Left ventricular regional asynchrony: Earliest marker for ischemic cardiomyopathy?

Aviral Vij, MD,^{a,b} and Saurabh Malhotra, MD, MPH, FASNC^{a,b}

^a Division of Cardiology, Cook County Health, Chicago, IL

^b Division of Cardiology, Rush Medical College, Chicago, IL

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Left ventricular asynchrony (LVAS) refers to abnormal myocardial activation during a cardiac cycle resulting in non-homogeneous left ventricular contraction. Phase analysis of gated radionuclide tomography is an established technique to assess global and segmental LVAS.^{1,2} Two validated indices of LVAS include: histogram band width (HBW) which is the range (in degrees) during which 95% of the myocardium initiates contraction and phase standard deviation (PSD) which is the standard deviation (in degrees) of the timing of contraction of all the myocardial samples.³ LVAS is common in patients with heart failure and has been established as a prognostic marker of adverse outcomes.⁴ LVAS has the ability to predict clinical response to cardiac resynchronization therapy,^{5,6} and also predicts the risk of ventricular arrhythmias in patients with heart failure.⁷ Recent reports have assessed the diagnostic value of LVAS for predicting coronary artery disease (CAD) and associated myocardial hypoperfusion. Chen et al reported stress-induced myocardial ischemia to be associated with early post-stress LVAS on gated rest/dipyridamole Thallium-201 SPECT.⁸ Huang et al further showed an incremental value of stress-induced LVAS on gated SPECT, to standard visual interpretation of myocardial perfusion. In their study the extent of LVAS was related to extent of epicardial coronary artery disease.⁹ Additional studies

have shown an improvement in LVAS with medical therapy¹⁰ and with revascularization.¹¹ These observational studies provide evidence for relationship of LVAS with CAD and myocardial ischemia. Much of the experience with LVAS by phase analysis stems from gated SPECT, though extrapolation of these principles has led to application of phase analysis to gated positron emission tomography (PET).¹² PET offers better spatial resolution, allows for list-mode acquisition, along with the assessment of myocardial blood flow. Real time imaging, immediately after vasodilator administration (as opposed to SPECT, where imaging is performed 45–60 minutes after the vasodilator injection) allows for the determination of both rest and stress function and thus rest and stress LVAS.

Van Tosh et al have previously studied the change in LVAS between rest and stress gated perfusion PET, and the presence of LVAS, improvement in LVAS and induction of LVAS to be related with myocardial blood flow (MBF) and myocardial flow reserve (MFR).¹³ In the current issue of the Journal, Van Tosh and colleagues have further investigated the presence and severity of LVAS on rest/stress gated PET with indices of myocardial perfusion and flow, across subgroups of anatomical CAD.¹⁴ The authors retrospectively analyzed data of 105 patients who underwent rest and Regadenoson stress Rubidium-82 PET and quantitative coronary angiography. “Apparently normal” coronary arteries were defined as those with territorial SRS of < 4, territorial SSS < 4 and quantitative angiographic stenosis of < 70%. Regional left ventricular wall thickening, HBW computation and visual LVAS analysis was performed. Visual asynchrony scoring was performed independently by a medical imaging physicist and a cardiologist on a 5-point scale, from rest and stress systolic and diastolic phase histograms and polar maps. A composite value was then obtained by summing all the territorial scores.

Reprint requests: Saurabh Malhotra, MD, MPH, FASNC, Division of Cardiology, Cook County Health, Chicago, IL; saurabh.malhotra@cookcountyhhs.org

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As expected, results of their analysis showed a higher resting and stress MBF in apparently normal coronary arteries when compared to abnormal coronary arteries ($> 70\%$ luminal stenosis on quantitative coronary angiography). Stratification of data by MFR showed, that apparently normal arteries with $MFR < 2.0$ were associated with lower stress MBF, larger HBW and larger “Asynch” score when compared to apparently normal arteries with $MFR > 2.0$. These results were noted in the context of normal relative perfusion scores and quantified stenosis. Apparently normal arteries with 20%-69% stenosis had lower resting ($0.77 \text{ mL}\cdot\text{gm}^{-1}\cdot\text{min}^{-1}$) and stress ($1.75 \text{ mL}\cdot\text{gm}^{-1}\cdot\text{min}^{-1}$) MBF compared to arteries with $< 20\%$ stenosis ($0.91 \text{ mL}\cdot\text{gm}^{-1}\cdot\text{min}^{-1}$ at rest and $2.15 \text{ mL}\cdot\text{gm}^{-1}\cdot\text{min}^{-1}$ at stress). However, this proportional difference in absolute myocardial blood flow, amounts to a near similar MFR among arteries with $< 20\%$ or 20%-69% stenosis. Furthermore, regional HBW was lower (narrower; less LVAS) in apparently normal arteries with $< 20\%$ stenosis compared to those with 20%-69% stenosis (wider HBW). Patients with significant epicardial coronary artery disease ($> 70\%$ luminal stenosis), had lower rest/stress MBF, MFR and greater LVAS (Figure 1).

Results of this study imply that rest and stress LVAS could serve as markers of ischemia when relative myocardial perfusion is normal. While the authors suggest that LVAS could be used to indicate ischemia in otherwise “non-obstructive” coronary arteries, it is possible that a proportion of coronary arteries with anatomically significant disease may continue to have normal MBF and a “synchrony reserve”,¹⁵ stemming from preserved robust microvascular function. Similarly, in a proportion of patients with none to mildly obstructive anatomical disease, abnormal LVAS measures may suggest the presence of ischemic cardiomyopathy which could portend poor cardiovascular prognosis, possibly similar to that noted in patients with diabetes or chronic kidney disease, but no significant anatomical disease.

Despite the findings of this study, several questions remain unanswered. Among those with luminal stenosis between 20%-69% it is critical to segregate those with normal myocardial perfusion and LVAS from those in whom these indices are abnormal and indicative of subclinical ischemic cardiomyopathy. Such a distinction is not evident from the current study. Furthermore, it is well established that measures of LVAS are influenced by LV function, volume, scar burden and conduction

Figure 1. Distribution of indices of myocardial flow and left ventricular asynchrony stratified by relative perfusion and anatomical stenosis. Data from Van Tosh et al.¹⁴

Figure 2. Ischemic cascade depicting a possible role of left ventricular asynchrony (LVAS) for predicting subclinical ischemic cardiomyopathy.

abnormalities,^{16–18} which also influence indices of myocardial perfusion.^{19,20} The effect of these confounders on the relationship between LVAS and myocardial perfusion indices needs to be excluded to clearly elucidate the relationship between LVAS and subclinical flow heterogeneity. Additional clarity will be needed on the clinical application of LVAS for diagnosis of CAD—overt or subclinical. It is not known if LVAS will provide incremental diagnostic and even prognostic value over indices of myocardial flow. Knowledge of this additional value of LVAS will guide routine assessment of LVAS on myocardial perfusion PET. Application with SPECT could be more challenging, given that routine gated rest imaging is not performed and assessment of rest LVAS could be degraded by low count density of rest images. While stress LVAS could be assessed with gated SPECT, assessment of a clinically relevant change in LVAS between rest and stress SPECT will be challenging. These hurdles could be overcome by imaging on CZT cameras that allow for high quality imaging even at low tracer dose. Additionally, peak stress or immediately post-stress LVAS assessment cannot be performed with SPECT given the inherent delay in image acquisition.

Nonetheless, this study adds to the growing evidence of the relationship between myocardial blood flow and LVAS. While incorporation of LVAS as a diagnostic paradigm for subclinical CAD requires further rigorous analysis, addition of LVAS assessment on myocardial perfusion imaging, could have a significant impact of management. Aggressive risk factor modification, high intensity statin and other lifestyle changes to halt atherosclerotic disease progression could be emphasized, when LVAS suggests the presence of subclinical ischemic cardiomyopathy. If the causal association between LVAS and myocardial blood flow is established, one could envision LVAS on gated myocardial perfusion imaging to become an integral part of the ischemic cascade (Figure 2).

Disclosures

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