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EDITORIAL

Echocardiographic Quantification of Left Ventricular Systolic Function

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Assessment of left ventricular (LV) systolic function is the most common indication for performing an echocardiogram and, correspondingly, the detection and quantification of systolic dysfunction hold major implications for patient diagnosis and management. However, no perfect measure of 'systolic function' exists and there are fundamental limitations inherent to all currently available surrogates. In this clinically focussed editorial, we examine what can actually be measured by echocardiography, identify the techniques with established practical utility and consider their current and potential roles in guiding clinical practice.

What can be measured by echocardiography? The physiological parameter that most accurately represents systolic function is *contractility* - the ability of myocardium to contract against a specific load for any given preload. Assessment of contractility requires simultaneous and continuous measurement of LV pressure and volume over multiple cardiac cycles with manipulation of preload to generate pressure-volume loops across a range of loading conditions. At present, this can only be achieved accurately by invasive methods using conductance catheters.

In contrast, all of the commonly utilised echocardiographic (and other non-invasive imaging) techniques for assessing systolic function measure *contraction* – essentially the degree of myocardial fibre shortening that occurs during systole. This is dictated by the degree of preceding myocardial stretch (preload) and the pressure against which it contracts (afterload) as well as intrinsic contractile function. Consequently, all techniques based on assessment of contraction provide 'load-dependent' measurements of systolic function. Nonetheless, a comprehensive echo study provides important insight into the prevailing loading conditions and integration of this information with the indices of LV contraction informs the overall evaluation of systolic function.

It should also be borne in mind that our aim, ultimately, is not to quantify systolic function as a physiological parameter but to detect and grade clinically meaningful systolic *dysfunction*. It is therefore preferable to evaluate echo-based indices of systolic function against a clinical standard rather than a pure physiological one. Clinically useful measures should ideally correlate with symptoms of heart failure, predict the subsequent development of adverse events and, most importantly, provide a proven basis for therapeutic decision making.

What are the strengths and limitations of LVEF as a measure of systolic function? LV ejection fraction (EF), as measured by Simpson's biplane method, is the most widely validated and commonly used echocardiographic index of LV systolic function. Reduced LVEF, particularly <45% is associated with pathological changes in the myocardium such as myocyte hypertrophy, interstitial fibrosis and scarring, and indicates clinically significant systolic dysfunction. Below the 45% threshold, LVEF correlates with symptom severity and is strongly related to prognosis with each 10% decrement conferring a 39% increase in risk of all cause mortality as well as an increased risk of HF hospitalisation [1]. Uniquely among measures of systolic function, LVEF has also served as a key entry criterion for almost all of the landmark therapeutic trials in heart failure. Accordingly its measurement is critical to guiding the optimal use of drug and device therapy. Nonetheless, LVEF has several important limitations as a surrogate of LV systolic function.

Measurement of LVEF by two-dimensional (2D) transthoracic echocardiography (TTE) suffers from poor reproducibility and is subject to errors arising from inadequate

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endocardial definition, apical foreshortening and geometric assumptions. Three dimensional (3D) TTE obviates the need for geometric assumptions, improves apical alignment and offers greater reproducibility for measurements of LVEF [2]. A limitation of 3D TTE is the continued dependence on adequate visualisation of the endocardial border.

The use of echo contrast to improve endocardial definition improves accuracy of LV volume measurement by both 2D and 3D TTE and should be considered in patients with suboptimal image quality. Moving forward, improved 3D TTE spatial resolution will be critical to achieving reliable automated endocardial detection and, in turn, integration of 3D LVEF into routine workflows. Meanwhile, some commercial platforms now permit acquisition of >40 volumes per second, obviating problems related to arrhythmias and irregular heart rates by allowing for real-time beat to beat volume measurements.

Even when accurately measured, LVEF may be misleading in the setting of altered loading conditions or pathological LV remodelling. The latter may distort the normal relationships between myocardial shortening, LVEF and LV stroke volume. In patients with concentric remodelling due to hypertensive heart disease, high relative wall thickness allows preserved endocardial excursion and LVEF despite reduced myocardial shortening in both the longitudinal and mid circumferential planes [3]. In addition, the low chamber volume results in a lower stroke volume for any given EF. As a consequence, both myocardial contraction and LV stroke volume may be reduced despite a normal LVEF. On the other hand, patients with very low LVEF often maintain a normal stroke volume due to concomitant LV dilatation that is proportionate to the fall in LVEF. Systolic function may, therefore, be severely impaired but nonetheless adequate to support a normal cardiac output and satisfy metabolic demands (at least at rest). Thus, in the setting of substantial LV remodelling, it is often helpful to consider LVEF alongside LV stroke volume (and cardiac output) which can be estimated by pulsed wave Doppler within the LV outflow tract.

In addition, as it is a measure of LV contraction rather than contractility, LVEF may over- or underestimate systolic function in the presence of markedly abnormal loading conditions. In severe mitral regurgitation, where LV contraction is augmented by increased preload (and possibly reduced afterload), LVEF values within the low normal range usually indicate significant intrinsic contractile impairment. The converse is true in the setting of severe hypertension or aortic stenosis where depressed LVEF may reflect the presence of increased afterload rather than abnormal contractile function.

One final and important limitation of LVEF is the lack of clinical utility once values exceed 45-50%. Beyond this threshold significant systolic dysfunction may still be present but changes in LVEF do not correlate with symptoms, inform prognosis or offer an effective guide to treatment. As described below, this is likely to be the setting in which alternative measures of systolic function offer the greatest potential for clinical application.

How can LV systolic dysfunction be detected when LVEF is normal or near normal? A plethora of echocardiographic techniques, other than LVEF, have been proposed to assess LV systolic function. These range from largely historical methods such as fractional shortening and M-mode measurement of mitral annular plane systolic excursion (MAPSE) to experimental techniques such as circumferential and torsional deformation imaging that, for now remain predominantly research tools. However, tissue Doppler assessment of mitral annular velocities and 2D speckle tracking derived longitudinal strain, both relatively novel techniques based on assessment of LV long axis contraction, appear to offer significant potential for clinical utility, particularly in the setting of a normal or near-normal LV ejection fraction.

Tissue Doppler Imaging (TDI) mitral annular velocities: The velocity of the mitral annular plane toward and away from the apex in systole and diastole respectively provides a quantitative assessment of LV long axis function. There are three main TDI signals obtained during the cardiac cycle (Figure 1): the s′, the e′ and the a′. Reduced s′ and e′ velocities provide a sensitive marker of myocardial dysfunction in patients with diabetes, hypertension, ischaemic heart disease or hypertrophic cardiomyopathy, even when LVEF is normal [4]. Moreover, reduced e′ and s′ are each strong and independent predictors of mortality and other adverse outcomes across a broad range of cardiac diseases including in patients with preserved EF.

The most common sites for mitral annular velocity measurement are at the basal septum and lateral wall. Both provide useful information, however septal velocities are more prone to interference from a number of sources including conduction abnormalities, right ventricular pacing, previous cardiac surgery and right ventricular pressure/volume overload. Lateral velocities are therefore a better guide to LV contraction in uniform myocardial pathologies, whilst the average of septal and lateral velocities is recommended in the setting of ischaemic LV dysfunction. An important advantage of the technique is that velocities are reliably obtainable, even when image quality is suboptimal. They are also highly reproducible and have well validated normal values, standardised across all major vendors.

Intriguingly e′ shows a more linear and predictable decline than s′ both with ageing and in relation to the severity of underlying myocardial disease. In addition, it appears to be a stronger predictor of adverse events including mortality and hospitalisation with heart failure. Although traditionally viewed as a measure of 'diastolic function', recent data suggest e′ is more closely determined by systolic long axis function than diastolic variables [5]. This makes intuitive sense when one considers the extent to which the systolic and diastolic velocities are interdependent: the overall upward displacement of the annulus in systole must be equivalent to its downward displacement in diastole; or, stated another way, the combined integrals of the e′ and the a′ must be equal to the integral of the s′. One advantage of e′ over s′ lies in the respective shapes of the signals. Whereas e′ exhibits a consistent, triangular shape with a

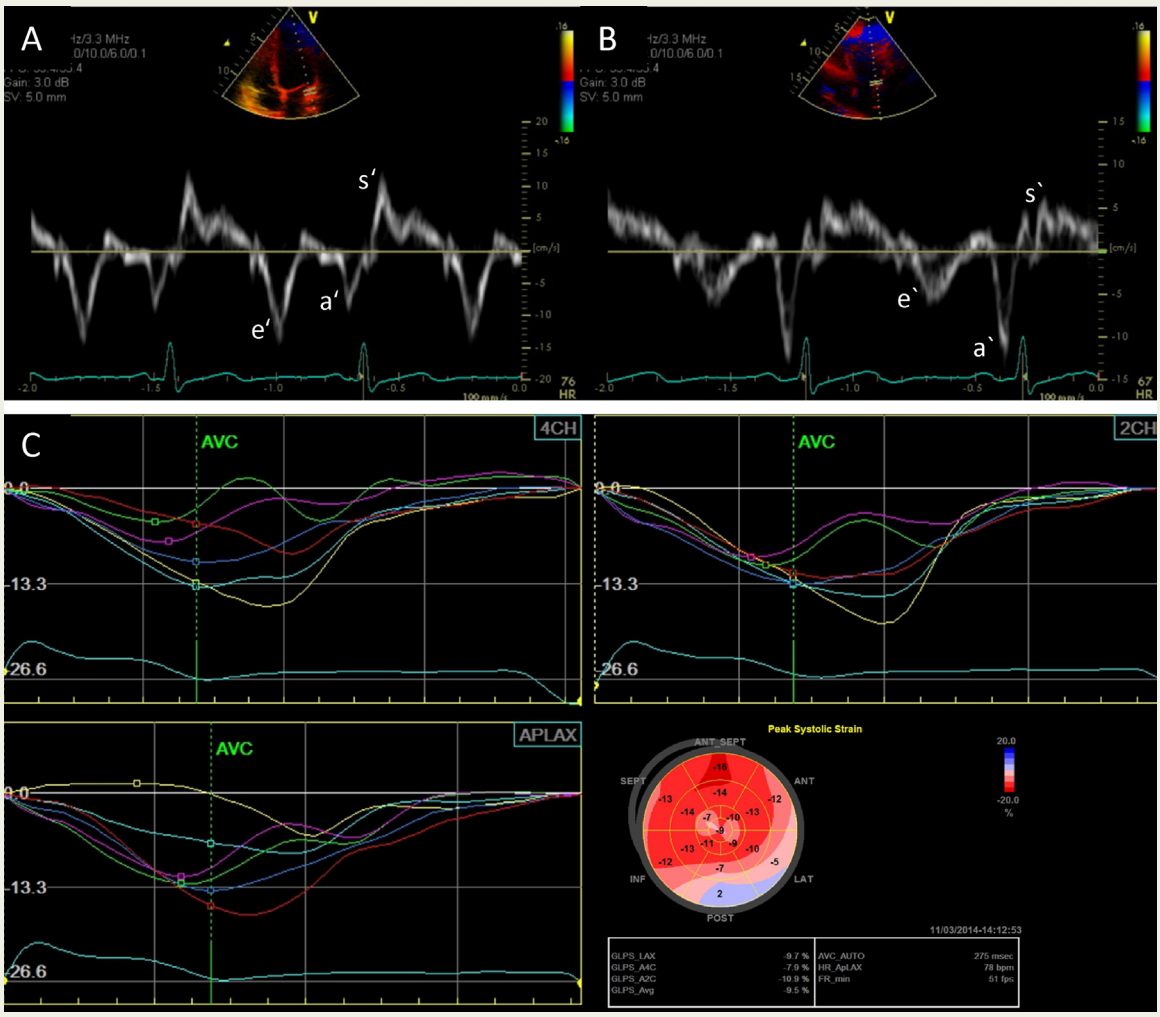

Figure 1 Echo measurements of LV long axis systolic function.
(A and B) TDI velocities at the lateral mitral annulus showing normal velocities in a healthy 31 year-old male (A) and reduced s′ and e′ in a 53 year-old male with longstanding hypertension and normal LV ejection fraction (B). Note the irregular shape of the s′ signal, particularly in panel B. **(C)** Longitudinal strain in individual myocardial segments across a cardiac cycle and a colour-coded 'bulls-eye' representation of peak systolic strain in each segment showing reduced GLS (-9.5%) with marked regional variation in a 51 year-old male with ischaemic cardiomyopathy and previous postero-lateral myocardial infarction. Abbreviations: TDI, tissue Doppler imaging; GLS, global longitudinal strain.

single clearly defined peak, s′ shows considerable variability, often containing two or more peaks, which may be partly related to 'contamination' of s′ with recoil from the preceding a′ signal. As a consequence, e′ is not only easier to measure but results in a better correlation between the peak velocity and annular displacement.

Global longitudinal strain: Myocardial strain refers to the extent of deformation of a portion of myocardium during contraction or relaxation – i.e. the change in length from its initial state. During systole, strain reflects the percentage of regional myocardial shortening and is expressed as a negative value. Assessment of strain by tissue Doppler velocities suffers from high noise-to-signal ratio, marked angle dependency and suboptimal reproducibility, and has now largely been superseded by 2D speckle-tracking techniques. Importantly, the amalgamation of regional strain values from each LV segment (global strain) has transformed strain from a regional technique to one that allows detection of uniform pathologies and quantification of overall LV systolic function. In keeping with the 3D arrangement of cardiac myofibres, strain may be assessed in a number of different directions eg. longitudinal, radial, and circumferential. However, to date, global longitudinal strain (GLS) has shown the greatest promise for clinical application, with typical normal GLS values approximately -20%. As a method of assessing LV systolic function, GLS overcomes some of the limitations of LVEF: it is more reproducible, does not rely on geometric assumptions and is unaffected by tethering. Nonetheless, it is also load dependent and relies on satisfactory 2D imaging with good endocardial definition. Moreover there is

currently a lack of consistency and standardisation of strain values between different vendors and cut-off values for clinical practice are less robust than for TDI mitral annular velocities.

As with mitral annular TDI velocities, measurement of GLS permits detection of LV systolic impairment in a range of conditions (e.g. diabetes, hypertensive heart disease) when LVEF is within normal limits. Most notably, in a cohort of patients with heart failure and preserved ejection fraction (HFpEF), reduced GLS was identified in two-thirds, and GLS correlated with N-terminal proBNP level, independently of all variables studied including indexed left atrial volume and indices of diastolic function [6]. Further study of GLS in HFpEF may therefore yield insight into the underlying pathophysiologic mechanisms and aid identification of distinct phenotypic subtypes in whom there is a contribution from LV systolic impairment.

In patients with moderate or severely reduced LVEF, GLS provides modest incremental value to LVEF in the prediction of adverse outcomes, however this is unlikely to offer major clinical utility. On the other hand, GLS may hold value in identifying high risk subgroups among patients with normal or near normal LVEF. For example, in patients post-myocardial infarction with LVEF >40%, GLS >-14% predicted 12-fold and 5-fold increases in the risk of cardiac death and hospitalisation with heart failure respectively, providing incremental value to multiple other established prognostic markers [7].

Finally, by permitting earlier detection of systolic impairment than LVEF, GLS has the potential to improve serial monitoring for myocardial dysfunction in a range of conditions including valvular heart disease and systemic or inherited diseases associated with heart muscle involvement. To date the strongest evidence is for cardiotoxicity related to chemotherapy. Subclinical detection in patients receiving chemotherapy is crucial because timely alterations to treatment regimens may prevent disease progression whereas systolic dysfunction is irreversible in up to 58% of cases once LVEF declines. A recent comprehensive systematic review suggests that reductions in GLS of $\geq$10%, consistently precede and predict the development of overt asymptomatic and symptomatic LV dysfunction [8]. A clinical trial is now underway to determine whether strain surveillance in this setting reduces the incidence of overt LV dysfunction or heart failure compared with conventional monitoring by LVEF [SUCCOUR; ACTRN12614000341628].

Despite conceptual and practical limitations, LVEF remains by far the most clinically useful echocardiographic method for detecting and quantifying overt LV systolic dysfunction. Contemporary measures of long axis contraction, particularly mitral annular TDI velocities and GLS are more sensitive than LVEF for detecting milder degrees of systolic impairment. In this setting they hold considerable promise for refinement of prognosis and early disease detection, however confirmation is still awaited of their ability to guide treatment decisions.

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