Novel electrocardiographic dyssynchrony criteria that may improve patient selection for cardiac resynchronization therapy

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ABSTRACT Cardiac resynchronization therapy (CRT) is an evidence-based effective therapy of symptomatic heart failure with reduced ejection fraction refractory to optimal medical treatment associated with intraventricular conduction disturbance, that results in electrical dyssynchrony and further deterioration of systolic ventricular function. However, the non-response rate to CRT is still 20%−40%, which can be decreased by better patient selection. The main determinant of CRT outcome is the presence or absence of significant ventricular dyssynchrony and the ability of the applied CRT technique to eliminate it. The current guidelines recommend the determination of QRS morphology and QRS duration and the measurement of left ventricular ejection fraction for patient selection for CRT. However, QRS morphology and QRS duration are not perfect indicators of electrical dyssynchrony, which is the cause of the not negligible non-response rate to CRT and the missed CRT implantation in a significant number of patients who have the appropriate substrate for CRT. Using imaging modalities, many ventricular dyssynchrony criteria were devised for the detection of mechanical dyssynchrony, but their utility in patient selection for CRT is not yet proven, therefore their use is not recommended for this purpose. Moreover, CRT can eliminate only mechanical dyssynchrony due to underlying electrical dyssynchrony, for this reason ECG has a greater role in the detection of ventricular dyssynchrony than imaging modalities. To improve assessment of electrical dyssynchrony, we devised two novel ECG dyssynchrony criteria, which can estimate interventricular and left ventricular intraventricular dyssynchrony in order to improve patient selection for CRT. Here we discuss the results achieved by the application of these new ECG dyssynchrony criteria, which proved to be useful in predicting the CRT response in patients with nonspecific intraventricular conduction disturbance pattern (the second greatest group of CRT candidates), and the significance of other new ECG dyssynchrony criteria in the potential improvement of CRT outcome.

The most recent European Society of Cardiology (ESC) guidelines recommend only the electrocardiographic criteria of QRS morphology and QRS duration (QRSd) for patient selection for cardiac resynchronization therapy (CRT). Only heart failure with reduced ejection fraction (HFrEF) patients with left bundle branch block (LBBB) pattern and a QRSd ≥ 150 ms or ≥ 130 ms and patients with non-LBBB pattern with a QRSd ≥ 150 ms have either a class I or class IIa recommendations for CRT. The guidelines are based on recent large randomized studies, which demonstrated benefits of CRT only in patients with LBBB pattern or with QRSd ≥ 150 ms, but CRT did not decrease the total mortality and/or non-fatal heart failure (HF) events in patients with non-LBBB pattern and a QRSd of 120−149 ms.[2−8] Moreover, a subgroup analysis of the EchoCRT trial demonstrated that CRT in patients with a QRSd < 130 ms may be harmful, therefore the current ESC guideline contraindicates CRT in these patients. For these reasons the indication of CRT in patients with non-LBBB pattern and a QRSd of 130−149 ms is questionable (class IIb recommendation). Although CRT is an evidence-based therapy of symptomatic HFrEF associated with intraventricular conduction disturbance and refractory to optimal medical treatment, the current criteria of patient selection for CRT are not optimal, as the non-response rate to CRT is still 20%−40%. In our opinion, the main determinant of CRT outcome is the presence or absence of significant ventricular electrical dyssynchrony and the ability of the applied CRT technique to eliminate it. The response to CRT depends on a great extent how effectively the patient selection criteria are able to determine the presence or absence of significant ventricular elec-
trical dyssynchrony. We think that the significance of QRS morphology in patient selection for CRT is currently somewhat overemphasized. A recent meta-analysis of randomized CRT trials using individual, instead of aggregate, patient data has shown that QRSd was the only independent predictor of CRT effect on all-cause mortality and HF hospitalizations.\(^9\) Especially QRSd > 140 ms indicated a high probability of benefit from CRT. After adjusting for QRSd in their analysis, QRS morphology was no longer a determinant of the clinical response to CRT.\(^9\) In another study\(^10\) the authors investigated 11,861 patients without an intracardiac device of the PARADIGM-HF and ATMOSPHERE trials. Among these patients 1,789 (15.1%) had LBBB, 524 (4.4%) right bundle branch block (RBBB), 454 (3.8%) non-specific intraventricular conduction disturbance (NICD) patterns, 2,588 (21.8%) mildly abnormal QRS (QRSd: 110–129 ms) and 6,506 (54.9%) a QRSd < 110 ms. During a median follow-up of 2.5 years the risk of primary composite endpoint (hospitalization for HF or cardiovascular death) and all-cause mortality was significantly higher in all patient groups with a QRSd ≥ 110 ms than in patients with a QRSd < 110 ms, irrespective of QRS morphology. Thus, the finding of similarly high risk in patients with modest increases in QRSd and in patients with RBBB and NICD as well as LBBB patterns, is in sharp contrast to the evidence that CRT is most clearly beneficial in HFrEF patients with a QRSd > 130 ms and LBBB pattern and may even be harmful in patients with NICD or RBBB patterns, without associated left hemiblock or without being an atypical RBBB, defined as the absence of characteristic S waves (S wave of greater duration than R wave or > 40 ms) in leads I and aVL, and may not be appropriate in patients with NICD pattern to eliminate dyssynchrony.\(^17–19\) The worse outcome after CRT applying the current CRT technique of HF patients with non-LBBB pattern compared with LBBB pattern in large randomized studies is not surprising at all, because the comparison of QRS morphology subgroups in these trials was biased, as the comparison of subgroups was unfair, because the applied CRT technique, originally devised to eliminate dyssynchrony caused by LBBB pattern, but it is not appropriate in patients with pure, typical RBBB pattern [without associated left hemiblock or without being an atypical RBBB, defined as the absence of characteristic S waves (S wave of greater duration than R wave or > 40 ms) in leads I and aVL, and may not be appropriate in patients with NICD pattern to eliminate dyssynchrony.\(^17–19\) The worse outcome after CRT applying the current CRT technique of HF patients with non-LBBB pattern compared with LBBB pattern in large randomized studies is not surprising at all, because the comparison of QRS morphology subgroups in these trials was biased, as the comparison of subgroups was unfair, because the applied CRT technique, originally devised to eliminate dyssynchrony caused by LBBB pattern, but it is not appropriate in patients with pure, typical RBBB pattern and its effectiveness is elusive in patients with NICD pattern, had not even the chance before the start of these trials to be equally effective in the investigated QRS morphology subgroups. For a fair comparison a CRT technique, that is at least theoretically potentially equally effective in all QRS morphology subgroups should have been applied in these trials.

**THE PURPOSE OF OUR STUDY**

The intraD and interD parameters measured by imaging modalities are based on alteration in the sequence of mechanical contraction of the ventricles. However, the primary determinant of dysyn-
chrony is the electrical activation of the heart, which determines the sequence of mechanical contraction. CRT can only eliminate mechanical dyssynchrony due to primary electrical dyssynchrony and ineffective in the treatment of mechanical dyssynchrony without primary electrical dyssynchrony (such as inflammation, myocardial ischemia, myocardial scar). Thus, ECG should be able to better or at least as reliably indicate ventricular dyssynchrony than imaging modalities.\cite{8,20} We sought to find electrocardiographic criteria that indicate better the presence or absence of electrical ventricular dyssynchrony than QRS morphology and QRSd, therefore we devised two novel surface ECG criteria for the estimation of interD and LV intraD in order to improve patient selection for CRT.

**OUR STUDY INVESTIGATING THE TWO NOVEL ECG DYSSYNCHRONY CRITERIA**

**Patients**

The results of our study\cite{17} we briefly discuss here were published in 2018. We retrospectively analyzed de-identified data of 124 consecutive patients who underwent CRT between February 2003 and January 2009 at the Heart and Vascular Center of Semmelweis University, Budapest and had pre-implantation 12-lead ECG as well as all pre-implantation and 6 months follow-up data necessary to determine the response to CRT. Among the 124 patients 70 had LBBB, 43 NICD, 7 RBBB plus left anterior fascicular block, 2 masquerading bundle branch block patterns and 2 had normal QRS duration. Intraventricular conduction disturbances were defined according to the 2009 AHA/ACCF/HRS recommendations.\cite{21} Response to CRT [clinical responder (R)] was defined as improvement of NYHA class ≥ 1, being alive and having no hospitalizations for HF during 6 months of follow-up as proposed by Packer.\cite{22} Patients were selected for CRT based on recommendations in use at the time of the study (traditional criteria = TC), i.e., they should have LV ejection fraction (EF) ≤ 35%, QRSd ≥ 120 ms, NYHA functional class III-IV HF refractory to optimal pharmacotherapy and their condition could not have been potentially improved by coronary revascularisation or valve surgery. The selection of patient for CRT using the TC meant that an expected R diagnosis was made using the TC. Thus, if the patient was a clinical R, the TC made a correct diagnosis, if the patient was a clinical non-responder (NR), the TC made an incorrect diagnosis.

**The Novel ECG Ventricular Dyssynchrony Criteria**

We developed two new 12-lead surface ECG criteria serving as surrogate markers of intraD and interD.

To estimate LV intraD, the absolute value of the difference between the times to onset of intrinsicoid deflections (ID) in leads aVL and aVF, reflecting the electrical potentials of LV lateral and inferior walls, was calculated and divided by QRSd: \(\frac{|aVL_{ID} - aVF_{ID}|}{QRSd}\) (%)

InterD was estimated by calculating the absolute value of the difference between the times to onset of the ID in leads V5 and V1, reflecting the electrical potentials of the LV and right ventricle (RV), divided by QRSd: \(\frac{|V5_{ID} - V1_{ID}|}{QRSd}\) (%)

The new criteria were applied on the pre-implantation ECG in patients selected for CRT by the TC. If their value was > 25%, the patient was diagnosed as electrical dyssynchrony present (ED+), if their value was ≤ 25%, electrical dyssynchrony absent (ED-) diagnosis was made. When the intraD and interD criteria (intra+interDC) were applied together, a final ED+ diagnosis was made if at least one of them indicated ED+ diagnosis and the patient was considered an expected responder (R), a final ED- diagnosis was made if both indicated ED-diagnosis and the patient was considered an expected nonresponder (NR). Figure 1 demonstrates the practical application of the new ECG dyssynchrony criteria. The more detailed description of the practical application is described in the original publication.\cite{17}

**THE RATIONALE BEHIND THE NEW ECG DYSSYNCHRONY CRITERIA**

The time to the onset of the ID measured in a unipolar lead represents the time elapsing from the onset of the ventricular activation until the electrical impulse reaches the myocardium located right under the exploring unipolar electrode.\cite{23} Physiologically, the anterior and posterior papillary muscles
Figure 1  The practical application of the new ECG dyssynchrony criteria. Long vertical continuous lines denote the onset of the QRS complexes and short vertical continuous lines mark the onset of the ID, the time interval between them is time to the onset of the ID. Dashed lines mark the measurement of QRS duration. Panel A: An ECG recorded in a patient with LBBB pattern is shown. With the LV intraventricular dyssynchrony criterion an ED+ diagnosis is made, as its value is 53% (i.e., > 25%). With the interventricular dyssynchrony criterion also an ED+ diagnosis is established, as its value is 32% (i.e., > 25%). When the two new ECG dyssynchrony criteria are applied together, a final ED+ diagnosis is made, if at least one of them indicates ED+ diagnosis. If both indicate ED- diagnosis, a final ED- diagnosis is made. Thus, using the two new ECG dyssynchrony criteria together predicted this patient as an expected R. Panel B: An ECG recorded in a patient with NICD pattern is shown. Since in lead V1 a QS complex is present, therefore we measured V2 ID instead of V1 ID. With the LV intraventricular dyssynchrony criterion an ED+ diagnosis is made, as its value is 31% (i.e., > 25%), with the interventricular dyssynchrony criterion an ED- diagnosis is made, as its value is 0% (i.e., ≤ 25%). Thus, this patient is an expected R applying the two dyssynchrony criteria together. Reproduced with permission from Ref. 17. ED: electrical dyssynchrony; ID: intrinsicoid deflection.
are activated earliest and synchronously in the LV via the left anterior and posterior fascicles and slightly later other areas of the LV are activated approximately simultaneously (Figure 2 upper panel). The left upper panel of Figure 2 is similar to a parasternal short axis view obtained during echocardiography. The aVL and aVF unipolar leads are located near to the anterior and posterior papillary muscles respectively, thus the onset of ID in these unipolar leads can be used as a surrogate marker of the time elapsing from the onset of the ventricular activation to the electrical activation of the papillary muscles. Since physiologically the papillary muscles are activated synchronously, the difference between aVLID and aVFID should be zero or very close to zero. LV intraD, when at least one LV myocardial region is activated later than during the normal LV myocardial activation sequence, usually results in a delayed activation of one papillary muscle compared with the other. Therefore, either aVLID or aVFID.
or aVFID will be longer than the other one, and the absolute value of their difference will be >> 0. Thus the [aVLID-aVFID] might be a good marker of any kind of LV intraD irrespective of which type of intraventricular conduction disturbance is the underlying cause. In patients with LBBB pattern the RV is activated initially and the LV is activated from the RV through the interventricular septum followed by a slow muscle to muscle conduction in the left side of the septum until the electrical impulse reaches the Purkinje fibers near to the left side of the septum (Figure 2 middle panel). The septal breakthrough site is much closer to the posterior than to the anterior papillary muscle, therefore the lateral and anterior LV free wall myocardium is activated later than the inferior LV myocardium in LBBB, resulting in a significantly longer aVLID than aVFID, thus, the [aVLID-aVFID] will be >> 0.\[11\]

The lower panel of Figure 2 shows the rationale of the interD ECG criterion. The onset of ID in leads V_1 and V_5 reflects approximately the time that elapses from the onset of ventricular activation until the RV and LV are activated respectively, since the unipolar leads V_1 and V_5 reflect the electrical activation potentials of RV and LV respectively. The difference between V_5ID and V_1ID is quite small but not zero during normal ventricular activation (approximately 20 ms), because the normal ID is < 30 ms in leads V_1 or V_2 and is < 50 ms in leads V_5 or V_6. \[24\] Therefore, the interDC should still have a low (≤ 25%) value during normal ventricular activation and/or in the absence of interD and a > 25% value in the presence of interD, which is associated with an increase in the value of [V_5ID-V_1ID] to >> 20 ms. \[11\]

**RESULTS AND CONCLUSIONS OF OUR STUDY**

We analyzed the data of two patient subgroups (LBBB and NICD) only, as the small number of other ECG morphologies was inappropriate for statistical analysis.

There were no significant differences in age, etiology, QRSD, LVEF and baseline rhythm between the LBBB and NICD subgroups, however the QRSD was longer in the LBBB subgroup in a borderline significant manner (171 ± 23.45 vs. 162.2 ± 24.97 ms, \[P = 0.0617\]). There were significantly (\[P = 0.01\]) more male patients in the NICD subgroup than in the LBBB subgroup.

As 35/124 (28%) of the patients were NRs and 89/124 (72%) were Rs the test accuracy (TA) of the TC was 72%. The TA of the intraD and interD criteria applied together with TC (intra + interDC + TC) was superior to that of TC applied alone in all patients [100/124(81%) vs. 89/124(72%), \[P < 0.001\] respectively], which was due to the superior TA of intra+interDC+TC achieved in the NICD subgroup [36/43 (84%) vs. 29/43 (67%), \[P < 0.05\], respectively]. The TA was not improved by the application of intra + interDC + TC compared to that of TC alone in the LBBB subgroup, which responds well to CRT anyway (Table 1).

Because the patient selection for CRT was done using the TC, by definition the TC had a sensitivity of 100%, a specificity of 0 and a negative predictive value (NPV) of 0. Therefore, only the positive predictive values (PPV) of the two methods were comparable by statistical methods. The intra + inter DC + TC showed only a trend for a superior PPV to that of TC applied alone (77.9% vs. 71.8% respectively), which was due to the better PPV (which showed only a superior trend as well) in the NICD subgroup (80.6% vs. 67.4% respectively). In the LBBB subgroup there were no between-methods differences in the PPV (Table 2).

The sensitivity, specificity, PPV and NPV values for ED+ diagnosis are identical to the specificity, sensitivity, NPV and PPV values for ED- diagnosis respectively. Since the ED+ diagnosis established

| Table 1  | The diagnostic accuracy of intra+interDC together with TC. |
|----------|----------------------------------------------------------|
|          | All patients; n = 124                                   | LBBB subgroup; n = 70/124 (56%) | NICD subgroup; n = 43/124 (35%) |
| Intra + inter DC + TC | 100/124 (81%)^\*                                          | 54/70 (77%)                       | 36/43 (84%)^\*                   |
| TC       | 89/124(72%)                                              | 56/70 (80%)                       | 29/43 (67%)                      |

^\*P < 0.05, ^\*\*P < 0.001 vs. TC alone. (Reproduced with permission from Ref. 17). Intra+interDC: intraventricular and intraventricular dyssynchrony criteria; LBBB: left bundle branch block; NICD: nonspecific intraventricular conduction disturbance; TC: traditional criteria.
using the new ECG criteria had a 100% sensitivity and NPV in the NICD subgroup, it follows that the ED- diagnosis by the new ECG criteria had a 100% specificity and PPV, meaning that all patients with NICD pattern diagnosed as expected NR by the new ECG criteria proved to be a NR after 6 months follow-up! On the other hand, when ED+ diagnosis was made in patients with NICD pattern by the application of the intra+interDC+TC, the PPV of these patients for ED+ diagnosis was 80.6%, which means that the expected NR rate in these patients is < 20%, identical to the expected NR rate in the LBBB subgroup (Table 2). Thus, the likelihood that a patient with NICD pattern predicted as an expected R with the new ECG dyssynchrony criteria will be a clinical NR after CRT is identical to that of a patient with LBBB pattern. Thus, the most important novel finding of our study was that our novel ECG dyssynchrony criteria may have a great value in the selection of patients with NICD pattern (the second greatest group of CRT candidates, comprising 10%–35% of them\(^{2,3,5,12}\)) and a QRSd of 130–149 ms, in whom the indication of CRT is questionable according to the current guidelines, who might benefit from CRT. If our results will be confirmed in future prospective, multicenter studies by independent investigators, our novel ECG dyssynchrony criteria may improve patient selection for CRT, mostly the selection of patients with NICD pattern, and decrease the number of NRs to CRT.

**LIMITATIONS**

The most important limitation of our study is that it was a single center, retrospective study conducted in a relatively small number of patients. Our results need to be confirmed in prospective, multicenter studies enrolling a greater number of patients. The short follow-up time is another limitation. Since LV end systolic volume data were available in only 10% and both pre- and post-CRT LVEF data in 82/124 (66%) patients and EF was measured by various investigators, who might have used different methods, we could not use these echocardiography parameters to determine CRT responders.

It should be tested whether the new ECG dyssynchrony criteria predict CRT response defined as LV volume response or reduction in total mortality or a composite endpoint of total mortality and hospitalization for HF during a longer follow-up period.

**THE VENTRICULAR ACTIVATION SEQUENCE IN PATIENTS WITH NICD PATTERN**

There are very scarce data about the ventricular activation sequence in patients with NICD pattern, except from three small studies. In the first study\(^{25}\) the ventricular activation sequence determined by electrocardiographic imaging in 15 patients with NICD pattern was highly variable, heterogeneous, characteristic activation pattern(s) could not be identified. The only consistent finding was the presence of fewer and smaller lines of slow conduction in the LV compared with LBBB pattern, which is responsible for the less dyssynchrony and shorter QRSd. In the second study\(^{26}\), it was demonstrated by ECG imaging in 23 patients with NICD pattern, that the right to left direction of activation delay vector (ADV) was similar to that of patients with LBBB pattern.
narrow QRS or LBBB pattern, but the magnitude of ADV was significantly greater in patients with NICD pattern compared with that of patients with narrow QRS and in patients with LBBB pattern compared with those of patients with NICD pattern and narrow QRS, indicating significant difference in the magnitude of dyssynchrony between narrow QRS, NICD and LBBB patients. ADV had a higher area under curve (AUC) than QRSd and tended to show a higher specificity than QRS morphology in the prediction of CRT response. Thus, in fact the extent of right to left activation delay identified best responders to CRT outperforming QRSd and QRS morphology. In the third study,[27] 23 consecutive patients with NICD pattern and a QRSd ≥ 120 ms referred for CRT were examined by coronary venous 3D electroanatomical mapping. A delayed LV lateral wall activation defined as maximal activation time measured at the LV lateral wall exceeding 75% of the total QRSd, was found in 12/23 (52%) of these patients, indicating that a significant percentage of patients with NICD pattern are potential CRT responders. In patients with delayed LV lateral wall activation the most delayed lateral region was usually confined to the basal lateral wall.

LITERATURE DATA SUPPORTING OUR RESULTS

We devised the LV intraventricular ECG criterion in 2010.[28] A later study,[29] has shown that delayed ID onset in lateral ECG leads predicted LV reverse remodeling after CRT. In this study the predictors of CRT response in subjects with LBBB and NICD after multivariate logistic regression analysis were longer preimplantation ID in leads I and aVL, a greater ID in lead I/QRSd ratio and a longer ID in lead I and V1ID difference. Preimplant QRSd was not a significant predictor of CRT response. Ploux, et al.[28] investigated patients with LBBB and NICD pattern selected for CRT by exactly the same criteria as in our study published very similar results to ours. They used ECG imaging, a promising new non-invasive method developed to provide an epicardial electrical activation map by combining body surface mapping with computed tomography and the use of a special software, which essentially corresponds to a non-invasive epicardial electrophysiological study. The total right ventricular activation time (RVTAT) was similar in the two patient groups, however the total left ventricular activation time (LVTAT) and the ventricular electrical uncoupling (VEU), calculated as the difference in the mean LVTAT and RVTAT, were longer in the LBBB group. VEU is a measure of both interD and LV intraD, because its duration can be increased both by a delay in the onset of LV activation relative to RV activation determined mainly by the transseptal activation time and LV intraventricular activation delay. A > 50 ms cutoff value of VEU predicted clinical CRT response better than QRSd irrespective of the presence of LBBB with 90% sensitivity, 82% specificity, 90% PPV and 82% NPV. Identical to our results, ECG imaging did not enhance the ability to predict clinical response in patients with LBBB pattern, but predicted clinical response in 3/5 (60%) patients and clinical non-response in 9/9 (100%) patients with NICD pattern. Thus, particularly NICD patients could benefit from the determination of VEU.

Similarly to our results Gold, et al.[30] found that electrical dyssynchrony measured by the interval from the onset of the QRS from the surface ECG to the first large peak of the LV electrogram (QLV interval), obtained at the LV stimulation site during CRT, predicted CRT response. Longer QLV was associated with a better CRT response even after adjusting for QRSd and LBBB, and a QLV > 95 ms predicted beneficial CRT response. Another study[31] showed in 1,342 patients of the PEGASUS trial undergoing CRT-D implantation, that the unpaced RV-LV interval in sinus rhythm, reflecting interventricular delay, proved to be a strong independent predictor of clinical response to CRT measured by hard clinical endpoints. In a later study[32] conducted in 419 patients enrolled in the SMART-AV trial, who underwent CRT-D implantation, the QLV and RV-LV intervals were determined. Reduction in LV end systolic volume (LVESV) > 15% was used to define CRT response. LBBB pattern was present in 74% of patients and RBBB and NICD patterns in 13.1% and 12.9% of patients respectively. In a multivariable model RV-LV interval, but not QLV interval remained associated with CRT response in all patients and in the different QRS morphology subgroups as well. An RV-LV interval ≥ 70 ms pre-
dicted response to CRT. Combining the two measures achieved better prediction of CRT response in the case of intermediate (45–65 ms) RV-LV interval. In this study the RV-LV interval proved to be a better predictor of CRT response than the QLV interval. Other authors also observed longer RV-LV interval in those patients with LBBB pattern who underwent CRT-D implantation and responded to CRT, than in those who were NRs.

Similarly to our results, in another study, it was found that the longest interval measured in the limb leads from the QRS onset to R wave offset (intersection between the descending limb of the R wave and baseline) (QR_max index) was a good surrogate of LV intraD (QLV interval) regardless of QRSd in 178 HF patients with non-LBBB (RBBB and NICD) pattern who received a CRT device. The QR_max index correlated better with the QLV interval than QRSd and was a better predictor of response to CRT than QRSd. A QR_max index cutoff value of > 120 ms predicted CRT response (decreased the risk of primary clinical endpoint of time to first HF hospitalization and of the composite secondary clinical endpoint of all-cause mortality or HF hospitalization or LV assist device implantation) with a PPV of 86.8% in the RBBB group and a PPV of 81.4% in the NICD group, indicating the presence of LV electrical delay in these patients.

Plesinger, et al determined ventricular electrical delay (VED), the longest time difference between maximal QRS amplitudes in the lateral (V_5, V_6) and septal (V_1, V_2) V-leads using high frequency QRS (HFQRS) maps obtained by body surface ECG using a 12-lead Holter recorder from the baseline digital ECG acquired before CRT implantation in patients of the CRT-D arm of the MADIT-CRT study. They examined 676 patients with LBBB, 113 patients with RBBB and 160 patients with NICD patterns. VED quartiles were determined in patients with LBBB pattern and the first quartile (Q_1) was 31.2 ms. VED values in the first quartile (< 31.2 ms) indicated less electrical dyssynchrony. They demonstrated that MADIT-CRT LBBB patients with a low VED (< 31.2 ms) before CRT implantation were at higher risk of study combined end points (HF or all-cause mortality) than patients with higher VED (≥ 31.2 ms). VED was a stronger predictor of CRT outcome in these patients with LBBB pattern than QRSd, but the combination of both VED and QRSd proved to be the best predictor of CRT outcome. This result of their investigation confirms the potential utility of our interventricular ECG dyssynchrony criterion, which uses the absolute value of the difference between V_{R-LV} and V_{L-LV} (practically the same interval as VED) divided by QRSd. VED proved to be an independent predictor of response to CRT and did not show interaction with other clinical markers of CRT response, such as age, ischemia, LVEF, LV end diastolic volume (LVEDV), LVESV. Patients with LBBB pattern with low (< 31.2 ms) VED values showed less LVEDV, LVESV and left atrial volume decrease, LVEF increase and LV dyssynchrony decrease measured by echocardiography, indicating worse CRT response and had a greater occurrence of VT/VF than patients with a higher VED (≥ 31.2 ms). In the RBBB and NICD subgroups the authors found opposite results to those found in the LBBB subgroup, in these subgroups patients with lower absolute VED values had a lower risk of combined end points than in patients with higher VED values.

There are two independent studies, which directly confirmed the diagnostic value of our novel ECG dyssynchrony criteria. Bonomini, et al determined the spatial variance of baseline ECG QRS complexes and normalized QRS complexes by non-selective His bundle pacing in several ECG lead pairs to estimate the extent of ventricular dyssynchrony. They found that our LV intraD ECG criterion would predict similarly well the intraD (AUC = 0.81) as the ECG lead pair of leads II-V_6 characterizing best the depolarization spatial variance in their study. This is not surprising, as the location of leads II and V_6 and leads aVF and aVL used to determine LV intraD in our study is quite similar, one lead was inferior the other lead was lateral in both studies. In the second study, the authors assessed the usefulness of our two novel ECG dyssynchrony criteria in 269 CRT-D patients with non-LBBB pattern (157 with NICD and 112 with RBBB patterns) from the MADIT-CRT study. Those with intraD had a similar risk of the combined HF/death endpoint (HR = 0.80, P = 0.276), but lower risk of death (HR = 0.53, P = 0.031) vs. those without intraD during a median follow-up of 5.6 years. Patients with or without interD had a similar risk of HF/death (HR = 1.1, P =
and death (HR = 1.27, P = 0.447). The prolonged QRS (QRSd ≥ 150 ms) subgroup patients with intraD had lower risk of both HF/death (HR = 0.41, P = 0.043) and death (HR = 0.36, P = 0.039) vs. those without intraD. No differences in HF and death were found in the presence of interD in the prolonged QRS subgroup.

VECTORCARDIOGRAPHIC 3D QRS AREA

3D QRS area determined by vectorcardiography is another promising parameter that identifies LV activation delay more accurately than the current ECG criteria and proved to be a better predictor of echocardiographic response to CRT and HF hospitalizations and cardiac mortality after CRT than the combination of QRSd and QRS morphology. Since there is a separate article in this Special Issue addressing the significance of QRS area in better patient selection for CRT, we do not discuss further this topic.

FRAGMENTED QRS

There are contradictory results about the role of fragmented QRS (fQRS) complexes in the prediction of CRT response. The presence of fQRS is thought to be due to inhomogenous activation due to myocardial scar and/or ischemia. However, fQRS may be present in patients who have smaller amount of myocardial fibrosis that does not preclude the favorable effects of CRT, or in patients with a significant amount of myocardial fibrosis that results in non-response to CRT. Therefore some studies reported that the mere presence of fQRS or its presence in more leads predicts poor response to CRT, while other studies did not confirm that the presence of fQRS was associated with CRT non-response. It was also reported that the quantitative assessment of QRS fragmentation by automated counting of abnormal QRS peaks was the only independent predictor of CRT response in multivariable analysis and could better discriminate CRT response than QRSd, while the qualitative assessment (presence or absence) of fQRS in the 12-lead ECG in patients with LBBB pattern was not predictive to CRT response.

HOW THE DEFINITION OF LBBB INFLUENCES THE RESPONSE TO CRT?

Strauss, et al. first suggested that approximately 1/3rd of patients diagnosed with LBBB by conventional ECG criteria do not actually have complete LBBB, but rather have a combination of LV hypertrophy and left anterior fascicular block, therefore do not respond to CRT. For this reason, they recommended stricter criteria for the definition of LBBB (Strauss criteria) including QRSd ≥ 140 ms (in men) or ≥ 130 ms (in women), QS or rS in leads V1 and V2 and mid-QRS notching or slurring in > 2 of leads V1, V2, V5, V6, I and aVL. It seems that QS or rS complexes in lead V1 and V2, mid-QRS notching/slurring in the above mentioned leads and the absence of q wave in leads I, V5 and V6 are the most important, whereas the time to intrinsicoid deflection in leads V5, V6 is less important, in the prediction of response to CRT. Strauss, et al. did not suggest to apply the absence of q waves in leads I, V5 and V6 for the definition of LBBB, because a large anterior-apical infarct can lead to q waves in the presence of LBBB. However, the addition of the absence of q wave in leads I, V5 and V6 criterion to the definition of LBBB may be still useful in the prediction of response to CRT in patients with LBBB pattern, because it may indicate the presence of scar tissue in the lateral wall, that likely precludes response to CRT. There are contradictory results in line with the application of strict LBBB definition improves or not the response to CRT in patients with LBBB pattern. In a study patients with strict LBBB pattern (using the Strauss criteria) responded better to CRT than patients without strict LBBB pattern, all patients with strict LBBB pattern were CRT responders (defined by > 5% increase of LVEF and >1 NYHA class improvement). In another study in patients with strict LBBB pattern (defined by the Strauss criteria) the LVEF increased to a significantly greater degree, the combined primary endpoint (death from any cause and hospital admission for heart failure) occurred less frequently and the secondary endpoint of ≥ 10% increase of LVEF was achieved more commonly than in patients without strict LBBB pattern. However, other authors did not find such significant difference in response to CRT between LBBB
patients with strict or without strict LBBB patterns. Although patients with strict LBBB pattern showed greater degree reverse LV remodeling, there was no significant difference either in echocardiography responders (defined by ≥ 15% decrease in LVESV or ≥ 5% increase in LVEF after CRT) or in all-cause mortality between patients with or without strict LBBB patterns. There was a significant difference between the two patient groups only in the rates of heart failure hospitalization. Bertaglia, et al.\[54\] found similar results, the application of stricter Strauss criteria did not improve the echocardiography response (defined by ≥ 15% decrease in LVESV) during the 12 months follow-up after CRT.

**Final Conclusions**

All the above mentioned studies support our view and results that the main determinant of response to CRT is the presence or absence of ventricular electrical dyssynchrony, and demonstrated better parameters than QRSd and QRS morphology for the assessment of electrical dyssynchrony. The results of these studies are controversial in the aspect whether both LV intraD and interD, or only interD, or only LV intraD are the best predictors of CRT outcome. They also showed that although the non-response rate to CRT is higher in patients with non-LBBB pattern than with LBBB pattern, a significant portion of patients with non-LBBB pattern benefit from CRT, therefore methods that can better identify the substrate responding to CRT can significantly decrease the non-response rate in patients with non-LBBB pattern and mildly to moderately decrease the non-response rate in patients with LBBB pattern. Another potential possibility to decrease the non-response rate to CRT is the use of a different CRT technique from the current one, devised to eliminate dyssynchrony in patients with LBBB pattern, in patients with RBBB and NICD patterns, which takes into consideration the ventricular activation sequence in these types of intraventricular conduction disturbances, that is able to eliminate dyssynchrony in these patients.

Our simple, novel ECG dyssynchrony criteria, which can be applied very quickly at the bedside by any physician, demonstrate the hidden potential still present in the 12-lead surface ECG, as they seem to be able to predict CRT response as well as the certainly more accurate, but much more complicated, still investigational and not widely available ECG imaging, high frequency QRS ECG mapping and the invasive and not pre-CRT QLV, RV-LV interval methods. The promising vectorcardiographic QRS area method, although may be more objective and accurate, as it is measured automatically, also requires special equipment, special software that is currently not widely available for everybody at the bedside. Therefore, although the diagnostic value of our novel ECG dyssynchrony criteria needs to be further confirmed by additional independent investigations on hard clinical endpoints in the future, the question is why we would like to use much more complicated, expensive, investigational techniques requiring special equipments and software with limited availability, if we have a simple, fast, very cheap, routine 12-lead ECG method available for everybody at the bedside with a similar accuracy for the same purpose.

**CONFLICT OF INTEREST**

None.

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