Left ventricular mechanical dyssynchrony in patients with heart failure: What is the next step?

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Left ventricular mechanical dyssynchrony (LVMD) is referred to incoordinate onset of mechanical contraction between the left ventricle (LV) segments,¹ leading to structural and functional alterations that may eventually result in heart failure (HF). LVMD is highly prevalent and has been extensively studied among patients with HF. It has been proven to be associated with an increased risk of major adverse cardiac events or presented incremental clinical value in prognosis and risk stratification among different subsets of HF patients with acute² or chronic,³ ischemic^{4,5} or nonischemic,⁶ reduced⁷ or preserved left ventricular ejection fraction (LVrEF or LVpEF),⁸ irrespective of narrow or wider QRS duration (QRSd).⁹ However, its major clinical application is to select candidate for better prediction of optimal cardiac resynchronization therapy (CRT) outcomes in HF patients.^{10–12}

Electrical dyssynchrony is defined by an asynchronous electrical activation of the LV, leading to a prolonged QRS duration on the electrocardiogram (ECG). Although electrical dyssynchrony and LVMD often occur together, they are not interchangeable.¹³ According to current ESC guidelines,¹⁴ the presence of electrical dyssynchrony, rather than LVMD, is among the inclusion criteria for CRT in HF patients. However,

there is still approximately one third of patients who meet guideline indications failing to benefit from CRT. Thus, there are ongoing efforts to optimize patient selection for this expensive therapy. It has been suggested that lack of response to CRT meeting otherwise traditional criteria may be due to the absence of LVMD.^{15,16} However, the large-scale, multicenter PROSPECT trial¹⁷ based on echocardiographic techniques failed to find a significant predict performance of LVMD for response to CRT, which challenged the role of LVMD in guiding CRT. Therefore, better tools to identify candidates for CRT are needed to optimize resource allocation. Due to high intra-observer and inter-observer repeatability and reproducibility, gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) may be such a tool for comprehensive integrated evaluation of the assessment of LVMD, site of latest mechanical activation, and myocardial scar for optimizing CRT with a single scan.^{18,19}

In the current issue of Journal of Nuclear Cardiology, Doi et al²⁰ have used gated SPECT MPI to evaluate the incremental risk-stratification value of LVMD when compared with conventional clinical indices including electrical dyssynchrony measured with QRSd and systolic dysfunction in HF patients. The enrolled patients (n = 829) had different range abnormalities of QRSd accompanied with LV dysfunction (LVEF < 50%). Patients were followed up with a primary endpoint of lethal cardiac events (CEs) for a mean period of 37 months. LVMD parameter measured by phase standard deviations (SDs) was identified as independently significant prognostic determinants in subgroups with both cut-off values of LVEF (LVEF < 35% and with 35% ≤ LVEF < 50%) and QRSd (130 ms or 150 ms), except the groups I (subgroups with 35% ≤ LVEF < 50% and QRSd < 130 ms or QRSd < 150 ms). The authors then

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concluded that LVMD assessed by gated MPI could further risk stratify over QRSd and LVEF in HF patients. This study adds to the existing literature that in addition to the established clinical parameters [including New York Heart Association (NYHA), brain natriuretic peptide (BNP), QRSd and LVEF, etc.], LVMD assessment is associated with poor prognosis of HF patients. The integrative analysis opens a new window for the identification of patients who are likely to benefit from CRT. The present results may also provide some valuable information for clinical strategy in the management of HF patients and lay the foundation for the routine use of phase analysis by gated SPECT MPI in the clinic—a technique that indices can derive retrospectively from prior acquired and saved images without any extra costs or risks. Moreover, using cut-off values for LVMD parameters may further aid clinical decision making regarding CRT implantation.

Nevertheless, as for every study, some certain weaknesses and limitations are deserved. First, the study is limited to the small proportion (17.4% or 11.6%, LVEF < 35% and QRSd > 130 ms or QRSd > 150 ms) of patients who clinically consistent with CRT indications in the enrolled population. Caution is warranted for translating the results into a “real-world” CRT clinical application. Second, the authors did not compare the prognosis value of other LVMD parameters obtained by gated MPI, jump to choose phase SD as the LVMD index directly in this study, which may lead to inaccurate and biased. Third, although the receiver operating characteristic (ROC) analysis for the prediction of CEs was statistically significant, using cut-off values of phase SD 36°, and the authors found 53.3% sensitivity and 65.8% specificity with an area under the curve (AUC) 0.606, which are not so satisfactory. We do admit the significance of cut-off values in clinical medicine and their utility for predictive tools. However, LVMD is not an all-or-none phenomenon but exists as a continuous variable with different grades of severity. Thus, considering the low currently predictive accuracy, if this cut-off value was to guide CRT in future trials, inevitably a substantial proportion of patients will have significantly opposite outcomes. At last, NYHA functional class, estimated glomerular filtration rate (eGFR), BNP, and amiodarone use as well as phase SD in the present study were confirmed together to have significant independent prognostic values by the multivariate Cox analysis. The literature to date suggests that there may not be one single predictor of CRT response.⁷ Therefore, LVMD parameters could be used as part of a model algorithm that includes other significant clinical variables to help come up with a decision about CRT implantation.

At present, while LVMD parameters have shown the ability to discriminate CRT responder in a paper or other, there is still no enough evidence to suggest that CRT selection criteria should include LVMD to amend guidelines. Any valuable research results should be based on whether the patients ultimately benefit or not in clinical practice. For clinicians to routinely utilizing LVMD, future studies are warranted to build a more appropriate prediction tool for the clinical choice of CRT. As to known, a large prospective, randomized, controlled trial (GUIDE-CRT, NCT03125720) was underway in China.²¹ GUIDE-CRT study applies pre-operation-gated SPECT MPI phase analysis to evaluate LVMD, the site of the latest activation segment away from scar as optimal pacing site and to verify the feasibility and effectiveness of SPECT MPI phase analysis in guiding LV lead implantation to improve CRT response. We look forward to encourage results from this study.

Besides, although the prevalence of HFpEF has obviously increased in the last two decades, there is still no effective therapeutic strategies.²² LV diastolic dyssynchrony may play an important role and show promising results in clinical practice in this cohort.²³ Recent study²⁴ shows that CRT therapy can also improve LV diastolic dyssynchrony. Because of limited medical resources and growing medical costs associated with the use of CRT therapy, there is a need to establish more appropriate selection of CRT candidates and more cost-effective management of HF. The next step is to conduct larger, prospective, multicenter randomized trials to build generalizable prediction models which integrated LVMD and other known conventional clinical parameters to optimize the selection criteria of CRT. Furthermore, with the advanced development of artificial intelligence, combining LVMD parameters and more novel approaches, for example, interventricular dyssynchrony, contraction patterns, image texture, with known predictors perhaps could yield an objective goal to improve the success rate for CRT and make solid changes for the guidelines.

In conclusion, LVMD has critical roles for improvement in the risk stratification of HF patients. Nevertheless, further studies are needed to deeply clarify its indispensable role in determining the indication and predicting therapeutic effect of CRT in HF patients under “real-world” conditions.

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Disclosures

The authors declare no conflicts of interest.

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