Assessment of Left Ventricular Function: Review Article

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Abstract:

Left ventricular (LV) ejection fraction (LVEF) is a simple measure of global systolic function that pervades the risk evaluation and management of many cardiovascular diseases. However, this parameter is limited not only by technical challenges, but also by pathophysiological entities where the ratio of stroke volume to LV cavity size is preserved. The assessment of global longitudinal strain (GLS) from speckle-tracking analysis of 2-dimensional echocardiography has become a clinically feasible alternative to LVEF for the measurement of myocardial function. Evidence gathered over the last decade has shown GLS to be more sensitive to left ventricular dysfunction (LVD) than LVEF and to provide additional prognostic information. The technology is validated, reproducible within an acceptable range, and widely available. GLS has been proposed as the test of choice in guidelines for monitoring of asymptomatic cardiotoxicity related to chemotherapy. It also has the potential to improve risk stratification, redefine criteria for disease classification, and determine treatment in asymptomatic LVD resulting from a variety of etiologies. GLS provides utility across the spectrum of heart failure (and LVEF) as well as in the evaluation of valvular heart disease. There is a strong case for incorporation of GLS into clinical decision making. This review appraises the evidence addressing the utility of GLS as a complementary metric to LVEF for incorporation into mainstream clinical practice.

Keywords: Left Ventricular Function, echocardiography, Global Longitudinal Strain.

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Introduction:

For the assessment of regional LV function, the ventricle is divided into segments. Segmentation schemes should reflect coronary perfusion territories, result in segments with comparable myocardial mass and allow standardized communication within echocardiography and with other imaging modalities (Figure 1). Accordingly, a 17-segment model is commonly used. Beginning at the anterior junction of the interventricular septum and the Right ventricle (RV) free wall and continuing counterclockwise, basal and mid ventricular segments should be labeled as anteroseptal inferoseptal inferior, inferolateral anterolateral and anterior. In this 17-segment model, the apex is divided into five segments, including septal inferior, lateral, and anterior segments, as well as the ‘‘apical cap’’ which is defined as the myocardium beyond the end of the LV cavity (Figures 1) **(1).**

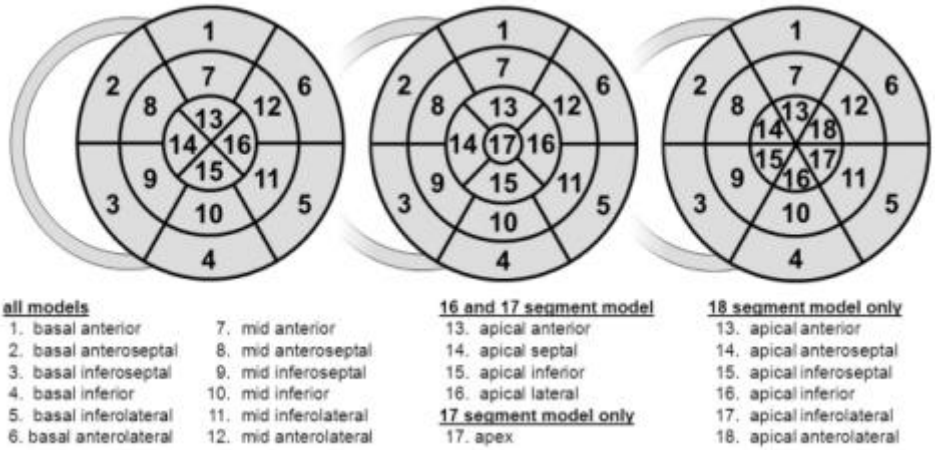

Figure (1): Schematic diagram of the different LV segmentation models: 16-segment model (left), 36 17-segment model (center), 35 and 18-segment model (right). In all diagrams, the outer ring represents the basal segments, the middle ring represents the segments at midpapillary muscle level, and the inner ring represents the distal level. The anterior insertion of the right ventricular wall into the left ventricle defines the border between the anteroseptal and anterior segments. Starting from this point, the myocardium is subdivided into six equal segments of 60. The apical myocardium in the 16- and 17-segment models is divided instead into four equal segments of 90. In the 17-segment model an additional segment (apical cap) is added in the center of the bull's-eye. **(2)**

The 17-segment model may be used for myocardial perfusion studies or when comparing between different imaging modalities, specifically single photon-emission computed tomography, positron emission tomography, and Cardiovascular magnetic resonance (CMR). When using this 17-segment model to assess wall motion or regional strain, the 17th segment (the apical cap) should not be included. Alternative segmentation models treat the apex differently: the 16- segment model divides the entire apex into the same four segments (septal inferior, lateral and anterior; Figure 2, left). Also, some segmentation schemes divide the apex into six segments, similar to the basal and mid ventricular levels, resulting in an 18-segment model (Figure 1, right) that is simple but results in a slight overrepresentation of the distal myocardium when scoring. All segments can be visualized by 2DE. On average, the two chamber view and the apical long-axis view intersect with the four-chamber view at angles of approximately 53 to 129 degree**(3).**

Respectively **Amzulescu et al., (4)** allowing the assessment of the central region of all segments from an apical window, independent of the model used. Although certain variability exists in the coronary artery blood supply to myocardial segments, segments are usually attributed to the three major coronary arteries (Figure 1).

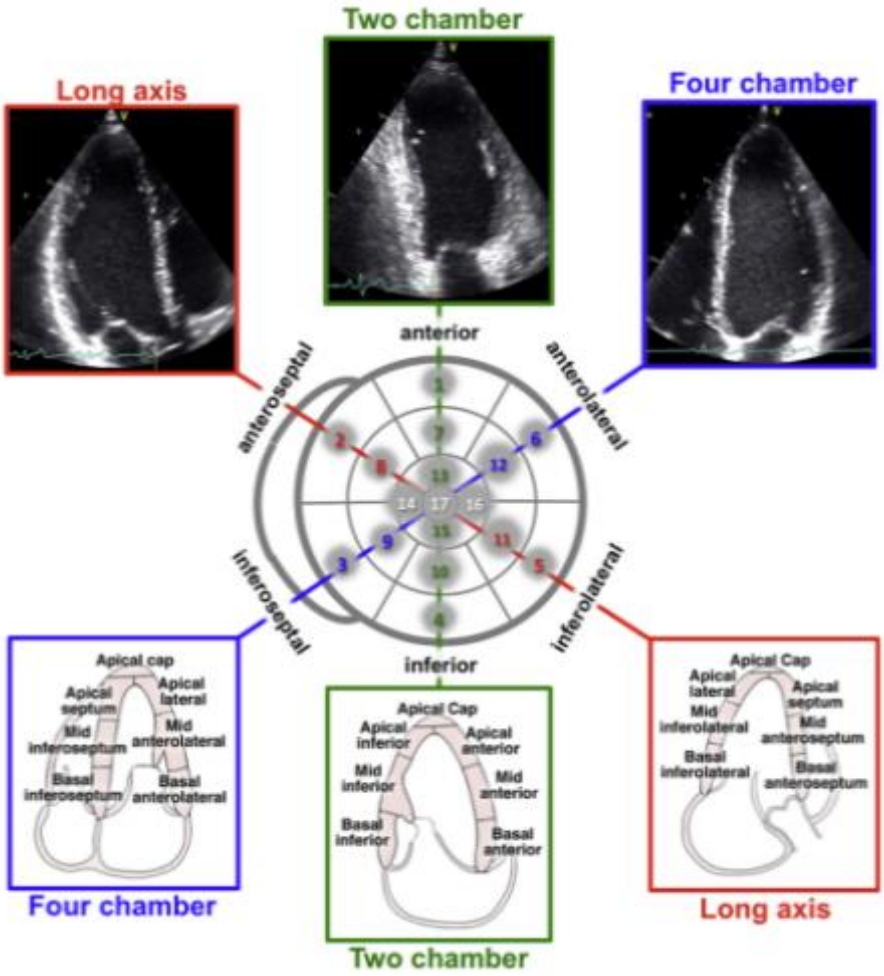

Figure (2): Orientation of apical four-chamber (A4C), apical two-chamber (A2C), and apical long-axis (ALX) views in relation to the bull's-eye display of the LV segments (center). Top panels show actual images, and bottom panels schematically depict the LV wall segments in each view. (Journal of the American Society of Echocardiography Volume 28 Number 1).

Regional Wall Motion during Infarction and Ischemia:

Depending on the regional coronary flow reserve, stress echocardiography may reveal significant coronary artery stenosis by means of inducing a wall motion abnormality. Myocardial scar may also result in regional dysfunction of variable severity. Echocardiography can over- or underestimates the amount of ischemic or infarcted myocardium, depending on the function of adjacent regions, regional loading conditions, and stunning **(3).**

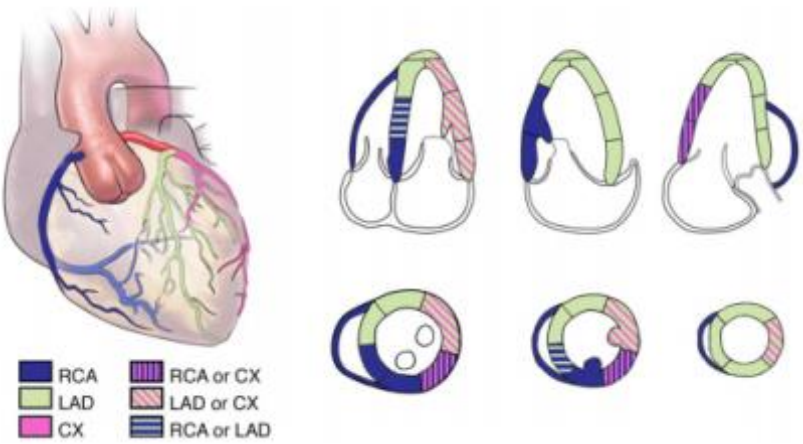

Figure (3): Typical distributions of the right coronary artery (RCA), the left anterior descending coronary artery (LAD), and the circumflex coronary artery (CX). The arterial distribution varies among patients. Some segments have variable coronary perfusion **(5).**

There is a growing body of evidence showing that the assessment of myocardial deformation by Doppler or speckle tracking techniques provides incremental information in the clinical setting **(6).**

Deformation imaging has been shown to provide unique information on regional and global ventricular function with some studies showing reduced inter and intra-observer variability in assessing regional left ventricular (LV) function **(7).**

The main areas of application of these techniques have been assessment of myocardial mechanics, ischemic heart disease, cardiomyopathies, LV diastolic dysfunction, and in detecting subclinical myocardial dysfunction in patients undergoing chemotherapy for cancer or in those affected by heart valve diseases. The Recognizing critical need for standardization in strain imaging, in 2010, the European Association of Echocardiography (now the European Association of Cardiovascular Imaging, EACVI) and the American Society of Echocardiography (ASE) invited technical representatives from all interested vendors to participate in a concerted effort to reduce inter vendor variability of strain measurement **(8).**

Ejection fraction:

The well accepted expression of global LV function is LVEF. It is a simple measure of how much end-diastolic volume is ejected from the LV with each contraction. Although it has many limitations, including load dependency, LVEF has been found to be a strong predictor of clinical outcome in almost all major cardiac conditions, and it is used to select optimal management strategies. In clinical practice, LVEF is frequently determined by "eye balling" 2D echocardiographic images of the LV **(9).** LVEF should be measured using volumetric measurements as described by the following equation:

LVEF= (LV EDV-LV ESV)/LV EDV

It is al so possible to calculate EF using linear rather than volumetric measurements (i.e., based upon M mode measurements alone). M-mode or 2D echocardiographic measurement of LV

dimensions from the mid ventricular level is used as:

LVEF= [(LVIDd) 3– (LVIDs) 3] ⁄ (LVIDd) 3

LVIDd and LVIDs – Left ventricular internal diameter end diastole and end systole

This equation is actually percentage change in LV area, or fractional shortening of the LV short axis, which equals LVEF if the apical long-axis dimension remains the same from diastolic phase to systolic contraction. For a symmetrically contracting ventricle, fractional area change directly reflects global ventricular function. Its obvious limitation is that it assesses ventricular function only at the level being interrogated. If regional dysfunction is present, which is not in the interrogation plane, it may result in a misleading estimate of global ventricular function. Because the apical long axis normally shortens 10 to 15 percent with systole, an apical correction factor is added on the basis of the contractility of the apex; 5 to 7 percent for normal to hyperdynamic apical contraction, 3 percent for hypokinetic contraction, and 0 percent for akinetic apex **(10).**

Simpson's Biplane Echocardiography Assessment of Left Ventricular Function:

Numerous studies during the 1980s validated the accuracy of 2D volumes and ejection fraction measurements by comparison with a variety of reference standards **(11).**

Left ventricular (LV) systolic function is one of the most important predictors of outcome in all cardiac conditions, and almost all therapeutic decisions in these patients are influenced by the status of LV systolic function. For cardiac anesthesiologists, preoperative knowledge of LV systolic dysfunction is crucial for anticipating and preparing for perioperative complications, whereas subsequent assessments are required for diagnosing and managing the cause of hemodynamic instability. Patients with LV systolic dysfunction who undergo coronary artery bypass graft surgery (CABG) are known to require more inotropic support after cardiopulmonary bypass (CPB) **(2).**

LV ejection fraction (LVEF) is the simplest and the most widely used measure of global LV systolic function. A number of echocardiographic methods are currently available for estimation of LVEF, but the biplane modified Simpson method is the most accurate and is al so the method recommended by the American Society of Echocardiography (ASE) **(3).**

LV Global Systolic Function Global LV function is usually assessed by measuring the difference between the end-diastolic and end-systolic value of a Two-dimensional 2D, or three-dimensional 3D parameter divided by its end-diastolic value. For this, end-diastole is preferably defined as the first frame after mitral valve closure or the frame in the cardiac cycle in which the respective LV dimension or volume measurement is the largest. End-systole is best defined as the frame after aortic valve closure or the frame in which the cardiac dimension or volume is smallest. In patients with regular heart rhythm, measurements of the timing of valve openings and closures derived from M-mode echocardiography, pulsed-wave (PW) or continuous-wave Doppler may be used for accurate definitions of ventricular time intervals **(12).**

Fractional Shortening Fractional shortening can be derived from 2D-guided

M-mode imaging or preferably from linear measurements obtained from 2D images. Deriving global LV function parameters from linear measurements is problematic when there are regional wall motion abnormalities due to coronary disease or conduction abnormalities. In patients with uncomplicated hypertension, obesity or valvular diseases, such regional differences are rare in the absence of clinically recognized myocardial infarction, and accordingly, this parameter may provide useful information in clinical studies. In patients with normal size of the LV base but enlarged mid ventricular and distal portions LV volume would be a better marker of LV size than linear dimension measured at the LV base **(3).**

Volumetric Measurements LV volumes are measured using 2DE or 3DE. Volume calculations derived from linear measurements may be inaccurate, because they rely on the assumption of a fixed geometric LV shape such as a prolate ellipsoid, which does not apply in a variety of cardiac pathologies. Accordingly, the Teichholz and Quinones methods for calculating LV volumes from LV linear dimensions are no longer recommended for clinical use. Volumetric measurements are usually based on tracings of the interface between the compacted myocardium and the LV cavity at the mitral valve level, the contour is closed by connecting the two opposite sections of the mitral ring with a straight line. LV length is defined as the distance between the bisector of this line and the apical point of the LV contour, which is most distant to it. The use of the longer LV length between the apical two- and four-chamber views is recommended. LV volumes should be measured from the apical four and two-chamber views. Two-dimensional echocardiographic image acquisition should aim to maximize LV areas, while avoiding foreshortening of the left ventricle, which results in volume underestimation. Acquiring LV views at a reduced depth to focus on the LV cavity will reduce the likelihood of foreshortening and minimize errors in endocardial border tracings **(13).**

The modified biplane Simpson's method, as recommended by the American Society of Echocardiography. End-diastolic and end-systolic endocardial borders were traced manually on frozen 2D images obtained from the apical two and four-chamber views to derive end-diastolic volume (EDV) and end-systolic volume (ESV). The LV EF was calculated according to the formula **(14).**

$$EF = (EDV - ESV)/EDV \times 100\%.$$

The Auto-EF tool Using dynamic 2D images of the apical four and two-chamber views, three anchor points were set within the LV cavity, two at the level of the mitral valve annulus and one at the LV apex. Endocardial borders were then detected and traced automatically by the software during a whole heart cycle to calculate EDV, ESV, and EF. When needed, corrections could be carried out manually **(14).**

Table (1): Normal Values for Two-Dimensional Echocardiographic Parameters of Left Ventricular Size and Function According to Sex **(3).**

Parameter	MAL E		FEMAL E	
	Mean ±SD	**2-SD Range**	**Mean ±SD**	**2-SD Range**
Left Ventricular (LV) Internal Dimension				
Diastolic dimension (mm)	50.2±4.1	42.0-58.4	45.0 ±3.6	37.8-52.2
Systolic dimension (mm)	32.4±3.7	25.0-39.8	28.2 ±3.3	21.6-34.8
LV Volumes (Biplane)				
LV EDV (mL)	106±22	62-150	76 ±15	46-106
LV ESV (mL)	41 ±10	21-61	28 ±7	14-42
LV Volumes Normalized by Body Surface Area				
LV EDV (mL/m 2)	54±10	34-74	45 ±8	29-61
LV ESV (mL/m 2)	21±5	11-31	16 ±4	8-24
LV EF (biplane)	62±5	52-72	64 ±5	54-74

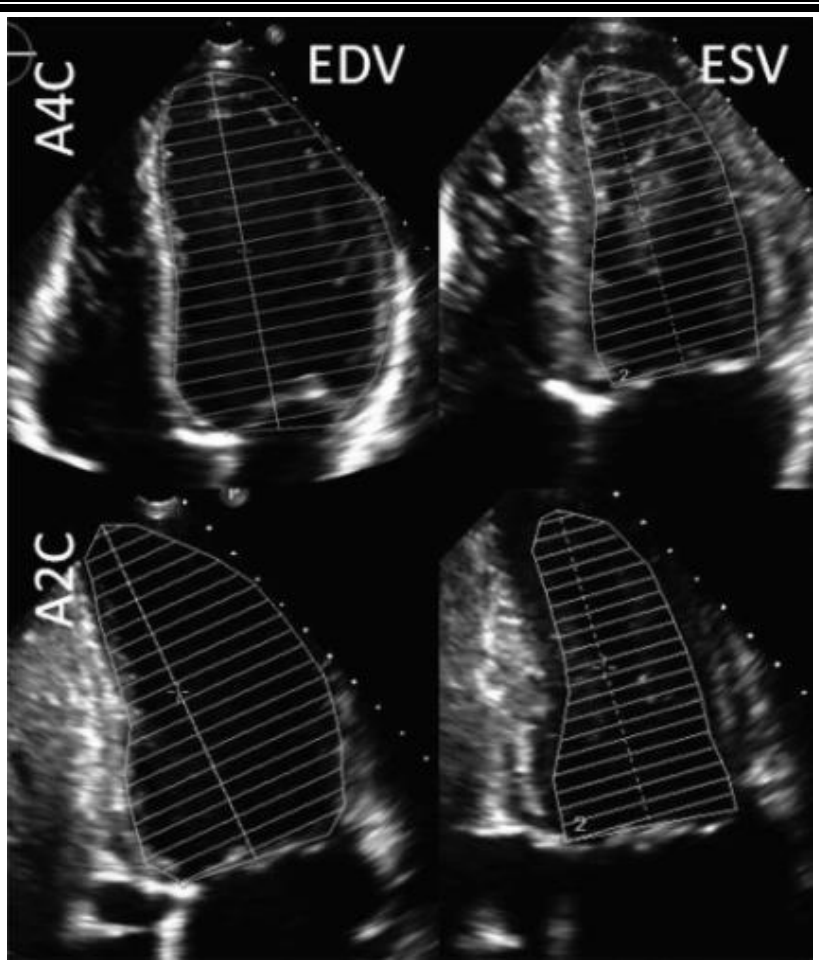

Figure (4): LV method of disk summation. Volume measurements are made by tracing the blood–tissue interface in the apical four and apical two-chamber views, at end-diastole and end-systole. The shape is closed by a virtual line made across the level of the mitral valve annulus. A4C, apical four-chamber; A2C, apical two-chamber; EDV, end-diastolic volume; ESV, end-systolic volume **(15).**

Linear LV measurement:

It is used in the diagnosis of valvular heart disease, but may misrepresent dilatation and dysfunction in patients with regional wall-motion abnormalities as a result of coronary artery disease. To obtain accurate linear measurements of interventricular septal wall thickness (SWT), posterior wall thickness (PWT), and LV internal dimensions, recordings should be made from the parasternal long-axis window. These linear measurements can be made directly from 2D images or using 2D-targeted M-mode echocardiography **(16).**

Left Ventricular Internal Dimension (LVID):

It was the only LV measurement performed in the M-mode era. It is measured from the posterior surface of the ventricular septum to the anterior surface of the LV posterior wall at the level of the mitral chordae tendinae. For a valid LVID, it is important that long axis of the LV chamber be perpendicular (or al most so) to the ultrasound beam (Fig.7). It is standardized to take LVID at end-diastole (LVIDd) and end-systole (LVlDs). End diastole can be defined at the onset of the QRS or after mitral valve closure or the frame in the cardiac cycle in which the cardiac dimension is largest. In sinus rhythm, this follows atrial contraction. End systole is best defined as the frame preceding mitral valve opening or the time in the cardiac cycle in which the cardiac dimension is smallest in a normal heart **(17).** Use of 2D echocardiographically derived linear dimensions overcomes the common problem of oblique parasternal images resulting in overestimation of cavity and wall dimensions from M-mode. If manual calibration of images is required, 6cm or larger distances should be used to minimize errors caused by imprecise placement of calibration points. Alternatively, chamber dimension and wall thicknesses can be acquired from the parasternal short-axis view using direct 2D measurements or targeted M-mode echocardiography provided that the M-mode cursor can be positioned perpendicular to the septum and LV posterior wall. The pitfalls of assessment of LV dimensions include failure to take measurements at the correct time points (end systole or end-diastole), failure to take measurements perpendicular to the long axis of the LV and failure to identify the endocardium correctly **(18).**

Reference ranges of left ventricular internal dimensions for men and women present in table (2).

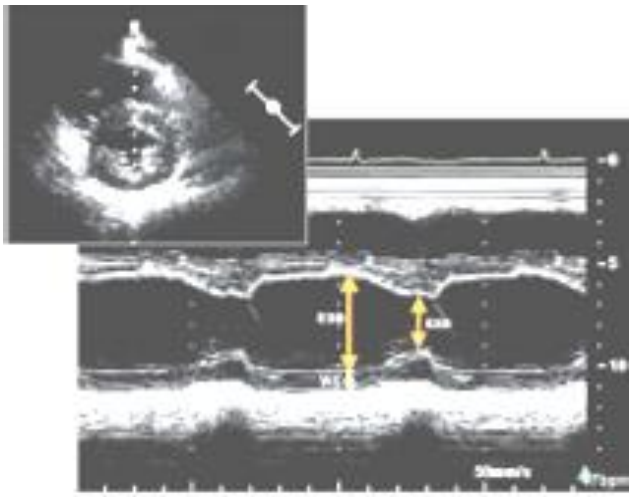

Figure (5): Measurement of left ventricular end-diastolic diameter (EDD) and end-systolic diameter (ESD) from M-mode, guided by parasternal short-axis image.**(5)**

Table (2): Reference ranges for men and women **(18)**

	Normal	**Mildly abnormal**	**Moderately abnormal**	**Severely abnormal**
Men				
lVSd (cm)	0.6-1.2	1.3-1.5	1.6-1.9	2.0
LVIDd (cm)	4.2-5.9	6.0-6.3	6.4-6.8	6.9
LVIDd/BSA (cm/m2)	2.2-3.1	3.2-3.4	3.5-3.6	3.7
LVPWd (cm)	0.6-1.2	1.3-1.5	1.6-1.9	2.0
Women				
IVSd (cm)	0.6-1.2	1.3-1.5	1.6-1.9	2.0
LVIDd (cm)	3.9-5.3	5.4-5.7	5.8-6.1	6.2
LVIDd/BSA (cm/m2)	2.4-3.2	3.3-3.4	3.5-3.7	3.8
LVPWd (cm)	0.6-1.2	1.3-1.5	1.6-1.9	2.0

Doppler Tissue Velocity:

Doppler echocardiography for blood flow measures the velocities of red blood cells (velocity usually higher than 20cm/sec and up to 800cm/sec in case of valvular disease). However, the velocities of myocardial tissue are much lower (<30cm/sec), but with larger amplitudes than those produced by blood. Velocities can be obtained in adjacent segments. The Doppler signal arising from relatively dense, slow-moving targets such as the myocardium and cardiac annulus are interrogated for their velocity. The pulsed wave Doppler was modified to record the low velocities of myocardial tissue and to reject the high velocities generated by blood, a pulsed Doppler sample volume is placed within an area of the myocardium or the annulus and the velocities at that point are then displayed for quantitation **(19).**

DTI has substantial spatial and temporal resolution. The spatial resolution is such that the sample volume can be placed in either the subendocardial or subepicardial regions, and differential velocities in adjacent wall segments can thereby be determined. When evaluating global performance, DTI velocities will show some regional variation based on which area of the mitral annulus is interrogated (septal vs. lateral). Because there is substantial spatial resolution inherent in the DTI method there are several secondary analyses as calculation of the endocardial-epicardial gradient. Alterations in this gradient with a selective decrease in the subendocardial velocities have shown promise as a very sensitive marker of ischemia. Because the endocardial

and epicardial velocities are determined in a single segment with the same angle of interrogation of the Doppler beam, this technique is relatively angle independent. Color M-mode DTI can also be used to assess differential velocities across the left ventricular wall thickness by using an offline analysis system that converts the color assignments to velocity values **(20).**

Assessment of diastolic function of left ventricle:

Assessment of diastolic function is a complex, inexact science in which multiple factors must be assessed and integrated with clinical information. For each parameter, a range of values exist that define normal and each of the stages of dysfunction. This is due to the fact that multiple factors, in addition to diastolic function, affect each marker. In all cases, some degree of overlap exists. This means that no one parameter can be used in isolation. Instead, a number of markers must be evaluated; including the clinical scenario. The first step involves the analysis of the mitral inflow pattern. The earliest form of diastolic dysfunction is usually impaired relaxation (Grade I), the result of delayed pressure decline following aortic valve closure. This is associated with a reversal of E/A ratio (usually<1) and a prolonged deceleration time (>240ms). Impaired relaxation is usually associated with a prolonged IVRT, although the multiple factors that affect IVRT limit the specificity of this finding. At this stage, E/E' is usually normal (indicating normal filling pressure) and left atrial volume is mildly increased **(21).**

With progression of disease, filling pressure rises, leading to the pseudonormal phase (Grade II). Here, the E/A ratio and deceleration time are within the normal range (hence the name). A number of markers can be used to differentiate between the normal and the pseudonormal including Valsalva maneuver, E', E/E', LA volume index and pulmonary vein S/D rate (Table 4). At this stage, the IVRT may fall within the normal range because of the combined and offsetting effects of increased left atrial pressure and delayed relaxation. Furthermore, the E/E' will be increased for the same reason **(21).**

With the development of restrictive filling (Grade III), the E/A ratio increases (usually >2, an indication of a high LA-LV pressure gradient at the time of mitral opening) and the deceleration time become very short (<160ms, due to noncompliant left ventricle). The left atrium is invariably enlarged and an E/E' ratio greater than 15 confirms elevated filling pressure. If this stage of dysfunction is reversible a decrease in the E/A ratio will occur with the Valsalva maneuver. As the last stage of restrictive filling progresses to irreversibility; restrictive filling (irreversible) (Grade IV), the E/A ratio become fixed and unresponsive to Valsalva **(21).**

Table (3): Distinguishing normal from pseudonormal using echo/Doppler parameters **(21).**

Parameter	Normal	Pseudonormal
E/A ratio **Change with Valsalva**	0.9-1.5 Both decrease No change in ratio	0.9-1.5 E decrease >A Ratio decreases(<1)
E'(cm/sec)	>10	<8
E/E'(septum)	<10	>15
LA volume index (ml/m2)	<28	>28
Pulmonary vein S/D	S>D	S<D

Echo/Doppler parameters of diastolic function:

Isovolumic Relaxation Time (IVRT):

IVRT measurement provides insight into the rate of early diastolic left ventricular relaxation. When relaxation is prolonged, mitral valve opening is delayed and IVRT is increased. It is derived using pulsed Doppler from a modified apical four-chamber view. The goal is to adjust the image to allow simultaneous visualization of the left ventricular inflow and outflow. Once this view is obtained, the Doppler sample volume is placed midway between the inflow and outflow areas so that mitral and aortic flows are captured simultaneously. IVRT is most easily obtained by measuring the time from the middle of the aortic closure click to the onset of the E wave of mitral flow. A major limitation is the fact that multiple factors influence the duration of the IVRT such as impaired relaxation, left atrial pressure, age, heart rate and systolic function **(21).**

Tissue Doppler Mitral Annular Velocity:

The velocity of the mitral annulus can be recorded throughout the cardiac cycle using the tissue Doppler method. From the four-chamber view, the sample volume is positioned on the annulus, near the insertion site of the mitral valve. Measurement of three or more consecutive cycles should be obtained at the end-expiration. The most useful measurement is the peak annular velocity in early diastole named E'. In practice, E' is not often reported in isolation. Instead, it is usually combined with the E wave velocity into the familiar ratio, E/E'. It was shown that the lateral E' may correlate better with filling pressures in the setting of a normal ejection fraction. The main use of the E/E' ratio is predict filling pressure in the setting of abnormal diastolic function **(21).**

Global Longitudinal Strain (GLS):

Lagrangian strain is defined as the change in length of an object within a certain direction relative to its baseline length: Strain %=(L1-L0) /LO; where Lt is the length at time t, and L0 is the initial length at time 0. The most commonly used strain-based measure of LV global systolic function is GLS. It is usually assessed by speckle-tracking echocardiography (STE) **(8).**

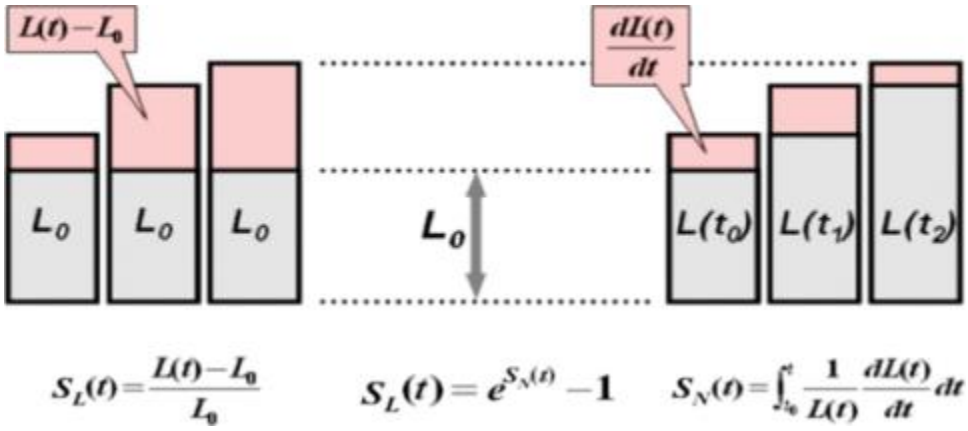

Figure (6): Graphical representation of the difference between strains. Left panel: Lagrangian strain SL relates the actual length always to the baseline length of the object. Right panel: Natural strain SN relates the instantaneous length changes to the variable instantaneous length Modified from **(2).**

On 2DE, peak GLS describes the relative length change of the LV myocardium between end-diastole and end-systole:

GLS%=MLS-MLD/MLD:

Where ML is myocardial length at end-systole (MLs) and end-diastole (MLd). Because MLs is smaller than MLd, peak GLS is a negative number. This negative nature of GLS can lead to confusion when describing increases or decreases in strain. We recommend that all references to strain changes specifically mention an increase or decrease in the absolute value of strain, to avoid confusion. After optimizing image quality, maximizing frame rate, and minimizing foreshortening, which are all critical to reduce measurement variability, GLS measurements should be made in the three standard apical views and averaged **(6).**

Measurements should begin with the apical long-axis view to visualize aortic valve closure, using opening and closing clicks of the aortic valve or aortic valve opening and closing on M-mode imaging. When regional tracking is suboptimal in more than two myocardial segments in a single view, the calculation of GLS should be avoided. In such cases, alternative indices may be used to gain insight into longitudinal LV function, such as mitral annular plane systolic excursion or pulsed Doppler tissue imaging (DTI)–derived mitral annular peak systolic velocity (s0). There are concurrent definitions as a basis for GLS calculation using endocardial mid wall, or average deformation **(2).**

This committee refrains from recommendations in this regard and refers to the ongoing joint standardization initiative of the ASE, EACVI, and the ultrasound imaging industry. Global longitudinal strain is emerging as a technique with utility in identifying systolic dysfunction prior to decrement in EF. Normal values vary across vendor platforms, but in general, a value of −20% (or more negative) would be expected in normal systolic function **(22).**

Because of inter vendor and inter software variability and age and load

dependency, serial assessment of GLS in individual patients should be performed using the same vendor's equipment and the same software. The preponderance of currently available data is for mid wall GLS. Although the evidence base for its use in routine clinical echocardiography is far smaller than that for EF, measures of mid wall GLS have been shown in several studies to be robust and reproducible and to offer incremental predictive value in unselected patients undergoing echocardiography for the assessment of resting function, as well as in predicting postoperative LV function in patients with valve disease **(23).**

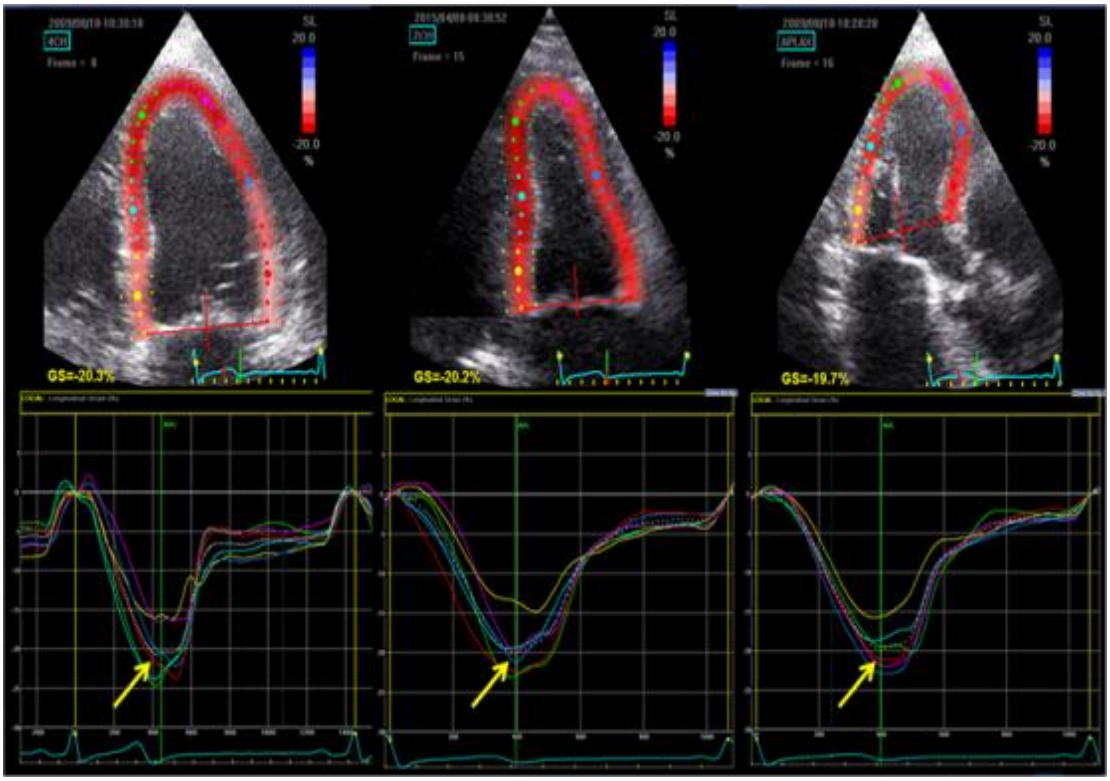

Figure (7): Example of calculation of global longitudinal strain (GLS) by 2Dspeckle tracking for the apical four-, two-, and three-chamber views. The strain throughout one cardiac cycle can be seen for each of the colour-coded LV segments (mean strain shown in white). In this example, the mean peak strains are −20.3, −20.2, and −19.7 % (indicated by the arrows), which occur during LV ejection. The calculated GLS is−20.1%; a more negative strain indicates better systolic function. **(24)**

Although −18.6 ± 0.1% was proposed as an average value of GLS in one large study of healthy volunteers **(23).** The published values of GLS vary considerably from −15.9% to −22.1% **(25).**

A variety of parameters might potentially influence the measurement of strain, including features specific to patients (age, gender, race, ethnicity, anthropometric variables), hemodynamic factors (heart rate, blood pressure), and cardiac factors (LV size, wall thickness). One cause for concern is the variation in recorded measurements among different vendors due to proprietary differences in the software used to calculate deformation **(23).**

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