Cardiac Resynchronization Therapy 101
If It’s Not Late, Pacing It Early Won’t Help*
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Cardiac resynchronization therapy (CRT) is an effective treatment for heart failure (HF) for patients who still have significant symptoms despite optimal medical therapy. Many patients with HF have interventricular and intraventricular conduction delays that cause delayed activation of the lateral wall of the left ventricle (LV). This delayed activation leads to ventricular dyssynchrony, which compromises diastolic filling time, decreases LV ejection fraction, and worsens mitral regurgitation and ventricular dilation. By placing a lead through the coronary sinus to a lateral or posterolateral branch, the LV can be paced simultaneously or near-simultaneously with pacing from the right ventricle, leading to resynchronization of the ventricles. New York Heart Association functional class, exercise tolerance, quality of life, and LV ejection fraction have all been shown to improve with CRT (1–4).

Although a consistent finding in these trials has been that the majority of patients improve, there is still a substantial minority who do not show any significant improvement either in symptoms or objective indexes of ventricular function after CRT. Placement of a lead to pace the LV can be technically challenging, potentially leading to long procedures in sick patients with advanced HF. Indeed, when transvenous lead placement fails, consideration is often given to epicardial lead placement, with its attendant surgical morbidity. Thus, identification of patients who are highly unlikely to benefit from CRT would be helpful so that implantation can be avoided and alternative treatments recommended.

Why is it that some patients do not improve while undergoing CRT? In some patients it is not possible to place a lead in an appropriate venous branch, either because of unfavorable anatomy or problems such as diaphragmatic stimulation or high pacing thresholds. In patients with ischemic cardiomyopathy, there may be large akinetic areas along the lateral wall from a previous myocardial infarction, leading to ineffective pacing (5,6). However, even patients with electrocardiographic conduction delays and non-ischemic cardiomyopathy do not always show improvement with CRT. How can we explain this observation?

All the major clinical trials of CRT used prolonged QRS duration on the surface electrocardiogram as a major entry criterion and marker for dyssynchrony. However, it has become clear that wide QRS duration alone does not assure that ventricular dyssynchrony is present. Recent studies using a variety of echocardiographic techniques have shown that ventricular dyssynchrony can be quantified and that some patients with HF have dyssynchrony despite normal QRS durations (7).

A recent state-of-the-art paper published in the Journal (8) provided an excellent review of the echocardiographic techniques currently available for evaluating ventricular dyssynchrony. Two types of ventricular dyssynchrony have been described: interventricular dyssynchrony, which is the delay in activation of the LV compared with the right ventricle; and intraventricular dyssynchrony, which is a measure of the delayed activation of the lateral or posterior walls of the LV compared with the septum. One simple technique using standard two-dimensional Doppler echocardiography involves determining interventricular delay by the difference in timing from the onset of the QRS to peak aortic flow (Q-Ao) versus peak pulmonic flow, whereas intraventricular dyssynchrony is measured by evaluating the timing difference between maximal systolic contraction of the septum compared with the posterior LV wall by M-mode (9). Despite the simplicity of this approach, adequate images to make these measurements cannot be obtained in all patients, thus leading to interest in other techniques such as tissue Doppler imaging or three-dimensional echocardiography to evaluate delays in LV activation (10–12). However, there is still no consensus as to which parameter(s) should be measured to assess ventricular dyssynchrony or what values best predict response to CRT.

In this issue of the Journal, Pitzalis et al. (13) studied the correlation of septal to posterior wall motion delay (SPWMD) with outcomes from CRT. The investigators had previously reported that the presence of such a delay correlated with reverse remodeling after CRT, and that this parameter was significantly better at predicting response to CRT than QRS duration, LV electromechanical delay (Q-Ao), or interventricular delay (9). In the current study, 60 patients with severe HF and left bundle-branch block underwent standard Doppler echocardiography that included assessment of SPWMD. Prolonged SPWMD, defined as >130 ms, correlated significantly with a reduced risk of HF progression and an improvement in LV ejection fraction.

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Does the study by Pitzalis et al. (13) provide the answer as to a useful predictor of response to CRT? Unfortunately, we are not there yet. An advantage to the investigators’ approach is that a simple echocardiographic technique was used to make the determination of dyssynchrony. For patients with adequate echocardiographic windows, including all but three of the eligible patients in the Pitzalis et al. (13) study, the timing differences that indicate dyssynchrony are simple enough to determine that other techniques, such as tissue Doppler imaging, that may be less readily available should not be necessary. However, although the investigators found that a cutoff value of 130 ms for SPWMD was predictive of response, SPWMD is a continuous variable with responders and non-responders found with values above and below the cutoff value. Thus, although the shorter the SPWMD, the less likely the response to CRT, it is unknown what values make a response unlikely enough to avoid pursuing this therapeutic option. Despite this shortcoming, the study does indicate that, although QRS duration was one of the primary inclusion criteria used in the major clinical trials of CRT, QRS duration alone is a poor predictor of likely response to CRT.

For electrophysiologists who perform CRT procedures and for HF specialists who wish to refer appropriate patients for this therapy, a simple and reliable technique is needed to determine whether ventricular dyssynchrony is present. It is not yet clear which parameter best indicates dyssynchrony and the likelihood of benefit from CRT: is it intraventricular dyssynchrony alone, interventricular dyssynchrony alone, or do both need to be present to make response likely? Is two-dimensional Doppler echocardiography sufficient to make these determinations, or are other techniques such as tissue Doppler imaging necessary? Even if we know which parameter is best, it is unclear what values best discriminate patients likely and unlikely to benefit. Finally, it would be most helpful to define when dyssynchrony is minimal or absent so that CRT will not be offered to a patient with HF who is highly unlikely to benefit. Whereas it is clear that if it (the lateral wall) is not late then you cannot make it early by pacing, the definition of “late” still needs work.

References