Prognostic Importance of a New Measure of Global Systolic Heart Function in Healthy Adults

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See related article, pp 770–778

Imaging left ventricular systolic function has functional and prognostic importance.1 Imaging with echocardiography has a broad range of indications,3 is usually straightforward to perform by trained staff, and is harmless. Compared with echocardiography, other heart imaging methods of systolic function, including magnetic resonance imaging (MRI), computed tomography, x-ray ventriculography, and radionuclide ventriculography, are less susceptible to measurement errors but are more expensive and, with the exception of MRI, are associated with ionizing radiation.

The appropriateness and use of different imaging tests of systolic function (Table) are influenced by several factors, including the known measurement accuracy, evidence of clinical use, safety, cost- and comparative-effectiveness, expert consensus, population characteristics, local availability, and quality.3–8 Echocardiography has high temporal resolution, whereas compared with echocardiography MRI has much higher spatial resolution for determination of endocardial and epicardial borders, and MRI is inherently less susceptible to errors resulting from measurements made in the wrong plane.9 Ventricular ejection fraction derived from radionuclide ventriculography is calculated from changes in gamma radiation intensity over time and has very high precision and accuracy. Unlike MRI, computed tomography, and echocardiography, nuclear ventriculography does not provide information on wall thickness or pathology in clinical practice. Therefore, each test for assessment of heart function differs in terms of methodology, type and quality of information provided, cost, and safety profile.

Regardless of the imaging method, the ejection fraction is the usual standard method for reporting left and right ventricular systolic function.1 Ejection fraction is defined as the ratio of stroke volume to end-diastolic volume.1 Stroke volume is defined as the difference between end-diastolic and end-systolic volumes.1 In fact, ejection fraction may be estimated in different ways. Ejection fraction may be estimated by measurement of 1-dimensional (D) fractional shortening using a single plane view of the heart, such as with M-mode echocardiography. Fractional shortening is the difference between end-diastole and end-systole divided by the end-diastolic dimension and multiplied by 100. Alternatively, measurement of ventricular areas and length is a more representative approach for estimation of ejection fraction. The Simpson Biplane method (method of discs) integrates ventricular area and length.8 With this method, cavity volume is estimated as the sum of cross-sectional areas of each slice multiplied by the distance between slices (including slice thickness and gaps between imaging planes) according to the following formula:

\[
\sum_a \left[\text{area} \times \left\{\text{length} / n\right\}\right], \text{where } n \text{ is the number of cross-sectional areas.}
\] (1)

Finally, there are fundamental differences between linear (M-mode), 2D, 3D, 4D (including time) volumetric, and geometric primary measurements.5 Volumetric measurements require delineation of the endocardial border, whereas linear measurements in a single plane do not. Because heart shape changes during the cardiac cycle in radial, circumferential, and long-axis directions, a 2D image will fail to capture through-plane motion, which could be detected by 3D imaging. A volumetric approach may not capture ventricular rotation and twist but could provide an assessment of ejection fraction with high precision.

Because assessing systolic function with the ejection fraction is reasonably straightforward, this parameter is widely used to describe heart function, including in epidemiology studies and clinical trials. However, there are several limitations with ejection fraction because it is a global index and is not informative of regional changes in systolic function. Other parameters of pump performance, such as wall motion, strain, and twist, may be much more informative about heart function (including early changes related to aging and subclinical cardiovascular disease). On the basis of advances with imaging technologies, these biomechanical parameters can be measured in the clinic, although the acquisition, analysis, and interpretation of some of these parameters may be less straightforward.10–12 In a large cohort of consecutive adults referred for echocardiography for the assessment of known or suspected impairment of left ventricular function, strain estimated from 2D speckle tracking had greater prognostic value than ejection fraction.13 However, some functional parameters, such as strain and wall motion, are less straightforward to analyze potentially meaning scans (or postprocessing) of longer duration and complexity. Furthermore, neither ejection fraction nor any of the other functional parameters include...
information on heart size or ventricular mass, which is positively influenced by afterload and a key measure of end-organ damage in cardiovascular disease and especially hypertension.

Based on the known limitations of the usual measures of systolic function, and especially ejection fraction, investigators in the Multi-Ethnic Study of Atherosclerosis (MESA) have developed a new index, Left Ventricular Global Function Index (LVGFI) which integrates global function (ejection fraction) with heart size, including left ventricular mass.14

The index is appealing because it is a simple concept and integrates prognostically important attributes, and is defined as follows:

\[
LVGFI (\%) = \frac{LVSV}{LV \text{ global volume}} \times 100
\]

where left ventricular (LV) global volume was defined as the sum of the LV mean cavity volume \([LVEDV+LVESV]/2\), where \(LVEDV\) and \(LVESV\) are the LV end-diastolic and end-systolic volumes, respectively, and the myocardium volume \((LV \text{ mass}/1.05 \text{ grams/mL})\). The definition of LVSV is left ventricular stroke volume.

Multi-Ethnic Study of Atherosclerosis was an MRI-based longitudinal study of community dwelling adults in North East United States and therefore represented an ideal opportunity to estimate LVGFI in a large number of people who were followed up for over 7 years for cardiovascular events, including heart failure.14 Mean LVGFI at baseline was 32±5% in the whole population, and an LVGFI at baseline <33% was associated with a 5-fold increased risk of future heart failure and a 2-fold risk of future adverse cardiovascular events (hard cardiovascular events, including hard coronary events [myocardial infarction, resuscitated cardiac arrest, and death from coronary disease]) plus fatal and nonfatal stroke.14 Given the large sample size, it is perhaps surprising that LV ejection fraction did not predict cardiovascular outcomes.

Given the complex nature of heart function, it is important that imaging methods have sufficient diagnostic accuracy to detect the effects of cardiovascular disease on the heart. There are four characteristics relevant to the usefulness of a diagnostic cardiac imaging test: (1) precision, (2) theoretical assumptions, (3) influence of hemodynamics, and (4) clinical use. First, as regards precision, LVGFI was developed with MRI, which is a gold standard test for measurement of ventricular dimensions. Second, there are theoretical assumptions made, and echocardiographic assessments may be susceptible to error because of nonsymmetrical ventricular shape (although this is less the case for 3D echocardiography).8 In this regard, LVGFI is a ratio (like ejection fraction) with systolic volume included in both denominator and numerator, and any errors in the original measurements may be compounded. Third, hemodynamic and loading conditions influence cardiac performance, and like ejection fraction, LVGFI will also be subject to these conditions, although because LVGFI incorporates heart volume, LVGFI may be an improvement because this method will account for ventricular mass and hypertrophy.

Finally, there is the clinical use of the method. On the one hand, the method should be straightforward to acquire, as well as being reliable and of prognostic significance. If these conditions are satisfied, then the method may be adopted in clinical practice, even if theoretical or methodological considerations are debated. Ejection fraction is an example of this because, in several ways, it is an error-prone method but it is straightforward to acquire,3–4 has prognostic value,2 and is benchmark for prescription of evidence-based medicines in patients with left ventricular systolic dysfunction.13 LVGFI could be in the same category. Although there may be methodological aspects which may stimulate debate, LVGFI has prognostic value in the Multi-Ethnic Study of Atherosclerosis study and its prognostic importance is superior to ejection fraction.14 In terms of clinical use, LVGFI has been developed and tested in one population using MRI data but how would it perform in others. Would LVGFI be clinically useful in patients with abnormalities in ventricular volume (eg, chronic heart failure) or mass (eg, left ventricular hypertrophy)? In the study by Mewton et al,14 LVGFI has been calculated using MRI data. Would the potential clinical use of LVGFI be maintained with less precise imaging methods, such as 2D echocardiography which is more widely used than MRI? Furthermore, in terms of transferability to the clinic, hopefully postprocessing algorithms could be developed to calculate LVGFI with minimal time delay.

Overall, LVGFI is an appealing new cardiac parameter because it incorporates heart size as well as function and has evidence to support its prognostic value. Future studies should be performed to assess its prognostic performance in patients with risk factors for cardiovascular disease and in individuals with established cardiovascular disease. LVGFI should be tested when derived using echocardiography. Further validation of LVGFI should include assessments of whether or not it is responsive to the effects of evidence-based antihypertensive drugs (which could be performed retrospectively using existing clinical trial databases). If this is the case then LVGFI could be considered as an end point in future clinical trials of antihypertensive interventions.

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