 4	0.070
Follow-up (%)	34 ± 12	28 ± 9*	28 ± 10*	29 ± 8	0.003
Absolute EF increase (%)	10 ± 9	5 ± 8*	5 ± 8*	4 ± 8*	<0.0001
Absolute increase ≥5% (n)	73/104 (70%)	36/100 (36%)	25/66 (38%)*	11/34 (32%)*	<0.0001

LBBB, left bundle branch block; IVCD, non-specific intraventricular conduction disturbance; RBBB, right bundle branch block; LV, left ventricular; NS, not significant. P-value indicates comparison across LBBB, IVCD, and RBBB.

*P < 0.05 vs. LBBB.

had quantitative follow-up echo data available for near-term LV functional analysis, but this was performed on a subgroup of 91%. Another limitation was that other CRT response markers such as heart failure hospitalizations, 6 min walk distance, or peak myocardial oxygen consumption were not part of the present study. Also, specific LV lead positioning data were not part of this study. It may be considered a limitation that ischaemic aetiology may influence response to CRT from scar burden or lead positioning and have confounding effects.^{41–43} We demonstrated that when adjusting specifically for ischaemic aetiology, IVMD and speckle-tracking radial strain remained independently associated with survival. Also, LBBB-like QRS morphology that is categorized as IVCD may be difficult to define. Future ECG methods of quantifying ventricular activation might be considered instead of QRS pattern recognition.⁴⁴ This study concludes that mechanical dyssynchrony and QRS morphology are associated with outcome following CRT and future study is warranted.

Acknowledgements

The authors are grateful to Stephanie Haberman for her skillful assistance with the figures and we thank the entire University of Pittsburgh Medical Center Electrophysiology Laboratory faculty and staff for their continued support and cooperation.

Funding

This study was supported in part by NIH award K24 HL04503-01 and AHA grant-in-aid (0855526D).

Conflict of interest: J.G. received research grant support from Biontronic, GE, Medtronic, St. Jude Medical, and Toshiba Medical. All other co-authors: none declared.

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