Cardiac resynchronization therapy (CRT) is an exciting advance for heart failure patients. As a result of a wealth of evidence from randomized clinical trials, guidelines for selecting patients for CRT have been established, including the New York Heart Association functional class III or IV on optimal medical therapy, QRS width $\geq 120$ ms, and ejection fraction $\leq 35\%$.\(^1,2\) The landmark Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial published in 2002 reported a 67% improvement in the group randomized to CRT using a clinical composite score in which patients were judged to be improved, unchanged, or worsened.\(^1\) Interestingly, the very recent Frequent Optimization Study Using the QuickOpt Method (FREEDOM) trial, designed to assess strategies for atrioventricular (AV) and interventricular (VV) interval optimization, reported a 67.5% improvement after CRT using the same clinical composite score.\(^3\) Despite tremendous advances in knowledge and experience with CRT, the proportion of patients considered clinical nonresponders has remained at one third over the last 8 years. Puzzling questions remain: Why are there nonresponders to CRT? Can we improve on current patient selection for CRT to reduce nonresponders? The important article by Delgado et al\(^4\) in this issue finds some pieces of the puzzle of nonresponse by focusing on a large series of patients with ischemic heart failure. They reported that mortality and heart failure hospitalizations after CRT in patients with routine indications are associated with dyssynchrony, left ventricular (LV) lead position, and estimates of regional scar. It is worthwhile to consider these factors individually, in combination, and in context of other variables that may influence response to CRT (the Figure).

**Lack of Dyssynchrony**

There is an abundance of data to support dyssynchrony as the major pathological derangement associated with mechanical inefficiency and deleterious biological effects that are improved by CRT.\(^5,6\) However, because clinical trials have used QRS widening as a surrogate for mechanical dyssynchrony, controversy as to its role in response to CRT has remained. This debate has centered on the perplexing dissociation between electric dispersion measured by QRS width and degree of mechanical dyssynchrony, usually measured by echocardiographic methods.\(^5\) Two negative studies in particular have influenced popular opinion regarding echocardiographic dyssynchrony and CRT: the Predictors of Responders to Cardiac Resynchronization Therapy (PROSPECT) study,\(^7\) and the Resynchronization Therapy in Normal QRS (RethinQ) trial, the first randomized trial of CRT in patients with narrow QRS width.\(^8\) PROSPECT revealed the technical complexities of echocardiographic methods for predicting response in patients with routine CRT indications.\(^7\) RethinQ used tissue Doppler and M mode to detect dyssynchrony in patients with narrow QRS, but failed to show a conclusive benefit of CRT using a relatively small sample size and a short follow-up of 6 months.\(^8\) The study by Delgado et al used the newer speckle tracking approach to assess dyssynchrony by radial strain\(^9,10\) and examined important long-term outcome after CRT. Delgado et al observed that the absence of significant dyssynchrony, defined as anteroseptal to posterior wall peak radial strain delay $\geq 130$ ms, was associated with less favorable all-cause mortality when considered alone or when combined with heart failure hospitalizations.\(^4\) The recent Speckle Tracking and Resynchronization (STAR) multicenter study supported the utility of speckle tracking radial strain to be associated with short-term and long-term outcomes after CRT.\(^11\) More recently, we reported our single-center experience in 229 CRT patients, associating the presence of echocardiographic dyssynchrony at baseline with freedom from death, heart transplantation, or LV assist device implantation over 4 years.\(^12\) Dyssynchrony by routine pulsed Doppler, tissue Doppler, and speckle tracking measures was significantly associated with long-term event-free survival. The present report by Delgado et al extends these observations that dyssynchrony by speckle tracking is predictive of outcome in patients with ischemic cardiomyopathy after CRT.\(^4\) However, speckle tracking can be technically challenging, particularly in regions of scar in which signal amplitude is markedly reduced. These data from Delgado et al demonstrate that speckle tracking information from an experienced laboratory has prognostic utility in CRT patients with ischemic cardiomyopathy.

**Myocardial Scar**

Delgado et al also demonstrated the utility of speckle tracking radial strain as an estimate of scar using a single short-axis plane at the mid-LV level.\(^7\) They associated a reduction in wall thickening $\leq 16.5\%$ to regions of scar on the basis of their previous work with gadolinium-enhanced cardiac magnetic resonance imaging.\(^13\) They reported that patients with...
LV lead tip position associated with segments of reduced strain had a less favorable long-term outcome. Although experience with speckle tracking for estimating scar is limited, this group also previously reported the association of scar location by cardiac magnetic resonance with LV lead positioning and response to CRT. Accordingly, their present work on a larger series of patients extends the concept that LV lead position in a region of potential scar is related to a poor clinical outcome. A limitation of speckle tracking, like other resting LV functional measures, is its inability to differentiate hibernating or stunned myocardium from scar. However, these limitations did not appear to be problematic in their study of chronic heart failure patients with ischemic cardiomyopathy.

Global scar burden in patients with ischemic cardiomyopathy appears to be another important determinant of response to CRT. Adelstein et al15 used the clinically widespread technique of single photon emission tomography imaging to assess scar burden in CRT patients. A large scar burden by single photon emission tomography thallium, defined as a summed rest perfusion score \( \geq 27 \), was associated with a poor prognosis after CRT. Furthermore, large scar burden appeared to be a more closely associated with outcome than dyssynchrony in patients with ischemic cardiomyopathy, underscoring the impact of scar on response to CRT.

**Lead Position**

It has been logical to assume that the anatomic location of the LV lead associated with the site of latest mechanical activation will result in optimal resynchronization. However, the clinical routine is to place the LV lead through the coronary sinus and to target the anatomic posterior or lateral LV region. On one hand, patients may have a large “sweet spot” where the LV lead may be placed and result in similar beneficial effects of CRT. In other words, it may be less important to target a specific anatomic region for LV lead placement, in particular in patients with nonischemic cardiomyopathy. On the other hand, LV lead positioning may be more important in patients with ischemic disease with heterogeneous regions of scar tissue adjacent to relatively preserved myocardium. The study by Delgado et al supports the association of LV lead positioning with the site of latest mechanical activation for achieving a more favorable response to CRT. This group used strain from the mid-LV short-axis plane to assess the site of latest mechanical activation, and used chest roentgenograms to estimate LV lead position. Although these approaches lack the spatial resolution for anatomic precision, the majority of their patients had mid-LV lead tip positioning (versus basal or apical locations), and the mid-LV short-axis plane often includes the site of latest mechanical activation, as shown by 3-dimensional techniques in other studies. Accordingly, the temporal regional strain information as it relates to LV lead position appears to have additive prognostic information. The ability to target anatomic LV lead positioning at the site of latest mechanical activation is limited by the accessibility of suitable epicardial coronary veins, although the possible evolution of epicardial or LV endocardial lead positioning in the future may overcome these anatomic restraints.

**AV and VV Optimization**

Another piece of the nonresponse puzzle has been AV and VV optimization after CRT, because these intervals must be programmed to deliver the therapeutic effects of CRT. The routine optimization approach has been to use echocardiographic Doppler measures of mitral inflow velocity and LV outflow velocity as markers for LV filling and ejection. Recent advances in automated device-based intracardiac ECG approaches have increased interest in AV and VV optimization. Unfortunately, the magnitude of contributions of AV and VV optimization to response to CRT is difficult to ascertain, because most clinical trials have incorporated echocardiographic Doppler optimization as their clinical routine. Existing data suggest that a minority of patients may have a major impact from AV and VV optimization, and that optimization has a modest effect on most patients. Recent preliminary data from the FREEDOM trial reported no differences in clinical outcome in patients randomized to frequent device-based AV and VV optimizations versus a routine optimization strategy. It appears that AV and VV optimization may not represent as large a piece of the nonresponse puzzle as other factors discussed.

**Irreversibly Advanced Heart Failure**

Although emerging data on dyssynchrony, scar location, scar burden, and LV lead position have enhanced our understanding of nonresponse to CRT, other pieces of the puzzle remain missing. Large randomized clinical trials and clinical experience have suggested that a subset of patients who meet current selection criteria have irreversibly advanced heart failure that will not respond to CRT. Current guidelines include New York Heart Association functional class IV patients, and there is no lower limit for ejection fraction accompanied by heterogeneous responses to CRT. Unfortunately, there is no simple means to identify patients who may have LV dysfunction that is too far advanced to reverse remodel, or who are on a relentless course of clinical deterioration that cannot be altered by CRT. Work continues to identify other missing pieces of the puzzle of CRT nonresponse.
Putting the Pieces Together

Currently, there is great motivation to pursue prospective recognition of nonresponders to CRT. Accurate identification of CRT nonresponders may prevent the risk of serious complications, such as coronary sinus dissection, and save the additional costs associated with the LV lead and CRT hardware rather than defibrillator implantation alone. The magnitude of clinical trial evidence has resulted in a strong basis of support for current selection criteria for CRT. However, the nonresponse rate remains at one third despite advances in procedural expertise and experience. Patients with ischemic heart failure represent a special challenge to predicting response because coronary disease is progressive, and future ischemic events are unrelated to CRT. The study by Delgado et al4 extends our understanding of nonresponse to CRT in patients with ischemic heart failure by demonstrating that dyssynchrony, scar location, and LV lead positioning are additive in their association with long-term outcome. This new information adds another piece to the puzzle of understanding nonresponse to CRT, which should eventually translate to continued improvements in patient care.

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References


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