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EDITORIAL COMMENT

Surrogate Survival

Battle Between Left Ventricular Ejection Fraction and Global Longitudinal Strain*

Gillian A. Whalley, PhD

Left ventricular ejection fraction (LVEF) is a commonly used surrogate for stroke volume (SV) and thus cardiac output. In the early 1970s, Richard Popp and Harrison (1) demonstrated it was possible to measure SV by echocardiography, but noninvasive measurements of SV remained somewhat unreliable. However, even when SV is reliably measured, measuring SV in isolation is not sufficient either, because the heart remodels in response to injury or disease. Thus, normal SV may be maintained in the presence of severe left ventricular (LV) dilation and dysfunction (2). In order to account for LV size, LVEF was derived.

Both LVEF and LV size are important predictors of outcome (3-5), and despite LVEF having no physiological nor anatomical equal, LVEF has become a widely used surrogate endpoint and a key component of many management guidelines. Presently, LVEF is assessed during almost all echocardiograms but remains subject to significant interobserver and test-retest variability, even with contrast and 3-dimensional (3D) approaches. Overall, echo LVEF is a useful endpoint in cohorts but is difficult to apply in individuals and lacks reproducibility between days. Furthermore, although LVEF is a useful prognostic marker in many patient groups (e.g., those with dilated cardiomyopathies or ischemic heart disease) it is not enough. In heart failure, for example, symptomatic patients increasingly present with preserved LVEF, and LVEF provides no additional prognostic information in that setting (4,5). Additional measurements of LV function are needed, and global longitudinal strain (GLS), assessed by speckle tracking, is potentially very useful in this setting.

Speckle tracking, which tracks individual reflected signals from the myocardium throughout the cardiac cycle, provides a measure of myocardial deformation and is a truly noninvasive measurement of myocardial performance. Through research-driven consensus, GLS, incorporating deformation in the apical 4-, 2-, and 3-chamber views, has been established as the universal measurement of LV deformation. GLS is particularly useful for detection of early systolic dysfunction, such as early detection of LV dysfunction in metabolic disorders (6) and associated with cardiotoxicity (7). In both cases, LVEF does not detect early dysfunction, whereas GLS detects important preclinical changes in these and other patient groups (8).

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Medvedofsky et al. (9) present a retrospective study demonstrating GLS has superior prognostic power to measure LVEF. The overall cohort in their study represents a highly select group of clinical patients (patients in nonsinus rhythm and with poor images were excluded). Differences in end-systolic volume, LVEF, and GLS were detected between survivors and nonsurvivors, but the novel finding is that GLS was better at differentiating groups on the basis of Kaplan-Meier survival than LVEF. GLS identified 3 distinct groups, whereas LVEF did not. The fact that GLS performed better in this cohort, where the mean LVEF was 52% and approximately one-half of the subjects had normal or near-normal LVEF, makes sense. Previous studies in heart failure populations have shown that LVEF does not predict survival when LVEF is >50% (4,5), and this is where GLS may be especially useful. This is the key message of this study: GLS is especially useful when LVEF falls in the mid-normal range.

Linking GLS with prognosis has garnered significant interest recently. Evidence that GLS is an important predictor of survival and *potentially* a better overall predictor than LVEF is supported by a recent meta-analysis (10). However, that meta-analysis included a

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From the Unitec Institute of Technology, Auckland, New Zealand. Dr. Whalley has reported that she has no relationships relevant to the contents of this paper to disclose.

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mixture of study cohorts (heart failure, acute myocardial infarction, amyloid hearts, aortic stenosis, and transplant patients), and LVEF was mostly in the normal-to-mildly impaired range. Importantly, the cause of LV dysfunction is different in each clinical cohort. For example, the usefulness of GLS to detect early systolic dysfunction in a patient with aortic valve disease is potentially greater than in a patient with stable systolic heart failure. Another recent meta-analysis confirmed that GLS is a tool with enough sensitivity to identify early systolic dysfunction in heart failure cohorts with preserved LVEF (11). These studies and the current study suggest that GLS is not a replacement for LVEF but is an adjunct measurement that is especially useful when LVEF is normal or nearly normal and will vary depending on clinical context.

Medvedofsky et al. (9) also present data for 3D-GLS. Although it is evident that 3D methods significantly improve measurements of LVEF, mostly in terms of variability and accuracy, the impact of adding 3D-GLS is modest at best in the current study. The authors present statistical models showing 3D-GLS is superior to 2D, but when the Kaplan-Meier survival curves are compared, there is really no overt benefit. The largest impact of this study comes from the addition of GLS to LVEF. Further addition of 3D-GLS is not supported by these data. Furthermore, GLS relies on good image quality and high frame rates, neither of which is consistently achieved with current 3D methods.

Medvedofsky et al. (9) provide some tantalizing data regarding LV shape and curvature of the inferior wall and septum. Survivors tended to have more cone-shaped ventricular cavities: sphericity, or roundness, which was associated with poor prognosis. This is consistent with early work showing that remodeling of the heart was deleterious and that larger LV volumes predicted poor outcomes alongside LVEF (3), highlighting the need to incorporate LV volume and shape into assessments of LV function. The current study also found that flattening of the septum (presumably due to right ventricular pressure overload) and the convexity of the inferior wall (presumably due to remodeling of the LV cavity) were linked to worse outcome. These represent 2 very different mechanisms, but both reflect deleterious pathophysiology. Sphericity reflects the global underlying pathophysiology leading to LV dysfunction and is an important piece of the systolic dysfunction puzzle. Sphericity provides information about remodeling, regardless of the cause, and alongside volumes, LVEF and GLS provides a comprehensive picture of LV status.

It is timely to remember that all echo measurements of LV systolic function are surrogates. Although GLS focuses on myocardial deformation and not the change in blood volume (as LVEF does), it remains a surrogate. Are researchers simply refining favorite surrogates and not getting closer to true measurements of the underlying pathophysiology? Is continuous improvement occurring at the expense of innovation? In a quote attributed to the late Oren Harari, a business professor at University of San Francisco, the electric light did not come from continuous improvement of candles. Are these surrogates our candles?

The current study supports previous work suggesting that GLS should be measured in all patients and considered alongside LVEF, primarily because GLS is the best method we currently have to identify early LV systolic dysfunction. Larger studies in individual disease cohorts (e.g., patients with hypertrophic heart disease, valve disease, heart failure, and so forth) are needed to clearly establish the complementary rather than competitive roles of GLS and LVEF. GLS is not a replacement for LVEF; GLS is an adjunct to LVEF. Neither measurement stands alone: LVEF *and* GLS should be used in a stepwise manner, and both should be reported in the context of LV volume and shape.

ADDRESS FOR CORRESPONDENCE: Dr. Gillian Whalley, Unitec Institute of Technology, 139 Carrington Road, Mount Albert, Auckland 1025, New Zealand. E-mail: gillianwhalleyphd@gmail.com.

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