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When does the E/e' index not work? The pitfalls of oversimplifying diastolic function

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Abstract

Since the E/e' ratio was first described in 1997 as a noninvasive surrogate marker of mean pulmonary capillary wedge pressure, it has gained a central role in diagnostic recommendations and a supremacy in clinical use that require critical reappraisal. We review technical factors, physiological influences, and pathophysiological processes that can complicate the interpretation of E/e'. The index has been validated in certain circumstances, but its use cannot be extrapolated to other situations—such as critically ill patients or children—in which it has either been shown not to work or it has not been well validated. Meta-analyses demonstrated that E/e' is not useful for the diagnosis of HFPeF and that changes in E/e' are uninformative during diastolic stress echocardiography. A similar ratio has been applied to estimate right heart filling pressure despite insufficient evidence. As a composite index, changes in E/e' should only be interpreted with knowledge of changes in its components. Sometimes, e' alone may be as informative. Using a scoring system for diastolic function that relies on E/e', as recommended in consensus documents, leaves some patients unclassified and others in an intermediate category. Alternative methods for estimating left heart filling pressures may be more accurate, including the duration of retrograde pulmonary venous flow, or contractile deformation during atrial pump function. Using all measurements as continuous variables may demonstrate abnormal diastolic function that is missed by using the reductive index E/e' alone. With developments in diagnostic methods and clinical decision support tools, this may become easier to implement.

KEYWORDS

diastolic function, Doppler echocardiography, left ventricular filling pressures, pulmonary capillary wedge pressure

1 | INTRODUCTION

A comprehensive assessment of diastolic function is an integral component of the complete echocardiographic examination of any patient referred with suspected heart failure, irrespective of their left ventricular (LV) systolic function. Diagnostic clues are provided

from all modalities including cross-sectional imaging, M-mode echocardiography, and both spectral blood pool and tissue Doppler (or myocardial velocity) recordings.

The first Doppler method that was applied to assess LV diastolic function was analysis of the mitral E/A ratio, but it was recognized that a ratio >1 may be ambiguous since it does not

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discriminate between normal and pseudonormal filling patterns—the E/A ratio is high in youth and health, falls with impaired relaxation, increases with pseudonormalization, and becomes very high if there is restrictive filling. Similarly, the LV isovolumic relaxation time (IVRT) and the mitral deceleration time (DT) both vary with the opposite biphasic pattern, since they are short in health, prolong when early diastolic relaxation is slowed, and shorten if restrictive filling develops.

In order to overcome uncertainties in interpreting those measurements, an index was proposed—the ratio of the early diastolic velocity of mitral inflow (E) to the early diastolic velocity of mitral annular motion (e')—that demonstrated a continuous progression with increasing mean pulmonary capillary wedge pressure.¹ The E/ e' ratio has since become established as the cornerstone of estimating LV filling pressure. It is even applied as an indicator of the severity of diastolic dysfunction in general, not infrequently to the exclusion of other measurements. Its status has been reinforced by a central position in diagnostic algorithms in consensus recommendations.^{2–5}

The popularity of the E/ e' index may derive in part from its simplicity, but as a composite index the reasons for its variation may be obscured. It was proposed as a load-insensitive index, but as discussed later, both E and e' are altered by changing LV preload. In diagnostic studies, the index has performed well in particular circumstances but not in others, and in all studies values that fall in an intermediate range are nondiagnostic such that some patients are unclassifiable.

In this review, we examine the evidence behind the use of the E/ e' index, highlighting technical and pathophysiological factors that affect its measurement or confound its interpretation. We summarize clinical circumstances in which its use has not been validated and when it should be used with caution. In any patient who needs comprehensive assessment of LV diastolic function, there are many other methods that can and should also be applied.

2 | TECHNICAL FACTORS AFFECTING THE MEASUREMENT OF E/E'

The mitral E velocity is measured only from a pulsed Doppler recording of flow between the tips of the mitral leaflets, but e' can be measured either from a pulsed spectral tissue Doppler recording in real time or by postprocessing of a color tissue Doppler loop. These two methods are not interchangeable; pulsed tissue Doppler gives peak myocardial velocities from the edge of the velocity profile, while color tissue Doppler displays mean myocardial velocities which are on average 25% lower.⁶ Using postprocessed measurements for e' therefore gives significantly higher values for E/ e' .⁷ The limits of agreement between the two methods for E/ e' have been reported at -7.7 to -0.3 .⁸ Even greater differences are found if gain settings for spectral Doppler are high (which increases measured E velocities) or if temporal smoothing of the tissue Doppler is increased (which lowers e').⁸

E and e' are both acquired using pulsed (or range-gated) techniques, and they are angle-dependent. Inter-observer variability is not trivial; in one study, the limits of agreement from Bland-Altman analyses of tissue velocities measured at the lateral mitral annulus were $\pm 9\%$ to 17% .⁹ A contributory factor may be the difficulty of distinguishing very small-amplitude e' waves from low velocity signals occurring during isovolumic relaxation or in mid-diastole. There are also differences in the accuracy of tissue Doppler measurements obtained from machines provided by different vendors. In an experimental study of four commercially available ultrasound systems against a precisely calibrated phantom, the largest errors occurred using tissue Doppler at 5 cm/s; all systems overestimated velocity, by a mean of 5.8%, while errors in the different systems ranged from $+1.1\%$ to $+12.5\%$.¹⁰ All these factors can be important if precise serial measurements of E/ e' are required in an individual patient or if results from different machines are combined during a research study.

Mitral annular longitudinal excursion is usually greatest around the free-wall portions of the left atrioventricular junction. Therefore, the early diastolic velocity of mitral annular motion varies at different sites, with e' normally being lower at the medial than at the lateral mitral annulus.^{11,12} Less annular excursion and lower velocities are thought to reflect the greater vulnerability of the septum to interstitial fibrosis, since it is subject to the highest regional wall stress.¹² Tissue velocities at the base of the septum are influenced also by disease that alters function of the right ventricular myocardial component of the septum.

The first report of the E/ e' index was based on measuring e' only at the lateral mitral annulus.¹³ Now, consensus recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend that e' should be averaged from pulsed tissue Doppler recordings obtained from medial and lateral sites.⁴ Ideally, these should be averaged over three consecutive beats for a patient in sinus rhythm and over 10 beats if the patient is in atrial fibrillation. Perhaps surprisingly, despite the importance of identifying and timing events accurately (so that E and e' are measured correctly), no major ultrasound vendor provides an easy mechanism for superimposing or time-aligning spectral blood pool Doppler and tissue Doppler traces.

3 | PHYSIOLOGICAL FACTORS AFFECTING THE VALUES OF E/E'

Both E and e' are velocity measurements that are obtained from early diastolic events. They are sometimes assumed to be useful to estimate left ventricular end-diastolic pressure, but the original study compared the E/ e' ratio to mean pulmonary capillary wedge pressure (PCWP) which equates with LV diastolic pressure just before the onset of atrial contraction. In that study of 60 subjects, E/ e' predicted a PCWP > 12 mmHg with 91% sensitivity and 81% specificity.¹³ Another study published earlier the same year reported that a preload challenge (the rapid infusion of 500 mL saline) did not

change the e' velocity in 20 patients who had a preexisting abnormality of relaxation, and secondly that reducing preload by giving an infusion of nitroglycerin did not change e' in 11 healthy subjects.¹⁴ Mitral annular velocities are related to heart rate, and the dose of nitroglycerin was increased in that study until the heart rate increased, but nonetheless the authors concluded that e' was independent of preload.

The same idea seems to have been extrapolated by default to E/e' , but many studies have cast doubt on that assumption.

3.1 | Influence of preload

Invasive hemodynamic studies in dogs demonstrated clearly that the e' velocity of LV early diastolic long-axis expansion is determined by lengthening load (preload), as well as by LV relaxation and restoring forces.¹⁵ The mitral E velocity is also load-dependent.

The consequences of reduced preload for calculating E/e' have been reported from clinical studies in which circulating volume and LV preload were reduced by hemodialysis. In one early study of 13 patients, both E and septal e' fell significantly after dialysis, by 32% and 26%, respectively.¹⁶ The septal E/e' was unchanged, but the lateral mitral annular E/e' was reduced by 17%. In another study, also of 13 patients, lateral E/e' fell after dialysis by 27% from 16.7 to 12.2.¹⁷ Of course, these changes can be interpreted as evidence that filling pressures have fallen, but for this discussion, it is relevant that E/e' was altered differently at the medial and lateral mitral annulus. Similar observations of differential effects of dialysis on E/e' measured using septal or lateral e' were made by Vignon et al.¹⁸

Santos et al did transthoracic echocardiography during right heart catheterization in 118 patients with unexplained dyspnea.¹⁹ On going from supine to upright posture, PCWP fell by an average of 5 mmHg but E/e' did not change because both E and e' fell by a similar degree. The correlation of E/e' with PCWP when supine was only 0.36 and changes in E/e' on standing were unrelated to changes in PCWP ($r = -.04$, $P = .77$); in half of the patients, PCWP and E/e' changed in opposite directions. Bhella et al performed similar studies in 47 subjects, the majority of whom were healthy volunteers aged <50 years or >65 years. Changes in E/e' during maneuvers to increase preload (by infusing saline rapidly) and to reduce it (by applying lower body negative pressure) again did not track changes in PCWP reliably.²⁰ In an experimental study of loading manipulations in open-chest dogs, E/e' was *inversely* related to LV end-diastolic pressure.²¹

During pregnancy, LV volumes, stroke volume, and cardiac output all increase. The mitral E velocity increases, but long-axis function and mitral annular e' velocities may fall (presumably due to a change in shape of the ventricle).²² In 63 women who underwent serial echocardiography during their pregnancy, there was no significant change in E/e' , which remained within the normal range, but there was a trend for it to increase. In a larger cross-sectional study of 104 women recruited at different stages of pregnancy, E/e' at

the lateral margin was 12% lower in the first two trimesters when compared to nonpregnant controls.²³ In 35 women with structural heart disease, the E/e' index did increase during pregnancy, more obviously in those in functional classes I and II.²⁴

3.2 | Exercise

The E/e' index at rest is unaltered in subjects who exercise regularly. It was similar in male athletes undertaking predominantly dynamic exercise (water polo) or combined dynamic and isometric exercise (wrestling) to that observed in sedentary controls,²⁵ and it was unchanged in female athletes after 16 weeks of intensive training.²⁶ In healthy subjects, the E/e' also does not change on exercise. For example, in 31 people aged 59 ± 14 years who were studied within 2 minutes after maximal treadmill exercise, the mitral E velocity had increased by 23% and the annular e' velocity by 25% so the E/e' index was constant.²⁷

What is controversial is whether or not the E/e' index can discriminate between normal and abnormal responses to exercise in heart disease. In a "positive" study of echocardiography, the E/e' ratio was unchanged immediately after treadmill exercise in 76% of 166 patients (in whom E increased by 31% and e' by 44%) while it was higher in the others by 24% (since E increased by 49% and e' by 24%).²⁸ There were 37 patients who performed supine bicycle exercise during left heart catheterization, of whom most had a normal ejection fraction and three quarters were taking beta blockers. E/e' was unchanged in those whose mean LV diastolic pressure (LVDP) was normal at rest, while it increased in those whose LVDP and E/e' were already high. In only 9 patients (25%) did the LVDP become high only during exercise; although their E velocity had increased by only 10%, the E/e' also increased, by 36%, because e' fell by 16%. Overall, E/e' was related to exercise capacity, but only 35% of the variance in LVDP was explained by the changes in E/e' .²⁸

In "negative" studies of patients with heart failure with preserved ejection fraction (HFpEF), mean E/e' was 11.4 at rest and also 11.4 during semi-supine bicycle ergometry,²⁹ and E/e' did not adequately predict increases in mean PCWP from 11 to 28 mmHg during exercise.³⁰ In patients with severe aortic stenosis, E/e' also did not predict mean PCWP during exercise.³¹ All these patients would be expected to have some diastolic dysfunction.

Numerous studies could be cited to support both sides of this debate, but the conclusion from a meta-analysis published in 2017 was that E/e' was not useful for assessing changes in LV filling pressure during exercise or pharmacological interventions.³² Thus, the problem here with using the E/e' index during exercise is not that it changes but that it may not, mainly because both E and e' are similarly sensitive to altered loading. Differences between studies may be due to variations in protocol such as the timing of measurements (during or early after exercise), posture, and coexisting drug treatment, as well as to the underlying pathophysiology and the stage or severity of disease.

3.3 | Cardiac rhythm and conduction

It was reported by the first proponents of the E/e' ratio that its good correlation with PCWP was retained in patients who had a sinus tachycardia—irrespective of whether the E- and A-waves were fused ($r = .86$).³³ When there is complete merging of the early and atrial flow components, however, the assumptions about using E and e' are no longer valid. The E and A (or e' and a') velocities can also become fused if there is first degree atrioventricular block.^{4,34}

In atrial fibrillation, beat-to-beat variability makes it more challenging to measure mean E and e' velocities from beats with similar RR intervals and preload. In 98 patients with heart failure with preserved ejection fraction, Hummel et al demonstrated poor overall correlation of E/e' to mean PCWP ($r = .24$, $P = .02$), while in their subset of 29 subjects in atrial fibrillation, E/e' was unrelated to PCWP ($r = .16$, $P = .42$).³⁵

In asymptomatic subjects with left bundle branch block, the E/e' index was 21% higher than in matched controls because their mitral annular e' velocities were lower while the mitral E velocities were equivalent.³⁶ In symptomatic heart failure with severely reduced LV ejection fraction and left bundle branch block, both RV pacing and biventricular pacing reduced E and e' and caused a small increase in E/e'.³⁷ That change in E/e' could be interpreted as evidence that both types of pacing worsen diastolic function whereas of course biventricular pacing reduces LV filling pressures.³⁸

3.4 | Age, gender, and ethnicity

The e' velocity decreases with age^{12,39,40} with changes being observed first and becoming most prominent at the medial mitral annulus. Thus, in a study of 174 normal patients, the E/e' ratio was 8.2 ± 2.2 at age <45 years and 12.4 ± 3.3 in those aged ≥ 75 years; the e' velocity fell from 10.1 to 6.2 cm/s (ie, by about 1 cm/s per decade), but the mitral E velocity did not change.⁴⁰ In that study, the mitral E/A ratio became <1 with aging because the mitral A velocity increased.⁴⁰ Secondly, in a larger population study of 453 healthy subjects, the mean e' velocity averaged from medial and lateral sites declined by 23% between the ages of 35 and 75 years, from 11.7 to 9.0 cm/s.³⁹ The mitral E velocity also declined but by less, 13% from 75 to 65 cm/s, so the E/e' increased from 6.9 to 7.6. There were wide confidence intervals for E/e' at all ages, but the trends were all significant. Thirdly, in 1168 healthy subjects, E/e' was greater in those with higher age, LV mass, LV end-diastolic volume, and left atrial volume.⁴¹

In all age groups in the study of De Sutter et al, E/e' was a little higher in women than in men.⁴⁰ Similarly, in age-matched groups of 180 men and 180 women with a mean age of 74 years, E/e' was slightly higher in women at 9.7 compared with 9.3 in men ($P = .03$).⁴² There were significant interactions between E/e' and systolic or mean blood pressure, even after adjusting for the aortic length or volume; women had higher aortic elastance and lower e'.⁴² It has also been reported from a single-center substudy of the ASCOT trial

that African-Caribbean patients had a higher mean E/e' than white European patients (8.9 vs 7.9, $P = .003$), because their mean e' was lower and even after adjusting for confounding variables such as age, gender, systolic blood pressure, ejection fraction, and LV mass index.⁴³

Variations of E/e' with age have been observed in 174 children and young adults aged 1–21 years (mean 8.4)⁴⁴ and in 369 healthy children aged 1–17 years (mean 6.4), all of whom had normal cardiac function.⁴⁵ In both studies, the E/e' index declined from birth to age 5–7 years and thereafter was constant with a mean value of about 6. Age was the strongest determinant of E/e'.^{44,45}

In the context of these reports, it is surprising that diagnostic recommendations do not suggest different normative reference values for e' and E/e'; their absence implies that very high proportions of asymptomatic older people are defined as having abnormal values. D'Andrea et al⁴¹ concluded that age-related cutoff values were “indispensable” for E/e'. Selmer et al analyzed 1,240 apparently healthy subjects from the HUNT population study in Norway and suggested that in older subjects, an E/e' ratio >15 can be regarded as a normal finding if the E/A ratio is <1 and/or e' is <7 cm/s.⁴⁶

4 | CLINICAL FACTORS AFFECTING THE DIAGNOSTIC UTILITY OF E/E'

Considering all the factors described in the previous sections (Table 1), it is unsurprising that the E/e' index does not predict left heart filling pressures reliably in many clinical circumstances. Recent diagnostic consensus statements which have been chaired by the first author of the original publication that proposed the E/e' index nonetheless continue to recommend its use, but now within an algorithm that includes other indices. The Eurofilling study of 159 subjects reported that the algorithm in the 2016 Recommendations,⁴ which includes E/e' >14 as its first criterion, predicted invasively measured LV end-diastolic pressure (LVedp) >15 mmHg with a sensitivity of 75% and a positive predictive value of 39%.⁴⁷ The overall performance of the model (area under the receiver-operator curve) was 0.78. In that study, however, the univariate correlation of the E/e' index to LVedp was only 0.34, with a sensitivity of 13%.⁴⁷

Any change in diagnostic consensus recommendations can have a major impact on the prevalence of disease, so it is problematic if new proposals are based on expert consensus more than hard evidence. Applying the 2016 recommendations,⁴ for example, reduced the prevalence of diastolic dysfunction in the Stanislas cohort of 1,485 subjects from 5.9% to 1.3%, compared with using the 2009 recommendations⁴⁸; in subjects aged >60 years, the estimated prevalence fell from 12.9% to 3.1%.⁴⁹ Inter-observer reproducibility for grading diastolic function was suboptimal using the 2009 recommendations, with a sensitivity of readers for identifying raised filling pressure of $66 \pm 37\%$ and with variations attributed to differences in the weighting of conflicting observations.⁵⁰

Ideally, diagnostic criteria should be selected because they predict clinical outcomes or because their use guides treatment with

TABLE 1 Some technical and physiological factors that affect the utility of the E/e' index

Technical considerations	
Measurement technique for e'—pulsed or processed tissue Doppler	
Doppler gain for mitral flow, influences E measurement	
Temporal smoothing of tissue Doppler, influences e'	
Measurement sites for e'	
Inter-vendor variability in accuracy of tissue Doppler	
Inter-observer variability	
Problems with time-aligning signals for measurements	
Physiological and demographic factors	Effect on E/e'
Increased LV preload	Septal unchanged, lateral reduced
Posture	No change
Increased LV afterload, LV mass	Increases
Heart rhythm—atrial fibrillation, sinus tachycardia, heart block	Becomes unreliable
Conduction—left bundle branch block, paced rhythm	Increases
Age	Decreases in infancy Increases with age
Gender	Slightly higher in women than men
Ethnicity	Higher in African-Caribbean than in European patients
Pregnancy	Increases or remains unchanged

Note: Details and references are given in the text.

e' = early diastolic velocity of mitral annular motion; E = early diastolic velocity of mitral inflow; LV = left ventricular.

evidence of benefit. In a recent study of >300 000 echocardiograms recorded in >170 000 patients, an algorithm developed by machine learning was able to predict survival after 5 years with an accuracy of 89%.⁵¹ The first selected echocardiographic variables in order were tricuspid regurgitant velocity (as an indirect marker of pulmonary arterial pressure), LV ejection fraction, diastolic functional class, and pulmonary arterial acceleration time. In a majority of patients, measurements of e' had not been recorded in the database that was analyzed. Thus, the independent contribution of E/e' could not be assessed, but it is unlikely that it could improve the model significantly.

There have now been thousands of published studies that have applied the E/e' index, which makes it very difficult to achieve a truly comprehensive overview. A second major challenge is that without correlative invasive data, it is impossible to determine whether a reported change in E/e' implies a real change in LV filling pressures (a true positive result) or whether E/e' remained constant despite a change in filling pressures (a false negative study). There have been well-conducted studies in which E/e' correlated better with invasively measured LV diastolic pressures than did

many other echocardiographic indexes⁵² but in general correlations have been modest. In a systematic review of 9 studies of patients with HFpEF, the pooled correlation coefficient was 0.56.⁵³ Our argument, based on the examples described below, is that the index should always be interpreted with caution and that it should never be relied upon as a single criterion either to estimate LV filling pressure or to diagnose diastolic dysfunction. Patients can have abnormal LV filling (early diastolic dysfunction) without increased myocardial stiffness (influencing end-diastolic pressures), and vice versa. In clinical trials, a change in E/e' that remains within the intermediate zone should not be accepted as proof of a change in diastolic function.

4.1 | Left ventricular hypertrophy

Mitral annular early diastolic velocity e' is reduced if there is LV hypertrophy caused by chronic arterial hypertension or hypertrophic cardiomyopathy.⁵⁴ Thus in a study of patients referred for cardiac catheterization, hypertension was an independent determinant of e' and LV mass index was an independent determinant of E/e'.⁵⁵ The E/e' ratio correlated with mean LV diastolic pressure in 36 patients with normal LV mass index ($r = .74, P < .001$) but not in 33 with increased LV mass index ($r = .29, P = .11$).⁵⁵ In a clinical trial for hypertension, mean E/e' had increased after more than two years of treatment with atenolol ± bendroflumethiazide despite some regression of LV hypertrophy.⁵⁵

In 35 patients with symptomatic hypertrophic cardiomyopathy due to undergo septal ablation, a good correlation was reported between E/e' and pre-A-wave LV diastolic pressure ($r = .76$).⁵⁶ More recently, a more modest correlation of 0.44 was found between E/e' and left atrial pressure in 100 symptomatic patients with hypertrophic cardiomyopathy.⁵⁷ The predictive power of E/e' in an individual patient was poor: mean LA pressure ranged between 5 and 40 mmHg in subjects with E/e' >15.⁵⁷ Possible reasons for the discrepancy between these studies include the degree of mitral regurgitation present and the direct measurement of left atrial or left ventricular pressure.

Figure 1 illustrates a patient who had LV hypertrophy and diastolic dysfunction but whose E/e' index was normal.

4.2 | Diabetes mellitus

Left ventricular long-axis function is reduced in subjects with diabetes, and the E/e' index may be elevated. For example, in age-matched groups, the mean E/e' was 7.4 in patients with type 2 diabetes compared with 5.9 in controls.⁵⁸ In diabetes, the E/e' index is further increased by coexisting obesity and hypertension.⁵⁹ In a large registry of patients who had had at least one hospital admission with acute heart failure, the mean E/e' index was higher in subjects with either HFrEF or HFpEF if they were also diabetic.⁶⁰ It was also higher in the control subjects who had not had heart failure but were diabetic.

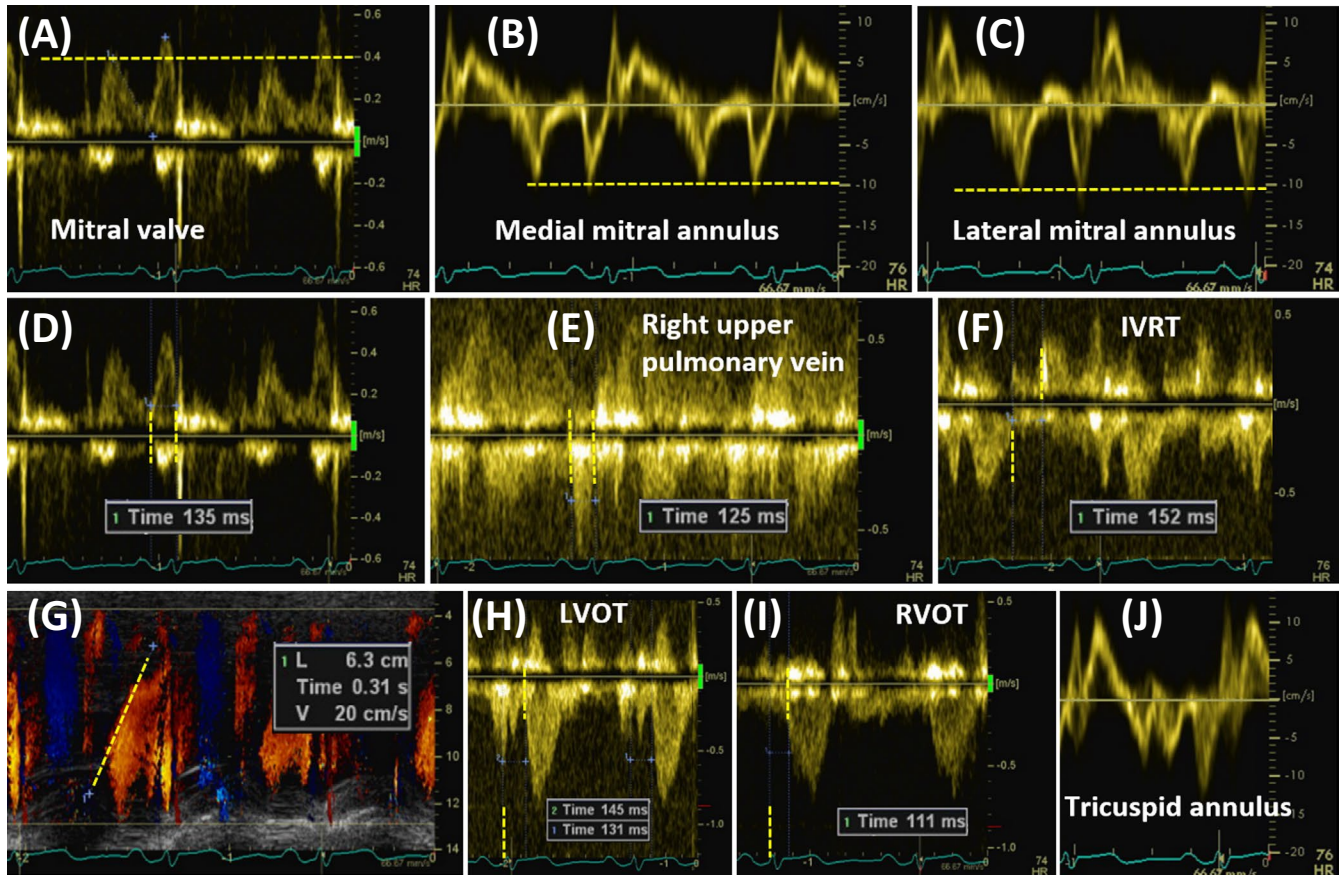


FIGURE 1 A breathless man with a normal E/e' index. Doppler echocardiography in a 56-year-old Afro-Caribbean man with polycystic kidney disease, renal failure requiring dialysis, and hypertension. He was breathless, in functional class II. The LV ejection fraction was normal. The mitral E velocity was 40 cm/s (panel A), the medial mitral annular early diastolic velocity e' 9.5 cm/s (B), and the lateral e' 10.5 cm/s (C), so his E/e' ratio was 4. The durations of antegrade mitral A and retrograde pulmonary venous 'a' flow during atrial contraction were normal at 135 and 125 ms, respectively (panels D and E). Thus, the estimated mean capillary wedge pressure (from E/e') and LV end-diastolic pressure (from the A – a difference) were both normal, but his LV diastolic function was abnormal: the mitral E deceleration time was long at 217 ms (see panel A), the LV isovolumic relaxation time IVRT was long at 152 ms (F), and the propagation velocity Vp of mitral inflow was low at 20 cm/s (G), all indicating impaired early diastolic relaxation and slow filling. There was some inter-ventricular mechanical dyssynchrony since the preejection periods measured in the LV and RV outflow tracts were 138 and 111 ms, respectively (panels H and I). There was also diastolic dysfunction in the right ventricle as shown by the abnormal early diastolic motion of the lateral tricuspid annulus (panel J). After renal transplantation and effective treatment of his hypertension, two years later, the IVRT was 93 ms and the Vp 36 cm/s; the E/e' ratio remained normal (and therefore still uninformative) while his E/A ratio was > 1 but shown by a Valsalva maneuver to be pseudonormal

4.3 | Heart failure with preserved ejection fraction

Both hypertension and diabetes mellitus or metabolic syndrome are strong risk factors for the development of HFpEF. Nonetheless, a majority of subjects with HFpEF and a raised LVEDp may have an E/e' index within the intermediate range where $8 < E/e' < 15$ and it is impossible to predict LVEDp accurately.⁶¹ A meta-analysis of 24 studies that compared E/e' and invasively derived LV filling pressure in subjects with HFpEF concluded that the correlation was poor, with a high E/e' index demonstrating good specificity (91%) but low sensitivity (37%).⁶²

Some patients with HFpEF have normal LV filling pressures at rest and raised PCWP only during exercise.³⁰ They can have normal NT-proBNP concentrations, and their E/e' values while on average higher than those found in control subjects demonstrate substantial

overlap and therefore have limited sensitivity.⁶³ Echocardiography during exercise improves the diagnostic sensitivity of E/e' but introduces a greater number of false positives; E/e' can remain within normal limits or in the indeterminate range despite a high PCWP.⁶³ This may be explained in part by the similar preload sensitivity of E and e' so that their ratio does not change.²⁹ This predictive unreliability makes it difficult to use E/e' as a marker of progression or response to treatment in patients with HFpEF.²⁰

4.4 | Myocardial ischemia and infarction

Myocardial ischemia or infarction that produces subendocardial or transmural contractile dysfunction or scar will have a major effect on regional longitudinal shortening and lengthening of the left ventricle.

Thus, after anterior myocardial infarction, e' was reduced at the septal or anterior mitral annulus ($P < .01$) but not at the lateral mitral annulus, while after inferior myocardial infarction, e' was reduced at the septum and inferior mitral annulus ($P < .001$) and also at the lateral annulus ($P < .01$).⁶⁴ Thus in a study of 41 patients with non-ST-segment elevation myocardial infarction (NSTEMI), the septal E/e' was a poor predictor of mean PCWP ($r = .35$, $P < .02$) while the lateral E/e' correlated moderately well ($r = .61$, $P < .0001$).⁶⁵ Another study of 120 NSTEMI patients demonstrated that an E/e' index > 14 had a sensitivity of 24% and overall accuracy of 59% for identifying an $LVedp > 15$ mmHg.⁶⁶

In 28 patients presenting with acute ST-segment elevation myocardial infarction, E/e' was unreliable for predicting raised filling pressures (with r ranging from .2 to .6 and nonsignificant, depending on the chosen annulus sampling point).⁶⁷ In subjects with stable angina, the highest correlation was in single vessel RCA disease with e' measured at the inferior mitral annulus ($r = .71$, $P < .001$).⁶⁸

4.5 | Impaired left ventricular global systolic function

It has been reported that an average $E/e' > 15$ has high sensitivity (89%) and specificity (91%) for a PCWP > 15 mmHg and that this relationship tends to be more certain in those with reduced systolic function,^{69,70} but some investigators have not confirmed this.

Cameli et al studied the concordance between E/e' and mean $LVedp$ in four groups each of 20 subjects, across a wide range of values of LV ejection fraction (EF). The correlations were highest in individuals with normal or only mildly impaired systolic function ($r = .72$ and $.73$, respectively), reduced in those with EF 30–44% ($r = .47$), and poor in those with EF $< 30\%$ ($r = .19$).⁷¹ In 110 patients with severely impaired LV systolic function and decompensated heart failure, no correlation was found between the E/e' ratio (which on average was 20) and PCWP ($r = 0.18$), particularly in those with larger LV volumes, more impaired cardiac indexes, and cardiac resynchronization therapy.⁷² There was also no association between changes in PCWP and changes in E/e' .

After cardiac transplantation in adults, E/e' and PCWP have been reported to be strongly related ($r = .8$) at rest and on exercise, but overlap of the confidence intervals limits the use of E/e' in this context in clinical practice.^{73,74} In children who had heart transplantation, there was no correlation between septal E/e' and PCWP ($r = .14$, $P = .28$) although a high septal E/e' was associated with high-grade cellular rejection.⁷⁵ In subjects with LV assist devices, there is a significant difference in E/e' between those with normal or elevated filling pressures but again considerable overlap between groups.⁷⁶

4.6 | Heart valve disease

In moderate to severe aortic stenosis, E/e' has been reported to have both high sensitivity (93%) and specificity (88%) for predicting raised

LV filling pressures.⁷⁷ In 65 young patients aged 14 to 23 years who had congenital heart disease and at least moderate aortic stenosis with or without aortic regurgitation, modest correlations were observed between E/e' and $LVedp$ ($r = .58$) or mean PCWP ($r = .63$); $E/e' > 9.5$ had a sensitivity of 84% and specificity of 76% to identify an $LVedp \geq 15$ mmHg.⁷⁸ These studies and others suggest that the E/e' index is useful in patients with aortic valve stenosis, but a recent study offers a cautionary note. Michaud et al found that 45% of their preoperative patients with coronary artery disease and/or aortic stenosis, who were graded using current consensus criteria to have low filling pressures, had prolonged retrograde pulmonary venous flow suggesting a high $LVedp$.⁷⁹

Figure 2 illustrates how the E/e' index cannot be used in a patient with acute pulmonary edema caused by torrential aortic regurgitation, despite extremely high LV diastolic pressures.

In patients with mitral stenosis, the E velocity is very high and thus the E/e' index also very high, but the ratio cannot be used to estimate mean PCWP (or even less, of course, the LV filling pressure); in one study, R was 0.34 (n.s.).⁸⁰ In patients with mitral annular calcification, E is increased and e' reduced⁸¹ so E/e' is unreliable if it is calculated using e' from the lateral annulus.⁸² In 50 patients with mitral annular calcification, E/e' demonstrated a weak correlation with mean LV filling pressure ($r = .42$; $P = .003$).⁸³

The E/e' index has been reported to correlate with $LVedp$ in patients with mitral regurgitation secondary to an ischemic or dilated cardiomyopathy ($n = 26$, $r = .61$, $P < .001$) but not in those with primary mitral regurgitation ($n = 11$, $r = .19$, n.s.).⁸⁴ In patients with secondary MR, a mitral E/e' ratio > 15 predicted an elevated $LVedp$ with a sensitivity of 80% and a specificity of 100%.

4.7 | Pericardial constriction

In severe constrictive pericarditis, the e' velocity is higher at the septal than the lateral mitral annulus, which is a reversal of the usual finding, but mean E/e' may be similar to healthy subjects.⁸⁵ The preservation or exaggeration of e' in constrictive pericarditis despite increased LV filling pressures, distinguishes it from restrictive cardiomyopathy.⁸⁶ Thus in 10 subjects with confirmed constrictive pericarditis, mean e' was positively correlated ($r = .69$, $P = .027$) while E/e' was inversely related to mean PCWP ($r = -.74$, $P = .014$).⁸⁷

4.8 | Right heart filling pressures

An E/e' index in the right heart, using the ratio of the early diastolic velocity of tricuspid inflow to the early diastolic velocity of lateral tricuspid annular excursion, has been used to estimate right heart diastolic function, but that is not supported by evidence. The tricuspid E/e' ratio had a sensitivity of only 23% to estimate mean right atrial pressure,⁸⁸ and this index was shown not to correlate with measured RV diastolic pressures in children with a heart transplant⁷⁵ or when there is pulmonary regurgitation.⁸⁹

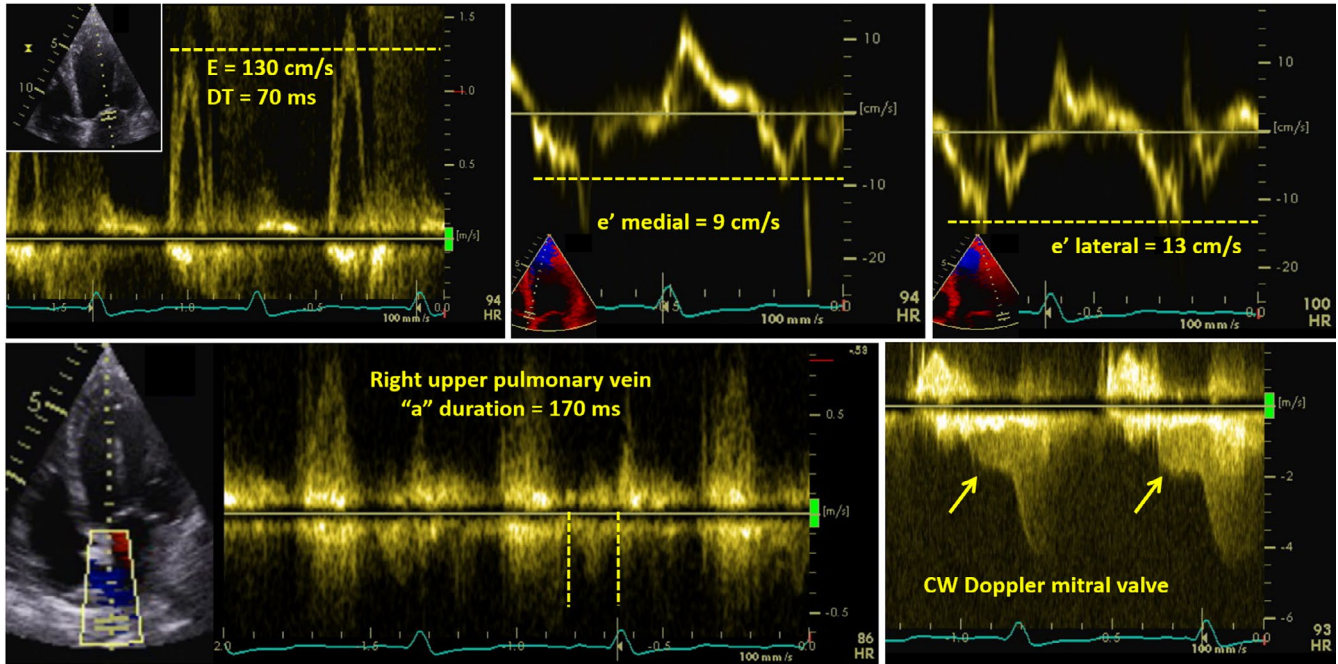
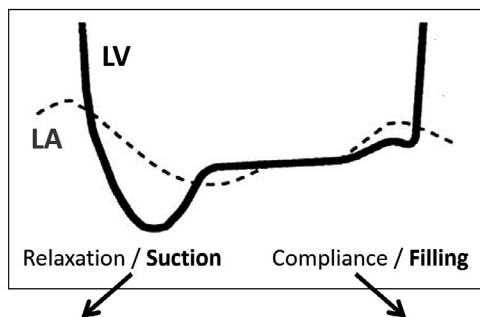


FIGURE 2 A patient in acute pulmonary edema with an E/e' index in the intermediate range. Doppler echocardiography in a 45-year-old man who presented in pulmonary edema after being pyrexial, breathless, and hypoxic for 3 days. He had torrential aortic regurgitation due to acute bacterial endocarditis. The left ventricle was volume-loaded and hyperdynamic. The E/e' ratio was 11.8 yet he had markedly elevated left ventricular diastolic pressures, as shown by an undetectable A-wave on mitral inflow although he was in sinus rhythm and by diastolic mitral regurgitation (arrows) with absent systolic forward flow from the pulmonary veins into the left atrium and greatly prolonged retrograde flow during atrial contraction



- Reduced $-dp/dt$ of mitral regurgitant velocity
- Reduced longitudinal early diastolic velocity (e)
- Reduced longitudinal early diastolic strain rate
- Slow mitral inflow propagation velocity (V_p)
- Prolonged isovolumic relaxation time (slow relaxation)
- Short isovolumic relaxation time (restrictive filling)
- Reduced mitral early diastolic velocity (E)
- Prolonged mitral E deceleration time
- Pronounced L wave
- Reduced untwisting rate
- Delayed peak untwisting
- Prolonged time interval between onsets of E and e
- Short deceleration time of mitral annular e' velocity
- Short deceleration time of pulmonary venous diastolic flow
- Short duration of mitral A wave
- Low amplitude mitral A wave (restrictive filling)
- Reduced longitudinal strain rate in left ventricle during atrial contraction
- Late diastolic (pre-systolic) mitral regurgitation
- Increased duration of pulmonary venous retrograde flow during atrial contraction
- Increased velocity of retrograde flow in pulmonary veins
- Increased left atrial strain rate during atrial contraction
- Increased diastolic myocardial stiffness by elastography

FIGURE 3 Echocardiographic indicators of specific aspects of diastolic function. Summary of alternative echocardiographic tests that can be used to estimate left ventricular suction and early diastolic filling, or left ventricular compliance/stiffness and end-diastolic filling and pressures. In particular circumstances in particular patients, all these methods may be more informative than the composite E/e' index. Some of the indices listed have been proposed recently, so their utility in routine clinical practice has not yet been confirmed

5 | CONCLUSIONS

Diastolic and systolic function are strongly inter-related, and many echocardiographic indices correlate with each other, so it is understandable that significant relationships have been found between the early diastolic E/e' ratio and LV mean or end-diastolic filling pressures. Nonetheless, the uncritical use of this index, without considering its individual components, can lead to diagnostic

imprecision or error. Many other echocardiographic measurements can be more informative about specific aspects of diastolic function during early or late filling; some are listed in Figure 3. The E/e' index is not synonymous with LV diastolic function, and more detailed and sophisticated measurements are needed in clinical trials and to guide treatment in individual patients. For example, reduction of heart rate will be helpful if there is abnormal relaxation but not when the main problem is poor compliance.⁶¹ There

are prospects that clinical decision tools can now be developed using unsupervised machine learning, in order to guide us which measurements to make and in which order to maximize impact on outcomes. Then, there could be new evidence-based diagnostic guidelines for diastolic function and it would not be unreasonable if they downgraded the role of the E/e' index.

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