CHEST

Evaluation of Left Ventricular Diastolic Function by the Intensivist

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VIDEO

The assessment of left ventricular diastolic function is an important element of advanced critical care echocardiography. Standard methods of evaluating diastolic function that are routinely performed on an elective basis in the cardiology echocardiography laboratory may be difficult to apply in the critical care unit. In this article, we review methods of measuring diastolic function with echocardiography that are of relevance to the intensivist and present two options for measurement: the standard cardiology method and a simplified approach.

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Competence in assessing left ventricular (LV) diastolic function is a required element of advanced critical care echocardiography (ACCE) as defined in the American College of Chest Physicians/Société de Reanimation de Langue Francaise Statement on Competence in Critical Care Ultrasonography[1] and in the International Statement on Training in ACCE.[2] It follows that intensivists with interest in developing competence in ACCE seeks to become skilled at the evaluation of diastolic function at a level similar to their cardiology colleague with emphasis on clinical applications that relate to critical care medicine.[3] This article will review the use of ACCE for evaluation of LV diastolic function and will serve as a companion article to the two-part series on the subject that was previously featured in *CHEST*.[4,5] Throughout this article, diastolic function will refer to left-sided cardiac diastolic function.

Relevance of LV Diastolic Function to the Critical Care Clinician

A regular challenge to the frontline intensivist is the patient on ventilatory support with bilateral opacities on chest radiography and diffuse bilateral B-lines on lung ultrasonography. Does the patient have lung disease because of an elevation in left atrial pressure (LAP), from primary lung injury (eg, ARDS), or both? Absent the ability to answer the question with a pulmonary artery catheter, echocardiography allows the intensivist to estimate LAP, which is a key component in the hemodynamic evaluation of the patient.

ABBREVIATIONS: 2D = two-dimensional; ACCE = advanced critical care echocardiography; AP4 = apical four; ASE = American Society of Echocardiography; CFD = color flow Doppler; CW = continuous wave; e′ = peak velocity of the mitral valve annulus; EACI = European Association of Cardiovascular Imaging; LA = left atrial; LAP = left atrial pressure; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MV = mitral valve; PW = pulsed wave; TDI = tissue Doppler imaging; TEE = transesophageal echocardiography; TR = tricuspid regurgitation; TTE = transthoracic echocardiography

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Although identification of an elevation in LAP in association with respiratory failure has major therapeutic implications, it has other uses as well. A new elevation of LAP during a spontaneous breathing trial indicates a load-related failure of the trial with the possibility of therapeutic intervention.[6,7] Elevation of LAP in any circumstance requires consideration of the mechanism for the elevation. Our opinion is that the estimation of LAP is a primary application of interest to the intensivist in evaluating diastolic function.

In addition to estimation of LAP, echocardiography allows the intensivist to identify normal diastolic function and to categorize the grade of diastolic dysfunction when it is present. Diastolic dysfunction in patients with sepsis occurs with a prevalence of 20% to 57%[8-11] and is associated with increased mortality.[9,10,12-15] Diastolic dysfunction has also been shown to be associated with mechanical ventilation liberation outcomes, and its presence is an independent risk factor for liberation failure.[16-18] The presence of diastolic dysfunction in the critically ill patient who is hemodynamically stable may not result in any immediate change in management; however, it cautions the intensivist of potential problems. For example, its presence may predict the risk of developing cardiogenic pulmonary edema with changes in cardiac loading conditions such as volume resuscitation, hypertension, tachycardia, or inadequate dialysis treatment. The patient with diastolic dysfunction may be at increased risk for hypotension related to hypovolemia and/or tachycardia.

Diastolic Function

Diastole is the interval of the cardiac cycle between the closure of the aortic valve and the closure of the mitral valve. This interval consists of four phases: isovolumic relaxation, early diastolic filling, diastasis, and late diastolic filling (Fig 1). There are numerous factors that influence diastolic function, including ventricular relaxation, ventricular compliance, ventricular recoil, ventricular suction effect, atrial compliance, atrial contractility, and mitral valve function. Added to these are the effects of pericardial pressure, intrathoracic pressure, right ventricular function through interventricular dependence, and LV systolic function with its derivatives. To further complicate matters,

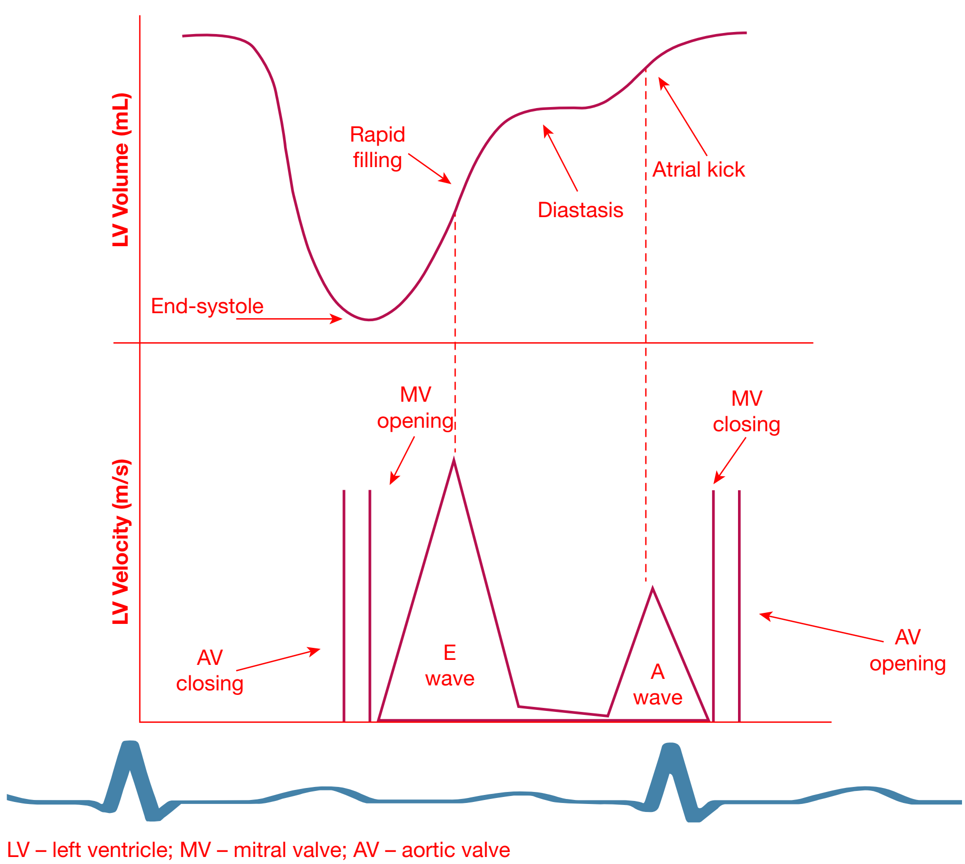

Figure 1 – *Diastolic filling curve. AV = atrioventricular; LV = left ventricular; MV, mitral valve.*

loading conditions that influence diastolic function change rapidly in critical illness. Echocardiography allows the physician to see and measure multiple indices of diastolic function noninvasively while maintaining good concordance with the gold standard of invasive hemodynamic monitoring.[19-21] We will limit the discussion to the elements of diastolic function that are addressed in the standard consultative cardiology echocardiography examination to estimate LAP and to grade diastolic function.

Cardiology Approach to Evaluating Diastolic Function

As a reflection of the enduring interest by cardiologists in assessing diastolic function, a search of PubMed using the key words “echocardiography” and “diastolic function” yields 22,310 citations. In view of the increasing complexity of the subject, in 2009, the American Society of Echocardiography (ASE) issued a guideline document titled “Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography.”[22] In addition to providing a comprehensive review of the subject, the document presented three figures that described an algorithmic approach to evaluating diastolic function. These allowed estimation of LAP (elevated or not elevated without specific numerical value) and classification of diastolic function as either normal diastolic function or into three separate grades of dysfunction (I, II, III). Although the 2009 ASE algorithms brought order to a complex field, intensivists have had difficulty using them in frontline practice in the ICU. The algorithm required measurement of a variety of parameters that could not be readily obtained in the critically ill patient. Patient-related factors (eg, obesity, edema, failure of ability to position the patient, surgical dressings) as well as time constraints characteristic of intensivist-performed ACCE regularly combined to yield indeterminate results when applying the ASE recommendations.[23]

In 2016, the ASE and the European Association of Cardiovascular Imaging (EACI) issued a guideline document titled “Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.”[24] This document is required reading for all intensivists who are interested in ACCE because it offers a comprehensive review of the field. It presents a revision of the algorithms for estimating LAP and for grading diastolic dysfunction. The two new algorithms are summarized in Figures 2A, 2B. The new ASE/EACI guidelines represent a welcome simplification from the previous standard. The question is whether the ACCE community can apply the new algorithms in frontline practice. Of note, the ASE/EACI algorithms are based upon expert consensus and have not been further validated.

Echocardiographic Assessment of Diastolic Function

Equipment

The echocardiographic assessment of diastolic function requires a machine capable of good quality two-dimensional (2D) ultrasonography with full Doppler capability: pulsed wave Doppler, continuous wave (CW) Doppler, tissue Doppler imaging (TDI), and color flow Doppler. Good-quality Doppler measurements may be obtained using a wide variety of small portable echocardiography machines common in critical care units. Large cardiology-type echocardiography machines are not required.

Doppler Measurements

Measurement of diastolic function requires knowledge of Doppler physics and signal acquisition. Because of space constraints, this article will not review Doppler physics in any detail. The reader is directed to standard texts on echocardiography for a full discussion of Doppler physics.[25,26] Table 1 summarizes important aspects of the different types of Doppler ultrasonography that are relevant to measurement of diastolic function.

A major difference between consultative cardiology echocardiography and ACCE is that that the intensivist is personally responsible for all aspects of image acquisition, image interpretation, and clinical applications at the point of care. Skill at acquisition of Doppler signals is a key component of competence for the intensivist.

Mitral Valve Inflow

Doppler ultrasonography allows the intensivist to visualize the phases of diastole. Following isovolumic relaxation, the mitral valve opens with rapid acceleration of blood flow from the left atrium (LA) to the left ventricle. This results in the E wave velocity curve. The peak velocity of the E wave is a required measurement for the assessment of diastolic function. After diastasis, which is the period of minimal flow after early diastolic filling, atrial contraction occurs, resulting in the late

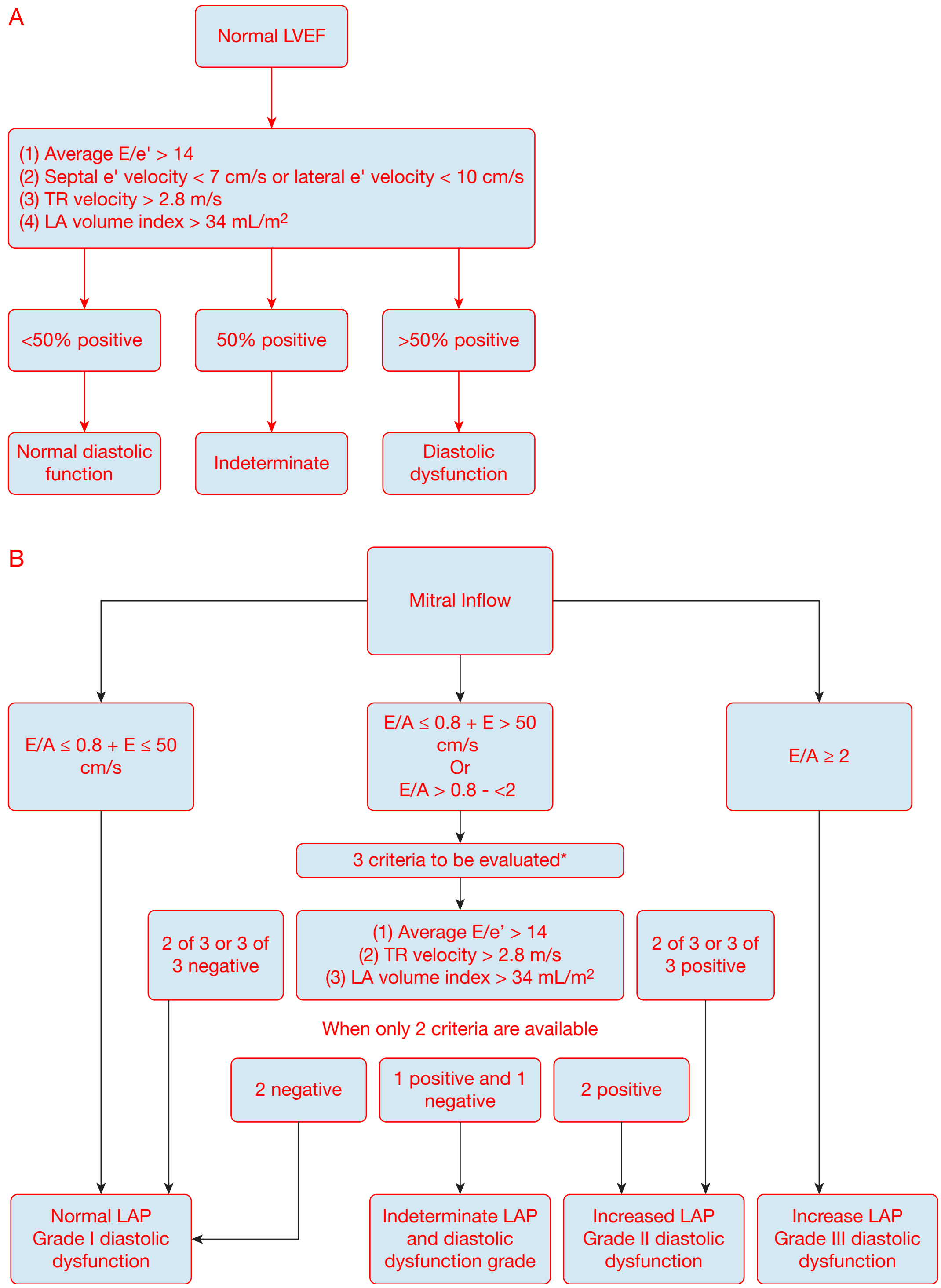

Figure 2 – *2016 American Society of Echocardiography/European Association of Cardiovascular Imaging algorithm for evaluation of LV diastolic function. A, In patients with normal LVEF. B, In patients with reduced LVEF. e′ = peak velocity of the mitral valve annulus; LA = left atrium; LAP = left atrial pressure; LVEF = left ventricular ejection fraction; TR = tricuspid regurgitation.*

diastolic A wave velocity curve. This is a required measurement for the assessment of diastolic function. The peak E wave velocity and peak A wave velocity are measured from the same image (Fig 3). This is accomplished by obtaining an apical 4 (AP4) chamber view of the heart and placing a pulsed wave Doppler echocardiography sample volume in the LV cavity between the tips of the mitral valve leaflets (Video 1).

TABLE 1] Types of Doppler

Doppler type	Typical applications	Advantages	Limitations
[redacted]	[redacted]	[redacted]	[redacted]
Pulsed wave	Measure of low velocities at a specific location (ie, LVOT VTI for SV measurement)	Range resolution	Unable to measure high blood flow velocities due to aliasing
[redacted]	[redacted]	[redacted]	[redacted]
Tissue Doppler imaging	Measurement of myocardial velocities	Ability to measure myocardial velocities	Small velocity range (low)

2D = two-dimensional; LVOT = left ventricular outflow tract; SV = stroke volume; VTI = velocity time integral.

With transthoracic echocardiography (TTE), the flow of blood into the LV cavity on the AP4 chamber view is toward the transducer, so the E and the A waves are positive deflections. With transesophageal echocardiography (TEE) using the mid-esophageal four-chamber view, the flow of blood is away from the transducer and the deflections are negative. Normal values for young healthy subjects for these measurements are presented in Table 2. The normative values for elderly patients are different, with the peak E wave velocity being somewhat lower. Patients with atrial fibrillation do not have a measurable A wave. Patients with tachycardia or prolonged atrial-ventricular nodal conduction may have fusion of the E wave and A wave, rendering measurement of the peak A wave velocity inaccurate.

The ASE/EACI algorithm for measurement of LV diastolic function algorithm requires, in some circumstances, measurement of the tricuspid regurgitation (TR) jet velocity when measurement of peak E and A wave velocity is not sufficient to categorize diastolic function. Peak TR velocity is measured from the right ventricular inflow view, the parasternal short-axis view at the level of the aortic and tricuspid valve, the AP4 chamber view (Fig 4), and/or the subcostal long axis view using CW Doppler. In recognition of the angle dependence with CW, the highest recorded velocity is

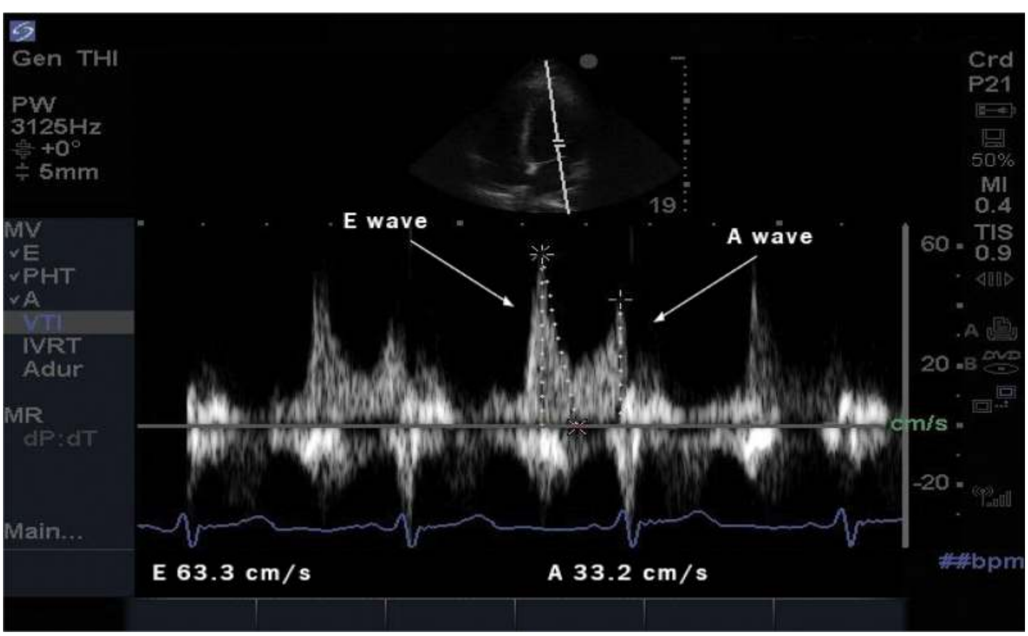

Figure 3 – *Pulsed wave Doppler analysis of early and late diastolic filling.*

TABLE 2] Normative Values for Young, Healthy Individuals[22,25]

Measurement	Normative range
[redacted]	[redacted]
Peak A wave velocity	0.19-0.35 m/s
[redacted]	[redacted]
Septal e′	10-15 cm/s
[redacted]	[redacted]
E/e′	< 8

e′ = peak velocity of the mitral valve annulus.

the relevant velocity. The TR jet may be eccentric in pattern, so a single velocity measurement is not sufficient. The color flow Doppler sample box is useful for placement of the CW interrogation line.

TDI

TDI allows for the analysis of myocardial velocities at specific locations throughout the cardiac cycle. For application of the ASE/EACI algorithm, the intensivist measures myocardial velocities along the longitudinal plane of mitral annular movement during diastole from the AP4 chamber view of the heart (or the mid-esophageal four-chamber view with TEE). When measured in this way, the myocardial velocity reflects changes in the length of the myocardial fibers along a longitudinal plane. TDI of the mitral annulus results in two velocity curves occurring in early and late diastole.

The ASE/EACI algorithm requires TDI measurement of the peak velocity of the mitral valve annulus (e′). The e′ TDI velocity reflects the rate of LV relaxation during diastole and is less load dependent than conventional Doppler parameters.[27,28] This peak velocity is measured by obtaining an AP4 chamber view of the heart with placement of the TDI sample volume on the mitral annulus (Fig 5, Video 2). The lateral or septal annulus can be used for this measurement; the normative values differ, with septal velocities being lower and more reproducible than lateral velocities (Table 2).[25] Care is taken to ensure that an AP4 chamber view is used because an apical five-chamber view will result in inaccurate measurements from the presence of the LV outflow tract. As opposed to the E and A wave velocities, the e′ velocity is directed away from the transducer during TTE and is represented by a negative deflection. If measuring the e′ velocity with TEE, it is represented by a positive deflection.

There are a variety of other measurements that can be made from mitral inflow, such as isovolumic relaxation time, E wave deceleration time, and duration of the A wave, which, when combined with Doppler-based analysis of pulmonary venous inflow, have been used to assess LV diastolic function. Although these measurements are not part of the new ASE/EACI algorithm, we recommend that the intensivist with interest in ACCE review their basis to have a comprehensive background in the field.

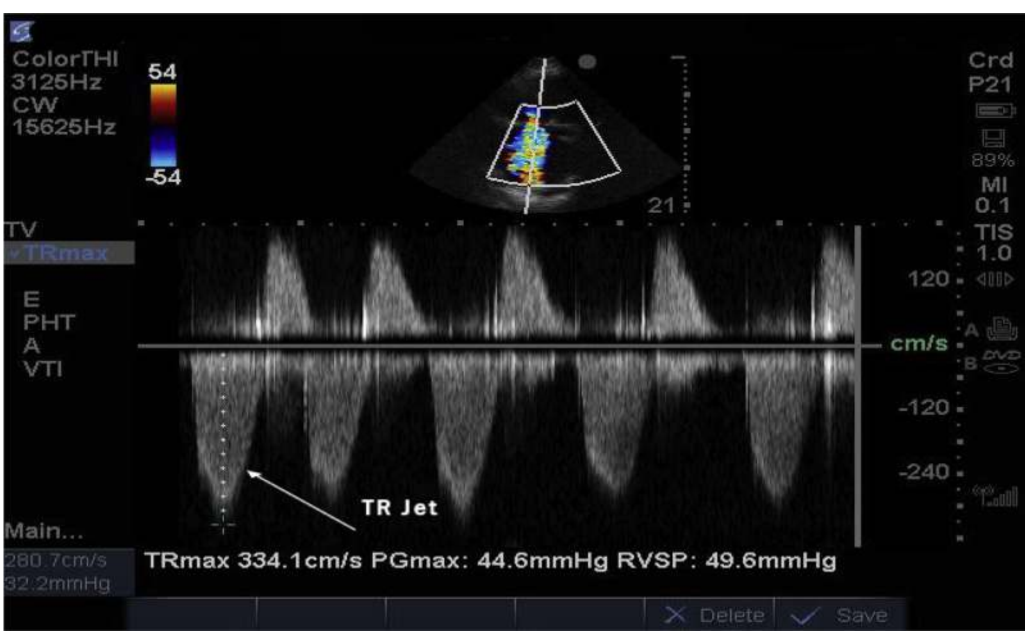

Figure 4 – *Continuous wave Doppler demonstrating tricuspid regurgitation.*

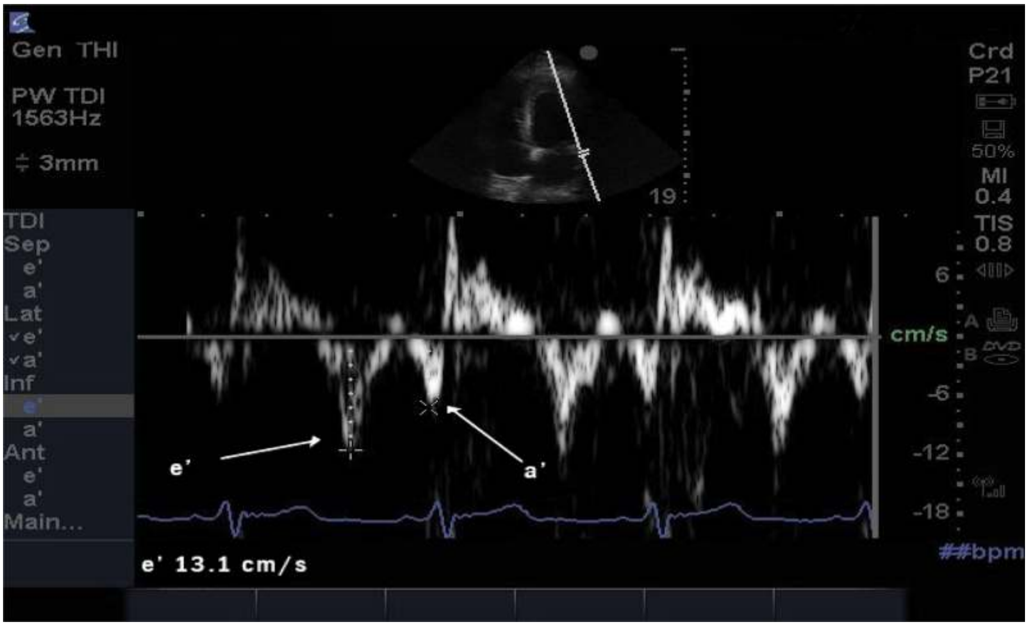

Figure 5 – *Tissue Doppler imaging of the lateral mitral valve annulus.*

Measurements Derived From 2D Echocardiography

Although Doppler measurements dominate assessment of LV diastolic function, 2D echocardiography findings are relevant. In the setting of normal LV systolic function and normal mitral valve function, an enlarged left atrium is a marker of diastolic dysfunction. This rule particularly applies when there is an increase in LV wall thickness (eg, hypertrophy, infiltrative myocardial disease). The intensivist performing bedside ACCE can assess the patient for LA enlargement qualitatively. This is best accomplished from the parasternal long axis view; LA enlargement is present if the transverse diameter of the left atrium is greater than the diameter of the proximal ascending aorta. A simple quantitative method of estimating LA size is the traditional M-mode technique, whereby the M-mode scan line is adjusted to pass through the aortic valve to measure the greatest systolic dimension of the left atrium. Although this has the advantage of simplicity, its disadvantage is that it uses a single linear measurement to represent a complex three-dimensional structure. In consultative cardiology echocardiography, LA volume is measured by using the disk summation method, whereby two orthogonal views of the LA in the AP4 chamber view and the apical two-chamber view are analyzed. The upper limit of normal for LA volume is 34 mL/m^2.[29] This measurement is time consuming and difficult to perform given the challenges of imaging the critically ill patient. The reader is referred to the 2015 ASE/EACI guidelines for more details.[29]

ASE/EACI Guidelines for Evaluation of Diastolic Function by Echocardiography

In 2016, the ASE/EACI revised their 2009 guidelines to simplify the assessment of diastolic function by echocardiography.[22,24] This algorithm is required reading for the intensivist with interest in ACCE. For patients with normal LV ejection fraction (LVEF), the guidelines recommend four measurements with cutoffs denoting an abnormal finding for identifying diastolic dysfunction: (1) e$'$ velocity (septal e$'$ $<$ 7 cm/s; lateral e$'$ $<$ 10 cm/s; (2) average E/e$'$ ratio $>$ 14 (lateral E/e; $>$ 13, septal E/e$'$ $>$ 15); (3) LA volume index $>$ 34 mL/m^2; and (4) peak tricuspid regurgitation velocity $<$ 2.8 m/s. In patients with normal LVEF, the guidelines define diastolic dysfunction if three or more measurements are abnormal (Fig 2A). Less than two abnormal measurements establish normal diastolic function, three or more abnormal measurements establish diastolic dysfunction, and two abnormal measurements indicate an indeterminate result. If diastolic dysfunction is present, the degree of diastolic dysfunction can then be determined by following an additional algorithm (Fig 2B). For patients with a depressed LVEF, the second algorithm is used with addition of the E/A ratio (Fig 2B). The 2016 ASE/EACI guidelines define normal LVEF $\geq$ 50%, indicating that an LVEF $< 50\%$ represents depressed systolic function.

In addition to classifying diastolic function, the algorithm can be used to determine the presence or absence of an elevated LAP (Fig 2B). A normal LAP is defined by $E/A \leq 0.8$ and $E \leq 50$ cm/s. If $E/A \geq 2$, then LAP is elevated. For patients whose mitral inflow measurements fall between these values, the average E/e', TR velocity, and LA can be measured. If two or more measurements are abnormal, the patient has increased LAP; if fewer than two measurements are abnormal, the LAP is indeterminate.

Limitations of the ASE Algorithm

For both the intensivist and cardiologist, certain conditions exclude the use of the algorithm. Mitral annular calcification and basal segmental wall motion abnormalities invalidate the measurement of mitral valve annular e'. Mitral stenosis and significant mitral regurgitation invalidate the measurement of mitral inflow velocities. Tachycardia and prolonged atrioventricular nodal conduction may lead to fusion of the E and A waves, resulting in inaccurate assessment of A wave velocities. Atrial fibrillation with variable RR intervals and absence of A waves makes it difficult to apply the algorithm. Alternative methods for evaluating diastolic dysfunction can be found in the ASE/EACI guideline document.[24] The assessment of LAP is limited to qualitative information (ie, high or low). The algorithm does not provide a quantitative assessment of LAP. Independent of the algorithm, the guidelines indicate that age is a consideration when assessing filling patterns because a normal filling pattern for an older patient may represent mild diastolic dysfunction for a younger patient.

From the intensivist's point of view, we have concerns about the practical application of the ASE/EACI algorithm. By definition, all aspects of the ACCE examination are performed and interpreted for immediate application at the bedside by the intensivist (unlike consultative cardiology in which the examination is typically performed by a qualified echocardiography technician). Given the challenge of time constraints, clinical pressure, and the high prevalence of patient-specific factors that degrade image acquisition, it is not practical for the intensivist to perform all parts of the ASE/EACI algorithm.

1. LA volume measurement: Accurate measurement of LA volume requires application of the Simpson method using two on-axis orthogonal views of the left atrium with clear endomyocardial visualization. Although this is practical in the consultative echocardiography laboratory, it is not so in the critically ill patient. Informally, we know of no ACCE expert who performs this measurement on a regular basis. We recommend that the intensivist performing ACCE not measure the LA volume on a routine basis. Instead, it is appropriate to use M-mode measurements, with an understanding of the technique's limitations.
2. Tricuspid regurgitation velocity: Although some degree of TR is commonly identified with color Doppler, in only a proportion of cases will a well-defined continuous wave spectral Doppler signal permit accurate measurement of peak systolic TR velocity. We agree that an attempt at the measurement is always indicated, but observe that it may not always be feasible.
3. The algorithm recommends using the average of the lateral and septal mitral valve annular e' velocity. This complicates the examination with unclear benefit. We recommend measuring either the lateral or septal e' velocity.
4. Valsalva maneuver: Although not included in the algorithm, the guidelines review the utility of the maneuver for assessment of LV diastolic function. Use of Valsalva maneuver is not relevant to critically ill patients given their inability to perform the maneuver.

A Simplified Approach

Lanspa et al[23] studied 167 patients with severe sepsis and septic shock and assessed a variety of echocardiographic parameters of diastolic function within the first 24 h of critical illness and their association with clinical outcomes. Using the 2009 ASE algorithm, the LV diastolic function of 35% of the patients could be categorized unambiguously. The remaining 65% could not be categorized, often from discordant results. LA volume index and deceleration time were not associated with clinical outcomes. Septal e' and E/e' allowed unambiguous categorization of 87% of the patients with correlation to clinical outcomes. Based upon statistical analysis of their data, the authors defined diastolic dysfunction by septal $e' < 8$ cm/s and proposed categorization into grade I ($E/e' \leq 8$), grade II ($8 < E/e' < 13$), and grade III ($E/e' \geq 13$). Although these findings need to be replicated and studied against an invasive gold standard with the updated ASE guidelines, there is a body of literature supporting the utility of e' and E/e' in the assessment of diastolic function. Gonzalez et al[11] defined diastolic dysfunction by an $e' < 10$ cm/s and demonstrated a trend toward increased mortality with reduced lateral e'. Mourad et al[14] defined diastolic dysfunction by an $e' \leq 8$ cm/s and demonstrated that this parameter was an independent risk factor associated with ICU mortality (OR, 7.7). Ritzema et al[30] compared echocardiographic parameters to an implanted LAP monitor in 15 patients and found that E/e' could reliably detect increased LAP. They found that an E/e' average $\geq$ 14, E/e' septal $\geq$ 15, or E/e' lateral $\geq$ 12 signified an LAP > 15 mm Hg with an area beneath the receiver-operator curve > 0.9. Sturgess et al[9] defined diastolic dysfunction using $e' < 9.6$ cm/s and $E/e' > 15$, finding that E/e' was an independent predictor of hospital survival in septic shock. In a study comparing echocardiography to invasive conductance catheter measurements, Kasner et al[21] reported that $E/e' > 8$ was the best echocardiographic parameter to detect diastolic dysfunction. None of these studies considered that LA volume index was a useful parameter for the assessment of LV diastolic function.

With this body of evidence, it is reasonable for the intensivist to define the presence of diastolic dysfunction on the basis of an e' and/or an E/e' value. Precisely which cutoff value to use is difficult to determine because of the sample size and heterogeneity of current studies.

It is inevitable that a proportion of ACCE assessments of diastolic function will be indeterminate. In these circumstances, the intensivist incorporates lung ultrasonography into the assessment of cardiac function. The presence of a normal aeration pattern on lung ultrasonography (lung sliding with A-lines) indicates that the pulmonary artery occlusion pressure is < 18 mm Hg.[31] In the setting of an indeterminate diastolic assessment by ACCE, this would effectively eliminate a significant elevation of LAP.

Summary

Competence in ACCE allows the intensivist to estimate LAP and to evaluate diastolic function. There are two approaches to estimation of LAP using Doppler based measurements:

1. The intensivist may apply the ASE/EACI algorithms with the understanding that the calculation of LA volume is not practical and that the TR regurgitation jet velocity may be difficult to measure in some patients. Because of these constraints, the estimation of LAP will be indeterminate in some patients using the ASE/EACI algorithm.
2. The intensivist may use a simplified approach in which the E/e' ratio is used to estimate LAP, with values > 14 indicating an increasing probability of an elevated LAP.

There are two approaches to the identification and grading of diastolic function:

1. The intensivist may apply the ASE/EACI algorithm with the understanding that the calculation of LA volume is not practical and that the TR regurgitation jet velocity may be difficult to measure in some patients. Because of these constraints, identification and grading of diastolic function will be indeterminate in some patients using the ASE/EACI algorithm.
2. The intensivist may use a simplified approach in which the e' and E/e' is used to determine whether the patient has diastolic dysfunction. Based upon current literature, it is reasonable to conclude that the patient with $e' < 8$ cm/s and/or $E/e' > 14$ has diastolic dysfunction. It is not clear that there is a need to grade diastolic dysfunction because the grade may have limited clinical utility in the critical care arena. This simplified approach designates diastolic function in a binary manner: either the patient has it or the patient does not have it.

e-Appendix 1 provides four case examples for the assessment of diastolic function and compares the ASE/EACI algorithm results to the simplified approach.

Some qualifications apply to these measurements:

1. The ASE/EACI Statement is based upon expert opinion, so the cutoff values used in the ASE/EACI algorithm are reasonable but arbitrary.
2. The simplified approach is derived from several relevant studies in the critical care literature, so the cutoff values are reasonable but arbitrary.
3. Doppler-based assessment of diastolic function has not been well validated against invasive measurements of diastolic function in critically ill patients.
4. The relevance of Doppler measurements of diastolic function to therapeutic intervention and patient outcome are not well validated.
5. The intensivist is mindful of the specific limitations to measurement of annular velocities and mitral inflow velocities that are used both in the ASE/EACI algorithms and the simplified approach *vide supra*.
6. Numerical cutoff values may not be the best approach to estimating LAP. A "gray zone" approach, similar to that proposed by Cannesson et al[32] may be more

appropriate. In this model, the E/e′ ratio occurs along a continuum of probability. Rather than assigning a single arbitrary value to define the presence of an elevated LAP, a given E/e′ would be associated with a probability that the LAP is elevated.

7. Lung ultrasonography is a useful adjunct to Doppler measurements for evaluation of whether respiratory failure is related to cardiogenic pulmonary edema or primary lung injury.[33]

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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