Extending the Use of Cardiac Resynchronization Therapy

Do We Need a New Algorithm?

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‘I’ll be more enthusiastic about encouraging thinking outside the box when there’s evidence of any thinking going on inside it.’
—Terry Pratchett, British author and commentator (1)

The current guidelines for cardiac resynchronization therapy include patients with New York Heart Association functional class III to IV heart failure, an ejection fraction of \(<35\%\), QRS duration \(>120\) ms, on optimal medical therapy, and in sinus rhythm (2,3). To this, the European guidelines add that patients should show evidence of left ventricular dilatation. Both American College of Cardiology/American Heart Association and European guidelines include atrial fibrillation as a Class IIa indication, as well as permanent pacing, although the American College of Cardiology/American Heart Association guidelines limit the indication to patients who are frequently dependent on ventricular pacing.

Interestingly, despite the homogeneity of these guidelines, there are significant variations in the performance of cardiac resynchronization therapy (CRT) in patients with heart failure in both the U.S. (4) and Europe (5). This heterogeneity is influenced by age, comorbidity, local reimbursement, the number of conventional implantable cardioverter-defibrillator implantations and training, and surprisingly less influenced by gross domestic product or health care spending. Indeed, clinical practice has drifted away from the evidence base from clinical trials, involving patients who are older and with more comorbidities, with 10% having ejection fraction of \(>35\%\) and 6% having an ejection fraction of \(>40\%\) (4) and often even borderline QRS durations. The appropriate implantation rate remains difficult to define, despite approximately 40% of patients with systolic heart failure having a QRS duration \(>120\) ms (6); only 12% of heart failure patients reported by Piccini et al. (4) underwent CRT. There is no doubt that defining the appropriate population for CRT remains an important challenge, as the technique is expensive (particularly when replacement devices are taken into account) and not without risk. A fundamental question is not only whether we should be satisfied with the populations recommended in the guidelines, but whether we should be satisfied with the application of the guidelines themselves.

The review of CRT indications in the current issue of the Journal suggests that guideline application is too restrictive (7). These authors focus particularly on additional groups of patients who are not captured by the current guidelines, including those with a narrow QRS and individuals with early heart failure. Nonetheless, although it is true that 40% to 50% of such patients may have evidence of mechanical dyssynchrony (by 1 of a multitude of published criteria), the published studies of the efficacy of intervention are far from encouraging. Despite favorable single-center studies, multicenter studies of CRT in patients with a narrower QRS failed to provide a uniform message (8,9). Likewise, of the 2 studies of CRT in early heart failure, the primary end point in the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial was not attained at 12 months, even though it was attained in a subgroup followed to 24 months and various secondary end points improved (10). In the second study (11), the primary end point of heart failure and death was attained due to a reduction of heart failure presentations with CRT. Generally, secondary end points should not be analyzed if the primary end point does not demonstrate clear statistical significance (12). Broadening of the indications for CRT to new populations will be dependent on a number of new studies, which are currently in progress (Table 1).

An alternative critique of the current CRT guidelines would perhaps be to question whether they are too broad. The current guidelines take no cognizance of a number of features that may compromise the ability of an individual patient to mount either a physiologic or survival response to CRT. CRT may face challenges in improving an already-synchronous ventricle—whether this is defined by mechani-
rical or electrical synchrony (13,14). Nonsynchrony issues include the impact of underlying etiology, the extremes of ventricular impairment, and comorbidities. A recurrent theme in CRT is the extent to which the presence of ischemic heart disease may limit the therapeutic response. Although it may not impact the survival benefit of CRT, failure to improve the physiologic response is often a problem for the patient’s expectations of the treatment. It now appears that there are a number of situations where the ventricle is unable to respond to CRT. Scarring, particularly involving the posterior wall, limits response (15,16), and extensive myocardial scar or lack of contractile reserve may also pose a problem (17). Ventricles that are at the extremes of left ventricular enlargement have been shown in previous studies to be unlikely to respond to myocardial revascularization and similarly may be unlikely to respond to CRT. The presence of extremes of dysynchrony may have a similar effect (18,19). Likewise, shorter QRS duration (<150 ms) and non-left bundle-branch block morphology have accumulating support for being associated with the lowest success rates. The presence of severe right ventricular dysfunction and pulmonary hypertension may have a similar effect, as may chronic pulmonary disease, valvular disease, peripheral vascular disease, and end-stage renal disease.

Understandably, the current guidelines reflect the evidence base for CRT. Nonetheless, the algorithm for this needs to be broadened to consider not only the degree of mechanical dyssynchrony, but also features of the left ventricle that will prevent response. Developing the evidence base within the population that we currently implant may be just as important as extending the population to other patients.

**Table 1** Existing and Pending Evidence for New CRT Indications

<table>
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<tr>
<th>Evidence</th>
<th>Pending</th>
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<tr>
<td>Narrow QRS</td>
<td>Favorable single-center studies</td>
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<td>Lack of VO2 change in RethinQ (7) and ESTEEM-CRT</td>
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<td></td>
<td>Favorable results in DESIRE (8)</td>
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<td>Early heart failure</td>
<td>Lack of 12-month response of primary HF composite end point in REVERSE</td>
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<td>(NYHA functional class I to II, EF &lt; 40%, EDD &gt; 55 mm) (8), but EF and volumes improved. Improvement of primary end point at 24 months in subgroup.</td>
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<td>MADIT-CRT (NYHA functional class I to II, EF &lt; 30%, QRS &gt; 130 ms) (9), CRT-D vs. ICD, difference HF + death, no difference in mortality.</td>
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CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; EchoCRT = Echocardiography Guided Cardiac Resynchronization Therapy; EDD = end-diastolic diameter; EF = ejection fraction; ESTEEM-CRT = Evaluation of CRT in Narrow QRS Patients With Mechanical Dyssynchrony From a Multicenter Study; HF = heart failure; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; RAFT = Resynchronization/Defibrillation for Ambulatory Heart Failure Trial; RethinQ = Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS; REVERSE = Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction.


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REFERENCES


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