Echocardiographic evaluation of diastolic heart failure

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The term "diastology" characterises left ventricular (LV) relaxation, filling dynamics and their integration into clinical practice[1]. Recent advances in echocardiography have enabled the understanding of this complex process, particularly relevant in the setting of an aging population and rising prevalence of heart failure (HF) with preserved systolic function. Data from the Mayo Clinic[2] and others[3] indicate that diastolic heart failure (DHF) accounts for approximately 50% of all HF cases[4] and carries a poor prognosis with survival being similar to those with a reduced ejection fraction[5,6], (5-year mortality ~ 50% in new onset symptomatic DHF)[4]. Additionally, the prevalence of asymptomatic diastolic dysfunction (DD) in the general community is ~ 25–30% in individuals ≥ 45 years[7].

Diastolic dysfunction (DD) is defined as "inability of the LV to fill during rest or exercise, to a normal end-diastolic volume without an abnormal increase in LV end diastolic pressure (LVEDP)"[8]. Diastolic function is frequently abnormal in patients with reduced LVEF and HF. Hence, the recent criteria of The European Society of Cardiology[9] recommends the diagnosis of DHF or HF with normal Ejection Fraction (HFNEF) be based on the following: (i) signs or symptoms of HF; (ii) normal or mildly abnormal LV systolic function without LV dilatation (LVEF > 50%, LV end-diastolic volume index (LVEDVI) < 97 mL/m^{2}.) and (iii) evidence of LV DD.

Likely mechanisms for diastolic dysfunction

Predisposing conditions for the development of DD include hypertension, LV hypertrophy (LVH), older age, female gender, obesity, diabetes, chronic kidney disease and coronary artery disease (CAD)[10,11]. LV filling is impaired (abnormalities of active relaxation and passive stiffness of the myocardium) in combination with abnormal ventriculo-arterial coupling[12,13]. However, with emerging technologies that question the accuracy of normal systolic function, the pathophysiology of HFNEF remains controversial[14].

The traditional concept of HFNEF is based on sophisticated catheter based conductance studies[15,16] demonstrating haemodynamically that HFNEF patients exhibit an upward and leftward shift in end-diastolic pressure-volume relationship, whereas the end-systolic pressure-volume relationship (end-systolic elastance) is unaltered or even steeper than in subjects without HF[17,18]. Zile, *et al.*[19] demonstrated that HFNEF patients have abnormalities of active LV relaxation (prolonged time constant of relaxation, tau (τ), and LV stiffness (increased LV passive stiffness constant (β)) with a resultant increase in left ventricular end-diastolic pressure (LVEDP) and pulmonary venous pressure even with small changes in LV end-diastolic volumes, resulting in exertional dyspnoea and even pulmonary oedema[20]. Exercise intolerance in HFNEF patients is likely due to the failure to increase cardiac output during exercise, secondary to impaired LV filling and a failure of the Frank-Starling mechanism. Definitive evidence of abnormal LV relaxation and filling, acquired invasively by cardiac catheterisation includes $\tau > 48$ ms, LVEDP > 16 mmHg or a mean pulmonary capillary wedge pressure (PCWP) > 12 mmHg[21,22,23]. Concomitant abnormalities in arterial mechanics and disturbance in ventriculoarterial coupling play a major role in the pathophysiology of HFNEF. The effective arterial elastance, a global measure of arterial stiffness, determined as the ratio of LV end systolic pressure/stroke volume[24], is typically raised in HFNEF patients. Moreover, the exaggerated increase in systolic blood pressure after small increases in LVEDV or in arterial elastance[24,25], as well as limited systolic reserve due to high baseline end-systolic elastance, support the notion of combined ventricular-arterial stiffening.

Coronary artery disease (CAD) has been implicated in the pathogenesis of HFNEF; ischaemia prolongs τ, which is reversed after reduction of ischaemic burden by coronary artery bypass grafting[26,27,28]. Mann, *et al.*[26] showed that in CAD, ischaemia provocation by rapid atrial pacing resulted in an upward shift of the diastolic pressure-volume curve.

The value of LVEF as a measure of LV systolic function has been questioned[14], given among other limitations its load dependence. Using Tissue Doppler Imaging (TDI), several groups[29,30] have described reduced systolic longitudinal myocardial velocities as well as reduced longitudinal and radial strain[31] in HFNEF patients compared to controls. Similarly, systolic abnormalities have been observed in hypertensive subjects with LVH[32] and in diabetics[33], both predisposing factors for HFNEF. Given various inter-related processes including the influence of systole on subsequent filling and the effect of passive ventricular properties on systolic function, it is difficult to separate cardiac cycle functionally into purely systolic and diastolic phases.

Echocardiography measures

Echocardiographic evaluation of DD requires comprehensive assessment and integration of all available information including two-dimensional left atrial (LA) volume, LV mass and systolic function that provides supportive evidence for DD. Concomitant valvular abnormalities, structural heart disease and pericardial disease are of particular relevance in the overall interpretation and are differential diagnoses of HFNEF. Traditional diastolic measures include mitral inflow velocity and pulmonary venous flow indices. Colour
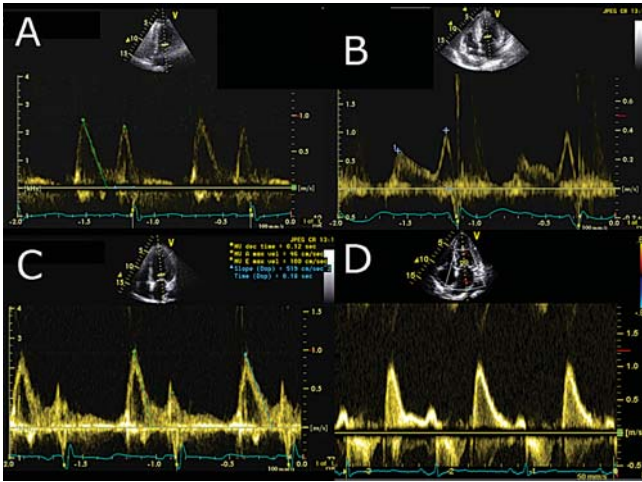
Fig. 1: Mitral inflow patterns of diastolic dysfunction; A = normal, B = Impaired relaxation, C = pseudonormal filling and D = restrictive filling.

M-mode and TDI have been introduced lately to overcome limitations of load dependency. Newer parameters in assessment of diastolic function are in development and include strain/strain rate, diastolic reserve and twist mechanics.

Transmitral flow and IVRT

Doppler derived mitral inflow forms the basis of evaluation of diastolic function and reflects acuity of left sided filling pressures. This includes peak early diastolic filling (E wave) and late diastolic filling (A wave) velocities, E/A ratio, deceleration time (DT) of early filling velocity and the isovolumic relaxation time (IVRT) (time from aortic valve closure to onset of mitral inflow). Secondary measurements include mitral A wave duration, A wave VTI, total mitral inflow VTI. Mitral E velocity reflects early diastolic LA-LV pressure gradient and is affected by preload and LV relaxation[34] while the A-wave velocity reflects late diastolic LA-LV pressure gradient and is affected by LV compliance and LA contractile function. E-wave DT is influenced by LV relaxation, LV diastolic pressures following mitral valve opening and LV compliance.

Apart from LV diastolic properties and filling pressures, many physiological determinants affect the mitral inflow profile. Age is an important consideration in interpretation; with increasing age, the mitral E velocity and E/A ratio decreases, whereas DT and A velocity increase[35]. Other determinants include loading conditions, heart rate and rhythm, PR interval, cardiac output, mitral annular size and LA function[36].

Based upon age-adjusted interpretation of the transmitral profile, diastolic function can be classified into normal, impaired LV relaxation, pseudonormal and restrictive LV filling (Fig. 1). These patterns represent progressively worsening diastolic function and increasing LV filling pressures. However, there is a non-linear relationship between these indices and severity of DD and filling patterns can vacillate with alteration of loading conditions.

With normal diastolic function, E/A ratio is 0.75–1.5, DT is < 220 ms and IVRT 70–90 ms. In mild DD (Grade I, impaired relaxation), the E/A ratio is < 0.75 and A velocity increases due to increased LA contraction while DT and IVRT are prolonged as a result of relaxation abnormality. Moderate or Grade II DD (pseudonormal) is characterised by reduced LV compliance with increased LA pressure and
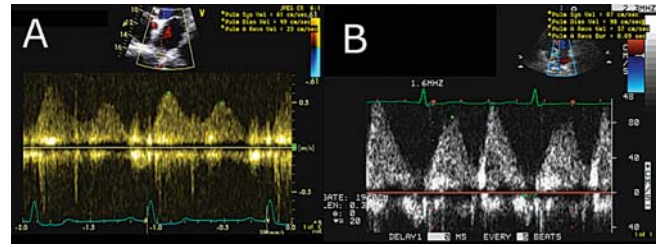

Fig. 2: Pulmonary vein flow with panel a demonstrating systolic dominant flow and pane B diastolic dominant flow patterns.

hence the E/A ratio appears normal but reversal occurs with Valsalva manoeuvre. With progression to severe or Grade III DD (restrictive filling), there is severely decreased compliance, causing further increase in LA pressure, resulting in a very elevated E wave and low A wave (E/A > 1.5) and a significantly reduced DT (< 150 ms) and IVRT (< 70 ms). When this pattern remains fixed with Valsalva, it is categorised as grade IV diastolic dysfunction (fixed restrictive filling). In assessing mitral inflow, apart from the above pattern, mid-diastolic flow ≥ 20 cm/s represents delayed LV relaxation and elevated filling pressures[37], although low velocities can be seen in normal individuals.

A number of the mitral inflow parameters have prognostic value, the commonest being a short DT and a persistent restrictive filling pattern[38,39]. In the clinical setting of acute myocardial infarction, a pseudonormal or restrictive filling pattern portends increased HF, unfavourable LV remodelling and increased cardiovascular mortality irrespective of LVEF[40,41]. Likewise, a restrictive filling pattern with LA enlargement in a patient with normal EF (e.g. amyloidosis with restrictive cardiomyopathy[42]), is associated with a poor prognosis similar to that of a restrictive pattern in dilated cardiomyopathy[43].

Pulmonary venous flow patterns

PW Doppler interrogation of pulmonary venous (PV) flow obtained from the apical four chamber view, comprises four variables; peak systolic flow velocity (S), peak diastolic flow velocity (D), peak atrial reversal (AR) flow velocity and AR duration (AR dur). Systolic forward flow is often biphasic with S1 related to atrial relaxation and LA pressure while S2 is related to stroke volume and propagation in the arterial tree[44,45] (S2 is used to derive S/D ratio). D velocity is influenced by LV filling and compliance and changes parallel to mitral E velocity[46]. AR velocity and duration are affected by LV late diastolic pressures, atrial preload and LA contractility[47].

When LA pressure is normal, most flow occurs in systole, shifting to diastole with increasing LA pressure[48]. There is an age related effect on PV flow. In normal subjects < 40 years, D velocity is dominant reflecting its parallel relationship with mitral E wave with the S/D ratio increasing with age. The AR velocity is usually < 35 cm/s; higher AR velocity values suggest increased LVEDP[49]. With DD, a decrease in LA compliance and increase in LA pressure reduces the S velocity with an increase in D velocity, resulting in an S/D ratio < 1 and a systolic filling fraction (S VTI/ S VTI+ D VTI) < 40%[50]. With increased LVEDP, AR velocity and duration increase, as does the difference between AR duration and mitral A-wave duration (AR-A duration)[51,52].
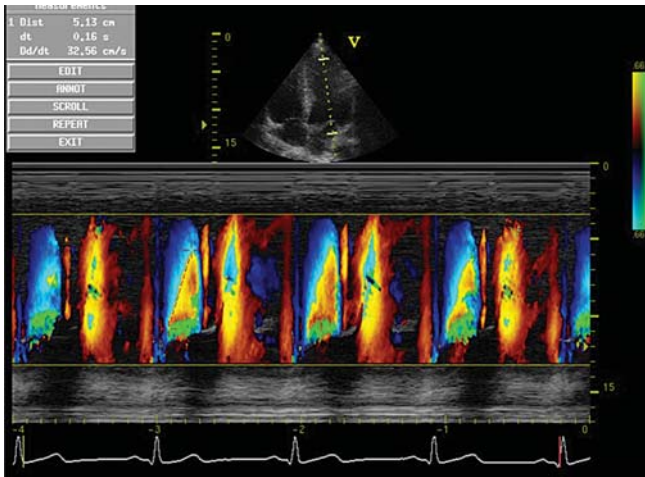
While peak S and D velocities do not add

Fig. 3: Abnormal Vp with slope measured at 33 cm/s.

Fig. 4: Septal annular TDI derived E' velocity that is normal in panel A and decreased in panel B.

incremental value in assessment of DD, a peak AR velocity > 35 cm/s correlates with elevated filling pressures[53] and AR-A duration has been validated as a useful parameter[54]. AR-A duration is age-independent [49] and a difference of > 30 ms indicates an elevated LVEDP[55], thereby identifying patients with abnormal LV relaxation with an elevated LVEDP. Importantly, the AR-A duration remains accurate in patients with normal LVEF[56]. However, there is difficulty in the acquisition of accurate AR-A duration measurement from a transthoracic window.

Pulmonary venous flow parameters are complementary to mitral inflow pattern in the diagnosis of DD. The strength of a combined use of the two modalities was observed in studies[57], when MV inflow parameters and PV flow Doppler were combined; 93% of patients suspected of HFNEF showed evidence of DD[58]. Unlike mitral inflow velocities, there have been limited studies in ascertaining the prognostic role of PV flow.

Flow propagation

Colour M-Mode provides high temporal and spatial resolution in the assessment of the early diastolic filling velocity as blood propagates through the mitral valve[59]. Flow propagation velocity (Vp) is obtained by measuring the slope of the isovelocity line demarcated by the colour wavefront, representing the pressure gradient between the LV base and apex. During myocardial ischemia or HF, there is slowing of the LV base to apical flow propagation[60,61]. A Vp > 50 cm/s is considered normal[62] while a value < 45 cm/s in patients > 30 years is consistent with DD[63].

Vp characterises LV relaxation, and has been correlated with invasive measurements and shown to be relatively independent of loading conditions[64]. The ratio of E/Vp has been used to estimate LV filling pressure, with an E/Vp > 1.5 suggestive of a PCWP > 15 mm Hg[65,66]. Vp is influenced by LV systolic function, which may act to normalise Vp in the presence of impaired LV relaxation[67,68]. All in all, although E/Vp ratio correlates with PCWP in patients with reduced LVEF, its utility in patients with normal systolic function is limited[69]. Currently, this modality is seldomly utilised in clinical practice, given its limitations such as accuracy of measurements and interobserver variability.

TDI and E' velocity

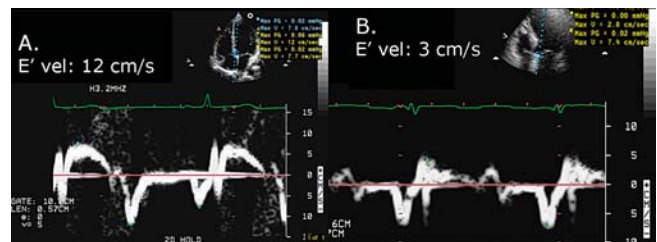Currently, the most sensitive echocardiographic technique for the assessment of DD is TDI[70] which measures low velocity, high amplitude intrinsic myocardial tissue velocity with high spatial and temporal resolution, providing a relatively load independent measure of both systolic and diastolic function[71]. Whereas the E/A ratio from mitral inflow exhibits a U-shaped relationship with LVEDP, TDI E' velocity declines from normal to advanced LV DD. As a consequence, the E/E' ratio increases with advanced LV DD[9]. In addition to its diagnostic utility, TDI velocities provide incremental prognostic value.

Longitudinal myocardial velocity is measured by Pulsed wave (PW) TDI, placing a sample volume at the septal or lateral mitral annulus in the apical four chamber view[72]. Colour TDI (CTDI) is an alternative method that permits offline analysis. However PW TDI is the preferred technique for routine clinical assessment of diastolic function. Published normal ranges are available for both methods, with CTDI velocities being significantly lower[73,67] as PW TDI measures peak whereas CTDI measures mean velocity[74]. Reference values must be adjusted for age given the normal age dependent reduction in diastolic function[75,76].

Mitral annular velocities can be regarded as an ''aggregate'' of segmental myocardial velocities and in the absence of regional LV dysfunction accurately reflect global longitudinal LV function[77]. The systolic velocity (S') corresponds to ventricular ejection while the early (E') and late (A') diastolic velocities correspond to ventricular filling and atrial contraction respectively.

S' velocity

The S' velocity correlates with LVEF[78], and an average S' velocity > 7.5 cm/s had a sensitivity of 79% and specificity of 88% in predicting normal global LV function. S' velocity is a sensitive marker of subclinical LV systolic dysfunction, even in those with apparently preserved LVEF such as DHF[14], or in diabetic subjects without overt heart disease[79]. Reduced S' velocities have been observed in carriers of hypertrophic cardiomyopathy mutations at a subclinical stage when LVH is not present[80].

The prognostic significance of S' velocity has been demonstrated in a follow up study of patients with cardiac disease; mortality was significantly higher when both S' and E' were < 3 cm/s, although E' had a stronger impact in multivariate analysis[81].

E' velocity

E' represents the early diastolic lengthening velocity of longitudinal LV fibers[82] that declines with normal ageing[83,84]. E' velocity is easily measured with low inter-observer variability[85] and has important prognostic value[81,86]. Decreased E' is one of the earliest markers for DD and is present in all stages of the condition[87], typically lowest in patients
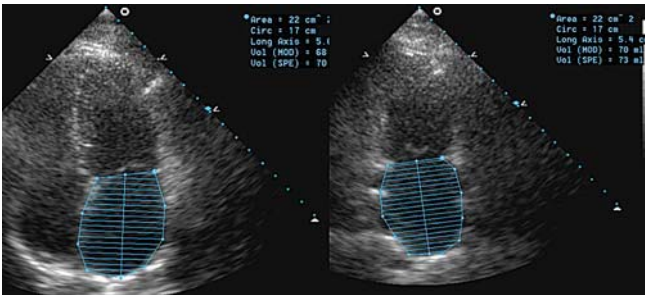
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Fig. 5: Biplane LA volume measured by Simpsons method of discs.

Fig. 6: Strain rate derived from TDI demonstrating early diastolic E-Sr.

with restrictive filling. In addition, close correlations have been observed between E' and invasive indices such as τ ($P < 0.001$) and LV dP/dt ($P < 0.001$) over a wide range of filling pressures[88]. Furthermore, compared to peak E, E' is relatively preload independent as was evident in patients with DD with pseudonormalisation of E velocity in which E' remained low during saline loading or after nitroglycerin[71]. E' also correlates closely with τ, even in atrial fibrillation[89], and with invasively measured LVEDP both at rest and during exercise[90,91].

In normal conditions, E' occurs coincident with, or just before, the transmitral E wave, whereas in HF, there is a progressive delay in E' with respect to E[92]. In terms of prognostic significance, in many studies E' appears superior to S'. Low E' velocity predicts mortality incremental to clinical and echocardiographic data as illustrated by Wang, *et al.*[93], where E'< 3 cm/s was the best prognostic marker on long-term follow-up, incremental to indexes of systolic or diastolic function, including a DT < 140 ms and E/E' > 15. Similar results were found in a hypertensive population where an E' value < 3.5 cm/s was implicated in the prognostic index[32].

A' velocity

Peak velocity during atrial contraction, the A' velocity, is an accurate marker of global atrial function[94] correlating with LA fractional area and volume change[95] and other traditional parameters of LA function (peak A velocity, atrial fraction, and atrial ejection force[94]). The main determinants of A' include LA systolic function and LVEDP; increased LA contractility increases A' velocity whereas an increased LVEDP leads to a corresponding decrease[96]. While there is an age related increase in A' velocity in healthy subjects[97], the converse is observed with atrial dysfunction where A' velocity is reduced. Although not as extensively studied as S' and E', A' provides prognostic information and an A' ≤ 5 cm/s in HF patients independently predicted worse prognosis with increased cardiac mortality or HF hospitalisation[98]. A' also predicts cardiac events and mortality in hypertension[32].

The major advantage of TDI is its feasibility, reproducibility, ease of application in the clinical setting[99] and its relative independence of 2D image quality. It should be noted that lateral annulus early diastolic velocity (E') is usually higher than septal annular E'[87], although there is no significant difference between such for peak A' velocity[100]. Recent evidence suggests that E' velocity at the septal and lateral annulus are affected by different variables and are not interchangeable[101]. Moreover, septal E' velocity has been demonstrated to be preload dependent in patients with normal LV function[102], although this effect may decrease as LV relaxation becomes progressively impaired. Additionally, septal E' velocity may be influenced by right ventricular
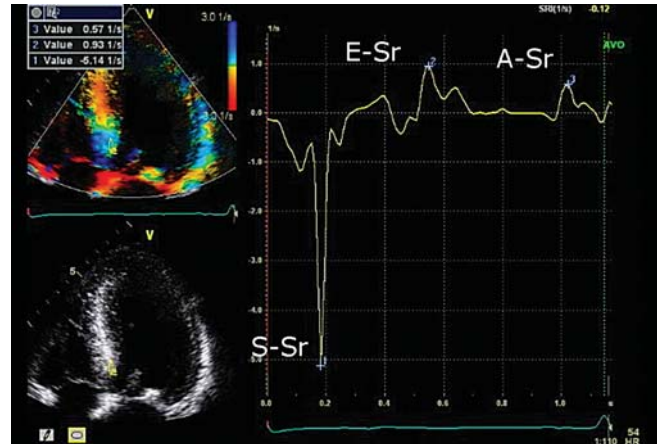
diastolic function.

One major limitation of E' velocity is the assumption that it reflects global LV relaxation. In subjects with segmental wall motion abnormality resulting in reduced annular velocity at the corresponding site, it leads to a spuriously low estimate of global LV relaxation. Therefore, it is recommended that an average E' velocity be obtained from sampling multiple sites to improve accuracy[103].

E/E' and T E-E'

E/E' has been demonstrated to correlate with LV filling pressures and mean left atrial pressure[104] and has been validated in various clinical settings[99]. Published values of the E' velocity and E/E' ratio vary depending on the annular sampling site. Nagueh and colleagues[104] demonstrated that E/E' > 10 using lateral mitral annular velocity reliably predicts a PCWP > 12 mmHg. In comparison, using the septal E' velocity, Ommen and colleagues[99] found that PCWP is normal if E/E' ratio is < 8 and likely elevated if > 15, while intermediate values were associated with a range of mean LV diastolic pressures. A number of recent studies[103,105] have found that lateral E/E' ratio is superior to septal E' ratio for predicting PCWP when LVEF is > 50%, although an average of both values is more accurate in the presence of regional dysfunction[106].

E/E' > 15 is a powerful prognosticator of adverse cardiac events[104] and is an independent predictor of cardiac mortality and HF hospitalisation in patients with systolic dysfunction[98]. Post myocardial infarction (MI), E/E' is a powerful predictor of survival and E/E' > 15 is superior as predictor of prognosis to other clinical or echocardiographic variables[107].

The close correlation between E/E' and LV filling pressures has been confirmed in HF patients with depressed (< 50%) or preserved LV ejection fraction[108] and in patients with impaired relaxation or pseudonormal filling patterns[104]. All in all, E/E' predicts HF events in a manner incremental to clinical factors and ejection fraction[109]. It is important however to note that there are circumstances that spurious results could occur. E' velocity is reduced in patients with significant annular calcification, surgical rings, mitral stenosis, and prosthetic mitral valves.

Information on LV filling pressures can be derived from the time interval between the onset of E and the onset of E' (T E-E')[110,111]. This is obtained by measuring the time interval between the QRS complex and the onset of E and subtracting that from the time interval between QRS complex and E'. With decreased LV relaxation, E' velocity is reduced

Table 1: Relative strengths and weaknesses.

Parameter	Strengths	Limitations	How/where to
Transmitral flow PW Doppler	• Easy to obtain • Prognostic value – restrictive pattern and short DT • Monitoring of DD	• Age & load dependent • Affected by HR, rhythm , PR interval • Only reflects acuity of left sided filling pressures • Values influenced by PW sample volume placement	• PW sample volume size (1–3 mm) placed between the mitral leaflet tips on LV side in diastole from A 4 C view
PV flow patterns	• Complementary to mitral inflow • AR-A duration is the only age independent marker	• Technical difficulty in obtaining accurate and adequate signals • Influenced by rhythm	• PW sample volume size (2–3 mm) placed 1 cm into right upper pulmonary vein posterior to LA from A4C view
Flow propagation	• High temporal and spatial resolution • Assess early diastolic filling	• Poor correlation with PCWP in patients with normal LVEF • Significant interobserver variability • Problems with reproducibility	• M-mode through mid axis of LV and MV with colour Doppler in A4C view
TDI	• High spatial and temporal resolution • Relatively load independent • Low interobserver variability • Prognostic value (S', E', A') • E' correlates with τ and dP/dt, even in AF • Early marker of DD	• Assumes E' reflects global LV relaxation- problematic in patients with wall motion abnormalities • Different E' velocities between septal and lateral annulus • Affected by translational motion due to tethering by neighbouring myocardial segments	• PW sample volume size (5–10 mm) at fibrous mitral annulus (septal and/or lateral) from A4C view
E/E'	• Close correlation with LVEDP/PCWP • Prognostic marker • T E-E' useful in evaluation of increased LV filling pressures when E/E'= 8-15	• Intermediate values between 8–15 non-diagnostic of DD • E' value altered by significant annular calcification, surgical rings, mitral prosthesis, mitral stenosis	• See above sections for E and E' measurements
LA volume	• Reflects chronicity of DD • Significant prognosticator for future CVS events • Change in phasic function reflects severity of DD	• Confounded by chronic volume overload (eg MR) and AF	• Bi-plane (A4C and A2C views) Simpsons method for volume calculation
Diastolic strain/ strain rate	• Independent of translation due to tethering • Validated by sonomicrometry/MRI • Higher frame rate than MRI • Evaluates diastolic stiffness differentiating stunning vs infarction and fibrosis • GSR_{IVR} represents true global index and predicts LV filling pressure, esp if E/E' inconclusive	• Technical aspects : TDI method angle dependent, subject to reverberation artefact, poor signal to noise ratio, problem of drift with respiration • Provides single plane estimation of deformation • Low reproducibility • Acquisition/analysis needs experience • Currently research tool • GSR_{IVR} dependent on quality of signals	• TDI and 2D speckle tracking of LV myocardium in longitudinal plane with offline analysis of strain parameters from A4C, A2C and apical long axis views

Torsion	• TDI and 2D speckle tracking methods both correlate
	    with MRI assessment
	• Speckle tracking- angle independent and high
	    reproducibility
		• Precise selection of image plane required
		• Difficulty of speckle tracking at LV base; alter reproducible measurements
		• Research tool
			• TDI and 2D speckle tracking of LV myocardial rotational motion in parasternal short axis LV views of basal and apical levels

and delayed, while mitral E velocity occurs earlier and may precede the onset of E' with pseudonormal or restrictive filling prolonging T E-E'. Animal[112] and human[110] studies have shown that T E-E' is strongly dependent on the time constant of LV relaxation and LV minimal pressure[113]. T E-E' is particularly useful in subjects with normal cardiac function[110], those with moderate to severe mitral regurgitation[111] and when the E/E' ratio is 8 to 15[114]. In particular, an IVRT/TE-E' ratio < 2 has reasonable accuracy in identifying patients with increased LV filling pressures[110].

LA size, volume and function

The left atrium (LA), being in continuum with the LV during diastole when the mitral valve is open, is constantly exposed

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to the LV loading pressure. In the setting of DD, the LA is subject to elevated filling pressures resulting in remodelling and changes in its volume and function. Left atrial size, expressed as a volume indexed to body surface area has been shown to be a robust biomarker of the severity and chronicity of DD and of cardiovascular disease risk[115]. The published reference values for mean indexed LA volume based on groups of healthy individuals reported by Thomas, *et al*.[97] and in population studies[116] were 23 ± 6 mL/m^{2} and 22 mL/m^{2} respectively. In persons free of cardiovascular disease, indexed LA volume is independent of age[117]; importantly, LA enlargement is a reflection of the pathophysiologic perturbations rather than a consequence of normal aging[94].

With DD whereby there is increased stiffness and non-compliance of the LV, the LA pressure rises to maintain LV filling and the increased atrial wall tension subsequently leads to chamber dilatation. As such, studies have demonstrated that LA volume increases with worsening severity and increasing duration of DD[118,119,120], and an indexed LA volume has the highest discriminative value in distinguishing between normal and pseudonormal transmitral filling pattern[121].

In a recent study of HFNEF patients, indexed LA volume was the strongest and most consistent multivariate predictor of N-terminal pro-brain natriuretic peptide level, a potent biomarker of heart failure[122]. It was additionally shown that a LA volume > 26 mL/m^{2} was a relatively load independent marker of LV filling pressures and of DD. Based on the recent consensus statement by the Heart Failure and Echocardiography Associations of the European Society of Cardiology[9], a LA volume index > 40 mL/m^{2} provides sufficient evidence of LV DD when the E/E' ratio is non-conclusive (i.e. 15 > E/E' > 8) or when plasma natriuretic peptides are elevated. Similarly, a LA volume index < 29 mL/m^{2} is proposed as a prerequisite to exclude HFNEF. LA volume index values of 29 and 40 mL/m^{2} correspond, respectively, to the lower cut-off values of mildly abnormal and severely abnormal LA size in the recent recommendations for cardiac chamber quantification of the American Society and the European Association of Echocardiography[123].

LA volume has prognostic value for future adverse cardiovascular events including myocardial infarction, cerebrovascular events, atrial fibrillation, HF as well as cardiac and all-cause mortality[124,125,126,127]. Tsang, *et al*.[118] demonstrated that increasing LA volume stratified risks of developing such adverse events. Particular to the individual adverse outcomes, studies revealed an indexed LA volume ≥ 32 mL/m^{2} to be associated with increased stroke risk[128] independent of age and other clinical risk factors. An increased incidence of congestive HF was noted with increased LA volume, independent of age, MI, diabetes, hypertension, LVH and mitral inflow velocities[124].

Apart from its effect on LA size, DD also alters LA phasic functions. LA function is described by three phases[129]; it functions as a "reservoir" in receiving blood from pulmonary veins, acts as a "conduit" for the passive transfer of blood into the LV from the pulmonary veins in diastasis and thirdly, it exerts its "contractile" function during atrial systole to augment the LV stroke volume by 20%[130]. It has been demonstrated that the relative contribution of this pump function becomes more dominant with LV dysfunction[97]. In normal subjects, the relative contribution of the reservoir, conduit and contractile function of the LA to the filling of the LV is approximately 40%, 35% and 25% respectively[131]. In the setting of abnormal relaxation, the relative contribution of the LA reservoir and contractile function increases and conduit function diminishes; while the LA functions primarily as a conduit as LV filling pressures increase with advancing DD[131].

Strain and strain rate in DHF

TDI derived strain rate (SR) and strain (S) measurements are quantitative indices of myocardial deformation[132], and are relatively independent of translational motion due to tethering by neighbouring myocardium in contrast to TDI myocardial velocities. S measures tissue deformation while SR measures the rate of tissue deformation[133]. Mathematically, strain is the integral of SR, with shortening expressed as a negative and lengthening as a positive value[134]. Depending on the direction of deformation, longitudinal, circumferential, and radial S and SR can be measured using TDI or two-dimensional speckle tracking. Both modalities have been validated against sonomicrometry and cardiac MRI[135,136]. Importantly, echocardiographic methods have higher frame rates than cardiac MR and are better suited to study temporal aspects of cardiac function.

Diastolic strain/strain rate

Recent studies suggest that myocardial S and SR may provide further information on diastolic function. Voigt, *et al*.[137] demonstrated that the quantification of postsystolic myocardial S estimated post-systolic shortening in ischemic myocardium. Pislaru, *et al*.[138] and Park, *et al*.[139] showed that regional diastolic SR can evaluate diastolic stiffness during myocardial stunning and infarction, aiding in viability assessment. There is evidence in an animal model that segmental early diastolic SR correlates with the degree of interstitial fibrosis[139]. Moreover, reduced early diastolic SR has been observed in patients with hypertension and DD[140] and a significant relationship was observed between segmental[141] and global[142] early diastolic SR and τ.

Global longitudinal SR obtained during isovolumeic relaxation time IVRT (GSR_{IVR}) is a newly developed parameter measured from the apical 4, 2, and long-axis views by speckle tracking. GSR_{IVR} has a number of advantages including its acquisition directly from LV myocardium, as opposed to indirect derivation from annulus and blood flow velocities. It is not affected by mitral annular or valvular disease and occurs when the valves are closed and therefore is not exposed to transmitral pressure gradient.

In a recent study that combined GSR_{IVR} and transmitral flow velocities, the mitral E velocity/GSR_{IVR} ratio predicted LV filling pressure in patients in whom the E/E' ratio was inconclusive and was more accurate than E/E' in patients with normal LVEF and those with regional dysfunction[142]. Although promising, accurate measurements of GSR_{IVR} are dependent on high-quality signals with good myocardial visualisation.

Limitations of S/SR imaging

Despite their utility, there are a number of pitfalls of S and SR imaging. The TDI-based method[143,144] is angle dependent, subject to reverberation artefacts, poor signal to noise ratio,

as well as the problem of drift when the strain curve demonstrates beat to beat variability due to minor angle changes as well as respiratory changes. In addition, measurements provide only a one dimensional estimation of myocardial deformation, and radial and circumferential axes can only be assessed in limited views. Combined with lower reproducibility, the widespread clinical use of this technology has not occurred. In contrast, speckle tracking is based on the recognition and tracking of speckles, which represent unique acoustic identification for each myocardial region. This method is not angle dependent, is more reproducible than TDI, and can determine circumferential strain, in addition to radial and longitudinal strain. However, speckle tracking has a lower frame rate than TDI and can therefore underestimate deformation rate.

Torsion/ twist mechanics

LV twist or torsion describes the wringing motion of the LV and occurs because of the helical arrangement of LV subendocardial and subepicardial fibers[145]. Contraction of these oblique and spirally orientated fibres causes "torsion" such that when viewed from the apex, systolic contraction of the ventricle is characterised by the counterclockwise rotation of the apex and clockwise rotation of the base[146]. During isovolumic contraction, brief apical clockwise rotation occurs that reverses rapidly becoming counterclockwise during LV ejection[147,148], followed by untwisting (clockwise rotation) during early diastole. In contrast, rotation of the base is lower in magnitude and opposite in direction.

Twist during ejection predominantly deforms the subendocardial fibres, with storage of potential energy. Subsequent elastic recoil of twist deformation during isovolumic relaxation releases restoring forces, contributing to LV relaxation and early diastolic filling[149,150]. LV torsion is a function of LV contractility and varies linearly with EF[151], while diastolic untwisting contributes to LV filling through suction generation[152,153]. Pertinent to the study of diastolic function is the dynamics of LV untwisting that commences in late systole but mostly occurs during the isovolumetric relaxation and is largely completed at the time of mitral valve opening[152]. The rate of untwisting correlates with τ, is independent of left atrial pressure[154] and was observed to remain constant during volume loading.

Torsion can be measured by TDI and 2D speckle tracking, with both methods correlating with MRI[155,156]. Speckle tracking is the preferred technique given its angle independence and higher reproducibility; however, studies utilising this modality have demonstrated incongruent results. Wang, *et al*.[157] demonstrated that in HF patients, LV twisting and untwisting rates were reduced in patients with reduced LVEF but not in those with HFNEF. The onset of untwisting was significantly delayed in both systolic and diastolic HF. Takeuchi, *et al*.[158], demonstrated in hypertensive patients that while twist was similar among groups of patients with or without LVH, diastolic LV untwisting and untwisting rates were delayed and reduced in parallel to the severity of LVH. Of note, DD associated with normal aging does not cause a reduction in diastolic untwist as studies have shown normal twist mechanics in elderly individuals[159,160].

Given the variability of study observations and technical limitations of twist mechanics including selection of image plane, difficulty of speckle tracking at LV base which can alter reproducibility, its clinical value in LV diastolic function assessment is as yet, not well defined.

Diastolic stress test

Many patients with DD have only exertional symptoms, as filling pressures rise to maintain adequate LV filling and stroke volume. DD may not be identified in these patients without provocation. Therefore, it is useful to evaluate LV filling with exercise or a "Diastolic Stress Test" that focuses particularly on diastolic parameters such as E/E' ratio, mitral inflow indices as well and pulmonary artery systolic pressures.

Only few studies have invasively assessed response to aerobic exercise; upright bicycle exercise testing with simultaneous right heart catheterisation and serial radionuclide ventriculography[161], demonstrated that cardiac index, stroke volume index, and LVEDVI at rest were similar between HFNEF patients and controls but were lower in HFNEF patients at peak exercise. PCWP at rest was higher in HFNEF patients compared with controls and increased significantly at peak exercise. Borlaug, *et al*.[162], demonstrated that HFNEF patients with a history of pulmonary oedema and LVEF > 50% showed a smaller increase in heart rate and cardiac index with a smaller decrease in systemic vascular resistance index during exercise compared to controls.

Echocardiographic diastolic stress testing provides comprehensive assessment of diastolic reserve, and E/E' relates significantly to exercise LV filling pressures acquired simultaneously with cardiac catheterisation[163,164]. In normal subjects, E and E' velocities increase proportionally with exercise, and the E/E' ratio remains unchanged or is reduced[165]. In contrast, in patients with DD, the increase in E' with exercise is much less than the mitral E velocity, such that the E/E' ratio increases[166]. In addition, mitral DT decreases slightly in normal individuals with exercise, but shortens > 50 ms in patients with markedly elevated filling pressures. The change in E' velocity with exercise is another index that has been reported to predict exercise capacity in patients with DD[167,168]. Diastolic stress echocardiography has also been performed with dobutamine infusion in patients with ischaemic cardiomyopathy and restrictive filling provided prognostic information[169].

Tan, *et al*.[170] combined traditional and newer echocardiographic parameters in their examination of patients at rest and during aerobic exercise. They proposed that in HFNEF, both systolic and diastolic abnormalities cause exercise limitation, particularly involving ventricular twist, delayed untwisting and deformation (strain). In HFNEF patients, resting systolic mitral annular velocity, apical rotation and deformation (longitudinal and radial strain) were all reduced and failed to increase with exercise. Apical untwisting was reduced and delayed, with reduced suction and increased end-diastolic pressure on exercise. The abnormalities of both systolic and diastolic function that become more apparent with exercise suggest that HFNEF is not an isolated diastolic disorder.

Possible therapies

In contrast to systolic HF, there is a paucity of large randomised placebo-controlled trials specifically addressing HFNEF treatment. In the absence of specific evidence based treatment, general principles and guidelines have been derived.

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Blood pressure control is the cornerstone of treatment because systemic blood pressure is a direct measure of afterload and is related to end-diastolic pressure, the key determinant of the pressure-volume relationship[171]. Currently, the only Class I level A recommendation by the *ACC/AHA Heart Failure Practice Guidelines*[172] is the control of systolic and diastolic hypertension for HFNEF patients. All other recommendations are evidence level C.

Given the high prevalence of diabetes and LVH, there is compelling indication for inhibitors of the renin-angiotensin-aldosterone system (RAAS) such as angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (AIIB) for blood pressure control. Both human[173] and animal[174] studies have shown that RAAS blockade improves LV diastolic distensibility. However, trials evaluating AIIB s irbesartan (I-PRESERVED trial[175]) and Candersartan (CHARM-PRESERVED trial[176]) and the ACEI perindopril (PEP-CHF trial[177]) in HFNEF patients demonstrated no survival benefit compared with placebo, although symptomatic improvement was noted.

On the other hand, the VALIDD study[178](VAL sartan In Diastolic Dysfunction study) demonstrated that blood pressure lowering in patients with hypertension and LV DD, either with valsartan or a regimen including beta blockers (BB), calcium channel blockers (CCB), diuretics and α blockers, elicited a similar reduction in blood pressure and improvement in diastolic relaxation.

Other general principles for the management of DD/DHF of level C evidence include control of heart rate, fluid volume control and relief of myocardial ischaemia. Tachycardia is particularly deleterious in patients suffering from DHF because an increase in heart rate shortens diastolic filling[171]. Ventricular rate control can be achieved with BBs and nondihydropyridine CCBs, both of which have been shown to improve exercise parameters[179]. In AF with rapid ventricular response, rate control or restoration of sinus rhythm by pharmacological or electrical cardioversion may improve diastolic filling[180]. The Digitalis Investigation Group[181], demonstrated reduction in hospitalisation for HF in patients with and without systolic dysfunction on Digoxin, the benefit perhaps due to its rate control effect. Fluid balance is achieved with the judicious use of diuretics. Treatment of exacerbating factors such as myocardial ischaemia need to be addressed and coronary revascularisation where appropriate should be considered[172].

When LVH is a major component of DHF, effecting LVH regression may have particular benefit[182]. A recent subgroup analysis from the Cardiovascular Healthy Study identified LVH as a predictor for the future development of HF independent of age, sex, obesity, diabetes, and hypertension[183]. Additionally, interstitial collagen deposition and fibrosis may account for the development of DD in hypertension[184]. Neurohormonal modulation of the RAAS is currently the only therapy with some effect on the pathophysiological mechanisms responsible for the increase in vascular and ventricular stiffness[185,186]. ACEIs[187,188], ARBs[189], and aldosterone receptor antagonists[190,191], independent of their hemodynamic effects, mediate potentially favourable effects of reduced smooth muscle cell growth, prevention of collagen deposition, reduced growth factor expression, and regression of myocardial fibrosis. Spironolactone, an aldosterone antagonist, has also been shown to reduce myocardial fibrosis and thus may aid in the treatment of DD[192].

Conclusion

Diastolic function is a complex integration of cardiac physiology and haemodynamics; a disturbed balance between LV compliance and filling results in DD and subsequent HFNEF, the exact pathophysiology of which remains debatable. Evolving technologies and advances in echocardiographic techniques have lent further insights into understanding the aetiologies and mechanisms by which they occur. They have also enabled detailed assessment of diastolic function, providing early detection and monitoring of treatment progress.

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