Indications for Cardiac Resynchronization Therapy

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KEYWORDS

• Heart failure • Biventricular pacing • Cardiac resynchronization therapy • Dyssynchrony

KEY POINTS

- CRT indications are evolving.
- EF less than 35% remains a cornerstone of indication.
- LBBB and QRS greater than 150 ms appear important criteria for favorable response.
- EKG remains most important indicator of dyssynchrony.

PACING FOR HEART FAILURE

The concept of using pacing to treat heart failure (HF) symptoms predates the development of techniques for left ventricular (LV) pacing and cardiac resynchronization therapy (CRT). There was hope that dual-chamber pacing techniques would improve HF outcomes by optimizing heart rate, atrioventricular (AV) timing, and cardiac output. Noting the adverse hemodynamic consequences of VVI pacing, dual-chamber pacing algorithms were developed that mimicked the natural AV interval with changing heart rates. Small, uncontrolled studies in the early 1990s suggested benefit of standard right atrial and right ventricular (RV) DDD pacing in HF patients.[1–3] When subjected to a randomized controlled trial,[4] however, DDD pacing failed to confirm positive outcomes. The deleterious effects of RV pacing and attendant left bundle branch block (LBBB) only became fully appreciated with the reporting of the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial in 2002.[5] DAVID enrolled 506 patients with LV ejection fraction (LVEF) less than or equal to 40%, randomized to VVI at 40 beats per minute (bpm) versus DDD pacing at 70 bpm, with death or HF hospitalization as the primary endpoint. This trial showed that those in the DDD arm were approximately 40% more likely to achieve the primary endpoint compared with controls at 1 year. Data from the Mode Selection Trial in Sinus Node Dysfunction (MOST) highlighted the potential of RV pacing to cause HF; a substudy from MOST that demonstrated an RV pacing threshold of approximately 40% was identified as putting patients at 3-fold increased risk of HF hospitalization.[6] The presumed mechanism by which RV pacing led to an apparent increase in HF was the LBBB and resulting mechanical dyssynchrony. In the general HF population, approximately 30% of patients with systolic HF have wide QRS intervals, also correlated with adverse outcomes.[7,8] In mechanistic support of this association, intraventricular conduction delay has been linked to a wide array of hemodynamic derangements, including reduced pulse pressure, impaired diastolic function, and functional mitral regurgitation.[9]

Early attempts to address this clinical problem by performing biventricular pacing (CRT) in the 1990s showed improvements in acute hemodynamics and medium-term functional measures.[10,11] In 1996, Cazeau and colleagues[12] reported a series of 8 advanced HF patients with

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widened QRS intervals. All received atrial-triggered biventricular pacemakers. Four died in the perioperative period, but of the 4 who survived, HF class improved from IV to II. CHF worsened when pacing was deactivated. These and other favorable early experiences set the stage for large-scale CRT trials.

INITIAL INDICATIONS

Presented in 1999, and later published in 2002, the PATH-CHF trial investigated pacing in patients with advanced HF.[13] Enrolled patients had 2 pulse generators implanted, then randomized to either univentricular (LV) or biventricular pacing. Both modes of pacing demonstrated improved oxygen consumption parameters and exercise capacity.

In 2001, the MUSTIC study[14] reported a convincingly positive impact of CRT in 67 randomized patients with reduced LVEF (mean 23%), New York Heart Association (NYHA) class 3 HF, Left LV end-diastolic diameter (LVEDD) greater than 60 mm, and QRS greater than 150 ms. The mean distance walked in 6 minutes was 23% greater with active pacing, the quality-of-life score improved by 32%, peak oxygen uptake increased by 8%, and hospitalizations decreased by more than 60% ($P<.05$).

In the same year, results of the MIRACLE trial[15] were presented. It was the largest multicenter, prospective, randomized clinical trial to date, enrolling 453 patients with QRS greater than or equal to 130 ms, LVEF less than or equal to 35%, LVEDD greater than or equal to 55 mm, and NYHA class 3–4. Compared with controls, CRT improved functional class, 6-minute hall walk distance, maximum oxygen consumption, and quality of life. Improvement was seen in 67% of CRT patients versus 39% of controls. In the years afterwards, the CARE-HF[16] and COMPANION[17] trials showed a reduction in the primary composite endpoint (all-cause mortality or hospitalization for MACE) from CRT compared with standard medical therapy alone. A further meta-analysis reported approximately a 30% reduction in both hospitalization and mortality.[18] Based on these trials, guidelines incorporated CRT as a treatment option for those with LVEF less than or equal to 35%, QRS greater than or equal to 120 ms, and NYHA 3–4.

In the current era, 3 separate expert groups have generated guidelines for utilization of CRT, each synthesizing their interpretation of the aforementioned landmark trials, coupled with expert opinion. The American Heart Association together with the American College of Cardiology and the Heart Rhythm Society,[19] the Heart Failure Society of America,[20] and the European Society of Cardiology[21] have recently published relevant guidelines. Although there are a few distinctions among the guidelines, a vast majority of recommendations put forth are concordant. The initial indications for CRT have evolved to incorporate the degree of QRS prolongation, QRS morphology, presence of atrial fibrillation, and lower NYHA class to provide a more nuanced approach to patient selection. **Fig. 1** summarizes these adjustments and **Box 1** attempts to incorporate and simplify these recommendations into a more practical approach.

In the past few years, the guidelines have been updated in such a way as to improve patient selection according to their likelihood of improvement with CRT. These adjustments arose from evolving evidence that QRS duration greater than or equal to 150 ms and an LBBB pattern seem to correlate with the most favorable outcomes after CRT.[22] Attempts to further refine selection criteria beyond ECG evidence of electrical dyssynchrony have largely involved echocardiographic assessments of mechanical dyssynchrony.[23–25] The largest multicenter trial to test the hypothesis,

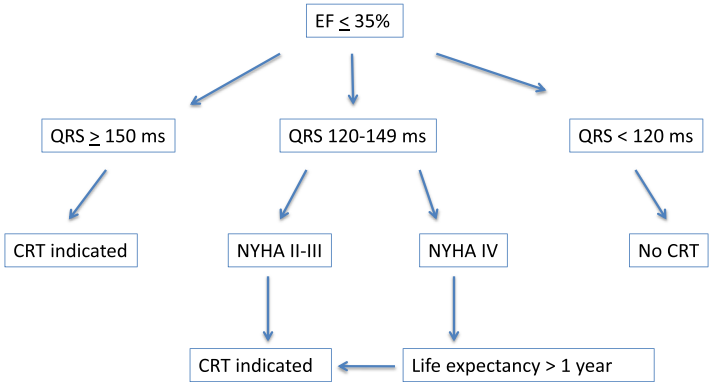

Fig. 1. Practical algorithm for CRT indication.