Spotlight on left ventricular dyssynchrony: Part 1—Performance, variability, and mechanisms

Saurabh Malhotra, MD, MPH, FASNC,^a and Ami E. Iskandrian, MD, MASNC^b

^a Division of Cardiology, John H Stroger Hospital of Cook County, Chicago

^b Medicine, University of Alabama at Birmingham, Birmingham

Received Oct 4, 2020; accepted Oct 5, 2020

doi:10.1007/s12350-020-02406-8

Left ventricular dyssynchrony (LVD) is typified by temporal differences in activation and contraction of various myocardial segments of the left ventricle (LV). LVD is not an all-or-none phenomenon and ranges from minor differences in normal ventricles to marked abnormalities in failing hearts or those with marked conduction abnormalities. Phase analysis of gated radionuclide imaging (RNI) is an established technique for assessment of LVD and is measured by many indices, the two most commonly used are the phase standard deviation (PSD) and the phase histogram bandwidth (HBW). Among patients with heart failure (HF), the presence of LVD is usually defined by cutoffs (typically mean + 2 SD) of PSD and HBW seen in normal populations, though alterations in LV contraction, under these thresholds, have been reported among patients with ischemia, but without significant LV dysfunction. Given that LVD can be easily assessed from routinely performed gated radionuclide studies (mostly tomographic imaging), many centers around the world are studying the application of LVD in clinical practice. Over the next few issues, the Journal will showcase several research studies focusing on LVD, that address mechanisms of LVD, and its ability to diagnose cardiovascular disease and to provide prognostic information. With this effort, we aim to increase awareness regarding the determination of LVD from gated RNI, which adds to its existing armamentarium of perfusion, function, and molecular imaging. We hope that many others will be enthused to further the research on LVD and its clinical applications.

Phase analysis improves the temporal resolution of an inherently low temporal resolution of gated RNI,

especially tomographic imaging, which typically employs 8- or 16-bin gating. In doing so, the timing of contraction of myocardial segments is now identified in degrees, ranging from 0 to 360. While this allows for an improved fidelity for assessing timing of myocardial activation, measurement of time in degrees is not intuitive in medicine, as we typically assess time in milliseconds (ms), e.g., when assessing electrocardiograms and measuring the duration of the QRS complex. In this issue, Barron and colleagues report the relationship between LVD indices measured in ms vs. degrees in a population of patients with normal perfusion and function on gated Tc-99m SPECT. They found that though these measurements of timing of myocardial contractility are strongly correlated, the two units of measurement are not interchangeable. Measurement in ms is strongly influenced by heart rate, while measurement in degrees is not. This has clinical implications, especially when comparing patients with differing heart rates and when performing serial imaging, wherein there may be variability in heart rates at the time of imaging. Use of degrees as a unit of timing seems more robust and not influenced by heart rate. Importantly, this report also found that PSD and HBW values did not significantly differ when measured by vasodilator or exercise stress test and confirmed the presence of gender-specific LVD cutoffs.

The excellent repeatability of phase analysis indices has been previously reported among normal and diseased patients. Legallois and colleagues further evaluated the repeatability of indices of LVD in a population with ischemic cardiomyopathy and LV ejection fraction < 50%, in a sub-analysis of a multicenter study. The authors performed two resting gated SPECT after administration of low-dose Tc-99m-based tracer and found repeatability to be somewhat inferior to that reported by prior studies. Additionally, in their study, a third index called entropy (Lin's concordance correlation coefficient = 0.80) had superior repeatability when

Reprint requests: Saurabh Malhotra, MD, MPH, FASNC, Division of Cardiology, John H Stroger Hospital of Cook County, Chicago; saurabh.malhotra@cookcountyhhs.org

J Nucl Cardiol 2020;27:1903–4.

1071-3581/\$34.00

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compared to PSD (0.75) and HBW (0.68). This report highlights several important concepts as they pertain to phase analysis for LVD assessment. Phase analysis uses changes in myocardial count density during a cardiac cycle to assess indices of LVD. Low-dose gated studies are count poor and are likely more subject to variability, even when the acquisitions are performed in quick succession. It is also known that gated information from low-dose studies is suboptimal to that obtained by high-dose studies, and thus, it is intuitive that phase indices will also be more prone to variability. Secondly, entropy, which is less influenced by noise in the phase distribution, had superior repeatability when compared to PSD and HBW. Hence, if PSD and HBW are being assessed as measures of LVD, then it is paramount that these be assessed with high-dose gated tomographic imaging, which is often the case in clinical practice. If low-dose gated imaging is employed for assessment of LVD, then entropy is probably a more robust marker.

Though primarily studied in refractory heart failure, presence of LVD has been reported in numerous other pathologic states, even when there is no overt LV dysfunction. As such, LVD likely represents a conglomerate of a variety of myocardial pathologies: scar, ischemia, flow heterogeneity, LV remodeling etc. However, many of these states may not co-exist in all the patients all the time. Myocardial pathologies can be reversible, such as ischemia, making LVD a dynamic process. As such, presence, severity, or change in LVD is likely to be predicted by underlying pathological myocardial processes. This is exemplified by two different research studies published in this issue. Camilletti et al. report the distribution of LVD indices among patients with normal perfusion to those with myocardial ischemia on bicycle ergometer stress-first gated myocardial SPECT. Those with perfusion abnormalities had no resting defects, and LV function among both the normal and abnormal perfusion groups was normal. Though post-stress gated SPECT images were acquired 45-60 minutes after stress,

the phase indices among those with myocardial ischemia were significantly worse when compared to those with normal perfusion. Among those with ischemia, gated rest SPECT showed a significant improvement in indices of LVD. This evaluation adds to the growing literature on the association of LVD with ischemia and its ability to predict more severe disease. Ischemia in this population was fairly extensive, ~15% LV myocardium, and is likely to result in myocardial stunning which caused the worsening of phase indices. Contrary to the report by Camilletti et al., Juarez-Orozco and colleagues used N-13 ammonia PET to assess the contributors to LVD in a population with chronic HF. PSD, HBW, and entropy were the indices of LVD that were evaluated from post-adenosine-stress gated PET. In this HF population with severely reduced LV ejection fraction (mean = 33%) and large scar burden (~15% LV myocardium), scar burden was an independent predictor of LVD indices. There were no significant differences in indices of LVD across tertiles of stress myocardial blood flow (sMBF) or myocardial flow reserve (MFR). Though many patients with HF may have concomitant reduced MBF, the severity of LV remodeling from large myocardial scars overshadows MBF as the major contributor for LVD. These studies highlight two extremes in myocardial pathology that produce LVD: severe reversible myocardial ischemia producing myocardial stunning and severe myocardial scarring. These mechanistic bases for generation of LVD are important to consider when developing diagnostic and prognostic studies of LVD. While induction of LVD due to flow heterogeneity and ischemia is likely to be more helpful in diagnosis of underlying CAD, the presence of fixed LVD in HF patients is more likely to favor the determination of prognosis w.r.t ventricular tachyarrhythmia or cardiac death.

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