REVIEW ARTICLE

ASSESSMENT OF ELECTRICAL DYSSYNCHRONY USING 12-LEAD ECG: A COMPARATIVE ANALYSIS OF PROPOSED METRICS

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Abstract

Cardiac resynchronization therapy (CRT) represents a well-established therapeutic strategy widely implemented in the treatment of patients with heart failure. By addressing electrical dyssynchrony, CRT improves mechanical cardiac function and reduces the risk of heart failure-related hospitalization. Current guidelines suggest QRS duration and left bundle branch block morphology for assessing electrical dyssynchrony. However, 30% of CRT patients do not respond to the therapy. This paper reviews the alternative metrics of electrical dyssynchrony derived from standard 12-lead ECG for patient selection and/or pacing programming in CRT. Specifically, a detailed analysis of recently proposed parameters of electrical dyssynchrony to elucidate whether they offer advantages over the currently used criteria was performed.

Keywords

CRT, Electrical Dyssynchrony, ECG, Heart Failure

Introduction

Heart failure (HF) remains a major cause of mortality and reduced quality of life [1]. Cardiac resynchronization therapy (CRT) is an evidence-based treatment for patients with left ventricular systolic dysfunction (LVSD) [2]. According to statistics, approximately 40% of HF cases are attributed to systolic dysfunction [3]. CRT reduces the mortality risk, particularly in patients classified as NYHA class II, III, and IV [4]. The efficacy of CRT may be influenced by the presence of electrical dyssynchrony with the specific type of conduction anomaly, such as left bundle branch block (LBBB). Identifying eligible candidates for CRT and optimizing pacing settings are critical for enhancing therapeutic outcomes. CRT plays a crucial role in the treatment of HF, particularly in patients with reduced ejection fraction (EF). CRT is primarily indicated for patients with heart failure who have evidence of electrical dyssynchrony [5]. It is now widely recognized that electrical dyssynchrony, rather than mechanical dyssynchrony, is crucial for CRT effectiveness. Electrical dyssynchrony is typically defined as ventricular conduction delay resulting in a QRS duration exceeding 120 ms [6].

More specifically, electrical dyssynchrony refers to heterogeneity in ventricular electrical activation timing, whereas mechanical dyssynchrony refers to delayed or discoordinated myocardial contraction secondary to abnormal electrical function. However, up to 30–40% of patients receiving conventional CRT do not show a positive response [7]. This lack of response has been partly linked to suboptimal placement of the left ventricular (LV) lead and suboptimal device programming [4, 8].

The aim of this review is to summarize alternative metrics of electrical dyssynchrony derived from the 12-lead ECG and to evaluate their impact in relation to currently used clinical parameters.

Current guidelines: 12-lead ECG for detecting electrical dyssynchrony

A routine marker of electrical dyssynchrony is QRS duration, particularly when accompanied by LBBB morphology [9]. LBBB morphology is considered a strong indicator of electrical dyssynchrony, and both parameters: prolonged QRS duration and LBBB are recommended as key selection criteria for CRT in the ESC Guidelines [4]. The current LBBB criteria can be found in Table 1 [10].

The minimum QRS duration threshold for CRT eligibility depends on LBBB morphology [11]. For symptomatic patients with HF in sinus rhythm with

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LBBB morphology and a left ventricular ejection fraction (LVEF) ≤ 35%, CRT should be considered if the QRS duration is between 130–149 ms. In contrast, for patients without LBBB, the minimum QRS duration for CRT is ≥ 150 ms [12]. However, defining "true LBBB" remains challenging due to ambiguous criteria given in different authoritative publications, as shown in Table 2 [4, 13, 14]. The selection criteria for LBBB patients also vary across studies, making it an unreliable sole marker of electrical dyssynchrony. Additionally, different CRT guidelines offer conflicting recommendations for non-LBBB morphology. While the National Institute for Health and Care Excellence (NICE) guidelines (2014) recommend a CRT in non-LBBB patients that have a QRS duration ≥ 150 ms, ESC guidelines do not recommend CRT in most non-LBBB patients, except in selected cases with a wide QRS duration [4, 15].

Table 1: ESC 2021 definition criteria for LBBB [4].

- QRS ≥ 120 ms
- Notches or slurring in the middle third of QRS in at least two of the following leads: V1, V2, V5, V6, I, and aVL—with a prolongation at the delayed peak in R in V5–V6 to longer than 60 ms
- Generally, the ST segment is slightly opposed to the QRS polarity, and particularly when it is at least 140 ms and is rapidly followed by an asymmetrical T wave also of opposed polarity
- Horizontal plane: QS or rS in V1 with small 'r' with ST slightly elevated and positive asymmetrical T wave and unique R wave in V6 with negative asymmetric T wave. When the QRS is less than 140 ms, the T wave in V6 may be positive
- Frontal plane: exclusive R wave in I and aVL often with a negative asymmetrical T wave, slight ST depression, and usually QS in aVR with positive T wave
- The QRS axis is variable

Although NICE guidelines recommend a CRT for non-LBBB patients with a wide QRS complex (≥ 150 ms) and NYHA class II, III, or IV groups, it remains unclear whether these patients with non-LBBB morphology truly benefit from CRT [16]. In the meta-analysis, CRT did not decrease the total mortality or HF events in patients with non-LBBB patterns, raising questions about the current non-LBBB patient selection criteria in the ESC guidelines [17]. The meta-analysis conducted by Cleland et al., evaluated QRS duration as an indicator of electrical dyssynchrony in patients with sinus rhythm and reduced LVEF, results showed QRS duration as a strong predictor of CRT response [18].

Limitations of QRS duration and LBBB morphology as markers of electrical dyssynchrony

The large study on cardiac resynchronization in HF indicated that QRS duration at baseline is not an effective predictor of CRT response [19]. Recent data showed that LBBB morphology predicts CRT response more accurately than QRS duration alone [20]. Interestingly, non-LBBB patients, namely those with right bundle branch block or intraventricular conduction disturbances, did not benefit from CRT, despite prolonged QRS interval. Since non-LBBB patterns are not characterized by interventricular electrical delay seen in LBBB, this further supports the view that QRS duration alone is not a reliable marker of electrical dyssynchrony. To improve clinical outcomes, CRT selection should prioritize QRS morphology over QRS duration [20]. The study by Dupont et al., on 496 patients, found that patients with LBBB and QRS duration ≥ 150 ms showed the greatest improvement in EF, followed by patients with LBBB and QRS duration < 150 ms, non-LBBB with QRS duration ≥ 150 ms, and non-LBBB with a QRS duration < 150 ms [21]. Patients with LBBB and a QRS duration of ≥ 150 ms also demonstrated improved survival with CRT treatment. This suggests that QRS duration alone is not effective for optimal patient selection for CRT, but rather in combination with LBBB morphology. A study by Ghio et al., which evaluated 158 patients, investigated ventricular dyssynchrony using echocardiography and Tissue Doppler Imaging [22]. The findings demonstrated that QRS duration alone is not a reliable predictor of response to CRT. A recent study by Nakai et al., reported that the CRT response rate in patients with narrow QRS complex was comparable to global data, with no significant difference observed between the narrow and wide QRS groups [23]. The study further identified NYHA class IV as a key predictor of mortality. Another study by Bleeker et al., involving a cohort of 66 patients with differing QRS durations (110 ± 8 ms vs. 175 ± 22 ms), found that mechanical dyssynchrony of the LV did not always correspond with electrical dyssynchrony indicated by QRS duration [7]. A study by Sassone et al., found that in patients with LBBB, a marked prolonged QRS duration (≥ 178 ms) was associated with a higher rate of non-response to CRT [24]. Current CRT patient selection guidelines do not specify a QRS duration cut-off, raising questions about the utility of this criterion.

A study by Mollema, involving 242 patients with LVEF < 35%, QRS duration > 120 ms and NYHA class III–IV symptoms, concluded that clinical response to CRT could not be reliably predicted by QRS duration alone [25]. The authors suggested incorporating additional markers to improve patient selection. Although QRS duration and LBBB morphology are key indicators of electrical dyssynchrony in CRT guidelines, they may be insufficient for optimal patient selection and device programming.

Alternative methods of measuring electrical dyssynchrony of the heart

Recently, several studies have proposed alternative ECG markers for assessing electrical dyssynchrony [26]. However, none of them have been implemented into clinical practice yet, and the QRS complex remains the primary criterion for CRT indication and programming [4]. A review of ECG parameters for evaluating electrical dyssynchrony was conducted (Table 3) to determine whether an optimal alternative to QRS duration exists.

SAI QRST

In a study of ventricular arrhythmia involving 355 individuals, the sum absolute QRST integral (SAI QRST) was identified as a unique predictor of ventricular tachyarrhythmia. It was also observed that QRS duration alone is not a perfect marker of conduction anomalies [27]. Based on this, Tereshchenko et al., analysed baseline 12-lead ECGs from 234 patients indicated for CRT implantation [28]. The pre-implant ECGs were digitized, transformed into XYZ leads using the inverse Dowel Transformation Matrix, and analysed using MATLAB software. SAI QRST metric, calculated as the averaged sum of absolute areas under the QRST curve, was assessed for its association with CRT response, defined as a ≥ 15 ml decrease in left ventricular end-systolic volume six months post-CRT. Logistic regression was adjusted for age, gender, LBBB morphology, LVEF, cardiomyopathy type, and QRS duration. High SAI QRST from the baseline ECG was independently associated with CRT response, suggesting its potential utility in estimating electrical dyssynchrony. However, this research needs to be conducted on patients meeting specific criteria to further validate the usefulness of this method: QRS duration of 120–149 ms, non-LBBB morphology, and ischemic cardiomyopathy. The results of this study align well with another study, which also suggested that SAI QRST can aid in selecting CRT patients [29].

QRS area

A vectorcardiogram (VCG) can be constructed from a 12-lead ECG using a mathematical transformation matrix; the unopposed electrical forces during ventricular depolarization and repolarization are thought to be represented by the 3D areas of the VCG QRS loop (QRS-area) and T-wave loop (T-area), respectively [30]. Currently, the QRS area derived from the VCG is considered one of the most promising VCG-based parameters for selecting candidates for CRT [26].

Table 2: Different proposed LBBB criteria.

Parameter	American College of Cardiology [13]	Strauss et al. [14]	European Society of Cardiology Guidelines [4]
QRS duration	≥ 120 ms	≥ 140 ms (men), ≥ 130 ms (women)	≥ 120 ms
R Wave Pattern	Broad notched or slurred R in I, aVL, V5, V6; RS pattern in V5-V6	Broad notched or slurred R in left-sided leads.	Notches/slurring in middle third of QRS in at least 2 leads (V1, V2, V5, V6, I, aVL)
Q Wave Absence	No Q waves in I, V5, V6 (except aVL)	-	-
R Wave Peak Time	> 60 ms in V5, V6	-	≥ 60 ms in V5, V6
QRS Morphology in Right-Sided Leads	-	Broad notched/slurred QRS in right-sided leads, QS or rS in V1-V2.	QS or rS in V1 with small "r"
ST-T Changes	ST-T opposite to QRS direction	-	ST opposite to QRS polarity
Frontal Plane Characteristics	-	-	R wave in I, aVL; QS in aVR; variable QRS axis

Table 3: Short summary of proposed markers for indication of an electrical dyssynchrony.

Reference	Sample size	Sample information	NYHA Classification	Marker	Finding
Tereshchenko et al. [28]	234	LBBB LVEF: 24.7 ± 6.9% QRS duration: 152 ± 10 ms	III-IV	SAI QRST	High SAI QRST derived from baseline ECG is a good CRT response predictor.
Jacobsson et al. [29]	496	LBBB, IVCD LVEF: 23 ± 6% QRS duration: 169 ± 28 ms	II-III	SAI QRST	High SAI QRST derived from baseline ECG is a good CRT response predictor.
Van Stipdonk et al. [31]	1492	LBBB LVEF: 25 ± 9% QRS duration: 160 ± 21 ms	II-IV	QRS area	Baseline QRS area is a better outcome predictor than QRS duration and LBBB morphology separately.
Van Deursen et al. [32]	81	LBBB LVEF: 26 ± 7% QRS duration: 161 ± 14 ms	II-IV	QRS area	Baseline QRS area was larger in CRT responders.
Nguyen et al. [26]	27	-	-	QRS area	Baseline QRS area is a strong marker of electrical dyssynchrony and CRT response in non-LBBB patients.
Yusuf et al. [35]	100	LVEF > 35% QRS duration < 120 ms	II-IV	Fragmented QRS	Fragmented QRS predicts significant presence of an intraventricular dyssynchrony.
Sedova et al. [38]	19	LBBB LVEF: 25% (IQR 10) QRS duration: 167 ± 16 ms	II-III	SDAT	SDAT derived from a standard 12-lead ECG provides similar results to a 96-lead Body Surface Mapping.
Jurak et al. [39]	17	LBBB LVEF: 31% QRS duration: 165 ms	-	e-DYS	e-DYS can be used as a marker for electrical dyssynchrony having a potential to predict patient response to CRT.
Leinveber et al. [41]	390	Normal/LBBB/RBBB LVEF ≤ 35% QRS duration ≤ 115 ms; ≥ 130 ms, ≥ 120 ms*	-	nd-DYS	nd-DYS significantly correlates with the volumetric e-DYS.
Plesinger et al. [40]	1820	LBBB LVEF ≤ 30% QRS duration > 130 ms	I-II	Ventricular Electrical Delay	Ventricular electrical delay derived from UHF-ECG in LBBB patients, predicted the primary endpoint of heart failure or death more effectively than QRS duration from a standard ECG.

*Different QRS duration thresholds in this study correspond to different patient groups (Normal / LBBB / RBBB); CRT—cardiac resynchronization therapy; ECG—electrocardiogram; e-DYS—electrical dyssynchrony; IQR—interquartile range; IVCD—intraventricular conduction delay; LBBB—left bundle branch block; LVEF—left ventricular ejection fraction; nd-DYS—non-dyssynchrony; RBBB—right bundle branch block; SAI—sum absolute integral; SDAT—standard deviation of activation times; UHF—Ultra-High-Frequency.

The significance of the QRS area as a marker of electrical dyssynchrony was demonstrated by Van Stipdonk et al., in a study conducted on 1492 patients [31]. Their analysis revealed that baseline QRS area, calculated by converting digitized 12-lead ECG signals into orthogonal X, Y, and Z leads using the Kors Conversion Matrix, was strongly associated with clinical outcomes following CRT treatment. This suggests that the QRS area may serve as an alternative to QRS morphology and duration. This observation aligns with findings by Van Deursen et al., which showed that QRS area derived from baseline 12-lead ECG predicts CRT response more accurately than QRS duration and is comparable to LBBB morphology in its predictive value [32].

Additional evidence supporting the effectiveness of the QRS area as a marker of electrical dyssynchrony was provided by Nguyen et al., in a study with a small sample size of 27 patients [26]. Findings confirmed that ventricular electrical uncoupling was strongly associated with a large QRS area. It is important to note that all the studies mentioned above were conducted primarily on LBBB patients, who have been shown to respond favourably to CRT treatment. Interestingly, a fully automated QRS area measurement for predicting response to CRT has been proposed. The resulting values are comparable to manual QRS area measurements and provide similar predictive outcomes [33].

Fragmented QRS

Fragmented QRS (fQRS) is defined as the presence of an R' wave or notching of the R or S wave within a narrow QRS complex [34]. fQRS has recently emerged as a promising marker of electrical dyssynchrony and, more importantly, as a predictor of CRT outcomes. The study conducted by Yusuf et al., focusing on a limited population of 100 individuals—50 with fQRS and 50 with normal QRS complexes—found that systolic dyssynchrony was significantly more prevalent in patients with fQRS than in those without. This study underscores the important role of fQRS as a marker of electrical dyssynchrony [35]. Apart from this, a systematic review and meta-analysis concluded that fQRS predicts nonresponse to CRT on its own and is associated with intraventricular dyssynchrony. fQRS may serve as a marker to identify patients, particularly those with broad QRS complexes, who are less likely to benefit from CRT. However, further research is required to determine if CRT is appropriate for patients with fQRS and narrow QRS complexes [36].

Standard deviation of activation times

Standard deviation of activation times (SDAT) is a parameter used to assess electrical dyssynchrony. SDAT can be obtained from activation times detected in electrocardiographic QRS complexes recorded by body surface mapping [37]. However, recent research suggested that SDAT can also be reliably obtained from a standard 12-lead ECG. Sedova et al., demonstrated absolute similarity of SDAT values derived from a 12-lead ECG and those obtained from 96-lead body surface mapping in CRT patients [38]. This finding is significant because it opens the door to a much simpler, faster, and more accessible method for calculating SDAT, without the need for specialized equipment or extensive lead placement. By utilizing the widely available 12-lead ECG, clinicians could potentially integrate SDAT analysis into routine cardiac assessments, broadening its clinical applicability and reducing costs and preparation time.

UHF-ECG derived parameters

The Ultra-High-Frequency ECG (UHF-ECG) technique is based on the analysis of higher frequency components of the QRS complex and has been proposed to obtain the detailed ventricular activation pattern. Jurak et al., initially presented the UHF-ECG technology in a proof-of-concept study with seventeen patients, assessing ventricular activation patterns before and after CRT implantation [39]. In comparison to traditional ECG approaches, UHF-ECG was suggested as a more sophisticated method for evaluating electrical dyssynchrony. This technique can detect small variations in ventricular activity patterns, which could potentially improve patient selection and optimization of CRT settings. The main parameter, e-DYS is calculated as the time difference between the peaks of depolarization in the amplitude envelopes of the high-frequency QRS complexes recorded from selected ECG leads, typically V1 and V6.

The results of the study showed that electrical dyssynchrony is not visible in a standard QRS; however, it can be identified from UHF-QRS-derived parameters. Moreover, the results also showed that focusing only on V1 and V6 leads might miss the location of maximal dyssynchrony, thus, a more comprehensive comparison across 8 precordial leads is more informative. In the same study, the time difference between peak depolarization in UHF-QRS envelopes was found to be beneficial for predicting patient response to CRT, with the potential to enhance patient selection and therapeutic outcomes.

In another study, a new parameter was introduced—ventricular electrical delay (VED), which measures the delay between the primary components of the filtered QRS measured in the septal and lateral leads of resting ECGs. VED derived from UHF-ECG in 676 LBBB patients predicted the primary endpoint of HF or death more effectively than QRS duration from a standard ECG. Interestingly, there was a significant but only moderate correlation between ventricular electrical delay and QRS duration [40]. Another study utilizing UHF-ECG was conducted by Leinveber et al., where the newly introduced parameter epicardial activation delay (nd-DYS) derived from the negative derivative of the QRS complex (nd-ECG) was compared with e-DYS and QRS duration [41]. The results demonstrated that QRS duration is a less precise marker of electrical dyssynchrony compared to the directly measured parameters, nd-DYS and e-DYS.

While UHF-ECG–derived parameters have shown promising results, their clinical applicability is currently limited by restricted availability and the absence of large prospective studies. Therefore, these parameters cannot yet be considered clinically established markers.

Discussion

LBBB morphology and prolonged QRS duration are currently the two primary ECG parameters recommended for selecting candidates for CRT. However, both parameters have produced inconsistent results, and current guidelines do not specify strict QRS duration cut-off values or detailed LBBB morphology requirements for predicting CRT success. As a result, approximately 30% of patients remain non-responders to CRT, highlighting the need for alternative strategies in patient selection and optimization of CRT in HF treatment. Moreover, patients with LBBB, an excessively prolonged QRS duration (≥ 178 ms), were associated with a higher rate of non-response to CRT [24]. This reflects that, paradoxically, beyond a certain QRS threshold, further widening may indicate more advanced myocardial disease or scarring, which can reduce CRT efficacy. In an effort to improve patient selection for CRT, novel metrics of electrical dyssynchrony derived from the standard 12-lead ECG have recently been proposed and evaluated. Additionally, the evaluated Strauss ECG criteria of LBBB have demonstrated enhanced predictive value: Shoman et al., showed that using these criteria correlates with improvements in NYHA class, ejection fraction, end-systolic volume, and speckle-tracking echocardiographic parameters [42]. Strauss's criteria for LBBB may offer improved predictive value and have been associated with a "super response" to CRT. It has been demonstrated that patients meeting Strauss criteria experienced a markedly higher rate of CRT super-response, defined by robust improvements in NYHA class, left ventricular systolic function, and reverse remodelling, as compared to those who did not [43].

From a clinical perspective, these findings suggest that refined ECG-based criteria, such as stricter LBBB definitions, may improve patient selection without increasing technical complexity, as they rely solely on conventional 12-lead ECG recordings.

When comparing the clinical validity of ECG-derived dyssynchrony parameters, it is important to distinguish between patients with LBBB morphology and those without LBBB. Novel ECG markers have been primarily evaluated in LBBB populations, whereas evidence in non-LBBB patients remains limited and less consistent. Accordingly, the application of these ECG markers could not be expected in non-LBBB patients.

The most studied alternative parameters for electrical dyssynchrony assessment are QRS area and SAI QRST. Both parameters demonstrated better prediction of CRT response than QRS duration and the same predictive value as compared to LBBB morphology [31, 32]. Moreover, Van Stipdonk et al., proposed that the QRS area can be used as an electrical dyssynchrony marker in non-LBBB patients [31]. Among the various proposed electrical dyssynchrony metrics, QRS area has been the subject of comparatively more extensive research, supporting its potential clinical utility. However, differences in methods used to quantify QRS area, such as transformation matrices and software, could impact repeatability across clinical settings. Additionally, many studies have been limited by small sample sizes, such as the study by Nguyen et al., with only a 27-patient population [26]. Despite these limitations, the QRS area remains applicable, as it can be derived from a standard 12-lead ECG using automated algorithms, making it potentially suitable for integration into routine ECG analysis.

In the SMART-AV study, Tereshchenko et al., calculated SAI QRST using digitized ECGs rather than digitally recorded waveforms, meaning their SAI QRST thresholds are not directly comparable to those from digital-ECG studies [28]. They emphasized the need for further validation of SAI QRST's predictive power in non-LBBB patients and those with narrow QRS durations (120–149 ms). Additionally, they proposed that integrating SAI QRST with QRS duration and morphology into a composite dyssynchrony score may enhance CRT patient selection in these subgroups.

Fragmented QRS as a marker of electrical dyssynchrony is also a good alternative to QRS duration and LBBB morphology, as it provides a relatively simple, affordable, and non-invasive method for detecting electrical dyssynchrony. It can be assessed using a standard 12-lead ECG and does not require specialized imaging or expertise. While fQRS helps detect electrical dyssynchrony, its definition varies across studies, affecting repeatability and highlighting the need for a standardized classification system. Furthermore, without additional imaging or clinical factors, fQRS may not be sufficient to predict CRT response independently. Pranata et al., suggest that interventricular dyssynchrony, particularly in patients with wide QRS complexes, is strongly associated with CRT response, raising questions about the utility of fQRS alone [36]. Apart from this, studies were carried out on a relatively small cohort.

UHF-QRS parameters, including e-DYS and nd-DYS, show promising results, but further validation through larger, multicentre trials is necessary to assess their applicability to CRT. The fundamental limitation of e-DYS, as of now, is that the clinical relevance of this parameter assessed with UHF-ECG is unknown, as no clinical trials have proven the association between dyssynchrony measured with UHF-ECG and patient clinical outcomes.

The SDAT parameter derived from body surface mapping was already studied previously as a marker of an electrical dyssynchrony [37]. However, another study demonstrated that the SDAT parameter can be accurately derived from a standard 12-lead ECG, yielding results matching those obtained from 96-leads [38]. Activation times obtained from body surface ECG for the calculation of SDAT remain questionable for the assessment of ventricular activation, and large prospective studies are needed to confirm the clinical utility of ECG-derived SDAT. If validated in larger cohorts, ECG-derived SDAT could represent a clinically accessible compromise between advanced mapping techniques and conventional ECG parameters.

Conclusion

In summary, while traditional ECG parameters such as QRS duration and LBBB morphology remain the gold standard for CRT patient selection, their predictive value is limited. New metrics such as QRS area, SAI QRST, SDAT, fQRS, and UHF-QRS-based parameters, including e-DYS, nd-DYS, and VED, offer promising alternatives for assessing electrical dyssynchrony, particularly in non-LBBB and narrow QRS patients. Based on current evidence, ECG-derived dyssynchrony parameters may be considered as complementary tools in LBBB patients. However, these novel tools require further standardization and validation in larger, varied patient populations. Moreover, the advantages of the newly proposed ECG markers, compared to the routine criteria currently used in clinical practice, have not been clearly demonstrated.

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