Left ventricular mechanical dyssynchrony in patient with CAD: The Saga continues

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Left ventricular mechanical dyssynchrony (LVMD) by phase analysis of gated single-photon emission computed tomography (SPECT) was initially introduced by Chen et al in 2005 as a simple reliable tool that is reproducible and repeatable, performed retrospectively on previously acquired gated images, and without the need for additional imaging.^{1,2}

LVMD has been used to identify patients with cardiomyopathy who would benefit from cardiac resynchronization therapy (CRT) beyond electrical dyssynchrony and ejection fraction criteria, and based on phase standard deviation cut-offs,^{3,4} contraction patterns (U versus non-U shape),^{5,6} and concordance of LV lead placement with site of latest mechanical contraction.⁷ The software, now commercially available, has also been used to differentiate ischemic versus non-ischemic cardiomyopathy⁸ and for many other clinical indications.⁹ Furthermore, it is a powerful prognostic tool validated in different cohorts.⁹⁻¹⁵

There have been many studies evaluating a potential role for LVMD in patients with coronary artery disease (CAD). Indeed, Gimelli et al showed that 38% of patients with extensive CAD have significant LVMD which is dependent on the presence of myocardial perfusion abnormalities and LV end-systolic volume.¹⁶ In the current manuscript, Hämäläinen et al from Kuopio University Hospital, Finland, evaluated LVMD in 326 patients with CAD.¹⁷ LVMD was assessed with the

phase analysis of ECG-gated myocardial SPECT and LVMD was described with phase histogram bandwidth, standard deviation or entropy values above limit of the highest normal using a control group as a reference. Almost a third of patients with CAD had LVMD. The size of the myocardial scar (fixed perfusion defect) and ischemia (reversible perfusion defect) correlated significantly with all dyssynchrony indices ($P < 0.001$ for all). Furthermore, on multivariate analysis, independent predictors of LVMD were myocardial infarction scar ($P = 0.004$), ischemia extent ($P = 0.003$), and QRS duration ($P = 0.003$).¹⁷

In a subgroup analysis, Hämäläinen et al also showed that patients with abnormal MPI in 2 or more vessel territories had more extensive LVMD.¹⁷ The effect of stress testing on LVMD is interesting. It has been postulated that significant stress-induced ischemia may cause myocardial stunning that translates into new or worsening LVMD on stress-gated images. Indeed, Hida et al nicely demonstrated that early post-stress worsening of LVMD identified patients with multivessel ischemia.¹⁸ However, few controversial issues remain regarding the significance of stress-induced changes in LVMD. First, the detection of stunning might be problematic with Tc-99m SPECT as imaging occurs 30-60 min after injection of the tracer, unlike Tl-201 imaging.¹⁹ Second, other studies have shown that LVMD indices tend to be smaller on stress imaging as opposed to rest imaging, independent of perfusion defect,¹⁹ and likely attributed to the higher tracer dose/uptake on stress images and more noise on rest images.²⁰ Third, vasodilator stress testing which was performed on all patients in the study by Hämäläinen et al (few had hybrid testing with low-level exercise) is less likely to cause myocardial stunning and induce ischemia as opposed to exercise stress testing.

Still, the association between LVMD and abnormal myocardial perfusion imaging remains interesting and valuable. In one of the largest studies, Hess et al evaluated 1244 patients with CAD undergoing gated SPECT

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MPI and showed not only high prevalence of LVMD in this cohort but also that mechanical dyssynchrony was a strong independent predictor of death.¹² While most studies evaluated the prevalence and prognostic value of systolic LVMD in patients with CAD, Fudim et al from Duke University showed that diastolic LVMD also had prognostic role with incremental value among 1310 patients with CAD.²¹

While most studies evaluated LVMD indices in patients with stable coronary artery disease, Murrow et al showed that new LVMD occurs in the absence of electrical dyssynchrony in patients with acute myocardial infarction as a sign of LV stunning, and tends to improve as LV function recovers.²²

Over the last decade, the clinical role and importance of LVMD has gained momentum as outlined in Table 1. Where do we go from here? When evaluating stress MPI, many parameters should be taken into consideration for a comprehensive and correct interpretation. These include non-perfusion parameters (ST changes, Duke treadmill score, heart rate recovery and reserve), ejection fraction, ejection fraction reserve, transient ischemic dilatation, perfusion defect (fixed, reversible, size, number of vessel territories involved), coronary and myocardial flow and flow reserve, and more recently added to the list LVMD indices (peak stress and stress-rest). In addition, when using CT attenuation correction, the presence and extent of

Table 1. Clinical relevance and applications of left ventricular mechanical dyssynchrony by phase analysis

<i>Coronary artery disease</i>	
Stable coronary artery disease	LVMD is associated with prior infarction or ischemia ¹⁷ LVMD is dependent on the extent of myocardial perfusion abnormalities ¹⁶
Acute myocardial infarction	Early post-stress LVMD: Marker of multivessel disease ¹⁸ LVMD is prevalent in the absence of electrical dyssynchrony; Improvement in LVMD correlates with beneficial ventricular remodeling ²²
<i>Heart failure</i>	
Predictor for CRT response	High LVMD at baseline SD >43°: better response to CRT ^{3,4} U shape contraction pattern is more likely to predict response to CRT as opposed to vs non-U shape contraction pattern ^{5,6} Concordance of LV lead placement and latest site of mechanical contraction ⁷
Differentiates ischemic vs. non-ischemic cardiomyopathy	Phase SD of >14° (odds ratio 16.7) and a summed stress score of >17 (odds ratio 8.0) best differentiated LV dysfunction of ischemic and non-ischemic etiologies, with a sensitivity of 89% and a specificity of 87% ⁸
<i>Prognostic value</i>	
Patients with implantable cardiac defibrillator	LVMD predicts ICD shock and death ¹⁰
Patients with coronary artery disease	LVMD predicts all-cause death ¹¹ Phase bandwidth is associated with death after clinical adjustment (Hazard Ratio per 10°: 1.06, $P < .0001$) ¹² Diastolic LVMD is an independent predictor of mortality with incremental value in addition to systolic LVMD ²¹
Post recent acute myocardial infarction	Stress phase SD $\geq 45.5^\circ$ and stress phase BW $\geq 126.0^\circ$ were predictive of MACE, as well as suboptimal non-culprit artery revascularization ¹³
Non-ischemic cardiomyopathy and EF 35-50%	Increased LVMD on peak stress SPECT was an independent predictor of all-cause mortality ¹⁴
End-stage renal disease on dialysis without known CAD	LVMD is highly predictive of the onset of MACEs at more than 2 years of follow-up and provides incremental value over perfusion scores alone ¹⁵

BW, histogram bandwidth; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; EF, (ejection fraction); ICD, implantable cardiac defibrillator; LVMD, left ventricular mechanical dyssynchrony; MACE, major adverse cardiovascular events; SD, standard deviation; SPECT, single-photon emission computed tomography

coronary artery calcification play an important role in risk stratifying patients and identifying those with high likelihood of multivessel disease and balanced ischemia.²³ While all these parameters might be available, it is extremely hard to integrate all of them effectively and uniformly in a single report. Therefore, I foresee a risk calculator that takes into account all these variables to predict the likelihood of CAD, significant ischemia, and provide prognostic value.

With the advancement of radiomics and artificial intelligence networking (currently being evaluated in SPECT imaging),^{24,25} I believe we should start taking advantage of the technology, find algorithms, combine these parameters and many more patterns identified by artificial intelligence, to identify patients with high-risk MPI and guide clinical decisions. At the end of the day, the stress MPI is ordered for a clinical reason and therefore, we should take advantage of all the parameters it offers to help the clinician make an informed decision.

Disclosure

Wael AlJaroudi has no conflict of interest.

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