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Strategies to Improve Selection of Patients Without Typical Left Bundle Branch Block for Cardiac Resynchronization Therapy

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ABSTRACT

Cardiac resynchronization therapy (CRT) is becoming increasingly controversial in patients without typical left bundle branch block (LBBB). Yet, several recent studies displayed that a distinct subgroup of patients with non-LBBB does benefit from CRT. Patients with non-LBBB should, therefore, not as a group be withheld from a potentially very beneficial therapy. Unfortunately, current clinical practice lacks validated selection criteria that may identify possible CRT responders in the non-LBBB subgroup. Consequently, clinical decision making in these patients is often challenging. A few studies, strongly differing in design, have proposed additive selection criteria for improved response prediction in patients with non-LBBB. There is accumulating evidence that more sophisticated echocardiographic dyssynchrony markers, taking into account the underlying electrical substrate responsive to CRT, can aid in the selection of patients with a non-LBBB who may benefit more favorably from CRT. Furthermore, it is important that cardiologists are aware of the shortcomings of current electrocardiographic selection criteria for CRT. Whereas these criteria provide an evidence-based approach for selecting patients for CRT, they do not necessarily guarantee the most optimal strategy for patient selection. Parameters obtained with vectorcardiography, such as QRS area, show potential to overcome the shortcomings of conventional electrocardiographic selection criteria and may improve response prediction regardless of QRS morphology. (J Am Coll Cardiol EP 2020;6:129–42) © 2020 by the American College of Cardiology Foundation.

Cardiac resynchronization therapy (CRT) has shown major favorable effects on the treatment of patients with symptomatic heart failure, severe left ventricular (LV) dysfunction, and prolonged QRS duration. However, several subanalyses of landmark trials and meta-analyses displayed that patients without a left bundle branch block (non-LBBB) QRS morphology benefit less from CRT than do patients with an LBBB (1–4). Non-LBBB is frequently encountered in the heart failure population, yet only a fraction of CRT devices is implanted in patients with a non-LBBB. Approximately 12% to
18% of all CRT devices are implanted in patients with non-LBBB and wide QRS complex (>150 ms), and only 9% of CRT devices are implanted in patients with non-LBBB with a relatively narrow QRS complex (130 to 149 ms) (5). Response rates in these patients are poor with volumetric responders varying from 38% to 50% to 31% to 38% of patients, respectively (5,6). Logically, the question arises whether to continue to implant CRT devices in patients with heart failure with a non-LBBB. Yet, the group of patients with non-LBBB is very heterogeneous, consisting of patients with both right bundle branch block (RBBB) and interventricular conduction delay (IVCD) and with a considerable diversity of underlying myocardial substrates. Hence, it seems unreasonable to expect a consistent response to CRT in these patients. Indeed, recent trials displayed that a subgroup of patients with a non-LBBB QRS morphology does benefit from the therapy (5,7,8). Striking is that current guideline recommendations are based on evidence that stems from subanalyses of studies that included limited patient numbers with RBBB and IVCD (Figure 1). The relevance of these subgroup analyses, therefore, should be questioned. Unfortunately, prospective randomized trials addressing the effect of CRT in patients with RBBB or IVCD are lacking. Consequently, deciding whether a patient with non-LBBB should be implanted with a CRT device often leads to clinical challenges.

This paper reviews the current publications regarding the use of CRT in patients with non-LBBB QRS morphology and sets out to evaluate existing and new parameters that could be helpful for clinical decision making in this subgroup.

THE PATHOPHYSIOLOGICAL MECHANISM FOR BECOMING A CRT RESPONDER

The assumed substrate for CRT is the existence of intrinsic LV electrical dyssynchrony. Through a process called electrical-mechanical coupling, electrical dyssynchrony leads to mechanical inefficiency, a reduction in stroke work, and the triggering of cardiac remodeling processes. Biventricular pacing, delivered by a CRT device, can improve electrical synchrony and, thereby, is able to improve mechanical efficiency and induce reverse remodeling (9). Yet, it is imperative to realize that (bi)ventricular pacing by itself induces a stage of dyssynchronous electrical activation, especially at the level of the LV (10). As a consequence, biventricular pacing can only be of benefit to patients with sufficient baseline electrical dysynchrony. In patients with little or no electrical dyssynchrony, biventricular pacing will prolong total and LV activation times and hence cause iatrogenic electrical dyssynchrony, which will result in worsening of cardiac function and poor patient outcomes (Figure 2) (10). This has been highlighted by the results of the multicenter randomized LESSER-EARTH (Cardiac Resynchronization Therapy in Patients With Heart Failure and a QRS Complex <120 ms: The Evaluation of Resynchronization Therapy for Heart Failure) and ECHO-CRT (Echocardiography in Cardiac Resynchronization Therapy) trials, which included patients with narrow QRS duration and were both terminated prematurely due to safety concerns (11,12). Being able to distinguish between patients that may or may not benefit from CRT, therefore, in large part depends on establishing the existence of sufficient baseline electrical dyssynchrony. Currently, only parameters derived from the 12-lead electrocardiogram (ECG) are used for this purpose.

HIGHLIGHTS

- CRT in patients with non-LBBB is often disputed, yet, 30% to 50% of these patients benefit from the treatment.
- Current ECG selection criteria have shortcomings, which, presumably result in a suboptimal patient selection.
- The establishment of sufficient baseline dyssynchrony (both electrical and mechanical) may enhance patient selection in the non-LBBB subgroup.
- Prospective randomized trials with sufficient power are needed to validate these dyssynchrony parameters.

LIMITATIONS OF CURRENT ELECTROCARDIOGRAPHIC CRITERIA FOR PATIENT SELECTION

When using current ECG guideline selection criteria to assess suitability for CRT, approximately one-third of all CRT recipients do not respond to the therapy. A disadvantage of using parameters derived from the ECG is that they provide only a general overview of ventricular electrical activation abnormalities. Therefore, ECG may not be the most optimal tool for determining the true electrical substrate for CRT (6).
Furthermore, it is noteworthy that multiple criteria exist to define LBBB on the ECG. These differ in their classification of patients and are not equally associated with clinical outcomes with regard to reverse remodeling, heart failure hospitalization, and survival rates. A recent retrospective multicenter study demonstrated that the frequency of LBBB in a CRT cohort of 316 patients strongly depended on the ECG classification used and varied from 29% for the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) (13) criteria, to 47% for the European Society of Cardiology (ESC) (14) criteria and 61% according to the Strauss et al. (15) criteria (16). In addition, clinical outcomes after CRT varied greatly depending on the LBBB definition used. Among the LBBB definitions (AHA/ACC/HRS, ESC [14], and Strauss), the association of LBBB definition and the combined study endpoint of heart failure and mortality was significant only for the ESC and the Strauss definitions (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.43 to 0.87, and HR: 0.57; 95% CI: 0.40 to 0.80, respectively). The ESC definition also showed the strongest association with reverse remodeling (ECS 2013: odds ratio [OR]: 8.7; 95% CI: 1.4 to 56.4). More striking perhaps is that defining LBBB, even when applying these specific criteria, seems subjective to personal interpretation. Furthermore, the interpretation of morphological criteria, such as notching and slurring, may be affected by the format and filtering of the ECG and the positioning of the lateral precordial leads (17). A recent study revealed significant interobserver (p range 0.81 to 0.88, kappa range 0.19 to 0.44), and to a lesser extent, intraobserver (p range 0.87 to 0.95, kappa range 0.47 to 0.74) variability in the classification of LBBB by the use of the various definitions (ESC, AHA/ACC/HRS, Strauss, and MADIT [Multicenter Automatic Defibrillator Implantation Trial]) (17). This means that 1 in every 5 or 6 ECG will be classified differently by different observers, and 1 in 10 ECG will be classified differently by the same observer, despite applying specific LBBB criteria.

With these results in mind, it should be appreciated that the exact LBBB definition used in a large proportion of the scientific publications on CRT is either not described or nonspecific (1,2). This is a problem because an important group of patients would have been classified differently when other LBBB criteria would have been applied or when different observers would have scored the presence of LBBB in these trials (16). This could explain why in a meta-analysis of data from 3,782 patients from 5 randomized key CRT trials (CARE-HF [Cardiac Resynchronization in Heart Failure], RAFT [Resynchronization/Defibrillation for Ambulatory Heart Failure Trial], MIRACLE [Multicenter InSync Randomized Clinical Evaluation], MIRACLE-ICD [Multicenter InSync Randomized Clinical Evaluation–Implantable Cardioverter-Defibrillator], REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction]) QRS morphology was not associated with response to CRT with regard to morbidity and mortality (18).

Clearly, evidence regarding the relationship between LBBB and CRT response is somewhat clouded. Nevertheless, finding the patient that may have a most favorable response to CRT will possibly not depend on defining true LBBB on the ECG but on defining a dominant leftward electrical delay. This dominant leftward electrical delay may be present or absent in patients classified as having LBBB or non-LBBB (10).

**VISUALIZING A DOMINANT LEFTWARD ELECTRICAL DELAY**

Comprehensive information regarding the underlying electrical activation patterns of the heart can be acquired with ventricular activation maps. Various techniques both invasive (e.g., 3-dimensional electroanatomical reconstruction contact or noncontact mapping) and noninvasive (ECG imaging or body surface mapping) allow for mapping of the electrical activation sequences (19-21). Previous work that
mapped the electrical activation of the ventricles exposed that in most patients with LBBB there is a dominant leftward electrical delay (20,22). This predominant leftward electrical conduction delay is a fundamental component of the electrical substrate, which is amenable to CRT. Hence the greater benefit from CRT in patients with LBBB. Still, some patients without a typical LBBB on the ECG may exhibit an electrical activation pattern that is very similar to that observed in patients with typical LBBB. These patients have an underlying electrical substrate that may be responsive to CRT (19-21).

IDENTIFYING THE ELECTRICAL SUBSTRATE RESPONSIVE TO CRT IN IVCD

Patients with IVCD generally exhibit more complex and heterogeneous ventricular activation patterns than do patients with a typical bundle branch block on the ECG. These are often not primarily related to conduction system disease but are predominantly caused by an underlying myocardial disease (e.g., ischemic) (22,23). Moreover, LV activation times in IVCD patients are generally shorter than those for patients with LBBB and the location of the region of the latest electrical activation is highly variable. The absence of sufficient LV electrical delay together with more extensive underlying myocardial disease likely results in the lower response rate observed in patients with IVCD (19,20,22). Despite an overall poorer response to CRT in patients with IVCD, there appears to be great variability in CRT response in this subgroup. This seems only logical given the diversity of underlying substrates and pathophysiological mechanism involved in IVCD (23). Several studies that mapped the ventricular activation sequences of patients with heart failure displayed that conduction disturbance at a similar level of that observed in patients with LBBB may exist in 20% to 52% of patients that display an IVCD on the ECG (19,20,23). Ploux et al. (10) demonstrated that visualizing these LBBB-like ventricular activation sequences has the potential to be a useful tool for selecting IVCD patients who may benefit from biventricular pacing. The investigators acquired both detailed ventricular activation maps (ECG mapping) and invasive LV pressure measurements (LV dP/dt) during baseline activation and biventricular pacing in patients with heart failure (10). Baseline ventricular electrical uncoupling (defined as the difference between left and right ventricular mean activation time) was significantly correlated with change in LV dP/dt in both patients with LBBB and IVCD (10) and with clinical response to CRT (based on change in New York Heart Association functional class and occurrence of major clinical events) (20).

Despite the positive results from studies that used ventricular activation maps for assessing the electrical substrate responsive to CRT, widespread clinical application of detailed electrical mapping is currently limited. This is because the existing techniques are time-consuming and sometimes only possible during the CRT implantation procedure. Unfortunately, identifying possible CRT responders using the 12-lead ECG is challenging in IVCD patients. A study that mapped the electrical activation sequences of hearts with IVCD showed that axis deviation, the presence of fascicular block, and QRS duration did not differ between patients with and without delayed LV lateral wall activation (19). Yet, a few studies suggested that specific ECG features might indicate an underlying electrical substrate responsive to CRT in IVCD patients (1,23). In patients with a pre-existing LBBB, a myocardial infarction might alter the typical LBBB morphology into an “atypical” LBBB (e.g., with QRS complex in the anterior leads and a QR-wave in leads V5 and/or V6). The electrical activation sequence of this patient can be assumed to be very close to that of a patient with typical LBBB and very different from a patient with a
widened QRS complex but relatively unchanged QRS morphology. Consequently, an atypical LBBB might—despite the presence of myocardial scar—indicate an underlying substrate better amendable by CRT. In an analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial, Zareba et al. (1) observed that IVCD patients with LBBB features (defined as predominantly negative QRS morphology in leads V1 to V3 and/or V4 and Q waves in V5 and/or V6 or without significant conduction delay in V3 and/or V4) may obtain some benefit after CRT. When the investigators combined the patients with LBBB with the IVCD patients displaying LBBB-like features, the HR for heart failure episode or death changed from 0.47 to 0.55 (p < 0.001), which still is a very significant reduction in the risk for heart failure or death. In addition, recently published data of 11,505 CRT-eligible patients with non-LBBB from the NCDR ICD (National Cardiovascular Data Registry Implantable Cardioverter-Defibrillator) registry, displayed that CRT implantation appeared to be associated with better outcomes than did implantable cardioverter-defibrillator (ICD) therapy alone in IVCD patients with a QRS duration of >150 ms, but not in patients with QRS duration<150 ms or an RBBB of any QRS duration (24). Yet, the nonrandomized retrospective study design, unclear definition of LBBB, and unclear reasons why certain CRT-eligible patients did not receive a CRT prevent the drawing of firm conclusions. An ongoing double-blind multicenter randomized controlled trial comparing a CRT on versus CRT off in IVCD patients will add substantial knowledge to the modest amount of existing data on CRT in patients with IVCD and should reduce uncertainties for guidelines and clinical practice (25).

IDENTIFYING THE ELECTRICAL SUBSTRATE RESPONSIVE TO CRT IN RBBB

In patients with RBBB, the earliest ventricular activation is located in the LV myocardium, whereas the electrical activation of the right ventricle occurs slowly (26). The absence of significant LV conduction delay in RBBB may explain why conventional CRT in these patients induces, rather than resolves, electrical dyssynchrony. This has been exposed by preclinical research and computer simulations assessing the hemodynamic consequences of pure RBBB failing hearts (26,27). Still, in some patients displaying an RBBB on the ECG, both right-sided and left-sided ventricular conduction systems can be affected (21). This was demonstrated in a case report series by Fantoni et al. (21), who in 2005 performed detailed 3-dimensional invasive electroanatomic mapping of the electrical activation patterns of 6 RBBB and 94 LBBB failing hearts. Interestingly, total and regional LV endocardial activation times were not significantly different between RBBB and LBBB patients (21). From this observation, the investigators hypothesized that some patients exhibiting an RBBB on the ECG might have an underlying substrate responsive to CRT. Computer simulations using the CircAdapt model later indeed established that in an RBBB model, stroke work only improves in the presence of sufficient coexisting LV conduction delay (26). These data further fuel the concept that RBBB patients with a coexisting LV activation delay may respond to CRT.

A few studies over time suggested that a specific ECG pattern resembling RBBB can be used to identify patients with RBBB and a coexisting LV activation delay. This pattern has first been introduced by Rosenbaum et al. (28) in the 1960s as “RBBB masking LBBB,” which is characterized by a broad slurred R-wave in leads I and aVL, together with a left axis deviation. A few decades later, Tzogias et al. (29) reported on the ECG consequences of transient RBBB occurring during right heart catheterization in patients with LBBB compared with in patients with either normal QRS complexes or left fascicular block. Whereas patients with a normal baseline QRS complex or left fascicular block developed a typical RBBB after catheter trauma to the right bundle, patients with baseline LBBB developed an atypical RBBB pattern (with RBBB pattern in lead V, and absent significant S-wave in the lateral leads I and aVL) (Figure 3). The investigators hypothesized that an atypical RBBB may be an indication of a coexisting left bundle branch delay. An atypical RBBB could, therefore, be an ECG pattern that identifies possible CRT responders within a group of patients with RBBB. A retrospective multicenter study recently tested whether this atypical RBBB pattern could identify possible CRT responders within a group of 66 patients exhibiting a RBBB morphology (8). Patients with an atypical RBBB, compared with patients with typical RBBB, at baseline (absent S-wave in leads I and aVL) indeed showed significantly longer LV electrical delay measured as the QLV-interval (the interval from the onset of the intrinsic QRS on the surface ECG to the first large peak of the LV electrogram). At follow up, these patients also (QLV 111.9 ± 17.6 ms and 73.2 ± 15.4 ms; p = 0.001). In addition, these patients also displayed improved echocardiographic (71.4% vs 19.4%; p = 0.001) and clinical outcome at 2-year follow-up after CRT implantation (Table 1).
Another characteristic on the RBBB ECG that has been suggested as a possible indicator for the presence of a leftward conduction delay is coexistence of a left hemiblock. Two previous studies (30,31) that assessed the effect of a coexisting left hemiblock on CRT volumetric response in patients with an RBBB showed conflicting results. Moreover, according to a MADIT-CRT substudy, there was no difference in the 3-year crude event rates for death or heart failure among RBBB patients with baseline left anterior hemiblock (22%), non–left anterior hemiblock (21%) who received a CRT, or patients who received ICD-only therapy (20%) ($p = 0.24$) (Table 1). The heterogeneity on outcomes with CRT in RBBB with left anterior hemiblock probably can be explained by the fact that this ECG pattern can be caused either by primary conduction system disease, with associated mechanical dyssynchrony, or by an infarction of the proximal left anterior descending coronary artery, in which a classical mechanical dyssynchrony pattern of opposing wall motion is often absent (32).

Despite the limited amount of studies performed on this subject, it is clear that pure RBBB without significant electrical delay of the LV is not a substrate that should be treated with CRT. RBBB with a significant leftward electrical delay can be established with ventricular activation maps. Unfortunately, it remains uncertain how these patients can best be identified using the ECG. An atypical RBBB pattern, with absent significant S-wave in the lateral leads I and aVL, may be useful as additive selection criteria in this subgroup, yet this parameter warrants further investigation in prospective trials (29).

**ATRIOVENTRICULAR DYSSYNCHRONY AS ELECTRICAL SUBSTRATE FOR CRT?**

The beneficial effect of CRT is often thought to be attributed to ventricular resynchronization. Interestingly, recent work suggested that the existence of atrioventricular dyssynchrony, represented by prolongation of the PR interval on the ECG, is a potential target for CRT (33). Proper atrioventricular coupling is of major importance for efficient pump function. Loss of atrioventricular coupling leads to elevated LV end-diastolic pressure, diastolic mitral regurgitation, and reduced stroke work. Heart failure is often accompanied by atrioventricular conduction disturbances, which, in a heart failure population, are associated with an increased risk for adverse outcomes (e.g., atrial fibrillation, heart failure hospitalization, and death) (34). It is therefore not surprising that several nonrandomized trials exhibited worsened outcomes after CRT in patients with prolonged PR compared with in patients with normal PR interval (35,36). In a large medical registry of CRT-eligible patients that were implanted with a CRT defibrillator or an ICD, the beneficial effect of CRT was confined to patients with a normal PR interval and was absent in patients with prolonged PR interval, even when these patients had an LBBB (35). Unfortunately, the reasons why CRT-eligible patients were implanted with a CRT or an ICD in this registry are unknown. Interestingly, on the other hand, are the results of several subanalyses of the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and MADIT-CRT trials, which showed a reduction of the
risk of all-cause mortality and heart failure hospitalization in CRT patients with prolonged PR interval (7,37,38). Two subanalyses of the MADIT-CRT trial, which focused exclusively on patients with non-LBBB, displayed that CRT reduced the risk of all-cause mortality and heart failure hospitalization in patients with non-LBBB with prolonged PR interval (HR: 1.45; 95% CI: 0.96 to 2.19; p = 0.078) and a 2-fold significantly higher mortality (HR: 2.14; 95% CI: 1.12 to 4.09; p = 0.022), which was sustained at long-term follow-up (7,39). These results suggest that the potential unfavorable effects of biventricular pacing in patients with non-LBBB could be over-ruled by the restoration of atrioventricular coupling in a subgroup of patients with prolonged PR interval.

The small number of studies, critically differing in design and outcome measures currently prevents the drawing of firm conclusions regarding atrioventricular dyssynchrony as electrical substrate that can be corrected with CRT especially in patients without a typical LBBB.

### Prognostic Value of Mechanical Dyssynchrony Markers in Non-LBBB

Due to electromechanical coupling, it seems plausible that abnormal electrical activation coincides with abnormal contraction patterns. However, several multicenter studies, like PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) and ECHO-CRT, were not able to show additive benefit of the use of echocardiographic markers for predicting the outcome of CRT (11,40). It is, therefore, interesting that recent data have presented a few emerging echocardiographic dyssynchrony parameters that show promising results for improving CRT response prediction (41,42). These new indices consist of (relatively complicated) strain-based speckle tracking echocardiography (STE)-derived dyssynchrony parameters and of the (simple) visual assessment of dyssynchrony (eyeballing) (Figure 4).

Two recent subanalyses of large international multicenter studies revealed that the presence of mechanical dyssynchrony can improve the prognostic value of guideline-based patient selection for CRT.
One of these studies analyzed patient data of the PREDICT-CRT (Relationship of Visually Assessed Apical Rocking and Septal Flash to Response and Long-term Survival Following CRT) database and evaluated the potential additive prognostic value of echocardiographic septal flash and apical rocking for the different CRT guideline recommendation classes (5). The presence of apical rocking and/or septal flash at baseline was associated with lower all-cause mortality (HR: 0.30; 95% CI: 0.24 to 0.39; \( p < 0.0001 \)) for the entire cohort, but, interestingly also for patients with intermediate ECG criteria according to the American and European guideline recommendations (43,44) (American: HR: 0.52; 95% CI: 0.35 to 0.77 for Class II, Level of Evidence: A patients [LBBB 120 to 149 ms or non-LBBB \( \geq 150 \) ms]; European: HR: 0.47; 95% CI: 0.27 to 0.82 for Class II, Level of Evidence: A patients [non-LBBB QRS duration \( \geq 150 \) ms], and HR: 0.35; 95% CI: 0.14 to 0.87 in Class II, Level of Evidence: B patients [non-LBBB QRS duration <150 ms]).

Additionally, adding mechanical dyssynchrony as selection criterion coincided with a significantly higher proportion of volumetric responders (\( \geq 15\% \) reduction in LV end-systolic volume) compared with patient selection based on QRS duration and morphology alone (77% vs. 65% in patients with LBBB, 75% vs. 50% in patients with non-LBBB with QRS duration \( \geq 150 \) ms, and 62% vs. 38% in patients with non-LBBB with QRS duration 130 to 149 ms) (5) (Table 2).

Complementary to this work are data from a recently published substudy of the multicenter Adaptive-CRT trial (42). When assessing the STE-derived dyssynchrony parameter “systolic stretch index” (SSI), the investigators found a strong association between baseline dyssynchrony and clinical outcome after CRT in patients with a QRS duration of 120 to 149 ms or non-LBBB (Class II indication according to American guideline recommendations [43]). This was observed for SSI derived from both longitudinal and circumferential strain curves (HR: 2.08; 95% CI: 1.27 to 3.42, and HR: 2.13; 95% CI: 1.24 to 3.67, respectively) (Table 2). In Kaplan-Meier survival analysis, patients with a QRS duration of 120 to 149 ms or non-LBBB (Class II American guidelines) and high SSI even had nearly identical outcomes compared with the outcomes of patients with LBBB and QRS duration \( \geq 150 \) ms (Class I American guidelines) (42). In line with the aforementioned analyses, a prospective single-center study reported similar positive effects of mechanical dyssynchrony at baseline on volumetric and clinical CRT response in patients with non-LBBB (45). Mechanical dyssynchrony (defined as interventricular mechanical delay of \( \geq 40 \) ms and a septal-to-posterior radial peak strain delay of \( \geq 130 \) ms assessed with STE-strain curves) was present in 28% to 52% of patients with non-LBBB.

Yet, despite these promising results, not all studies focusing on the association of mechanical dyssynchrony parameters with CRT response found that...
patients with non-LBBB with mechanical dyssynchrony have improved outcomes. A retrospective multicenter study with 137 patients with non-LBBB did not show a lower incidence of death, transplant, or LV assist device (adjusted HR: 0.66; 95% CI: 0.32 to 1.36; p = NS) when mechanical dyssynchrony was present (46) (Table 2). It should, however, be noted that the investigators used exclusively timing-based STE dyssynchrony parameters (Δtime-to-peak septal to posterior wall strain ≥130 ms) for CRT response prediction. Time-to-peak indexes of dyssynchrony have been shown to be inferior to the assessment of a strain-based contraction pattern (e.g., early systolic shortening of the septum and pre-stretch of the lateral wall) by Risum et al. (47).
Both the identification of sufficient baseline electrical dyssynchrony as well as mechanical dyssynchrony—taking into account paradoxical left ventricular (LV) stretching during systole—can be used for selection of patients with a non–left bundle branch block (LBBB) who may benefit more favorably from cardiac resynchronization therapy (CRT). All promising parameters warrant prospective multicenter validation. ECG = electrocardiography; RBBB = right bundle branch block; VCG = vectorcardiography.
been further exposed by computer simulations (48). Via these stimulations, Lumens et al. (48) displayed that different myocardial substrates exist that may lead to some degree of LV mechanical dyssynchrony. These substrates include electrical substrates, which are generally responsive to CRT, and nonelectrical substrates, such as hypocontractility and myocardial scar, that do not respond to CRT. All 3 substrates are likely to exist in patients with heart failure. Interestingly, computer simulations showed that both electrical and nonelectrical substrates cause time-to-peak mechanical delay, yet, the strain pattern of mechanical dyssynchrony differs considerably between electrical and nonelectrical substrates. These findings nicely illustrate that time-to-peak dyssynchrony measures are not specific to the electrical substrates responsive to CRT, and therefore, they are not likely to be effective for selecting patients that may benefit from CRT. This could explain why several multicenter studies that primarily used timing-based dyssynchrony measures, such as PROSPECT and ECHO-CRT, found that (timing-based) measures of dyssynchrony were not able to improve patient selection for CRT (11,40). Implementation of specific strain patterns, on the other hand, may improve patient selection because they are specific to the electrical substrate responsive to CRT. These strain patterns consist of the systolic pre-stretch of the lateral wall (caused by an early septal contraction), systolic rebound stretch of the septum (caused by delayed lateral wall contraction) or the combination of both, which, covers all LV stretching during systole (SSI) (41,48) (Figure 4).

To conclude, there is increasing evidence showing that more sophisticated mechanical dyssynchrony measurements, taking into account the underlying electrical substrate responsive to CRT, can aid in the selection of patients who may benefit more favorably from CRT. Nonetheless, because current evidence stems primarily from retrospective studies, randomized trials with sufficient power are still needed to determine: 1) whether mechanical dyssynchrony parameters can indeed improve response prediction; and 2) which parameter is most robust and feasible.

**FUTURE DIRECTIONS IN PATIENT SELECTION**

The field of medicine is moving fast, from treating patient groups based on statistical averages (e.g., being cautious towards CRT implantation in non-LBBB patients) towards a more personalized medicine. In this review, several new and existing markers have been proposed that might aid in the selection of patients with a non-LBBB but with a substrate amendable by CRT (Central Illustration). To improve CRT patient selection, we believe that physicians should be encouraged to look further than QRS duration and morphology on the ECG. The demand...
TABLE 3 Prognostic Value of VCG-Derived QRS Area Versus Conventional Guideline Selection Criteria in Overall CRT Population Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Inclusion period</th>
<th>Patients</th>
<th>Dyssynchrony parameters tested</th>
<th>Long-term outcome data</th>
<th>Volumetric response</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Deursen et al (2015) (51)</td>
<td>Prospective, single-center</td>
<td>Not described</td>
<td>81</td>
<td>1. QRS area $\geq$98 $\mu$Vs</td>
<td>All-case mortality, Htx, LVAD</td>
<td>LVE ESV reduction $\geq$15%</td>
<td>~6 months</td>
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<td>2. QRS duration $\geq$156 ms</td>
<td>Unadjusted HR</td>
<td>Unadjusted OR</td>
<td>Median: 3.1 (IQR: 1.8-5.4) yrs</td>
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<td>3. LBBB* AHA/ACCF/HRS</td>
<td>Adjusted HR</td>
<td>Not collected</td>
<td>3.4 ± 2.4 yrs</td>
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<td>4. LBBB* Strauss</td>
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<td>5. LBBB* MADIT-CRT</td>
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<tr>
<td>Emerek et al (2018) (49)</td>
<td>Retrospective, single-center</td>
<td>2006-2015</td>
<td>705</td>
<td>1. QRS area $\geq$95 $\mu$Vs</td>
<td>Survival free from Htx or LVAD</td>
<td>LVE ESV reduction $\geq$15%</td>
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<td>2. QRS duration $&lt;150$ ms</td>
<td>Adjusted HR</td>
<td>Unadjusted OR</td>
<td></td>
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<td>3. LBBB (nonstrict/undefined)</td>
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<td></td>
<td></td>
<td>2. LBBB* ESC + QRS duration</td>
<td>Adjusted HR</td>
<td>Unadjusted OR</td>
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</tbody>
</table>

Values are n, unless otherwise indicated. *LBBB according to: AHA/ACCF/HRS (13), ESC (14), Strauss criteria (15), and criteria used in MADIT-CRT (1). HR adjusted for QRS duration and morphology, age, sex, ischemic heart disease, and atrial fibrillation/flutter. OR adjusted for sex, age, cardiomyopathy, atrial fibrillation, device type, LV lead, position, baseline New York Heart Association, baseline ejection fraction, and medication. ESC = European Society of Cardiology; Htx = heart transplant; OR = odds ratio; VCG = vectorcardiography; other abbreviations as in Tables 1 and 2.

for an easy, widely applicable, and noninvasive robust parameter to assess suitability for CRT has recently led to renewed interest in vectorcardiography (VCG). VCG is a method for recording 3-dimensional information regarding the magnitude and direction of the electrical forces generated by the heart (Figure 5). The area under the 3-dimensional QRS complex (QRS area) and 3-dimensional T-wave (T area) are assumed to reflect unopposed electrical forces during ventricular depolarization and repolarization, respectively. In particular, the QRS area, but also T area and sum of QRS and T areas (QRST area), have been shown to be strong predictors of volumetric response and survival after CRT (49,50). Both retrospective analyses and prospective studies have recently evaluated QRS area as a predictor for CRT response. All of these trials demonstrated QRS area to be a strong predictor of CRT response, superior even to QRS duration and morphology (6,49,51,52) (Table 3). One retrospective multicenter study displayed that this was not only true for a whole cohort of patients that received CRT but, interestingly, also for patients without a Class I indication for CRT according to American guideline recommendations (43) (QRS duration 120 to 149 ms or non-LBBB) (6). In these patients, only the QRS area was significantly associated with all-cause mortality (adjusted HR: 0.49; 95% CI: 0.34 to 0.71). With regard to volumetric CRT response, both QRS area and LBBB morphology were associated with an LV end-systolic volume reduction of $\geq$15% (adjusted OR: 1.70; 95% CI: 1.05 to 2.76, and adjusted OR: 2.02; 95% CI: 1.12 to 3.62, respectively) (6). Yet, some caution should be taken when interpreting these results because patient data were retrospectively analyzed.

It is noteworthy that the combination of VCG QRS area and echocardiographic dyssynchrony indices may improve CRT response prediction even further. This was demonstrated in a multicenter prospective trial, in which QRS area and echocardiographic dyssynchrony markers (apical rocking and intraventricular mechanical delay) were associated with volumetric CRT response in multivariable analysis—whereas QRS duration or QRS morphology were not—and also predicted clinical outcomes assessed by heart failure hospitalizations and all-cause mortality (52).

Although not yet commercially available in clinical practice, QRS area seems to be a promising alternative selection criterion for identifying possible CRT
and not the beginning and end of the QRS area is a continuous variable, but variability in LBBB is operator-dependent. Like QRS duration, QRS independent parameter, whereas the definition for LBBB is operator-dependent. Like QRS duration, QRS area is a strong determinant of outcome. Current ECG selection criteria for CRT have shortcomings because various definitions for LBBB exist, which are subjective to personal interpretation and are all differently associated with outcomes. In daily practice, this presumably leads to a suboptimal patient selection. There is accumulating evidence that the presence of baseline dysynchrony on echocardiography (apical rocking, septal flash, systolic stretch index) can identify volumetric and clinical responders. A promising and observer-independent new ECG marker, which could improve response prediction irrespective of QRS morphology, is the VCG-derived QRS area. In current clinical practice, these tools could especially be useful for selecting patients without a typical LBBB on the ECG, but with a possible underlying substrate responsive to CRT.

CONCLUSIONS

Current ECG selection criteria for CRT have shortcomings because various definitions for LBBB exist, which are subjective to personal interpretation and are all differently associated with outcomes. In daily practice, this presumably leads to a suboptimal patient selection. There is accumulating evidence that the presence of baseline dysynchrony on echocardiography (apical rocking, septal flash, systolic stretch index) can identify volumetric and clinical responders. A promising and observer-independent new ECG marker, which could improve response prediction irrespective of QRS morphology, is the VCG-derived QRS area. In current clinical practice, these tools could especially be useful for selecting patients without a typical LBBB on the ECG, but with a possible underlying substrate responsive to CRT.

REFERENCES


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**KEY WORDS** cardiac resynchronization therapy, dyssynchrony, heart failure, non-left bundle branch block, patient selection.