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Echocardiographic Evaluation of Left Ventricular Diastolic Function: an Update

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Abstract Echocardiographic evaluation of diastolic properties and assessment of hemodynamic status of the right and the left ventricle have been traditionally applied for many years in clinical practice. Establishment of diagnosis of diastolic dysfunction, grading, and estimation of filling pressures noninvasively adds prognostic information to the clinician, which may affect treatment management. Novel methods, including left atrium strain, left ventricular diastolic strain rate, and left ventricular untwisting rate, have been imported in clinical practice attempting to provide a more comprehensive and more accurate understanding of the mechanisms and diagnosis of diastolic dysfunction.

Keywords Diastole · Doppler · Echocardiography · Left ventricle · Left atrium · Mitral inflow

Introduction

Left ventricular (LV) diastolic properties were first characterized invasively using the rate of left ventricular pressure decline, LV relaxation time constant, and measurements of myocardial and chamber stiffness. Currently, noninvasive evaluation of diastolic function is used in the day-to-day evaluation of LV function. It is based on Doppler echocardiography and utilizes measurements of transmitral flow, pulmonary vein flow velocities and patterns, mitral annulus tissue Doppler imaging, and pulmonary artery pressure (PAP) estimation by echocardiography. A comprehensive approach that takes into consideration LV ejection fraction (EF), presence or absence of left ventricular hypertrophy, and left atrial (LA) volume is recommended for the grading of diastolic dysfunction and the estimation of LV filling pressures [1]. In addition, there are relatively novel indices including global diastolic strain rate (SR), regional diastolic strain rate, LV untwisting rate, and LA strain based on speckle tracking imaging that can be implemented to study LV diastolic function. In this article, we present a guideline-based approach to assess LV diastolic function and the emerging role for the more recently introduced parameters.

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Grading Diastolic Function

The presence of diastolic dysfunction by Doppler echocardiography is not uncommon in the general population and has been associated with increased all-cause mortality [2]. Further, progression of diastolic dysfunction has been related to the development of heart failure symptoms [3] and to higher mortality in patients with normal EF [4•]. In a recent study, a simple marker of diastolic dysfunction, *e′* velocity, was shown to be a significant predictor of fatal and nonfatal cardiovascular events in the general population [5•].

The initial step in diastolic function assessment is the evaluation of mitral annular *e′* velocity by tissue Doppler, a marker that correlates significantly with the time constant of LV relaxation [6]. This is done in conjunction with biplane LA volume measurements. Patients with impaired diastolic function usually have a septal *e′* velocity <8 cm/s and a lateral *e′* <10 cm/s, and depending on the stage of the disease, LA volume index may be increased (≥34 ml/m^2). However, tissue Doppler annular velocities are not reliable for evaluation of LV relaxation in patients with primary mitral valve disease and normal EF; patients with LBBB, paced rhythms, or prosthetic valves or rings; and patients with constrictive pericarditis.

The American Society of Echocardiography/European Association of Echocardiography (ASE/EAE) guidelines use three grades of diastolic dysfunction: grade I (mild), grade II (moderate), and grade III (severe) [1]. The separation into three grades is primarily based on the mitral inflow pattern. Important measurements of mitral inflow Doppler signal include peak early filling velocity (*E*), late diastolic filling velocity (*A*), the *E*/*A* ratio, the deceleration time (DT) of the early filling velocity, and the time interval between the aortic closure and mitral valve opening called isovolumic relaxation time (IVRT).

In grade I, an abnormal relaxation pattern is seen and defined by an *E*/*A* ratio <0.8 and a DT >200 ms. DT reflects the rise in ventricular pressure during diastole and is related to LV ventricular stiffness. Those patients usually have normal diastolic LV filling pressures. However, there is a subset of patients where LV filling pressures are elevated despite an *E*/*A* ratio <1. This is more frequently seen in patients with markedly prolonged LV relaxation, often in the setting of hypertrophic cardiomyopathy and advanced hypertensive cardiovascular disease. These patients can be recognized by an elevated *E*/*e*′ ratio.

Patients in grade III diastolic dysfunction have abnormal LV relaxation and elevated filling pressures. By Doppler, *E*/*A* ratio is ≥2 and DT is <160 ms. Additional Doppler parameters that can be used to support the grading include *E*/*e*′ (using average *e*′) ≥13 cm/s, *Ar-A* ≥30 ms (difference in duration between atrial reversal signal in pulmonary veins and mitral *A* duration at the level of mitral annulus), and change in *E*/*A* ratio ≥0.5 with Valsalva maneuver. Moderate or grade II diastolic dysfunction is characterized by a pattern similar to a normal pattern defined by an *E*/*A* ratio 0.8–1.5. In those patients, the duration of the mitral inflow (duration of the *A* wave at the level of the mitral annulus) is usually shorter than the duration of atrial reversal velocity (*Ar*) in the pulmonary veins by at least 30 ms (*Ar-A*≥30 ms). The average *E*/*e*′ often falls in the range of 9–12, and the change in *E*/*A* ratio ≥0.5 with Valsalva maneuver.

Estimation of LV Filling Pressures

LV filling pressures as assessed by *E*/*e*′ have been shown to predict outcome in patients following myocardial infarction [7]; in patients with hypertension [8], moderately severe to severe secondary MR [9], heart failure due to reduced EF and heart failure with normal EF [10], end-stage renal disease [11], or atrial fibrillation [12]; in patients with cardiomyopathies [13, 14]; and in patients with aortic stenosis after aortic valve replacement [15]. Several studies have confirmed the significant correlation of this ratio with filling pressures in several patient populations [16–23]. However, Mullens et al. reported that *E*/*e*′ ratio may not be as reliable in decompensated patients with advanced systolic heart failure and the presence of resynchronization therapy [24]. Of note, the latter study had several limitations related to pressure and Doppler acquisition signals [25]. In a more recent study, Nagueh et al. showed in a similar population of patients with advanced decompensated heart failure that several Doppler indices including *E*/*e*′ ratio have good accuracy in identifying patients with elevated mean wedge pressure (>15 mmHg). Further, the latter study showed that the comprehensive approach recommended by the ASE/EAE guidelines had the highest accuracy [25]. Likewise, Ritzema et al., using direct measurements of LA pressure in patients with various grades of diastolic dysfunction and chronic heart failure due to reduced EF, have shown *E*/*e*′ ratio to be the most accurate parameter in identifying patients with increased left atrial pressure (LAP) [26]. Changes in LAP in repeat studies were tracked well by *E*/*e*′ ratio [26]. Another recent study successfully applied a simplified approach using *E*/*e*′ ratio ≥15, LA area ≥20 cm^2, and DT <140 ms for evaluation of filling pressures in a population with heart failure and reduced EF and cardiac transplant patients with normal or reduced EF [27].

While the above presentation discussed the role of the more commonly applied Doppler measurements, it is also important to recognize other parameters which can help in patients with equivocal findings. In the presence of LV diastolic dysfunction, a short DT indicates increased LV chamber stiffness and can be of value even in the presence of significant functional mitral regurgitation [1]. The IVRT is another parameter for differentiating normal from elevated LAP as it is often <60 ms with elevated LAP. In addition, the ratio of IVRT to the time interval delay between onset of *E* velocity and that of *e*′ ($T_{E\text{-}e'}$, Fig. 1) relates inversely with mean wedge pressure and can be applied in cases of mitral stenosis, mitral regurgitation, and atrial fibrillation which pose challenges to many Doppler signals [28, 29]. For pulmonary vein signals (1), a decrease in LA compliance along with an increase in LA pressure is associated with reduced forward systolic flow (systolic filling fraction <40 %). As noted above, *Ar-A* duration >30 ms occurs in the setting of elevated LVEDP (>20 mmHg), but its clinical utility is limited in the presence of atrioventricular block or arrhythmias.

Filling Pressures in Patients with Normal EF

According to the ASE/EAE guidelines [1], LV filling pressures are elevated if septal *E*/*e*′≥15, lateral *E*/*e*′≥12, or average *E*/*e*′≥13. An *E*/*e*′ ratio <8 occurs in the presence of a normal LAP, whereas an *E*/*e*′ ratio 9–14 requires a more comprehensive approach that includes parameters as LA volume index (increased LAP with ≥34 ml/cm^2); pulmonary artery systolic pressure estimate (increased LAP with >35 mmHg); time difference between duration of atrial

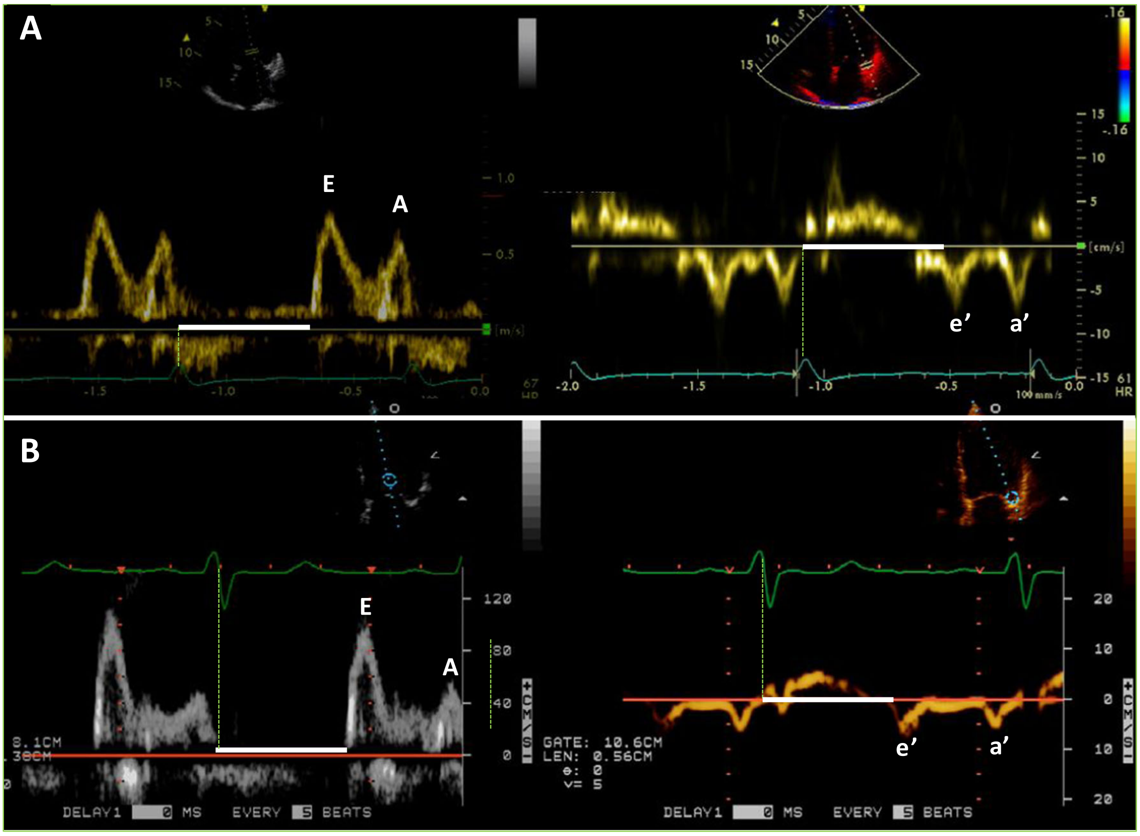

Fig. 1 **a** A patient with normal LV relaxation where $T_{E\text{-}e'}$=20 ms. Pulmonary artery systolic pressure was normal and estimated at 25 mmHg. **b** A patient with impaired LV relaxation and elevated LV filling pressures where $T_{E\text{-}e'}$=38 ms. Pulmonary artery systolic pressure was elevated at 40 mmHg

reversal wave at the pulmonary veins and the duration of the *A* wave at the level of the mitral annulus, or *Ar*-*A* duration; ratio of IVRT to time interval delay between onset of mitral *E* and annular *e′* (increased LAP with IVRT/$T_{E\text{-}e'}$<2); and the change in *E*/*A* ratio with Valsalva maneuver ≥0.5.

Filling Pressures in Patients with Reduced EF

In patients with depressed EF, the noninvasive LAP estimation algorithm initially uses the mitral inflow pattern *E*/*A* ratio to differentiate patients with normal and elevated LAP. Patients with a restrictive filling pattern (*E*/*A*≥2, DT<150 ms) usually have elevated LAP, while those with an impaired relaxation pattern and peak *E* velocity <50 cm/s have normal LAP [1]. In patients with pseudonormal filling (*E*/*A* ratio 1–2 in the setting of impaired LV relaxation) or impaired relaxation pattern with peak *E*>50 cm/s, additional parameters are needed. Thus, several other variables are needed to conclude that LAP is elevated and include an average *E*/*e′* ratio ≥15, *E*/*Vp* ratio ≥2.5 (*Vp* stands for flow propagation velocity by color M-mode), pulmonary vein inflow systolic/diastolic ratio <1, *Ar*-*A*≥30 ms, IVRT/$T_{E\text{-}e'}$<2, change in *E*/*A* ratio ≥0.5 with Valsalva maneuver, and noninvasive pulmonary artery systolic pressure estimate >35 mmHg [1]. It should be noted that not all of the above parameters will fall in the range of expected values, and based on technical and pathophysiological factors, one or more of these parameters may have limitations and thus should not be used.

Filling Pressures in Atrial Fibrillation

The accuracy of LV filling pressures in patients with atrial fibrillation has been addressed in several studies. Deceleration time of mitral *E* velocity (DT) has been shown to correlate well with mean wedge pressure in patients with depressed EF [30]. The authors also demonstrated that peak acceleration rate of mitral diastolic flow velocity (increased LAP with peak acceleration rate ≥1900 cm/s^2) correlated well with LV filling pressures. In addition, the ratio of early transmitral flow velocity to flow propagation velocity (increased LAP with *E*/*Vp*>1.4) identified patients with wedge pressure ≥15 mmHg [30]. Furthermore, Sohn et al. have shown that a septal *E*/*e′* ratio ≥11 predicts LV filling pressure ≥15 mmHg with reasonable accuracy [17]. Pulmonary venous diastolic velocity deceleration time ≤220 ms appears to identify patients in atrial fibrillation with mean wedge pressure ≥18 mmHg [31]. $T_{E\text{-}e'}$>34 ms using dual Doppler assessment has improved the accuracy of evaluation of filling pressures when added to *E*/*e′*

ratio in patients with atrial fibrillation [32]. Likewise, single-beat acquisition of mitral *E* and annular *e*′ velocities resulted in a better correlation with plasma BNP and mean wedge pressure in patients with atrial fibrillation and normal EF than an *E*/*e*′ ratio obtained by velocity averaging from nonsimultaneous beats [33] .

Diastolic Stress Test

Diastolic stress testing has become a valuable method to unveil elevated LV filling pressures in patients with exertional dyspnea of a cardiac etiology. A diastolic stress test is performed using supine bicycle exercise allowing a detailed stage-by-stage analysis of diastolic properties during which mitral inflow velocities, mitral annular velocities by tissue Doppler, and tricuspid valve peak regurgitation velocity are recorded at the different stages and the early recovery period. In patients with diastolic dysfunction, peak *E* velocity increases more profoundly than the change in annular e′ velocity [34], and thus, *E*/*e*′ ratio increases with exercise reflecting the elevated LV filling pressures [35, 36]. Importantly, the elevated *E*/*e*′ ratio with exercise has been associated with adverse cardiovascular outcomes even when detectable ischemia is considered [37]. Diastolic stress testing with intravenous dobutamine infusion, although infrequent in current clinical practice, has also been shown to predict clinical events in cardiac patients [38].

Deformation Measurements (Strain and Strain Rate)

Myocardial deformation and the rate of deformation during the different phases of the cardiac cycle can be currently measured by tissue Doppler imaging and speckle tracking imaging techniques. Strain represents the fractional length change of a myocardial segment with respect to an original length (could be the length in the absence of any stress or at end diastole), and strain rate is the speed that deformation occurs (unit: s^{-1}). Many patients with diastolic dysfunction, including those with heart failure and normal EF, have impaired longitudinal strain (Fig. 2). With respect to relation of diastolic strain and strain rate (Fig. 3), both regional and global measurements have been correlated with the time constant of LV relaxation; this applies to signals during the isovolumic relaxation period as well as during early diastole [39–41].

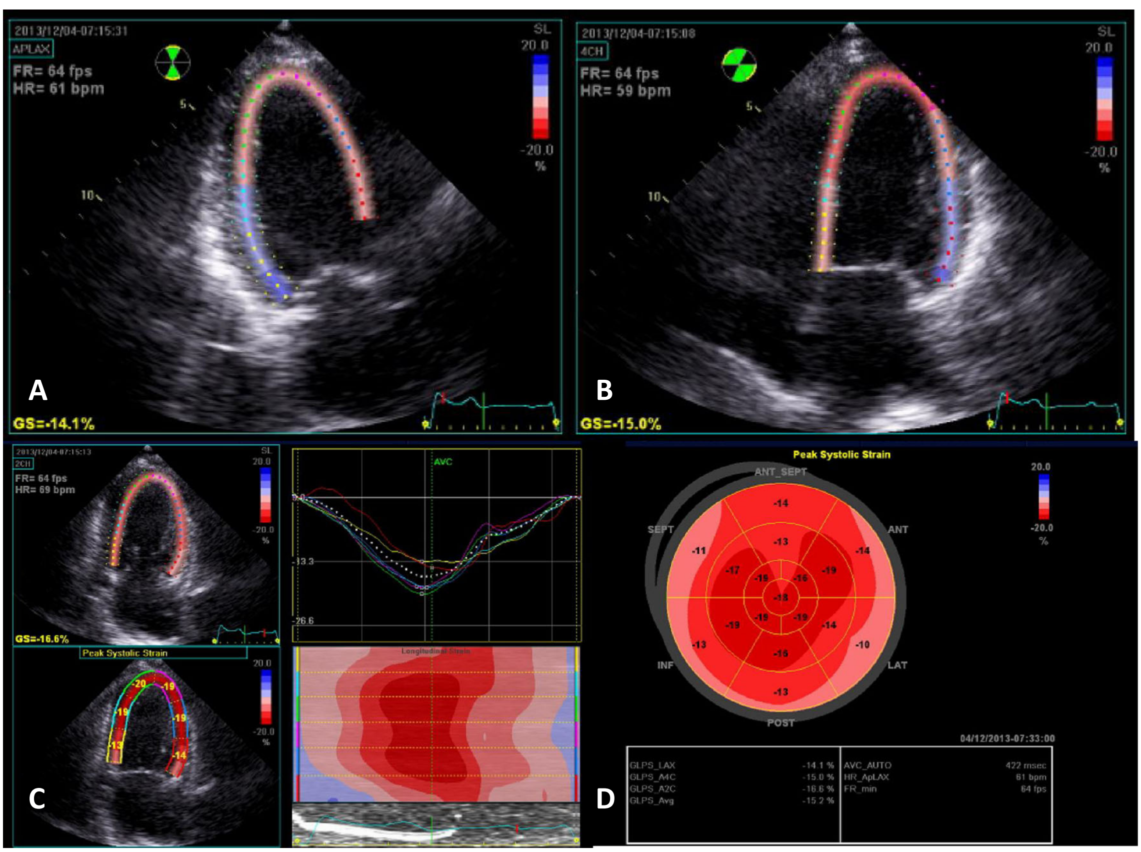

Fig. 2 Strain imaging and calculation of global longitudinal strain in a heart failure patient with preserved EF using measurements from apical three-chamber view (**a**), apical four-chamber view (**b**), and apical two-chamber view (**c**). Segmental strain results are displayed in a polar map (**d**). Global LV longitudinal strain is impaired at −15.7 %.

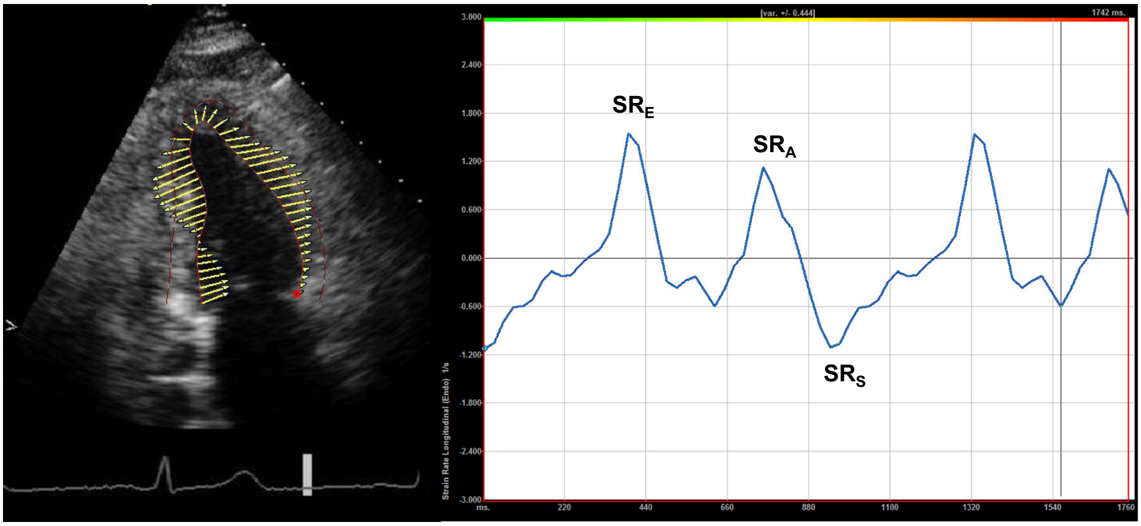

Fig. 3 An example of regional strain rate during early diastole (SR_E), late diastole (SR_A), and during systole (SR_S)

Regarding segmental function, time to onset of regional relaxation was used to identify ischemic segments during dobutamine stress echocardiography [42]. In another report, early diastolic strain rate predicted segmental viability in STEMI patients with an akinetic apex following reperfusion therapy [43]. Similarly, diastolic strain rates have been used for differentiating segments with myocardial viability in patients with prior myocardial infarction [44]. More recently, regional increased strain in early diastole (described by strain imaging diastolic index and using end systolic strain at aortic valve closure and strain at one-third diastole) was noted in patients undergoing percutaneous coronary revascularization not only during balloon inflation but also after the ischemia has resolved [45]. With respect to outcome studies on diastolic strain rate measurements, strain rate during the isovolumic relaxation period (SR_{IVR}) was an independent predictor of outcome in patients with ST-elevation myocardial infarction in one study [46].

There are growing data supporting the notion that diastolic strain rate in conjunction with mitral E velocity can provide reasonable estimation of LV filling pressures. In one study, Kimura et al. [47] used the ratio of mitral E velocity to early diastolic global longitudinal strain rate (E/SR_E) as surrogate of LV filling pressures. In another study that included animal experiments and patients' data [40], the ratio of E velocity to diastolic strain rate during isovolumic relaxation (E/SR_{IVR}) was a good measure of mean wedge pressure. In addition, there are data [48] that E/SR_E and E/SR_{IVR} are significantly related to LV stiffness constant. With respect to diastolic strain, one study used the ratio of mitral E to global longitudinal diastolic strain (and strain rate) during peak mitral filling (E/D_S) to successfully predict LV filling pressures in patients with preserved EF [49]. While most studies used longitudinal deformation, one report utilized the ratio of mitral E velocity to circumferential strain at the time of peak E velocity to identify dilated cardiomyopathy patients with

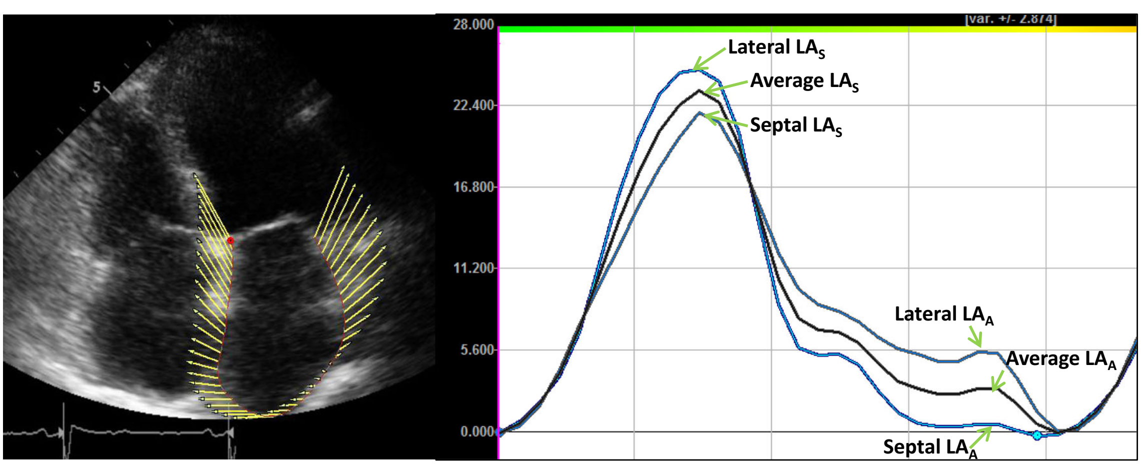

Fig. 4 Left atrium (LA) strain curves in a patient with heart failure and preserved EF. Signals are obtained from LA mid-lateral and mid-septal regions in the apical four-chamber view. LA_S refers to LA strain during left ventricular systole, and LA_A refers to LA strain during atrial systole before the QRS complex

mean wedge pressure >12 mmHg [50]. These ratios provided incremental prognostic information in several patient populations including myocardial infarction and atrial fibrillation [46, 51•, 52•].

Twist and Untwisting

Twisting of the LV results in storage of potential energy during systole, and untwisting is in part related to the recoil forces and favorably influences early diastolic filling. LV twist is obtained as the net difference between anticlockwise rotation of the apex and clockwise rotation of the base [53]. CMR, tissue Doppler imaging, and speckle tracking can be used to study torsional mechanics [54, 55].

Several studies have shown that patients with diastolic dysfunction can have delayed untwisting and a reduced peak untwisting rate with exercise [56–58]. Several factors affect peak untwisting rate and include the diastolic time constant of LV [59], LV early diastolic load which increases it [60••], as well as LV elastic recoil which can result in normal peak untwisting rate in patients with diastolic dysfunction [61]. Recently, 3D speckle tracking has been evaluated to study twist mechanics. However, the low frame rate could lead to underestimation of LV peak twisting and untwisting velocities. At the present time, these measurements are useful in evaluating myocardial function in several disease states but are not essential for day-to-day clinical studies.

2D and 3D LA Volumes

An LA volume index ≥34 ml/cm^2 is associated with adverse cardiovascular outcomes [62]. In one study, LA volume index was highly sensitive and specific for detecting diastolic dysfunction in a patient population older than 45 years [63]. Although LA size is usually increased in patients with elevated filling pressures, LA volume may not be increased in early stages of diastolic dysfunction [64]. Notwithstanding the findings in early and mild disease, LA maximal volume can be taken as an index of diastolic dysfunction in the absence of significant mitral regurgitation and atrial arrhythmias. LA enlargement is not specific for diastolic dysfunction as the LA can be enlarged in patients with anemia, high-output states, bradycardia, athletes, mitral valve disease, and atrial arrhythmias [1].

Most labs obtain biplane measurements of LA volumes. However, 3D echocardiography appears to be more accurate in determining true LA size. This is in part due to the asymmetrical enlargement of the left atrium [65••]. Additional studies are needed to examine the advantage of using 3D LA volume measurements in the clinical setting.

LA Strain

LA strain (Fig. 4) provides insights into LA reservoir (LA_S), conduit, and pump (LA_A) functions. Additionally, a surrogate of LA stiffness may be calculated using the ratio of E/e' to LA_S. This index is abnormally elevated in patients with diastolic heart failure when compared to healthy subjects and patients with diastolic dysfunction who are not in heart failure [66]. Importantly, LA_S relates inversely to LV filling pressures, especially in patients with depressed EF [67]. Studies have also shown that LA_S is a significant predictor of maintenance of sinus rhythm after cardioversion in patients with atrial fibrillation [68]. While promising, measurement of LA strain is not standardized. Similar to LV strain measurements, the results depend on the ultrasound system used for acquisition and the software used for analysis. In addition, the number of sites and the location of sampling in the LA have varied between the studies.

Conclusion

Doppler echocardiography can be used to obtain reliable noninvasive assessment of LV diastolic function. There are several promising new indices, but their ultimate adoption in clinical practice awaits standardization of measurements and additional clinical studies.

Compliance with Ethics Guidelines

Conflict of Interest Dimitrios Maragiannis and Sherif F. Nagueh declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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