

# The Role of Left Atrial Strain in Detecting Left Ventricular Diastolic Dysfunction: Comparison between the 2009 and 2016 Recommendations

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## Abstract

**Background:** The frequency of left ventricular diastolic dysfunction (DD) is overestimated by earlier recommendations. We compared the 2009 and 2016 guidelines regarding the detection of DD and explored the potential of adding left atrial (LA) strain to the current guideline.

**Methods:** Consecutive patients with heart failure were enrolled. All the patients were examined using 2-dimensional speckle-tracking echocardiography (2D-STE) and tissue Doppler imaging. DD was evaluated in terms of E/e', e' velocity, E, A, tricuspid regurgitation velocity, LA volume, and LA strain.

**Results:** This study evaluated 147 patients (101 males, 68.7%) at a mean age of 54.73±14.42 years. LA strain decreased with increasing grades of DD in both guidelines. The rate of reclassification between the 2 guidelines was 41%. The detection rate of normal diastolic function increased after the implementation of the 2016 guideline. LA strain discriminated individuals with normal diastolic function from those with DD more accurately than did LA volume index (area under the curve [AUC] =0.816 vs AUC=0.759, respectively). When LA strain <23% was incorporated into the 2016 guideline, 2 out of 4 patients with indeterminate diastolic function were reclassified as normal and 2 patients as grade I DD. The rate of reclassification was 4.1% after the addition of LA strain to the current guideline ( $\kappa=0.939$ ,  $P<0.001$ ).

**Conclusion:** This study showed that the current guideline detected lower rates of DD than did the earlier recommendations. Furthermore, the incorporation of LA strain into the current guideline resulted in lower rates of indeterminate diastolic function.

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**Keywords:** Heart failure; Heart failure, diastolic; Heart Atria; Echocardiography

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## Introduction

The evaluation of left ventricular function is an integral component of a comprehensive cardiovascular examination. The presence of left ventricular diastolic dysfunction (DD) in the setting of different cardiac problems is strongly associated with patients' prognoses.<sup>1</sup> Besides invasive methods, noninvasive imaging modalities, including transthoracic echocardiography (TTE), magnetic resonance imaging, and nuclear scanning, can be implemented to evaluate left ventricular function.<sup>2</sup> The current recommendations for the evaluation of diastolic function published in 2016,<sup>2</sup> in comparison with the earlier guideline in 2009,<sup>3</sup> have been simplified for clinicians. Nonetheless, they fail to confer higher accuracy in detecting left ventricular filling pressure compared with invasive modalities.<sup>4</sup>

Left atrial (LA) function is also considered a crucial element in the assessment of left ventricular function. The importance of LA function in left-sided diastolic function has prompted investigators to focus on the evaluation of LA via different methods.<sup>5,6</sup> In the setting of failed left ventricular filling (ie, DD), the LA myocardium demonstrates some adaptations, which can be easily studied using TTE. Strain imaging by 2-dimensional speckle-tracking echocardiography (2D-STE) is a valuable and noninvasive echocardiographic modality for the evaluation of LA function. LA function has 3 components, namely reservoir, conduit, and booster functions, to modulate left ventricular filling in a cardiac cycle.<sup>7</sup> According to the prior investigations concerning the functional features of the LA, systolic strain (S) and strain rate (S-Sr) represent the atrial reservoir function and early diastolic Sr (E-Sr) and late diastolic Sr (A-Sr) represent the conduit and booster functions of the LA, respectively.<sup>6,8,9</sup> Several studies have shown that LA strain is correlated with the invasive measurement of left ventricular filling pressures<sup>7</sup> and left ventricular DD severity.<sup>10</sup>

In this study, we sought to evaluate the differences between earlier and current recommendations concerning the identification of left ventricular diastolic function using echocardiographic examinations in patients with a new diagnosis of heart failure (HF) with preserved or reduced ejection fraction (EF). We also explored the potential of adding LA strain imaging values to the current protocol for the detection and grading of left ventricular diastolic function.

## Methods

From January 2012 through August 2012, this observational study enrolled 147 consecutive patients with HF who were referred to the echocardiographic laboratory of our institution, a tertiary center for cardiovascular medicine in the Middle East. The study protocol was approved by the Ethics Committee of

Iran University of Medical Sciences, Tehran, Iran. All the procedures performed in this investigation were in accordance with the ethical standards of the committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and later revisions. Consent forms were also obtained from all the participants.

The inclusion criteria included a new diagnosis of HF based on the Framingham criteria, preserved or reduced left ventricular EF, and normal sinus rhythm regardless of the status of left ventricular diastolic function (ie, ranging from normal diastolic function to grade III DD). Before echocardiographic examinations, all the patients had classic symptoms of HF (ie, chest pain and dyspnea) upon enrollment. Patients were excluded if they had atrial fibrillation or any conduction defects or paced rhythms, pericardial diseases, mitral annular calcification, any degree of mitral or aortic valve stenosis, greater than mild-to-moderate degrees of mitral or aortic valve regurgitation, greater than the moderate degree of right ventricular dysfunction, significant right-sided valvular heart diseases, and valvular heart surgery or intervention.

All the echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI)<sup>11</sup> using a MyLab 60 ultrasound system (Esaote, Italy) with a 3.0 MHz transducer. Three cardiac cycles were analyzed offline. The data were analyzed by 2 independent experienced echocardiographers. Left ventricular EF was evaluated by eyeball assessment and the biplane Simpson method. The LA diameter and area were measured in end-systole. The LA volume was measured using the biplane area length method.<sup>12</sup> The indexed volume of the LA (LAVI) was calculated as the LA volume divided by the body surface area.<sup>11</sup>

Mitral inflow velocities were measured using a 1 to 2 mm sample volume placed at the mitral valve tip in the apical 4-chamber view. The velocities were composed of diastolic peak early (E) and peak late (A) transmitral flow velocities, the peak E to peak A velocity ratio (E/A), and the deceleration time of peak E velocity (EDT). The isovolumic relaxation time (IVRT) was measured using continuous-wave Doppler in the apical 5-chamber view. Right pulmonary vein velocities (S and D waves) were also studied in the apical 4-chamber view with the sample volume at 3 mm from the pulsed-wave Doppler. Pulmonary pressure was estimated based on the tricuspid regurgitation velocity, the diameter of the inferior vena cava, and respiratory variations. For all the measurements, the average of 3 consecutive beats was used. Right ventricular dysfunction was evaluated via 4 methods: the eyeball assessment, the tricuspid annular plane systolic excursion, the right ventricular S velocity in tissue Doppler imaging (TDI), and the fractional area change.

TDI was carried out at more than 100 frames per second, and the provided loops were digitally stored and analyzed

in an offline mode. The recorded walls were positioned at the center of the sector to minimize artifacts and to align the myocardial wall parallel to the direction of the insonating beam. TDI-derived mitral valve annular velocities, composed of systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities, were measured with a 2 to 5 mm sample volume placed at the septal part of the annulus. The E/Em ratio was measured for the evaluation of DD. With the aid of XStrain software (Esaote, Italy), LA longitudinal strain and strain rate were measured from the apical 2-, 3-, and 4-chamber views. The size of the sample volume upon the TDI of the LA was 2 to 3 mm. During the measurement of the LA wall strain, the pulmonary vein and the LA appendage were not included in image tracing, and interatrial septum strain values were also not included in the final calculation of LA strain.

Peak systolic strain (S) and strain rate (S-Sr) were obtained in segments during systole, early diastole (E-Sr), and late diastole (A-Sr). The average measurements of 15 segments of 6 LA walls were used to simplify the analysis. Recorded values were excluded if a smooth Sr curve could not be provided or if the angles of interrogation were higher than 30°.

The diagnosis and grading of DD were evaluated based on the 2009<sup>3</sup> and 2016<sup>2</sup> guidelines for the assessment of ventricular diastolic function. The participants were categorized into 4 groups according to the 2009 recommendations: without DD, grade I DD, grade II DD, and grade III DD. Based on the 2016 recommendations, the patients were categorized into 5 groups: without DD, grade I DD, grade II DD, grade III DD, and indeterminate diastolic function. In the first step among patients with a normal EF, evaluation was done based on septal E/e' >15, septal e' velocity <7 m/s, tricuspid regurgitation velocity >2.8 m/s, and LAVI >34 mL/m<sup>2</sup>. Lateral e' was not measured in this study; thus, septal E/e' >15 was used rather than averaged E/e' >14 in the 2016 guideline. The other criteria were the same as those mentioned in the recommendations.<sup>2</sup> The clinical value of septal E/e' and lateral E/e' is equal, and there is no additive predictive value in measuring both or one of them.<sup>13</sup> Moreover, in the current study, patients with coronary artery disease were considered grade I as well.

The assessment of LA function comprised 3 parts: the reservoir, conduit, and booster functions. During left ventricular systole, while the mitral valve is closed, the LA is stretched, which leads to longitudinal lengthening, recorded as positive S and systolic Sr waves (ie, the reservoir function). During left ventricular diastole, there is LA wall shortening, which is considered the negative value of the Sr measurement. The LA acts as a conduit for passive emptying in early diastole (E-Sr) and as a booster pump for active emptying during atrial contraction in late diastole (A-Sr). LA strain imaging was measured in the 2-, 3-, and 4-chamber views, and the values were averaged for either of the parameters for use in this study. Furthermore, LA

stiffness was calculated via a noninvasive method as "E/e' ratio divided by averaged LA strain".<sup>7</sup>

Based on the cutoff point of LA strain for the discrimination of left ventricular DD from normal diastolic function, LA strain was utilized to categorize the patients regarding left ventricular diastolic function. In line with the 2016 recommendations, the participants were evaluated using septal E/e' >15, septal e' velocity <7 m/s, tricuspid regurgitation velocity >2.8 m/s, LAVI >34 mL/m<sup>2</sup> and LA strain <23%. If 3 of the 5 variables met the criteria, the patient was defined as DD, and if fewer than 3 variables were positive, the patient was defined as normal diastolic function. LA strain was also added to identify the grading of DD.

According to the criteria mentioned in the earlier and current guidelines, the study population was categorized. Continuous variables were reported as the mean±the standard deviation, and categorical variables were presented as numbers (percentages). The one-way ANOVA test was used to evaluate differences in the continuous variables between the study groups, and the post hoc Tukey test was also implemented to examine differences between the paired groups. The  $\chi^2$  test was employed to evaluate differences between the groups regarding the categorical variables. Inter- and intraobserver variabilities were assessed through the random interpretation of LA strain and LAVI measurements twice in 10 individuals (a group of patients with or without a reduced EF). An observer evaluated these 10 new images on a separate occasion to determine the intraobserver variability by calculating the intraclass correlation coefficient (ICC). Both inter- and intraobserver variabilities were calculated using the ICC. The agreement was performed using the  $\kappa$  test to compare the significance of the reclassification after the incorporation of LA strain into the 2016 guideline.<sup>2</sup> The correlation between the continuous variables was evaluated using the Pearson correlation coefficient. The receiver operating characteristics (ROC) curve was constructed to assess the accuracy of the echocardiographic parameters in discriminating patients with DD and different grades of DD. Two-sided P values were calculated. All the statistical analyses were performed using STATA software, version 21.0, (College Station, TX, USA).

## Results

Out of 147 patients with HF, 101 patients (68.7%) were male, and 49 patients (33.3%) had a left ventricular EF  $\geq 55\%$ . The patients' mean age was 54.7±14.4 years. The patients were categorized into 4 groups according to the 2009 recommendations (normal and grades I, II, and III DD) and 5 groups based on the 2016 guideline (normal, indeterminate, and grades I, II, and III DD) for the evaluation of left ventricular diastolic function. Hypertension was reported in 34% of the study population and diabetes mellitus in 23.1%.



The baseline characteristics of the study participants are summarized in Table 1 and Table 2.

The components of LA strain (ie, LA strain, S-Sr, E-Sr, and A-Sr) were significantly impaired with the increasing severity of DD in both classifications (Table 1 & Table 2). LA strain was significantly lower in patients with left ventricular DD in comparison with those with normal diastolic function except for A-Sr, which was comparable between patients with grade I DD and those with normal diastolic function in the classification based on the 2009 recommendations (Table 1). LA strain parameters were also significantly

different between the groups by the 2016 recommendations but were comparable between the grade I and II groups (Table 2). The E/A ratio, LAVI, and septal E/e' ratio were progressively enhanced with the increasing grade of DD in both classifications ( $P < 0.001$ ); still, some of them were comparable between the normal diastolic function group and the indeterminate or grade I group in both classifications (Table 1 & Table 2). LA stiffness was also significantly enhanced in the groups with an increase in the grade of DD in both classifications. Other parameters are listed in Table 1 and Table 2.

Table 1. Baseline characteristics and echocardiographic parameters in the groups based on the 2009 recommendations for ventricular diastolic function

	Total (n=147)	No DD (n=29)	Grade 1 DD (n=59)	Grade 2 DD (n=28)	Grade 3 DD (n=31)	P
Age (y)	54.69±14.14	45.17±16.47	60.10±11.09*	54.10±12.18	53.84±14.20	<0.001
Male	101 (68.7)	19 (65.5)	37 (62.7)	24 (85.7)	21 (67.7)	0.179
Body surface area (m <sup>2</sup> )	1.81±0.17	1.80±0.18	1.80±0.17	1.81±0.13	1.84±0.19	0.701
Systolic BP (mmHg)	123.61±17.08	119.65±12.67	126.00±18.19	121.67±14.18	124.51±20.46	0.372
Diastolic BP (mmHg)	75.10±12.28	74.31±9.97	76.08±13.17	74.50±12.32	74.51±12.86	0.890
Hypertension	50 (34)	6 (20.7)	24 (40.7)	10 (35.7)	10 (32.3)	0.316
Diabetes mellitus	34 (23.1)	1 (2.9)	13 (22)	7 (25)	13 (41.9)	0.006
left ventricular ESD (mm)	4.50±1.27	3.61±0.73**§	4.30±1.09*§	4.71±1.14*§	5.55±1.35**‡	<0.001
left ventricular EDD (mm)	5.69±1.02	5.01±0.76**§	5.52±0.88§	5.84±0.85*§	6.53±1.07**‡	<0.001
left ventricular EF (%)	36.73±16.86	52.41±7.14**§	38.72±16.28*§	30.89±14.08*	23.54±13.73**‡	<0.001
IVRT	89.25±24.48	85.06±13.08*§	112.28±13.81*§	79.75±11.24*§	57.90±10.67**‡	<0.001
EDT (ms)	206.80±62.30	195.41±25.93*§	265.10±32.61*§	189.21±29.25*§	122.41±31.34**‡	<0.001
E (cm/s)	70.51±24.33	76.79±15.95*§	50.16±12.05**§	79.82±18.35*§	94.96±22.57**‡	<0.001
A (cm/s)	58.78±22.20	57.89±12.26*§	75.59±17.66**§	53.17±17.04*§	32.70±10.30**‡	<0.001
S (cm/s)	41.78±13.45	49.75±10.73*§	46.62±11.22*§	36.85±13.28*†	29.54±9.26*†	<0.001
D (cm/s)	43.19±14.70	44.82±12.77*§	33.38±8.60**§	49.85±14.31†	54.32±14.53**‡	<0.001
E/A	1.50±1.04	1.34±0.23*§	0.71±0.31**§	1.59±0.49*§	3.10±0.97**‡	<0.001
LA volume (mL)	32.93±15.22	22.41±4.17*§	24.69±6.81*§	38.60±10.55**§	53.32±14.89**‡	<0.001
LAVI	18.24±8.31	12.57±2.97*§	13.88±4.28*§	21.38±6.20**§	28.99±7.83**‡	<0.001
Septal e' velocity (cm/s)	6.28±2.32	9.94±1.76**§	5.62±1.17*§	5.58±0.96*	4.72±1.73**‡	<0.001
E/e'	9.03±4.03	6.35±1.22*§	6.58±1.32*§	10.80±2.73**§	14.61±3.75**‡	<0.001
TR velocity (m/s)	2.49±0.41	2.51±0.28	2.35±0.31§	2.46±0.49§	2.75±0.48**‡	<0.001
PAP (mmHg)	32.36±11.09	25.96±5.59*§	27.57±6.30*§	35.00±10.18**§	45.09±11.88**‡	<0.001
LA strain parameters						
LA strain (%)	24.93±11.64	38±9.65**§	27.11±7.57**§	21.37±8.17**§	11.75±5.95**‡	<0.001
S-Sr (s <sup>-1</sup> )	1.18±0.48	1.64±0.37**§	1.29±0.35**§	1.03±0.35**§	0.66±0.34**‡	<0.001
E-Sr (s <sup>-1</sup> )	-0.92±0.54	-1.66±0.52**§	-0.80±0.40*§	-0.77±0.33*	-0.57±0.27*†	<0.001
A-Sr (s <sup>-1</sup> )	-1.28±0.64	-1.56±0.45*§	-1.68±0.50*§	-0.99±0.39**§	-0.52±0.31**‡	<0.001
LA stiffness	0.59±0.30	0.17±0.06*§	0.26±0.11§	0.60±0.36§	1.57±0.94**‡	<0.001

\*Data are presented as mean±SD or n (%).

\*\*P < 0.05 for this group vs no DD;

†P < 0.05 for this group vs grade I DD;

‡P < 0.05 for this group vs grade II DD;

§P < 0.05 for this group vs grade III DD. Paired analyses were performed using the Tukey test.

DD, Diastolic dysfunction; EF, Ejection fraction; BP, Blood pressure; EF, Ejection fraction; ESD, End-systolic diameter; EDD, End-diastolic diameter; IVRT, Isovolumetric relaxation time; EDT, Deceleration time of peak E velocity; E, Peak early diastolic mitral velocity; A, Peak late diastolic mitral velocity; S, Peak systolic pulmonary vein velocity; D, Peak diastolic pulmonary vein velocity; LA, Left atrial; LAVI, Left atrial volume index; e', peak Early velocity; PAP, Pulmonary arterial pressure; S-Sr, Peak systolic strain rate; E-Sr, Early diastolic strain rate; A-Sr, Late diastolic strain rate

Based on the intra- and interobserver variabilities, the ICC values for LA strain were 0.875 (95% confidence interval [CI], 0.58 to 0.97) and 0.837 (95% CI: 0.47 to 0.96) for inter- and intraobserver variabilities, respectively. The ICC values for LAVI were 0.971 (95% CI: 0.89 to 0.99) and 0.895 (95% CI: 0.63 to 0.97), respectively.

Based on the 2009 recommendations, the number of patients in each of the normal, grade I DD, grade II DD, and grade III DD was 29 (19.7%), 59 (40.2%), 28 (19%), and 31 (21.1%), respectively. When all the patients were reclassified by the 2016 recommendations, the majority of those with normal diastolic function and grade I DD were recategorized as normal or grade I. However, out of 28 patients with grade II DD, 21 patients (75%) were defined as grade I DD. Most of the grade III patients (28 out of 31, 90%) were reclassified

as the same. In addition, 1 and 3 patients from grade I and III, respectively, were categorized as indeterminate (Figure 1). In our study population, the reclassification rate was 41% between the earlier 2009 guideline<sup>3</sup> and the current 2016 guideline.<sup>2</sup>

There was a significant direct correlation between LA stiffness and LAVI, E-Sr, and A-Sr ( $P < 0.001$ ). Moreover, significant inverse correlations were detected between LA stiffness and LA strain, left ventricular EF, and S-Sr ( $P < 0.001$ ). All the correlations are provided in Figure 4.

The ROC curve was constructed to differentiate patients with DD from those with normal diastolic function based on the 2016 guideline using LA strain or LAVI. LA strain discriminated individuals with normal diastolic function from those with DD more accurately than did LAVI (area

Table 2. Baseline characteristics and echocardiographic parameters in the groups based on the 2016 recommendations for ventricular diastolic function

	Total (n=147)	No DD (n=45)	Indeterminate (n=4)	Grade 1 DD (n=64)	Grade 2 DD (n=3)	Grade 3 DD (n=31)	P
Age (y)	54.69±14.13	52.88±16.32	55±24.91	56.4±12.47	52.33±21.12	53.96±12.28	0.394
Male	101 (68.7)	20 (44.4)	6 (60)	50 (86.2)	2 (66.7)	23 (74.2)	<0.001
Body surface area (m <sup>2</sup> )	1.81±0.17	1.80±0.19	1.66±0.14	1.81±0.14	1.63±0.03	1.86±0.19	0.049
Systolic BP (mmHg)	123.61±17.08	126.08±17.35	115±5.77	121.35±15.32	136.66±15.27	124.51±20.46	0.212
Diastolic BP (mmHg)	75.10±12.28	77.71±11.94	65±5.77	73.32±11.87	83.33±20.81	75.48±12.60	0.108
Hypertension	50 (34.0)	18 (40.0)	0	19 (32.8)	2 (66.7)	11 (35.5)	0.118
Diabetes mellitus	34 (23.1)	4 (8.9)	4 (40.0)	12 (20.7)	2 (66.7)	12 (38.7)	0.006
left ventricular ESD (mm)	4.50±1.27	3.42±0.58 <sup>  </sup>	3.12±0.61 <sup>  </sup>	4.74±1.02 <sup>**  </sup>	4.43±1.44	5.77±1.09 <sup>**‡</sup>	<0.001
left ventricular EDD (mm)	5.69±1.02	4.81±0.46 <sup>  </sup>	4.95±0.72 <sup>  </sup>	5.87±0.84 <sup>  </sup>	5.66±1.02	6.70±0.90 <sup>**‡</sup>	<0.001
left ventricular EF (%)	36.73±16.86	55.44±1.43 <sup>  </sup>	55.50±1.00 <sup>  </sup>	30±12.56 <sup>**  </sup>	40±17.32 <sup>  </sup>	20.80±10.00 <sup>**‡§</sup>	<0.001
IVRT	89.25±24.48	95.71±19.07 <sup>  </sup>	94.00±25.60 <sup>‡</sup>	100.98±20.03 <sup>**  </sup>	77.66±9.23	59.25±11.24 <sup>**</sup>	<0.001
EDT (ms)	206.80±62.30	225.64±45.79 <sup>  </sup>	243.31±67.64	233.50±48.41 <sup>  </sup>	219.33±11.75 <sup>  </sup>	125.70±35.74 <sup>**§</sup>	<0.001
E (cm/s)	70.51±24.33	65.35±19.61 <sup>  </sup>	82.50±22.17	60.25±18.07 <sup>  </sup>	113.33±15.27 <sup>**</sup>	93.51±23.52 <sup>**</sup>	<0.001
A (cm/s)	58.78±22.20	64.71±18.42 <sup>  </sup>	47.50±22.10	670.30±19.11 <sup>  </sup>	80±10 <sup>  </sup>	32.58±10.43 <sup>**§</sup>	<0.001
S (cm/s)	41.78±13.45	48.46±11.02 <sup>  </sup>	47.00±16.87	41.74±11.73 <sup>  </sup>	47.00±17.57	30.03±10.91 <sup>**</sup>	<0.001
D (cm/s)	43.19±14.70	39.15±11.13 <sup>**  </sup>	43.71±15.62 <sup>**</sup>	39.15±12.46 <sup>**  </sup>	70.00±15.62 <sup>**</sup>	53.67±15.11 <sup>**</sup>	<0.001
E/A	1.50±1.04	1.11±0.54 <sup>**  </sup>	1.23±0.90 <sup>**  </sup>	1.00±0.40 <sup>**  </sup>	1.41±0.30 <sup>  </sup>	3.10±1.00 <sup>**‡§</sup>	<0.001
LA volume (mL)	32.93±15.25	23.51±6.54 <sup>**  </sup>	34.74±12.41 <sup>*</sup>	28.96±9.71 <sup>  </sup>	49.00±6.00 <sup>**</sup>	52.16±15.69 <sup>**</sup>	<0.001
LAVI	18.24±8.31	13.21±4.00 <sup>**  </sup>	25.35±12.25 <sup>**</sup>	16.03±5.44 <sup>**  </sup>	30.12±4.31 <sup>  </sup>	28.03±8.15 <sup>**</sup>	<0.001
Septal e' velocity (cm/s)	6.28±2.32	7.88±2.36 <sup>**  </sup>	7.00±3.39	5.93±1.90 <sup>**  </sup>	5.16±1.04	4.67±1.47 <sup>**</sup>	<0.001
E/e'	9.03±4.03	6.59±1.60 <sup>**  </sup>	8.62±2.31 <sup>**  </sup>	7.73±2.27 <sup>**  </sup>	15.90±0.79 <sup>**‡</sup>	14.50±3.91 <sup>**‡</sup>	<0.001
TR velocity (m/s)	2.49±0.41	2.46±0.46 <sup>**  </sup>	2.40±0.32 <sup>**  </sup>	2.37±0.35 <sup>**  </sup>	3.15±0.33 <sup>**</sup>	2.78±0.45 <sup>**</sup>	<0.001
PAP (mmHg)	32.36±11.09	26.48±6.24 <sup>**  </sup>	30.81±34.23	29.18±7.49 <sup>**  </sup>	50.00±8.66 <sup>**</sup>	45.58±11.47 <sup>**</sup>	<0.001
LA strain parameters							
LA strain (%)	24.93±11.64	33.27±8.67 <sup>**  </sup>	24.93±11.64 <sup>  </sup>	25.50±9.60 <sup>**  </sup>	27.68±15.17 <sup>  </sup>	11.42±5.35 <sup>**‡§</sup>	<0.001
S-Sr (s <sup>-1</sup> )	1.18±0.48	1.57±0.39 <sup>**  </sup>	1.16±0.60 <sup>  </sup>	1.16±0.32 <sup>**  </sup>	1.23±0.60 <sup>  </sup>	0.62±0.28 <sup>**‡§</sup>	<0.001
E-Sr (s <sup>-1</sup> )	-0.92±0.54	-1.32±0.58 <sup>**  </sup>	-0.92±0.43	-0.80±0.42 <sup>*</sup>	-1.02±0.57	-0.56±0.35 <sup>*</sup>	<0.001
A-Sr (s <sup>-1</sup> )	-1.28±0.64	-1.57±0.50 <sup>**  </sup>	-0.94±0.63	-1.47±0.56 <sup>  </sup>	-1.17±0.61	-0.53±0.30 <sup>**</sup>	<0.001
LA stiffness	0.58±0.70	0.21±0.12 <sup>**  </sup>	0.58±0.69 <sup>  </sup>	0.35±0.18 <sup>  </sup>	0.73±0.47	1.60±0.94 <sup>**‡</sup>	<0.001

\*Data are presented as mean±SD or n (%).

\*\*P<0.05 for this group vs no DD;

\*P<0.05 for this group vs indeterminate DD;

‡P<0.05 for this group vs grade I DD;

§P<0.05 for this group vs grade II DD;

||P<0.05 for this group vs grade III DD;

Paired analyses were performed using the Tukey test.

DD, Diastolic dysfunction; EF, Ejection fraction; BP, Blood pressure; EF, Ejection fraction; ESD, End-systolic diameter; EDD, End-diastolic diameter; IVRT, Isovolumetric relaxation time; EDT, Deceleration time of peak E velocity; E, Peak early diastolic mitral velocity; A, Peak late diastolic mitral velocity; S, Peak systolic pulmonary vein velocity; D, Peak diastolic pulmonary vein velocity; LA, Left atrial; LAVI, Left atrial volume index; e', Peak early velocity; PAP, Pulmonary arterial pressure; S-Sr, Peak systolic strain rate; E-Sr, Early diastolic strain rate; A-Sr, Late diastolic strain rate



under the curve [AUC]=0.816, 95% CI: 0.75-0.88 and AUC=0.759, 95% CI: 0.68 to 0.84; P<0.001, respectively). The comparison between the ROC curves was not statistically significant (P=0.156) (Figure 2). The  $\chi^2$  statistic for the comparison between the 2 ROC curves was 466.87 (P<0.001). LAVI was more accurate than was LA strain in discriminating grade I DD from grade II DD (AUC=0.974, 95% CI: 0.93-1.02; P<0.001 and AUC=0.448, 95% CI:

0.01-0.89; P<0.001, respectively). On the other hand, LA strain was more accurate than LAVI in discriminating grade I DD from III DD and grade II DD from grade III DD. Furthermore, only LA strain significantly discriminated indeterminate DD from grade III DD (AUC=0.847, 95% CI: 0.63-1.07; P=0.026) (Table 3).

We also implemented abnormal LA strain <23% based on studies showing a lower limit of 23% for LA strain

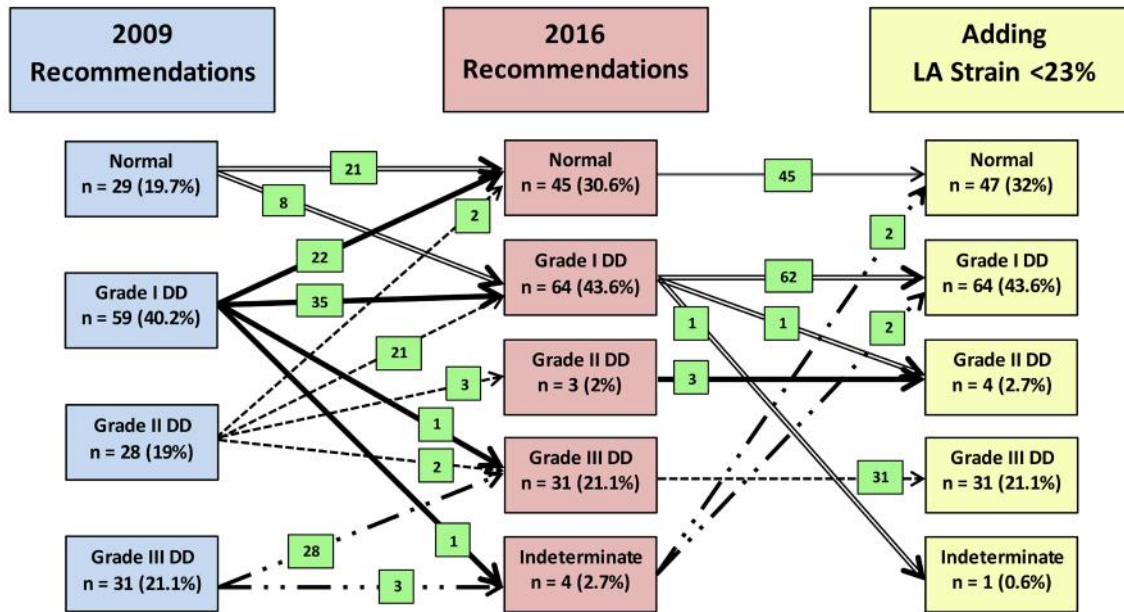


Figure 1. This schematic chart shows the rates of reclassification in this study between the earlier and current guidelines and after the addition of left atrial strain values.

DD, Diastolic dysfunction; LA, Left atrial

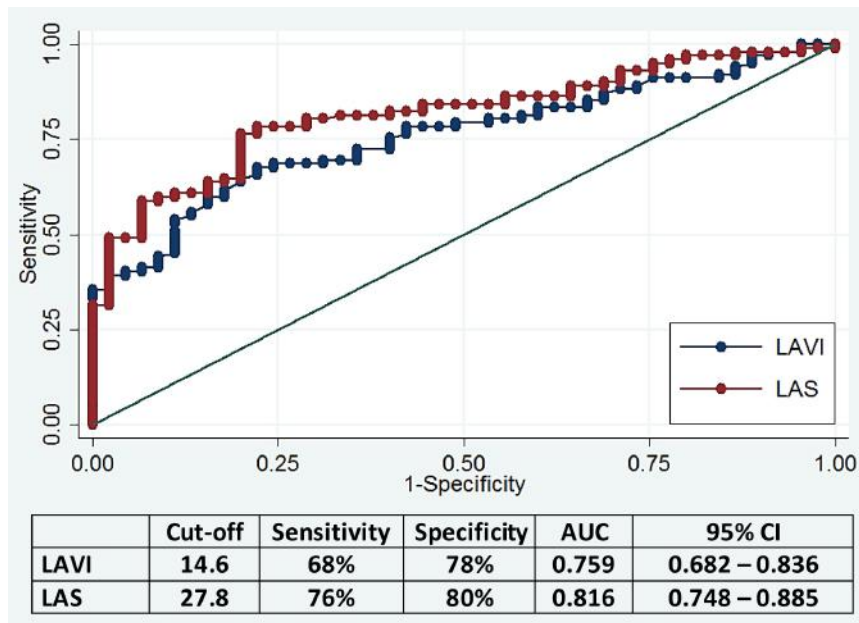


Figure 2. The ROC analysis shows the discrimination of patients with normal diastolic function from those with diastolic dysfunction based on the current guideline.

AUC, Area under the curve; CI, Confidence interval; LAS, Left atrial strain; LAVI, Left atrial volume index; NPV, Negative predictive value; PPV, Positive predictive value

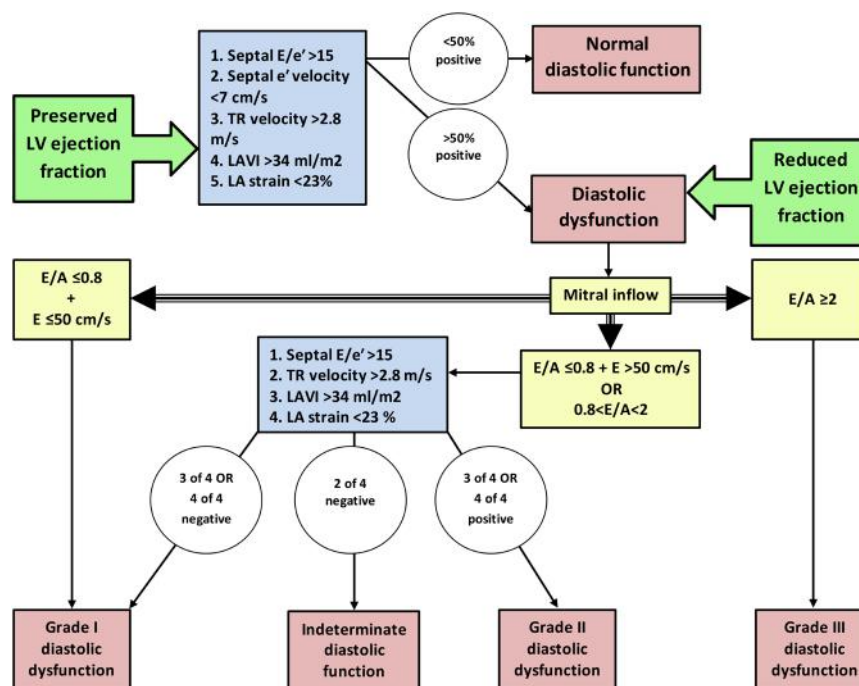


Figure 3. The figure shows the incorporation of left atrial strain values into the current guideline to detect and grade diastolic dysfunction.

Table 3. ROC curve analyses discriminating the grades of left ventricular DD according to the 2016 classification

Differentiating DD grades	Cutoff	AUC	95% CI	Sensitivity	Specificity	P
<b>LAVI</b>						
Grade I from II	25.5	0.974	0.931 – 1.017	100%	94%	0.006
Grade I from III	23.3	0.894	0.818 – 0.970	84%	88%	<0.001
Grade II from III	34.7	0.366	0.168 – 0.563	26%	100%	0.448
Indeterminate from grade I	12.5	0.266	-0.027 – 0.558	70%	25%	0.118
Indeterminate from grade II	21.8	0.583	0.124 – 1.043	100%	50%	0.724
Indeterminate from grade III	18.7	0.565	0.187 – 0.942	90%	50%	0.678
<b>LA strain</b>						
Grade I from II	13.2	0.448	0.003 – 0.893	33%	97%	0.762
Grade I from III	16.1	0.929	0.871 – 0.988	90%	81%	<0.001
Grade II from III	13	0.882	0.700 – 1.064	68%	100%	0.031
Indeterminate from grade I	34.6	0.477	0.109 – 0.844	50%	83%	0.844
Indeterminate from grade II	30.4	0.417	-0.052 – 0.886	67%	5%	0.724
Indeterminate from grade III	17.1	0.847	0.626 – 1.068	90%	75%	0.026

ROC, Receiver operating characteristics curve; DD, Diastolic dysfunction; AUC, Area under the curve; CI, Confidence interval; LA, Left atrial; LAVI, Left atrial volume index

in a healthy population.<sup>14</sup> When LA strain <23% was incorporated into the variables used in the ASE/EACVI 2016 recommendations (Figure 3), 4 patients with indeterminate diastolic dysfunction were reclassified as normal or grade I DD (100% reclassification of indeterminate DD) and 1 patient with grade I was redefined as indeterminate diastolic dysfunction (Figure 1). Only 1 patient with grade I DD was reclassified as grade II DD, and the others were redefined as grade I DD. On the other hand, all patients with grades II and III DD were categorized as the same grades. The rate of reclassification was 4.1% after the addition of LA strain to

the 2016 guideline ( $\kappa=0.939$ ,  $P<0.001$ ).

## Discussion

In this observational investigation, the use of the 2016 recommendations of the ASE/EACVI<sup>2</sup> for the assessment of left ventricular diastolic dysfunction led to the identification of more patients with normal diastolic dysfunction (30.6%) and grade I DD (43.6%) and fewer patients with grade II DD than did the use of the earlier 2009 recommendations.<sup>3</sup> In addition,

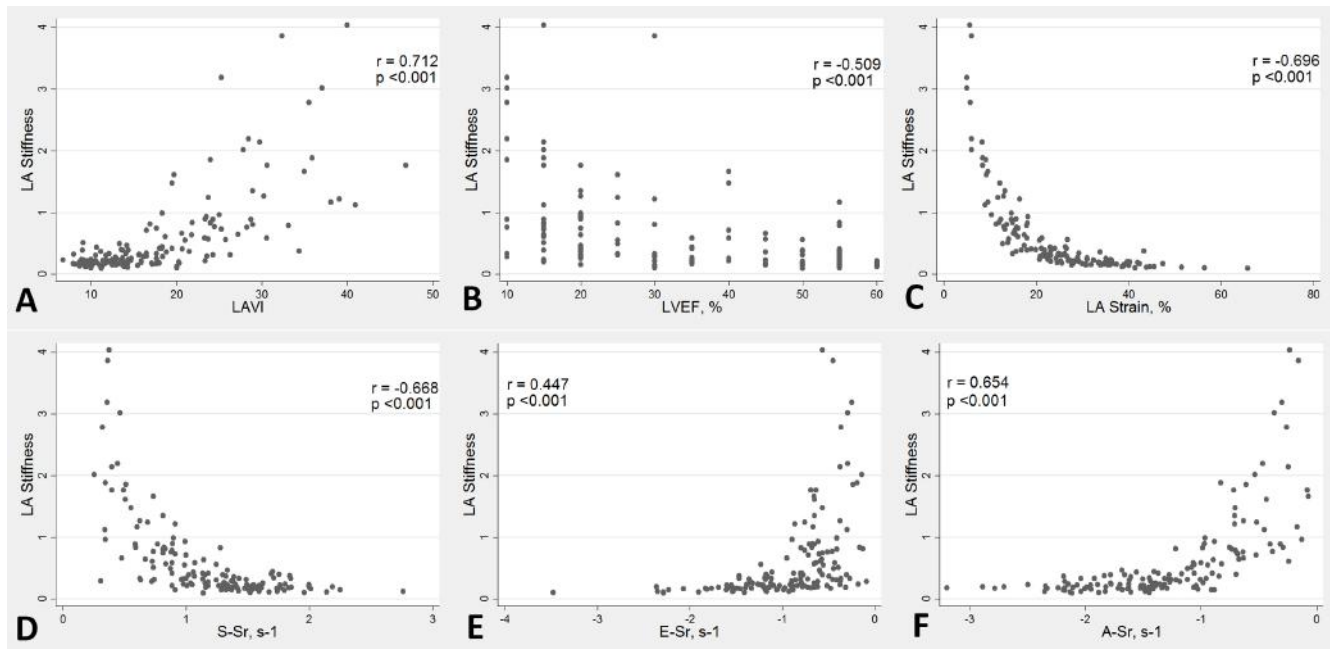


Figure 4. The correlation analysis shows the relationship between LA stiffness and A) LAVI, B) LVEF, C) LA strain, D) S-Sr, E) E-Sr, and F) A-Sr. LVEF, Left ventricular ejection fraction; LA, Left atrial; LAVI, Left atrial volume index; S-Sr, Peak systolic strain rate; E-Sr, Early diastolic strain rate; A-Sr, Late diastolic strain rate

we found that LA strain was accurate in discriminating patients with normal diastolic function from those with DD. Adding LA strain values to the updated recommendations resulted in the identification of lower rates of patients with indeterminate diastolic function and relatively similar rates for other grades of diastolic function in our population.

Despite the accurate measurement of left ventricular filling pressure by invasive modalities, echocardiography has emerged as an important tool in this setting; however, there have been some limitations in its use. Anderson et al<sup>15</sup> found that the 2016 guideline had 87% accuracy for the detection of left ventricular DD and that the percentage was enhanced when the clinical status of patients was incorporated into the recommendations. Lancellotti et al<sup>16</sup> also demonstrated that the 2016 guideline was relatively reliable in the detection of DD compared with invasive measurements in patients with or without a reduced EF and that it was associated with higher accuracy than the 2009 guideline. Likewise, Balaney et al<sup>4</sup> concluded that the 2016 guideline was more accurate than the 2009 guideline in comparison with invasive measurements. Two other studies compared the 2 guidelines in community-based populations. Huttin et al<sup>17</sup> showed that among individuals without HF and EF >50%, the rate of left ventricular DD was 1.3% and 5.9% by the 2016 and 2009 recommendations, respectively. Almeida et al<sup>18</sup> evaluated healthy individuals without known cardiac diseases with EF >50% and found 1.4% and 38.1% rates of DD by the 2016 and 2009 guidelines, respectively. These findings are in accordance with our findings insofar as the current recommendations<sup>2</sup> are associated with a significantly lower

prevalence rate of DD. The significant difference between the 2 guidelines can be explained by the notion that the updated guideline has been designed with high specificity to detect DD.

The grading of DD is another aspect of the clinical evaluation of patients with HF. The clinical consequence of DD grading is of great importance, but the exact discrimination of DD grades underscores invasive measurements. On the other hand, another approach is to perform grading based on echocardiographic parameters (2 or 3 positive parameters of averaged  $E/e' > 14$ , tricuspid regurgitation velocity  $> 2.8$  m/s, and LAVI  $> 34$  mL/m<sup>2</sup>).<sup>2</sup> Sanchis et al<sup>19</sup> showed that the 2016 guideline conferred more accurate diagnostic and prognostic implications than did the 2009 guideline. While the proportions of grades II and III DD were relatively similar in both recommendations, the rates of normal diastolic function (10.8% vs 44.6% in the 2009 and 2016 guidelines, respectively) and grade I DD (67.5% vs 7% in the 2009 and 2016 guidelines, respectively) were greatly different between the 2 recommendations. The study by Sanchis et al<sup>19</sup> and our report consisted of small populations, and any robust conclusions to be drawn upon in daily practice need further large-scale studies.

In patients with diastolic HF who have preserved left ventricular EF, a reduction in LA strain components can be seen earlier than conventional parameters for DD. Furthermore, LA strain components are more accurate than the measurements of LA size and volume.<sup>20-23</sup> It has been revealed that in diabetic and hypertensive patients with a normal left ventricular EF, reductions in the deformational



indices of the LA may be an early sign of the development of DD.<sup>21, 24</sup> The findings of the present study are in line with previous studies. In this study, we found that LA deformational indices correlated with left ventricular EF and LA volume, and echocardiographic features impaired with increasing the grade of DD, advocating the notion that decreases in LA myocardial deformational indices might occur before the development of overt LA enlargement. Therefore, LA deformational indices would be a better surrogate for the estimation of left-sided filling pressures in the setting of advanced HF.<sup>25</sup>

Singh et al<sup>26</sup> demonstrated that LA strain discriminated grade III DD from the other grades with an excellent accuracy rate of 0.91, whereas LAVI was not significantly different between the severe forms of DD. Brecht et al<sup>10</sup> in a large cohort of patients suffering from DD with preserved EF compared the utility of LA function and conventional parameters. They demonstrated that LA reservoir (AUC=0.82) and conduit (AUC=0.87) functions had greater diagnostic accuracy in the detection of early DD than did LAVI (AUC=0.65). These findings are in accordance with our study insofar as we found that LA strain had higher accuracy than did LAVI in the detection of DD.

Morris et al<sup>27</sup> evaluated the diagnostic value of adding LA strain to the current guideline. They observed that the incorporation of LA strain into the 2016 guideline enhanced the detection of left ventricular DD. Moreover, the frequency of abnormal LA strain in indeterminate patients was lower than abnormal LAVI (48.6% vs 69.1%). These findings revealed that the LA myocardium was involved in the HF process, which could be either in consequence of the direct involvement of myocardial fibers or an abnormal hemodynamic load caused by DD and can be used to improve the diagnostic and prognostic implications of noninvasive imaging in such a population.

The present study suffers from some limitations, which should be considered in future studies. Firstly, our findings may have been influenced by the observational design and small sample size of this study. Secondly, we did not evaluate filling pressure by invasive measurements, nor did we perform clinical follow-ups, precluding us from concluding how many patients were truly classified as DD and how many patients were categorized into different grades of DD. Thirdly, we did not measure lateral  $e'$  velocity, which might have influenced the prevalence of patients with DD.

## Conclusion

The implementation of the 2016 recommendations of the ASE/EACVI for the evaluation of ventricular diastolic function resulted in the identification of more individuals with normal diastolic function and grade I DD and fewer patients with grade II DD than did the use of the earlier 2009

recommendations, leading to a reclassification rate of 41%. In addition, LA strain accurately discriminated individuals with a normal diastolic function from those with DD. Adding LA strain values to the updated recommendations led to the identification of lower rates of indeterminate diastolic function and relatively similar rates for the other grades of diastolic function in our population.

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