Measuring mechanical cardiac dyssynchrony in the 3-D era

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The use of dobutamine in heart failure (HF) patients can be connected to either a therapeutic or a diagnostic strategy. When dilated cardiomyopathy patients with acute decompensated heart failure (ADHF) and low left ventricular ejection fraction (LVEF) are treated with inotropic agents in an hospital setting, the main goal is that of improving cardiac function and relieving symptoms until definitive therapy (coronary revascularization, heart transplantation, etc.) is performed, or the acute precipitating problem has resolved.^{1–3} While there are concerns that inotropic agents may adversely affect mortality and clinical outcomes,^{4,5} dobutamine is nevertheless widely used in ADHF patients with low LVEF and is effective in inducing improvements in both myocardial contractility and vascular endothelial function,⁶ with the effects sometime lasting up to a month or longer and inspiring the term “dobutamine holiday.”⁷

From a diagnostic perspective, dobutamine stress testing has been employed to identify potential cardiac resynchronization therapy (CRT) responders. Logically speaking, CRT can be expected to be effective only if dyssynchrony exists, either at rest or at stress, and dobutamine stress may help bring about regional differences in myocardial contractility. Moreover, a

dobutamine-induced variation in dyssynchrony, whether positive or negative, may bear a greater relationship to clinical outcomes than rest dyssynchrony, similarly to what has been reported for exercise stress.⁸ Of note, dyssynchrony may compensate the typical stress-induced increase in contractile reserve (CR), resulting in a paradoxical lack of increase in ejection fraction in spite of greater myocardial contractility.⁹

While the standard for referral to CRT is still a wide (>120 ms) QRS complex,¹⁰ it has been reported that one-third of heart failure patients with a wide QRS do not have mechanical dyssynchrony, while 40–50% of those without a wide QRS do,¹¹ these findings probably representing a major reason why about 30–40% of patients referred to CRT do not benefit from it.¹² If dyssynchrony is a better predictor of response to CRT than QRS width, as well as possibly better correlated to adverse outcomes—for example, dyssynchrony that develops under exercise stress has been reported to be associated with a higher frequency of adverse cardiac outcomes in patients with dilated cardiomyopathy (DCM) and narrow QRS complex¹³—it would appear important to expend the effort to measure cardiac dyssynchrony in the most accurate and precise (reproducible) manner.

Cardiac dyssynchrony has been typically measured using echocardiographic techniques, which are mostly two-dimensional and not as standardized as one might want, in terms of both study performance and image analysis. Indeed, the Predictors of Response to CRT (PROSPECT) multicenter trial, whose results suggested that no individual echocardiographic measure of mechanical cardiac dyssynchrony could predict response to CRT with good sensitivity and specificity, suffered from unacceptably high inter-observer variabilities (32–72%) and intra-observer variabilities (16–24%).¹⁴ The implied message here is perhaps that a three-dimensional, standardized and automated imaging modality is the most natural and suitable choice to measure a

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Figure 1. Wall motion phase analysis of a 59-year-old male patient with LAD disease and an apical LV aneurysm. *Top row* GBPS study, processed with an automated algorithm.²⁵ *Bottom row* resting MPI study of the same patient, acquired 4 months later and processed with an automated algorithm²¹ modified to perform endocardial motion phase analysis. From *left to right* End-diastolic (ED) contours, end-systolic (ES) contours, wall motion phase polar map, and wall motion phase histogram. Both BPGS and MPI allow the visualization and quantification of apical dyskinesia, as demonstrated by the similarity of the phase polar maps and histograms, despite the large apical perfusion defect evident in the MPI data.

“difficult” parameter such as dyssynchrony, which ought to retain an essential role in the evaluation of the prospective CRT patient.⁸

Cardiac Magnetic Resonance Imaging (cMRI) allows high-resolution tracking of myocardial surfaces in the 3-D space (albeit via non-isotropic voxels), using advanced techniques such as myocardial tagging, harmonic phase analysis, and strain encoding.¹⁵ While promising, cMRI suffers from high equipment cost, complexity of image acquisition, and lack of fully automated algorithms for image quantification, leading to its narrowly spread application to the measurement of mechanical cardiac dyssynchrony. Similarly, multi-detector computed tomography (MDCT), although capable of acquiring high-resolution images of the entire heart in the time of a breath-hold, is challenged both by a still limited temporal resolution and by the lack of standardized and automated analysis tools.¹⁶

In historical and practical terms, the main alternatives to echocardiography for the assessment of mechanical dyssynchrony have been nuclear cardiology techniques, with the planar radionuclide ventriculography (PRNV) approach originally described in 1980,¹⁷ eventually evolving into gated blood pool SPECT (GBPS) to better quantify the 3-D heart.¹⁸ Both PRNV and GBPS can measure mechanical dyssynchrony associated with endocardial motion by analyzing the variation of counts within, or at the periphery of, a

region of interest over the cardiac cycle. Accordingly, the paper by Salimian et al. in this issue of the Journal¹⁹ uses a previously described and validated GBPS algorithm to measure intra- and inter-ventricular dyssynchrony, as a function of varying degrees of dobutamine stress, in eight dogs with tachycardia-induced dilated cardiomyopathy (DCM). With the caveats that coronary artery disease (CAD) rather than DCM causes systolic heart failure in most cases in the United States,²⁰ and that induced DCM in a canine model is not by its nature equivalent to chronic HF in humans, this study contributes to the growing body of literature seeking to clarify the relationship between mechanical cardiac dyssynchrony and heart failure.

Of interest, gated myocardial perfusion imaging (MPI) can also be used to measure dyssynchrony. Because of the high prevalence of clinical use of MPI, which accounts for perhaps 10 times as many studies as GBPS in the USA, automated and highly reproducible algorithms for the quantification of MPI motion and thickening have been developed, validated, and widely used for the past 20 years,²¹ and phase analysis of the onset of MPI-derived regional left ventricular (LV) contraction has been proposed over 10 years ago for the specific purpose of assessing dyssynchrony.²² As demonstrated in Figure 1, regional LV motion as well as its phase histogram are substantially equivalent when measured by GBPS and MPI in the same patient. Partial

Figure 2. LV and RV segmentation of F-18 flurpiridaz PET MPI images. The high resolution of PET (compared to SPECT) along with the favorable imaging characteristics of F-18 allow for clear delineation of both LV and RV.

volume effect, which is supposedly less of a problem for GBPS due to the larger dimensions of the blood pool compared to the myocardium, is actually used in MPI as a tool to more accurately estimate myocardial thickening through image “brightening.”²¹

While this is obviously not a concern in DCM patients, GBPS is often thought to offer increased robustness in the presence of large perfusion defects; however, a simulation study has demonstrated the accuracy of MPI phase analysis in ventricles where defect uptake is as low as 10% of that in normal regions,²³ as also shown in Figure 1. Perhaps more importantly, myocardial thickening may better assess the dyssynchrony of myocardial contraction by being less susceptible to tethering effects of defect areas²⁴—indeed, in some MPI quantitative algorithms, endocardial motion is defined as a combination of mid-myocardial wall motion and myocardial thickening.²¹

A potential advantage of GBPS over MPI is its ability to assess both LV and right ventricular (RV) motion, and consequently inter-ventricular dyssynchrony. Using phase analysis, inter-ventricular dyssynchrony is measured by evaluating the delay between the LV and RV onset of contraction, and can be calculated as the difference between the means of the LV and RV phase histograms, or through cross-correlation of LV and RV time-activity curves approach.¹⁹ This advantage may become less relevant in the future, as the increasing use of PET MPI and high-resolution,

dedicated cardiac SPECT hardware and reconstruction algorithms allow us to better visualize and quantify RV function, as shown in Figure 2.

Disclosure

The authors have no conflict of interest to disclose with respect to this editorial.

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