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REVIEW TOPIC OF THE WEEK

# QRS Duration or QRS Morphology

## What Really Matters in Cardiac Resynchronization Therapy?

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**ABSTRACT**

The beneficial effects of cardiac resynchronization therapy (CRT) have been well established in large, randomized trials. Despite the documented success of this treatment strategy, a significant proportion of patients with heart failure do not achieve the desired response. The aim of this review was to delineate factors contributing to a successful CRT response, emphasizing the interrelated roles of QRS morphology and QRS interval duration. More data are available on QRS duration, as this factor has been used as an enrollment criterion in clinical trials. Response to CRT seems to increase as the QRS duration becomes longer, with greatest benefit in QRS duration ≥150 ms. Recent data have placed more emphasis on QRS morphology, demonstrating variability in clinical response between patients with left bundle branch block, non–left bundle branch block, and right bundle branch block morphology. Notably, myocardial scarring and cardiac dimensions, among other variables, may alter heterogeneity in ventricular activation. Understanding the electrophysiological underpinnings of the QRS complex has become important not only to predict response but also to facilitate the patient-specific delivery of resynchronization therapy. (J Am Coll Cardiol 2016;67:1104–17)


Cardiac resynchronization therapy (CRT) has effectively had an impact on the natural trajectory of symptomatic heart failure (HF) in patients with coexisting conduction tissue disease. CRT brings its physiological impact to bear through synchronizing cardiac contraction, resulting in favorable ventricular remodeling and improvement in ejection fraction (EF). Prospective randomized studies of patients with both ischemic and nonischemic causes of HF have shown that this effect of CRT translates into long-term clinical benefits, such as improved quality of life, increased functional capacity, reduction in hospitalization for HF, and overall mortality (1–11). Despite the success of this therapeutic modality, a significant proportion of patients may not respond sufficiently or in a predictable way to this pacing therapy. There are several determinants of successful response to CRT; QRS duration and QRS morphology are of considerable importance in this response.

Although surface electrocardiographic (ECG) evidence of electrical dyssynchrony due to the presence of an intraventricular conduction delay (IVCD) serves as a surrogate for ventricular mechanical dyssynchrony, its precision in predicting response may be limited by the complexity of electrical and mechanical dyssynchrony in the diseased heart. Dyssynchrony can exist at numerous levels within the heart: within the atria; between the atrium and ventricles; and at different levels within the ventricles (i.e., at the

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interventricular, intraventricular, and intramural levels) (12,13). These factors may operate to greater or lesser degrees in an individual patient, such that a simple approach based on the ECG markers (QRS morphology and QRS duration) may not adequately represent the conduction patterns within any single heart. Nevertheless, these ECG surrogates of electromechanical dyssynchrony are the clinical tools on which we rely to help select patients for CRT. This review focuses on dyssynchrony within the ventricle, the electrical conduction abnormalities that underlie mechanical dyssynchrony, and the clinical trial data defining appropriate patient selection for CRT.

## MECHANICS OF ELECTRICAL ACTIVATION

As discussed in detail later, there is a large amount of data confirming the variability in the clinical response between patients with left bundle branch block (LBBB) and non-LBBB morphology. Much of this response is driven not only by the altered electrical activation of the left ventricle but by the current lack of individualized pacing approaches within these variable substrates. Mechanical dyssynchrony due to pure conduction block in the right or left bundles is the easiest to appreciate. Typically, an LBBB is linked with a U-shaped activation pattern that courses through the apex, with delayed activation of the lateral and posterolateral portions of the left ventricle. This spread of electrical activity parallels the mechanical activation and constitutes the basic reasoning behind the conventional left ventricular (LV) lead implantation strategy of targeting the lateral wall.

However, even in a pure LBBB, a high level of heterogeneity remains in the LV activation pattern, accompanied by a wide variance in the line of functional block. Some of this may be linked to the axis of activation, but it can be affected by other underlying characteristics, such as myocardial scarring and cardiac dimensions. Another important factor is that as the QRS duration increases, the band of electrical and mechanical dyssynchrony widens, such that some patients may respond to CRT, even with nonconventional pacing lead locations (14). Patients with HF and impaired left ventricular ejection fraction (LVEF) are complex and may manifest variable degrees of mechanical dyssynchrony due to scarring from infarction/ischemia or primary myocardial disease, even in the situation of an LBBB. Some have suggested that unless a "true" LBBB is present, patients are unlikely to respond to CRT. For instance, Strauss et al. (15) suggested revised ECG criteria for determining if a true LBBB can be confirmed. Risum et al. (16) used echocardiographic longitudinal strain methods to determine if LV late activation was present in 234 patients with an LBBB ECG pattern. These investigators found that only two-thirds of the patients, those with both an ECG LBBB pattern and late LV activation, were CRT responders.

As will be discussed later, patients with non-LBBB morphology generally have responded poorly to CRT, perhaps driven by the abnormal and variable electrical activation pattern of their left ventricle. Some patients with non-LBBB may not manifest mechanical dyssynchrony at all; some do, but late activation does not occur at the lateral LV wall, where LV leads are generally targeted. Non-LBBB has included an examination of nonspecific IVCD patient subsets, who consistently demonstrate outcomes inferior to LBBB patients and to those with a right bundle branch block (RBBB), who generally fare even worse (17–22). Examination of the activation sequence in non-LBBB conduction lends further understanding to the physiology behind CRT response (**Figure 1**). As shown in the example, the segment of the heart with the most delayed activation can be markedly different in patients with a non-LBBB morphology compared with those with an LBBB (13,23). In the situation of an RBBB, there is delayed right ventricular activation, with relatively early LV activation.

The patterns of activation in the myopathic heart can affect patients manifesting an RBBB pattern. Electroanatomic mapping of such patients has found significant LV conduction delay (especially in very prolonged QRS duration), albeit with wide variability in the degree of mechanical dyssynchrony. There is evidence that in some patients, the presence of an RBBB ECG pattern may mask a coexistent LBBB as an explanation for this finding. This situation may be recognized by the concomitant presence of broad, slurred, and occasionally notched R waves in leads I and aVL, along with left-axis deviation (23–27). Several other proposed explanations for a worse outcome in patients with RBBB include: 1) ventricular dyssynchrony patterns, which are simply not favorable for CRT; 2) concomitant right ventricular dysfunction; and 3) more extensive conduction disease (28).

As will be discussed further, QRS morphology is simply 1 determinant of CRT response. Although areas of delayed activation result in mechanical dyssynchrony, the duration of activation delay also seems to be a critical component.

### ABBREVIATIONS AND ACRONYMS

**CRT** = cardiac resynchronization therapy

**CRT-D** = cardiac resynchronization therapy combined with a defibrillator

**CRT-P** = cardiac resynchronization therapy combined with a pacemaker

**ECG** = electrocardiographic

**EF** = ejection fraction

**HF** = heart failure

**ICD** = implantable cardioverter-defibrillator

**IVCD** = intraventricular conduction delay

**LBBB** = left bundle branch block

**LV** = ventricular

**LVEF** = left ventricular ejection fraction

**NYHA** = New York Heart Association

**OR** = odds ratio

**RBBB** = right bundle branch block