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Review

Is mechanical dyssynchrony still a major determinant for responses after cardiac resynchronization therapy?

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Summary The assessment of mechanical dyssynchrony by advanced echocardiographic technologies and its importance in selecting more appropriate candidates for cardiac resynchronization therapy (CRT) have been disputed, after the announcement of the Predictors of Response to CRT (PROSPECT) trial, as the first evidence derived from a multicenter study. However, attempts in this field have never been stopped, as it appears that the fundamental mechanism of CRT is the correction of dyssynchrony where the detection of baseline dyssynchrony is of particular significance. The QRS width provides simple but very limited information. On the other hand, non-invasive imaging tools such as echocardiography have the capacity for more detailed analysis of mechanical dyssynchrony. We reviewed a number of clinical studies published in the post-PROSPECT era, designed to figure out a predictive algorithm where dyssynchrony measure is included, for identifying the most suitable patients before device implantation. From the analysis, mechanical dyssynchrony remains to be a major determinant for clinical outcomes after CRT, although discrepancies have arisen with respect to the single-center nature, echocardiographic methodologies, and relative merit when compared with other predicting factors.

Contents

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Introduction

Cardiac resynchronization therapy (CRT) is one of the most rapidly evolving fields in heart failure management over the last decade [1]. There has been compelling evidence from multicenter clinical trials that CRT not only improves symptoms and cardiac function, but also reduces heart failure hospitalization and cardiovascular mortality in patients with advanced heart failure. However, it remains to be a major issue that based on the current guidelines for patient selection, non-responders to the therapy are constantly observed in about 30—40% of patients receiving CRT [2,3]. As the correction of left ventricular (LV) mechanical dyssynchrony has been suggested to be one of the major mechanisms for CRT, its detection should be of clinical importance in estimating the probability of response to the therapy. Not surprisingly, lack of mechanical dyssynchrony assessed by noninvasive echocardiographic techniques is found to be closely correlated to non-response in numerous single-center clinical trials, while other factors also attributable are extensive myocardial scar at the posterolateral wall or even the whole LV, lack of adequate contractile reserve, high pulmonary pressure, severe mitral regurgitation, non-posterolateral LV lead position, and suboptimal atrioventricular or interventricular delay programming [2,4,5]. Nevertheless, the results of the Predictors of Response to CRT (PROSPECT) trial, the first multicenter trial, indicated that no single echocardiographic measure of mechanical dyssynchrony could predict CRT responses with a good sensitivity and specificity, and therefore it is not recommended to improve patient selection beyond the current criteria of QRS durations [6]. Since then, researchers continue to quest for potential dyssynchrony-related parameters which may predict a positive outcome in CRT population. The current review will provide a comprehensive description of the role of dyssynchrony in the post-PROSPECT era.

Learning lessons from the PROSPECT trial

The PROSPECT trial was a multicenter, prospective, non-randomized study designed to evaluate selected echocardiographic indices of mechanical dyssynchrony for their capability in predicting responses to CRT. There were 12 parameters tested for a clinical composite score and LV end-systolic volume (LVESV) at 6 months as the primary outcomes, which being useful in previous single-center studies. Echocardiographic parameters were measured by conventional M-mode, Doppler echocardiography to advanced tissue Doppler imaging (TDI). The study reported a large variability in the analysis of mechanical dyssynchrony by echocardiography (up to 70% when using M-mode method) and a low area under the curve (AUC) in the prediction of the endpoints by mechanical dyssynchrony ($\leq$0.62 for all parameters). The results suggested that measures of mechanical dyssynchrony had limited incremental value in patient selection, including those indices derived from TDI that had demonstrated a large body of evidence before PROSPECT [6,7].

Of note, the PROSPECT study had a number of major limitations in the design and execution which raised further controversies and biased the conclusion [8—11]. The trial commenced in 2003 when the implantation technique of CRT devices became quite mature due to systematic proctoring, hands-on training, and high-volume implantation in centers selected and supported by device companies. On the contrary, there were only a few laboratories in the world that regularly performed dyssynchrony analysis by echocardiography at that time where knowledge sharing and hands-on training had yet to develop. Inevitably, some technical problems were introduced in this study, including methodology in dyssynchrony assessment by offline analysis was not standardized, training was inadequate, and echocardiographic equipment was not uniform and in some centers too obsolete for adequate TDI images. Dyssynchrony measurements adopted in the PROSPECT trial were criticized by their unexpected high interobserver variabilities, which ranged from 32% to 72% and intraobserver variabilities from 16% to 24%, presented by the reproducibility test within the core laboratories [6]. This may reflect the general difficulty in dyssynchrony analysis by echocardiography. However, it is worth mentioning that the variability test was conducted retrospectively after all the offline analysis had been completed, but not before the study. It is arguable that these 3 core laboratories should have been trained and adopted a common algorithm for dyssynchrony analysis before offline analysis was commenced. Of note, the interobserver variability for the measurement of LVESV by Simpson's method was as high as 14.5% [6]. Moreover, in about half of the images, the image quality was not adequate for offline TDI analysis. Consequently, concerns are raised that ''failure'' of mechanical dyssynchrony by echocardiography could be attributed to the lack of standards in online acquisition and offline analysis due to insufficient training and feedback between the core laboratories and the study sites, in particular during the initial phase of the trial. Furthermore, the use of modern echocardiographic equipment capable of decent TDI image quality cannot be overemphasized. Therefore, the PROSPECT trial should not be regarded as a final conclusion that dyssynchrony has little role in predicting CRT response, but rather, an appeal to physicians to emphasize training with knowledge and skill transfer if the role of echocardiographic dyssynchrony is to be explored, sim-