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EDITORIAL COMMENT

Predicting Benefit From CRT

When Is it Too Little, Too Late?*

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Cardiac resynchronization therapy (CRT) is a standard adjunctive treatment for patients with symptomatic heart failure, significant left ventricular (LV) systolic dysfunction, and delayed ventricular conduction as manifest by an increased QRS duration (1,2). Despite the clear utility of CRT in preventing death, reducing hospitalizations for heart failure, and enhancing quality of life (3), approximately one-third of CRT recipients do not appear to derive a measurable benefit from this therapy (4). The issue of nonresponse to CRT is complicated by variability and marked discrepancy in how response to CRT is defined in various studies (5), the notion that patients who do not clearly benefit, but do not worsen, after CRT are considered as responders by some (4), and the wide array of factors that are known to modify the benefit from CRT in individual patients (6). Nonetheless, the quest to better identify which patients with heart failure are most likely and least likely to benefit from CRT is a laudable goal given the cost, complexity, and challenging long-term management of these patients (7). Improved LV systolic function and reduced LV systolic/diastolic dimensions are often used as a measure of benefit for CRT. These remodeling outcomes have the clear advantage of being quantifiable, having reasonable reproducibility, and, most importantly, correlating with long-term clinical outcomes in CRT recipients (8). However, hard clinical outcomes are desirable given the lack of a linear relationship between the degree of favorable LV remodeling and long-term clinical outcome.

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Too Little, Too Late?

As reflected in present guidelines for CRT (1,2), many consider that patients with very advanced heart failure symptoms, manifest as intractable heart failure symptoms at rest (i.e., nonambulatory New York Heart Association functional class IV), do not clearly benefit from CRT. While these patients have a high risk of death, CRT is not indicated due to a lack of evidence regarding its efficacy (i.e., their heart failure is too advanced and CRT is too little, too late). Furthermore, the presence of advanced chronic kidney disease (9) and other comorbidities (10) are associated with poor outcomes in CRT recipients. These patients were largely excluded from the pivotal guidelines from which CRT indications were derived. Thus, the decision to implant a CRT system in such a patient is driven by other factors, chiefly clinical judgment. Hence, it would seem reasonable to hypothesize that patients with very severe LV systolic dysfunction, manifest as severely compromised LV systolic function or marked LV dilation, may not benefit from CRT to the same extent as patients with more modest impairment in LV systolic function.

Relationship Between Baseline LV Size and Function and Response to CRT

There is both data supporting and data refuting the notion that severely compromised LV systolic function is associated with a lesser response to CRT. In addition to the work cited in the paper by Carluccio

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et al. (11) in this issue of *iJACC*, António et al. (12) reported that patients with very favorable LV remodeling (i.e., CRT *super-responders*) had smaller baseline LV end-diastolic and -systolic volumes versus CRT recipients who experienced lesser benefit. Likewise, the SCART (Selection of Candidates for CRT) study investigators found that a smaller baseline LV end-diastolic volume was associated with a more favorable outcome after CRT than were larger volumes. However, baseline LV volumes were neither an overly sensitive nor specific predictor of response to CRT, making the translation of these findings into clinical practice problematic (13). In contradistinction, baseline LV ejection fraction and differences in LV end-systolic and -diastolic dimensions did not discriminate between patients with better or poorer long-term clinical outcomes in the pivotal CARE-HF (Cardiac Resynchronization in Heart Failure) trial (14) or in another large cohort study recently published by Shanks et al. (15). Furthermore, Vidal et al. (16) reported that larger, not smaller, LV end-diastolic volumes were predictive of a greater likelihood of clinical response to CRT. Thus, additional data are needed to better understand the relationship of baseline LV systolic function and subsequent response to CRT.

Should Baseline LV End Systolic Volume Index be Used to Select Patients for CRT?

Carluccio et al. (11) report the outcomes of 78 patients with heart failure. LV parameters were evaluated at baseline and again 6 to 8 months after CRT using echocardiography. In addition to the standard criteria for CRT implantation (symptomatic heart failure, severe LV systolic dysfunction, and QRS duration ≥120 ms), patients in this study were required to have echocardiographic evidence of mechanical dyssynchrony on tissue Doppler imaging. The majority of patients had a nonischemic etiology of LV systolic dysfunction, the mean QRS duration was 165 ms, and more than one-quarter of patients had only minimally symptomatic heart failure. Patients were followed an average of 40 months and the outcomes assessed were cardiac death and hospitalization for heart failure.

Change in LV ejection fraction at follow-up was found to be independently and negatively associated with the baseline LV end-systolic volume index ($p = 0.001$). Moreover, baseline LV end-systolic volume index was identified as the most powerful predictor of clinical events (hazard ratio 2.5 for patients with LV end-systolic volume index values above vs. below the study population median). Clinical events rates rose with increasing LV end-systolic volume index. Patients with the lowest values at baseline had an event rate that was approximately one-fourth that of patients in highest tertile of LV end-systolic volume index (6.3% vs. 23.8%). Patients in the middle tertile had intermediate event rates (10.2%).

The work by Carluccio et al. (11) adds important information to the existing and discrepant results in this area. As with all studies, there are limitations to their work. In addition to the limitations noted by the authors, drop out was significant, with 17 of 95 patients (18%) being excluded or lost to follow-up. Moreover, important factors that may impact long-term clinical outcome such as comorbid illness, chronic kidney disease, along with the presence and extent of myocardial scarring were not reported in the paper or adjusted for in the statistical models. Finally, the characteristics of patients in their study differ from those of patients in recent pivotal clinical trials (MADIT CRT [Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy], RAFT [Resynchronization in Ambulatory Heart Failure Trial]). Nonetheless, the results presented add to a growing literature regarding the relationship between severely compromised LV systolic function and outcome after CRT.

Carluccio et al. (11) conclude that "despite the presence of intraventricular dyssynchrony, patients with more [a]dilated LV enjoy no or limited benefit after implant." Although this conclusion does reflect their results, there are a number of caveats that need to be considered. It is difficult to tease out the importance of individual predictors in a relatively small study, such as that by Carluccio et al. (11). This is particularly relevant when the population includes a diverse range of patients. For example, most patients had a nonischemic etiology of their LV systolic dysfunction and it is unclear whether their findings apply equally well to patients with an ischemic etiology. The authors stress the value of limiting enrollment to patients with documented intraventricular dyssynchrony, but the role of echocardiographic assessment of dyssynchrony is unclear at present. Furthermore, more complex analysis of LV and right ventricular geometry, LV systolic and diastolic function, and the extent of myocardial scarring may be helpful in identifying patients more likely or less likely to respond to CRT. Finally, it is premature to deprive a patient of a potentially beneficial and life-extending therapy such as CRT based on a single measure such as the LV end-systolic volume index.

It is undoubtedly true that some patients are too sick to benefit from CRT. The challenge at present is *how do we reliably identify these patients*? While the work by Carluccio et al. (11) adds to a growing literature in this area, it is too early to rely on LV end-systolic volume index or any other parameter, possibly aside from QRS duration, in guiding the prescription or nonprescription of CRT. However, the work by Carluccio et al. (11) will undoubtedly aid in the design of larger, more definitive studies where LV end-systolic volume index and other parameters can be prospectively assessed on a representative population of CRT recipients in order to determine which parameters or combination of parameters can be used to identify, with certainty, those patients more likely or less likely to benefit from CRT.

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