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Chapter 8

Predictors of Long-Term Benefit of Cardiac Resynchronization Therapy in Patients with Right Bundle Branch Block

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Cardiac resynchronization therapy (CRT) has demonstrated efficacy at reducing morbidity and mortality among patients with advanced heart failure, reduced left ventricular (LV) ejection fraction (EF), and QRS duration >120 ms.[1,2] Left bundle branch block (LBBB) has been the prevailing QRS morphology in all CRT trials (~70% of the cases). Existing studies comparing CRT recipients with right bundle branch block (RBBB) or LBBB have found poorer outcome among RBBB patients.[3–8] However, only limited data are available on the differences between CRT patients with RBBB or LBBB regarding cardiac mechanics before implantation, and the effect of CRT on LV performance. Furthermore, potential parameters that might help in the selection of CRT candidates with RBBB have not been well elucidated. The aims of this evaluation were therefore: (i) to characterize consecutive CRT recipients with RBBB in comparison with LBBB and (ii) to identify independent predictors of death or heart failure hospitalization among CRT recipients with RBBB.

METHODS

Patient population

The study population consisted of 747 consecutive patients from the ongoing registry of patients treated with CRT between 1999 and 2010.[9] Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and subsequently analysed. The indication for CRT was heart failure with LVEF ≤35%, QRS duration >120 ms, and New York Heart Association (NYHA) functional class III or IV, despite optimal medical therapy. In order to examine specifically the relationship between bundle branch block morphology, cardiac mechanics, and outcome following CRT, patients with non-specific intraventricular conduction disturbance and those receiving upgrades to bi-ventricular pacing from right ventricular (RV) pacing were excluded. Heart failure aetiology was considered ischaemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery on coronary angiography) and/or history of prior myocardial infarction or revascularization.

Prior to CRT, patients underwent clinical evaluation for identification of co-morbid conditions, medications, and functional status, which was quantified by NYHA class. In addition, 12-lead electrocardiography, 6 min walk testing, and Minnesota Living with Heart Failure questionnaire were performed. Transthoracic echocardiography was undertaken to evaluate LV size and systolic function, and the extent of interventricular and LV dyssynchrony. Echocardiography employing an identical protocol was repeated at a median 6-month follow-up (inter-quartile range 6–7 months).

Electrocardiography

Bundle branch block was confirmed by the presence of QRS duration >120 ms. Left bundle branch block was diagnosed by broad, notched, or slurred R-waves and absent q-waves in the lateral leads.[10] Right bundle branch block was defined by an rsR′ morphology in Lead V1 or V2, and an S-wave greater than 40 ms or than the R-wave duration in Leads I and V6.[10] Non-specific intraventricular conduction disturbance was identified in individuals with a QRS duration of >120 ms who failed to meet the above criteria for a discrete bundle branch block.[10] Co-existent left anterior hemi-block was diagnosed in the presence of RBBB if the frontal plane axis was −45° to −90° and there was a qR pattern in aVL. Concomitant left posterior hemi-block was diagnosed in the presence of RBBB if the frontal plane axis was 90–180° and there was either an rS pattern in Leads I and aVL or a qR pattern in Leads III and aVF, and there was no alternative explanation for right-axis deviation.[10,11]

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system equipped with a 3.5 MHz transducer (Vingmed Vivid Seven, General Electric Healthcare, Horten, Norway). Two-dimensional grey-scale, pulsed, continuous, and colour Doppler data were acquired at parasternal and apical views. For tissue Doppler imaging, the sector width was adjusted to obtain a frame rate of at least 115 frames/s. Images were recorded digitally in a cine-loop format and analysed off-line with commercial software EchoPAC (108.1.5, GE-Vingmed). Left ventricular end-systolic and end-diastolic volumes were measured from the apical two- and four-chamber views and LVEF was calculated using the biplane Simpson's technique.[12]

Mitral regurgitation (MR) severity was graded according to the current guidelines.[13] Pulse-wave Doppler recordings in the LV and RV outflow tracts were used to measure time-to-onset of antegrade flow relative to the beginning of the QRS complex (pre-ejection time). Interventricular mechanical delay (IVMD) was calculated as the absolute difference in the LV and RV pre-ejection times, with ≥40 ms IVMD regarded as a significant delay.[1] The ventricular pre-ejection difference was defined as the LV pre-ejection time – RV pre-ejection time. The ventricular pre-ejection difference has therefore a negative value if the RV pre-ejection time exceeds the LV pre-ejection time and reflects the extent of interventricular dyssynchrony.

Left ventricular dyssynchrony was assessed by septal-to-lateral delay as described previously.[14] Using colour tissue Doppler imaging, sample volumes were positioned in the basal septal and lateral myocardial segments in the apical four-chamber view. Septal-to-lateral delay was measured as the time interval between peak systolic velocities of the two segments and was considered significantly elevated if ≥60 ms.[14]

Device implantation

The LV lead was inserted transvenously into the coronary sinus and advanced where possible to the posterolateral cardiac vein under the guidance of venography. The RV and atrial leads were positioned at the RV apex and right atrial appendage, respectively. Implanted devices included Contak Renewal, Contak TR, or Contak CD (Guidant, USA), Insync Marquis, Insync III, or Insync Sentry (Medtronic Inc., USA), Atlas HF (St Jude Medical, USA), and Lumax (Biotronic, Germany).

Outcomes

Six-month response to CRT was defined as a reduction in LV end-systolic volume of ≥15%[15] Long-term follow-up to determine the incidence and cause of death or hospitalization was performed by case record review, telephone contact with patient primary health care providers, and through the national death registry. The primary composite endpoint was all-cause mortality and heart failure hospitalization.

Statistical analysis

Continuous variables are presented as mean ± SD. Categorical data are summarized as frequencies and percentages. Comparisons between RBBB and LBBB groups at baseline were performed using analysis of variance and the $\chi 2$ test as appropriate. For repeated-measures analysis, mixed-effects modelling was employed. The patient group (i.e. RBBB vs. LBBB) was entered into a mixed model as part of an interaction term with subjects' visit time (i.e. baseline vs. follow-up). If this group–time interaction term was significant, then it was retained in the model, and it implied that the group influence on the outcome variable was time- (i.e. visit-) dependent. Post hoc testing was then performed to determine whether the group influence on the dependent variable was significant at both baseline and follow-up visit.

For identifying predictors of response to CRT among RBBB patients, as defined by a reduction in LV end-systolic volume of ≥15% at 6 months, logistic regression analysis was performed for the following covariates: age, gender, heart failure aetiology, renal function, QRS duration, the presence of fascicular block, atrial fibrillation, 6 min walk distance, LVEF, LV end-systolic volume, MR grade, ventricular pre-ejection difference, and LV dyssynchrony.

For survival analysis, a continuous covariate functional form was checked by visual inspection of martingale residuals and transformed where appropriate. Rates of mortality or hospitalization for worsening heart failure were estimated using the Kaplan–Meier technique. The proportional-hazards assumption was tested using scaled Schoenfeld[16] residuals, and in the case of categorical variables by visual inspection of log–log survival curves. We fitted Cox's proportional hazards models to evaluate the predictive value of the above-listed patient characteristics for the primary endpoint of all-cause mortality or hospitalization for worsening heart failure. Predictors associated with a P-value of <0.1 on univariate analysis were entered into a multivariate analysis using stepwise selection to identify independent predictors of death or hospitalization for worsening heart failure. Results are expressed using hazard ratios. All statistical tests were two-sided, and a P-value of <0.05 was considered statistically significant. Analyses were undertaken using STATA software, Version 12 (Stata Corp., College Station, TX, USA).

RESULTS

Patient population

Seven hundred and forty-seven consecutive patients undergoing CRT were evaluated. Eighty (10%) individuals with non-specific intraventricular conduction disturbance and 106 (13%) receiving upgrades to CRT from RV pacing systems were excluded. The following analysis therefore pertains to the remaining 561 patients, of whom 89 (16%) exhibited RBBB and 472 (84%) LBBB. The clinical and echocardiographic characteristics of these individuals are displayed in Table **1**. Thirty-three (37%) RBBB patients exhibited concomitant left hemi-block (24 left anterior hemi-block and 9 left posterior hemi-block). Patients with RBBB were of similar age, NYHA functional class, and QRS duration to those with LBBB; however, male gender, ischaemic aetiology, and atrial fibrillation were more prevalent (P< 0.03). His bundle ablation for atrial fibrillation was performed in 3 (13%) RBBB and 12 (21%) LBBB patients, respectively (P= 0.7). Patients with RBBB displayed lower 6 min walk distance (P= 0.02) and smaller LV volumes (P= 0.02) than their LBBB counterparts, although MR severity did not differ between groups.

Significant difference in the temporal sequence of mechanical activation was observed between the two groups. Left bundle branch block patients exhibited a ventricular pre-ejection difference of 43 ± 33 ms, indicating a delayed onset of LV outflow compared with RV outflow. In contrast, RBBB patients displayed a ventricular pre-ejection difference of −21 ± 29 ms consistent with a delayed onset of RV outflow relative to LV outflow (P< 0.001 compared with LBBB patients). In addition, IVMD was significantly smaller in RBBB patients compared with LBBB (29 ± 20 vs. 47 ± 28 ms, P< 0.001). Using a cut-off value for IVMD ≥40 ms,**1** a marked disparity between the proportions of RBBB and LBBB patients featuring significant interventricular mechanical dyssynchrony was observed (29 vs. 57% respectively, P< 0.001).

Left ventricular dyssynchrony was not quantifiable owing to image quality in 1 RBBB and 22 LBBB patients. Among the remaining individuals, LV dyssynchrony was observed to be significantly less among RBBB patients when compared with LBBB

(55 ± 45 vs. 74 ± 48 ms, P= 0.002). Using a ≥60 ms threshold to indicate significant LV dyssynchrony,[14] a significantly greater proportion of LBBB patients exhibited LV dyssynchrony (62 vs. 47%, P= 0.006).

Table 1. Patient baseline characteristics

Characteristic ±SD	RBBB (n= 89)	LBBB (n= 472)	P-value
Age (years)	68 ± 12	66 ± 11	0.3
Gender, male (%)	75 (84)	344 (73)	**0.02**
Ischaemic aetiology, n (%)	64 (72)	250 (53)	**0.001**
NYHA class, n (%)			
III	77 (87)	433 (92)	0.3
IV	12 (13)	39 (8)	
eGFR (mL/min)	68 ± 33	69 ± 30	0.8
Medications, n (%)			
ACE-I/ARB	75 (84)	426 (90)	0.1
β-Blocker	58 (65)	327 (69)	0.4
Spironolactone	36 (40)	232 (49)	0.1
Diuretics	78 (88)	394 (83)	0.3
QRS duration (ms)	161 ± 19	165 ± 22	0.1
AF, n (%)	23 (26)	58 (13)	**0.002**
MLWHFS	36 ± 22	36 ± 19	0.8
6 min walk distance (m)	266 ± 137	307 ± 123	**0.02**
LVEF (%)	26 ± 8	25 ± 8	0.09
LVEDV (mL)	206 ± 67	228 ± 86	**0.02**
LVESV (mL)	153 ± 58	174 ± 76	**0.02**
MR grade, n (%)			
0	9 (10)	68 (14)	0.1
I	44 (49)	182 (39)	
II	24 (27)	145 (31)	
III	5 (6)	54 (11)	
IV	7 (8)	23 (5)	
IVMD (ms)	29 ± 20	47 ± 28	**<0.001**
Ventricular pre-ejection difference (ms)	−21 ± 29	43 ± 33	**<0.001**
Septal-to-lateral delay (ms)	55 ± 45	74 ± 48	**<0.001**

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IVMD, interventricular mechanical delay; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction, LVESV, left ventricular end-systolic volume; MLWHFS, Minnesota Living with Heart Failure Score, MR, mitral regurgitation; RBBB, right bundle branch block; SD, standard deviation.

Response to cardiac resynchronization therapy: right bundle branch block vs. left bundle branch block

At 6-month follow-up, by mixed-effects modelling, both CRT recipients with LBBB and RBBB exhibited significant reverse LV remodelling; however, those with LBBB displayed a significantly greater absolute reduction in LV end-systolic volume compared with RBBB patients (34 ± 44 vs. 13 ± 35 mL, P< 0.001) and with a significant group–time interaction (Table 2). In addition, using a cut-off of ≥15% reduction in LV end-systolic volume to define CRT response, a significantly greater proportion of patients with LBBB were identified as CRT responders compared with RBBB (64 vs. 49%, P= 0.01). Notwithstanding, LV dyssynchrony was still observed to be the only predictor of response to CRT among RBBB patients (odds ratio 4.5, 95% confidence interval 1.7–12, P= 0.002).

Table 2. Changes in left ventricular remodelling and inter- and left ventricular dyssynchrony after 6 months of cardiac resynchronization therapy

Parameter ±SD	Baseline	Six months	P-value*	P-value for the group–time interaction
LVESV (mL)				
LBBB	174 ± 76	139 ± 69	<0.001	<0.001
RBBB	153 ± 58†	139 ± 55#	<0.001	
IVMD (ms)				
LBBB	46 ± 28	26 ± 20	<0.001	<0.001
RBBB	29 ± 20†	23 ± 19#	0.03	
Ventricular pre-ejection difference (ms)				
LBBB	43 ± 33	20 ± 26	<0.001	<0.001
RBBB	−21 ± 29†	7 ± 29†	<0.001	
Septal-to-lateral delay (ms)				
LBBB	74 ± 48	38 ± 36	<0.001	0.02
RBBB	55 ± 45†	35 ± 33#	<0.001	

*P-value for the baseline–6 month comparison by mixed-effects modeling †P< 0.05 for the comparison with LBBB at the given time point by mixed-effects modelling.#P≥0.05 for the comparison with LBBB at the given time point by mixed-effects modelling. The statistical significance of these associations was unaffected by adjustment for heart failure aetiology and the presence of atrial fibrillation. For abbreviations, see Table 1.

Six months after CRT, RBBB patients showed a reversed temporal sequence of ventricular activation, as indicated by a change in pre-ejection difference from −21

± 29 to 7 ± 29 ms (P< 0.001; Table **2**). Meanwhile, CRT recipients with LBBB continued to show delayed activation of the LV when compared with the RV, but with a significantly reduced magnitude of pre-ejection difference from 44 ± 32 to 20 ± 26 ms (P< 0.001; Table **2**). In both patients with RBBB and LBBB, a significant reduction in interventricular dyssynchrony was observed, with loss of the previously significant baseline difference in IVMD between the two groups by 6-month follow-up (Table **2**).

By mixed-effects modelling, both groups of patients demonstrated significant improvement in LV dyssynchrony 6 months after CRT (P< 0.001), but with a greater reduction in LBBB patients (Table **2**). Consequently, despite greater baseline LV dyssynchrony in LBBB patients, septal-to-lateral delay at 6-month follow-up was similar to that of RBBB patients (38 ± 36 vs. 35 ± 33 ms, P= 0.5).

To examine the effects of potential confounding factors, both heart failure aetiology and the presence of atrial fibrillation were included in the mixed-effects models as covariates. The influence of QRS configuration on LV remodelling, IVMD, ventricular pre-ejection difference, and LV dyssynchrony was found to be independent of either ischaemic heart failure aetiology or the presence of atrial fibrillation.

Event-free survival: right bundle branch block vs. left bundle branch block

The median follow-up duration was 45 months (inter-quartile range 29–66 months). During follow-up, 185 (33%) patients died and 57 (10%) were hospitalized for worsening heart failure. Over the study period, there was a trend towards a higher incidence of the composite primary endpoint of all-cause mortality or heart failure hospitalization among CRT recipients with RBBB at baseline compared with LBBB (Figure **1**). Predictors of death or heart failure hospitalization among right bundle branch block patients

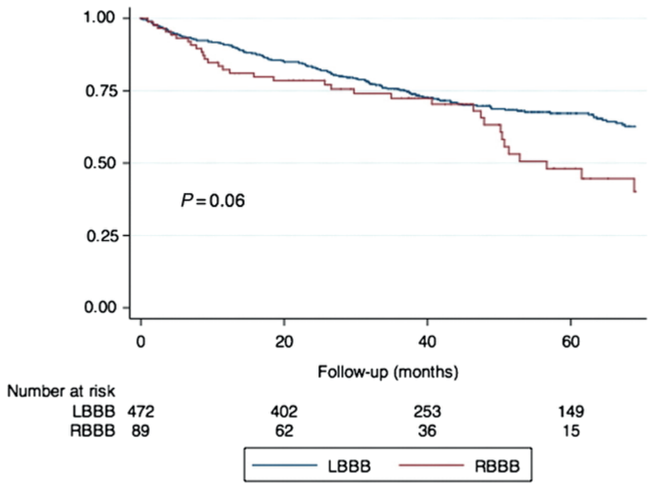

Figure 1. The Kaplan–Meier estimate of the primary composite endpoint of death or heart failure hospitalization by QRS morphology: left bundle branch block (LBBB) vs. right bundle branch block (RBBB).

To identify potential predictors of the primary endpoint of all-cause mortality or heart failure hospitalization after CRT in RBBB patients, Cox's proportional hazards modelling was applied and the following parameters showed a significance level of P< 0.1: atrial fibrillation, estimated glomerular filtration rate, LVEF, MR severity, and LV dyssynchrony (Table **3**). When these parameters were included in a multivariate model, LV dyssynchrony (Figure **2**) and MR grade were identified as independent predictors of this composite endpoint (Table **3**).

Table 3. Predictors of all-cause mortality or heart failure hospitalization among cardiac resynchronization therapy recipients with right bundle branch block

	Univariate		Multivariate	
Parameter	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age (years)	1.02 (0.989–1.05)	0.2		
Gender (female)	1.1 (0.41–2.7)	0.9		
Non-ischaemic aetiology	1.2 (0.53–2.5)	0.7		
eGFR (mL/min)	0.988 (0.975–1.00)	**0.07**	0.987 (0.973–1.00)	0.07
QRS duration (per 10 ms increase)	0.99 (0.97–1.0)	0.3		
Left hemi-block	1.0 (0.48–2.1)	1.0		
AF	2.3 (1.1–4.9)	**0.03**	2.1 (0.99–4.5)	0.06
6 min walk distance (per 50 m increase)	0.999 (0.996–1.00)	0.6		
LVEF (%)a	0.95 (0.91–1.0)	**0.04**	0.98 (0.94–1.0)	0.2
LVESV (per 10 mL increase)	1.0 (0.99–1.0)	0.8		
MR (per 1 grade increase)	1.7 (1.2–2.4)	**0.001**	1.7 (1.2–2.5)	**0.002**
Ventricular pre-ejection difference (ms)	1.00 (0.993–1.02)	0.5		
LV dyssynchrony ≥60 ms	0.45 (0.22–0.93)	**0.03**	0.46 (0.22–0.94)	**0.03**

For abbreviations, see Table 1. Bold P-values are the ones <0.1 in the univariate analysis and <0.05 in the multivariate analysis

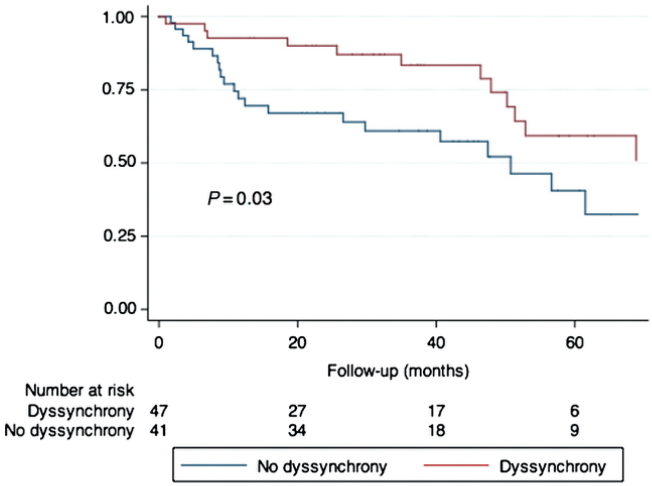

Figure 2. The Kaplan–Meier estimate of the primary composite endpoint of death or heart failure hospitalization among right bundle branch block patients dichotomized by the presence of baseline left ventricular dyssynchrony (using a ≥60 ms septal–lateral delay threshold).

DISCUSSION

This study has illustrated the differences between consecutive patients with RBBB and LBBB undergoing CRT for conventional, guideline-driven indications. Importantly, LV dyssynchrony was identified as an important predictor of long-term outcome among CRT recipients with RBBB.

Characterization of cardiac resynchronization therapy patients with right bundle branch block: comparison with left bundle branch block

The present study has demonstrated a different clinical profile among patients referred for CRT with RBBB when compared with LBBB, including aetiology of heart failure and atrial fibrillation, which is consistent with previously published evidence.[8,17] In addition, reversed temporal sequence of RV and LV mechanical activation was observed in RBBB patients, with a delay in RV ejection. The current study therefore illustrates in a large group of patients the mechanical consequences of the electrophysiological observations of Fantoni et al.,[18] who performed a three-dimensional endocardial activation mapping study in 6 patients with heart failure and RBBB and 94 heart failure patients with LBBB. The authors demonstrated a significant delay in transseptal and RV activation time in RBBB patients compared with LBBB patients.

The results of the current study also indicate the presence of significant LV dyssynchrony, as measured by tissue Doppler imaging, in RBBB patients referred for CRT. Therefore, the presence of RBBB morphology on the electrocardiogram does not exclude the presence of LV dyssynchrony, which may be due to dual bundle branch disease or disease affecting conduction through the myocardium. Notably, however, LV dyssynchrony extent was less in RBBB patients when compared with LBBB patients. In a canine model of heart failure with selective RBBB or LBBB, Byrne et al.**19** have also shown less LV dyssynchrony associated with RBBB when compared with LBBB, although with the same QRS duration. They also demonstrated a limited effect of CRT on dP/dtmax in the animals with RBBB when compared with LBBB.

Prediction of outcome of cardiac resynchronization therapy in patients with right bundle branch block

The current study is the first single-centre evaluation of the changes in echocardiographic parameters after CRT implantation, together with long-term outcomes in a substantial cohort of RBBB patients. Importantly, less LV reverse remodelling was observed among CRT recipients with RBBB when compared with LBBB. Similarly, in a study including de novo CRT recipients, Wokhlu et al.**5** demonstrated less improvement in NYHA class and LVEF among 36 patients with RBBB when compared with 228 patients with LBBB. The present study showed in addition that LV dyssynchrony was an important predictor of LV reverse remodelling among RBBB patients.

At long-term follow-up, this study observed a trend towards a difference between RBBB and LBBB patients in the primary composite endpoint of all-cause mortality or heart failure hospitalization. In larger populations, Wokhlu et al.,[5] Bilchick et al.,[7] and Zareba et al.[8] have shown RBBB to be associated with worse clinical outcome (all-cause mortality and heart failure hospitalization) than LBBB.

Despite evidence of poorer CRT response among patients with RBBB as a group, an unfavourable outcome is not a uniform finding in this population. Therefore, this study sought to identify independent predictors of death or heart failure hospitalization among RBBB patients. In fact, no studies to date have evaluated potential prognostic factors for long-term outcome after CRT in RBBB patients. Garrigue et al.[20] demonstrated in a sample of 12 RBBB patients that those with greater LV dyssynchrony tended to respond better to CRT in terms of treadmill performance. Chandra et al.[21] reported in 44 patients that the presence of concomitant left hemiblock among RBBB patients referred for CRT was associated with greater response to therapy (defined as improvement in LVEF of ≥5% or NYHA class).

The current study has shown that LV dyssynchrony, as measured by a widely available technique,[22] may be a key predictor of long-term outcome following CRT in RBBB patients. This observation has important implications. From a mechanistic perspective, it supports the paradigm that amelioration of LV dyssynchrony can improve LV remodelling and thus long-term outcome. In LBBB patients, reduction of the delay in LV activation by bi-ventricular pacing restores LV synchrony, which has been shown to be an important factor in determining clinical response to CRT.[23] In contrast, in RBBB patients, preserved impulse conduction to the LV through an intact left bundle branch may be expected to be associated with less LV dyssynchrony, thus diminishing the potential therapeutic effect of CRT. Despite clinical observations consistent with this model, the presence of focal or diffuse myocardial fibrosis in heart failure patients with RBBB may still cause LV dyssynchrony. The beneficial effects of CRT seen in these particular individuals with greater LV dyssynchrony support this postulate and suggest that echocardiographic evaluation of LV dyssynchrony may be a ready, non-invasive measure that may help distinguish those CRT candidates with RBBB who are most likely to benefit from this therapy. However, further research is needed to confirm these results.

The present study also found MR severity as an independent predictor of the primary endpoint in RBBB patients, as previously shown in a mixed population referred for CRT.[9] The finding of a lack of prognostic value of left hemi-block in RBBB patients undergoing CRT in the current study may reflect a limited sensitivity of surface electrocardiographic measures for electromechanical events within the myocardium.

Limitations

Although this evidence represents the experience of a single high-volume centre, the absolute numbers of RBBB patients and thus clinical events are small compared with LBBB. The findings with respect to long-term patient outcome should therefore be taken with caution and require confirmation in a larger cohort, which may be better powered to identify additional prognostic factors among RBBB patients. These prognostic factors also ideally require validation in an independent cohort. Patients with non-specific intraventricular conduction disturbance were excluded from this study owing to the heterogeneity of this form of conduction abnormality. This study's findings can therefore not necessarily be extrapolated to these individuals.

Clinical implications

At the present time, published guidelines do not include QRS morphology as a criterion for CRT prescription, although they do highlight emerging evidence on this subject.[24] In certain RBBB patients for whom the risk–benefit ratio of CRT is thought equivocal, the current study suggests that the measurement of LV dyssynchrony may help the decision-making process.

CONCLUSIONS

Patients referred for CRT with RBBB exhibit interventricular and LV dyssynchrony, albeit less than their LBBB counterparts. Pre-implantation LV dyssynchrony may be an important determinant of death or heart failure hospitalization among CRT recipients with RBBB.

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