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Estimating Left Ventricular Filling Pressure by Echocardiography

Oyvind S. Andersen, MD,[a] Otto A. Smiseth, MD, PhD,[a] Hisham Dokainish, MD,[b] Muaz M. Abudiab, MD,[c] Robert C. Schutt, MD,[d] Arnav Kumar, MBBS,[e] Kimi Sato, MD,[e] Serge Harb, MD,[e] Einar Gude, MD, PhD,[a] Espen W. Remme, MSc, PhD,[a] Arne K. Andreassen, MD, PhD,[a] Jong-Won Ha, MD,[f] Jiaqiong Xu, PhD,[c] Allan L. Klein, MD,[e] Sherif F. Nagueh, MD[c]

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CME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) identify patients with elevated left ventricular filling pressure based on clinical and echocardiographic data; 2) select the grade of diastolic dysfunction based on echocardiographic findings; and 3) compare the accuracy of echocardiography for the estimation of LV filling pressure with that of clinical assessment.

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From the [a]Oslo University Hospital, Rikshospitalet, Center for Cardiological Innovation and University of Oslo, Oslo, Norway; [b]McMaster University, Hamilton, Ontario, Canada; [c]Methodist DeBakey Heart and Vascular Center, Houston, Texas; [d]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [e]Cleveland Clinic, Cleveland, Ohio; and the [f]Cardiology Division, Yonsei University College of Medicine, Seoul, Korea. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABSTRACT

BACKGROUND The diagnosis of heart failure may be challenging because symptoms are rather nonspecific. Elevated left ventricular (LV) filling pressure may be used to confirm the diagnosis, but cardiac catheterization is often not practical. Echocardiographic indexes are therefore used as markers of filling pressure.

OBJECTIVES This study investigated the feasibility and accuracy of comprehensive echocardiography in identifying patients with elevated LV filling pressure.

METHODS We conducted a multicenter study of 450 patients with a wide spectrum of cardiac diseases referred for cardiac catheterization. Left atrial volume index, in combination with flow velocities and tissue Doppler velocities, was used to estimate LV filling pressure. Invasively measured pressure was used as the gold standard.

RESULTS Mean left ventricular ejection fraction (LVEF) was 47%, with 209 patients having an LVEF $<$50%. Invasive measurements showed elevated LV filling pressure in 58% of patients. Clinical assessment had an accuracy of 72% in identifying patients with elevated filling pressure, whereas echocardiography had an accuracy of 87% ($p < 0.001$ vs. clinical assessment). The combination of clinical and echocardiographic assessment was incremental, with a net reclassification improvement of 1.5 versus clinical assessment ($p < 0.001$).

CONCLUSIONS Echocardiographic assessment of LV filling pressure is feasible and accurate. When combined with clinical data, it leads to a more accurate diagnosis, regardless of LVEF. (J Am Coll Cardiol 2017;69:1937–48)

Heart failure (HF) is a major public health problem that accounts for >1 million hospitalization discharges annually in the United States (1) and nearly as many emergency room visits (2). For patients presenting with dyspnea, the clinical diagnosis can be challenging because HF symptoms are relatively nonspecific and may be due to noncardiac disease. In that regard, cardiac imaging can be helpful for reaching the correct diagnosis and subsequently guiding patient management. Echocardiography is usually the first imaging test to obtain, as it provides immediate information on left ventricular (LV) size and function, including ejection fraction (EF) and valvular function (3). However, the presence of normal EF does not exclude a cardiac etiology for dyspnea, as approximately 50% of patients with HF have only mildly reduced EF or preserved EF (heart failure with preserved ejection fraction [HFpEF]) (4). A diagnostic hallmark of HF is elevated LV filling pressure, a compensatory response to maintain cardiac output that is observed regardless of LVEF.

Information about filling pressure is important not only to diagnose HF, but also to better appreciate its severity and, subsequently, the response to treatment. Although cardiac catheterization remains the gold standard, it is not practical to submit many patients presenting with dyspnea and suspicion of HF to invasive studies. Accordingly, there is a continuing search for noninvasive markers of elevated LV filling pressure. In that regard, there are recent guidelines on how to apply echocardiography to estimate LV filling pressures that are based on expert consensus but have not been validated against invasively measured filling pressure (5). This multicenter study sought to evaluate the feasibility and accuracy of echocardiographic parameters recommended in recent clinical practice guidelines in identifying the presence of elevated LV filling pressure and to determine the incremental value of combined echocardiographic and clinical assessment for estimating LV filling pressure.

METHODS

The multicenter study sites included Methodist DeBakey Heart and Vascular Center (Houston, Texas), McMaster University (Hamilton, Ontario, Canada), Oslo University Hospital (Oslo, Norway), Yonsei University Severance Hospital (Seoul, South Korea), and the Cleveland Clinic (Cleveland, Ohio). Echocardiography was performed in 450 patients referred for right- and/or left-sided heart catheterization (180 patients from previous studies [6–8] and 270 patients included prospectively), either during or immediately post-procedure and without intervening clinical change or administration of medications. Catheterization was obtained to help guide diagnosis and patient management. All patients age >18 years were included if willing and able to give informed consent. Patients with prior cardiac transplantation or complex congenital heart disease that limited the application of standard 2-dimensional (2D) echocardiography Doppler methodology were excluded.

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Clinical data were evaluated by an experienced cardiologist. The evaluation, based on chart review, determined whether patients were in HF or not given their symptoms (exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea); physical examination findings (S3, pulmonary rales, increased jugular venous pressure, hepatomegaly, hepatojugular reflux, and pedal edema or anasarca); additional tests (such as electrocardiography for rhythm analysis and evidence of LV hypertrophy, acute coronary syndrome, or old myocardial infarction; or chest x-ray to look for cardiomegaly, pulmonary congestion, pulmonary edema, or pulmonary infiltrates); laboratory tests for abnormally elevated biomarkers; plus past and present medical history, blinded to invasive measurements of LV filling pressure and echocardiographic estimation of LV filling pressure. We investigated whether the available clinical information could be used to determine whether LV filling pressure was elevated. Echocardiographic data (2D and Doppler) were applied to estimate LV filling pressure as recommended in recent guidelines (5).

ECHOCARDIOGRAPHIC IMAGING AND ANALYSIS. Patients were imaged with ultrasound systems equipped with multifrequency transducers. A complete echocardiographic study was performed using standard views, with care taken to avoid foreshortening. From the apical window, pulsed wave Doppler was used to record mitral inflow for 3 to 5 cardiac cycles at the level of the mitral valve annulus and at the mitral tips. Pulmonary venous flow was recorded from 1 of the pulmonary veins, guided by color Doppler. Tissue Doppler was applied to record mitral annular velocities at the septal and lateral sides of the annulus. The resulting annular velocities by pulsed wave Doppler were recorded for 3 to 5 cardiac cycles at a sweep speed of 100 mm/s. Tricuspid regurgitation signals were recorded by continuous wave Doppler from multiple windows. Saline contrast was used in 11 patients, and echocardiographic contrast was injected intravenously in another 11 patients. It was feasible to record inferior vena caval diameter (IVC) and its collapse and hepatic venous flow from the subcostal view in 314 patients. The **Central Illustration** shows a schematic illustration of the parameters used to estimate LV filling pressure (5).

Measurements were performed on computerized off-line analysis stations without knowledge of invasively derived hemodynamic data. LV volumes, EF, and left atrial (LA) maximal volume were measured as recently recommended (9). Right ventricular function and valvular regurgitation were evaluated following American Society of Echocardiography (ASE) recommendations (10,11). Mitral inflow from tips level was analyzed for peak early diastolic velocity (E) as well as late diastolic velocity (A), E/A ratio, and deceleration time. Pulmonary venous flow was analyzed for the peak velocity of systolic, diastolic, and atrial reversal signals. The ratio between pulmonary vein peak systolic and diastolic velocity and the difference in duration between pulmonary vein atrial reversal velocity and mitral A velocity were obtained (5). Mitral annulus early diastolic velocity (e′) and late diastolic velocity were measured at septal and lateral mitral annulus and E/e′ ratios were computed. Interobserver error (mean $\pm$ SD) for mitral E velocity was 4 $\pm$ 3%, and for annulus e′ velocity was 5 $\pm$ 2%. Intraobserver error (mean $\pm$ SD) for mitral E velocity was 3 $\pm$ 2% and for annulus e′ velocity was 3 $\pm$ 2% (analysis reproducibility). Measurements were averaged over 3 cardiac cycles when patients had sinus rhythm, and over 5 cycles for patients in atrial fibrillation (AF).

CARDIAC CATHETERIZATION. Mean right atrial pressure, pulmonary artery pressures (systolic, diastolic, and mean), and pulmonary capillary wedge pressure (PCWP) were measured with a pulmonary artery catheter during right heart catheterization in

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

A = mitral inflow peak late diastolic velocity

AUC = area under the receiver-operating characteristic curve

E = mitral inflow peak early diastolic velocity

e′ = mitral annulus early diastolic velocity

EF = ejection fraction

HFpEF = heart failure with preserved ejection fraction

IDI = integrated discrimination improvement

LV = left ventricular

PCWP = pulmonary capillary wedge pressure

pre-A = pre-atrial contraction

CENTRAL ILLUSTRATION **Noninvasive Assessment of LV Filling Pressure**

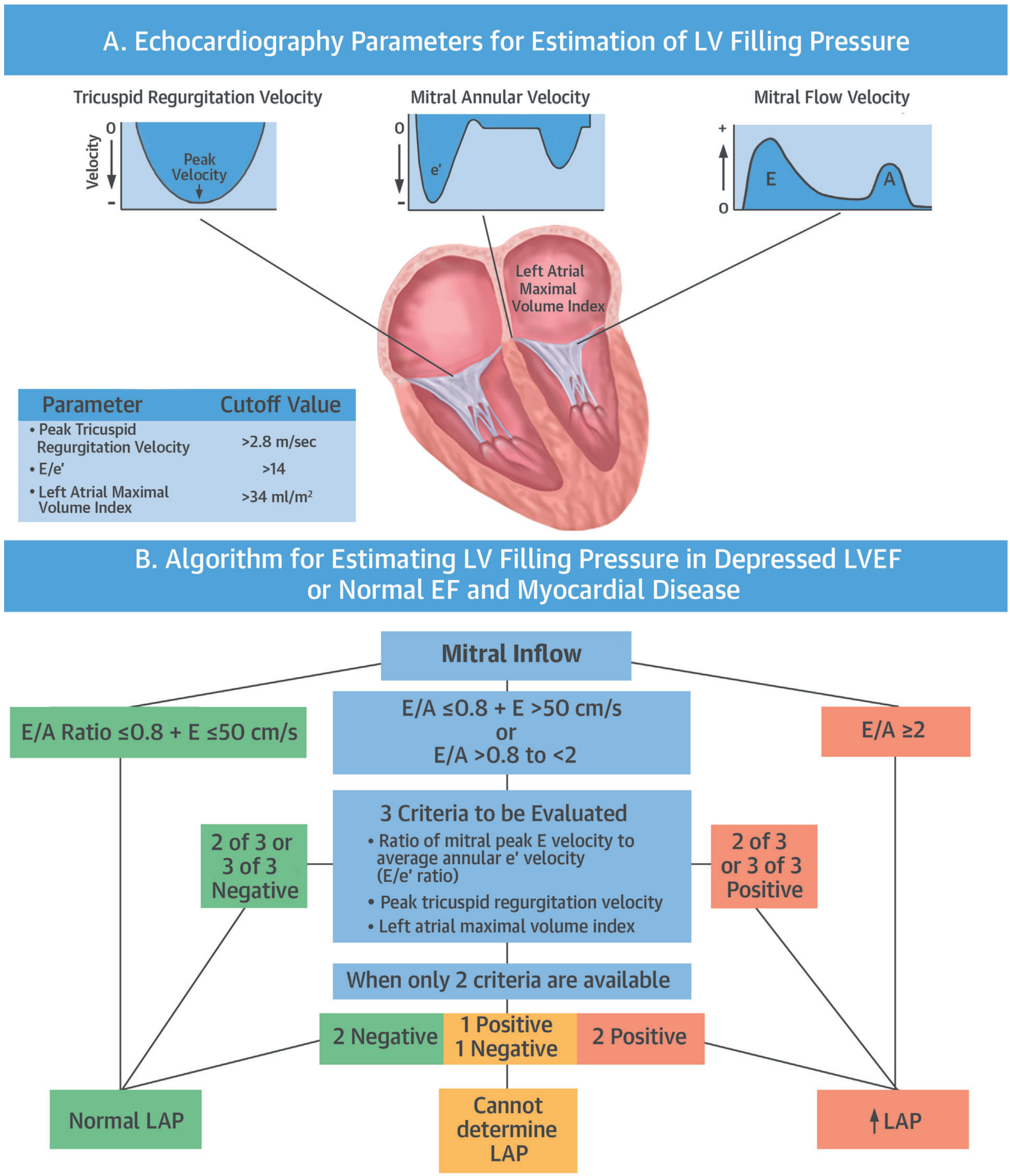

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TABLE 1 Clinical, Echocardiographic, and Hemodynamic Characteristics

Age, yrs	59.00 ± 11.65
Male, %	61
Body surface area, m^2	1.95 ± 0.25
Diabetes mellitus	47 (10.4)
Chronic kidney disease	46 (10.2)
Hypertension*	139 (31.0)
Coronary artery disease†	117 (26.0)
LV end-diastolic volume, ml	154 ± 90
LVEF, %	47 ± 21
LAV index, ml/m^2 (n = 445)	45 ± 27
E/A (n = 387)	1.6 ± 1.1
E/e′ (n = 437)	13.9 ± 7.5
Heart rate, beats/min	75 ± 15
Stroke volume, ml	61 ± 24
Cardiac output, l/min	4.5 ± 1.8
Cardiac index, l/min/m^2	2.3 ± 0.9
Systolic blood pressure, mm Hg	126 ± 24
Diastolic blood pressure, mm Hg	73 ± 14
Pulmonary artery systolic pressure, mm Hg	47 ± 19
Pulmonary artery diastolic pressure, mm Hg	20 ± 9
Pulmonary capillary wedge pressure, mm Hg	17 ± 9
LV end-diastolic pressure, mm Hg	21 ± 9
Mean right atrial pressure, mm Hg	10 ± 7

Values are mean ± SD, %, or n (%). *On medications and/or having hypertension at time of study. †Indicated by wall motion abnormalities and coronary angiography results.

E/A = mitral early diastolic velocity/atrial diastolic velocity ratio; E/e′ = mitral early diastolic velocity/average early diastolic e′ velocity ratio; LAV = left atrial volume; LV = left ventricular; LVEF = left ventricular ejection fraction.

TABLE 2 Correlation of 2D and Doppler Measurements With LV Filling Pressure

	r	p Value
Left atrial maximal volume index	0.23	<0.0001
Mitral E velocity	0.44	<0.0001
Mitral A velocity	−0.28	<0.0001
Mitral E/A ratio	0.53	<0.0001
Deceleration time of mitral E velocity	−0.42	<0.0001
Isovolumic relaxation time	−0.44	<0.0001
Pulmonary veins: systolic velocity/diastolic velocity ratio	−0.57	<0.0001
Pulmonary veins: atrial reversal duration-mitral A duration	0.39	<0.0001
Septal E/e′ ratio	0.46	<0.0001
Lateral E/e′ ratio	0.5	<0.0001
Average E/e′ ratio	0.52	<0.0001
Doppler pulmonary artery systolic pressure	0.58	<0.0001

2D = 2-dimensional; other abbreviations as in Table 1.

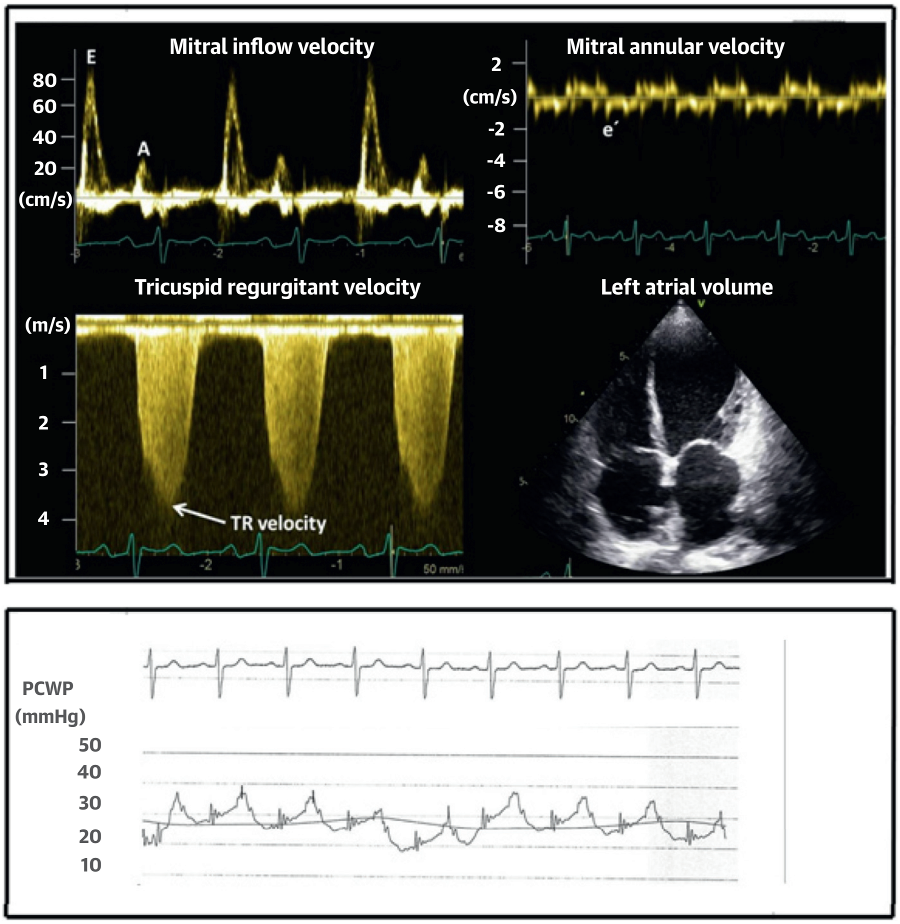
293 patients. The wedge position was verified by fluoroscopy, changes in the waveform, and when needed, changes in pulmonary vein oxygen saturation (O_2 saturation >95%). Invasive measurements were acquired without knowledge of echo data. All of them were derived at end expiration at an average of 5 cycles. Fluid-filled transducers were balanced before the study with the 0 level at the midaxillary line. Cardiac output (average of 3 cycles with <10% variation in patients in sinus rhythm and 5 cardiac cycles in patients with AF) was derived by thermodilution only or both thermodilution and the Fick method using nomograms for oxygen uptake in conjunction with the Fick method. When a discrepancy was present between both methods, cardiac output by thermodilution was used. In 157 patients, left heart catheterization only was performed and LV diastolic pressures were obtained. In these 157 patients, LV pre-atrial contraction (pre-A) pressure was measured and used as an estimate of PCWP, as PCWP and LV pre-A are known to correlate well (12). All patients in AF (except for 2 cases) underwent right heart catheterization, and PCWP measurements were used for analysis, whereas mid-LV diastolic pressure was used in the 2 patients who underwent left heart catheterization only. PCWP or LV pre-A pressure >12 mm Hg was considered abnormally elevated (13).

STATISTICAL ANALYSIS. Baseline characteristics are presented as mean ± SD for continuous variables or numbers (percentage) for categorical variables. Accuracy and 95% confidence interval of comprehensive echocardiography in detecting elevated PCWP and clinical assessment versus echocardiography Doppler

CENTRAL ILLUSTRATION Continued

Elevated left ventricular (LV) filling pressure may be used to confirm a diagnosis of heart failure. We sought to determine if echocardiographic indexes could be used instead of cardiac catheterization for such a confirmation. **(A)** Of the echocardiographic parameters used, tricuspid regurgitation velocity is related to peak systolic pulmonary artery pressure, the early diastolic mitral annulus velocity (e′) and the early (E) and atrial induced (A) mitral inflow velocities are related to LV diastolic pressures, and left atrial volume index is related to left atrial pressure (LAP). **(B)** In the algorithm to estimate LV filling pressure, we incorporated recommendations from recent guidelines (5), setting criteria of elevated LV filling pressures as either E/A ratio ≥2 in the presence of myocardial disease, or if E/A is <2, at least 2 of the 3 parameters shown must be above cutoff values **(table in A)**. The algorithm was applied in patients with depressed left ventricular ejection fraction (LVEF) or normal LVEF but with myocardial disease. Echocardiography had an accuracy of 87% versus 72% for clinical assessment (p < 0.001), and the combination of clinical and echocardiographic assessment demonstrated a net reclassification improvement of 1.5 versus clinical assessment (p < 0.001). E/A = mitral early diastolic velocity/atrial diastolic velocity ratio; E/e′ = mitral early diastolic velocity/average early diastolic e′ velocity ratio.

FIGURE 1 Assessment: Patient With Depressed LVEF



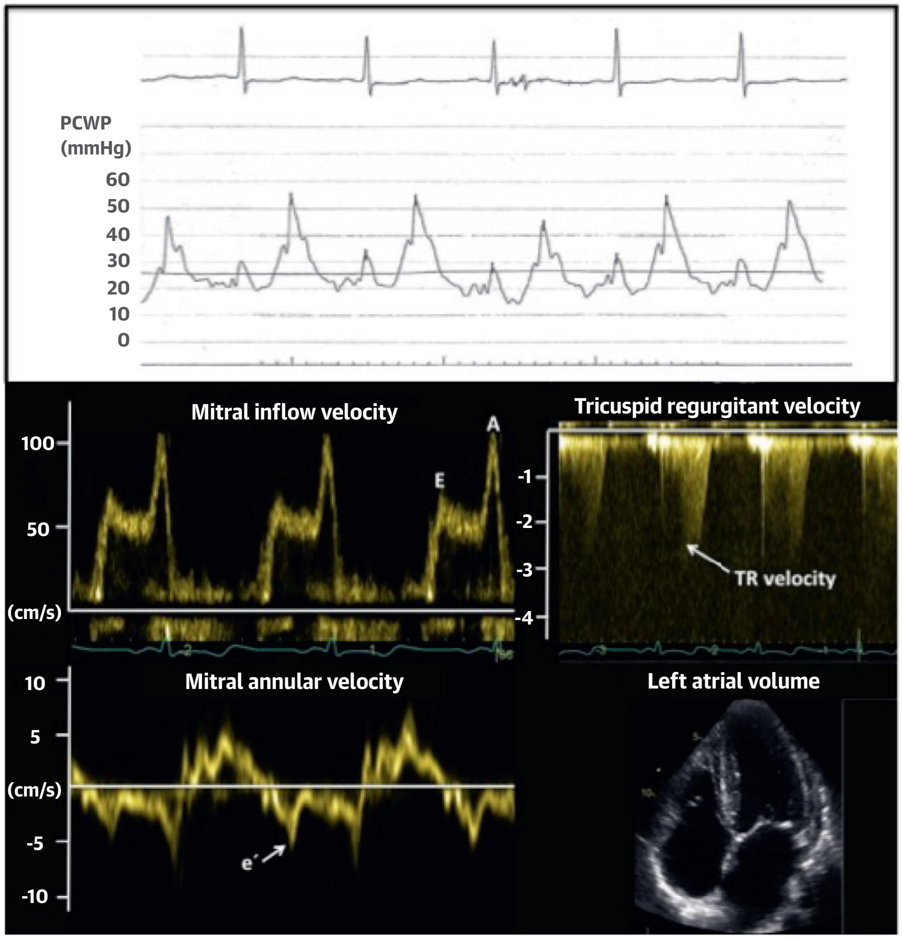
(Upper panel) Obtained during right heart catheterization, echocardiographic images demonstrated elevated left ventricular (LV) filling pressure: mitral inflow velocities showed a restrictive filling pattern; average E/e′ ratio was 21; peak tricuspid regurgitation (TR) velocity was 3.7 m/s; and left atrial (LA) maximal volume index was 61 ml/m^2. **(Lower panel)** Pressure recordings obtained during right heart catheterization showed pulmonary capillary wedge pressure (PCWP) was 27 mm Hg. E/e′ = mitral early diastolic velocity/average early diastolic e′ velocity ratio; LVEF = left ventricular ejection fraction.

were calculated, and the McNemar test was used to compare the accuracy. Area under the receiver-operating characteristic curve (AUC) was calculated from logistic regression analysis and compared using the DeLong method. Regression analysis was used to relate Doppler variables to LV filling pressure. Analysis of variance on ranks was used to compare LV filling pressure among the 3 grades of diastolic dysfunction, and Dunn's method was used for pairwise comparisons. Global chi-square analysis determined the incremental value of the combination of clinical assessment and echocardiography over either alone in identifying patients with elevated LV filling pressure. The increased discriminative value of the combination of clinical assessment and echocardiography was examined with net reclassification improvement and integrated discrimination improvement (IDI) methods. All analyses were performed with STATA version 14 (StataCorp, College Station, Texas). Statistical significance was defined as a 2-tailed $p < 0.05$ for all tests.

RESULTS

PATIENT POPULATION. Table 1 presents a summary of the clinical, echocardiographic, and hemodynamic data of the study population. Mean LVEF was 47%, with normal right ventricular function in 68% of patients. LVEF was <50% in 209 of 450 patients (46.4%). Elevated LV filling pressure was seen in 58%

FIGURE 2 Assessment: Patient With Normal LVEF



(Upper panel) Mean PCWP was 25 mm Hg. The prominent "a" and "v" waves are elevated above the mean pressure. **(Lower panel)** The enlarged LA had a maximal volume index of 51 ml/m^2. Mitral annulus e′ velocity (average of the 3 beats) is reduced at 5 cm/s, and E/e′ ratio is 15. Although the TR jet was incomplete, the other parameters—mitral annulus e′ velocity was 5 cm/s and E/e′ ratio was 15—and the presence of 2 of 3 variables meeting cutoff values was consistent with elevated LV filling pressure. Abbreviations as in Figure 1.

of patients, mean PCWP was 17 ± 9 mm Hg, and mean LV pre-A pressure in the patients who underwent left heart catheterization was 15 ± 8 mm Hg. Elevated LV filling pressure, as verified by invasive pressure measurements, was present in 60% of patients with EFs <50% and in 57% of patients with EFs ≥50%. Moderately severe or severe mitral regurgitation (MR) was present in 19 patients (elevated LV filling pressure in 14 but normal in 5 patients), aortic stenosis of at least moderate severity in 8 patients, pulmonary parenchymal or vascular disease (type I pulmonary arterial hypertension) in 71 patients, and end-stage liver disease in 5 patients. The majority were in sinus rhythm, with 41 patients having left bundle branch block (LBBB) or paced rhythm and 18 patients with AF.

PERFORMANCE OF INDIVIDUAL DOPPLER AND 2D PARAMETERS. When all patients were considered, significant correlations were observed between 2D and Doppler signals and LV filling pressure (Table 2). Figures 1 and 2 show examples of echocardiography Doppler and pressure recordings. For average E/e′ ratio, the correlation coefficient ($r = 0.65$; $p < 0.0001$) (Figure 3) was higher in patients who were not in LBBB or on ventricular pacing and who did not have significant MR ($r = 0.48$; $p < 0.01$). The relation of LA maximal volume index with LV filling pressure was unchanged when patients in AF were excluded.

Using the cutoff values recommended in the recent guidelines (5), the distribution of mitral E/A ratio, E/e′ ratio, LA maximal volume index, and peak tricuspid

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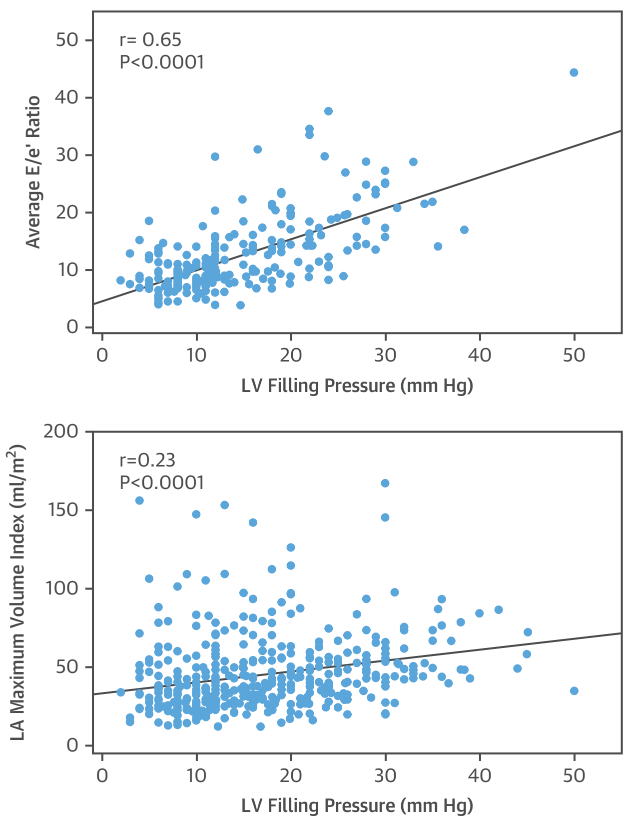
FIGURE 3 Regression Plot: LV Filling Pressure



Regression plots demonstrated the relation between LV filling pressure and either **(upper panel)** average E/e′ ratio (patients with normal LV ejection fraction [EF] and depressed LVEF are included in the plot but patients in left bundle branch block, paced rhythm, and significant mitral regurgitation were excluded) or **(lower panel)** LA maximal volume index. Abbreviations as in Figure 1.

regurgitation velocity identified patients with elevated LV filling pressure (Table 3) excluding patients with moderately severe or severe MR, paced rhythm, and AF (which have different algorithms) and the 31 patients where the method was inconclusive.

To investigate the accuracy of the algorithm in patients with markedly reduced systolic function, an additional analysis was carried out in the 159 patients with EF ≤35%. In this subgroup, LV filling pressure could not be assessed by echocardiography in 11 patients (indeterminate per the algorithm). In 129 patients with low EF and elevated LV filling pressure by cardiac catheterization, the algorithm correctly identified elevated filling pressure in 117 (91%); in 12, however, filling pressure was incorrectly classified as normal. Prediction was correct in 18 of the 19 (95%) patients with normal LV filling pressure; the incorrect prediction in 1 patient was elevated. When testing average E/e′ ratio as a single predictor of LV filling pressure, in these patients with low EF, prediction was correct in 18 of 24 (75%) with normal filling pressure during cardiac catheterization. Of the 135 patients with elevated LV filling pressure, prediction by E/e′ was correct in 111 (82%).

LV filling pressure was significantly different between the 3 grades of diastolic dysfunction (analysis of variance on ranks: $p < 0.001$). It increased from 10 mm Hg in grade I (interquartile range [IQR]: 7 to 12 mm Hg) to 18 mm Hg in grade II (IQR: 14 to 24 mm Hg) and 24 mm Hg in grade III (IQR: 19 to 30 mm Hg) (grade I vs. grade II: $p < 0.001$; grade I vs. grade III: $p < 0.001$; grade II vs. grade III: $p = 0.006$ by Dunn method).

ECHOCARDIOGRAPHIC ASSESSMENT OF FILLING PRESSURES VERSUS CLINICAL EVALUATION. Clinical assessment of LV filling pressure was feasible in 448 of 450 (99.6%) patients; clinical status could not be reliably assessed in 2 patients. The echocardiographic approach was feasible in 419 (93.1%) and inconclusive in 31 due to inability to acquire the complete set of signals needed for estimating PCWP as recommended in the guidelines. The comparison of clinical diagnosis against echocardiographic diagnosis of elevated filling pressure (with invasive measurement as the gold standard) is presented in Tables 4 and 5. The clinical diagnosis of HF and normal LVEF had a sensitivity of 45%, a specificity of 76%, and an accuracy of 64% in identifying patients with HFpEF (13). N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels obtained on the same day as cardiac catheterization were related to LV filling pressure in a subset of 123 patients. In 41 patients with normal LVEF and normal LV filling pressure, NT-proBNP levels were <300 pg/ml, and levels were elevated and consistent with increased filling pressure in 7 patients who met the invasive diagnostic criteria of HFpEF. However, the biomarker level was also elevated in 7 patients with normal LV filling pressure and normal EF, and was <300 pg/ml in another 12 patients who had an LV filling pressure >12 mm Hg. NT-proBNP levels correctly identified 28 patients with depressed LVEF and elevated LV filling pressure and 5 patients with depressed LVEF and normal LV filling pressure. However, 17 patients with depressed EF and elevated LV filling pressure and 2 with normal LV filling pressure were not correctly identified by NT-proBNP levels.

On logistic regression analysis, AUC increased from 0.71 for clinical assessment to 0.87 for echocardiographic assessment to 0.91 for the combination of clinical and echocardiographic assessments ($p = 0.0002$ vs. echocardiographic assessment only and $p < 0.001$ vs. clinical assessment only). Global chi-square analysis showed a significant increment when clinical and echocardiographic data were combined (259.14 vs. 240.55 for echocardiography only and 83.16 for clinical evaluation only; $p < 0.0001$ vs. clinical evaluation only and vs. echocardiography alone). Net reclassification improvement for the combination of echocardiography and clinical assessment over clinical assessment alone was 1.5 ($p < 0.0001$) as was the IDI at 0.293 ($p < 0.0001$). The combination of both clinical and echocardiographic assessment over echocardiographic assessment alone was smaller at 1.08 but was still significant ($p < 0.0001$); the same trend was observed for IDI analysis at 0.034 ($p = 0.0002$).

Echocardiographic accuracy in detecting elevated PCWP was 91% in patients with EF <50% and 84% in patients with EF ≥50% (**Table 5**). The echocardiographic diagnosis of elevated LV filling pressure against the invasive gold standard was good for patients with LBBB or a paced rhythm (AUC = 0.84), AF (AUC = 0.83), or moderately-severe to severe MR (AUC = 0.96). For these disorders, the specific approach recommended in the guidelines was applied (5).

TABLE 3 Distribution of 2D and Doppler Variables*

		Elevated Filling Pressure (n = 165)	Normal Filling Pressure (n = 155)
Mitral E/A ratio ≤0.8 + E ≤50 cm/s		0	23
Mitral E/A ratio ≥2		53	5
None of the cutoff values met for the 3 variables in patients with diastolic dysfunction†		15	70
3 abnormal	LAV >34 ml/m^2, E/e′ >14, and TRV >2.8 m/s	25	0
2 abnormal (2 of 3 listed)	LAV >34 ml/m^2, E/e′ >14, TRV <2.8 m/s	35	7
	LAV >34 ml/m^2, E/e′ <14, TRV >2.8 m/s	11	8
	LAV <34 ml/m^2, E/e′ >14, TRV >2.8 m/s	8	1
1 abnormal	LAV >34 ml/m^2	6	32
	E/e′ >14	8	4
	TR >2.8 m/s	4	5

Values are n. *In patients in sinus rhythm and without atrial fibrillation, paced rhythm, or significant mitral regurgitation where a conclusion on LV filling pressure could be reached. †Diastolic dysfunction was diagnosed based on the presence of pathological LV hypertrophy, coronary artery disease (CAD), and/or depressed LVEF.
TRV = tricuspid regurgitation velocity; other abbreviations as in Table 1.

DISCUSSION

The current study demonstrated that echocardiography can reliably identify patients with elevated LV filling pressure with high feasibility and good accuracy. This was observed in a large sample from multiple institutions, including several patients who pose challenges to the acquisition and interpretation of echo data. Our study validated the recently published ASE/European Association of Cardiovascular Imaging (EACVI) guidelines (5).

The study was unique given the large sample size, the inclusion of patients with a wide spectrum of underlying cardiac diseases, and a proportion of patients with normal LVEF, which is consistent with what is seen in clinical practice (4). As recommended in the guidelines, the study combines LA volume index as an indicator of long-term elevation of LV filling pressure with Doppler velocities, which reflect filling pressure at the time of echocardiographic examination (5). Given the performance of individual signals, an approach combining different measurements, as recommended in the 2016 guidelines, is essential to correctly estimate LV filling pressure.

ECHOCARDIOGRAPHIC ESTIMATION OF LV FILLING PRESSURE BY EF. Patients with depressed LVEF and normal wedge pressure usually have an impaired LV relaxation pattern. However, when LV filling pressure increases, predominant early diastolic filling occurs (grade II and III diastolic dysfunction) with short deceleration time and isovolumic relaxation time, elevated E/e′ ratio, and increased pulmonary artery pressures. These findings were verified in stable patients with HFrEF (14–24) as well as in patients with acute decompensated heart failure (6,25). The current study supports the important role of echocardiography in estimating LV filling pressure in patients with HFrEF, where concerns were raised about the accuracy of single indexes and reproducibility of technique (26,27). These concerns were expressed despite numerous published studies from several laboratories across the globe showing not only the diagnostic aspect of the methodology but also its ability to predict outcome events. Notably, some of the studies tried to apply the methodology to patients with normal EF, but without cardiac disease where the hemodynamic variables that affect Doppler signals

TABLE 4 Accuracy of Diagnosis of Elevated LV Filling Pressure: Total Population

	Clinical (95% CI)	Echocardiographic (95% CI)	p Value* Clinical vs. Echo
Sensitivity	74 (68–79)	87 (81–91)	0.001
Specificity	69 (62–75)	88 (82–93)	<0.001
PPV	77 (71–82)	91 (86–94)	<0.001
NPV	65 (58–72)	83 (76–88)	<0.001
Overall accuracy	72 (67–76)	87 (84–91)	<0.001

Values are %. *Based on McNemar test.
CI = confidence interval; echo = echocardiography; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 1.

TABLE 5 Accuracy of Diagnosis of Elevated LV Filling Pressure: Subgroup Analysis

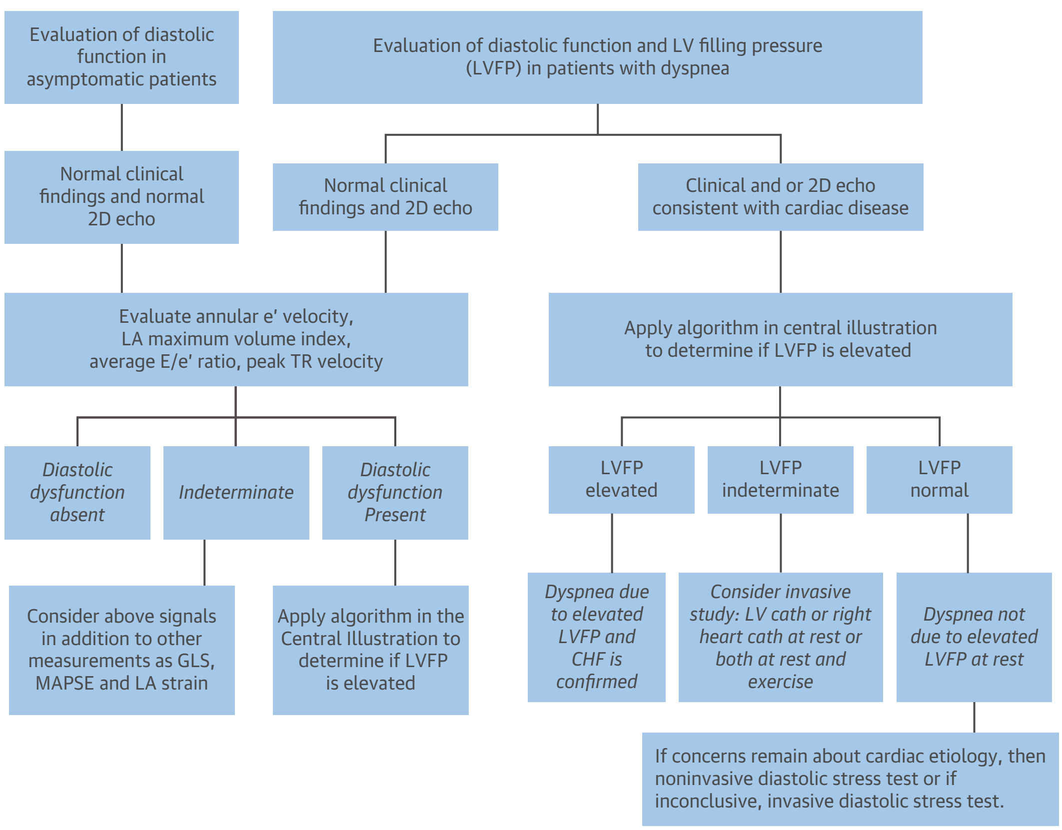
	Clinical Accuracy	Echocardiographic Accuracy	p Value Clinical vs. Echo
LVEF <50% (n = 209)	81	91	0.01
LVEF ≥50% (n = 241)	64	84	<0.001
Obesity (n = 193)	76	87	0.015
Diabetes mellitus (n = 48)	70.8	88	0.08
Chronic kidney disease (n = 47)	61.7	79	0.12
Hypertension (n = 167)	68	86.7	<0.001
CAD (n = 155)	73.5	92.7	<0.001
Pulmonary parenchymal or vascular disease (n = 71)	53.5	81	0.001

Values are %.
Abbreviations as in Tables 1, 3, and 4.

are different from those in patients with abnormal myocardial function (for example mitral annulus e′ velocity, which is directly related to filling pressure in normal subjects). Other studies had technically challenging signals that were nevertheless still used to derive conclusions or used the same general approach to special patient groups where a specific approach is recommended. Patients with EF <50% constituted 46% of our study population, and we noted similar results. The comprehensive approach recommended in the 2016 guidelines improved the diagnostic accuracy, which was 81% for clinical assessment alone to 91% by echocardiography (Table 5).

Estimation of LV filling pressure is more challenging in patients with normal EF. In our study, individual 2D and Doppler signals had significant but

FIGURE 4 Evaluation of Diastolic Function and LV Filling Pressure



To identify patients with cardiac disease in whom the algorithm (Central Illustration) can be applied, the evaluations start with clinical and 2-dimensional (2D) findings, followed by Doppler signals, and if needed, cardiac catheterization with or without noninvasive or invasive diastolic stress testing. For diastolic function assessment in the absence of abnormal clinical and 2D findings, the evaluation begins with mitral annular velocities, LA maximal volume index, average E/e′ ratio, and peak TR signal. When findings are indeterminate, other abnormalities that point to cardiac disease could be considered, including LV global longitudinal strain (GLS), mitral annulus systolic plane excursion (MAPSE), and LA strain. The latter approach needs validation. CHF = congestive heart failure; echo = echocardiography; LVFP = left ventricular filling pressure; other abbreviations as in Figure 1.

modest relations with LV filling pressure, similar to previous studies (19–22). However, a comprehensive approach, as recommended in the guidelines, resulted in good accuracy that surpassed clinical assessment alone (84% vs. 64%; $p < 0.001$).

CLINICAL IMPLICATIONS. There are practical implications to our findings, as patients with previous HF history, whether with normal or reduced EF, can have other reasons for dyspnea, such as chronic obstructive pulmonary disease. By accurately identifying the correct cause of dyspnea in a patient, the appropriate treatment can be implemented.

The starting point for evaluation is the history and physical examination and, as needed, chest x-ray and laboratory tests. In some patients, this can be enough to reach the correct diagnosis. However, there are challenges for clinical assessment, as noted in this study for obese patients and for patients with pulmonary disease, 2 groups with a high frequency of concomitant cardiac pathology. Our findings highlighted the important role of echocardiography in estimating LV filling pressure in patients who pose problems to clinical evaluation.

Many clinicians utilize echocardiography mainly to assess LV volumes and EF in trying to draw conclusions about the etiology of dyspnea. LV filling parameters are often overlooked and some physicians assume that patients with depressed EF have elevated LV filling pressure as the reason for shortness of breath. We have shown that this is not the case for 40% of patients with LV systolic dysfunction and depressed EF, highlighting the need to acquire and analyze Doppler signals in this patient population. Likewise, although the majority of patients (57%) with normal EF had elevated LV filling pressure, many patients did not. **Figure 4** presents our recommended approach to the evaluation of patients suspected of having dyspnea due to elevated LV filling pressure.

STUDY LIMITATIONS. The current ASE/EACVI algorithm recommends performing the diastolic stress test in symptomatic patients who have normal filling pressure at rest. Stress testing was not performed, and it is possible that echocardiographic Doppler measurements during exercise could have revealed elevated filling pressure in some of these patients (28,29). For other subgroups with nonsinus rhythm and for patients with hemodynamically significant MR, the existing echocardiographic methodology is promising but needs additional validation in larger samples given the small number of patients in these subgroups in our study. The algorithm is based on the interpretation of 2D and Doppler signals in patients with cardiovascular diseases and not in patients without cardiac diseases, who are explicitly excluded from the algorithm (5). The accuracy of echocardiographic evaluation of LV filling pressure likely will be lower when applied in populations with lower prevalence of cardiac disease. Echocardiography and cardiac catheterization were not simultaneous in all patients. However, there were no significant differences in heart rate and blood pressure between the 2 studies. The evaluation of the accuracy of clinical and echocardiographic assessment was performed in the same sample and needs validation in a separate group.

CONCLUSIONS

Echocardiographic assessment of LV filling is readily available with high feasibility and good accuracy to estimate LV filling pressure. Our study validated the recently published ASE/EACVI guidelines. When used in the proper context, it leads to a more accurate diagnosis of elevated LV filling pressure, irrespective of LVEF.

ADDRESS FOR CORRESPONDENCE: Dr. Sherif F. Nagueh, Methodist DeBakey Heart and Vascular Centre, 6550 Fannin Street, SM-677, Houston, Texas, 77030. E-mail: snagueh@houstonmethodist.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Combining echocardiographic measures of left atrial volume index with diastolic Doppler filling velocity can identify patients with elevated LV filling pressure and, when interpreted in conjunction with clinical data, enhances diagnostic accuracy, regardless of LV ejection fraction.

TRANSLATIONAL OUTLOOK: Additional studies are needed to assess the utility of echocardiographically estimated LV filling pressure to guide therapy for patients with and without heart failure.

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