One prospective, observational, multicenter trial has squashed the hopes of heart failure physicians and electrophysiologists that a single echocardiographic dyssynchrony measure would improve the patient response rate for cardiac resynchronization therapy (CRT). In the aftermath of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study (1), echocardiography seems to have completely lost its reputation for assessment of dyssynchrony in this field, despite the fact that most basic research on the CRT-related pathophysiology has been performed with the aid of echocardiographic techniques and ignoring the pathophysiologic link between delayed electrical activation, mechanical dyssynchrony, and left ventricular-based resynchronization. Echocardiography is clearly the most versatile routine imaging technique for the cardiologist, because it combines bedside technology with high spatial and temporal resolution and provides hemodynamic and functional information. However, despite all the promise from mostly single-center evaluations, several tested echocardiography parameters failed to predict the CRT response with sufficient sensitivity and specificity in the multicenter PROSPECT study.

Why did echocardiography fail to show a prognostic benefit in the PROSPECT study? Numerous reasons have been discussed, mainly focusing on the study design, echocardiographic training, and equipment. Outside of the specifics of that trial, however, the fundamental concerns were whether mechanical dyssynchrony might simply be irrelevant or that echocardiographic measures were too imprecise to quantify dyssynchrony reliably. Inherent in the latter are the limitations of categorical cut points. The cutoffs for defining the presence of dyssynchrony have largely been based on previous single-center publications but have never been rechecked. For example, the >40-ms cutoff for defining abnormal interventricular mechanical delay (IVMD) by pulsed wave Doppler might be revisited in light of the CARE-HF (Cardiac Resynchronization in Heart Failure) trial data showing a significant survival benefit for patients with an IVMD >49 ms (2).

Perhaps one of the other lessons of the PROSPECT study relates to the limitations of tissue Doppler-derived dyssynchrony parameters, which were less robust and less reproducible than “old-fashioned” conventional Doppler parameters. These problems should not be a major surprise, because the limitations of this analysis with a poor correlation between the velocity of motion and the deformation sequence were observed some years ago (3) and confirmed recently (4). Peak systolic velocities might provide misleading information on the contraction sequence (Fig. 1) and might suggest the presence of dyssynchrony in completely normal hearts and vice versa (5). Strain imaging might solve some of the problems and limitations, but it is technically very demanding when derived from tissue Doppler velocity information. Newer strain techniques are based on 2-dimensional (2D) speckle information and might provide more robust and reliable strain information (6).
Similar negative conclusions were drawn from the RETHINQ (Resynchronization Therapy in Patients with Narrow QRS) trial, which showed that patients with a narrow QRS complex <130 ms but mechanical dyssynchrony did not benefit from CRT (7). We might focus on, in addition to the explanation that a minimal amount of electrical delay (evident by QRS prolongation of at least 120 to 130 ms) is a prerequisite for CRT response (7), how much mechanical dyssynchrony is needed to engender benefit from CRT? In the RETHINQ trial, only the tissue Doppler parameters (septal-to-lateral wall delay in peak systolic velocities, and the like) showed pathologic values, whereas the conventional M-mode and Doppler parameters did not show any significant dyssynchrony! Thus, the real problem was that patients were mainly selected by tissue Doppler velocity analysis, a highly sensitive technique that has to be analyzed properly and with caution (see the following text).

The most important message from these studies is not that echocardiographic dyssynchrony assessment should be completely abandoned but that a single measure is probably insufficient to characterize global cardiac dyssynchrony comprehensively and that a multiparametric strategy might be required to increase the response rate significantly (8).
In this issue of *JACC*, Buss et al. (9) present a new method for dyssynchrony assessment: echocardiographic phase imaging (EPI). Echocardiographic phase imaging measures the cyclic changes in gray level intensities of the left ventricular myocardium throughout the cardiac cycle, which allows calculation of a global dyssynchrony index (EPI index). At first sight, the technique seems similar to the 2D strain analysis by speckle-tracking. However, EPI only quantifies motion changes and does not assess true myocardial deformation. Despite this clear limitation, this new approach adds new and hopefully robust and reproducible information to our echocardiographic armamentarium.

Is EPI just another measure for dyssynchrony that performs well in the instance of an experienced laboratory but will fail in a multicenter evaluation? Maybe, but such techniques are particularly attractive, because they incorporate information from the complete left ventricular myocardial circumference (although currently limited to a single imaging plane) and have the potential to provide a semi-automatic measure of dyssynchrony with minimal operator interaction. In the present study, the authors still contoured the endocardial borders manually, but this can be overcome with the incorporation of modern automatic boundary detection methods.

The diagnostic value for the detection of CRT responders by EPI is comparable to the global dyssynchrony assessment by the timing of regional peak systolic velocities by tissue Doppler imaging (TDI-SD), a parameter that did not perform particularly well in the multicenter studies (1,3). As discussed in the preceding text, TDI-SD might work better in the hands of an experienced operator and if the data are obtained and analyzed properly with care. However, it is obvious that more studies and comparisons are required before the real diagnostic value of such a new technique can be appraised properly.

As in many other trials, the diagnostic sensitivity (88% to 95%) of echocardiographic CRT responder identification by EPI dyssynchrony assessment clearly outperforms the corresponding specificity (67% to 75%). In other words, the vast majority of CRT responders present with significant dyssynchrony by EPI, but not every patient with baseline dyssynchrony can be expected to respond. This reminds us that mechanical dyssynchrony cannot be the only predictor for CRT success, no matter which technique is applied. Other factors such as correct lead placement and individual optimization of the pacing configuration and patient factors such as advanced remodeling, arrhythmias, and regional scar distribution all have a significant impact on CRT efficacy (10,11). The importance of post-implant assessment of CRT efficacy in each individual is frequently underestimated and has been ignored in most echocardiographic studies that focused only on pre-implant dyssynchrony quantification. Recent evidence has supported the clinical relevance of post-implant verification of CRT efficacy (12,13).

In summary, echocardiographic dyssynchrony assessment will remain an integral part before and after CRT implantation but has to be applied with expertise and knowledge of the inherent technical and pathophysiological limitations. A comprehensive multiparametric approach will probably be required for an appropriate dyssynchrony assessment in future studies and for individual patient management (8). If we keep this in mind, new echocardiographic approaches such as the EPI technique will complement our diagnostic spectrum and continue to contribute to decision-making for our patients.

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