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Identification of Typical Left Bundle Branch Block Contraction by Strain Echocardiography Is Additive to Electrocardiography in Prediction of Long-Term Outcome After Cardiac Resynchronization Therapy

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ABSTRACT

BACKGROUND Current guidelines suggest that patients with left bundle branch block (LBBB) be treated with cardiac resynchronization therapy (CRT); however, one-third do not have a significant activation delay, which can result in nonresponse. By identifying characteristic opposing wall contraction, 2-dimensional strain echocardiography (2DSE) may detect true LBBB activation.

OBJECTIVES This study sought to investigate whether the absence of a typical LBBB mechanical activation pattern by 2DSE was associated with unfavorable long-term outcome and if this is additive to electrocardiographic (ECG) morphology and duration.

METHODS From 2 centers, 208 CRT candidates (New York Heart Association classes II to IV, ejection fraction ≤35%, QRS duration ≥120 ms) with LBBB by ECG were prospectively included. Before CRT implantation, longitudinal strain in the apical 4-chamber view determined whether typical LBBB contraction was present. The pre-defined outcome was freedom from death, left ventricular assist device, or heart transplantation over 4 years.

RESULTS Two-thirds of patients (63%) had a typical LBBB contraction pattern. During 4 years, 48 patients (23%) reached the primary endpoint. Absence of a typical LBBB contraction was independently associated with increased risk of adverse outcome after adjustment for ischemic heart disease and QRS width (hazard ratio [HR]: 3.1; 95% CI: 1.64 to 5.88; $p < 0.005$). Adding pattern assessment to a risk prediction model including QRS duration and ischemic heart disease significantly improved the net reclassification index to 0.14 ($p = 0.04$) and improved the C-statistics (0.63 [95% CI: 0.54 to 0.72] vs. 0.71 [95% CI: 0.63 to 0.80]; $p = 0.02$). Use of strict LBBB ECG criteria was not independently associated with outcome in the multivariate model (HR: 1.72; 95% CI: 0.89 to 3.33; $p = 0.11$. Assessment of LBBB contraction pattern was superior to time-to-peak indexes of dyssynchrony ($p < 0.01$ for all).

CONCLUSIONS Contraction pattern assessment to identify true LBBB activation provided important prognostic information in CRT candidates. (J Am Coll Cardiol 2015;66:631–41) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

2DSE = 2-dimensional strain echocardiography

CRT = cardiac resynchronization therapy

ECG = electrocardiography/electrocardiographic

LBBB = left bundle branch block

LV = left ventricle/ventricular

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

TDI = tissue Doppler imaging

Striking improvement in the prognosis for patients with symptomatic heart failure and left bundle branch block (LBBB) has been obtained in some patients treated with cardiac resynchronization therapy (CRT) (1,2). Current guidelines recommend LBBB with QRS duration of ≥150 ms by electrocardiography (ECG) alone, whereas the role for CRT in patients with intermediate QRS duration and LBBB or non-LBBB QRS morphology is less well established (3). However, approximately one-third of patients do not benefit, and some may even experience worsening after CRT (4). The relationship between LBBB electrical activation and the consequent mechanical dysfunction that results in heart failure is therefore not fully understood.

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CRT, an electrical intervention aimed at resolving the LBBB-related abnormal activation of the left ventricle (LV) associated with dyssynchronous heart failure, may alleviate the mechanical dysfunction caused by this electrical delay (5). In contrast, if heart failure is caused by underlying myocardial disease, such as scar, CRT is unlikely to benefit the patient (5). Thus, methods that reliably reflect a significant activation delay of the LV are thought to be of potential value in selection of candidates for CRT (6). Unfortunately, current modalities have generally proven suboptimal in this regard. Indeed, not all LBBBs by ECG reflect a true LV activation delay (7). Studies using LV endocardial mapping have reported that up to one-third of patients thought to have LBBB are misdiagnosed (8,9). Progressive evidence suggests that an LBBB activation delay can be identified from LV mechanical deformation patterns (6,10–16). True LBBB activation leads to a unique contraction pattern of opposing wall motion (12) with apical rocking motion (15). We recently demonstrated the use of 2-dimensional strain echocardiography (2DSE) to specifically identify LBBB-related wall deformation (6,14), which can be reversed by CRT and is highly predictive of LV remodeling response (14). It is, however, unknown whether such patterns are associated with long-term outcome after CRT.

Using a larger, 2-center group of patients with LBBB undergoing CRT, we hypothesized that: 1) the absence of a typical LBBB contraction pattern identified by 2DSE would be associated with unfavorable long-term outcome in comparison with those with evidence of typical LBBB contraction; 2) risk prediction of adverse outcome would be improved beyond conventional ECG criteria, QRS duration, and LBBB morphology by identification of a typical LBBB contraction pattern; and 3) risk prediction of adverse outcome would be improved beyond traditional time-to-peak indexes of mechanical dyssynchrony.

METHODS

STUDY POPULATION. Inclusion criteria. The study design was prospective, with analysis of the typical LBBB pattern applied to a consecutive patient series meeting the inclusion and exclusion criteria. The population included patients eligible for CRT at 2 centers. Patients had native LBBB by conventional ECG criteria (left ventricular ejection fraction [LVEF] ≤35%, QRS duration ≥120 ms, and New York Heart Association class II to IV, despite optimal pharmacological therapy) (17). Overall, 234 patients with LBBB were included (139 from the University of Pittsburgh Medical Center and 95 from Gentofte University Hospital, Denmark). The decision to implant a CRT device was on the basis of routine ECG criteria. Pre-implant dyssynchrony was not among the selection criteria.

Exclusion criteria. Patients were excluded if they had significant primary valve disease, atrial fibrillation, acute coronary syndrome, or revascularization within 3 months of the baseline echocardiography or if baseline echocardiographic images were not of suitable quality for quantitative strain analysis. All patients were implanted with a CRT device with defibrillator capacity, according to standard clinical practice, with 1 lead in the high right atrium, a right ventricular apical or septal lead, and an LV lead positioned through the coronary sinus in an epicardial vein targeting posterolateral or lateral branches. Data collection included pre-implant ECG, echocardiography, routine laboratory work, and demographic and clinical data. The study protocol was approved by the Institutional Review Boards at both centers and complied with the Declaration of Helsinki.

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ECHOCARDIOGRAPHY. A full standard echocardiographic examination, including gray-scale images optimized for 2D strain analysis (mean frame rate 62 ± 17 frames/s) was performed within 1 month before CRT implantation. All echocardiographic studies were acquired with a Vivid 7 Dimension or Vivid 9 using a 3.5-MHz ultrasound probe (GE-Vingmed Ultrasound, Horten, Norway). Two experienced readers performed off-line analysis using EchoPac PC version BT11 (GE-Vingmed Ultrasound). The LV end-systolic volume, LV end-diastolic volume, and LVEF were assessed using the biplane Simpson method.

TWO-DIMENSIONAL STRAIN ECHOCARDIOGRAPHY. Two-dimensional strain echocardiography analysis was performed from the apical 4-chamber view as previously described (18). The reference point was placed at the beginning of the QRS complex. Aortic valve closure and opening were defined using a pulsed-wave Doppler ultrasound in the LV outflow tract with a 2-mm sample volume. The endocardial border was traced in end-systole and the automatically generated region of interest was adjusted to exclude the pericardium. The integrity of speckle tracking was automatically detected and visually ascertained. In case of poor tracking, the region of interest tracing was readjusted. Segments with persistent inadequate tracking were excluded from analysis. In case of inadequate tracking in 2 or more segments, the patient was excluded from analysis. All strain analysis was performed blinded to outcome.

DEFINITION OF A TYPICAL LBBB CONTRACTION PATTERN. Identification of a typical contraction pattern reflecting a true LBBB was performed as previously described (14). All 3 of the following criteria were required for a study to be read as a typical LBBB pattern from longitudinal strain curves in the 4-chamber view: 1) early shortening of at least 1 basal or mid-ventricular segment in the septal wall and early stretching in at least 1 basal or midventricular segment in the lateral wall; 2) early septal peak shortening (within the first 70% of the ejection phase); and 3) lateral wall peak shortening after aortic valve closure. If 1 of these 3 criteria was not present, the patient was categorized as having an atypical pattern. **Figure 1A** shows an example of a typical LBBB contraction pattern, and **Figure 1B** shows an example of an atypical pattern. Both patients had LBBB by ECG criteria.

STRICT LBBB ECG CRITERIA. The value of improved LBBB ECG criteria, as recently proposed by Strauss et al. (7), was investigated. A complete LBBB was defined as QRS duration of ≥140 ms in men or ≥130 ms in women, QS or rS in leads V_1 and V_2, and mid-QRS complex slowing or notching in ≥2 of leads V_1, V_2, V_5, V_6, I, and aVL (7).

TIME-TO-PEAK DYSSYNCHRONY INDEXES. The performance of LBBB contraction pattern assessment was compared with methods for time-to-peak dyssynchrony. Radial strain dyssynchrony was determined by the time difference in peak strain between the anteroseptal and posterior walls, with ≥130 ms defined as significant (19). Longitudinal strain dyssynchrony was determined by the maximal time difference in peak strain between opposing walls in the apical 4-chamber view, with ≥130 ms defined as significant (20). Tissue Doppler imaging (TDI)-derived time-to-peak opposing-wall delay was defined as the maximal difference in peak velocity at basal segments and midsegments in opposing walls for the 3 apical views, with ≥80 ms defined as significant dyssynchrony (13,19).

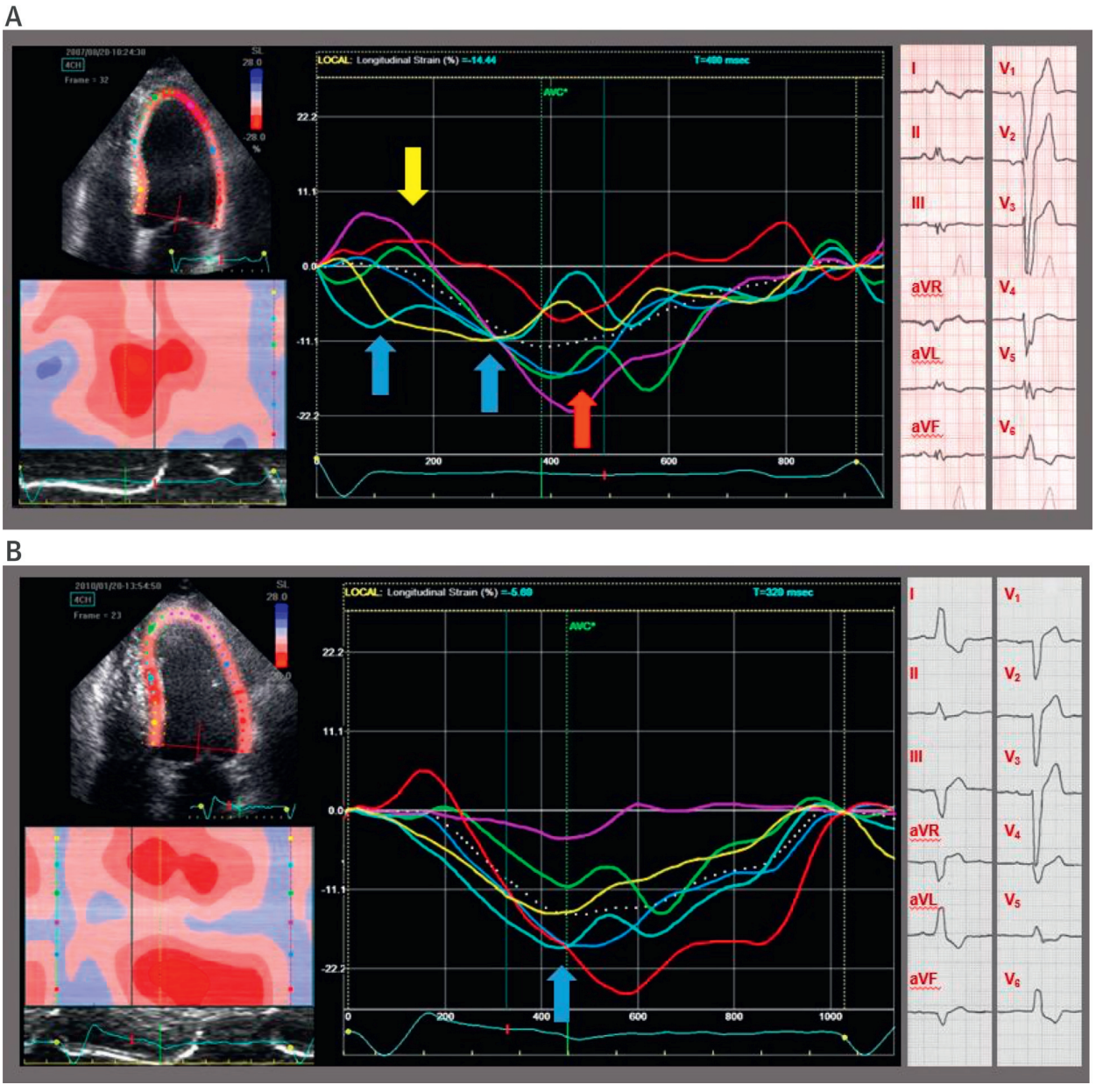
INTRAOBSERVER AND INTEROBSERVER REPRODUCIBILITY. The presence of a typical LBBB pattern was evaluated in 30 randomly selected pre-implantation examinations and re-evaluated by the original observer and a second, independent observer. The intraobserver and interobserver concordance on identifying the typical pattern was evaluated by kappa statistics.

LONG-TERM OUTCOME AND SUBGROUP ANALYSES. The primary outcome was a composite of all-cause mortality, cardiac transplantation, and implantation of an left ventricular assist device (LVAD). Vital status for all patients was ascertained by May 2014 through chart review, the U.S. Social Security Death Index, and the Danish civil registration register, respectively. Pre-defined subgroup analysis was planned in patients with QRS duration between 120 and 150 ms and >150 ms.

STATISTICAL ANALYSIS. Descriptive statistics. Relevant variables were tested for normality using visual inspection of histogram plots and are presented as mean ± SD. Continuous variables were compared using the Student *t* test. Proportional differences were tested using chi-square statistics or the Fisher exact test, as appropriate.

Survival statistics. Proportional hazards assumptions were verified graphically. For all survival analyses, follow-up was truncated at a maximum of 4 years (1,460 days). The cumulative probability of the endpoint was illustrated using the Kaplan-Meier method, with significance testing using log-rank statistics. Univariate and multivariate predictors of event-free survival after CRT device implantation were assessed in Cox proportional hazards models. Candidate variables with p values <0.05 in univariate analysis were included in the multivariate model, using

FIGURE 1 Different Contraction Patterns by 2-Dimensional Strain Echocardiography in 2 Patients With LBBB by Electrocardiography



(A) A characteristic left bundle branch block (LBBB) opposing wall motion is present, indicating typical LBBB activation, including early terminated shortening in the septal wall **(blue arrows)** with early (pre-stretch) in the lateral wall **(yellow arrow)** and late lateral peak contraction **(red arrow)**. **(B)** Atypical LBBB pattern. Segments show synchronous peak shortening timed at aortic valve closure **(blue arrow)**.

backward selection to test the independent association between the outcome and the presence of the LBBB contraction pattern, as well as each of the dyssynchrony indexes and use of strict LBBB ECG criteria.

Risk reclassification by adding LBBB pattern assessment. Receiver-operating characteristic curve analysis with use of a nonparametric estimate of the area under curve and C-statistics with 95% CI was performed for the multivariate model. For comparison between assessment of LBBB contraction pattern and dyssynchrony indexes, the strength of association with outcome for each index was compared using −2 log likelihood statistics. The ability to reclassify patient risk when patterns were added to

the multivariate model was evaluated by assessment of the net reclassification index (NRI) and the integrated diagnostic improvement (21). Patients were initially classified at a low or high risk of an event if their predicted risk was < or ≥10%, respectively, a predefined cutoff derived from previous studies (13,22). Patients might then be reclassified into a different category with the added information of whether or not the LBBB contraction pattern was present. A 2-tailed p value <0.05 was considered significant in the final models. All statistical analyses were performed using SAS for Windows version 9.3 (SAS institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Of the 234 patients with native LBBB, 26 (11%) were excluded because of atrial fibrillation (3%) or poor image quality (8%); Accordingly, 208 patients with complete baseline data were included. The patients' mean age was 66 ± 10 years, 57 (27%) were female, and 120 (58%) had ischemic heart disease. One hundred and thirty patients (62.5%) had a typical LBBB contraction pattern, 78 (37.5%) patients had an atypical pattern, and 97 ± 4% had biventricular pacing percentage, with no difference between groups. Table 1 shows baseline characteristics according to whether a typical contraction pattern was present or not. Baseline characteristics among patients with and without a pattern differed significantly: patients with typical patterns were more often female (35% vs. 14%; p < 0.001) and had a wider QRS duration (163 ± 23 vs. 153 ± 22; p = 0.004), and fewer had evidence of ischemic heart disease (47% vs. 76%; p < 0.001).

FOLLOW-UP. The median follow-up was 4.0 years (IQR: 3.25 to 4 years). During follow-up, 38 patients (18%) died, 4 (2%) had a heart transplant, and 6 (3%) received LVADs. Eleven patients (5%) died during the first 6 months after device implantation.

OUTCOME IN RELATION TO TYPICAL VERSUS NOT TYPICAL LBBB CONTRACTION PATTERN. The absence of a typical LBBB contraction pattern by 2DSE was highly associated with a poor outcome (Figure 2). During 4 years, 40% in the group without a typical pattern had an adverse event, compared with 14% in the typical pattern group (hazard ratio [HR]: 3.57; 95% CI: 2.00 to 6.66; p < 0.001). Among the covariates, significant associations with outcome could be demonstrated for QRS duration and ischemic etiology by univariate analysis (Figure 3). In multivariate analysis, the absence of a typical LBBB contraction pattern remained independently associated with outcome (HR: 3.13; 95% CI: 1.64 to 5.88; p < 0.005) (Figure 3). Adding sex to the multivariate model did not significantly change the results.

TABLE 1 Baseline Characteristics

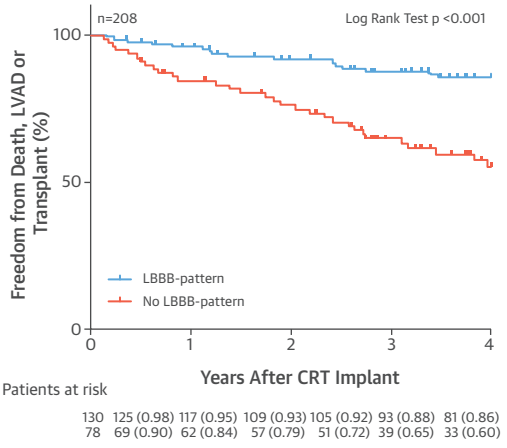
	Total Cohort (N = 208)		
	LBBB Contraction (n = 130)	No LBBB Contraction (n = 78)	p Value
Age, yrs	66.1 ± 10	66.3 ± 10	0.9
Female	46 (35)	11 (14)	<0.001
NYHA functional class	2.7 ± 0.4	2.7 ± 0.4	0.9
QRS, ms	163 ± 23	153 ± 22	0.004
QRS >150 ms	91 (70)	38 (49)	0.002
Ischemic etiology	61 (47)	59 (76)	<0.001
eGFR, ml/min	73 ± 23	70 ± 22	0.44
LVEF, %	24 ± 6	24.5 ± 6	0.7
LVESV, ml	157 ± 64	154 ± 72	0.8
LVEDV, ml	203 ± 74	202 ± 83	0.9
Beta-blocker	118 (91)	72 (92)	0.8
ACEI/ARB	121 (93)	71 (91)	0.6

Values are mean ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; EGFR = estimated glomerular filtration rate; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.

INTRAOBSERVER AND INTEROBSERVER REPRODUCIBILITY. The intraobserver and interobserver concordances on identifying the typical pattern were 30/30, kappa = 1.0 and 28/30, kappa = 0.87, respectively.

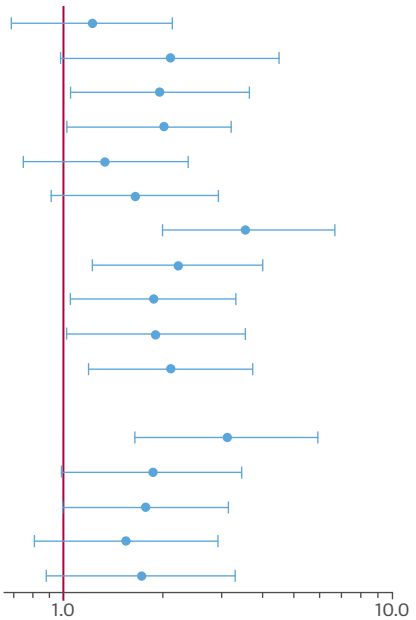
FIGURE 2 Kaplan-Meier Curves Showing Freedom From Death, LVAD, or Heart Transplant After CRT



These curves are in relation to the presence or absence of a typical LBBB contraction pattern. CRT = cardiac resynchronization therapy; LVAD = left ventricular assist device; other abbreviation as in Figure 1.

FIGURE 3 Univariate and Multivariate Risk Analyses of Long-Term Adverse Outcome After CRT

	Hazard Ratio (95% CI)*	p Value
Univariate		
Age ≥ 66 years	1.22 (95% CI 0.69-2.13)	0.50
Male	2.10 (95% CI 0.98-4.48)	0.06
Ischemic etiology	1.95 (95% CI 1.05-3.64)	0.03
QRS 120- 150 ms	2.01 (95% CI 1.02-3.20)	0.04
LVEF < 24%	1.33 (95% CI 0.75-2.38)	0.33
eGFR < 60 ml/min	1.64 (95% CI 0.92-2.93)	0.09
No typical LBBB contraction	3.57 (95% CI 2.00-6.66)	<0.001
No radial strain dyssynchrony	2.22 (95% CI 1.22-4.00)	0.001
No TDI dyssynchrony	1.86 (95% CI 1.05-3.30)	0.03
No longitudinal strain dyssynchrony	1.89 (95% CI 1.02-3.53)	0.04
No strict LBBB by ECG	2.11 (95% CI 1.19-3.73)	0.01
Multivariate†		
No typical LBBB contraction	3.13 (95% CI 1.64-5.88)	0.005
No radial strain dyssynchrony	1.85 (95% CI 0.99-3.44)	0.05
No TDI dyssynchrony	1.76 (95% CI 0.99-3.14)	0.05
No longitudinal strain dyssynchrony	1.54 (95% CI 0.81-2.94)	0.19
No strict LBBB by ECG	1.72 (95% CI 0.89-3.31)	0.10



*Cox proportional hazards modeling with composite outcome of death, LVAD, or heart transplant; †Etiology and QRS duration were added to each of the variables in the multivariate model. CI = confidence interval; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; TDI = tissue Doppler imaging; other abbreviations as in Figures 1 and 2.

RISK RECLASSIFICATION BY ADDING LBBB PATTERN ASSESSMENT. The addition of LBBB pattern assessment to a model including etiology and QRS duration (>150 ms or ≤150 ms) significantly improved risk prediction. Figure 4 shows receiver-operating characteristic curves for a model including etiology and QRS duration versus the same model with contraction pattern assessment added. C-statistics were 0.63 (95% CI: 0.54 to 0.72) and 0.70 (95% CI: 0.62 to 0.79), respectively ($p = 0.02$).

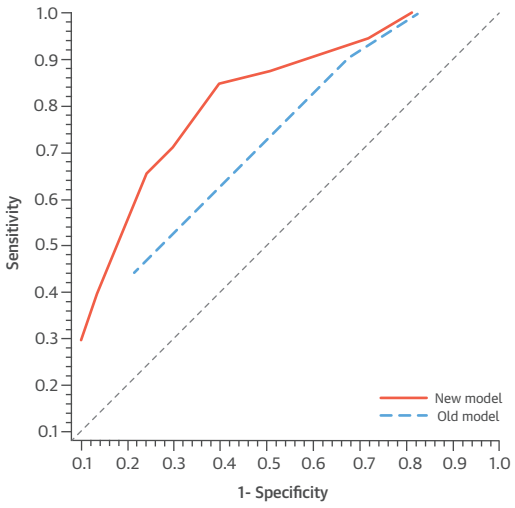
NRI analysis showed that adding pattern assessment to a 4-year 10% risk model with QRS duration and ischemic heart disease yielded a significant integrated diagnostic improvement (0.067; $p < 0.001$) and NRI (0.14; $p = 0.04$), driven by a correct downward risk classification of 45 patients among those without events ($p < 0.001$) and an incorrect downward risk reclassification in 7 patients with events ($p = 0.008$).

LBBB CONTRACTION PATTERNS IN RELATION TO QRS DURATION. The relationship between the absence of a typical LBBB contraction and an unfavorable outcome was independent of QRS duration (Figure 5). For patients with QRS duration of 120 to 150 ms, absence of typical pattern versus presence of typical pattern resulted in an HR of 2.9 (95% CI: 1.22 to 7.01; $p = 0.02$). For QRS duration of ≥150 ms, absence of typical pattern versus presence of typical pattern resulted in an HR of 3.8 (95% CI: 1.67 to 8.64; $p = 0.002$). No statistically significant differences were found in the risk of an adverse outcome between groups with typical pattern (QRS duration of 120 to 150 ms vs. >150 ms; HR: 1.6; 95% CI: 0.60 to 4.16; $p = 0.35$) or between groups without a typical pattern (QRS duration of 120 to 150 ms vs. >150 ms; HR: 1.2; 95% CI: 0.60 to 2.49; $p = 0.58$).

Of note, only 30% of the patients with QRS width between 120 and 140 ms showed evidence of typical LBBB contraction. Among patients with QRS duration of >140 ms, 65% had a typical LBBB pattern.

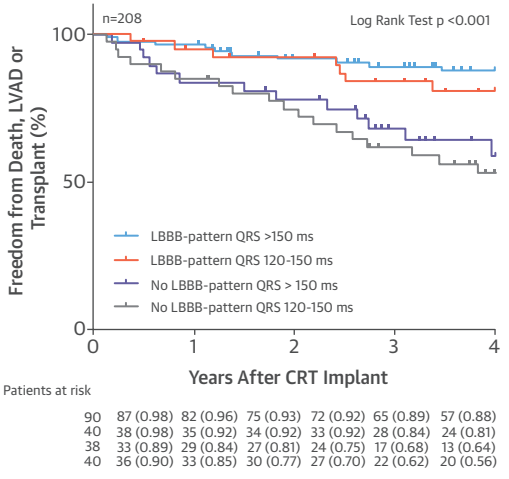
OUTCOME IN RELATION TO STRICT LBBB ECG CRITERIA. Analysis of strict LBBB by ECG was possible in 206 of 208 patients; 2 ECGs were excluded due

FIGURE 4 ROC Curves for Associations With Outcome of Models With and Without Echocardiographic Assessment of the Contraction Pattern



Receiver-operating characteristic (ROC) curves for the associations of a model including QRS duration and etiology (**blue line**/old model) and a model including assessment of LBBB contraction pattern, QRS duration, and etiology (**red line**/new model) with survival free from heart transplant or LVAD after CRT. Abbreviations as in Figures 1 and 2.

FIGURE 5 Kaplan-Meier Curves Showing Freedom From Death, LVAD, or Heart Transplant After CRT



These are according to baseline QRS duration and the presence or absence of typical LBBB contraction. Abbreviations as in Figures 1 and 2.

to baseline artifacts. Strict LBBB was present in 136 of 206 patients (66%). Absence of strict LBBB was significantly associated with an unfavorable outcome (HR: 2.1; 95% CI: 1.2 to 3.7; p = 0.01). However, an independent association was not found after adjustment for etiology and QRS duration (HR: 1.72; 95% CI: 0.89 to 3.33; p = 0.11).

Addition of LBBB pattern assessment to a model including strict LBBB ECG criteria etiology and QRS duration significantly improved risk prediction, with a C-statistic of 0.63 (95% CI: 0.54 to 0.72) versus 0.71 (95% CI: 0.63 to 0.80; p = 0.02).

COMPARISON WITH TIME-TO-PEAK DYSSYNCHRONY INDEXES. Time-to-peak dyssynchrony analysis was performed by TDI (n = 205), longitudinal strain (n = 208), and radial strain (n = 201). All indexes showed a statistically significant association with outcome in univariate analysis; however, only radial strain dyssynchrony and TDI opposing-wall delay showed a (borderline) significant relation with outcome in the multivariate model (Figure 3). LBBB pattern assessment had a significantly higher association with outcome compared with each of the dyssynchrony indexes in the multivariate models (p < 0.01 for all for difference between parameters).

DISCUSSION

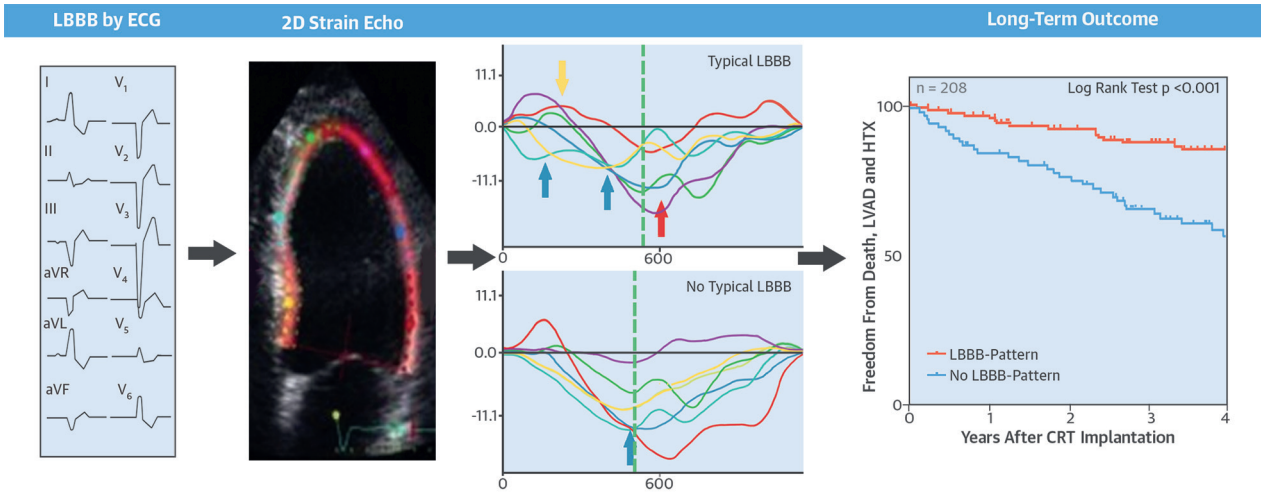
The presence or absence of an electrical activation delay is an important reason why some patients respond to CRT and others do not. Identification of the underlying electrical substrate for CRT by assessment of the mechanical manifestation using strain echocardiography may be clinically useful.

The main findings of the current study were:

1. In more than one-third of patients with LBBB by conventional ECG criteria, a typical LBBB contraction pattern was absent; this was independently associated with a more than 3-fold increase in the risk of adverse events.
2. Assessment of LBBB-specific contraction by 2DSE improved risk prediction beyond ECG (QRS duration and morphology) and etiology.
3. Assessment of LBBB contraction pattern improved risk prediction beyond time-to-peak dyssynchrony measurements.

A recent substudy of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) study demonstrated long-term survival benefit in patients with LBBB, whereas CRT was not beneficial in patients without LBBB (those with right bundle branch block and

CENTRAL ILLUSTRATION **Left Bundle Branch Block Contraction and Long-Term Outcome**



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CRT = cardiac resynchronization therapy; ECG = electrocardiography; HTX = heart transplant; LBBB = left bundle branch block.

intraventricular conduction delay morphology) (4). It seems reasonable to believe that the main mechanism underlying the differential effect from CRT according to QRS morphology is whether a significant activation delay is present in the LV. In patients without LBBB, the left bundle is usually preserved, resulting in normal LV activation times (7,23). Consequently, there is no obvious target for CRT (5), and lack of response to CRT among patients without LBBB is expected. In contrast, most patients with LBBB by ECG have a significant LV activation delay. However, electrophysiological mapping studies have demonstrated that approximately one-third of patients do not have a significant activation delay (8,9). Combinations of LV hypertrophy, dilation, isolated fascicular block, and slowed intraventricular conduction velocity can cause ECG changes that may be falsely interpreted as a complete LBBB by conventional criteria (24).

NEED FOR PHYSIOLOGICAL UNDERSTANDING. Methods that reliably reflect the physiology of a significant activation delay of the LV are needed if selection of CRT candidates is to be improved and therapeutic expectations are to be more refined. The current study investigated the importance of a typical LBBB mechanical deformation pattern for CRT outcome (**Central Illustration**). A strong association between LBBB mechanical contraction and long-term survival after CRT could be demonstrated, and high-risk patients were identified independently of and incrementally to LBBB, QRS duration, and heart failure etiology, which are the most important decision-making indexes for CRT. NRI analysis further suggested that adding pattern assessment to a predictive model including QRS duration of >150 ms and etiology among patients with LBBB will considerably improve risk reclassification, primarily by identifying patients at low risk (death, LVAD insertion, or transplant) if they have an implanted CRT device. Thus, the present study supports a valuable role for 2DSE in risk stratification and refinement of treatment in patients undergoing CRT.

CONTROVERSIES IN ECHOCARDIOGRAPHY-DERIVED PATIENT SELECTION. Following the PROSPECT (Predictors of Response to CRT) (25) and ECHO-CRT (Echocardiography Guided Cardiac Resynchronization Therapy) (26) trials, the role for echocardiography in selection of CRT candidates has been controversial. In both studies, the mechanical delay in contraction was addressed by methods that rely on the time-to-peak principle (19,20,27). However, this approach may have some limitations (28). Timing of peak motion alone, whether by velocities or strain, does not provide any information on the nature of the wall deformation, such as whether differences are due to scarring or activation timing differences (13). Relatively large time-to-peak differences can be observed in the presence or absence of a true activation delay (5,29). In particular, patients with ischemic heart failure due to scarring (30), or with an exacerbation in heart failure or other conditions causing

changes in regional loading conditions, may manifest time-to-peak differences that are not due to a true electrical activation delay (31). In the present study, dyssynchrony by time-to-peak indexes was significantly associated with outcome, with HRs similar to those previously reported (19), although this relation had only borderline significance ($p = 0.05$) in the multivariate model. This observation is likely due to the current study including only patients with LBBB ECG morphology, whereas previous studies had also included a significant number of patients without LBBB (19). Overall, the results indicate that some echocardiography-derived indexes of mechanical dysfunction may occasionally be inadequate. By assessment of the entire contraction pattern reflecting the target for resynchronization therapy, risk prediction was significantly improved beyond the use of simple time-to-peak numbers in patients with LBBB ECG morphology.

PHYSIOLOGY MAKES A DIFFERENCE. Distinguishing mechanical dyssynchrony induced by an electrical activation delay (likely to benefit from CRT) from mechanical dyssynchrony from other causes (unlikely to benefit from CRT) may be quite difficult. The present study suggests that more attention should be paid to the complex interplay between walls, which reflects the physiology of activation delay-induced heart failure. In fact, any method, whether by echocardiography or ECG, should reliably reflect this substrate. Strict ECG criteria for complete LBBB were recently proposed (7) but were not found to be independently associated with adverse outcome in the present study. Furthermore, strict ECG criteria were found inferior for risk stratification compared with assessment of contraction patterns by 2DSE. This is in agreement with observations by Jackson et al. (32), who reported different contraction patterns in patients with strict LBBB related to different outcomes. The data imply that mechanical contraction patterns using echocardiography-based strain inherently hold useful information beyond the activation delay for prediction of outcome after CRT. Computer simulations have shown that LBBB deformation patterns are primarily determined by wall contractility and the degree of activation delay in the LV (33). Absence of typical LBBB mechanical contraction despite LBBB by ECG indicates that the patient either does not have a true LBBB or that contractility is decreased to such a degree that patterns are abolished (6). Either scenario or a combination of both scenarios is associated with a poor prognosis and is critical to identify. LBBB pattern assessment may provide a more logical and reliable method for identifying such scenarios than is currently available.

CLINICAL PERSPECTIVES. Identification of typical LBBB contraction was found to be beneficial, independent of QRS duration and morphology, but assessment of contraction patterns may be particularly useful in pre-implantation evaluation of patients in the intermediate QRS duration range of 120 to 150 ms. Patients with a wide QRS duration of >150 ms have a high a priori likelihood of response, whereas the role for CRT in the intermediate QRS duration group is not entirely clear, as reflected by guidelines (3).

In the present study, a majority of patients in the intermediate QRS group did not have evidence of LBBB contraction. This was associated with a poor outcome, with more than a 3-fold increase in risk of death, LVAD implantation, or heart transplant. In particular, only a minority of patients with a QRS duration of between 120 and 140 ms showed mechanical evidence of true LBBB. These findings further emphasize the importance of careful attention in selection of CRT candidates in the intermediate QRS group. The importance of determining the mechanisms behind heart failure is essential, and ECG reading in these patients cannot stand alone.

STUDY LIMITATIONS. The present study was not randomized, and there was no comparison with patients who did not undergo CRT. Accordingly, the treatment effect from CRT could not be ascertained nor could any adverse effects from CRT be established.

At present, assessment of LBBB patterns is semiquantitative, and a simple number is difficult to obtain along a continuum of disease. However, as reflected by the interobserver analysis, the method is highly reproducible. In our experience, this method can be relatively easily taught to colleagues, fellows-in-training, and sonographers (14). In addition, development of an automated algorithm to facilitate reading of patterns is currently underway.

Myocardial viability was not investigated in the current study. This may be important to further understand the relationship between LBBB electrical activation and the consequent mechanical dysfunction in future selection of CRT candidates.

CONCLUSIONS

Among patients with LBBB by ECG, those with a typical LBBB contraction pattern displayed a markedly improved response to CRT compared with those without a typical LBBB contraction. Patients without a typical contraction pattern had a 3-fold increased risk of adverse outcome following implantation. Risk

prediction of an adverse outcome was improved beyond current selection criteria of QRS duration and morphology by ECG and was superior to previously used dyssynchrony indexes. The importance of the contraction pattern was independent of QRS duration but may be particularly useful for selection of patients with LBBB and QRS duration between 120 and 150 ms, in which the role for CRT is still debated.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: One-third of patients with LBBB on ECG do not have significant LV activation delay, as assessed by 2DSE, and this discordance is associated with poor clinical responses to CRT.

TRANSLATIONAL OUTLOOK: The clinical value of assessing delayed LV activation by 2DSE in candidates for CRT should be evaluated in larger prospective trials targeting those with QRS durations in the range of 120 to 150 ms and long-term outcomes.

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