The independent prognostic value of left ventricular dyssynchrony

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Stress Gated SPECT myocardial perfusion imaging (MPI) provides powerful prognostic information that is incremental to myocardial perfusion pattern including left ventricular ejection fraction (LVEF), transient ischemic dilation, exercise-specific parameters (functional capacity, heart rate response and recovery and electrocardiographic changes), vasodilator-specific parameters (inability to exercise, heart rate response and electrocardiographic changes), and absolute quantitation of myocardial blood flow.[1,2] MPI, using phase analysis, can also assess the synchrony of LV contraction. The development of this technique, its validation, and the advantages it provides to the field has been reviewed elsewhere.[3,4] Although phase analysis has been used primarily to guide resynchronization therapy, there has been recent interest in the prognostic information provided by its parameters. This has been fueled by the realization that LV mechanical dyssynchrony is common even in patients with narrow QRS on electrocardiography and in those with normal or only mildly depressed LVEF.[5-7] Studies have shown that dyssynchrony on phase analysis is associated with worse outcomes in patients with heart failure and in those with end-stage renal disease.[7-11]

In this issue of the *Journal*, Zafrir et al.[12] examine whether LV dyssynchrony is associated with worse cardiac outcomes in all patients studied at a single university-affiliated laboratory over a 2-year period. After excluding 86 patients due to incomplete data, they report findings on a cohort of 787 patients (42% exercise, 45% dipyridamole, 9% rest only) followed for 18.3 ± 6.2 months. During this time, 55 patients died (26 from cardiac causes), 16 patients were hospitalized with heart failure, and three were hospitalized with ventricular tachycardia or fibrillation. Patients with cardiac events (composite of cardiac death and hospitalization for heart failure or ventricular tachycardia or fibrillation) had wider phase standard deviation (SD) and bandwidth (BW) than those without events but this association was not statistically significant after multivariate adjustment. NYHA functional class, diabetes, and LVEF <50% were the only independent predictors of the composite outcome of cardiac events. In contrast, phase SD (hazard ratio for 10° increase 1.2, 95% CI 1.01-1.45, $P = .043$) and NYHA, but not LVEF, were the independent predictors of cardiac death. When an abnormal phase SD cutoff was used (40°), composite cardiac events occurred in 12.4% of patients with abnormal phase SD and 3.5% of patients with normal phase SD ($P < .001$). The respective numbers for cardiac deaths were 7.8% and 1.9% ($P < .001$).

In a separate report, Pazhenkottil et al.[14] studied 202 consecutive patients (197 patients with follow-up) who underwent 1 day adenosine stress-rest MPI for evaluation of known or suspected coronary artery disease at a university hospital. During 3.2 ± 1.2 years of follow-up, 62 major adverse cardiac events (a composite of cardiac death, hospitalization for cardiac reason including heart failure, nonfatal myocardial infarction, unstable angina, and coronary revascularization occurring after 30 days of the index MPI) occurred in 41 patients including 5 cardiac deaths. LV dyssynchrony, based on previously derived cutoffs,[13] was associated with major adverse cardiac events in univariate (hazard ratio 3.6, 95% CI 1.9-6.8, $P < .001$) and multivariate analyses (hazard ratio 2.0, 95% CI 1.0-4.2, $P < .05$) that adjusted for age, gender, cardiovascular risk factors, myocardial perfusion, and LVEF.

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In both the studies of Zafrir et al.[12] and Pazhenkottil et al.,[14] LV dyssynchrony by phase analysis was independently associated with worse outcomes in patients referred to MPI. Although LVEF and phase SD are correlated as shown by Zafrir et al., phase SD, but not LVEF, was a significant predictor of poor outcome in the multivariate models (for cardiac death in the study of Zafrir et al. and for major adverse cardiac events in the study by Pazhenkottil et al.). A theoretical argument as to why parameters from a phase histogram may be more sensitive than LVEF is that LVEF reflects volume measurements at only two points in the cardiac cycle whereas the phase histogram reflects the mechanical thickening information of every LV segment at every point in the cycle.[13] Moreover, there is no guarantee in the LVEF measurement that every endocardial segment in the LV will reach end-diastole or end-systole at the same exact time point in the cardiac cycle. This is especially important in malfunctioning LVs, thus reducing the magnitude of the LVEF calculation.

As noted by Zafrir et al.,[12] both of these studies used LVEF cutoff values of 50% rather than continuous values which are known to be a stronger prognostic predictor. The same can be said for using a single cutoff for phase SD. The information provided by using continuous variables to better characterize disease may be gleamed from Fig. 2 in Zafrir et al. [12] where phase SD is plotted vs LVEF in each patient. Note that for an LVEF of 50% (cutoff) phase SDs approximately range from a very normal 10° to a very abnormal 60°. Note that the lower the LVEF the wider the spread in phase SD highlighting the variation in dyssynchrony in patients with the same abnormal LVEF. Similarly, for a phase SD of 40% (cutoff) LVEF approximately range from 10% to 70%. Thus, in specific patients, using a single cutoff of one variable can significantly limit the clinical information given by the other variable even though the correlation between the two variables is 0.52. Thus, in the study by Zafrir et al.[12] phase SD, but not LVEF, was an independent predictor of cardiac death, while LVEF, but not phase SD, was an independent predictor of the composite endpoint of cardiac events.

This last statement reflects the importance of endpoint selection. We are proponents of all-cause mortality as an unbiased, accurate, and clinically meaningful endpoint.[15] Use of composite endpoints can be problematic and may lead to confusion in the interpretation of studies.[16] The use of cause-specific mortality and composite outcomes are further exaggerated in retrospective studies where the outcomes are not adjudicated. Nevertheless, a case can be made for composite outcomes to increase the power of a study when event rates and/or study population are small if the elements of the composite outcome are meaningful to patient care. Both studies included hospitalization for cardiac causes in their composite endpoint, an event that is valuable but dependent on the subjective assessment of the physician taking care of the patient and the healthcare system where the study is conducted and may therefore limit the generalization of the findings. Furthermore, Zafrir et al. [12] included hospitalization for ventricular arrhythmias in their endpoint but did not include appropriate therapy by implantable cardioverter defibrillators. The importance of this is highlighted by recent studies showing the association of LV dyssynchrony with sudden cardiac death events.[9,11]

A limitation of using a single cutoff value for phase SD (or BW), particularly when determined from ''normal controls'' is that it depends on the definition of normal in the context of the disease being studied. Note that in the article by Zafrir et al. [12,] the abnormal phase SD cutoff value used was 40° (18 + (2 × 11)) where in the 2005 article that originally defined these results by Chen et al.[13] and used by Pazhenkottil et al.,[14] the phase SD cutoff values reported were 24.4° (14.2 + (2 × 5.1)) for men and 22.2° (11.8 + (2 × 5.2)) for women. The difference between these two reports is explained by the differences in how the normal populations were defined. In Chen et al.[13,] the normal population was defined from MPI studies of 45 men and 45 women with <5% likelihood of coronary artery disease where in Zafrir et al.,[12] they are defined based on the subset of patients (n = 226) with normal perfusion, normal electrocardiogram QRS width <100 ms and LVEF ≥50%. Thus, it is important for clinicians to realize that a patient should not be automatically treated because their LV is slightly dyssynchronous with their phase SD just exceeding a normal cutoff defined from normal controls. For example, for predicting response to resynchronization therapy, Henneman et al.[17] determined that a phase SD of 43° (almost double the normal cutoff values by Chen et al.[13]) best separated responders from non-responders.

One obstacle to the widespread clinical use of LV mechanical dyssynchrony as a diagnostic or prognostic tool is that parameters like phase SD or phase BW do not instinctually portray the same straightforward clinical information as LVEF. One attempt to address this, albeit with a different technique, is to examine mechanical efficiency (defined as effective stroke work divided by theoretical maximal work) which deteriorates as a result of LV mechanical dyssynchrony.[18] Similarly, thickening efficiency may be defined as effective thickening divided by theoretical maximal thickening, where the latter is measured by assuming that every segment in the LV thickens maximally at one point in time. Parameters like thickening efficiency and mechanical efficiency, properly validated, can be used in the future to convey information on LV synchrony using parameters that are easier to understand in a clinical setting.

With this recent data showing an independent association of LV mechanical dyssynchrony with adverse outcomes, we are coming closer to the development of a comprehensive risk assessment tool using MPI based on complementary risk predictors. It is important to stress the need for the verification of these findings in other centers, and preferably in multicenter studies with pre-defined endpoints.

References

1. Shaw LJ, Hage FG, Berman DS, Hachamovitch R, Iskandrian A. Prognosis in the era of comparative effectiveness research: Where is nuclear cardiology now and where should it be? J Nucl Cardiol 2012;19:1026-43.
2. Hage FG, Gupta A, Iskandrian AE. Risk assessment in the era of high-speed myocardial perfusion imaging. J Nucl Cardiol 2012;19:1102-5.
3. Chen J, Henneman MM, Trimble MA, Bax JJ, Borges-Neto S, Iskandrian AE, et al. Assessment of left ventricular mechanical dyssynchrony by phase analysis of ECG-gated SPECT myocardial perfusion imaging. J Nucl Cardiol 2008;15:127-36.
4. Chen J, Garcia EV, Bax JJ, Iskandrian AE, Borges-Neto S, Soman P. SPECT myocardial perfusion imaging for the assessment of left ventricular mechanical dyssynchrony. J Nucl Cardiol 2011; 18:685-94.
5. Samad Z, Atchley AE, Trimble MA, Sun JL, Shaw LK, Pagnanelli R, et al. Prevalence and predictors of mechanical dyssynchrony as defined by phase analysis in patients with left ventricular dysfunction undergoing gated SPECT myocardial perfusion imaging. J Nucl Cardiol 2011;18:24-30.
6. Atchley AE, Trimble MA, Samad Z, Shaw LK, Pagnanelli R, Chen J, et al. Use of phase analysis of gated SPECT perfusion imaging to quantify dyssynchrony in patients with mild-to-moderate left ventricular dysfunction. J Nucl Cardiol 2009;16:888-94.
7. Goldberg AS, Alraies MC, Cerqueira MD, Jaber WA, Aljaroudi WA. Prognostic value of left ventricular mechanical dyssynchrony by phase analysis in patients with non-ischemic cardiomyopathy with ejection fraction 35-50% and QRS <150 ms. J Nucl Cardiol 2014;21:57-66.
8. AlJaroudi W, Alraies MC, Hachamovitch R, Jaber WA, Brunken R, Cerqueira MD, et al. Association of left ventricular mechanical dyssynchrony with survival benefit from revascularization: a study of gated positron emission tomography in patients with ischemic LV dysfunction and narrow QRS. Eur J Nucl Med Mol Imaging 2012;39:1581-91.
9. Aljaroudi WA, Hage FG, Hermann D, Doppalapudi H, Venkataraman R, Heo J, et al. Relation of left-ventricular dyssynchrony by phase analysis of gated SPECT images and cardiovascular events in patients with implantable cardiac defibrillators. J Nucl Cardiol 2010;17:398-404.
10. AlJaroudi W, Aggarwal H, Venkataraman R, Heo J, Iskandrian AE, Hage FG. Impact of left ventricular dyssynchrony by phase analysis on cardiovascular outcomes in patients with end-stage renal disease. J Nucl Cardiol 2010;17:1058-64.
11. Hage FG, Aggarwal H, Patel K, Chen J, Jacobson AF, Heo J, et al. The relationship of left ventricular mechanical dyssynchrony and cardiac sympathetic denervation to potential sudden cardiac death events in systolic heart failure. J Nucl Cardiol 2014;21:78-85.
12. Zafrir N, Roman N, Tamir B, Boris S, Ariel G, Israel M, et al. Prognostic value of left ventricular dyssynchrony by myocardial perfusion-gated SPECT in patients with normal and abnormal left ventricular functions. J Nucl Cardiol 2014. doi:10.1007/s12350-014-9852-1.
13. Chen J, Garcia EV, Folks RD, Cooke CD, Faber TL, Tauxe EL, et al. Onset of left ventricular mechanical contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. J Nucl Cardiol 2005;12:687-95.
14. Pazhenkottil AP, Buechel RR, Husmann L, Nkoulou RN, Wolfrum M, Ghadri JR, et al. Long-term prognostic value of left ventricular dyssynchrony assessment by phase analysis from myocardial perfusion imaging. Heart 2011;97:33-7.
15. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: Time for a reassessment? J Am Coll Cardiol 1999;34:618-20.
16. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, et al. Problems with use of composite end points in cardiovascular trials: Systematic review of randomised controlled trials. BMJ 2007;334:786.
17. Henneman MM, Chen J, Dibbets-Schneider P, Stokkel MP, Bleeker GB, Ypenburg C, et al. Can LV dyssynchrony as assessed with phase analysis on gated myocardial perfusion SPECT predict response to CRT? J Nucl Med 2007;48:1104-11.
18. Di Donato M, Toso A, Dor V, Sabatier M, Barletta G, Menicanti L, et al. Surgical ventricular restoration improves mechanical intraventricular dyssynchrony in ischemic cardiomyopathy. Circulation 2004;109:2536-43.