EDITORIAL

The potential role of gated myocardial perfusion SPECT imaging in patient selection for cardiac resynchronization therapy

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Cardiac resynchronization therapy (CRT) is currently recommended in patients with wide QRS complex (≥120 ms), heart failure symptoms, and depressed left ventricular (LV) function (ejection fraction ≤ 35%) despite optimal medical therapy.[1] Several randomized clinical trials provided evidence that in these patients CRT can improve symptoms, LV function, heart failure hospitalizations, and overall mortality.[2-4] However, this beneficial effect is not homogenous among CRT recipients and previous studies have observed that a substantial group of patients who received CRT according to these selection criteria do not respond favorably to CRT.[4-7] More importantly, there is no consensus on the definition of response to CRT, and both symptomatic improvement (in New York Heart Association functional class) and echocardiographic improvement (LV reverse remodeling, decrease in LV end-systolic volume, and increase in LV ejection fraction) have been used; when comparing these two definitions of CRT response, it appears that symptomatic improvement occurs more often than echocardiographic improvement,[8] but that up to 30% of patients may not show significant improvement in symptoms and/or LV performance.[4-7]

The attention has therefore shifted toward understanding how to improve prediction of CRT response and identify the best candidates for this therapy. Presence of cardiac dyssynchrony (either atrio-ventricular, inter-ventricular of intra-ventricular) seems to be the logic pre-requisite for a good effect of CRT. Current guidelines indicate that a dyssnchronous contraction might be better reflected by a significantly prolonged QRS interval (>150 ms) and by a typical left-bundle branch block QRS morphology, for which a class IA indication was given.[1] However, several observational studies have also suggested that the direct assessment of LV mechanical dyssynchrony could improve outcomes in CRT recipients.[9-17] Different imaging techniques have been proposed for this purpose, including echocardiography, magnetic resonance imaging, computed tomography, and nuclear imaging.[9-17] Echocardiography is the most widely used technique, providing several imaging tools for LV dyssynchrony assessment, such as tissue Doppler imaging (TDI), speckle tracking two-dimensional strain analysis, and three-dimensional echocardiography.[9-12] TDI was first introduced and widely applied in single-center studies, with promising results for predicting CRT response. However in a multi-center setting, TDI measures of dyssynchrony showed reduced feasibility and reproducibility mainly due to technical issues and differences in vendors.[18] It also became evident that pathophysiological issues, such as the presence, extent, and location of scar tissue, are of additional importance.[7] Particularly, the presence of scar tissue may limit the response to CRT, as demonstrated in several studies using contrast-enhanced magnetic resonance[15,19]; the larger the extent of scar tissue, the lesser the response to CRT. It has also been demonstrated that when the LV lead is positioned in areas of transmural scar tissue or outside LV site of latest mechanical activation, the response to CRT is limited.[15,19-22]

Gated myocardial perfusion single photon emission computed tomography (GMPS) has been also proposed for LV dyssynchrony assessment using phase analysis. This is a count-based method that extracts the phase from the regional LV count changes during the cardiac

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cycle. Phase information is related to the onset of mechanical contraction in the 3D myocardial wall and therefore provides information on the synchrony of LV contraction. This technique has been implemented in various software programs, including the Emory Cardiac Toolbox (ECTb) and the Quantitative Gated SPECT (QGS) from Cedars-Sinai Medical Centre and two main parameters of dyssynchrony can be derived: (1) histogram bandwidth, which includes 95% of the elements of the phase distribution; and (2) phase standard deviation (SD), which is the standard deviation of the phase distribution. In a normal heart, LV contraction is homogeneous and phase distribution is nearly uniform with a highly peaked distribution. With increasing LV dysssynchrony, histogram bandwidth, and phase SD are expected to increase. Assessment of LV dyssynchrony by these two parameters, being a relatively automated process, is also characterized by a high reproducibility, overcoming the limitation abovementioned for TDI. Previous studies have demonstrated the value of these quantitative indices for predicting CRT response.[16,17] However, the optimal cut-off values for histogram bandwidth and phase SD to define substantial LV dyssynchrony differed among the ECTb and the QGS software programs,[16,17] and a head-to-head comparison between software packages was not been performed so far. It was therefore unclear whether this difference related to intrinsic characteristics of the sampling systems of the two software programs or might be related to differences in patient populations.

In the current issue of the Journal, Rastgou et al[18] performed a direct comparison of the two quantitative software packages for assessment of LV dyssynchrony parameters in 31 patients with reduced LV ejection fraction (21% ± 6%) and QRS duration of 124 ± 36 ms. The authors reported a good correlation between the two software programs, both for histogram bandwidth ($r = 0.664$) and phase SD ($r = 0.731$), suggesting that both quantitative packages are providing the same information and can be used to assess LV dyssynchrony. However, the values derived by ECTb were significantly higher than those derived by QGS with a mean difference of 38 for histogram bandwidth and 19.7 for phase SD. These findings suggest that the two software packages cannot be used interchangeably and support the use of different cut-off values for the two software packages to eventually define the range of normal synchrony or significant LV dyssynchrony for both histogram bandwidth and phase SD. This remains to be determined in future studies in patients undergoing CRT, validating cut-off values for LV dyssynchrony by predicting CRT response.

Rastgou et al[18] also compared the different LV dyssynchrony parameters derived by GMPS with measurements derived from echocardiography using TDI, and only modest correlations were noted. Previous studies comparing LV dyssynchrony assessment by GMPS (using either ECTb or QGS software packages) reported good correlations in patients referred for CRT.[16,23] The modest correlations between echocardiography and GMPS for assessing LV dyssynchrony may be related to the fact that the population evaluated by Rastgou et al. included a small group of patients with relatively narrow QRS complex (124.2 ± 36.3 ms), and therefore with a subset of patients without electrical LV dyssynchrony (QRS duration < 120 ms), in whom mechanical dyssynchrony may be minimal or absent.

An important advantage of using GMPS for assessing LV dyssynchrony is that it provides also comprehensive information on LV ejection fraction, LV volumes, myocardial ischemia, scar tissue, and viability. The majority of patients referred for CRT have ischemic heart failure (with underlying cause chronic coronary artery disease), and in these patients GMPS is usually performed during the diagnostic and prognostic work-up. In the therapeutic decision-making process, all the abovementioned information can be integrated and can help to decide on therapeutic options: revascularization, medical therapy, or device (CRT or implantable cardioverter defibrillator) therapy.

Future studies could therefore be performed in classical candidates for CRT (wide QRS complex—$\geq$120 ms, depressed LV function—ejection fraction $\leq$35%, and heart failure symptoms despite optimal medical therapy) to determine the additional value of GMPS in the selection of patients for CRT. Particularly, information on the presence of LV dyssynchrony and the presence/location of LV scar tissue may further improve prediction of CRT response. In addition, GMPS may prove useful in the guidance of LV lead positioning, specifically to avoid placement of the LV lead in areas of (transmural) scar tissue or outside the site of latest mechanical activation.

Disclosure

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Conflict of interest

Authors have no conflict of interest to disclose.

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