Three-dimensional left ventricular mechanical dyssynchrony assessed by myocardial perfusion gated-SPECT: Is there a role in cardiac resynchronization therapy?

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Nuclear cardiology techniques have wide and emerging applications in heart failure patients undergoing Cardiac Resynchronization Therapy. Left ventricular function and dyssynchrony can be assessed by ECG-gated myocardial perfusion SPECT and equilibrium radionuclide angiography with Fourier phase analysis.^{1,2} Moreover, myocardial viability, assessed by SPECT, has been shown to be a predictor of response to Cardiac Resynchronization Therapy.^{1,2} Studies with positron emission tomography have documented changes in myocardial metabolism and efficiency after Cardiac Resynchronization Therapy,¹ and more recently phase analysis of gated positron emission tomography has been developed for the evaluation of mechanical ventricular synchrony.³

Cardiac Resynchronization Therapy is currently indicated in symptomatic heart failure patients with wide QRS complex (≥ 130 ms) and reduced left ventricular ejection fraction ($\leq 35\%$).⁴ To date, nearly one-third of heart failure patients who fulfil the standard indications⁴ for Cardiac Resynchronization Therapy still do not respond to this device therapy, and the reasons

are not known completely.⁵ Assessment of left ventricular dyssynchrony appears to be a more promising factor in the evaluation of Cardiac Resynchronization Therapy response than QRS duration, which usually reflects only interventricular dyssynchrony.¹ To increase the individual benefit from Cardiac Resynchronization Therapy, efforts have been made to optimize patient selection, left ventricular lead positioning, and device programming.^{5,6} Despite these efforts, the quote of non-responders remains an unresolved issue.

Whether Cardiac Resynchronization Therapy may be an option in heart failure patients with less severe abnormalities of QRS duration and systolic function has been debated. In a previous multicenter randomized trial, Cardiac Resynchronization Therapy did not reduce the rate of death or heart failure hospitalization in patients with systolic heart failure and QRS duration of less than 130 ms, despite echocardiographic evidence of mechanical dyssynchrony.⁷ The results provide support to the concept that QRS prolongation is a pre-requisite for favourable response to Cardiac Resynchronization Therapy. In the REVERSE study, Cardiac Resynchronization Therapy induced a significant left ventricular reverse remodelling which was linked to improved heart failure morbidity in patients with mild heart failure symptoms, left ventricular ejection fraction $\leq 40\%$, and QRS duration ≥ 120 ms.⁸ Of note, the REVERSE study slightly extended the cut-off value of left ventricular ejection fraction used as selection criteria for Cardiac Resynchronization Therapy implantation.

In the past years, interest has focused on the assessment of left ventricular mechanical dyssynchrony in the attempt to integrate conventional selection criteria for Cardiac Resynchronization Therapy based on QRS

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duration and left ventricular systolic function. It is known that the presence of left ventricular dyssynchrony is an important determinant of the response to Cardiac Resynchronization Therapy.^{1,5} However, there are different types of mechanical dyssynchrony, and it is not known which is most significant in determining the response to Cardiac Resynchronization Therapy.^{1,5} Several studies have investigated the feasibility, clinical applicability, and prognostic role of various dyssynchrony indexes assessed by echocardiography, nuclear cardiology techniques, and cardiac magnetic resonance.⁹ However, the PROSPECT trial showed a low feasibility and high interlaboratory variability of echocardiographic dyssynchrony indexes.¹⁰ Moreover, dyssynchrony variables derived from different cardiovascular imaging methodologies have often been investigated in small population studies and have not been standardized. Therefore, although many studies on mechanical dyssynchrony have given promising results in predicting the response to Cardiac Resynchronization Therapy,^{5,9} the role of left ventricular dyssynchrony in patient selection has not been validated yet.

In this clinical scenario, the identification of potential responders among patients with standard indications for Cardiac Resynchronization Therapy or with less severe abnormalities of QRS duration and systolic function is still a matter of debate. In this issue of the Journal, Doi et al.¹¹ have focused on risk stratification and prediction of outcomes in heart failure patients with mid-range to severe abnormalities of QRS duration and systolic function. Interestingly, the authors found that three-dimensional left ventricular mechanical dyssynchrony assessed by gated-SPECT may improve conventional risk stratification based on QRS duration and systolic dysfunction.

The study by Doi et al.¹¹ highlights the potential applications and clinical utility of three-dimensional left ventricular mechanical dyssynchrony assessment by phase analysis of myocardial perfusion-gated SPECT. In the past years, scintigraphic methods to assess myocardial perfusion and function have been implemented for dyssynchrony evaluation by Fourier phase analysis.^{1,2,12} Previous data have shown that left ventricular dyssynchrony assessed by phase analysis of gated-SPECT is predictive of cardiac death in patients with left ventricular dysfunction.¹³ In the study by Doi et al., left ventricular mechanical dyssynchrony was assessed as standard deviation on a phase histogram calculated by Fourier phase analysis applied to three-dimensionally obtained regional time-activity curves.¹¹ Three-dimensional left ventricular mechanical dyssynchrony assessed by gated-SPECT was previously shown to be a reliable and reproducible variable,^{14,15} and to improve the prognostic stratification of heart failure patients

when used in combination with clinical variables¹⁴ and cardiac sympathetic nerve activity assessment.¹⁵

The results of the study by Doi et al.¹¹ extend while confirming previous findings suggesting that three-dimensional left ventricular mechanical dyssynchrony assessed by gated-SPECT may be an independent predictor of lethal cardiac events in heart failure patients.^{14,15} The specific contribution of the study is that three-dimensional left ventricular mechanical dyssynchrony may further discriminate heart failure patients with mid-range to severe grades of QRS prolongation and systolic dysfunction, thus improving the prognostic assessment of such patients. Accordingly, in a previous study left ventricular mechanical dyssynchrony by phase analysis of gated-SPECT was shown to be an independent predictor of all-cause mortality in patients with non-ischemic cardiomyopathy, ejection fraction 35%-50%, and QRS duration < 150 ms.¹⁶ Furthermore, the results of the study by Doi et al.¹¹ reflect the possibility that QRS duration may not be a parameter directly related to the presence of left ventricular dyssynchrony and therefore to the response to Cardiac Resynchronization Therapy, especially in the absence of left bundle branch block. Previous studies have shown that about 30% of patients with wide QRS do not have left ventricular dyssynchrony; in turn, about one third of patients with narrow QRS show significant left ventricular dyssynchrony.¹⁷ SPECT assessment of left ventricular dyssynchrony may be therefore combined with the analysis of QRS duration to improve the prognostic evaluation of heart failure patients with left ventricular dysfunction and class 2 indication to CRT according to current guidelines.

The findings of the study by Doi et al.¹¹ may be helpful to better stratify candidates for Cardiac Resynchronization Therapy beyond customary criteria. Moreover, the analysis of three-dimensional left ventricular mechanical dyssynchrony may improve the prognostic stratification of patients with less severe abnormalities of QRS duration and systolic function, who are not included in current guidelines for Cardiac Resynchronization Therapy implantation.⁴ In particular, SPECT evaluation of left ventricular dyssynchrony with Fourier phase analysis may allow for a better selection of candidates to Cardiac Resynchronization Therapy among those patients with a 120–149 ms QRS duration. In addition, SPECT imaging allows to analyze in a single exam several information about LV functionality, which are paramount in the appropriate selection of candidates to Cardiac Resynchronization Therapy, like left ventricular ejection fraction, myocardial perfusion, and extent of viable myocardium.

Further prospective, large-scale studies are required to confirm the prognostic role of three-dimensional left ventricular mechanical dyssynchrony assessed by gated-SPECT in Cardiac Resynchronization Therapy

recipients. In a previous study on 42 heart failure patients undergoing Cardiac Resynchronization Therapy, a cut-off value for left ventricular phase standard deviation of 43 degrees by gated myocardial perfusion SPECT was found to be predictive of Cardiac Resynchronization Therapy response with good sensitivity and specificity.¹⁸ Both histogram bandwidth and phase standard deviation assessment by phase analysis of myocardial perfusion-gated SPECT have shown high accuracy for prediction of response to Cardiac Resynchronization Therapy.¹⁸ Of note, the cut-off values of bandwidth, phase standard deviation, and entropy for left ventricular dyssynchrony assessment may vary depending on the software program used for phase analysis in gated-SPECT.¹⁹ Moreover, SPECT myocardial perfusion imaging measures of dyssynchrony seem to be influenced by proper valve plane alignment and test type (rest vs. stress).²⁰ Therefore, standardized protocols for left ventricular dyssynchrony assessment should be implemented and validated by larger prospective studies. Finally, whether three-dimensional left ventricular mechanical dyssynchrony assessed by gated-SPECT may provide incremental prognostic information in comparison with other dyssynchrony variables requires further investigation.

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