Corrected mechanical dyssynchrony is believed to be the primary mechanism by which cardiac resynchronization therapy (CRT) improves clinical status and reduces left ventricular (LV) volume. The use of QRS duration as a surrogate for mechanical dyssynchrony has been intensely investigated, based on the suspicion that a direct measurement of mechanical rather than electric dyssynchrony might be more relevant in CRT. Indeed, although the majority of patients improve after CRT using the current treatment criteria, significant numbers of patients do not appear to derive a detectable benefit, either clinically or structurally. Conversely, there are patients with normal QRS who manifest mechanical dyssynchrony by echocardiographic techniques. Therefore, various imaging-based methods of detecting segmental systolic timing have been developed to enhance the sensitivity and specificity of patient selection criteria for response to CRT.

Multiple relatively small studies have shown a high correlation between numerous echocardiographic measures and LV reverse remodeling. These methods generally use M-mode, cardiac cycle intervals, tissue Doppler (TDI)-derived velocities, and speckle tracking–based strain. However, when tested in a larger, multicenter study, Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT), these findings were not confirmed. The study concluded that at the time (May 2008), echocardiographic measures of dyssynchrony should not be widely incorporated in patient selection and that treatment criteria should remain those established by the landmark trials of CRT. In retrospect, this finding is not entirely surprising, given subsequent studies in which significant proportions of normal control patients were measured to have dyssynchrony using the existing methods, and, in fact, the mean value for standard deviation of time to peak tissue velocity (TV-SD) in 122 healthy patients was found to be above the cutoff for dyssynchrony. The authors of PROSPECT did not recommend that imaging-based dyssynchrony measures had no validity and should be discarded. Rather, the authors thought that at the time of the study, the accurate and reliable applications of these methods required too much training, time, and dedication to be widely incorporated into general practice. After all, QRS-based treatment criteria had revolutionized therapy of advanced heart failure patients, and to improve on that standard would be a tall order. Nonetheless, among the criticisms of PROSPECT included an impassioned editorial in which PROSPECT is suggested to have “major flaws such that it is effectively a study of laboratory error rather than a test of a hypothesis.” In a more reasoned commentary, Bax and Gorcsan have attempted to provide perspective and suggest future directions. They categorize potential pitfalls encountered in generalizing the dyssynchrony methods: patient selection, technical issues, and pathophysiological issues. Assuming that correction of dyssynchrony is in fact the basis of CRT effect and that the echocardiographic measures indeed measure dyssynchrony, the set of suggestions put forth in this article are a reasonable basis for further study.

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Echocardiographic Assessment of Dyssynchrony
Moving Forward

Review of Miyazaki et al
In the current issue of Circulation: Heart Failure, Miyazaki et al at the Mayo Clinic present the findings of a single-center, prospective evaluation of the relationship between multiple echocardiography-derived parameters (more than in any study to date) and outcomes after CRT. One hundred thirty-one patients with heart failure receiving CRT were extensively investigated at baseline and 6 months with 2 echocardiograms (conventional, tissue Doppler, speckle tracking imaging with the GE platform, and real-time 3D imaging with the Philips machine), 6-minute walk test, Minnesota Living with Heart Failure Questionnaire (ML-WHFQ), and cardiopulmonary exercise testing. Dyssynchrony evaluation consisted of techniques based on M-mode (1 method), tissue velocity (2 methods), TDI-based strain (2 methods), 2D speckle tracking–based strain (4 methods), 3D imaging (1 method), and major cardiac time intervals (4 intervals). Patients were categorized as a reverse remodeling responder at 6 months if LV end-systolic volume was reduced by ≥15%. Binary definitions of response for the secondary endpoints were >10% improvement in MLWHFQ, 6-minute walk test, and cardiopulmonary exercise test.

Baseline patient characteristics hold no major surprises. With regard to outcomes, LV end-systolic volume was reduced by 21% after 6 months of CRT (20% in PROSPECT), and the percentage of patients with ≥15% reduction of LV end-systolic volume is 55 (56% in PROSPECT). Feasibility of obtaining adequate baseline dyssynchrony measurements varied from a low of 65% (circumferential and radial speckle tracking) to 98% (cardiac timing intervals). Generally, feasibility was higher in the Miyazaki study that...
was performed at a single, highly experienced center compared with PROSPECT. Furthermore, Miyazaki et al included the newer methods and techniques that were not available at the time of PROSPECT, speckle tracking and 3D imaging. It is of interest that these methods’ feasibility rates were the lowest in the study, although the criteria used to exclude a study for analysis were relatively stringent (>2 longitudinal or >1 circumferential or radial segments that were suboptimal). Variability analyses showed the measures with the lowest feasibility demonstrated the greatest variability (speckle tracking and 3D imaging). Both intraobserver and interobserver variability were greater in PROSPECT than in Miyazaki et al for the parameters that were common: pre-ejection period, standard deviation of time to peak of 12 segments (Tv-SD), and septal-posterior wall motion delay.

All 15 putative “predictors” of reverse remodeling are analyzed for correlation with the outcome, sensitivity and specificity, as well as area under the receiver operating characteristic curve (AUC). The 4 measures in common between Miyazaki et al and PROSPECT demonstrate qualitatively similar AUC: septal-posterior wall motion delay, 0.63 and 0.62; pre-ejection period, 0.67 and 0.59; tissue Doppler septal-lateral delay, 0.5 and 0.61; and Tv-SD, 0.61 and 0.55, respectively. In fact, the best AUC are noted with the simple time intervals and the TDI strain methods. These comparatively similar AUC: septal-posterior wall motion delay.

Comparison With PROSPECT
Miyazaki et al have addressed some of the pitfalls encountered in PROSPECT. First, there was the potential variability introduced by using multiple investigators, echocardiographic vendors, and core laboratories. Indeed, observed intraobserver and interobserver variability are less than in PROSPECT, although there remains a concern that the newest techniques, (3D and speckle tracking imaging) have relatively low yield and reproducibility. This may represent a barrier for widespread use of these methods, even if they could be proven to be of significant clinical benefit before CRT. Furthermore, the criticism that the PROSPECT investigators and core laboratories were not adequately experienced with tissue Doppler techniques is not valid for Miyazaki et al, who are a dedicated group experienced in the appropriate techniques. There were concerns that in PROSPECT, significant number of patients had an ejection fraction >35% and relatively small LV diameter when baseline studies were remeasured by the core laboratories and that these patients might have negated the potential of echocardiographic predictors of response. Miyazaki et al do not report LV diameters, but severely dilated volumes (LV end-diastolic volume, 212 mL) and low ejection fraction would suggest an advanced heart failure population, further evidenced by peak oxygen consumption of 13.7 mL/kg/min.

Lingering Questions
The first question to ask is whether application of the resources necessary for such evaluation is clinically warranted. If approximately 70% of the treated patients improve clinically, and 50% to 60% improve structurally, then does that require an exhaustive search to find reasons to exclude patients from therapy? Given the severity of the disease state and the fact that many of these patients will receive an implantable device anyway, the threshold for further costly, time-intensive workup should be necessarily high. Nonetheless, the search for accurate, evidence-based enhancements to clinical practice is difficult to criticize.

Second, echocardiographic dyssynchrony parameter development has been predicated on the hypothesis that correction of mechanical dyssynchrony is the underlying mechanism of CRT action. Although that may be true in significant proportion of patients, there are other plausible hypothesized mechanism of action of LV pacing, including chronic pre-excitation of dysfunctional delayed regions19,20 and enhancement of contractility and relief of external constraint.21 Furthermore, the anatomy of dyssynchrony probably is more complex in the ischemic patient, requiring more in-depth analysis before optimal pacing configuration can be determined. These issues point out the pitfalls of using echocardiographic measures of one particular form of mechanical dyssynchrony in attempting to predict response to an intervention that is likely to be far more complex.

Third, are the dyssynchrony parameters measuring mechanical dyssynchrony? If so, what other factors affect these measures? As shown by Fornwalt et al,18 these measures do not correlate well with each other, suggesting that whatever phenomenon being measured by these echocardiograms is not a black and white event with well-defined borders. Hypothetically, if measures A, B, and C are not correlated with each other, and yet, predict response to similar degrees, then A, B, and C are probably not measuring the same phenomenon.

Future Directions
Because indications for CRT are likely to expand beyond New York Heart Association class 3 to 4 (based on results of REVERSE22 and MADIT-CRT23), QRS >120 (ongoing EchoCRT trial) and ejection fraction ≤35% (exploratory subanalysis of PROSPECT of ejection fraction >35% patients24), resulting in both more responders and nonresponders, it becomes even more important to develop tools to fine-tune patient selection. Newer methods of using current technologies, such as meaningfully combining scar burden and location with cardiac venography and regional function may yield greater ability to distinguish those who are more or less likely to benefit from CRT. To interpret CRT response in a more clinically relevant way, on a continuum rather than a binary scale, would be helpful in practice.25 Are there new technologies that might be more powerful than the previously
described echocardiographic methods? Although methods based on time to peak strain are sensitive to noise and the influence of outliers, an alternative approach is measurement of temporal uniformity of strain, whereby a time plot of regional strains, arranged for LV location is subjected to Fourier analysis.26 Dyssynchrony index by circumferential temporal uniformity of strain was more reproducible and yielded greater AUC for response than time to peak strain methods.26 The cross-correlation delay method in which all data points from the velocity curves are incorporated, rather than a manual selection of peak velocities, appears to be a better discriminator of dyssynchrony between control subjects and CRT responders, although its ability to predict CRT response is only marginally better than the conventional TDI-based methods.27

Conclusion
The first generation of echocardiographic methods to assess mechanical function before CRT appears to be weakly correlated with outcomes as determined by various clinical parameters and reverse remodeling. There are enough conflicting data to demonstrate that they should not be used routinely for CRT patient selection. The second generation of methods based on strain appears to be more powerfully correlated with outcomes, although variability, sensitivity, and specificity appear to be suboptimal. Potential future methods include different ways to analyze echocardiograms as well as different modalities, in particular MRI.

It is possible that in trained hands, some of these measures will be accurate enough to at least enhance the doctor-patient conversations before CRT. If these are ever to be widely incorporated into clinical practice, the echocardiography community must establish training and quality assurance procedures that will lead to accurate data acquisition, measurement, and interpretation.

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References


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