Hype and Hope in the Use of Echocardiography for Selection for Cardiac Resynchronization Therapy

The Tower of Babel Revisited

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Editorial

Behold, the people is one, and they have all one language, and now nothing will be restrained from them, which they have imagined to do. Let us go down, and there confound their language, that they may not understand one another’s speech.

—The story of the Tower of Babel, from Genesis 11.

Initially, the rationale behind the use of echocardiography to assess mechanical synchrony seemed straightforward. Not all patients with left bundle-branch block (LBBB) have mechanical dyssynchrony, and this entity could be identified by measuring the contraction delay between different cardiac walls. It was hoped that better selection with echocardiography would minimize the nonresponder rate of cardiac resynchronization therapy (CRT).

Articles p 2608 and p 2617

Then matters started to get complicated. In addition to a variety of measurements of the onset, peak, and offset of contraction, many individual centers have reported a dozen or more permutations of these measurements with different imaging modalities that could be used to predict responsiveness to CRT.1 This Tower of Babel of markers of mechanical dyssynchrony was compounded by the use of a variety of definitions of procedural success, including clinical evaluation (composite scores, New York Heart Association class, and quality-of-life scores), exercise capacity (10% improvement), and indices of left ventricular (LV) function (>15% reduction of LV volumes, >5% increase in LV ejection fraction, decrease in Tei index, and reduction of mitral regurgitation). To the astute observer, the fecundity of this field should ring alarm bells: A truly effective modality is unlikely to beget so many variants.

With the publication of the Predictors of Response to CRT (PROSPECT) trial in this issue of Circulation,2 the use of echocardiography for clinical decision making in CRT has progressed from ambiguity to negativity. This landmark multicenter study of nearly 500 patients at 53 centers, involving 3 core laboratories, examined whether echocardiographic indices of dyssynchrony could be used to predict response to CRT (defined by 15% reduction of end-systolic volume or a clinical score). The predictive value of echocardiographic parameters was modest, and large intraobserver and interobserver variations of tissue Doppler parameters were documented (respectively, 10% to 15% and >30%). The core laboratory identified 20% of the enrolled subjects as having an ejection fraction that exceeded that usually used in the selection of CRT candidates. These findings could hardly have been less favorable for echocardiography.

There are important lessons to be learned from this study. First, the inconsistency between these findings and the lack of negative reports from smaller studies should remind us that like heart failure itself, publication bias remains an intractable problem. The failure of this study will not be completely unexpected by echocardiographers who struggle with the difficult measurement of mechanical dyssynchrony, but it might seem surprising given the literature. Unfavorable trials of dyssynchrony markers are rare indeed, and when they have been published, the results may be ascribed to technical issues3 or the definition of clinical response.4

Second, we should consider a number of aspects of study design that could be improved in the next such study. Apart from issues related to training and core laboratories referred to by the investigators,2 the study did not consider a number of determinants of the CRT response. This is dependent not only on dyssynchrony and the presence of impaired LV function but also on viable muscle and location of the pacing lead in the appropriate position. It is important to recognize that echocardiography and other imaging techniques may provide important information on each of these latter aspects, but at the stage that the study was designed, their importance was less clear, and therefore, they were not included in the study design. The use of 3D echocardiography may be useful in the accurate measurement of ejection fraction and volumes. Perhaps there is a threshold of LV size at which reduction of end-systolic volume is harder to satisfy; certainly, very dilated ventricles have been shown to be unlikely to respond to revascularization therapy.5 The identification of nonviable tissue in the lateral wall is critical; such tissue is unlikely to respond to pacing.6 Finally, failure to pace at the site of maximum mechanical dyssynchrony has been associated with CRT failure.7 Additional reasons proposed by the investigators for the failure of PROSPECT, such as the need for special training and variations derived from the use of equipment from multiple vendors, are “real-world”
issues that reflect the limited feasibility of this technique in daily practice.

Third, the result will support the reservations of many clinicians regarding the suitability of tissue Doppler imaging in the selection of patients undergoing CRT. Current guidelines do not include mechanical indices of dyssynchrony in the selection criteria for CRT. The trials of this expensive therapy show an improvement in functional status and survival in patients in New York Heart Association class III with LV ejection fraction <35% who are undergoing appropriate medical therapy and who have a wide QRS, usually involving LBBB. Only 1 of these large trials used echocardiographic indices: CARE-HF (Cardiac Resynchronization in Heart Failure) used markers of interventricular dysynchrony to identify suitable CRT candidates among those with QRS duration 120 to 150 ms. The rationale of identifying a group of likely nonresponders is a strategy unfamiliar to clinical trialists. The protagonists of the responder/nonresponder strategy argue that the frequency of nonresponse (30% to 40%) and the cost of device therapy mandates this characterization. The problem is that few, if any, imaging techniques have a sensitivity >90%, which implies that at least 10% of patients who could experience benefit would be denied potentially prognostically beneficial therapy if imaging tests were used in patient

Figure. Tissue velocity and strain measurements in the “rocking heart.” The lateral and septal walls follow an opposing trajectory with almost mirror image velocity curves, whereas the strain curves are close to synchronous.
selection. With this in mind, it will be difficult to justify not proceeding to CRT in patients with QRS duration >150 ms, whatever the echocardiography findings, and future analogs of PROSPECT should focus on patients with QRS duration 120 to 150 ms.

Although tissue Doppler has high temporal resolution, there are several technical problems with its use for timing measurements, including the difficulty in defining peak contraction in the flat velocity contour of the failing heart, signal noise, and the spatial and temporal variations of the signal. Another major issue is that Doppler measures motion relative to the transducer, whether active or passive. The failing heart may demonstrate a rocking motion that is very difficult to interpret with tissue Doppler and that may not represent dysynchronous contraction (Figure).

A second article in this issue of Circulation addresses whether myocardial strain might be a preferred technique to tissue velocity in the assessment of dysynchrony.\textsuperscript{11} Strain measures deformation and therefore contraction and may overcome some of the problems cause by the inability of velocity to distinguish contraction from rocking movements and tethering. Miyazaki et al\textsuperscript{11} compared measures of dysynchrony with tissue velocity imaging (TVI) and strain in 120 subjects (40 normal, 20 LBBB with normal LV, 20 LV dysfunction and no LBBB, and 40 LV dysfunction and LBBB). TVI measurements were recorded both with use of the ejection phase alone and with the inclusion of postsystolic motion. Although the variance of TVI was greater in patients with LV dysfunction and LBBB, there was considerable overlap between groups, and approximately half of the healthy subjects had TVI results that indicated dysynchrony. In contrast, the use of a strain marker resulted in less overlap between the groups. Although the comparison of these 4 groups has no intrinsic value (the issue is really to identify responders and nonresponders in the fourth category), it does have some important messages. First, the standard deviation of TVI measures should be small in normal subjects but has been reported to measure up to 40 ms.\textsuperscript{12} The reasons for this degree of variation may be patient related, but this should not hide a variety of possible technical explanations. Second, intraobserver variability of repeated measurements of velocity and strain were both low (6±7\% and 6±10\%). Finally, the authors concluded that strain may be the better option because it includes postsystolic motion and avoids translational motion due to rocking. However, the application of strain to decision making for CRT will require outcome data, which were not provided in this study, and existing data have not been encouraging.\textsuperscript{13,14} Problems with TVI-based strain may be attributable to signal noise and angle dependency; initial data with the more robust technique of speckle-based strain are encouraging.\textsuperscript{15}

Once a suitably robust technique for the clinical assessment of mechanical dysynchrony has been identified, we will need to address some fundamental questions relating to the measurement of mechanical dysynchrony. Should dysynchrony be measured in the long or short axis? Should the measurements be restricted to systole or include postsystolic events, which may reflect ischemia? The variation of electromechanical delay (TSSD, the standard deviation of the time from the ECG Q wave to peak myocardial systolic contraction) is likely a good marker of global LV dysynchrony for work relating to pathophysiology, but is wall-to-wall delay a more relevant parameter for CRT decisions, which involve the pacing of discrete points to try to restore synchrony? Should alternative imaging strategies (including MRI and gated heart-pool scanning, which may not have the temporal resolution to identify 50- to 60-ms delays) be used in light of the problems with echocardiography documented by the PROSPECT trial?\textsuperscript{16}

In conclusion, the PROSPECT trial results indicate that current iterations of echocardiographic and tissue Doppler–based indices of mechanical synchrony are unsuited to everyday clinical use in CRT selection. These measurements are too variable, their sensitivity is currently too low to use in the hope of avoiding nonresponders, and their use with regard to expanding the CRT population (eg, mechanical dysynchrony and narrow QRS) foundered with the RETHINQ (Resynchronization Therapy in Normal QRS) trial.\textsuperscript{16} Large, preferably multicenter, observational studies will be required to understand the fundamental questions posed above regarding the optimal measurement of mechanical dysynchrony, taking account of the determinants of CRT responsiveness, including viability and appropriate pacing lead location. The story is far from over for mechanical markers of LV dysynchrony, and new modalities such as speckle tracking, as well as spatial and temporal averaging to reduce signal noise, will make important contributions. However, whatever the modality, we should seek a single (or a few) robust measurements, or we will be revisiting the Tower of Babel.

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References
5. Pasquet A, Lauer MS, Williams MJ, Seeknus MA, Lytle B, Marwick TH. Prediction of global left ventricular function after bypass surgery in patients with severe left ventricular dysfunction: impact of pre-operative


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