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ORIGINAL ARTICLE

Cardiac resynchronization therapy in heart failure based on Strauss criteria for left bundle branch block

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Abstract

Aims The left bundle branch block (LBBB) is a strong predictor of response to cardiac resynchronization therapy (CRT). However, a significant number of patients do not respond to the treatment. The study sought to evaluate the impact of the stricter Strauss criteria for left bundle branch block (St-LBBB) on CRT response, hospitalizations, ventricular arrhythmia (VA) events and mortality.

Methods This study is a retrospective analysis of prospectively collected data on heart failure (HF) patients with LBBB admitted for CRT implantation. Patients were divided into two groups according to the fulfilment or not of St-LBBB criteria.

Results The study included 82 patients with ischaemic (ICM) and non-ischaemic (NICM) cardiomyopathy [46 (56%) with St-LBBB and 36 (44%) with non-St-LBBB]. Patients with St-LBBB showed higher CRT response rates compared with those with non-St-LBBB ($P < 0.01$), while the group with NICM exhibited the greatest benefit ($P < 0.01$). St-LBBB CRT responders displayed significantly lower rates of HF hospitalization ($P < 0.0001$) compared with the non-St-LBBB group. According to Kaplan–Meier time curves, this was primarily evident in patients with NICM ($P < 0.0001$). CRT responders displayed significantly fewer VA events ($P < 0.001$) and lower mortality rates ($P < 0.0001$) than non-responders. Kaplan–Meier estimates demonstrated a significantly lower incidence of VAs in NICM patients with St-LBBB ($P = 0.049$) compared with ICM patients with St-LBBB ($P = 0.25$). Lower mortality rates were observed in CRT responders than non-responders ($P < 0.0001$), with the group of NICM with St-LBBB criteria exhibiting the greatest benefit ($P = 0.0238$).

Conclusions Patients with NICM and St-LBBB present the greatest benefit concerning CRT response, HF hospitalizations, VA events and mortality. Although St-LBBB criteria seem to improve patient selection for CRT, more data are needed to elucidate the role of St-LBBB criteria in this setting.

Keywords CRT response; ischaemic cardiomyopathy; non-ischaemic cardiomyopathy; Strauss LBBB; ventricular arrhythmias

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Introduction

Cardiac resynchronization therapy (CRT) improves clinical outcomes in eligible patients with symptomatic heart failure (HF) who are already receiving optimal medical treatment. In particular, CRT improves symptoms and exercise capacity and reduces mortality and hospitalizations.[1] Although the benefits following CRT implantation have been demonstrated in large clinical trials, the benefit for each patient is difficult to predict. Left bundle branch block (LBBB) on the electrocar-

diogram (ECG) is an important prognostic factor for patient response to CRT.[1] However, 20%–40% of patients with LBBB will not respond to this treatment modality.[2,3]

The stricter Strauss criteria for left bundle branch block (St-LBBB) have been proposed to define true LBBB, and their implementation in patient selection concerning CRT response has been addressed in a small number of studies with conflicting results.[4–7] Limited data exist regarding the impact of St-LBBB employment on hospitalizations, ventricular arrhythmias (VAs) and mortality in CRT patients.[8,9] This study aimed to investigate whether patients with St-LBBB have a better response to CRT than patients with LBBB that do not fulfil the Strauss criteria (non-St-LBBB). We also sought to evaluate whether these patients have reduced hospitalizations, malignant VA events [non-sustained ventricular tachycardia (NSVT), sustained VT, polymorphic VT or ventricular fibrillation (VF)] and mortality rates.

Methods

Patients

This study is a retrospective analysis of prospectively collected data on consecutive HF patients admitted for CRT implantation in two centres between January 2013 and June 2021. The inclusion criteria were (1) New York Heart Association (NYHA) class II–III HF despite adequate medical treatment; (2) chronic left ventricular (LV) systolic dysfunction caused by ischaemic (ICM) or non-ischaemic (NICM) cardiomyopathy [left ventricular ejection fraction (LVEF) $\leq$ 35%]; (3) presence of LBBB with QRS duration $\geq$ 130 ms on an ECG before implantation; (4) $\geq$98% stable paced rhythm post-implantation in patients with either atrial fibrillation (AF) or sinus rhythm; and (5) comprehensive echocardiographic evaluation at baseline and 6 month follow-up. Patients were divided into two groups based on the presence of St-LBBB or non-St-LBBB. Data on cardiovascular risk factors, functional status and current HF therapy were collected before CRT implantation. Exclusion criteria were (1) patients that underwent a device upgrade to CRT; (2) poor echocardiographic windows; (3) intraventricular conduction delay (IVCD) or right bundle branch block (RBBB); and (4) an inadequate percentage of paced rhythm ($<$98%) due to irreversible causes (e.g., failure of LV capture, LV lead dislodgement, LV lead fracture, anodal stimulation, premature ventricular contractions and atrial arrhythmias with a fast ventricular response that cannot be controlled).

Data extraction

Patient demographics, type of HF, medications, echocardiographic data [interventricular septum (IVS) thickness, left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular end-systolic diameter (LVESD), left atrial diameter (LAd), left atrial volume (LAv) and LVEF] and electrocardiographic data [QRS duration, fragmented QRS (fQRS), LBBB, LBBB Strauss and QTc] were extracted from each patient. Echocardiographic examinations were performed with GE Vivid 7 (GE Healthcare, Chalfont St. Giles, UK) during the week prior to CRT implantation in a standardized manner. LVEDV, LVESV, LVEF and LAv were calculated by a modified Simpson biplane method from apical imaging planes. LVEDD, LVESD and LAd were measured in the parasternal long-axis view. The analysis of the 12-lead ECG was performed after scanning so that it could be studied in digital form. The recording rate of the ECG was 25 mm/s, and the sensitivity was 10 mm/mV. Two independent electrophysiologists measured the parameters. Outcomes of interest (LVESV, LVEF, deaths, AF episodes and VAs) were extracted during follow-up. The institutional ethics committee approved the study protocol, and written informed consent was obtained from all patients.

Definitions

The response to CRT was defined as an increase in LVEF $\geq$ 10% or a decrease in LVESV $\geq$ 15% at 6 months of follow-up.[10] The clinical response to CRT was described as a reduction in NYHA class by at least 1 point. Strauss LBBB criteria were defined as a QS or rS morphology in V1–V2 leads, a QRS duration of $\geq$140 ms for males and $\geq$130 ms for females, along with mid-QRS notching or slurring in $\geq$2 leads between I, aVL, V1, V2, V5 and V6.[11]

CRT implantation

All devices were implanted by physicians experienced in the field of biventricular pacing. All patients received a CRT device combined with a cardioverter-defibrillator (CRT-D) as primary prevention due to an LVEF $\leq$ 35% despite optimal medical therapy over 3 months.[3] The implantation was performed transvenously using the left or right axillary, subclavian or cephalic vein approach. Coronary sinus venography was performed before the introduction of the LV lead. The LV lead was preferentially inserted into a lateral or postero-lateral branch of the coronary sinus. The right atrial and right ventricular (RV) leads were conventionally placed.[12] Optimization of the atrioventricular interval was performed using adaptive CRT algorithms that have been proven to be non-inferior to echocardiographic optimization in clinical composite scores.[13,14] Optimal ICD programming regarding detection, zones, antitachycardia pacing (ATP), ICD shocks, supraventricular tachycardia (SVT) discriminators and

oversensing rejections was based on the 2019 HRS/EHRA/APHRS/LAHRS expert consensus document.[15] In brief, devices were programmed with VT detection at 150 beats per minute (or less if slower clinical VT had been documented), requiring at least 30 intervals for initial detection. Fast VT and VF intervals were specified, as well as standardized discriminator algorithms. ATP was programmed in all zones.

Follow-up

HF hospitalization was defined as the admission of a patient to a health care unit for at least 24 h with symptoms and signs of congestive HF requiring medical treatment or invasive management. Malignant VAs that were included in our study were NSVT, sustained VT, polymorphic VT or VF. NSVT was defined as three or more consecutive ventricular beats, a rate of $>$100 beats per minute and a duration of $<$30 s, while sustained VT had a duration of $>$30 s.[15] The occurrence of at least one episode of NSVT or VT was classified as malignant VA. Telephone interviews with a first-degree relative evaluated deaths and causes of death.

Statistical analysis

Continuous variables were presented as medians [min–max], while categorical variables were presented as absolute and relative frequencies (percentages). Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables with and without a normal distribution were compared using Student's *t*-test or the Mann–Whitney *U* test. Pearson's χ^2 or Fisher's exact test was used to test for any associations between two categorical variables. A paired *t*-test was used to compare two related continuous variables' averages and standard deviations. The incidence rates for CRT response, hospitalizations, VA events and all-cause mortality were analysed based on Kaplan–Meier time curves. Analyses were performed using the SPSS software (Version 22.0, SPSS Inc., Chicago, IL, USA). All reported *P*-values are two-tailed with a significance level of 0.05.

Results

Characteristics of the study cohort

The study population consisted of 82 patients [65 males (79.3%), median age: 67 [42–89] years old]. ICM was the cause of HF in 32 (39%) patients, and NICM in 50 (61%) patients (Figure 1). The clinical, echocardiographic and ECG characteristics of the study cohort are depicted in Table 1. Most patients were in the NYHA III class [68 patients (82.9%)]; the remaining patients were in the NYHA II class [14 patients (17.1%)]. The median LVEF was 25 [15–35]%, while the median LVEDD was 65.5 [52–95] mm. The median LVEDV and LVESV were 239 [120–430] and 164.5 [74–282] mL, respectively. QRS width prior to CRT implantation was 160 [130–200] ms. Forty-six patients (56.1%) displayed St-LBBB. The mean follow-up of the entire cohort was 52.2 months.

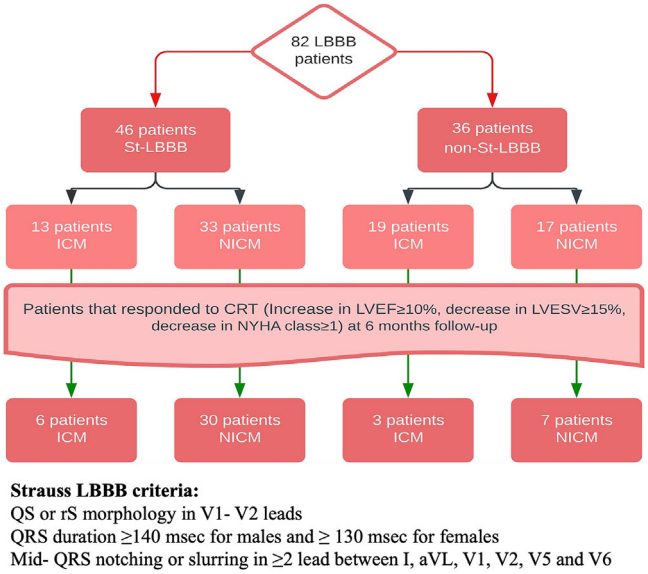
CRT response in relation to cardiomyopathy type and LBBB definition

A flowchart demonstrating the type of cardiomyopathy, St-LBBB criteria and CRT response rates in the study cohort is depicted in Figure 1. Forty-six patients (56.1%) responded to CRT at a 6 month follow-up. The post-implantation QRS duration was significantly shorter in both ICM (from 160 [130–190] to 139 [120–160] ms, $P = 0.011$) and NICM patients (from 160 [130–200] to 130 [100–200] ms, $P < 0.001$). Patients with NICM ($n = 37$, 74%) displayed a significantly higher rate of response compared with patients with ICM ($n = 9$, 19.6%) ($P < 0.01$). Post-implantation LVEF was significantly increased in NICM patients (from 25 [15–35]% to 35 [17–55]%, $P < 0.001$), while ICM subjects exhibited a trend towards improved LV function (from 26 [15–35]% to 36 [15–60]%, $P = 0.071$). Both ICM (from 157.5 [103–265] to 104 [40–259] mL, $P = 0.012$) and NICM patients (from 166.6 [74–282] to 105.5 [50–260] mL, $P < 0.001$) displayed a statistically significant reduction of LVESV. Of note, in the responder group, there were four patients (one with ICM and three with NICM) with only a clinical response (NYHA class increase).

Thirteen patients with ICM (41%) and 33 patients with NICM (66%) fulfilled the St-LBBB criteria. Irrespective of cardiomyopathy type, subjects with St-LBBB criteria exhibited increased QRS duration compared with non-St-LBBB patients (160 [140–200] vs. 140 [130–190] ms, $P < 0.0001$). Patients fulfilling St-LBBB criteria displayed significantly higher CRT response rates compared with patients with non-St-LBBB [36 (78.3%) vs. 10 (27.8%), $P < 0.01$] (Table 2). A statistically significant increase in LVEF (40 [20–60] vs. 30 [15–55], $P < 0.0001$) and reduction in LVESV (88.5 [40–250] vs. 130 [50–260] mL, $P < 0.0001$) during follow-up were seen in St-LBBB patients in relation to those with non-St-LBBB. Patients with St-LBBB exhibited a higher incidence of LV reverse remodelling (Δ-LVESV $>$ 15%) [37 (80.4%) in the St-LBBB group vs. 17 (47.2%) in the non-St-LBBB group, $P < 0.01$] (Table 3).

Six months post-CRT implantation, most patients in the St-LBBB group were classified as NYHA I (73.9%), while most non-St-LBBB patients were classified as NYHA III (66.7%). Patients with NICM and St-LBBB criteria exhibited a statistically significant CRT response ($P < 0.01$) (Table 2). A trend towards a better response was also seen in ICM patients with St-LBBB, but this was not statistically significant ($P = 0.11$).

Figure 1 The flowchart demonstrates the type of cardiomyopathy, Strauss criteria for left bundle branch block (St-LBBB) criteria and cardiac resynchronization therapy (CRT) response rates in the study cohort. ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NICM, non-ischaemic cardiomyopathy; NYHA, New York Heart Association.



HF hospitalizations in relation to cardiomyopathy type and LBBB definition

Total HF hospitalizations and hospitalizations per month were significantly reduced in CRT responders in both ICM and NICM ($P < 0.0001$ in both groups) (Table 2). Patients fulfilling St-LBBB criteria displayed significantly lower rates of total HF hospitalizations (0 [0–3] vs. 1 [0–8], $P < 0.0001$) and hospitalizations per month of follow-up (0 [0–0.2] vs. 0.03 [0–0.125], $P < 0.0001$) compared with those with non-St-LBBB (Table 3).

Kaplan–Meier time curves demonstrated significant benefit in CRT responders [hazard ratio (HR): 0.05, 95% confidence interval (CI): 0.03–0.15; $P < 0.0001$ by the log-rank test], and particularly in patients with NICM with true LBBB (HR: 0.07, 95% CI: 0.02–0.22; $P < 0.0001$ by the log-rank test) (Figure 2). On the contrary, patients with ICM with true LBBB failed to show this benefit.

VAs in relation to cardiomyopathy type and LBBB definition

During follow-up, 29 (35.4%) patients exhibited at least one VA episode in the device interrogation. In total, CRT responders displayed fewer VA events than non-responders (19.6% vs. 55.6%, $P < 0.001$) (Table 2). In particular, this was evident only for NICM responders (16.2% vs. 61.5%, $P = 0.004$) but not for ICM responders (33.3% vs. 52.2%, $P = 0.44$).

Kaplan–Meier estimates demonstrated a significantly lower incidence of VAs in CRT responders than in non-responders ($P < 0.0001$ by the log-rank test) (Figure 3). The HR of the Kaplan–Meier analysis between these two groups was 0.19 (95% CI: 0.09–0.41), indicating an 81% reduction in the relative risk. Patients fulfilling St-LBBB criteria displayed a trend towards lower rates of VAs than those with non-St-LBBB (28.3% vs. 44.4%, $P = 0.0989$). Kaplan–Meier analysis showed that subjects with NICM and St-LBBB (HR: 0.36, 95% CI: 0.12–1.1; $P = 0.049$ by the log-rank test) demonstrated significant benefit compared with ICM and St-LBBB (HR: 0.60, 95% CI: 0.25–1.41; $P = 0.25$ by the log-rank test) (Figure 3).

Mortality in relation to cardiomyopathy type and LBBB definition

During follow-up, 21 (25.6%) deaths occurred. Kaplan–Meier estimates of survival during the follow-up period demonstrated a significantly lower mortality in CRT responders than non-responders ($P < 0.0001$ by the log-rank test). The HR of the survival analysis between these two groups was 0.06 (95% CI: 0.02–0.14), indicating a 94% reduction in the risk of death. Furthermore, the Kaplan–Meier estimates of survival in the NICM patients showed significantly lower mortality in those with St-LBBB than without ($P = 0.0238$ by the log-rank test), with an HR of 0.12 (95% CI: 0.02–0.79) between these two groups, indicating an 88% reduction in the risk of death. In contrast, no statistically significant difference was found in the ICM patients between St-LBBB and non-St-LBBB ($P = 0.616$ by the log-rank test) (Figure 4).

Table 1 The clinical, echocardiographic and electrocardiographic characteristics of the study population. Continuous variables are presented as the mean ± standard deviation.

Variables	Value
Demographics	
Mean age (years)	66 ± 10
Males, *n* (%)	65 (79.3%)
Clinical characteristics	
NICM HF, *n* (%)	50 (61%)
ICM HF, *n* (%)	32 (39%)
NYHA I, *n* (%)	0 (0%)
NYHA II, *n* (%)	14 (17.1%)
NYHA III, *n* (%)	68 (82.9%)
NYHA IV, *n* (%)	0 (0%)
Echocardiographic pre-CRT data	
LAd (mm)	46 ± 6
LAv (mL)	83 ± 20
LVESD (mm)	56 ± 8
LVESV (mm)	168 ± 52
LVEDD (mm)	66 ± 8
LVEDV (mL)	247 ± 68
LVEF (%)	26.8 ± 5.2
ECG data	
QRS duration (ms)	157.3 ± 19.6
St-LBBB, *n* (%)	46 (56.1%)
QTc Fridericia (ms)	459 ± 40
fQRS, *n* (%)	3 (3.7%)
Drugs	
ACEi/ARBs, *n* (%)	66 (80.5%)
Beta-blocker, *n* (%)	79 (96.3%)
MRAs, *n* (%)	75 (91.5%)
Ivabradine, *n* (%)	6 (7.3%)
Diuretics, *n* (%)	76 (92.7%)
Nitrates, *n* (%)	6 (7.3%)
Digoxin, *n* (%)	7 (8.5%)
CCB, *n* (%)	1 (1.2%)
Anticoagulants, *n* (%)	34 (41.5%)
Antiplatelets, *n* (%)	33 (40.2%)
AADs, *n* (%)	31 (37.8%)
Statins, *n* (%)	44 (53.7%)
SGLT2, *n* (%)	1 (1.2%)

Abbreviations: AADs, antiarrhythmic drugs; ACEi/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCB, calcium channel blockers; fQRS, fragmented QRS; HF, heart failure; ICM, ischaemic cardiomyopathy; LAd, left atrial diameter; LAv, left atrial volume; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MRAs, mineralocorticoid receptor antagonists; NICM, non-ischaemic cardiomyopathy; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter-2 inhibitors; St-LBBB, Strauss criteria for left bundle branch block.

Discussion

The main findings of the present study are the following:

i CRT responders displayed lower rates of HF hospitalizations, VA events and mortality rates compared with non-responders.
ii Patients fulfilling St-LBBB criteria exhibited significantly higher CRT response rates compared with patients with non-St-LBBB; in particular, patients with NICM and St-LBBB criteria showed the greatest benefit.
iii St-LBBB patients exhibited significantly lower rates of total HF hospitalizations, HF hospitalizations per month and mortality rates.
iv Patients with NICM and St-LBBB criteria demonstrated the greatest benefit concerning HF hospitalizations, VA events and mortality rates.

ECG criteria for CRT patient selection

Non-response to CRT is multifactorial and remains a significant limitation of this therapeutic modality. Considerable effort has been made to elucidate and resolve the determinants of non-response, including ECG criteria, to improve its effectiveness. CRT is more effective in patients with LBBB than non-LBBB morphology, and its effectiveness increases with QRS duration.[16] Patients experiencing the highest benefit in improved exercise capacity, quality of life and functional status display the longest conduction delays, as indicated by a QRS duration $>$ 150 ms.[17]

Invasive measurements of interventricular conduction delay using parameters such as the QLV interval, measured from the onset of QRS in the surface ECG to the local activation time of the LV at the site of the LV lead, and the RV–LV interval, which measures the time difference between the activation of the RV and the LV, have been proposed as predictors of improved response.[18–20] A sub-study of the SMART-AV trial suggested that the RV–LV interval is a predictor of reverse remodelling with CRT, even in patients with traditionally low response rates (ICM, non-LBBB). An RV–LV interval exceeding 80 ms is considered a positive marker for LV lead position, while repositioning is suggested in cases of shorter intervals.[20]

Auricchio *et al*. performed a three-dimensional endocardial mapping study of patients considered to have LBBB by conventional ECG criteria. In this study, one third of patients did not have significant delays between the start of activation of the RV endocardium and the start of activation of the LV endocardium. Specifically, 32% of patients had $<$20 ms between the beginning of activation in the RV endocardium and that of the LV endocardium. Patients with transseptal times $<$ 20 ms had a mean QRS duration of 133 ± 28 ms, compared with 170 ± 16 ms in patients with transseptal times $>$ 40 ms. This provides further evidence that patients with LBBB by conventional ECG criteria and transseptal times of $<$20 ms do not have complete LBBB. Patients with LBBB morphology have a specific 'U-shaped' activation sequence that turns around the apex and inferior wall of the LV.[21] This activation pattern is generated by a functional line of the block that is oriented from the base towards the apex of the LV. Patients with QRS duration $<$ 150 ms demonstrate a more homogeneous electrical activation process with shorter transseptal time and a line of the block that is usually

Table 2 The clinical, echocardiographic and electrocardiographic characteristics of the study population are based on the type of cardiomyopathy and CRT response outcome. Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented as absolute and relative frequencies (percentages).

	All patients			ICM patients			NICM patients		
	Responders	Non-responders		Responders	Non-responders		Responders	Non-responders	
Variables	46 (56.1%)	36 (43.9%)	*P*-value	9 (19.6%)	23 (63.9%)	*P*-value	37 (74%)	13 (26%)	*P*-value
Age (years)	67 ± 10	66 ± 10	0.67	76 ± 7	68 ± 10	0.04	65 ± 10	63 ± 11	0.53
Males, *n* (%)	34 (73.9%)	31 (86.1%)	0.18	8 (88.9%)	21 (91.3%)	1.0	26 (70.3%)	10 (76.9%)	0.73
LVEF pre-CRT (%)	27.2 ± 4.9%	26.3 ± 5.5%	0.48	28 ± 2.9	26.7 ± 5.4	0.48	27 ± 5.3%	25.5 ± 6%	0.40
LAd (mm)	45 ± 6	47 ± 4	0.12	44 ± 2	47 ± 4	0.03	46 ± 7	48 ± 4	0.10
LAv (mL)	81 ± 21	87 ± 17	0.24	72 ± 11	83 ± 16	0.12	83 ± 23	95 ± 19	0.21
LVESD pre-CRT (mm)	56 ± 9	57 ± 8	0.27	55 ± 6	57 ± 7	0.49	56 ± 10	58 ± 8	0.37
LVESV pre-CRT (mL)	165 ± 53	172 ± 51	0.54	166 ± 51	168 ± 48	0.93	165 ± 54	178 ± 58	0.45
LVEDD pre-CRT (mm)	66 ± 10	67 ± 7	0.22	64 ± 8	67 ± 6	0.33	66 ± 10	67 ± 8	0.55
LVEDV pre-CRT (mL)	239 ± 66	257 ± 69	0.20	250 ± 81	251 ± 64	0.98	236 ± 63	266 ± 79	0.17
St-LBBB	36 (78.3%)	10 (27.8%)	<0.01	6 (66.7%)	7 (30.4%)	0.11	30 (81.1%)	3 (23.1%)	<0.01
QRS duration (ms)	163.1 ± 19	150 ± 19	0.02	166 ± 11	151 ± 20	0.053	163 ± 20	150 ± 17	0.051
QTc Fridericia (ms)	459 ± 43	458 ± 36	0.96	473 ± 45	458 ± 33	0.29	456 ± 42	460 ± 42	0.74
fQRS, *n* (%)	1 (2.2%)	2 (5.6%)	0.58	0 (0%)	2 (8.7%)	1.00	1 (2.7%)	0 (0%)	1.00
NT-proBNP (pg/mL)	2193 ± 900.5	2340 ± 844.5	0.47	2565 ± 620.3	2322 ± 782.6	0.35	2102 ± 940.7	2373 ± 977.6	0.41
ACEi/ARBs, *n* (%)	40 (86.95%)	26 (72.2%)	0.15	7 (77.8%)	17 (73.9%)	0.69	33 (89.2%)	11 (84.6%)	0.64
Beta-blocker, *n* (%)	45 (97.8%)	34 (94.4%)	0.58	9 (100%)	22 (95.7%)	1.00	36 (97.3%)	12 (92.3%)	0.46
MRAs, *n* (%)	41 (89.1%)	34 (94.4%)	0.46	8 (88.9%)	21 (91.3%)	1.00	33 (89.2%)	13 (100%)	0.56
Ivabradine, *n* (%)	2 (4.3%)	4 (11.1%)	0.40	0 (0%)	1 (4.3%)	1.00	2 (5.4%)	3 (23.1%)	0.10
Diuretics, *n* (%)	43 (93.5%)	33 (91.7%)	1.00	9 (100%)	22 (95.7%)	1.00	34 (91.9%)	11 (84.6%)	0.60
Nitrates, *n* (%)	2 (4.3%)	4 (11.1%)	0.40	2 (22.2%)	4 (17.4%)	1.00	0 (0%)	0 (0%)	
Digoxin, *n* (%)	4 (8.7%)	3 (8.3%)	1.00	1 (11.1%)	1 (4.3%)	0.49	3 (8.1%)	2 (15.4%)	0.60
CCB, *n* (%)	0 (0%)	1 (2.8%)	0.44	0 (0%)	0 (0%)		0 (0%)	1 (7.7%)	0.26
Anticoagulants, *n* (%)	16 (34.8%)	18 (50%)	0.17	4 (44.4%)	10 (43.5%)	1.00	12 (32.4%)	8 (61.5%)	0.1
Antiplatelets, *n* (%)	13 (28.3%)	20 (55.6%)	0.01	6 (66.7%)	17 (73.9%)	0.69	7 (18.9%)	3 (23.1%)	0.71
AADs, *n* (%)	13 (28.3%)	18 (50%)	0.04	6 (66.7%)	10 (43.5%)	0.43	7 (18.9%)	8 (61.5%)	0.01
Statins, *n* (%)	20 (43.5%)	24 (66.7%)	0.04	9 (100%)	20 (87%)	0.54	11 (29.7%)	4 (30.8%)	1.00
SGLT2, *n* (%)	0 (0%)	1 (2.8%)	0.25	0 (0%)	0 (0%)	0.49	0 (0%)	1 (7.7%)	0.31
LVEF post-CRT (%)	42.1 ± 7.9	26.6 ± 5.8	<0.01	43.3 ± 9.1%	27.4 ± 5.2%	<0.01	41.8 ± 7.7%	25.3 ± 6.8%	<0.01
LVESV post-CRT (mL)	90 ± 33	160 ± 53	<0.01	90 ± 22	156 ± 52	<0.01	90 ± 35	167 ± 56	<0.01
AF interrogation, *n* (%)	10 (21.7%)	9 (25%)	0.73	1 (11.1%)	6 (26.1%)	0.64	9 (24.3%)	3 (23.1%)	1.00
Total HF hospitalizations	0.13 ± 0.34	1.89 ± 1.83	<0.0001	0.11 ± 0.33	1.57 ± 1.44	0.001	0.13 ± 0.35	2.46 ± 2.33	<0.0001
HF hospitalizations per month of follow-up	0.0019 ± 0.006	0.0052 ± 0.044	<0.001	0.0012 ± 0.004	0.0588 ± 0.049	<0.001	0.0021 ± 0.006	0.0415 ± 0.033	<0.0001
VA events, *n* (%)	9 (19.6%)	20 (55.6)	0.001	3 (33.3%)	12 (52.2%)	0.44	6 (16.2%)	8 (61.5%)	0.004
Deaths, *n* (%)	2 (4.3%)	19 (52.8%)	<0.001	2 (22.2%)	14 (60.9%)	0.11	0 (0%)	5 (38.5%)	0.001

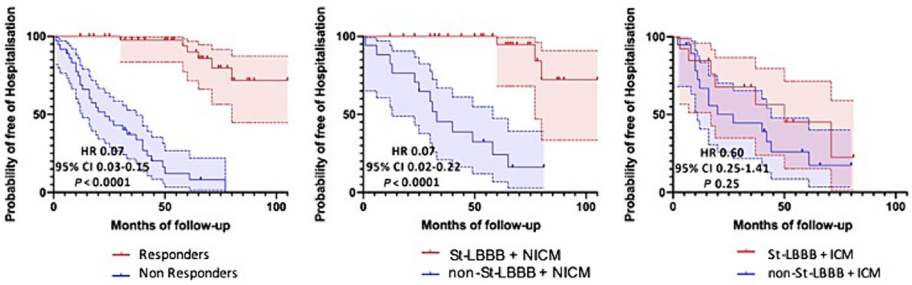
Abbreviations: AADs, antiarrhythmic drugs; ACEi/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCB, calcium channel blockers; fQRS, fragmented QRS; HF, heart failure; ICM, ischaemic cardiomyopathy; LAd, left atrial diameter; LAv, left atrial volume; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MRAs, mineralocorticoid receptor antagonists; NICM, non-ischaemic cardiomyopathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; SGLT2, sodium-glucose cotransporter-2 inhibitors; St-LBBB, Strauss criteria for left bundle branch block; VA, ventricular arrhythmia.

Table 3 The clinical, echocardiographic and electrocardiographic characteristics are based on St-LBBB criteria. Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented as absolute and relative frequencies (percentages).

	St-LBBB	Non-St-LBBB	
Variables	46 (56%)	36 (44%)	*P*-value
Age (years)	67.9 ± 10.6	64.5 ± 9.3	0.072
Height (cm)	173 ± 7.4	172 ± 6	0.51
Weight (kg)	80.6 ± 14.9	77.1 ± 10.1	0.52
QRS duration (ms)	167 ± 15	144 ± 17.2	<0.0001
QTc Fridericia (ms)	467 ± 38.7	449 ± 25	0.0485
LVEF pre-CRT (%)	27.4 ± 5.2	26 ± 5.2	0.198
LAd (mm)	45.4 ± 6.6	47.5 ± 4	0.0026
LVESD (mm)	55.4 ± 8.7	57.6 ± 7.9	0.118
LVEDD (mm)	65.6 ± 9.4	67.2 ± 7.1	0.124
LVEDV (mL)	232 ± 67.8	265 ± 63.8	0.017
LVESV pre-CRT (mL), *n* (%)	161 ± 49.3	177 ± 54.2	0.223
NYHA class I pre CRT, *n* (%)	0 (0%)	0 (0%)	-
NYHA class II pre CRT, *n* (%)	11 (23.9%)	3 (8.3%)	0.079
NYHA class III pre CRT, *n* (%)	35 (76.1%)	33 (91.7%)	0.063
NYHA class IV pre CRT, *n* (%)	0 (0%)	0 (0%)	-
LVEF post-CRT (%)	39.7 ± 9.6	29.7 ± 8.9	<0.0001
LVESV post-CRT (mL)	99.7 ± 43.8	147 ± 57	<0.0001
Δ-LVESV > 15% post-CRT, *n* (%)	37 (80.4%)	17 (47.2%)	<0.01
NYHA class I post-CRT, *n* (%)	34 (73.9%)	9 (25%)	<0.0001
NYHA class II post-CRT, *n* (%)	4 (8.7%)	1 (2.7%)	0.379
NYHA class III post-CRT, *n* (%)	5 (10.9%)	24 (66.7%)	<0.0001
NYHA class IV post-CRT, *n* (%)	3 (6.5%)	2 (5.6%)	0.999
Total HF hospitalizations	0.3 ± 0.67	1.67 ± 1.9	<0.0001
HF hospitalizations per month of follow-up	0.012 ± 0.036	0.040 ± 0.036	<0.0001
VA events, *n* (%)	13 (28.3%)	16 (44.4%)	0.0989
Deaths, *n* (%)	8 (17.4%)	13 (36.1%)	0.0475
Follow-up (months)	54.6 ± 25.6	49 ± 25.8	0.39

Abbreviations: HF, heart failure; LAd, left atrial diameter; LAv, left atrial volume; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; St-LBBB, Strauss criteria for left bundle branch block; VA, ventricular arrhythmia.

Figure 2 Kaplan–Meier estimates of the freedom of HF hospitalizations for cardiac resynchronization therapy responders (left), non-ischaemic cardiomyopathy (NICM) patients with and without Strauss criteria for left bundle branch block (St-LBBB) criteria (middle) and ischaemic cardiomyopathy (ICM) patients with and without St-LBBB criteria (right). CI, confidence interval; HR, hazard ratio.



located in the lateral region of the LV.[21] The clinical implication of the latter is the lower likelihood of improving LV ventricular function during acute resynchronization therapy. These data highlight the importance of better patient selection based on ECG criteria.

Strauss *et al*. have proposed more specific criteria to identify a complete LBBB and to distinguish this conduction delay from other IVCDs mimicking LBBB. These criteria specifically include mid-QRS notching. The beginning of the notch reflects the time when the electrical depolarization wave front breaks through the endocardium of the LV, and the end of the notch reflects the time when the wavefront reaches the epicardium of the lateral wall.[11] In a high-resolution mapping study of LV activation in humans with true LBBB based on Strauss criteria, the earliest LV septal breakthrough was recorded after the QRS onset at 44 ± 29 ms with unipolar recordings. The presence of QRS notching on I, aVL, V5 and V6 leads is therefore an accurate

Figure 3 Kaplan–Meier estimates of the freedom of ventricular arrhythmia (VA) events for cardiac resynchronization therapy responders (left), non-ischaemic cardiomyopathy (NICM) patients with and without Strauss criteria for left bundle branch block (St-LBBB) criteria (middle) and ischaemic cardiomyopathy (ICM) patients with and without St-LBBB criteria (right). CI, confidence interval; HR, hazard ratio.

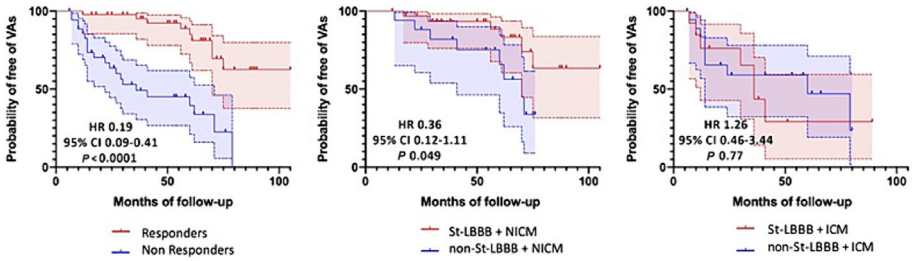
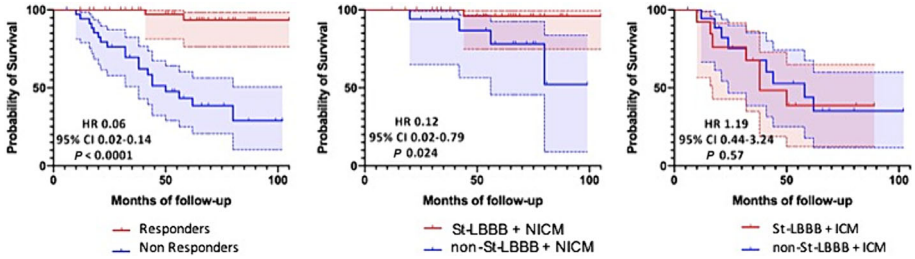


Figure 4 Kaplan–Meier estimates of survival for cardiac resynchronization therapy responders (left), non-ischaemic cardiomyopathy (NICM) patients with and without Strauss criteria for left bundle branch block (St-LBBB) criteria (middle) and ischaemic cardiomyopathy (ICM) patients with and without St-LBBB criteria (right). CI, confidence interval; HR, hazard ratio.



criterion for prolonged transseptal times if present 40–50 ms after QRS onset and may distinguish patients that may benefit from CRT.[22]

Strauss criteria for LBBB and CRT responses

The implementation of the stricter St-LBBB criteria in patient selection with respect to CRT response has been addressed in previous studies with conflicting data. García-Seara *et al*. demonstrated that patients with St-LBBB had a greater echocardiographic response and a lower incidence of HF hospitalization than non-true LBBB patients.[7] However, in this study, the percentage of responders defined as LVESV reduction $\geq$ 15% or LVEF increase $\geq$ 5% or a combination of them was not significantly different among the subgroups analysed, although there was a trend towards a better response in the true LBBB group. In a similar study of 335 patients with LBBB, the implementation of Strauss criteria did not improve CRT response.[4] Caputo *et al*. evaluated the impact of different ECG criteria for LBBB definition (a QRS duration of $\geq$150 ms and LBBB according to AHA/ACC/HRS, ESC 2006, ESC 2009, ESC 2013 and the classification proposed by Strauss) on CRT response. In this study, reverse remodelling, defined as a $\geq$15% reduction of baseline LVESV, was significant only for the ESC 2009 and ESC 2013 definitions but not for Strauss criteria.[9] On the contrary, in a study of 58 patients, Tian *et al*. demonstrated that patients with St-LBBB displayed greater improvement in LV function after 6 months of CRT than did patients with traditionally defined LBBB with no notch or notches in $<$2 of the leads. In multivariate analysis, St-LBBB was an independent predictor of the super-response to CRT.[5] In a different report, patients with strict LBBB exhibited a significant increase in LVEF compared with conventional LBBB and non-LBBB. In a recent retrospective analysis, the implementation of Strauss criteria has been associated with greater echocardiocardiographic response (74% responders and 26% non-responders) compared with conventionally defined LBBB (40% responders and 60% non-responders).[8] The presence of QRS duration of $>$140 ms in men and $>$130 ms in women, as well as the presence of notch or slurring in at least two contiguous leads, was higher in responders than non-responders. The definition of LBBB according to Strauss criteria had an odds ratio (OR) of 4.40 for CRT response, while the definition of LBBB according to the current guidelines offered an OR of 1.93.[6] Our study shows promising data, particularly in demonstrating the advantage of using St-LBBB criteria to predict echocardiographic response and statistically significant LV reverse remodelling (80.4% in the St-LBBB group exhibiting $>$15% LVESV reduction vs. 47.2% in the non-St-LBBB group). Patients with NICM and St-LBBB criteria exhibited a statistically significant CRT

response, a finding that was not evident in ICM patients with St-LBBB.

The small sample size of our study, as well as the baseline characteristics of the included patients and the different definitions of CRT response, could explain the observed differences among the existing studies.

Strauss criteria for LBBB for CRT patient selection and hospitalizations, VA events and mortality

Previous data have demonstrated lower HF hospitalizations among patients with St-LBBB than in those with non-St-LBBB.[9] In our study, patients fulfilling St-LBBB criteria displayed significantly lower rates of total HF hospitalizations and HF hospitalizations per month during follow-up, with the greatest benefit among patients with NICM, an event possibly related to the fact that 6 months post-CRT implantation, most of the patients in the St-LBBB group were classified as NYHA I (73.9%), while the majority of non-St-LBBB patients were classified as NYHA III (66.7%).

VA burden is a powerful predictor of subsequent mortality in CRT patients.[23] Several studies have demonstrated an association between CRT response and a reduced risk of VAs compared with CRT non-responders.[24–26] In a meta-analysis, patients with an improvement in LVEF of ≥45% exhibited significantly lower rates of ICD therapy compared with patients without such recovery. Several mechanisms have been proposed to explain the VA reduction in CRT responders. Reverse electrical (reduction of ventricular conduction delay) and structural remodelling (reduction in LVESV, LV mass and increase in LVEF) appear to be the most plausible explanations for this beneficial effect.[27] In MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy), the extent of reverse remodelling was inversely related to the development of future VA events.[28]

Data regarding VA events in CRT patients selected based on Strauss criteria do not exist. To the best of our knowledge, this is the first study addressing this issue. Patients fulfilling St-LBBB criteria displayed significantly lower rates of VAs (NSVT, sustained VT, polymorphic VT or VF) than those with non-St-LBBB (28.3% vs. 44.4%). Kaplan–Meier estimates demonstrated that patients with NICM and St-LBBB exhibited greater benefit compared with ICM and St-LBBB with respect to VA burden. A possible explanation is that patients with ICM may be less likely to respond in terms of LVEF improvement, LVESV reduction and reverse remodelling than patients with NICM,[29,30] due to the greater percentage of myocardial scarring.[31] In addition, CRT therapy may have a proarrhythmic effect due to the reversal of LV wall activation in patients without true LBBB. This may lead to QT interval prolongation and increased transmural dispersion, creating the substrate and triggering a re-entrant arrhythmia.[32]

Thus far, two studies have addressed mortality outcomes based on the St-LBBB selection of patients for CRT. In the study by Caputo *et al*., no differences regarding mortality rates were observed among different ECG definitions of LBBB, including the Strauss criteria.[9] On the contrary, Hadjis *et al*. demonstrated that the implementation of strict LBBB criteria is associated with a significant reduction in mortality compared with conventional LBBB,[8] most likely due to effective resynchronization. In accordance with this study, we showed that treatment with CRT, based on Strauss criteria, resulted in an 88% risk reduction of death among patients with NICM. On the contrary, no benefit was seen in ICM patients.

According to our results, the beneficial role of St-LBBB was greater among NICM patients compared with ICM patients. The lower adherence to medical therapy, the increased comorbidity burden and the worse general clinical status of ICM patients could explain these results. Other reasons for the observed differences could be the greater CRT response and the fewer VA events that can result in higher biventricular pacing rates in NICM compared with the ICM group.

Limitations

The limited sample size of the cohort may affect the power of our study to extract general results. Current research may serve as a pilot study that needs to be confirmed in larger prospective trials. Interobserver variability may exist in the analysis of ECG parameters. In order to minimize the subjectivity of distinguishing the QRS from fQRS waves, measurements were conducted by two electrophysiologists.[33–35] The echocardiographic measurements were not evaluated by two independent investigators, and the measurements were not performed in a 'blind' fashion. The issue of competing risks should also be noted in the survival data analyses. As a result, the VAs and hospitalization curves could be affected by survival differences.

Conclusions

Patients with NICM and St-LBBB present the greatest benefit concerning CRT response, HF hospitalizations, VA events and mortality. The results of the present study propose that St-LBBB criteria may improve patient selection for CRT. However, further studies are needed to elucidate the role of St-LBBB criteria in this setting.

Conflict of interest statement

The authors declare no conflicts of interest.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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