Evaluation of Left Ventricular Diastolic Function by Echocardiography

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Despite the knowledge that the heart spends almost two-thirds of its time in diastole (relaxing and filling), its contractile activity was for a long time considered the core of its mechanical function and over which major concerns had been focused. It was after the 1980s that the scientific community began to realize the clinical significance of diastolic dysfunction among patients with signs and symptoms of heart failure (HF) but in whom ejection fraction was rather preserved. The recognition of the latter condition as "heart failure with preserved ejection fraction" (HF-PEF) impelled major efforts in order to identify the pathophysiological mechanisms underlying this emerging concept.[1;2] The impact of diastolic dysfunction on cardiac morbidity and mortality is becoming increasingly understood. [1]

The hallmark of diastolic dysfunction is the impaired capacity to fill or maintain stroke volume without a compensatoy increase in filling pressures.[3] Historically, invasive hemodynamics have provided useful information with respect to diastolic filling pressures, e.g., left atrial (LA) pressure and left ventricular (LV) end-diastolic pressure; left ventricular relaxation (time constant of relaxation-dP/dt) and operant chamber stiffness (pressure-volume loops, diastolic pressure contour). However, advances in echocardiographic assessment of LV diastolic function can lead to the replacement of invasive hemodynamics in the vast majority of patients.[2;4] In the crucial question "can echocardiography accurately measure diastolic function?", there are reasoned arguments on either side of the debate.[5] Undoubtedly echocardiography has played a central role in the evaluation of LV diastolic function over the past two decades.

Diastole starts at aortic valve closure and includes LV pressure fall, rapid filling, diastasis (at slower heart rates), and atrial contraction.[6] Many factors can affect LV filling and the diastolic pressure-volume relation (**Fig**. 1). Female gender, older age, arterial hypertension, diabetes, obesity, and LV hypertrophy are currently well-established risk factors, showing a strong association with impaired diastolic function with a concomitant normal systolic function.[1] Elevated filling pressures are the main physiologic consequence of diastolic dysfunction. Filling pressures change minimally with exercise in healthy subjects. Exercise-induced elevation of filling pressures limits exercise capacity and can indicate diastolic dysfunction.[7]

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The echocardiographer must attempt to answer 3 major questions in making a diagnosis of diastolic dysfunction.[8] Is there a substrate for diastolic dysfunction? Are there markers consistent with the diagnosis of diastolic dysfunction? Are there markers of elevated LV filling pressure?

The different factors that influence diastolic function of LV and their importance at the different phases of diastole

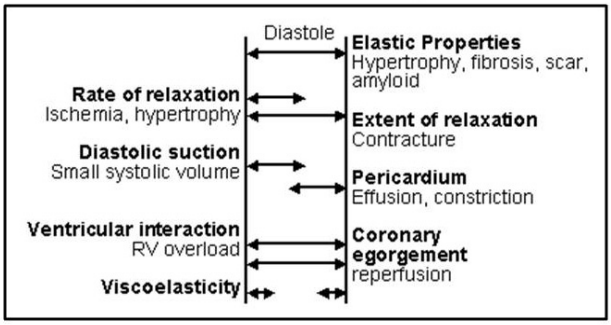

Figure 1. The different factors that influence diastolic LV function and their importance at the different phases of diastole.

Current framework for echocardiography assessment of diastolic function

1) Cardiac Morphology as Marker of Diastolic Dysfunction (substrate)

Diastolic function assessment should be framed in the context of the echocardiographic phenotype such as LV wall thickness, mass, and LA size. These morphologic descriptors may be either the cause or the consequence of diastolic dysfunction, and they often connote the severity or chronicity of dysfunction. The interaction between morphology and diastolic function has therefore formed a growing trend of combining echocardiographic measures of morphology and function in assessing diastolic function.[9]

- **LV hypertrophy/LV mass.** Increased LV mass correlates with LV relaxation impairment, LV end-diastolic pressure, and LV stiffness, whereas improvement in diastolic function is associated with regression of LV hypertrophy. LV mass may be best measured using 3-D echocardiography. Nevertheless, it is possible to measure it in most patients using 2-D echocardiography, using the recently published guidelines of the American Society of Echocardiography. For clinical purposes, at least LV wall thickness should be measured in trying to arrive at conclusions on LV diastolic function and filling pressures. [6]
- **LA volume.** Left atrial enlargement is commonly associated with severe diastolic dysfunction and with markers of both LV compliance and LV volume. However, one must recognize that dilated left atria may be seen in patients with bradycardia and 4-chamber enlargement, anemia and other high-output states, atrial

flutter or fibrillation, and significant mitral valve disease, in the absence of diastolic dysfunction. Therefore, it is important to consider LA volume measurements in conjunction with patient's clinical status, other chambers' volumes, & Doppler parameters of LV relaxation.[6;10] In order to calculate LA volume index (LAVI), we have to use the biplane method of disks and divide the LA volume by body surface area (BSA) (**Fig**. 2). More recently, LA volumes have been obtained by 3D echocardiography.

Observational studies including 6,657 patients without baseline histories of atrial fibrillation and significant valvular heart disease have shown that LAVI $\geq$ 34 mL/m^2 is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke. [6;11;12] In 2005, Pritchett et al concluded that in the general population, atrial remodelling as assessed by LAVI is closely associated with the severity of diastolic dysfunction, a relationship that persists after adjustment for pertinent clinical and echocardiographic covariates. [3;10]

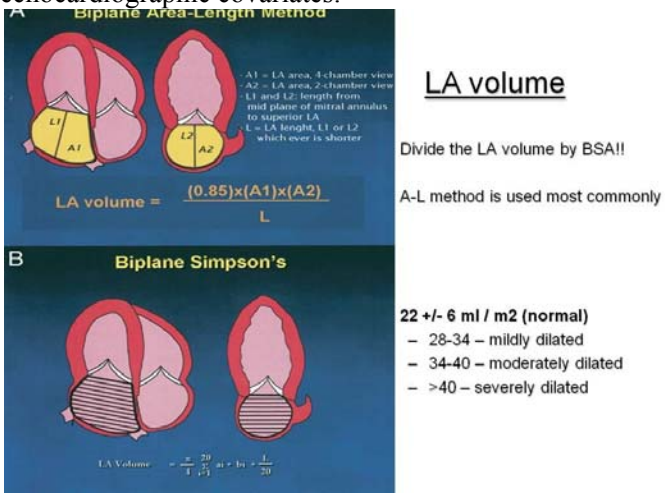

Figure 2. Calculation of left atrium volume index

2) Functional Correlates of Diastolic Dysfunction

● **LA function.** The atrium modulates ventricular filling through its reservoir, conduit, and pump functions. The reservoir, conduit, and stroke volumes of the LA can be computed and expressed as percentages of LV stroke volume.[13;14] Aside from LA stroke volume, LA systolic function can be assessed using a combination of 2D and Doppler measurements as the LA ejection force (preload dependent, calculated as 0.5 x 1.06 x mitral annular area x [peak A velocity]^2) **&;** kinetic energy (0.5 x 1.06 x LA stroke volume x[A velocity]^2). In addition, recent reports have assessed LA strain and strain rate and their clinical associations in patients with atrial fibrillation. Accordingly, the direct assessment of LA function is preferable and is now feasible by measuring LA strain by tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) (**Fig**. 3).[13-15]

● **Pulmonary artery systolic pressure (PASP) and pulmonary artery diastolic pressure (PADP).** In the absence of pulmonary disease, increased pulmonary artery (PA) pressures may be used to infer elevated LV filling pressures. A significant correlation was noted between PASP and noninvasively derived LV filling pressures. PADP by Doppler echo usually correlates well with invasively measured mean pulmonary wedge pressure and may be used as its surrogate.

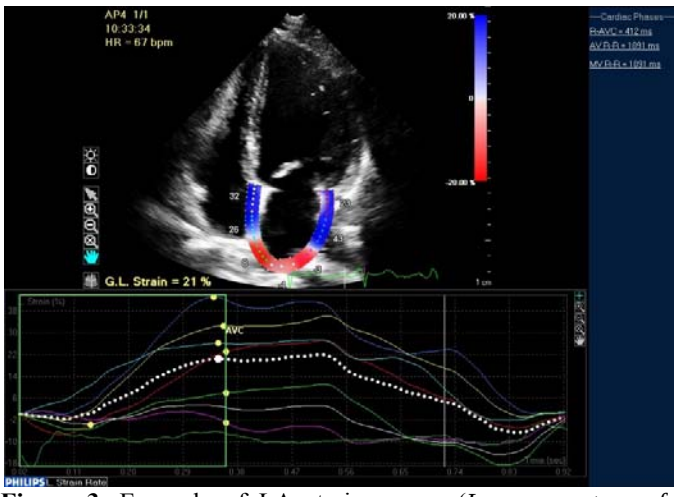

Figure 3. Example of LA strain curves (*Image courtesy of Medic View, Hellas and Philips Medical, Hellas)*

3) Traditional Doppler approach for evaluation of diastolic function

Traditional methods for evaluating diastolic function primarily focused on the dynamics of flow across the **mitral valve**. Consequently both the changes downstream related to the pressure and volume changes within the LV and the upstream changes in the temporal flow of blood across the ***pulmonary veins*** dominate diastolic function assessment. This traditional approach necessitated the classification of diastolic function into 4 patterns, namely, normal, abnormal relaxation pattern, pseudonormal filling pattern, & restrictive filling pattern (reversible/irreversible). The major pitfalls of the traditional paradigm are **age & load dependency**, its **focus on flow after mitral valve opening** (an event occurring after the onset of diastole), and **failure to adequately account for the effect of LV compliance** after rapid LV filling.[8]

● **Mitral Inflow.** Primary measurements include peak E and A velocities, E/A ratio, deceleration time (DT), and isovolumic relaxation time (IVRT) (**Fig**. 4). Secondary measurements include mitral A-wave duration (obtained at the level of the mitral annulus), diastolic filling time, A-wave velocity-time integral, and the total mitral inflow velocity-time integral (thus the atrial filling fraction) with the sample volume at the level of the mitral annulus.[6]

Age is a primary consideration when defining normal values of mitral inflow velocities and time intervals. With increasing age, mitral E velocity and E/A ratio decrease, whereas DT and A velocity increase. Factors that make mitral variables more difficult to interpret are sinus tachycardia, conduction system disease, and arrhythmias. In patients with dilated cardiomyopathies, filling patterns correlate better with filling pressures, functional class, and prognosis than LV ejection fraction (EF). In patients with coronary artery disease and those with hypertrophic cardiomyopathy in whom the LV EFs are ≥50%, mitral velocities correlate poorly with hemodynamics.[6;16]

- **Valsalva Maneuver (preload manipulation).** The Valsalva maneuver is performed by forceful expiration (about 40 mmHg) against a closed nose and mouth, producing a complex hemodynamic process involving 4 phases. A pseudonormal mitral inflow pattern is caused by a mild to moderate increase in LA pressure in the setting of delayed myocardial relaxation. Because the Valsalva maneuver decreases preload during the strain phase, pseudonormal mitral inflow changes to a pattern of impaired relaxation (Fig. 5). In cardiac patients, a decrease of ≥50% in the E/A ratio is highly specific for increased LV filling pressures, but a smaller magnitude of change does not always indicate normal diastolic function. One major limitation of the Valsalva maneuver is that not everyone is able to perform this maneuver adequately, and it is not standardized.[6]
- **Pulmonary Venous Flow.** Measurements of pulmonary venous waveforms include peak systolic (S) velocity, peak anterograde diastolic (D) velocity, the S/D ratio, systolic filling fraction (Stime-velocity integral/ [Stime-velocity integral + Dtime-velocity integral]), and the peak Ar velocity in late diastole. Other measurements are the duration of the Ar velocity, the time difference between it and mitral A-wave duration (Ar - A); and D velocity DT. There are two systolic velocities (S1 and S2), mostly noticeable when there is a prolonged PR interval, because S1 is related to atrial relaxation. S2 should be used to compute the ratio of peak systolic to peak diastolic velocity (**Fig**. 6).[6]

With increased LV end-diastolic pressure (LVEDP), Ar velocity and duration increase, as well as the Ar - A duration. Sinus tachycardia and first-degree AV block often result in the start of atrial contraction occurring before diastolic mitral and pulmonary venous flow velocity has declined to the zero baseline. This increases the width of the mitral A-wave velocity and decreases that of the reversal in the pulmonary vein, making the Ar-A relationship difficult to interpret for assessing LV A-wave pressure increase. With atrial fibrillation, the loss of atrial contraction and relaxation reduces pulmonary venous systolic flow regardless of filling pressures. In patients with depressed EFs, reduced systolic filling fractions (<40%) are related to decreased LA compliance and increased mean LA pressure.

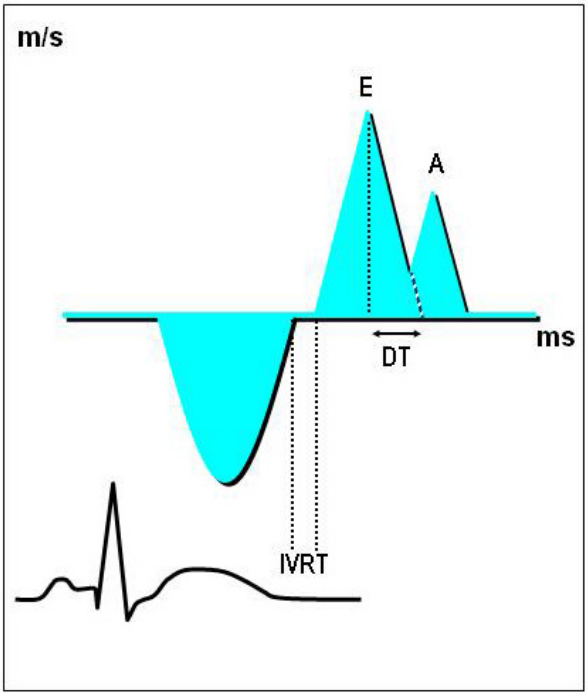

Figure 4. Doppler assessment of mitral valve inflow and IVRT. DT = time interval for the E wave velocity to reach 0; PHT = 0.29 DT; IVRT = time interval of AV closure to MV opening

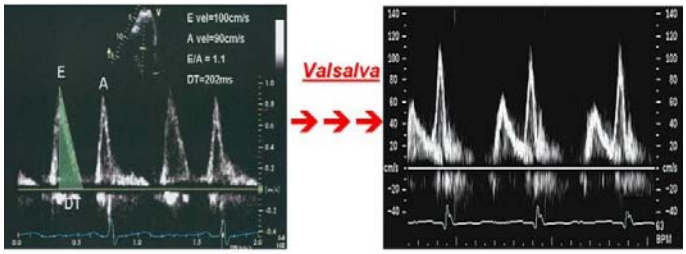

Figure 5. Valsalva manoeuvre changes a pseudonormal mitral inflow to a pattern of impaired relaxation.

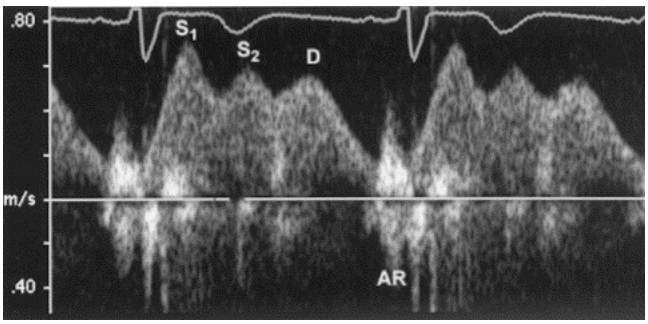

Figure 6. Pulmonary venous flow

The hallmark of diastolic dysfunction is the impaired capacity to fill or maintain stroke volume without a compensatory increase in filling pressures. Recently, it

has been proposed that **intraventricular pressure gradients (IVPGs), as derived by color M-mode echocardiography,** correlate with LV elastic recoil and LV contractility; IVPGs could be a useful method to improve the assessment of LV diastolic function using Doppler echocardiography. Similar to transmitral filling, normal LV intracavitary filling is dominated by an early wave and an atrial-induced filling wave. Most of the attention has been on the early diastolic filling wave, because it changes markedly during delayed relaxation with myocardial ischemia and LV failure.

In the normal ventricle, the early filling wave propagates rapidly toward the apex and is driven by a pressure gradient between the LV base and the apex. This gradient represents a suction force and has been attributed to LV restoring forces and LV relaxation. During heart failure and during myocardial ischemia, there is slowing of mitral-to-apical flow propagation, consistent with a reduction of apical suction. However, evaluation and interpretation of intraventricular filling in clinical practice is complicated by the multitude of variables that determine intraventricular flow. Not only driving pressure, inertial forces, and viscous friction but geometry, systolic function, and contractile dyssynchrony play major roles. Furthermore, flow occurs in multiple and rapidly changing directions, forming complex vortex patterns. The slow mitral-to-apical flow propagation in a failing ventricle is in part attributed to ring vortices that move slowly toward the apex. In these settings, the relationship between mitral-to-apical Vp ***(propagation velocity)*** and the intraventricular pressure gradient is more complicated. The complexity of intraventricular flow and the limitations of current imaging techniques make it difficult to relate intraventricular flow patterns to LV myocardial function in a quantitative manner.[3;17;18]

● **Color M-Mode Flow Propagation Velocity.** There is a well-defined intraventricular flow disturbance that has proved to be a semiquantitative marker of LV diastolic dysfunction, that is, the slowing of mitral-to-apical flow propagation measured by color M-mode Doppler. In addition, it is possible to use Vp in conjunction with mitral E to predict LV filling pressures. Studies in patients have shown that the ratio of peak E velocity to Vp is directly proportional to LA pressure, and therefore, E/Vp can be used to predict LV filling pressures by itself and in combination with IVRT.

The M-mode scan line is placed through the center of the LV inflow blood column from the mitral valve to the apex. Then the color flow baseline is shifted to lower the Nyquist limit so that the central highest velocity jet is blue. Flow propagation velocity (Vp) is measured as the slope of the first aliasing velocity during early filling, measured from the mitral valve plane to 4 cm distally into the LV cavity. Alternatively, the slope of the transition from no color to color is measured (Fig 7) Vp>50 cm/s is considered normal.[6]

In most patients with depressed EFs, Vp is reduced, and should other Doppler indices appear inconclusive, an E/Vp ratio ≥2.5 predicts PCWP >15 mmHg with reasonable accuracy. Caution should be exercised when using the E/Vp ratio for the prediction of LV filling pressures in patients with normal EFs. In particular, patients with normal LV volumes and EFs but abnormal filling pressures can have a misleadingly normal Vp. Advances in echocardiography have produced measurements that are less load dependent than the traditional markers such as **tissue Doppler imaging (TDI)**, and these measurements have facilitated differentiation of the true normal from the pseudonormal filling pattern.[6]

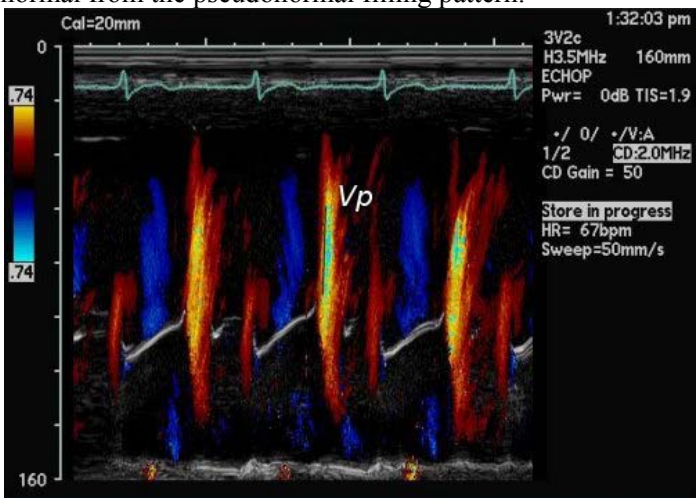

Figure 7. Color M-Mode flow propagation velocity (Vp) (*Image courtesy of Philips Medical, Hellas)*

● **Tissue Doppler Annular early and late Diastolic Velocities *(the historic search for a single echocardiographic marker of diastolic dysfunction).*** Given the limitations of preload dependency, atrial fibrillation, tachycardia, and regurgitant valvular lesions and the commonly observed pseudonormalization pattern, TDI has taken the "front-stage" in the transthoracic echocardiographic assessment of diastolic function as it is less hindered by preload dependency. [8]

TDI focuses on the high intensity, low velocity echoes of the myocardium. It can be displayed either by pulsed-wave Doppler or color M-mode flow velocity. Most current ultrasound systems have tissue Doppler presets for the proper velocity scale and Doppler wall filter settings to display the annular velocities. The sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5–10 mm) to cover the

longitudinal excursion of the mitral annulus in both systole and diastole. Primary measurements include the systolic & early (e´) & late (a´) diastolic velocities (**Fig**. 8). For the assessment of global LV diastolic function, it is recommended to acquire and measure tissue Doppler signals at least at the septal and lateral sides of the mitral annulus and their average. The joint Diastology Working Group recommends using an average value of medial and lateral e'velocities, especially when there is a regional wall motion abnormality involving the septal basal or lateral basal segment. An E/E'≤ 8 (5-12 mmHg), in most circumstances, predicts normal filling pressures and E/E' >15 (at any annular site) predicts elevated filling pressures (≥20 mmHg). When E/e is between 8 and 15, other parameters and maneuvers are necessary to estimate filling pressures. [8;19]

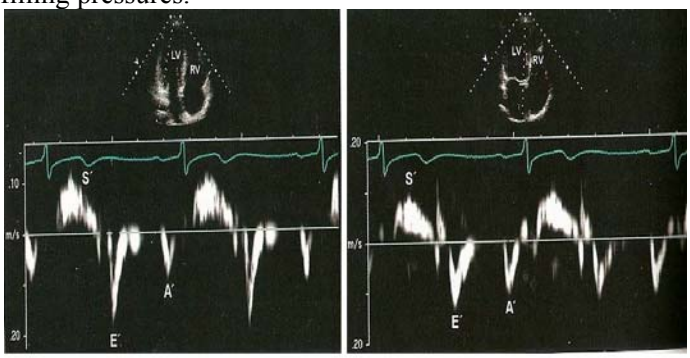

Fig. 8. Tissue Doppler early (e´) & late (a´) diastolic velocities

The European Working Group even recommended that E/E' ratio can be used in certain circumstances *as a sole marker of diastolic dysfunction*. This oversimplified reliance on single measures may be difficult to justify, given the modest correlation between LV pressures and other direct measures of mechanical diastolic function. Recently, Mogelvang et al[20] found that early diastolic annular velocity predicted mortality in a general population of patients, most of whom were free of apparent systolic and diastolic dysfunction by conventional echocardiographic methods.[6;8]

Limitations to TDI

Like all Doppler measures, tissue velocity is angle dependent.

1) **Sinus tachycardia (HR > 100)**: If e' and a' fuse (as they do with mitral inflow Doppler), the "fused" E and "fused" e' ("fused" E/ "fused" e') velocities can be used to predict filling pressures.

2) **AV conduction disturbances**: Asynchrony between contraction and relaxation events will manifest as impaired relaxation, thus, interpret with caution (e.g., VVI pacing will produce dissociated e'and a' waves, depending on the underlying rhythm; synchronous DOO pacing should have little affect on the TDI pattern).[21]

3) **Local wall motion abnormalities**: Because e' represents only the net effect of myocardial relaxation, elastic properties and the potential translational and tethering effects at the "sample" segment, it is recommended to avoid sampling a wall affected by pronounced wall motion abnormalities. However, if regional wall motion abnormalities are widespread, averaging multiple segments will offer a good estimate of global ventricular relaxation. In general, in patients with cardiac disease, e´ can be used to correct for the effect of LV relaxation on mitral E velocity, and the E/e´ ratio can be applied for the prediction of LV filling pressures. Normal values of TDI-derived velocities are influenced by **age**, similar to other indices of LV diastolic function. With age, e´ velocity decreases, whereas a´ velocity and the E/e´ ratio increase.

Mullens et al reported that E/e' may not be reliable in predicting LV filling pressures in decompensated patients with advanced systolic heart failure. The E/e´ ratio is not accurate as an index of filling pressures in patients with heavy annular calcification, mitral valve disease, and constrictive pericarditis.[6;22]

Novel techniques - New echocardiographic tools based on evaluation of cardiac mechanics

1) Deformation Measurements

Strain means deformation and can be calculated using different formulas. During the heart cycle, the LV myocardium goes through a complex 3-dimensional deformation that leads to multiple shear strains, when one border is displaced relative to another. In this case there are 3 normal strains (along the x, y & z axes) and 6 shear strains. To completely define the deformation of 3D objects, all 9 strain components must be defined. Until recently, the only clinical method to measure myocardial strain has been magnetic resonance imaging with tissue tagging, but complexity and cost limit this methodology to research protocols. [23;24]

A number of novel indices of regional and global LV diastolic function were developed in recent years. Some are based on TDI, whereas others are obtained using speckle tracking echocardiography (STE). Today, echocardiographic deformation imaging allows 1D measurements based on tissue Doppler imaging and 2D strain measurements based on speckle-tracking imaging.[8;23]

TDI was the initial approach to assessment of LV mechanics and **measures velocities of myocardial tissue** using the Doppler principle. Hence, it highly depends on minimal angulation (<15°) between the ultrasound beam and the plane of motion while having the advantage of a

high temporal resolution. Longitudinal mechanics of the LV are evaluated from apical (long-axis) views, whereas circumferential and radial mechanics are evaluated from short-axis views.

To achieve its high temporal resolution, it is essential to have a high frame rate of >100/s, which necessitates imaging of individual walls. Signals derived by color TDI are processed off line and can be displayed either as color 2D images or reconstructed time versus distance or deformation (ie, strain) curves.[6;25]

Myocardial deformation imaging by **2D speckle tracking echocardiography (STE)** is a newer technique, based on tracking myocardial "speckles" from frame to frame in grayscale images. With speckle tracking a new physiological window to the heart facilitates evaluation of both longitudinal and circumferential axis deformation (**Fig**. 9a,b). STE is based on tracking myocardial "speckles" from frame to frame in grayscale images. Speckles are very small structures in the image that can be recognized after filtering out noise. STE can be used to determine myocardial velocity and strain. The technique does not have the limitations of angle dependency as TDI and is obtained from images acquired at a frame rate of 50 to 80/s. Velocity vector imaging is based on the same concept, and deformation measurements by velocity vector imaging have been validated against sonomicrometry.[24;26] Problems with tissue Doppler–based strain include significant signal noise and signal drifting. STE is limited by relatively lower frame rates.

Using these techniques, it is possible to measure displacement (cm), velocity (cm/s), strain (a dimensionless parameter expressed in %), and strain rate (SR) (s_1). **SR** is the rate of change in length calculated as the difference between two velocities normalized to the distance (d) between them: (Va_Vb)/d, where Va_Vb is the instantaneous velocity difference between points a and b. **Strain** is the percent change in length during a given time period. It is obtained by integrating the SR over time or by the following equation: (L_Lo)/Lo (L is the final length & Lo the original length). It is possible to measure strain by STE in the longitudinal, circumferential, transverse, & radial directions.

Longitudinal axis deformation is more commonly evaluated by longitudinal strain and by strain rate, which focuses on the temporal changes in the base-to-apex length of the LV. A number of studies suggest that myocardial strain & SR may provide unique information regarding diastolic function. Comparing the strain and SR obtained by speckle tracking based 2D- strain imaging with those obtained in the same patients by TDI, Dandel et al found no significant differences (**Fig** 10a,b).

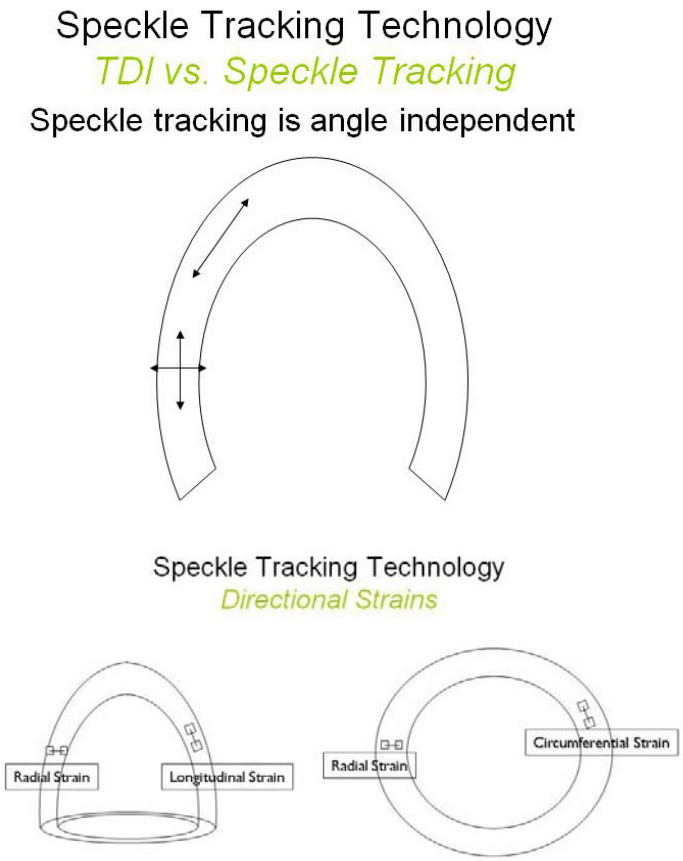

Figure 9. Tissue Doppler Imaging vs Speckle Tracking technology. Speckle tracking is a new imaging modality capable of providing information about myocardial motion in all 3 directions: longitudinal, circumferential and radial (*Image courtesy of Medic View, Hellas and Philips Medical, Hellas).*

Approaches to obtain global parameters were developed using SR during the IVRT (**SRIVR**) and during **SRe**. Both SR measurements are not affected by mitral valve disease or annular calcification, which can alter mitral annulus velocities. Furthermore, deformation measurements take into account resting length, which is not the case for velocity measurements. Finally, SRIVR occurs during the isovolumic relaxation period when the mitral valve is closed; therefore, it is not affected by the transmitral pressure gradient.[27;28]

Global diastolic strain rate during the isovolumetric relaxation time **(SRIVR)** has been used as a preload independent marker of diastolic relaxation similar to tissue Doppler imaging–derived annular early diastolic velocity. Global SRIVR by STE provided incremental information over baseline clinical, angiographic, and other echocardiographic variables (including ejection fraction and TD velocities). Patients with SRIVR ≤0.24

s_1 had a significantly higher event rate than those with a higher SRIVR.[29;30]

The ratio of mitral E to SRIVR was shown to be superior to the ratio of E to E' as a means of estimating LV filling pressure in patients with normal EFs and those with regional dysfunction. The evaluation of diastolic function by deformation imaging is promising but needs more study of its incremental clinical value.[31]

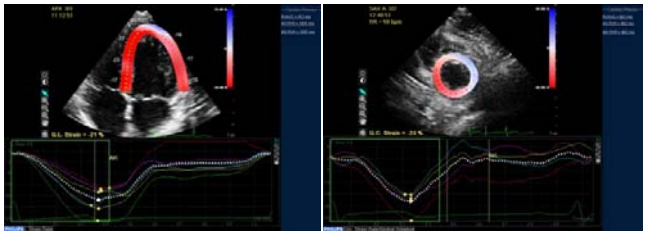

Figure 10. Speckle tracking of 2D images is a new technique for measuring myocardial deformation & velocity. **Left:** 2-D strain of LV, apical 4-chamber view; **Right:** 2-D strain of LV, short axis view (rotation) (*Image courtesy of Medic View, Hellas & Philips Medical, Hellas)*

2) LV Twist and Untwisting

LV twisting & untwisting are important aspects of cardiac mechanics and function. Viewed from the apex, the apical LV portion normally twists counterclockwise and the basal segment twists clockwise during systole, storing potential energy. The LV untwists immediately after systolic contraction, contributing to generating an intraventricular pressure gradient (**Fig**. 11).[32]

LV torsion is the summation of the apical and the basal twisting (**Fig** 12a,b). It is now possible to measure twist using **TDI & STE** from short-axis images of the LV. LV twist is calculated as the difference between basal and apical rotation measured in LV short-axis images. Under normal circumstances, apical rotation exceeds basal rotation and accounts for most of the observed twisting.[33;34]

The clinical value of assessing LV untwisting rate is not defined. When LV twist and untwisting rate were assessed in patients with diastolic dysfunction or diastolic heart failure, both twist and untwisting rate were preserved and no significant relation was noted with the time constant of LV relaxation whereas longitudinal and radial deformation are reduced. In fact, torsion is increased during the initial stage of diastolic dysfunction so that it may be helpful in identifying patients with mild diastolic dysfunction.[35;36]

On the other hand, in patients with depressed EFs, these measurements were abnormally reduced. Other studies showed that loading conditions strongly influence the untwisting rate. The abnormalities in LV torsion and untwisting can be uncovered with exercise in patients with diastolic heart failure. In normal subjects, exercise leads to an increase in both torsion and untwisting. However, in patients with heart failure, there is minimal augmentation of torsion and untwisting with a detrimental impact on LV filling during exercise.[37]

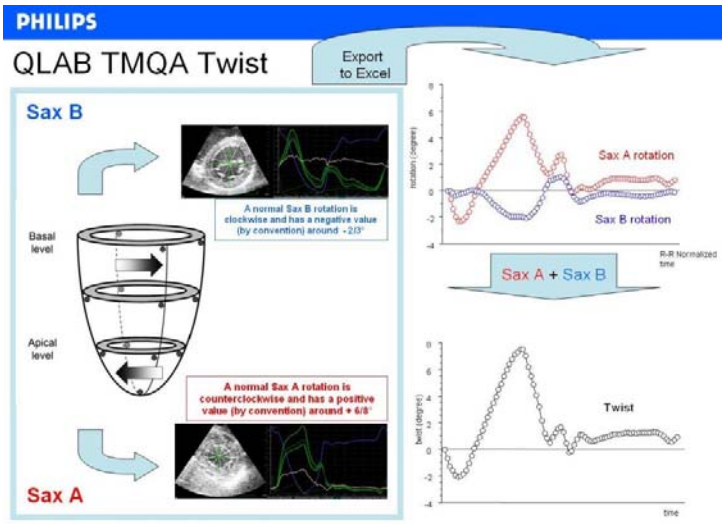

Figure 11. Terms such as LV rotation, twist, and torsion are often used interchangeably for explaining the wringing motion of the LV. QLAB software (Phillips, Andover, MA, USA) with advanced tissue motion quantification module (TMQA) (*Image courtesy of Philips Medical, Hellas)*

*The limitations of newer echocardiographic modalities that prevent widespread implementation can be broadly categorized into 3 domains.*1) Need for additional echocardiographic infrastructure (probes and/or machines, networked workstations, software modules). This should not be underestimated, because laboratories outside academic centers that do not have any niche clinical applications for new technologies may not find a convincing business case for developing new echocardiographic infrastructure, especially in the current economic environment. 2) Human resources are another important consideration. Aside from the time needed to train sonographers and echocardiographers to acquire and interpret images properly and perform measurements accurately and reproducibly, the extra time needed for acquisition and measurements (most of the time offline) poses a considerable burden for echocardiographic laboratories. 3) Cross-laboratory and cross-vendor standardization.

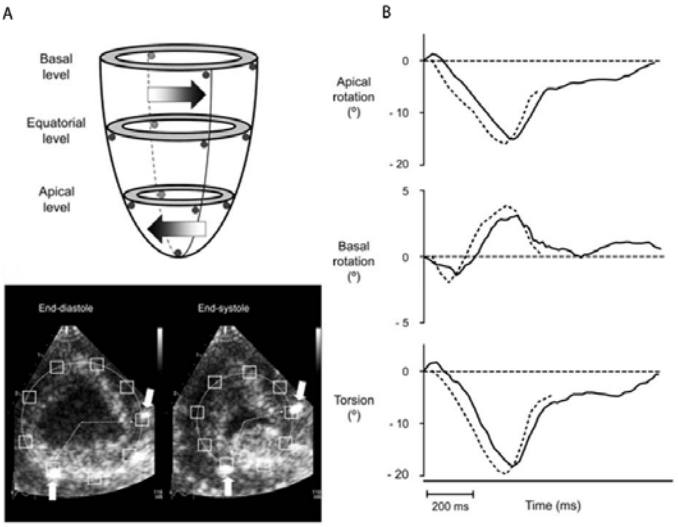

Figure 12. A: The base and apex of the LV rotate in opposite directions. **B**: The terms twist and torsion refer to the same phenomenon and should be used for defining the base-to-apex gradient in the rotation angle along the longitudinal axis of the LV (*Image courtesy of Medic View, Hellas & Philips Medical, Hellas)*

Diastolic Stress Test

Normal diastolic function allows adequate filling of the heart without an excessive increase in diastolic filling pressure both in the resting state and with stress or exertion. There is growing evidence that the diastolic stress test is most useful in patients with unexplained exertional dyspnea who have mild diastolic dysfunction and normal filling pressures at rest and can provide important diagnostic findings helpful in the management of patients presenting with dyspnea of an unclear etiology. It is useful to evaluate LV filling pressure with exercise as well, similar to the use of exercise to evaluate patients with coronary artery or mitral valve disease. The **E/e= ratio** has been applied for that objective**.** Ha et al were the first to introduce the concept of the diastolic stress test. Subsequently, exercise E/e' ratio was validated against invasive measurements. Importantly, exercise septal E/e' ratio was an important determinant of exercise capacity, and its decline with age was noted in a large series of patients referred for exercise echocardiography. Furthermore, a recent study showed the incremental prognostic value of exercise E/e' ratio over clinical variables and exercise wall motion score index. Because dobutamine is a vasodilator as well as an inotrope, the hemodynamic response to dobutamine is very different from that of exercise. It is unusual for a diastolic filling pattern to improve with exercise, but it is not uncommon with dobutamine. Diastolic filling that becomes worse with dobutamine is a very poor prognostic sign. However, the paucity of clinical data and the potential limitations in patients with regional LV dysfunction, mitral valve disease, and atrial fibrillation preclude recommendations for its routine clinical use.[6;12;24;38-42]

Other Reasons for Heart Failure Symptoms in Patients with Preserved EFs (PEF-HF)

● **Pericardial diseases.** It is important to consider the possibility of constrictive pericarditis when evaluating patients with the clinical diagnosis of heart failure with normal EFs, because it is potentially curable. Restrictive LV filling, prominent diastolic flow reversal during expiration in the hepatic veins, and normal or increased tissue Doppler annular velocities should raise suspicion of constrictive pericarditis in patients with PEF-HF, even when the respiratory variation in mitral inflow is absent or not diagnostic.[6]

● **Mitral stenosis.** Typically, patients with mitral stenosis have normal or reduced LV diastolic pressures, except for the rare occurrence of coexisting myocardial disease. Mitral stenosis renders the assessment of LV diastolic function more challenging, but IVRT, *T* E-e', and mitral inflow peak velocity at early and late diastole can be of value in the semiquantitative prediction of mean LA pressure.[24]

● **Mitral regurgitation (MR).** Primary MR leads to LA and LV enlargement and an increase in the compliance of both chambers, which attenuates the increase in LA pressure. The time intervals Ar _ A, IVRT, and IVRT/*T*E-e' may be applied for the prediction of LV filling pressures in patients with MR and normal EFs, whereas the E/e= ratio is applicable only in the presence of a depressed EF.

Estimation of LV filling pressures in special populations (see Table)

● **Atrial fibrillation.** Measurements from 10 cardiac cycles are most accurate. In general, septal e´<8 cm/s had reasonable accuracy in identifying patients with $\tau \geq 50$ ms. Likewise, an E/e´ratio ≥11 predicts LVEDP ≥15 mm Hg. The variability of mitral inflow velocity with the RR cycle length should be examined, because patients with increased filling pressures have less beat-to-beat variation._When LV EF is depressed, mitral DT (≤150 ms) has reasonable accuracy for the prediction of increased filling pressures and adverse clinical outcome. Other Doppler measurements that can be applied include the peak acceleration rate of mitral E velocity (≥1,900 cm/s2), IVRT (≤65 ms), DT of pulmonary venous diastolic velocity (≤220 ms), the E/Vp ratio (≥1.4), and the E/e´ ratio (≥11). [6;43-45]

● **Sinus Tachycardia.** A ratio of Doppler peak E-wave velocity to lateral mitral annular e´ velocity (E/e´) >10 predicts a mean pulmonary wedge pressure >12 mm Hg with sensitivity of 78% and specificity of 95%.

● **Restrictive cardiomyopathy.** Regardless of whether idiopathic or infiltrative in nature, mitral, pulmonary venous, and tissue Doppler variables are all good indicators of the marked elevation in filling pressures in patients with restrictive cardiomyopathy.

● **Hypertophic obstructive cardiomyopathy.** In contrast to restrictive cardiomyopathies, the mitral variables of E/A ratio and DT have weak to no correlations with LV filling pressures in patients with hypertrophic cardiomyopathy. A comprehensive approach is recommended when predicting LV filling pressures in patients with hypertrophic cardiomyopathy, with consideration of all echocardiographic data, including PA pressures and LA volume (particularly in the absence of significant MR).[46]

● **Pulmonary hypertension.** If the etiology is related to pulmonary parenchymal or vascular disease, LV filling pressures are usually normal or low, and an impaired relaxation mitral filling pattern is usually observed due to reduced LV filling rather than diastolic dysfunction per se. Typically, these patients have normal lateral annular e' velocities and lateral E/e' ratios <8. Conversely, patients with pulmonary hypertension secondary to diastolic dysfunction have increased E/e' ratios, because the mitral E velocity is increased because of increased LA pressure, and lateral e'velocity is reduced because of myocardial disease. The use of septal e' and the E/e' ratio is limited in patients with noncardiac etiologies of pulmonary hypertension because septal e' is reduced because of right ventricular contribution to septal velocity signals. With successful lowering of pulmonary vascular resistance, cardiac output increases, the LV filling pattern reverts to being more normal, and the lateral E/e' ratio increases. These changes may be of value in monitoring the response to medical and surgical treatment of pulmonary hypertension.

Prognosis associated with diastolic dysfunction

Regardless of etiology, or predisposing condition, the mortality and morbidity associated with the finding of diastolic dysfunction are significant. The stage of diastolic dysfunction correlates with the impairment of exercise capacity in patients without myocardial ischemia; LVEF does not. The presence of severe diastolic dysfunction in clinically stable patients identifies patients likely to subsequently develop heart failure. Progression of LV filling abnormalities in outpatients with preserved LV systolic function is a strong, independent predictor of all-cause mortality. As demonstrated by AlJaroudi et al, echo-Doppler progression of diastolic dysfunction can detect LV dysfunction at an early stage and indicates increased risk for future events. In elderly subjects with normal LVEF and evidence of abnormal relaxation, the most significant correlate of exercise tolerance is echocardiographic evidence of elevated LV filling pressure.

Diastolic function assessment is also important in evaluating prognosis in response to therapy or in serial echo evaluations. Achong et al reported worse outcomes for patients who either deteriorated from mild to severe diastolic dysfunction or failed to improve from an initial diagnosis of severe dysfunction. It is recommended that echocardiographic assessment of diastolic filling pressure can be used as "noninvasive Swan-Ganz catheter."[6;47;48]

New proposed classification of diastolic dysfunction & stepwise algorithm for evaluation of diastolic function

Traditional classification of diastolic dysfunction uses an incremental grade, from grade 1 (abnormal relaxation) to grade 3 (restrictive pattern) (**Fig**. 13). But the transition between various levels of abnormal LV filling pressure is dynamic and depends on the ambient heart rate and preload.[49] This dynamic transition makes accurate depiction of severity by means of just 1 snapshot of imaging, or single parameters in isolation, problematic. Furthermore, there is no evidence to support the assumption that there is a natural progression through the different grades of diastolic dysfunction inherent in the numeric assignment of incremental grades. The confusion created by assigning grades is further complicated by having a pseudonormal stage (grade 2), which refers to a situation when filling pressures are elevated but the mitral inflow pattern appears normal. When an algorithm not centered on mitral flow characteristics was used to identify subjects with elevated filling pressure, the pseudonormal grade was found to be dispensable as the prognosis associated with pseudonormal diastolic dysfunction is similar to that of severe diastolic dysfunction.[8;50]

A new prognosis-centered paradigm implies that diastolic function need only be stratified into **"normal"**, **"mildly abnormal" (compensated dysfunction)**, or **"severely abnormal" (uncompensated diastolic dysfunction)** categories and adequately captures the prognostic implications. The new paradigm centered on the prognostic value of diastolic dysfunction aims to determine the presence or absence of morphologic substrates or functional markers of elevated filling pressure.[8;24] Normal diastolic function in this context is identified by absence of markers of abnormal relaxation, abnormal compliance, and morphologic or functional abnormalities suggestive of elevated LV filling pressure.

An algorithm for application of currently used echo measurements is necessary to perform this simplified classification consistently. The algorithm does not require use of LVEF as an initial screening criterion. Reduced

LVEF is just one of the morphologic substrates for abnormal diastolic function. Subtle abnormalities of contractile function are present in most people with discernible evidence of diastolic dysfunction.[8;50] For patients who have a substrate but apparently normal markers of LV relaxation and no echocardiographic markers of elevated LV filling pressure, a repeat evaluation after exercise may unmask the presence of elevated LV filling pressure.[51] The prognostic data related to diastolic dysfunction as discussed above depend on whether LV filling pressures are elevated or remain elevated over time in spite of therapy.[2;47]

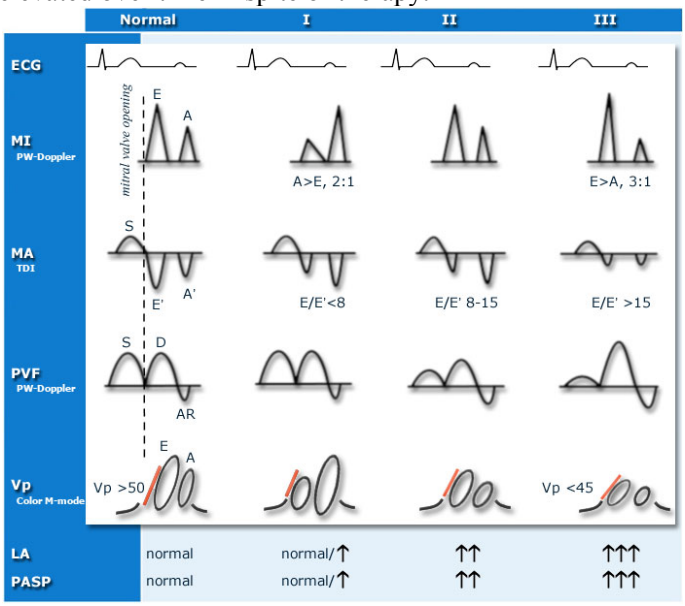

Figure 13. Traditional classification of diastolic dysfunction algorithm. I: impaired relaxation; II: moderate diastolic dysfunction (pseudonormal); III: restrictive left ventricular filling (impaired LV compliance). *Source:* www.echobasics.de

Systematic approach to evaluate diastolic function

1. With use of age- and gender-based reference values, determine whether each of the following is normal or abnormal (at least 1 must be abnormal for a diagnosis of diastolic dysfunction to be made): ● LV mass and relative wall thickness; ● LA volume; ● LV end-systolic or end-diastolic volume; ● Presence of clinical pathologic substrate such as hypertrophic cardiomyopathy, wall motion abnormalities, pericardial disease; ● Unexplained elevation of RV systolic pressure

2. a) *Use at least 2 high-order markers of diastolic dysfunction or 1 high-order criterion plus 4 abnormalities from mitral inflow & pulmonary vein flow (see below).* **High-order criteria** for diastolic dysfunction include TDI velocity of mitral annulus, global longitudinal strain, early diastolic strain rate, or strain rate during isovolumic relaxation (SRIVR). Of these, annular diastolic velocities and global longitudinal strain are preferable because of good reproducibility. Annular velocities by either color or pulsed wave TDI represent high-order markers that detect abnormalities at multiple phases of diastole. It is helpful to use age- / gender-based normograms for normal values

b) *Next, use age- / gender-corrected cut points for indices of blood-flow Doppler markers of diastolic dysfunction. Preferably use a representative measure from each of the following phases of diastole:* (1) isovolumetric relaxation; (2) rapid filling and; (3) late filling phases, respectively. Also, determine pulmonary vein flow systolic/diastolic ratio, and atrial reversal velocity and duration. Calculate indices to identify findings suggestive of abnormal filling pressure. These include E/E', E/FPV, mitral *a*-wave duration minus pulmonary vein atrial reversal duration >30 ms; and E/SRIVR. There are extensive prognostic data regarding the ratio of E/E' from either lateral annulus alone or a mean of lateral and septal annuli

3) Classify diastolic function according to this hierarchy:

● Severe dysfunction: Morphologic substrate markers of abnormal filling pressure are present in addition to abnormal age- and gender corrected markers from annular velocity, or abnormal blood flow marker with at least 1 morphologic substrate abnormality, or appropriate clinical context (such as diagnosis of heart failure or biochemical abnormalities)

● Compensated diastolic dysfunction: there are no markers suggestive of elevated filling pressure in the presence of either morphologic substrate, or age-/ gender-corrected annular velocity or mitral inflow abnormalities

● Normal diastolic function: absence of a morphologic substrate and absence of abnormal annular velocity markers without any marker of elevated filling pressure: *E, mitral inflow; E', early diastolic annular velocity; FPV, flow propagation velocity.*

European Association of Echocardiography *(EAE)*/ American Society of Echocardiography *(ASE)* Recommendations *(2009)* [6;52]

- Estimation of LV filling pressures in patients with depressed EFs (**Fig**. 14) **or** normal EFs **(Fig**. 15)
- Grading diastolic dysfunction **(Fig**. 16)

On the basis of a clearly formulated question, one should define the needs: to examine changes in relaxation, stiffness, and/or filling pressures.

Myocardial Relaxation is an *active* process influencing the isovolumic relaxation phase and part of the early filling phase. The main indicators **of abnormal relaxation** are IVRT and isovolumetric or early diastolic annular motion or LV strain rate. It is possible to combine IVRT with noninvasive estimates of LV end-systolic pressure and LA pressure to derive τ (IVRT/[ln LV end-systolic pressure - ln LA pressure]). This approach has

been validated and can be used to provide a quantitative estimate of τ in place of a qualitative assessment of LV relaxation. **Ventricular compliance** is a *passive* process that influences all 3 filling phases of diastole. Indicators **of reduced operating compliance** are DT of mitral E velocity, A-wave transit time, ratio of LVEDP to LV end-diastolic volume, and surrogates of increased LVEDP, namely, an abbreviated mitral A-wave duration, reduced a´, and prolonged Ar duration in pulmonary venous flow.

Besides myocardial relaxation and ventricular compliance, characteristics of the **pulmonary veins, left atrium and mitral valve** are also involved in diastolic function. Indicators **of early diastolic LV and LA pressures** are the E/e´ ratio, DT of mitral E velocity in patients with depressed EFs, and to some extent LA enlargement, which reflects chronic rather than acute pressure changes. Correlations and mechanistic links between slowing of relaxation (i.e., increases in tau) and development of heart failure are not well established but need to be investigated. LV untwisting rate can be useful in studying the effects of suction on LV filling and the link between LV systolic and diastolic function.[53]

Each question should be addressed with the most suitable echocardiographic approach that gives an answer, as outlined in the recommendations. We have to keep in mind that diastolic dysfunction differs from diastolic heart failure in that heart failure is a clinical diagnosis that may or may not be present at the time an echocardiogram is performed (**Fig**. 17). In addition, caution should be exercised when drawing inferences about changes in LV relaxation, because these may occur due to load changes per se rather than an intrinsic improvement in myocardial function. When selecting among the echocardiographic methods for investigating problems related to diastolic function, it is possible to entertain either a general simple approach with high feasibility and reproducibility or a more tailored and sophisticated one. Although the former approach is suited for clinically oriented trials, the latter approach may be superior for answering mechanistic questions. Strain measurements by speckle tracking appear to have good reproducibility and can be applied to study segmental deformation and to address mechanistic issues.

Areas of Future Research

Assessing the validity and reproducibility of commonly used measurements should become a routine of all echocardiography laboratories. Three-dimensional evaluation of cardiac mechanics and function and studies of the spatial displacement of flow vortices may further

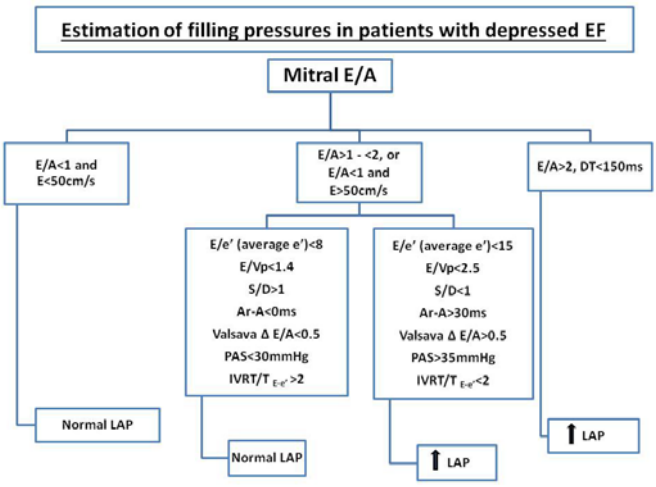

Figure 14: Diagnostic algorithm for the estimation of LV filling pressures in patients with depressed EFs.

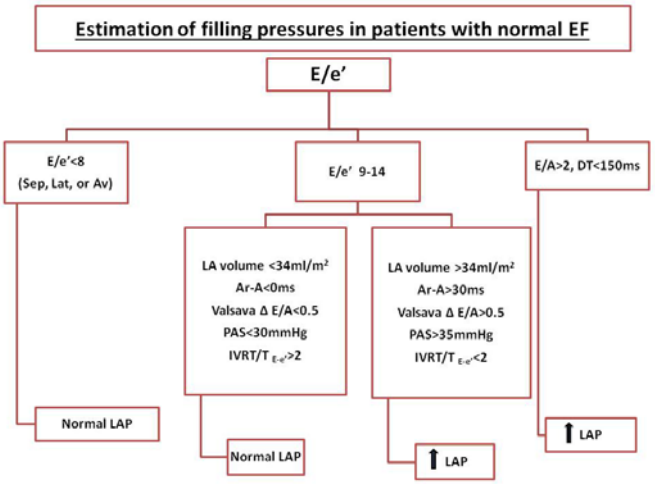

Figure 15. Diagnostic algorithm for the estimation of LV filling pressures in patients with normal EFs.

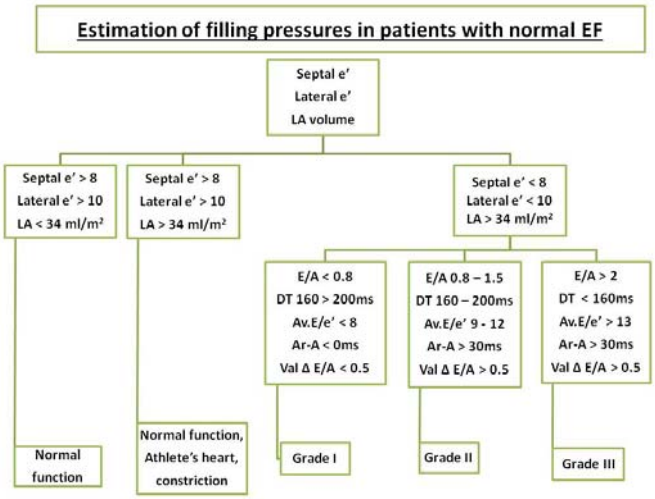

Figure 16. Scheme for grading diastolic dysfunction. Av = average; EF = ejection fraction; LA = left atrium; Val=Valsalva

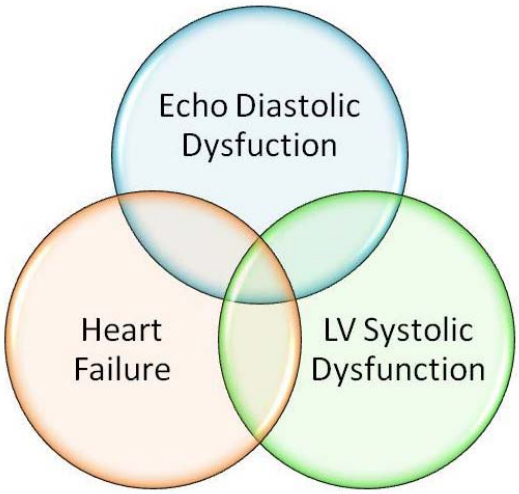

Figure 17. Diagram shows overlap among systolic and diastolic dysfunction and manifestation of heart failure.

enhance the study of diastolic function. There are special circumstances in which quantitative myocardial deformation may be an especially helpful diagnostic tool.[8;54]

Conclusion

Diastolic function assessment is a clinical reality with important prognostic consequences. The science of echocardiography has matured enough for a meaningful evaluation to be performed by most echocardiographers.[8] There is a consensus of opinion that no single echo measure is sufficient for diagnosis of diastolic dysfunction without consideration of the clinical or morphologic substrate. A tailored strategy with preferential use of an echocardiographic index in a specific clinical setting involves circular reasoning because it requires pretest knowledge of a diagnosis, which precisely depends on evidence of diastolic LV dysfunction.[55] A systematic approach which incorporates the pathologic context into the analysis of multiple echocardiographic measurements can provide adequate prognostic stratification.

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