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REVIEW TOPIC OF THE WEEK

A Test in Context

E/A and E/e′ to Assess Diastolic Dysfunction and LV Filling Pressure

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CME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) explain the physical and physiological underpinnings of the Doppler and tissue Doppler parameters of diastolic function; 2) delineate the stepwise echocardiographic assessment of diastolic function in order to accurately diagnose individuals with diastolic dysfunction and elevated left ventricular filling pressure; and 3) describe the pathophysiology underlying the pearls and pitfalls of mitral inflow and tissue Doppler imaging in special scenarios such as constrictive pericarditis and pulmonary arterial hypertension.

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A Test in Context

E/A and E/e′ to Assess Diastolic Dysfunction and LV Filling Pressure

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ABSTRACT

Diastolic dysfunction represents a combination of impaired left ventricular (LV) relaxation, restoration forces, myocyte lengthening load, and atrial function, culminating in increased LV filling pressures. Current Doppler echocardiography guidelines recommend using early to late diastolic transmitral flow velocity (E/A) to assess diastolic function, and E to early diastolic mitral annular tissue velocity (E/e') to estimate LV filling pressures. Although both parameters have important diagnostic and prognostic implications, they should be interpreted in the context of a patient's age and the rest of the echocardiogram to describe diastolic function and guide patient management. This review discusses: 1) the physiological basis for the E/A and E/e′ ratios; 2) their roles in diagnosing diastolic dysfunction; 3) prognostic implications of abnormalities in E/A and E/e′; 4) special scenarios of the E/A and E/e′ ratios that are either useful or challenging when evaluating diastolic function clinically; and 5) their usefulness in guiding therapeutic decision making.
(J Am Coll Cardiol 2017;69:1451–64)

Diastolic function is a catch-all term referring to several different physiological processes that allow the left ventricle (LV) to fill with sufficient blood for the body's current needs at a low enough pressure to prevent pulmonary congestion. *Diastole* (Table 1) actually begins in systole, as energy stored in titin within the myocyte and as torsion in the interstitial fibers of the myocardium. As systole ends, an abrupt untwisting occurs, which lowers pressure in the LV until the mitral valve (MV) opens, and blood flows along a negative pressure gradient (suction) toward the apex until the pressure equilibrates between the left atrium (LA) and the LV, resulting in diastasis until the final component of ventricular filling occurs with atrial contraction. Derangement of any of these components may produce the pathophysiological entity of *diastolic dysfunction* (Table 1), a leading cause of the important and growing clinical syndrome of heart failure with preserved ejection fraction (HFpEF), which now accounts for ≥50% of all heart failure cases (1).

TABLE 1 Components of Healthy Diastole and Disorders That May Affect Them

Diastolic Component	Potential Disruptors
Storage of energy in systole	Systolic dysfunction
Rapid untwisting and relaxation	LV hypertrophy, ischemia, dyssynchrony
Highly compliant fully-relaxed LV and compliant pericardium	LV hypertrophy, infiltration, scarring; constrictive pericarditis; RV overload with extrinsic compression of the LV
Effective atrial contraction	Atrial fibrillation, atrial systolic failure

LV = left ventricle; RV = right ventricle.

Herein we present a comprehensive review of the echocardiographic early to late diastolic transmitral flow velocity (E/A) ratio and the E to early diastolic mitral annular tissue velocity (E/e′) ratio, placing each of these tests in clinical context for the practicing clinician. We discuss: 1) the physiological basis for the E/A and E/e′ ratios; 2) the role of these parameters in diagnosing diastolic dysfunction; 3) prognostic implications of abnormalities in E/A and E/e′; 4) special scenarios of the E/A and E/e′ ratios that are useful when evaluating diastolic function clinically; and 5) the usefulness of these indexes in guiding therapeutic decision making.

THE PHYSIOLOGICAL BASIS FOR ECHOCARDIOGRAPHIC ASSESSMENT OF DIASTOLIC FUNCTION

Definitive assessment of diastolic function requires intraventricular pressure measurements (to measure the relaxation time constant, tau [τ], left ventricular end-diastolic pressure [LVEDP] before and after atrial contraction, and ventricular stiffness [which requires additional simultaneous ventricular volume measurement]) (2). Because these measurements are impractical for daily clinical practice, attention has been directed toward noninvasive methods,

particularly echocardiography. Unfortunately, despite 40 years of work in this field, there remains no theoretically sound way to measure absolute pressures inside the heart (and therefore no way to measure ventricular compliance accurately), critically affecting the unambiguous assessment of diastolic function. All echocardiographic estimates of LVEDP rely on observed relationships between echocardiographic parameters that are predictive in a population-based statistical sense, but must be interpreted with caution in the individual patient. In this paper, we discuss the physiological basis for transmitral flow profiles (the early [E] wave and the atrial [A] wave) (**Figure 1**, left panel), tissue Doppler measurement of mitral annular velocity (particularly the early diastolic component [e′]) (**Figure 1**, right panel), the ratio E/e′, and the role of these markers in assessment of diastolic function and LVEDP.

HYDRODYNAMIC DETERMINANTS OF TRANSMITRAL FLOW

MAXIMAL E-WAVE VELOCITY. Although physics cannot predict absolute LV pressures, it can provide a great deal of insight into the components of transmitral flow (3). Weiss et al. (2) showed 40 years ago that LV pressure ($p_{LV}[t]$) during isovolumic relaxation falls as a zero-asymptote exponential curve: $p_{LV}(t) = p_0 e^{-t/\tau}$, where p_o is the pressure at aortic valve closure, t is time from that point, and τ is an exponential time constant, where shorter values indicate faster relaxation. The MV opens when this pressure falls below LA pressure, p_{LA}, and simple differentiation shows that the rate of pressure decay at this time (dp_{LV}/dt) is $-p_{LA}/\tau$. At this time point, assuming relatively constant LA pressure, the growth in the pressure gradient across the MV (Δp) at the start of filling (the "kick" that drives early, passive filling [E] of the LV) is p_{LA}/τ, empirically shown by Choong et al. (4). Active, late diastolic blood flow into the LV is driven by atrial contraction (A). The E/A ratio in healthy, euvolemic, recumbent young adults is typically >1. When τ is prolonged (often seen with aging), $d\Delta p/dt$ is lower, and the E-wave is smaller, leading to the grade I diastolic dysfunction filling pattern where E/A <1 (5,6). This pattern of impaired relaxation also occurs with hypertension, hypertrophic cardiomyopathy, ischemia, and myocardial infarction (6–8). To compensate, LA pressure may rise, increasing $d\Delta p/dt$ and E-wave height, leading to the grade II ("pseudonormal") or grade III ("restrictive") diastolic dysfunction filling pattern, with consequent risk for pulmonary congestion (9). The Valsalva maneuver can be helpful to distinguish a pseudonormal mitral inflow pattern (grade II diastolic dysfunction) from normal diastolic function. In patients with normal diastolic function, the Valsalva maneuver will lead to a reduction in the amplitude of both the E-wave and the A-wave due to decreased preload. In patients with grade II diastolic dysfunction, by reducing preload with the Valsalva maneuver, filling will occur on the flatter portion of the LV diastolic pressure-volume

ABBREVIATIONS AND ACRONYMS

A = late (atrial) diastolic transmitral flow velocity

a′ = late (atrial) diastolic mitral annular velocity

DT = deceleration time

E = early diastolic transmitral flow velocity

e′ = early diastolic mitral annular velocity

HFpEF = heart failure with preserved ejection fraction

LA = left atrium/atrial

LAVI = left atrial volume, indexed to body surface area

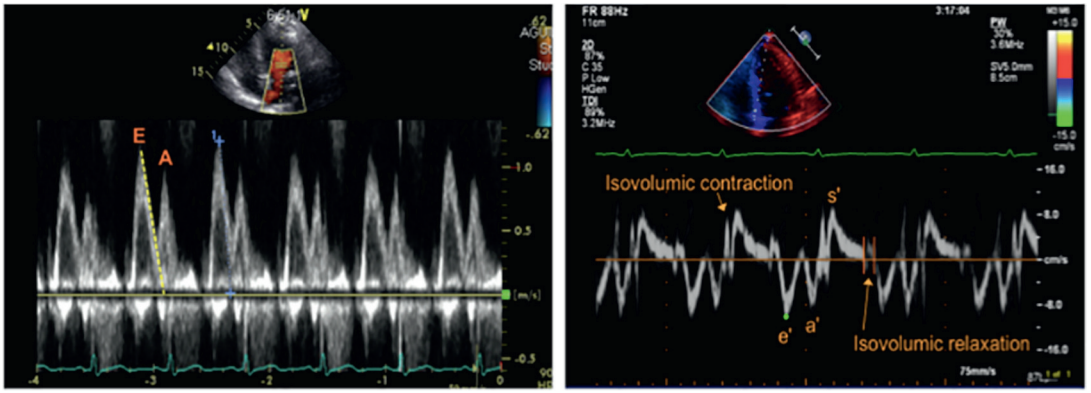
LV = left ventricle/ventricular

LVEDP = left ventricular end-diastolic pressure

MV = mitral valve

τ = time constant of left ventricular relaxation

FIGURE 1 Doppler (E/A Ratio) and Tissue Doppler (e′ Velocity) Profiles for the Assessment of LV Diastolic Function



(Left) Transmitral flow demonstrating early (E) and late/atrial (A) waves on pulsed-wave Doppler imaging at the mitral leaflet tips in the apical 4-chamber view. Dashed line = E deceleration time. **(Right)** Pulsed-wave tissue Doppler velocities at the lateral mitral annulus (e′ = early diastolic, a′ = late/atrial diastolic, and s′ = systolic tissue velocities). LV = left ventricular.

relationship; thus, whereas E-wave amplitude decreases, A-wave amplitude falls less and may actually increase, resulting in E/A reversal (i.e., E/A ratio <1).

E-WAVE DECELERATION TIME. A second place where physics can help us to understand transmitral flow is the E-wave deceleration time (DT), which was derived originally for the pressure half-time in mitral stenosis (10). As blood flows across the MV, pressure decreases in the LA and increases in the LV until Δp becomes 0, and the flow stops. It can be shown that the rate at which the E-wave velocity decreases is inversely proportional to the net compliance of the LA and LV. Thus, the stiffer the ventricle, the shorter the DT. Although this prediction holds most closely for a restrictive MV, its application in the normal MV has been demonstrated in animals and humans (11,12). E-wave morphology assumes a rapid increase and decay with a short DT (<150 ms), and the A-wave is blunted as the atrium contracts against an increasingly stiff ventricle. This grade III diastolic filling pattern is associated with an adverse prognosis in a variety of disease states (3,13,14).

In neither of these situations is the physics perfectly clean, with compliance neglected in the derivation of maximal E-wave velocity and ongoing relaxation neglected in derivation of the DT. Nevertheless, their theoretical underpinnings are strong enough to provide useful guidance in the clinical interpretation of transmitral flow patterns. Of note, however, are that both E and A are heart rate and conduction system disease dependent, whereby tachycardia, atrioventricular block, and left bundle branch block can lead to fusion of E and A waves, and ambiguity in diastolic assessment.

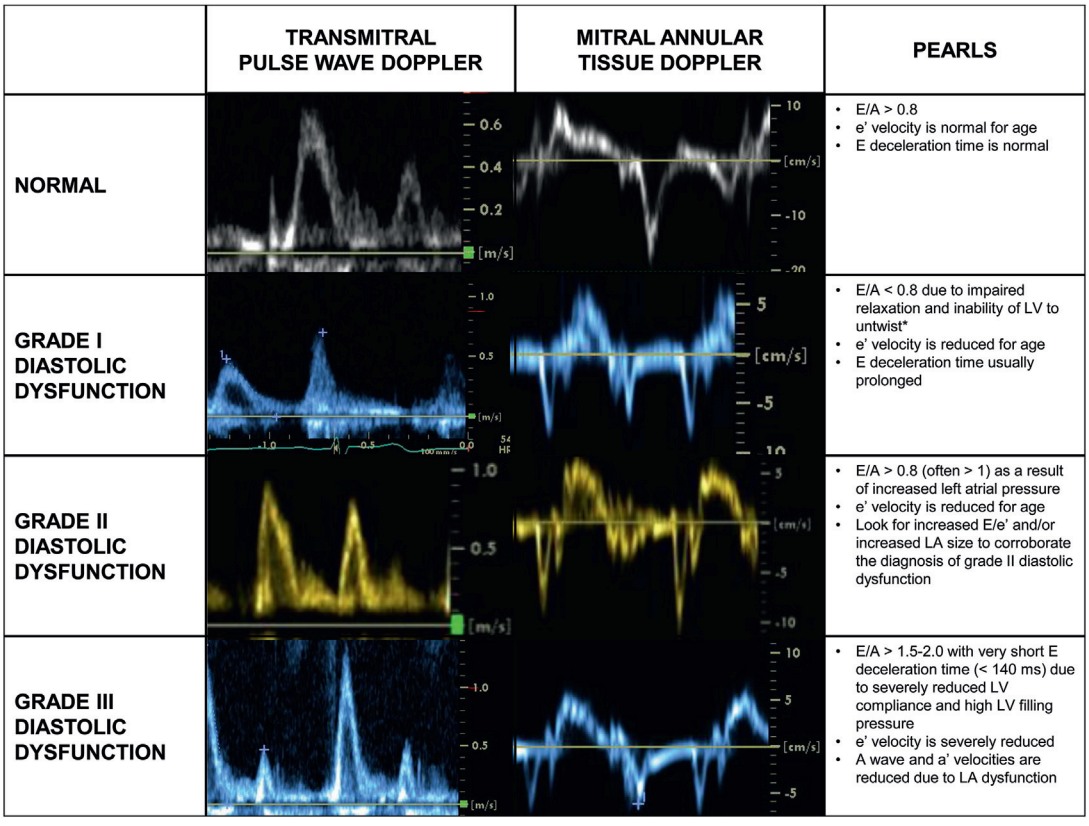
MITRAL ANNULAR e′ VELOCITY. The usefulness of mitral annular velocity measurement lies in the observation that, in healthy hearts, a significant amount of LV ejection and LA filling results from descent of the mitral annulus toward the apex. This longitudinal motion normally precedes filling. This motion can be both decreased and delayed in either the setting of global dysfunction (all motion is reduced) or in various settings associated with LV hypertrophy (contraction shifts from longitudinal shortening to radial thickening). Furthermore, there are a variety of comorbidities (e.g., hypertension, obesity, diabetes) that lead to impaired myocardial relaxation and restoration forces, and increased lengthening load (LA pressure), which results in reduced and delayed longitudinal motion and e′ velocity (15). The normal mitral annular tissue velocity pattern (**Figure 1**) contains 3 dominant waves: s′, representing systole; the e′-wave, reflecting relaxation in early diastole; and the a′-wave, due to atrial contraction in late diastole. Also seen are sets of biphasic waves during isovolumic contraction and relaxation. Because the annulus ends up in the same place on each beat, the area under the s′-wave (distance the annulus descends toward the apex) must roughly equal the sum of the areas under the e′ and a′ waves (16). This is physics and almost axiomatic. What is empiric is the observation that the e′ velocity is roughly inversely related to τ in some pathological conditions (17).

This observation leads to the prediction that E/e′ can be used to predict LV filling pressure in the following manner: recall that $E \propto p_{LA}/\tau$ and now we observe that $e' \propto 1/\tau$. If we divide the first of these equations by the second, the 2 τs cancel out, leaving us with $E/e' \propto p_{LA}$. Tissue Doppler e′ reflects relaxation of the long axis of the LV, and can be unreliable in the setting of incorrect sample volume placement, poor visualization of a dilated MV annulus, mitral annular calcification, severe mitral regurgitation, tachycardia, atrial fibrillation, constrictive physiology, ventricular dyssynchrony, or focal wall motion abnormalities (18). Echocardiography only allows the reader to say there is an higher likelihood of increased filling pressures if lateral E/e′ >12 (or septal E/e′ > 15), there is no significant mitral annular calcification, and the aforementioned clinical scenarios are not present. The certainty of this finding (elevated E/e′ indicative of elevated LV filling pressures) is increased in the presence of other echocardiographic parameters that suggest elevated filling pressures. For simplicity purposes, we recommend using the lateral e′ velocity for the evaluation of diastolic function and LV filling pressures given the potential influence of the RV on septal e′ velocity. However, in light of potential regional variability, both septal and lateral mitral annular tissue velocities (provided correct sample volume placement) should be considered when interpreting e′ and a′. Much of the remainder of this review focuses on the evidence base supporting this simplified approach.

DIAGNOSTIC USEFULNESS

The 2009 joint guidelines from the American Society of Echocardiography and the European Association of Echocardiography on grading diastolic dysfunction and the estimation of LV filling pressures rely primarily on the previously mentioned pulsed-wave transmitral and tissue Doppler velocities, as well as LA volume indexed to body surface area (LAVI) (18). The recently updated 2016 joint guideline from the American Society of Echocardiography and the

FIGURE 2 Stages of Diastolic Dysfunction

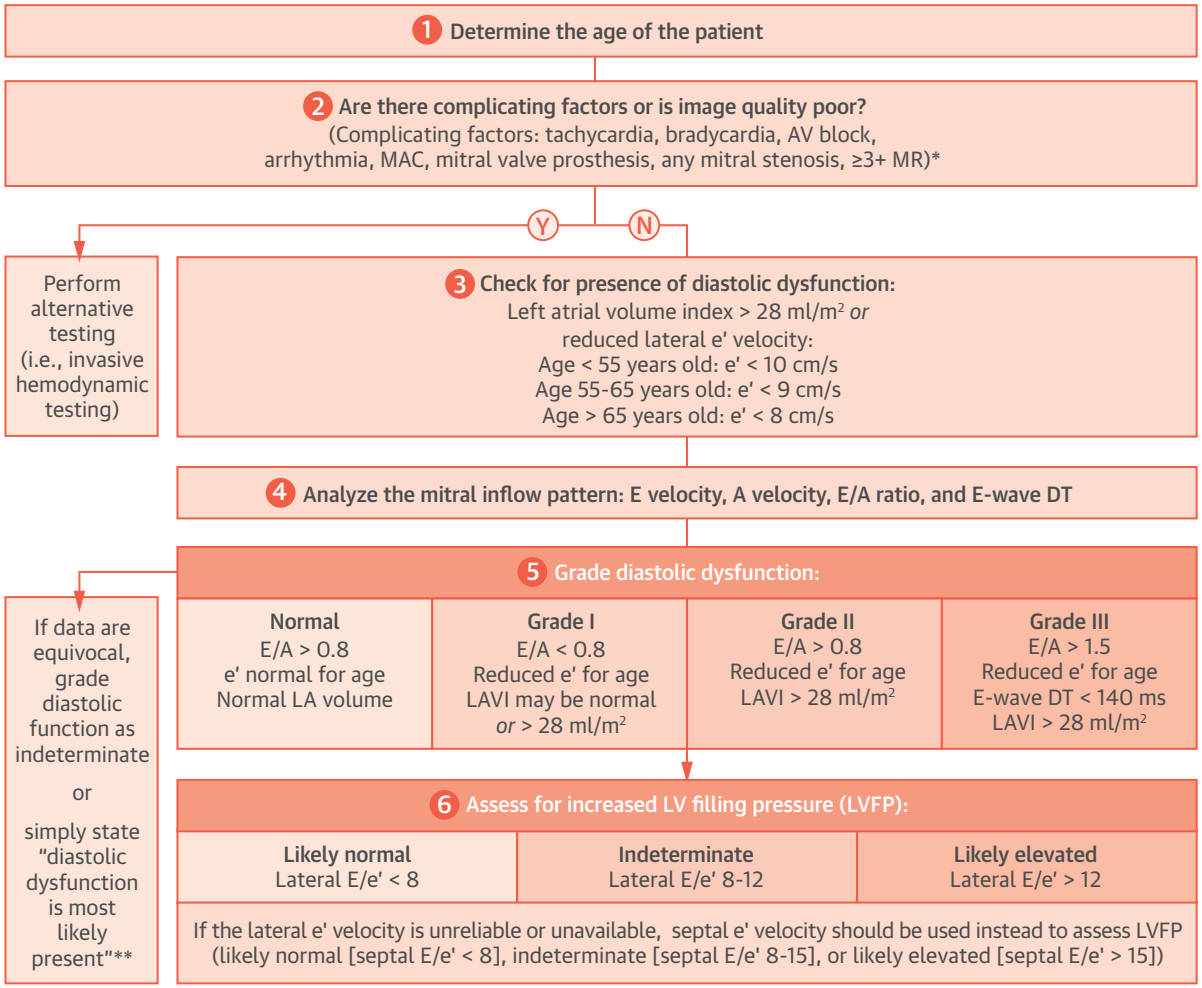


Transmitral pulsed-wave Doppler and mitral annular tissue Doppler signals of various stages of diastolic dysfunction. For all stages of diastolic dysfunction, e′ is reduced regardless of the mitral inflow patterns. *Nagueh et al. (18). A = late (atrial) transmitral pulse-wave Doppler flow; a′ = late (atrial) mitral annular tissue Doppler velocity; E = early transmitral pulsed-wave Doppler flow; e′ = early mitral annular tissue Doppler velocity; LA = left atrium; LV = left ventricle.

European Association of Cardiovascular Imaging also factor in an elevated tricuspid regurgitation velocity of >2.8 m/s as one of the main criteria for determining the presence of diastolic dysfunction (19). However, given their recent publication and lack of validation, it is difficult to comment on their performance in clinical practice. Per the 2009 guidelines, septal and lateral e′ velocity and LAVI are considered as 3 dichotomous variables to differentiate normal individuals from those with diastolic dysfunction. Once diastolic dysfunction is established, other echocardiographic parameters, including E/A patterns, DT, average E/e′, and the difference between pulmonary vein atrial reversal wave duration and A-wave duration determine whether the patient has grade I, II, or III diastolic dysfunction (**Figure 2**). Furthermore, E/A and E/e′ should not be used in isolation in assessing diastolic function and LVEDP, but rather used in conjunction with clinical characteristics, such as age and medical history, and other echocardiographic parameters from the study in its entirety to accurately classify diastolic function.

Unfortunately, the more commonly used 2009 joint guidelines do not address all parameter possibilities, resulting in many indeterminate evaluations. For example, there can be 8 ($2 \times 2 \times 2$) possible combinations from the 3 dichotomous variables (septal and lateral e′ velocity and LAVI), and the guidelines address only 3 combinations, ignoring the other 5, meaning that many patients, perhaps a majority, cannot be classified at all. An examination of the echocardiograms of 20 patients by 14 experienced echocardiography readers in 8 countries (a total of 280 reads) revealed that only 5 patients satisfied all criteria in their prespecified diastolic function class when applying the guidelines and a Fleiss κ of only 0.68 for concordance in assigning diastolic grades (20). Selmeryd et al. (21) noted in a recent meta-analysis of

CENTRAL ILLUSTRATION Algorithm for Diagnosing Diastolic Dysfunction With Doppler Echocardiography



Mitter, S.S. et al. J Am Coll Cardiol. 2017;69(11):1451–64.

A stepwise approach using E/A and E/e′ to diagnose diastolic dysfunction. Proper assessment is dependent on an accurate acquisition of transmitral flow and tissue Doppler imaging. A LAVI of >28 ml/m² (as opposed to a cutoff of >34 ml/m²) is used in the algorithm presented to indicate an increased LA size, because obesity is a risk factor for diastolic dysfunction; thus, LAVI can underestimate LA enlargement in these individuals (due to indexing to body size). *Although grading of diastolic dysfunction is not possible in these cases, the LVFP can still be estimated using surrogate markers, such as the estimated pulmonary artery systolic pressure or the end-diastolic pulmonary regurgitation gradient (as long as pulmonary arterial hypertension is not present). In older patients with normal sinus rhythm, systolic blunting of the pulmonary vein flow can be a sign of increased LA pressure. **It is not always possible to assign a diastolic dysfunction grade. In cases where equivocal data exists (e.g., an E/A ratio >0.8, reduced e′ velocity, indeterminate range E/e′, and normal LAVI), one can simply state that, "diastolic dysfunction is most likely present," without assigning a specific grade of diastolic dysfunction. In other cases, the e′ velocity may be normal, but LA volume may be increased and an E/A ratio of >1, which can be seen in cases of increased cardiac output or athlete's heart. In these cases, one can simply state, "diastolic function is most likely normal." A = late (atrial) transmitral flow velocity; AV = atrioventricular; DT = deceleration time; E = early diastolic transmitral flow velocity; e′ = early diastolic mitral annular velocity; LA = left atrial; LAVI = left atrial volume index; LVFP = left ventricular filling pressure; LVEF = left ventricular ejection fraction; MAC = mitral annular calcification; MR = mitral regurgitation; NYHA = New York Heart Association.

60 studies applying the 2009 consensus guidelines on diastolic function that only 17 used a definition of e′ and LAVI to define diastolic dysfunction, under which there was even greater heterogeneity within the definitions, as well as further classification. The resulting prevalence of diastolic dysfunction in the studies ranged from 12% to 84%, depending on the definition used.

The updated 2016 joint guideline to assess diastolic function also creates situations wherein diastolic dysfunction would be underdiagnosed. For example, impaired relaxation with normal LA size should ideally

fall under diastolic dysfunction, but would be considered indeterminate in the absence of an elevation in peak tricuspid regurgitation velocity under the new classification scheme. Grading diastolic function by peak tricuspid regurgitation velocity is troublesome in that it suggests diastolic dysfunction and clinical HFpEF to be synonymous. Elevations in peak tricuspid regurgitation velocity are not solely determined by an elevation in LV filling pressure, and can be the result of a pre-capillary component of pulmonary hypertension. Elevations in LV filling pressure leading to increased pulmonary arterial systolic pressure and peak tricuspid regurgitation velocity are seen in advanced stages of diastolic dysfunction; thus, cases of early diastolic dysfunction may be underdiagnosed upfront and lead to missed opportunities to prevent clinical syndromes of HFpEF as diastolic dysfunction progresses. Furthermore, treated HFpEF patients with reductions in LAVI and peak tricuspid velocity may not meet the criteria for definitive background diastolic dysfunction under the new 2016 guideline.

With respect to the estimation of LV filling pressures, early work suggested that E/e′ could be used to reliably estimate of LV filling pressure in settings such as systolic and diastolic HF, and even in atrial fibrillation (22–25), but later studies have shown greater scatter. For example, Ommen et al. (26) showed poor predictive accuracy among the large group of patients with septal E/e′ between 8 and 15. Firstenberg et al. (27) showed essentially a flat response in normal subjects. In a series of patients with symptomatic hypertrophic cardiomyopathy, Geske et al. (28) showed that correlation between E/e′ and direct LA pressure measurement by transeptal puncture resulted in Pearson r coefficients of 0.41 and 0.33 for septal and lateral e′, respectively, thus accounting for 17% and 11% of the respective variances in LA pressure. Mullens et al. (29) also found that, in patients with acutely decompensated systolic heart failure, E/e′ was poorly correlated with PCWP due, in part, to the use of inotropes and resynchronization therapy. Furthermore, Unzek et al. (20) found a Fleiss κ of only 0.71 among 14 experienced echocardiography readers in the estimation of LV filling pressures.

In assessing patients for diastolic dysfunction and possible HFpEF, application of the 2009 consensus guideline on diastolic function yielded a sensitivity of 47% to rule out HFpEF, whereas other proposed classification schemes actually yielded higher sensitivities of between 72% and 77% to rule out of HFpEF (18,30–32). It remains to be seen how the updated 2016 consensus guideline on diastolic function (which were proposed without validation data to support their use) compare with other classification schemes in assessing diastolic function. Given the limitations of these prior diastolic function classification schemes, there remains a need for a straightforward, easy-to-use diastolic function grading system. The **Central Illustration** displays an algorithm for the classification of diastolic function that we find useful clinically. Although this algorithm also has not been validated clinically, it focuses on commonly used criteria to assess diastolic function and LV filling pressures from the well-known 2009 guidelines, including LAVI, E, A, E-wave DT, e′, and E/e′. Notably, this algorithm highlights that even a LAVI of >28 ml/m^2 can suggest early diastolic dysfunction and that population-based, age-related criteria for an abnormal lateral e′ should be used to assess diastolic function. Furthermore, this algorithm helps echocardiogram readers to identify pitfalls quickly, limiting adequate assessment of diastolic function and LV filling pressures. In validating the proposed algorithm, it may be worthwhile to assess not only its accuracy, but also whether Bayesian analyses can be incorporated to help echocardiogram readers increase or decrease the predictive nature of diastolic dysfunction and increased LV filling pressure assessments. Additionally, newer echocardiographic parameters, specifically LA strain and LV early diastolic strain rate, will aid in assessment of diastolic function in the coming years, as new technology further penetrates community practices (33–35).

PROGNOSTIC IMPLICATIONS

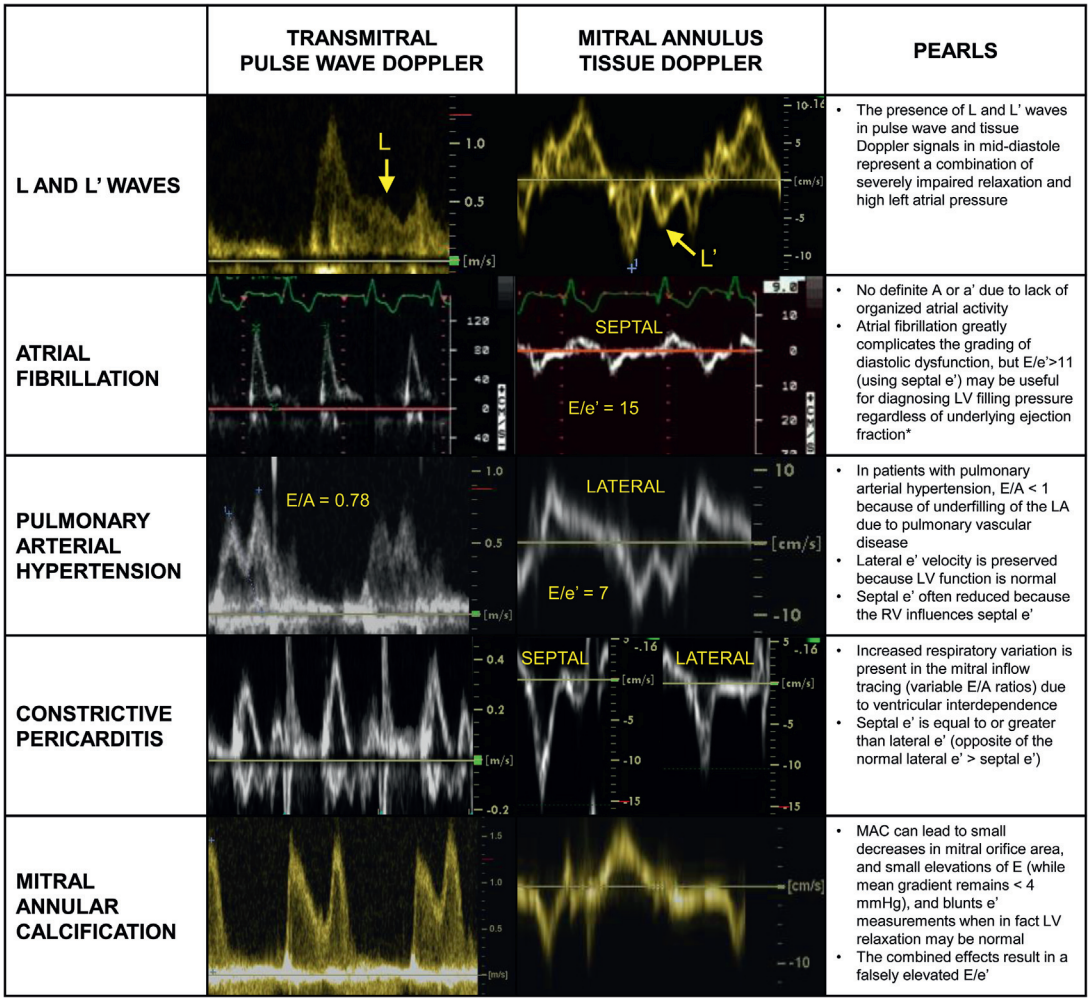
At a population level, E/A and E/e′ have been used numerous times to predict all-cause mortality, cardiovascular death, and heart failure hospitalizations in several disease states, including acute myocardial infarction, cardiomyopathy, and heart failure with preserved and reduced ejection fraction (36–40).

In asymptomatic individuals with risk factors for HFpEF (age, hypertension, diabetes mellitus, and obesity), worsening stages of diastolic dysfunction on the basis of E/A and E/e′ are also predictive of adverse cardiovascular outcomes (41,42). Furthermore, 4-year longitudinal follow-up of 2,042 patients randomly selected to participate in the Olmsted County Heart Function Study showed that progressive worsening in E/A and E/e′ is associated with an increased incident heart failure (43). Although these indexes clearly have important epidemiological meaning in large populations, their application in individual patients is more problematic.

SPECIAL CLINICAL SCENARIOS

Although E/A and E/e′ ratios can be very helpful clinically in diagnosing heart failure, predicting the

FIGURE 3 Special Scenarios for Assessing Diastolic Function and LV Filling Pressures



Clinically helpful patterns of transmitral pulsed-wave Doppler and mitral annular tissue Doppler signals for diastolic function and left ventricular filling pressure assessment. *Al-Omari et al., 2008 (49). L = mid-diastolic transmitral pulse wave Doppler flow; L′ = mid-diastolic tissue Doppler velocity; MAC = mitral annular calcification; RV = right ventricle; other abbreviations as in Figure 2.

risk for heart failure, and determining prognosis, these tests are not perfect and should be examined within the context of the rest of the echocardiogram and the clinical scenario. As previously mentioned, the use of E/e′ to estimate LV filling pressures is controversial, failing to correlate with invasive measurements in various clinical situations (22,26,28,29,44). Its usefulness rests largely on the "preload independence" of e′ velocity, as measured in a recumbent position. Although e′ typically shows less variation with preload alterations than E in pathological conditions, in normal subjects this is often not the case, with E/e′ showing an almost flat response to variable LVEDP (27). As noted previously, E/e′ showed poor correlation with direct LA pressure measurements in patients with hypertrophic cardiomyopathy (28).

Despite challenges in the interpretation of E/A and E/e′ ratio, specific patterns of these indexes can be quite helpful clinically, because they provide important diagnostic clues. Figure 3 displays some of these special scenarios in which specific E/A patterns and/or E/e′ ratio cutoffs can be used to guide diagnosis and management, and others where caution must be observed. In the case of atrial fibrillation, beat-to-beat variability and the absence of A waves make the

assessment of diastolic dysfunction difficult (18). Other Doppler parameters, such as e′ <8 and E/e′ >11 that are associated with tau >50 ms and LV filling pressures of >15 mm Hg, respectively, are needed to help assess diastolic function and increased LA pressure in atrial fibrillation (45). Furthermore, the presence of a second filling wave after the E-wave (L-wave) in patients with atrial fibrillation is correlated with advanced diastolic dysfunction (46). Even in the absence of atrial fibrillation, the L-wave and the L′ (its tissue Doppler correlate) are markers of worse diastolic function and filling pressure in a variety of settings, and predict future heart failure events (47,48). Other parameters associated with higher LV filling pressures in individuals with atrial fibrillation include shortened diastolic pulmonary vein flow DT (<220 ms), regardless of LV function, and an E-wave DT of <150 ms in the presence of LV systolic dysfunction (49–51).

Mitral inflow (respirophasic variation in E/A ratio, due to ventricular interdependence) and patterns of lateral and septal e′ velocities can be very helpful in diagnosing constrictive pericarditis. During expiration, E is highest, falling with inspiration as the right ventricle is filled preferentially. A 25% decrease in the E-wave with inspiration is suggestive of constriction, although it can also be seen with tamponade and chronic obstructive lung disease, and must be used with caution in isolation. Mitral annular e′, which is often reduced severely in restrictive cardiomyopathies, is typically increased in the setting of constrictive pericarditis, resulting in an inverse relationship between E/e′ and LV filling pressure (annulus paradoxus) (13). Constrictive pericarditis can also result in tethering of the lateral LV wall such that the lateral e′ velocity is now similar to or lower than septal e′ velocity (annulus reversus because the lateral e′ is normally higher than the septal e′) (52).

The mitral inflow pattern can also help to determine the subtype of pulmonary hypertension (pulmonary arterial vs. pulmonary venous hypertension). In patients with significantly elevated pulmonary artery systolic pressure (e.g., >50 mm Hg), an E/A ratio <1 is indicative of pulmonary arterial hypertension because the LA is underfilled (due to pulmonary vascular disease obstructing blood flow through the lungs), and extrinsic compression of the LV by the right ventricle, resulting in decreased LV compliance. In these patients, lateral e′ velocity is typically normal, but septal e′ velocity is often reduced because the septal mitral annulus is also influenced by an abnormal right ventricle in the setting of pulmonary arterial hypertension. In patients with pulmonary venous hypertension, the lateral e′ velocity is typically reduced, lateral E/e′ is increased, and the E/A ratio should be >1 (53,54).

THERAPEUTIC DECISION MAKING

Echocardiography can be a powerful tool for the diagnosis of diastolic dysfunction and increased LV filling pressures. Given the high prevalence of heart failure in the population, and the frequency with which clinicians manage volume status in clinical practice, echocardiography is a routine test that influences therapeutic decision making. Furthermore, diastolic parameters, such as the E/A and E/e′ ratios, are often used as surrogate endpoints in clinical trials. Thus, clinicians must understand how to interpret the E/A and E/e′ ratios so that they can manage patients correctly and interpret clinical trial data that use these parameters.

As explained, both the E/A and E/e′ ratios have their limitations; therefore, these parameters must not be viewed in isolation to determine whether or not a patient requires diuretic agents or other heart failure therapies. When diagnosing increased cardiac filling pressures, other clinical and echocardiographic parameters should be used to support the conclusions from E/A and E/e′ ratios. These include elevated jugular venous pressure, rales, and dilation and decreased collapsibility of the inferior vena cava. When used appropriately, the E/A ratio and/or E/e′ ratio can be very helpful diagnostically and therapeutically (**Figure 3**). Additional examples include the benefits of goal-directed therapy in advanced HFpEF on the basis of diastolic parameters, and the potential usefulness of E/A ratios in guiding heart rate management in HFpEF patients. In advanced HFpEF patients with E/A ratio of >1, continued diuresis until the E/A is <1 and the E/e′ has decreased from baseline may help to define therapeutic success (55). In patients with HFpEF who have an E/A ratio of <1, slowing the heart rate may help, because this will allow for adequate time for LV filling and atrial contraction, which helps to lower the LA pressure and boost cardiac output. In patients with HFpEF who have an high E/A ratio (>1.5 to 2.0), the majority of LV filling occurs in early diastole; therefore, slowing the heart rate down does not help, and may actually be harmful because stroke volume is often fixed in these patients. In this clinical scenario, adequate heart rate is necessary to maintain cardiac output.

Besides being useful in clinical practice, diastolic parameters have demonstrated potential usefulness in clinical trials of patients with diastolic

TABLE 2 Recent Randomized, Controlled Trials Using Echocardiography to Evaluate for Changes in Diastolic Markers in Patients With or at Risk for HFpEF

First Author, Year, Trial (Ref. #)	Patient Characteristics; Intervention	Trial Duration	N	Echocardiographic Outcome(s)	Results	Conclusions
Solomon et al., 2007, VALIDD (56)	Hypertension, diastolic dysfunction valsartan 320 mg vs. placebo in addition to standard therapy	38 weeks	384	Change in e′ (lateral)	e′ (lateral) velocity: intervention Δ = +0.6 cm/s* placebo Δ = +0.44 cm/s*	LV relaxation (e′ velocity) improves with blood pressure reduction, regardless of the agents used.
Solomon et al, 2010, EXCEED (57)	Hypertension LVEF ≥ 50%, intense (<130 mm Hg) vs. standard (<140 mm Hg) systolic blood pressure reduction	24 weeks	228	Change in e′ (lateral)	e′ (lateral) velocity: intervention Δ = +1.54 cm/s* standard Δ = +1.48 cm/s*	The degree of improvement in e′ velocity depends on the amount of blood pressure reduction.
Deswal et al., 2011, RAAM-PEF (58)	HFpEF, LVEF ≥ 50%, NYHA functional class II and III; eplerenone 50 mg vs. placebo	26 weeks	44	Change in E/A, e′ (lateral) and E/e′ (lateral)	E/A ratio: intervention Δ = -0.18 placebo Δ = -0.11 e′ (lateral): intervention Δ = +0.8 cm/s placebo Δ = -0.06 cm/s E/e′ (lateral) ratio†: intervention Δ = -1.8 placebo Δ = +1.2	Despite improvements in E/e′ and markers for decreased collagen cell turnover, the effects of mineralocorticoid receptor antagonism are cardiac specific and do not help improve skeletal muscle, which could contribute to residual impairment in exercise tolerance.
Edelman et al., 2013, ALDO-DHF (59)	HFpEF, NYHA functional class I and II; spironolactone 25 mg vs. placebo	12 months	422	Change in E/e′ (septal)	E/e′ (septal) ratio†: intervention Δ = -0.6* placebo Δ = +0.8*	Spironolactone decreases E/e′, but does not improve peak oxygen consumption on CPET (reduction in E/e′ does not necessarily correlate with improved exercise tolerance in early-stage HFpEF).
Shah et al., 2015, TOPCAT (pre-specified echocardiography substudy) (60)	HFpEF, NYHA functional class II and III LVEF > 45%; spironolactone 15-45 mg vs. placebo	12-18 months	239	Change in LA volume, E/A and E/e′ (septal)	LA volume: intervention Δ = +1.1 mL placebo Δ = +2.2 mL E/A ratio†: intervention Δ = -0.09 placebo Δ = +0.5 E/e′ ratio (septal): intervention Δ = +0.3 placebo Δ= +0.5	After multivariate analysis, increasing LA volume and E/A ratios in the entire study population were associated with the primary outcome of cardiovascular death, heart failure hospitalization, and aborted sudden death. Spironolactone was associated with significant reductions in E/A vs. placebo during follow-up.
Solomon et al., 2012 PARAMOUNT (61)	NYHA functional class II and III LVEF > 45% NT-proBNP > 400 pg/ml, LCZ696 200mg BID vs. valsartan 160 mg BID	36 weeks	301	Change in LA volume, E/A, e′ (lateral), and E/e′ (lateral)	LA volume†: LCZ696 Δ = -4.6 mL valsartan Δ = 0.37 mL E/A ratio: LCZ696 Δ = -0.05 valsartan Δ = -0.03 e′ (lateral) velocity: LCZ696 Δ = 0.55 cm/s valsartan Δ = 0.92 cm/s E/e′ (lateral) ratio: LCZ696 Δ = -1.3 valsartan Δ = -1.0	LCZ696 reduced LA volume. LA volume may be a better target than E/A or E/e′ ratio for assessing improvements in diastolic function and LV filling pressures.

Continued on the next page

TABLE 2 Continued

First Author, Year, Trial (Ref. #)	Patient Characteristics; Intervention	Trial Duration	N	Echocardiographic Outcome(s)	Results	Conclusions
Bergstrom et al., 2004, SWEDIC (62)	HFpEF NYHA functional class I, II, and III; carvedilol up to 25-50 mg BID vs. placebo	6 months	97	Change in E/A, IVRT, E-wave DT and S/D	E/A†: intervention Δ = +0.11 placebo Δ = +0.05 IVRT: intervention Δ = -1 ms placebo Δ = -7 ms E-wave DT: intervention Δ = +10 ms placebo Δ = +8 ms S/D: intervention Δ = -0.04 placebo Δ = +0.07	LV relaxation (E/A ratio) improves more in patients with increased heart rate control.
Kosmala et al., 2013 (63)	HFpEF, NYHA functional class II and III, LVEF ≥ 50%, ivabradine 5 mg BID vs. placebo	7 days	61	Change in e′, and E/e′ (average) with exercise	e′ (septal) velocity: ivabradine Δ = +0.7 cm/s* placebo Δ = +0.4 cm/s e′ (lateral) velocity: ivabradine Δ = +0.8 cm/s placebo Δ = +0.7 cm/s E/e′ (average) ratio: ivabradine Δ = -1.8* placebo Δ = -0.7	Ivabradine vs. placebo, improved exercise tolerance, but had no effect on between-group diastolic function or LV filling pressure.
Pal et al., 2015 (64)	HFpEF NYHA functional class II and III LVEF > 50%, ivabradine 7.5 mg BID vs. placebo	14 days	44	Change in E/e′ (average)	E/e′ (average) ratio: ivabradine Δ = -0.4 placebo Δ = -0.7	Ivabradine had no effect on exercise capacity or LV filling pressure.

*p≤0.05 for within-group differences. †p ≤ 0.05 for between-group differences.

A = late (atrial) transmitral flow velocity; ALDO-DHF = Aldosterone Receptor Blockade in Diastolic Heart Failure; BID = twice a day; CPET = cardiopulmonary exercise testing; DT = deceleration time; E = early diastolic transmitral flow velocity; e′ = early diastolic mitral annular velocity; EXCEED = Amodipine/valsartan [Exforge] Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction Trial; HFpEF = heart failure with preserved ejection fraction; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PARAMOUNT = Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion; RAAM-PEF = Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial; SWEDIC = Swedish Doppler-echocardiographic study; TOPCAT = Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; VALIDD = Valsartan In Diastolic Dysfunction.

dysfunction and/or HFpEF (**Table 2**). The VALIDD (Valsartan In Diastolic Dysfunction) and EXCEED (Amodipine/valsartan [Exforge] Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction Trial) trials demonstrated that the degree of improvement in e′ velocity is dependent on blood pressure reduction (56,57). In the RAAM-PEF (Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction) and ALDO-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trials, which examined patients with early phase HFpEF, treatment with spironolactone improved diastolic parameters but did not result in improved exercise capacity, a finding that supported the notion that in HFpEF, exercise intolerance is due to both cardiac and skeletal muscle dysfunction (58,59). In the TOPCAT trial (Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), which studied patients with more overt HFpEF (i.e., elevated B-type natriuretic peptide or history of heart failure hospitalization), a prespecified echocardiographic substudy showed that spironolactone reduced the E/A ratio, which was associated with reduced cardiovascular death and heart failure hospitalizations (60). Additional trials listed in **Table 2** show the usefulness of the E/A and E/e′ ratios to vary by trial. PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) showed that in HFpEF, neprilysin inhibition reduced LA volume, but had no effect on the E/A or E/e′ ratios (61). The SWEDIC study (Swedish Doppler-echocardiographic study) showed a signal that echocardiographic improvement in LV relaxation (E/A) could be dependent on heart rate control (62). In 2 relatively small trials of ivabradine in HFpEF, the baseline E/A ratio proved to be quite informative; in earlier stages of HFpEF (denoted by lower E/A ratio), Kosmala et al. (63) found that ivabradine improved exercise capacity, whereas in later stage HFpEF (denoted by higher E/A ratio), Pal et al. (64) found no benefit with ivabradine. Although clear evidence is lacking, these findings suggest that heart rate reduction may be helpful only in the early stages of diastolic dysfunction and concomitant HFpEF when the E/A ratio is <1 (63,64).

CONCLUSIONS

Echocardiographic evaluation of diastolic function with the E/A and E/e′ ratios, widely used in the clinical setting, is an important tool for the diagnosis, treatment, and prognosis of a wide variety of patients. Therefore, it is important for clinicians who care for patients with known or suspected cardiac disease to understand the pathophysiological underpinnings, and strengths and limitations, of these parameters so that they can be effective tools to guide clinical practice. Our understanding of the pathophysiology of heart failure and heart disease in general has advanced markedly due to the availability of echocardiographic diastolic function assessment. Herein we have provided a guide for the interpretation of the E/A ratio, E/e′ ratio, and diastolic function grading, with the hope that it can be used to complement the rest of the echocardiographic and clinical assessment to improve patient care.

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