Assessment of left ventricular mechanical dyssynchrony in coronary artery disease

Chetan D. Patel, MD,^a and Anirban Mukherjee, MD^a

^a Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India

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The assessment of left ventricular mechanical dyssynchrony (LVD) using phase analysis of gated myocardial perfusion SPECT (MPS) was introduced in 2005, allowing for the simultaneous assessment of left ventricular (LV) perfusion, function, and mechanical dyssynchrony.¹ Phase analysis has shown excellent reproducibility and repeatability for assessing LVD.² Also, compared to other imaging modalities, such as echocardiography, magnetic resonance imaging, and equilibrium radionuclide angiography, phase analysis of MPS has shown several advantages, such as simplicity, widespread availability, superior reproducibility, applicability to retrospective data, and ability to simultaneously assess myocardial scar location and severity for optimizing cardiac resynchronization therapy (CRT) in heart failure patients.^{3,4} Aljaroudi⁵ outlined other potential clinical applications of LVD including prognostication and risk stratification of patients with ischemic,⁶ non-ischemic cardiomyopathy,⁷ implantable defibrillators⁸, and end-stage renal disease.^{9,10}

Several studies have demonstrated the relation of LVD with myocardial ischemic and/or scar burden,^{11–13} coronary artery disease (CAD) extent¹⁴, and LV contractile function.¹⁵ However, there are conflicting data in the literature about the effect of different patterns of perfusion abnormality on LVD in CAD patients. Aljaroudi et al¹² in their study on CAD patients who

underwent stress-rest Tc99m-sestamibi, reported that the rest and stress phase-derived standard deviation (PSD) and the rest and stress bandwidth (PHB) were similar in patients with reversible perfusion defect compared to patients with normal perfusion and that presence of even large reversible perfusion defects did not alter the indices of mechanical dyssynchrony on MPS. This was attributed to delayed image acquisition after stress in Tc99m-sestamibi study. So it was proposed, that stress-induced changes in LVD may be better evaluated using thallium-201 (Tl-201) MPS, as the post-stress images are acquired within 10 minutes of stress in Tl-201 study. Chen et al¹³ evaluated this aspect in their study on 75 patients who underwent stress-rest Tl-201 MPS. The authors suggested that stress-induced ischemia causes dyssynchronous contraction in the ischemic region, leading to worsening of LVD whereas normal myocardium showed more synchronous contraction during stress. However, in a similar study, Singh et al¹¹ found that LVD parameters were smaller on post-stress as compared to rest study on Tl-201 MPS, regardless of perfusion pattern. Stress-induced worsening of LVD was observed only in patients with perfusion abnormalities, but this is not related to the type of perfusion abnormality. Therefore, there is still a lack of clarity on the exact relationship of the LVD with the type of perfusion abnormalities on MPS performed with different radiotracers and study protocol. There are limited publications on prognostic value of LVD in patients with CAD.^{15,16} Zafir et al¹⁵ in a study group of 787 patients followed for mean duration of 18.3 ± 6.2 months observed that LVD can successfully predict cardiac death together with NYHA class, in patients with LV dysfunction.

In this issue of the Journal of Nuclear Cardiology, Gimelli et al¹⁷ have evaluated the relative interactions between coronary anatomy, myocardial perfusion, and LV function with LVD in patients with known or suspected CAD. Although LVD can be an important parameter in predicting adverse prognosis in patients

Reprint requests: Chetan D. Patel, MD, Department of Nuclear Medicine, All India Institute of Medical Sciences, B-54, South Extension Part-1, New Delhi, 110049, India; chetantruptipatel@hotmail.com
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with CAD, this article has not evaluated the prognostic implication but merely observed the prevalence of LVD and evaluated its determinants in these patients. The authors studied 657 consecutive patients with angina pain and known or suspected CAD who underwent Tc99m-Tetrofosmin MPS on a dedicated cardiac camera equipped with cadmium-zinc-telluride (CZT) detectors. Further, the coronary anatomy was assessed by either CT or invasive coronary angiography. A coronary stenosis $\geq 70\%$ was considered significant. Summed stress score (SSS), sum rest score (SRS), and summed difference score (SDS) were calculated. The authors also quantified end diastolic volume (EDV), end systolic volume (ESV), ejection fraction (EF), and peak filling rate (PFR) both for the rest and the stress studies. However, only resting LV dyssynchrony was determined in this study.

Cardiac cameras equipped with CZT detectors allow myocardial perfusion imaging at a reduced radiation burden and acquisition time with a significantly improved spatial resolution.^{18,19} However, the values of PSD and PHB as a marker of dyssynchrony indices may change with conventional vs. CZT cameras, different radiotracers, study protocol, and software used for dyssynchrony assessment and in different population. Appropriately, the authors in this study, defined the normal cut-off values of PSD and PHB from 'normal' sub-group comprising patients with normal LVEF ($>55\%$), normal coronary anatomy, and normal MPS. Thus, defining the cut-offs values which are imaging system, quantitative software (Corridor4DM), and population specific. The normal cut-off values for PSD and PHB (at rest) in this study are {men (bandwidth $89^\circ \pm 38^\circ$; SD $20^\circ \pm 10^\circ$) and women (bandwidth $88^\circ \pm 31^\circ$; SD $21^\circ \pm 11^\circ$)}.

In our experience, the normal cut-off values of PSD and PHB on Tc99 m-sestamibi derived on our own population {men (bandwidth 30.6 ± 7.6 ; SD 8.9 ± 2.9) and women (bandwidth 25.3 ± 8.6 ; SD 7.7 ± 2.7)} (unpublished data) were different from the LVD parameters reported by Chen et al¹ {men (bandwidth 38.7 ± 11.8 ; SD 14.2 ± 5.1) and women (bandwidth 30.6 ± 9.6 ; SD 11.8 ± 5.2)} using TI-201/Tc-99m sestamibi rest/exercise study. Both studies were performed on conventional cameras using same quantitative software ('SyncToolTM' Emory Cardiac Toolbox). But after taking into consideration other factors like dose of radiotracer and study protocol, the study population was found to be the most important reason for the difference in normal cut-off values of PSD and PHB. One possible explanation is that Asian population usually have a lower BMI as compared to people in the western population.²⁰ The effect of BMI is of particular importance since people with larger BMI will have more attenuation

and less counts. Lesser the counts per pixel, the higher is the noise and potential measurement errors leading to higher PSD and PHB indices.²¹ Interestingly, the normal cut-off values derived by Chen et al¹ and our values are markedly different and lower than the values obtained by Gimelli et al¹⁷ in this study which was performed on CZT system using different study protocols and quantitative software. Given these variables, it is more ideal to establish the normal cut-off values of synchrony based on specific radiotracer, dose of radiotracer, study protocol, quantitative software, and preferably specific population. The normal cut-off values of synchrony are also dependent on selection criteria of 'normal group' from which these values are derived.²²

In the present study by Gimelli et al,¹⁷ significant CAD ($\geq 70\%$ on CT/invasive angiography) was present in 415/657 (63%) patients of which 187 (45%) showed LVD. In remaining 242 (37%) patients with non-obstructive CAD, LVD was present in 60 (25%) patients. The prevalence of LVD in patients with non-obstructive CAD on angiography is high in this study population. Although, 415 (63%) patients had significant obstructive CAD on angiography, 567 (86%) patients had abnormal MPS (scar/ischemia/scar & ischemia). By convention these positive MPS results in 152 patients would be considered false positive. While LVD was present in 10/90 patients (11%) with normal MPS, it was noted in 237/567 (42%) patients with abnormal MPS. So overall, out of 247 patients with LVD, 50 patients with LVD had abnormal MPS but non-significant CAD on angiography. The authors have, therefore, observed a stronger association between the presence of LVD and perfusion abnormalities on MPS, even in the absence of significant CAD on CT or conventional angiography. But, can the presence of dyssynchrony in this subset of patient be considered as a marker of early ischemia is uncertain. A large prospective trial with long-term follow-up for cardiac events could resolve this issue and provide guidelines for management.

Stress-induced worsening of LVD is a reflection of myocardial stunning and, therefore, a marker for multivessel disease (MVD). Detection of stress-induced worsening of LVD is dependent on the time interval between peak stress and imaging.⁵ Post-stress images in TI-201 study are acquired within 10 minutes of peak stress and, therefore, it is possible to detect post-stress LVD. Huang et al¹⁴ observed that patients with MVD had significantly more global and territorial dyssynchrony at early post-stress than at rest on TI-201 study. On the other hand, in Tc99m-labeled MPS post-stress imaging usually begins 30-60 minutes after the peak stress, often resulting in the recovery of stress-induced worsening of LVD. So post-stress worsening of LVD, may often be missed during Tc99m-labeled MPS.

Interestingly, Gimelli et al¹⁷ on Tc99m-tetrofosmin study, observed higher prevalence of MVD in patients with LVD at rest than those without dyssynchrony. Since post-stress LVD was not determined in this study, it is difficult to assess the relation of MVD with post-stress or change in the post-stress and rest LVD parameters. Relation between dyssynchrony at rest on Tc99m-labeled MPS and MVD needs further validation and if established can serve as a marker for MVD.

In addition, the post-stress LVD could have provided more information on any post-stress alteration of dyssynchrony and its relation with the perfusion abnormality and other functional parameters, especially since this study was performed on CZT camera which has better count statistics (for relatively low-dose stress study) and as per protocol followed in this study, the stress images were acquired within 10-15 minutes of stress injection.

The study further investigated the interactions among myocardial functional parameters at rest (EDV & ESV index, PFR, EF), perfusion parameters (SRS, SDS) and significant CAD ($\geq 70\%$) and LVD derived on rest study. All these parameters showed significant association on univariate analysis. On multivariate analysis, the resting ESV index and SDS remained only independent predictors of LVD, overwhelming the effects of CAD extent and of LV systolic dysfunction. The authors have suggested that association of these parameters with LVD at rest might allow a better risk stratification of anginal patients, possibly helping clinical decision making.

The retrospective study by Gimelli et al has demonstrated the prevalence of LVD and its determinants in patients with known or suspected CAD. Its importance can be known only, after its prognostic implication and, therefore, its value in the management of the CAD patients is proved. A large prospective trial revealing its prognostic utility can translate LV dyssynchrony into clinically important parameter and add a new dimension in gated MPS study.

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Disclosure

The authors declare no conflict of interest.

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