Cardiac resynchronization therapy (CRT) is a highly effective treatment for some patients with heart failure. Current guidelines recommend the implantation of CRT devices in patients with left ventricular (LV) dysfunction and electrical dyssynchrony, evidenced by a left bundle branch block (1). Unfortunately, not all patients suitable for CRT derive symptomatic benefit—an unsatisfactory situation, because device implantation is costly and carries a small risk.

Despite the failure of previous CRT selection strategies involving echocardiographic techniques (2), there have been continued efforts to predict those most likely to benefit. Because device implantation itself provides a placebo effect, responsiveness has been defined on the basis of imaging changes or survival benefit. There are problems with this approach (3). The use of imaging to identify reverse remodeling or improvement in ejection fraction is limited by the test-retest reliability of the reference measurement. The statistical challenges of using echocardiography for identifying CRT response have been previously emphasized in jJACC (4). Moreover, the additional problem of using reverse remodeling as an endpoint is that a 15% change of a severely remodeled LV is substantially different biologically from that in a small ventricle. Unfortunately, arguing for CRT responsiveness based on survival is also problematic. In the absence of a control group, it is impossible to discern whether treated patients would have survived for a shorter time frame had a device not been implanted.

Of the 3 aspects of synchrony that may be improved by CRT (atrioventricular [AV] delay, interventricular delay, and intraventricular delay), most previous attempts to use mechanical synchrony as a response marker have focused on the latter. In fact, AV synchrony may be the most important, at least in terms of the benefits of optimization (5). The consequences of left bundle branch block explain the mechanical markers of intraventricular dyssynchrony. Transient premature activation of the septum and delayed activation of the lateral wall causes inefficient contraction (6). Previous efforts to predict CRT response have been compromised by the limitations of methods for measuring mechanical dyssynchrony. The initial attempts for this assessment were based on imaging tests to measure intraventricular delay. As these delays are short, methods of high temporal resolution were used, such as M-mode and tissue Doppler (6). Despite success within individual centers, these technically challenging and relatively noisy methods were not well-suited to this purpose, and a large multicenter study showed them to be unable to provide useful predictive information (5). In addition, most such studies focused on single parameters.

In this issue of jJACC, investigators from Spain (7) present the findings of a study of 200 CRT recipients who were examined for 3 previously validated markers of intraventricular, interventricular, and AV dyssynchrony (8). In this study, intraventricular dyssynchrony was evidenced by septal flash, defined as a rapid contraction and relaxation of the septum occurring during the isovolumetric contraction period. This finding is analogous to other myocardial motion markers that reflect dyssynchrony, such as apical rocking (9). Dyssynchronous interventricular motion was identified by exaggerated right-left interaction (abnormal passive motion of the septum). Long AV delay was identified by the presence of fused...
E and A waves and diastolic mitral regurgitation, and short left AV delay by A-wave truncation. Those with a correctable abnormality were shown to have more reverse remodeling at 12 months and better survival over an average of 3 years. The predictive value of these findings was independent of other predictors (renal function, LV size, functional class, and transmural extent of scar).

These results emphasize that a number of cardiac findings, other than just synchrony markers, appear to influence CRT responsiveness. Clinical variables are important; in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) population with mild heart failure, prior hospitalization for heart failure, female sex, and nonischemic etiology were important predictors of response, independent of left bundle branch block, QRS duration, and LV and left atrial volumes (10). As shown in this study, imaging of myocardial scar may be of value. The extent of myocardial scarring can facilitate the prediction of reverse remodeling or functional improvement, and the localization of scar to the posterior wall is an important predictor of CRT nonresponse (11).

In addition to the LV markers used in this study, a neglected association of reverse remodeling is the status of the right ventricle (12). Both RV size (end-diastolic area index \(>10.0 \text{ cm}^2/\text{m}^2\)) and RV dysfunction (fractional area change \(\geq35\%\)) are important independent predictors of failure of reverse remodeling. Additionally, LV function (measured as global longitudinal strain, cutoff \(<-7\%\)), and left atrial size area \(<26\text{ cm}^2\) are important determinants of response. The site of the implanted pacemaker lead is an important determinant of response (13)—mal-located leads have been documented as a source, not of only nonresponse, but also of deterioration. Targeting the lead to the site of maximum dyssynchrony has been known for several years to maximize the chances of success (14). All of these considerations reinforce the need to consider, not only dyssynchrony, but also a variety of other imaging parameters.

These new markers of cardiac synchrony as well as the other cardiac findings associated with CRT responsiveness are fruits of ongoing efforts to improve patient selection for CRT. Despite these positive findings, however, more work needs to be done before this approach can be incorporated into patient selection. First, we need to remain mindful of the perils of single-center studies, especially given that the shortcomings of previous synchrony markers were exposed in the PROSPECT (Predictors of Response to CRT) study (2), so this work needs to be repeated in a multicenter trial. Second, markers of CRT responsiveness need also to be found to predict improvement of functional capacity and quality of life, as this (maybe even more than remodeling and survival) is the motivation for CRT implantation in many patients. New “responder analysis” strategies (15) will provide information about what we and our patients really want to know—whether they will feel better.

The underutilization of CRT is probably based upon the fact that its expense is hard to justify when a substantial number of patients—at least 30\% (in this study, 50\%)—fail to respond. Historically, the rationalization of failure to more appropriately select patients for therapy has been based on the argument that intervention showed a prognostic benefit in the studied populations, raising the specter of fatal consequences of not providing therapy. The current acceptance in the guidelines of CRT implantation into a large number of nonresponders, in order to provide benefit to some patients, carries an opportunity cost for provision of other services in most resource-constrained health systems, and seems unlikely to be a sustainable strategy. Perhaps after the additional developments mentioned in the previous text, imaging markers will enter the guidelines for CRT implantation.

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