Delayed Response to Cardiac Resynchronization
Better Late Than Never*

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Cardiac resynchronization therapy (CRT) has become a cornerstone of treatment in heart failure patients with reduced left ventricular (LV) systolic function and left bundle branch block. Although CRT has been shown to improve LV size and function, reduce symptoms and hospitalizations, and improve survival (1,2), >30% of patients do not experience clinical improvement after implantation of a CRT device (3). In this issue of JACC: Heart Failure, Burns et al. (4) investigate the incidence and clinical outcomes of delayed echocardiographic response to CRT. In this single-center, retrospective study, the authors identified 294 patients who had echocardiograms ~1 year after implantation and ≥3 years after implantation. Patients with a reduction in left ventricular end-systolic volume (LVESV) ≥15% were defined as responders. At 1 year, 174 (59%) patients had a ≥15% LVESV reduction (mid-term responders). Of the 120 nonresponders at 1 year, 52 (43%) experienced a delayed positive response (long-term responders). Long-term responders had mortality and hospitalization rates similar to mid-term responders, and these rates were significantly better than the rates of nonresponders.

The study design has some limitations, including the exclusion of more than one-third of patients who did not have long-term echocardiograms (4). Patients who have worsening symptoms and present again to the clinic or emergency department are more likely to have follow-up imaging, skewing the data to include sicker patients. Because there was no standardization for imaging follow-up, the exact time course in a given patient cannot be charted or compared with other patients. Echocardiograms were not performed at a core laboratory, and echocardiogram readers were not blinded to the timing of CRT device implantation.

Because of the study design (4), we can only speculate about the reasons for the delayed response to CRT in this subset of early nonresponders. One potential reason is that some patients may truly have slow LV improvement from CRT. The time course of response to CRT likely occurs on a continuum, and some patients may be on the tail-end of the response curve. Doppler imaging performed early after implantation of the CRT device suggests that improvement of LV dyssynchrony plays a critical role in the development of reverse remodeling, which leads to decreases in LVESV (5). CRT responders who have a >15% decrease in end-systolic volume exhibit LV volume decreases at 3 months that continue to improve at 6 months, suggesting that CRT can stop the cycle of negative remodeling and instead initiate a positive succession of reverse remodeling and further resynchronization (6). It is possible that in some patients undergoing CRT, the positive cycle of reverse remodeling occurs very slowly, and significant improvements measured by echocardiography are not detected until after more than 1 year. Long-term follow-up of patients with peripartum cardiomyopathy found that LV recovery continues well beyond the first 6 to 12 months into the second and third year after diagnosis (7). Although the

*Editorials published in JACC: Heart Failure reflect the views of the authors and do not necessarily represent the views of JACC: Heart Failure or the American College of Cardiology.

From the Division of Cardiology, Virginia Commonwealth University Pauley Heart Center, Richmond, Virginia. Dr. Ellenbogen has received honoraria, consulting fees, and research grants from Medtronic, Boston Scientific, and St. Jude Medical; and honoraria and consulting fees from Biotronik. Dr. Kron has reported that she has no relationships relevant to the contents of this paper to disclose.
etiology of peripartum cardiomyopathy is unknown, the protracted time course of healing suggests that the myocardium is capable of functional improvements long after an initial insult. In cases in which the left bundle branch block is a causative or aggravating factor for cardiomyopathy, functionally removing the left bundle branch block through biventricular pacing may initiate a long process of recovery. Similar to findings in many CRT trials, 41% of the patients in the study by Burns et al. (4) were nonresponders at 1 year. There are numerous potential causes for nonresponse to CRT. Many physicians have either a formal or informal troubleshooting strategy they use to diagnose and treat factors that may be contributing to lack of clinical response. Possible causes for nonresponse include atrial fibrillation, volume overload, cardiac ischemia, loss of right ventricular or LV lead capture, and atrioventricular or interventricular dyssynchrony; these factors have been reviewed in the European Heart Rhythm Association/Heart Rhythm Society expert consensus statement on CRT in heart failure (8,9). In the study by Burns et al., 32% of the included patients had atrial fibrillation. The number of patients who received antiarrhythmic drug therapy, pulmonary vein isolation, or atrioventricular junction ablation during the study period was not noted. Biventricular pacing >90% confers a reduced risk of heart failure and death, and recent data show that biventricular pacing ≥97% yields an additional reduction in risk of heart failure and death (10). Routine follow-up after device implantation could have led to rate or rhythm control strategies to increase the amount of biventricular pacing. These strategies may have been implemented and optimized over months to years. Similarly, treatment of premature ventricular contractions, which can also lead to a decreased amount of biventricular pacing, may have been instituted in some patients over the study period. One-half of the patients in the trial had known ischemic disease (4), and medication adjustments or interventions to treat ischemia may have been performed in nonresponders. Although there was no difference in the proportion of long-term responders versus nonresponders receiving a new prescription or dosage increase in beta-blockers or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, a subset of delayed responders may have achieved significant clinical benefit from late optimization of heart failure medical therapy. Device reprogramming or interventions were not evaluated in this study, and patients with suboptimal initial programming or lead malfunction may have fared well long term after system modification. Conversely, patients who are nonresponders due to a problem that is not easily correctable are unlikely to have long-term improvement even after their physician “troubleshoots” their lack of response to CRT. For example, a patient with an LV lead that is positioned anteriorly, apically, or in scar tissue would not be expected to become a long-term responder unless the lead is repositioned or another factor is addressed that is preventing LV remodeling, independent of the CRT (e.g., ischemia, heart failure optimization).

In their thought-provoking research, Burns et al. (4) identify a subset of patients with heart failure who have a delayed echocardiographic response to CRT. Importantly, the survival and hospitalization rates of these patients match those with earlier responses to CRT. Due to the limitations of the study, the mechanism of the delayed response cannot be determined and, in fact, may be different in different patients. Although future research should be designed to elucidate the reasons for the delayed response, the findings are meaningful even without fully understanding the etiology. In a real-world group of CRT nonresponders, standard of care treatment (including device troubleshooting, arrhythmia control, and heart failure medication titration) could lead to delayed echocardiographic response to CRT that portends an improved clinical outcome. The authors showed that for patients with heart failure, having an echocardiographic and clinical response to CRT is, in fact, better late than never.

**REPRINT REQUESTS AND CORRESPONDENCE:**

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KEY WORDS cardiac resynchronization therapy, nonresponders