Evaluation of dyssynchrony with nuclear cardiac imaging: New evidence for an old parameter

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In the last years, the assessment of cardiac mechanical dyssynchrony has gained increasing relevance for patients' management, with specific regard to the evaluation of subjects with advanced congestive heart failure (CHF) candidates to cardiac resynchronization therapy (CRT).¹ While all the different non-invasive imaging modalities are valuable for the assessment of myocardial synchronicity, phase analysis with nuclear cardiac imaging has been always regarded as the reference standard for the assessment of the presence and quantification of the regional extent of myocardial dyssynchrony.^{2,3} In this regard, conclusive evidence has demonstrated that measures of left ventricular (LV) mechanical dyssynchrony (MD) derived from phase analysis may both allow the identification of patients that would likely benefit from CRT,⁴ and to guide LV lead replacement,⁵ likely improving the success rate of the procedure.

Accordingly, in patients with CHF, the evaluation of ventricular synchronicity has almost become a mandatory step in disease management, guiding risk stratification and therapeutic decision making.⁶ The common theory behind the evaluation of ventricular dyssynchrony with all the available nuclear imaging techniques is the application of Fourier harmonic (phase) analysis to gated datasets to define the moment in which the contraction of each myocardial segment starts (the onset of mechanical activation).² While the feasibility of this analysis has been

originally demonstrated with planar nuclear imaging techniques, phase analysis is more conveniently performed with three-dimensional imaging modalities, which could allow a better evaluation of regional myocardial contraction patterns.^{2,3} In this respect, studies performed in the last 2 decades, mostly with single-photon emission computer tomography (SPECT) cameras, have demonstrated how information on LVMD may be conveniently obtained in the context of traditional myocardial perfusion imaging (MPI) studies, complementing perfusion data with relevant LV functional parameters.^{3,7} This aspect seems of particular value, considering that accurate information on regional myocardial ischemia and viability may have a central role in determining whether a patient may benefit or not from CRT. In fact, it is now clear that patients with ischemic cardiomyopathy, particularly in the presence of extensive myocardial scar, do infrequently show significant LV reverse remodeling following CRT implantation, even in the presence of nominally significant LVMD.⁸ Similarly, phase analysis has been instrumental in demonstrating the presence of significant LVMD in different categories of patients that would not be generally considered for CRT implantation, such as subjects with relatively preserved LV ejection fraction and those with non-left bundle branch block (LBBB) QRS morphology.⁹ In this respect, recent evidence suggested that clinically relevant LVMD may develop independently of the underlying ECG pattern and QRS duration, demonstrating the limits of the currently employed criteria used for the identification of CRT recipients.⁹ However, the relationship between LVMD and ischemic heart disease (IHD) is even more complex. Due to its semi-automatic and intrinsically quantitative nature, phase analysis performed on MPI datasets is particularly suited for the evaluation of subtle alterations of LV wall contraction, likely allowing a better depiction of stress-induced LV wall motion anomalies secondary to inducible myocardial ischemia. Accordingly, it has been

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suggested that the systematic implementation of phase analysis in MPI protocols could increase the overall diagnostic accuracy of the test, with minimal increase in the overall computation time.¹⁰ In this setting, MPI on positron emission tomography (PET) cameras, with its generally superior spatial resolution and image quality, would seem particularly suited for such an assessment, possibly allowing combining information on LV perfusion and viability with the finer assessment of regional LV dynamics allowed by phase analysis.¹¹ While phase analysis on SPECT MPI has been progressively perfected in the last years, also with the validation of the technique on the novel dedicated cardiac cameras,³ the implementation of the same technique on PET imaging has been still limited. On one hand, PET would allow to explore the intrinsic relationship between myocardial perfusion and LVMD, shading more light on the possible determinants of progressive LV dysfunction in patients with CHF. On the other hand, the excellent quality of PET MPI datasets, devoid of the most relevant imaging artifacts of myocardial SPECT imaging, would likely expand the potential of phase analysis further toward its limits, likely allowing a better selection of patients that could benefit from CRT implantation.¹² However, as a result of the limited availability of dedicated cardiac PET cameras and, possibly, of the intrinsically higher complexity of the technology, only limited clinical evidence exists on the evaluation of LVMD with PET.

Specifically, despite initial validation studies, it has been recently reported that phase parameters derived by SPECT and PET are not interchangeable, and only moderate agreement should be expected between the two modalities.¹³ While the presence and extent of myocardial scar can explain most of the discrepancy between the two imaging techniques,¹³ the actual clinical impact of this difference has to be still determined. The possible functional and prognostic impact of stress-related LVMD on PET MPI is even more obscure, with some evidence showing that it might associate with adverse prognosis.¹⁴

Accordingly, a better understanding of the possible role of phase analysis on PET imaging is needed. In this number of the Journal, Mazzeletti et al. evaluated the possible interaction between myocardial perfusion patterns and stress-induced changes of LVMD in patients submitted to MPI with ¹³N-ammonia PET imaging.¹⁵ Seventy-four patients were submitted to regadenoson stress/rest PET MPI. To eliminate major confounding factors, subjects with LBBB, paced rhythm and scarred myocardium were excluded. The presence of inducible myocardial ischemia was evaluated through the computation of the summed difference score (SDS) and only patients with completely homogeneous perfusion (SDS = 0) were considered normal. The main results of the study were that, while stress had no significant impact on phase

parameters in patients without myocardial ischemia, a numerical stress-induced increase of both phase standard deviation and histogram bandwidth was observed in ischemic patients. Hence, after stress, ischemic patients showed significantly more compromised phase parameters than normal patients. Interestingly, no significant relationship existed between global myocardial perfusion parameters and measures of LVMD.

While the study of Mazzeletti et al. is significantly limited by the retrospective design, small patient populations, and selection of patients with modest signs, if any, of LVMD, it may represent a stimulus for the future in-depth evaluation of the interaction between myocardial perfusion patterns and LVMD.

Evidence accumulated during the last years confirmed the strict relationship between myocardial perfusion abnormalities and LVMD.^{3,16} Specifically, in a large population of patients submitted to combined evaluation of coronary anatomy by means of invasive coronary angiography and stress/rest myocardial perfusion with SPECT imaging performed using a dedicated cardiac camera equipped with Cadmium-Zinc-Telluride (CZT) detectors, it was demonstrated that LVMD was associated with a peculiar cardiac anatomic-functional profile, characterized by LV systolic dysfunction, LV dilatation, and more severe ischemic burden.³ Even after extensive correction for CAD burden and major clinical data, the presence of significant LVMD was ultimately predicted by the SDS and the LV end-systolic volume, as a direct measure of cardiac overload.³ Starting from those data, a complete understanding of the interaction between myocardial perfusion (regional and global) and LVMD is eagerly needed. Recent advances in the field of CZT imaging have shown the feasibility of quantitative myocardial blood flow (MBF) assessment in a PET-like fashion, as a result of the increased photon sensitivity, and energy resolution of those devices, coupled with the possibility to image the entire heart without any movement of the detector.^{17,18} However, while the accuracy and additive diagnostic value of MBF assessment with CZT cameras has been already demonstrated, the technique suffers from the intrinsic limitations of ^{99m}Tc-labeled tracers, still providing only accurate estimates of the real MBF values, especially in the high range of MBF. For these reasons, reports like the one by Mazzeletti et al.¹⁵ evaluating the possible interaction between MBF patterns derived by PET and LVMD are most welcome. Nevertheless, such an assessment would require the selection of a population of patients with variable degrees of LVMD and MBF. Finally, considering the intrinsically regional nature of LVMD, only a truly regional cardiac functional evaluation would allow the in-depth assessment of the interconnection between key parameters.^{19,20}

It is reasonable to believe that regional stress-induced myocardial ischemia would impair myocardial synchronicity, thus altering phase parameters. Accordingly, stress-induced abnormalities of phase parameters could represent specific markers of myocardial ischemia, likely increasing the accuracy of MPI in individuating clinically significant CAD.^{10,16}

On one hand, multiparametric cardiac imaging seems necessary to unmask the possible regional interplay between MBF and dyssynchrony and to individuate patients that would likely benefit from CRT, possibly guiding the procedure (i.e., correct lead placement), and stratifying long-term cardiac risk.⁵ On the other hand, the systematic implementation of phase analysis of MPI datasets could allow to refine the diagnostic capabilities of the technique and provide the unique opportunity to gather information on multiple major cardiac functional parameters within the same imaging session.

Disclosures

Dr. Riccardo Liga and Dr. Alessia Gimelli have nothing to disclose.

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