Simpler Is Better
New Lessons Learned From the 12-Lead Electrocardiogram

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“It has long been an axiom of mine that the little things are infinitely the most important”
—Sherlock Holmes in “A Case of Identity” by Arthur Conan Doyle

Cardiac resynchronization therapy (CRT) can have a profound therapeutic impact on appropriately selected patients. However, even when the current clinical guidelines for CRT are rigorously applied, the response rate is ~70%.

Nearly a third of patients who undergo implantation of a CRT device are clinical nonresponders and more may be “remodeling nonresponders.” An extensive body of literature reports on a wide variety of methods that can be better used to identify potential responders by measurement of mechanical dyssynchrony. Factors responsible for nonresponse include comorbid conditions, cardiac substrate, left ventricular (LV) lead location, and device programming. Comorbid conditions such as obstructive sleep apnea, right-sided heart failure, and type of intraventricular conduction delay should be considered at the preprocedural stage. Device programming may help minimize the number of nonresponders. Prediction of responders by invasive hemodynamic assessment is impractical for daily clinical practice. Cardiac magnetic resonance imaging is too expensive for routine use and is not an option for many patients who already have devices and need upgrades. The appeal of echocardiography for predicting responders by identifying mechanical dyssynchrony has been dampened by its limited reproducibility and poor predictive value. It is also impractical to perform echocardiography during implantations. The prolonged QRS duration (QRSd; electric dyssynchrony), as measured on a standard 12-lead ECG, remains the best method for identifying candidates for CRT. In an elegant and important study reported in this issue of Circulation, Sweeney and colleagues use the 12-lead ECG to show that, despite its apparent simplicity, analysis of the standard 12-lead ECG can yield both pitfalls and impressive rewards.

Current clinical guidelines specify a QRSd >120 ms on a standard 12-lead ECG as one of the criteria for CRT eligibility but do not specify the method: mean or maximum and in which leads or combination of leads. Furthermore, it is known that when QRSd is defined as the earliest QRS activation in any lead to the termination of the QRS complex in any lead, the results can be vary significantly compared with the mean or maximum duration in any lead. This is not likely to be important when the QRSd is >140 ms. Even the accuracy of manual QRSd assessment has been questioned. Significant interobserver variability and discordance with computer measurements have been demonstrated when the QRSd is >120 ms. This is important in light of recent findings of the Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS (RethinQ) that suggested that patients with relatively narrow QRSd (110 to 120 ms) do not benefit from CRT. Studies have yielded divergent results when baseline QRSd alone is evaluated as a predictor for clinical response. There have also been conflicting results when patient populations have been divided on the basis of a higher threshold value for QRSd (>150 ms).

Baseline QRS morphology is not specifically addressed in current guidelines. Patients with a prolonged QRSd may have a left bundle-branch block (LBBB), right bundle-branch block, nonspecific intraventricular conduction delay, or paced ventricular rhythm. Evidence is mounting that patients with a right bundle-branch block pattern are much less likely to respond to CRT than those with other forms of conduction delay. Patients with nonspecific intraventricular conduction delay or paced ventricular rhythm have an intermediate probability of response. Even the definition of LBBB, which includes QRSd ≥120 ms has been questioned. Strauss and Selvester have suggested that a QRSd of 120 to 140 ms is often due to LV hypertrophy rather than true LBBB. The basis, in part, of endocardial catheter mapping data, they have proposed that a true LBBB requires a QRSd >140 ms. This is important because in true LBBB the depolarization of the anteroseptal and posterolateral walls is completely uncoupled. This is not the case in LV hypertrophy.

Areas of scar from myocardial infarction result in slow conduction and are manifested as notching on the surface ECG. In fact, early studies correlating notching on surface ECG with ventriculograms suggested significant dyssynchrony even in the absence of an LBBB. QRS notching may be a sensitive predictor of prior myocardial infarction and scar, but recent echocardiographic studies suggest that is not an independent predictor of dyssynchrony in patients with a wide QRS complex. QRS notching and Q waves are not the only signs of myocardial scar. Selvester et al used computer modeling and data from ventriculograms to derive a QRS score corresponding to the amount of LV myocardial scar.
The Q- and R-wave duration, R- and S-wave amplitudes, R/Q ratios, R/S ratios, and QRS slurs and notches in 10 of 12 standard leads (all except aVR and III) were examined to calculate the QRS score. The use of data derived from ventriculograms, despite validation, has obvious limitations. Scar burden may now be better assessed with contrast-enhanced magnetic resonance imaging and may have a negative predictive value in terms of response to CRT. A prolonged QRSd associated with an LBBB alone is not synonymous with mechanical dyssynchrony. Assessment by 2- and 3-dimensional echocardiography and magnetic resonance imaging suggests that a significant number of patients do not have mechanical dyssynchrony despite having a LBBB. Furthermore, the pattern of LV activation and dysynchrony is not uniform among patients with LBBB. This is very important when target veins are selected on the basis of anatomic considerations only. It is generally assumed that a lateral or posterolateral vein is a better target than an anterolateral vein because the basal posterolateral region of the LV is the latest to activate. This assumption is not valid in some patients. ECG imaging is a functional noninvasive mapping modality in which activation sequences are reconstructed from 250 body-surface ECG traces and thoracic computed tomography images. It also provides insight into lines of block that can result in delayed activation of anatomically adjacent areas. Jai and associates report ECG imaging from a small number of patients with heart failure and LBBB. ECG imaging of these patients revealed them to be a heterogeneous group with variable LV activation patterns, regions of delayed conduction, and lines of block. Marked delay in activation of the anterolateral wall was rarely seen. ECG imaging is not available for routine clinical use, but this modality highlights the importance of electric substrate in our understanding of nonresponders.

QRSd shortening has also been studied as a predictor of clinical response. The ΔQRS was initially thought to have limited value as a predictor of clinical and echocardiographic response, but there is growing evidence that ΔQRS is an independent predictor of response. One study also showed that a longer QRSd after biventricular pacing was associated with worse mortality or need for transplantation.

Another ECG measurement that has been studied as a useful predictor of hemodynamic and clinical response is the LV electric delay. Sometimes referred to as the Q-LV time, it is measured from the onset of the QRS on a surface lead to the sense marker on the LV lead and can be expressed as a percentage of the QRSd or an absolute value. Singh et al showed that an LV electric delay of <50% of the QRSd was associated with worse clinical outcome.

At best, the analytic approaches described above modestly improve our ability to identify responders and nonresponders. In this issue of Circulation, Sweeney and colleagues take a big step forward in the analysis of the ECG and present an alternative method of using the standard 12-lead ECG to better predict responders on the basis of volumetric remodeling. This approach combines and extends the same conceptual basis for the previously discussed techniques, yielding a method that addresses the potential role of substrate on the response to CRT. Use of these findings during CRT implantation is practical and can have implications for device programming.

Patients received a CRT device on the basis of standard clinical indications and LBBB only. Volumetric response was evaluated by 2-dimensional echocardiography with excellent interobserver and intraobserver reproducibility. A standard 12-lead ECG was recorded as baseline and after implantation. The QRS was characterized on the basis of morphology expressed as a hieroglyphic framework with the 4 waveform elements (R, S, Q, QS). Ventricular activation was then characterized by the hieroglyphic expression of the QRS in the frontal and horizontal planes. The portion of QRSd resulting from LV activation was represented by the LV activation time (LVATmax). QRS notching, when present after 40 ms of QRS onset, was assumed to indicate the transition from right ventricular to LV depolarization. LV activation time essentially corrects for the component of the QRSd resulting from right ventricular depolarization. The Selvester QRS score for LBBB was used to quantify LV scar. This score has not been extensively validated and is therefore limited in this method. The ΔQRS represents ventricular activation fusion during biventricular pacing. ECG evidence of fusion in this study included change in frontal plane axis to right-axis deviation (and the corresponding changes in QRS hieroglyphs) and the emergence of anterior force in leads with dominant posterior forces. Expected changes in R-wave amplitude in the lateral (I, aVL) and precordial leads also represented fusion. Another important assumption made by the authors is that LV lead position was not relevant because electric resynchronization during CRT does not correlate with stimulation site.

Analysis of multiple variables identified 2 baseline and 2 post-CRT predictors for the primary end point (10% reduction in end-systolic volume). These include LVAT, QRS score, increasing R-wave amplitude in V1 to V2, and an axis shift from the left axis deviation to right axis deviation. Adverse and favorable values were determined for each. The post-CRT predictors of response are both indicative of fusion. Increasing LVATmax was associated with a greater probability of remodeling up to a plateau value of 125 ms. Taken on its own, a low QRS score was associated with a higher likelihood of response. The predictive value of LVATmax was offset by a higher QRS score. The highest predictor of response was increasing R-wave amplitude in V1 to V2 when R-wave amplitude was ≳4.5 times the baseline value.

It is possible that no baseline characteristic, ECG or otherwise, can predict CRT clinical response to a greater degree than existing parameters. A 60% to 70% clinical and volumetric response to therapy compares favorably with treatment modalities in other disease processes. The ECG markers of fusion described in the present study can help guide device programming on a real-time basis, potentially reducing the percentage of nonresponders. The remainder of the nonresponders may have factors related to substrate, including high scar burden or absence of dyssynchrony despite having an intraventricular conduction delay. The study does not provide any details regarding the programming of the CRT device with respect to the degree of LV preexcitation. It is conceivable that LV capture latency and
conduction delay can be overcome by preexcitation of the LV guided by the amplitude of the R wave in V1 to V2. Furthermore, the findings in this study imply that lead positioning guided by the longest Q-LV time may not be as important as achieving a stable lead position and then preexciting the LV enough to yield adequate fusion as measured by change in R-wave amplitude. The findings of Sweeney and colleagues are an important step forward, providing clinicians with an effective set of ECG markers for predicting CRT response. Further investigation testing the ability of these markers to guide device programming and patient selection is welcomed.

Disclosures

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References


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