Echocardiographic Predictors of Response to Cardiac Resynchronization Therapy in 2016: Can Quantitative Global Parameters Succeed Where Segmental Parameters of Dyssynchrony Have Fallen Short?

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From almost the time of the initial randomized controlled trials demonstrating a benefit to cardiac resynchronization therapy (CRT) in the early 2000s,1,2 clinicians, investigators, and industry have all been drawn to the concept that quantitative parameters derived from echocardiographic images might be a powerful tool to enhance patient selection. The need for a tool was magnified by the early observation that approximately one third of patients remain nonresponders despite implantation of a CRT device—an observation that remains mostly unchanged today.

The task seemed simple at first: because CRT is designed to resynchronize the mechanical motion of the left ventricular (LV) walls, all one needs is a tool that can measure the degree of dyssynchrony—the patients with the most dyssynchrony should have the most to gain. The high temporal resolution available through M-mode seemed well suited to the task of measuring differences in timing, and some of the earliest reports demonstrated that in patients with a left bundle branch block, a simple parasternal long-axis view with a septal to posterior delay of ≥130 ms on M-mode was associated with an improved likelihood of response to CRT.1 Around this same time, there were significant advances in echocardiographic technology with tissue Doppler that applied Doppler principles to the low velocity of the LV walls (tissue). These quantitative tools display the change in speed or distance over time, allow for simultaneous sampling of multiple sites, have inherent advantages compared with tissue Doppler including Doppler, were unable to match the success of the earlier studies. Most notably, poor reproducibility and controversy surrounding the defined clinical cutoff points of tissue Doppler measurements came more into question at that time as a result of this trial as well as other investigator observations.8

By 2010, the tethering effects and angle dependency of tissue Doppler seemed to be obstacles that might be insurmountable and what seemed to be so simple to measure (dyssynchrony and its association with clinical response) started to appear more complex. In addition, studies on the importance of pacing site location, atrio-ventricular optimization, and infarct burden all started to emerge as important additional variables.

Although some active research on tissue Doppler remains ongoing, the introduction of 2D strain on clinical platforms reinvigorated the field and provided new opportunities with more robust tools to retest old questions (ie, Can dyssynchrony be measured reliably? Can it predict response?). In this issue of Circulation: Cardiovascular Imaging, Delgado-Montero et al9 present the findings of their study, Additive Parameters of Dyssynchrony Have Fallen Short?

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report intraclass correlation coefficient with a range from 0.92 to 0.97) consistent with some of our previous experience. Many of the tissue Doppler formulas to define dyssynchrony were recycled (variations in time to peak strain: septal versus lateral, 5D of 12 segments) with the hope that the superior applicability and reproducibility of 2D strain would have a different result. Although these efforts initially seemed promising, further study which included dyssynchrony indices derived from 2D strain as well as 3D segmental volume curves failed to have strong predictive value for reverse remodeling. Overall, 2D strain has perhaps improved our ability to measure regional LV mechanics and dyssynchrony, but the association with clinical response may not be linear as scar burden, scar location, atrio-ventricular delay, and lead location may all continue to be important variables that are not accounted for in dyssynchrony analysis alone.

The short title for the study by Delgado-Montero et al in this issue is Global Strain in Resynchronization Therapy and represents a major shift away from a measurement of regional differences in timing to a measurement of global function as a predictor of CRT response. Both GLS and GCS represent a quantitative version of global LV mechanics in long axis and short axis, respectively. Although changes in global longitudinal and circumferential mechanics after CRT was recognized by velocity vector imaging >10 years ago, the focus in this field has remained on the differences in regional timing as a predictor of response. However, the current study not only changes the measurement tool (from a regional one to a global one) but also changes the clinical end points traditionally associated with CRT studies. Perhaps this is a reflection of CRT itself which started as a therapy to improve quality of life, but more recent studies demonstrated survival advantages as well. Therefore, survival end points as part of pre-CRT echo analysis studies may at times be appropriate.

Although various studies have proposed different cutoff values for normal, recent American Society of Echocardiography Guidelines suggest that a GLS of ~20% (or more negative) can be expected in a healthy person. The authors selected a predefined cutoff value for GLS of ~9% (or more negative) to be associated with less risk based on previous literature of prognosis in patients with heart failure. The authors applied this same cutoff value in a novel way to a global LV mechanics so the observation that they can outperform left ventricular ejection fraction (Simpson’s biplane) as a predictor of survival in this high-risk population with heart failure and CRT is intriguing. However, the fact that a line in the sand has to be drawn for the GLS/GCS measurements creates a simplified binary clinical classification system of high risk and low risk, but the Cox regression analysis in the multivariable analysis applied GLS and GCS as continuous variables using a forward stepwise method; therefore, it is not entirely clear as to whether the proposed cutoff value still applies in the multivariate analysis and sequential Cox models.

Regardless, assuming that these quantitative measurements of global function in the short axis and long axis are reproducible and have predictive value for long-term prognosis, the question remains as to whether they are helpful beyond just prognosis but also in patient selection for CRT—particularly in the intermediate ECG group. As the authors note, there is no comparison group as a control (ie, a non-CRT group) and the predictive value of GLS and GCS may apply for patients with heart failure in general and not necessarily be specific to CRT. On the contrary, because the nonresponder rate has not significantly changed in over a decade, perhaps it is time to take another approach to both our measurement tools and clinical end points in CRT candidate studies.

Rather than searching to identify regional timing differences and dyssynchrony as a mechanistic target for intervention, recent reports including this one seem to be suggesting that markers of global LV structure and function may place the patient at greater risk and thus greater potential for improvement. At the recent American College of Cardiology 2016, a moderated poster session titled, How to Better Resynchronize the Heart? was started by a study that simply divided the QRS duration by left ventricular end-diastolic
volume and demonstrated an improvement in CRT response that was inversely related to LV size. This was followed by presentations on multipoint pacing and the possible role of lead placement at the site of latest delay—both derived from electric mapping. All of these factors may play a role and the truth may be that a patient population that was once thought to be fairly homogenous with a single mechanism in common turns out to be heterogenous and thus highly variable in clinical response, but global markers of risk may remain useful.

There may be a paradigm shift occurring in the field of echocardiography-based CRT research which is represented by this study in that for some investigators the emphasis seems to be shifting away from regional differences in LV dyssynchrony and moving toward global parameters of LV structure and function and not necessarily as a predictor of short-term clinical response, but rather long-term prognosis. It remains to be determined as to which investigative line may ultimately be most clinically useful but the significant shift from regional differences versus global parameters should not be ignored because this relatively new field continues to evolve and likely has yet to reach its full potential.

Disclosures

None.

References


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