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Impact of Updated 2016 ASE/EACVI VIS-À-VIS 2009 ASE Recommendation on the Prevalence of Diastolic Dysfunction and LV Filling Pressures in Patients with Preserved Ejection Fraction

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ABSTRACT

BACKGROUND: Assessment of diastolic dysfunction (DD) and left ventricular filling pressures (LVFP) by echocardiography is complex in patients with preserved ejection fraction (EF). The American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) jointly published recommendations in 2016 to simplify the diagnosis and classification of DD and the assessment of LVFP. We aimed to study the impact of the updated 2016 ASE/EACVI guidelines vis-à-vis the 2009 ASE recommendations on prevalence of DD and LVFP in patients with preserved EF.

METHODS: Five hundred patients referred to the echocardiography laboratory from March 2020 to May 2020 were analyzed. Patients with left ventricular ejection fraction (LVEF) < 50% were excluded. All patients underwent comprehensive transthoracic echocardiography. DD and LVFP were assessed by the 2016 ASE/EACVI and 2009 ASE recommendations. The concordance between the guidelines was analyzed by kappa coefficient and overall proportion of agreement.

RESULTS: Mean age was 53 ± 13 years and 63.4% were men. Prevalence of DD and abnormal LVFP were significantly lower with the 2016 recommendations than with the 2009 recommendations (9.4% vs. 16.8%, p < 0.001 and 8.4% vs. 12.8%, p < 0.05). Patients with Grade 1 DD (100%) and Grade 2 DD (46.4%) were reclassified by the 2016 recommendations. Indeterminate diastolic function (9.8%) was strikingly high according to the 2016 recommendations. The concordance between the two recommendations was moderate (kappa = 0.569). The overall proportion of agreement was 85.4%.

CONCLUSIONS: Prevalence of DD and abnormal LV filling pressures were lower with application of the 2016 ASE/EACVI recommendations in patients with preserved EF. There was moderate agreement between the 2009 and 2016 recommendations.

Keywords: Doppler echocardiography; Left ventricle; Diastole; Dysfunction; Heart failure; Guidelines

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INTRODUCTION

Diastolic dysfunction (DD) is common, especially in the elderly, and is considered an important prognostic indicator for various cardiac diseases.[1] The prevalence of asymptomatic DD is reported to be approximately 25% to 30% in individuals over 45 years of age.[2] DD can coexist with left ventricular systolic dysfunction. DD contributes to the development and progression of heart failure with preserved ejection function (HFpEF), accounting for almost one-half of patients with heart failure.[3)4] Elevated left ventricular filling pressure (LVFP) is the main physiological consequence of DD.[5] The diagnosis of HFpEF is straightforward when patients are acutely decompensated. However, among stable people presenting with chronic dyspnea, diagnosis is challenging and relies on identifying direct or indirect evidence of elevated LVFP.[6-8] Assessment of diastolic function (DF) and LVFP by echocardiography is complex and rather more difficult in patients with normal LV systolic function, requiring interpretation of multiple parameters. LVFP assessed non-invasively by echocardiography when incorporated into HFpEF diagnostic algorithms has limited ability to identify HFpEF accurately when compared to invasive testing.[9)10] However, invasive testing is neither routinely advisable nor desirable. Recently, the H2FPEF score, comprising six clinical and echocardiographic characteristics, was proposed by Reddy et al. to noninvasively estimate the likelihood of HFpEF.[11]

In 2009, the American Society of Echocardiography (ASE) proposed the first guideline document based on an algorithmic approach incorporating multiple parameters to simplify and standardize the assessment of DF.[12] Due to multiple parameters, DF couldn't be categorized reliably when the values of the parameters were discordant and not confined to a single category. Acknowledging the complexity of the 2009 guidelines, the American Society of Echocardiography and the European Association of Cardiovascular Imaging (EACVI) jointly published an update in 2016 to simplify the diagnosis and classification of DD.[13] A two-step algorithm incorporating a restricted number of feasible and reproducible variables was recommended. Studies have reported low but varying prevalence of DD with the 2016 ASE/EACVI guidelines.[14-16] The heterogeneity in the reported prevalence of DD with the new guidelines is due to the differences in the study setting, sampling strategy, subjects studied, and consideration of 'myocardial disease' for diastolic function assessment. As per the 2016 ASE/EACVI guidelines, patients with myocardial disease are considered to have DD, and the second step is used for DD grading and estimation of LVFP. There is no clarity regarding which diseases and their severities constitute myocardial disease. The impact of the 2016 ASE/EACVI guidelines on the prevalence of DD grades and LVFP in patients with preserved ejection fraction (EF) without considering myocardial disease remains undefined.

We aimed to evaluate the impact of the 2016 ASE/EACVI guidelines on the prevalence of DD, DD grades, and elevated LV filling pressures vis-à-vis the 2009 guidelines in a cohort of patients with preserved EF. We also examined the association between H2FPEF scores and DD as well as the DD grades diagnosed by the 2009 and 2016 guidelines.

METHODS

The echocardiography laboratory in the Department of Cardiology, JSS Hospital, Mysore provides services to both outpatients and inpatients. In the present study, 500 consecutive adult patients with preserved left ventricular ejection fraction (LVEF) fulfilling the inclusion

and exclusion criteria were prospectively enrolled from March to May 2020. Informed consent was taken. This study was approved by our institutional ethical committee.

Inclusion criteria

Patients over 18 years of age, both genders, and preserved LV systolic function (LVEF >50%) on echocardiography were included in the study.

Exclusion criteria

Patients with congenital heart disease, valvular heart disease, mitral regurgitation more than mild, acute coronary syndrome, rhythm other than sinus rhythm, permanent pacemaker, complete left bundle branch block (LBBB), LV systolic dysfunction (LVEF <50%), inadequate image quality, and not willing to give consent were excluded from the study.

Medical record review

Each subject's medical record was reviewed for their baseline characteristics. History of hypertension, diabetes mellitus, and dyslipidemia was recorded.

Echocardiographic evaluation

Transthoracic echocardiography was performed by using the Vivid T8 (GE Medical Systems Co Ltd, Wuxi, China) ultrasound machine. Each subject underwent comprehensive 2D echocardiography, pulsed and continuous wave Doppler examination, and tissue Doppler imaging. LVEF was measured by the biplane disc summation technique. Left atrial volume was calculated by the biplane area length method and indexed for body surface area (LAVi). Stored images were analyzed offline by two cardiologists who were blinded for clinical data.

Assessment of LV diastolic function and LV filling pressure by the 2009 and 2016 ASE guidelines

As per the 2009 guidelines,[12] initially septal e', lateral e', and left atrial volume index (LAVi) were assessed. Patients with septal e' ≥ 8 cm/sec, lateral e' ≥ 10 cm/sec and LAVi ≤ 34 mL/m^2 were considered to have normal diastolic function. Patients with septal e' < 8 cm/sec or lateral e' < 10 cm/sec and LAVi > 34 mL/m^2 were considered to have DD. Further, DD was graded from 1 to 3, based on at least two out three variables among average E/e' (< 8, between 9–12 and > 13 respectively), mitral inflow E/A ratio (< 0.8, between 0.8–1.5 and > 2, respectively), and E velocity deceleration time (> 200, between 160–200, and < 160 msec, respectively) reaching the given cut-offs. In the event of a discrepancy between different variables in which DD grade could not be assigned, DD was considered as 'cannot be determined.' In patients with normal LVEF, LVFP was assessed based on the lateral E/e' ratio. LVFP was considered as normal when E/e' was ≤ 8 and elevated if either lateral E/e' was ≥ 12 or if E/e' ratio ranged from 8 to 12 with concomitant presence of LAVi ≥ 34 mL/m^2 and/or pulmonary artery systolic pressure (PASP) > 35 mmHg. DD and LVFP were 'indeterminate' if no precise conclusion or even discordant conclusions were reached with the given cut-off points.

As per the 2016 ASE/EACVI guidelines,[13] a two-step approach was used. The first step was to identify the presence of DD in patients with normal LV systolic function based on four variables (septal e' < 7 cm/sec or lateral e' < 10 cm/sec, average E/e' ratio > 14, tricuspid regurgitation (TR) velocity > 2.8 m/sec, and LAVi > 34 mL/m^2). Diastolic function was considered as normal if < 50% variables were positive, indeterminate if 50% were positive, and abnormal if > 50% variables were positive. If patients were found to have DD in the first step, the second algorithm was used for estimation of LVFP and grading of DD. By this

algorithm, Grade 1 DD was assigned if E/A ratio was < 0.8 along with E velocity ≤ 50 cm/sec, Grade 2 DD was assigned if E/A ratio was > 0.8–< 2 or E/A ratio < 0.8 along with E velocity > 50 cm/sec with at least two criteria: average E/e′ ratio > 14, LAVi > 34 mL/m^2, and TR velocity > 2.8 m/sec. Grade 3 DD was assigned if E/A ratio > 2. Patients were assigned to the 'cannot be determined' category if there was a discrepancy between the only two available variables or if only one variable was available. LVFP was considered increased if E/A ratio > 2 or E/A ratio < 0.8 along with E velocity > 50 cm/sec, or for E/A ratio > 0.8 to < 2 and at least two of the following criteria: average E/e′ ratio > 14, LAVi > 34 mL/m^2, and TR velocity > 2.8 m/sec. According to the 2016 recommendations, indeterminate DF means that the diastolic function couldn't be assessed and 'cannot be determined' DD grade means that the DD grade couldn't be assigned even in the presence of DD.

Echocardiographic parameters, such as pulmonary venous flow-derived systolic-to-diastolic ratio, atrial reverse–trans mitral A (Ar-A) difference, and Valsalva delta E/A ratio suggested in the 2009 guidelines were not used in our study due to lower feasibility and reproducibility as stated in previous studies.[14)17)49)]

H2FPEF score
H2FPEF score was calculated using six clinical and echocardiographic variables: 1) obesity (body mass index > 30 kg/m^2), 2 points; 2) atrial fibrillation, 3 points; 3) age > 60 years, 1 point; 4) treatment with two or more antihypertensive drugs, 1 point; 5) E/e′ ratio > 9, 1 point; and 6) PASP > 35 mmHg, 1 point. The H2FPEF score ranges from 0–9. A score of 0–1 corresponds to a low probability (< 20%) of HFpEF. Conversely, a score of 6–9 corresponds to a high probability (> 90%) of HFpEF. Patients with a score of 2–5 have an intermediate probability of HFpEF.[11)]

Statistical analysis
Data were entered in MS Office Excel 2019 and analyzed using the Statistical Package for the Social Sciences (SPSS) v25 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were presented as absolute numbers and percentages. Comparisons between normal DF, DD, and indeterminate DF individuals were performed using Kruskal–Wallis H test or Friedman test whichever was appropriate. The concordance between the guidelines was determined by using the kappa coefficient and the proportion of agreement. The concordance was described as poor (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), and optimal (0.81–1). The reclassification percentage was derived as 100 - the proportion of agreement. All tests were two-tailed. The p-value < 0.05 was considered statistical significance.

RESULTS

The mean age of the study population was 53 ± 13 years. The majority of patients were men (n = 319, 63.8%). Hypertension (n = 156, 31.2%) and type 2 diabetes mellitus (n = 133, 26.6%) were the most common comorbidities. Patient characteristics between the groups (normal DF, DD, indeterminate DF) by 2009 and 2016 guidelines are shown in **Tables 1** and **2**. According to the 2009 guidelines, 97 patients (19.4%) had DD. According to 2016 guidelines, 47 patients (9.4%) had DD and 49 patients (9.8%) had indeterminate diastolic function. Despite the presence of DD, a grade could not be assigned to 13 patients by the 2016 recommendations and three patients by the 2009 recommendations.

Table 1. Comparison of clinical and echocardiographic characteristics between patients with normal diastolic function and diastolic dysfunction by 2009 guidelines

Parameters	2009 guidelines		
	Normal (n = 403)	Diastolic dysfunction (n = 97)	p-value
Age (year)	52.40 ± 12.90	58.71 ± 12.20	0.352
Men	260 (64.5)	57 (58.7)	0.554
Women	143 (35.5)	40 (41.3)	0.280
Hypertension	109 (27)	47 (48.5)	0.001*
Diabetes	97 (24)	36 (37.1)	< 0.001*
BMI (kg/m²)	26.48 ± 5.06	25.95 ± 4.62	0.586
WC (cm)	89.06 ± 11.46	89.41 ± 11.02	0.324
LVEF (%)	64.54 ± 6.66	62.76 ± 5.67	0.521
LV mass index (g/m²)	78.62 ± 17.90	93.20 ± 28.62	0.050
E velocity (cm/sec)	79.76 ± 18.71	88.89 ± 20.65	0.012†
Transmitral E/A ratio	1.00 ± 0.31	1.18 ± 0.51	0.036†
Lateral e′ velocity (cm/sec)	11.74 ± 2.64	9.09 ± 2.10	< 0.001†
Septal e′ velocity (cm/sec)	9.69 ± 2.87	6.65 ± 2.10	< 0.001†
E/e′ (average)	8.56 ± 1.66	13.20 ± 3.21	0.001†
LAVi (mL/m²)	26.21 ± 3.40	38.16 ± 5.22	< 0.001†
TR jet velocity > 2.8 m/sec	11 (2.5)	22 (22.7)	< 0.001
E velocity DT (msec)	168.34 ± 19.65	163.72 ± 26.57	0.124
H2FPEF score (mean ± SD)	0.96 ± 1.10	2.83 ± 1.51	< 0.001†

Values are presented as number (%) or mean ± SD.
BMI: body mass index, DT: deceleration time, LAVi: left atrial volume index, LVEF: left ventricular ejection fraction, SD: standard deviation, TR jet: tricuspid regurgitation jet, WC: waist circumference.
*Statistically significant p-value has been obtained by performing Kruskal Wallis H test; †Statistically significant p-value has been obtained by performing t-test.

Table 2. Comparison of clinical and echocardiographic characteristics between patients with normal diastolic function, diastolic dysfunction, and indeterminate diastolic function by 2016 guidelines

Parameters	2016 guidelines			
	Normal (n = 404)	Diastolic dysfunction (n = 47)	Indeterminate diastolic function (n = 49)	p-value
Age (year)	52.48 ± 12.80	58.46 ± 12.61	56.30 ± 13.62	0.921
Men	260 (64.4)	28 (59.6)	29 (59.2)	0.803
Women	144 (35.6)	19 (40.4)	20 (40.8)	0.230
Hypertension	111 (27.4)	24 (51)	21 (42.9)	0.001*
Diabetes	96 (23.8)	23 (48.9)	14 (28.6)	< 0.001*
BMI (kg/m²)	26.37 ± 4.90	26.02 ± 4.46	26.83 ± 5.10	0.125
WC (cm)	88.81 ± 10.80	90.14 ± 11.39	89.91 ± 10.90	0.625
LVEF (%)	64.70 ± 6.62	61.80 ± 4.82	63.36 ± 6.59	0.673
LV mass index (g/m²)	78.67 ± 18.90	96.41 ± 18.50	86.40 ± 19.90	0.009†
E velocity (cm/sec)	79.27 ± 18.14	91.85 ± 21.76	85.63 ± 22.97	0.040†
Trans-mitral E/A ratio	11.75 ± 2.62	8.08 ± 1.19	10.31 ± 2.20	< 0.001†
Lateral e′ velocity (cm/sec)	11.75 ± 2.62	8.08 ± 1.19	10.31 ± 2.20	< 0.001†
Septal e′ velocity (cm/sec)	9.70 ± 2.85	5.45 ± 1.15	8.03 ± 2.10	< 0.001†
E/e′ (average)	8.55 ± 1.60	14.85 ± 2.98	10.66 ± 2.42	< 0.001†
LAVi (mL/m²)	26.26 ± 3.52	40.27 ± 5.50	32.83 ± 4.98	< 0.001†
TR jet velocity > 2.8 m/sec	10 (2.4)	20 (42.5)	3 (6.1)	0.012*
E velocity DT (msec)	168.83 ± 19.90	153.10 ± 22.06	170.34 ± 22.61	< 0.001†
H2FPEF score (mean ± SD)	0.94 ± 1.07	3.51 ± 1.34	1.87 ± 1.33	< 0.001†

Values are presented as number (%) or mean ± SD.
BMI: body mass index, DT: deceleration time, LAVi: left atrial volume index, LVEF: left ventricular ejection fraction, SD: standard deviation, TR jet: tricuspid regurgitation jet, WC: waist circumference.
*Statistically significant p-value has been obtained by performing Friedman test; †Statistically significant p-value has been obtained by performing analysis of variance.

All patients with Grade 1 DD and 46.4% of patients with Grade 2 DD by the 2009 guidelines were reclassified according to the 2016 guidelines. None of the patients with Grade III by 2009 guidelines were reclassified. The concordance between the 2016 and 2019 guidelines analyzed by kappa coefficient showed moderate agreement (kappa = 0.569, SE of kappa = 0.037, 95% CI = 0.496–0.643). The overall proportion of agreement was 85.4%. The overall reclassification rate was 14.6%. As per the 2016 guidelines, most of the patients (89.4%)

Table 3. Reclassification of diastolic dysfunction grades by 2009 and 2016 guidelines

2009 guidelines	2016 guidelines					
	Normal	Grade 1	Grade 2	Grade 3	ID/CD[*]	Total
Normal	383	0	0	0	20	403
Grade I	6	0	0	0	6	12
Grade II	4	2	26	0	24	56
Grade III	0	0	0	16	0	16
ID/CD[*]	11	0	0	0	2	13
Total	404	2	26	16	52	500

Kappa = 0.569, SE of kappa = 0.037, 95% CI = 0.496–0.643, weighted kappa = 0.546 (moderate agreement).
ID/CD: indeterminate diastolic function/cannot determine diastolic dysfunction grade.
[*]No specific category has been assigned in 2009 guidelines for patients in whom diastolic dysfunction grading was not possible in view of discordant echocardiographic parameters.

Table 4. Comparison of echocardiographic characteristics and H2FPEF scores between grades of diastolic dysfunction by 2009 guidelines

Parameters	2009 guidelines			
	Grade 1 (n = 12)	Grade 2 (n = 56)	Grade 3 (n = 16)	p-value
LVEF (%)	62.66 ± 4.90	63.39 ± 5.52	60.63 ± 6.44	0.050[*]
LV mass index (g/m²)	95.33 ± 31.30	89.82 ± 26.58	104.84 ± 34.78	0.050[*]
E velocity (cm/sec)	74.16 ± 18.41	92.14 ± 19.22	88.56 ± 23.31	< 0.001[*]
Trans mitral E/A ratio	0.66 ± 0.046	1.09 ± 0.323	1.90 ± 0.52	< 0.001[*]
Lateral e′ velocity (cm/sec)	10.24 ± 3.02	9.03 ± 1.78	7.49 ± 1.49	< 0.001[*]
Septal e′ velocity (m/sec)	8.29 ± 2.49	6.80 ± 1.94	4.91 ± 1.40	< 0.001[*]
E/e′ (average)	8.12 ± 2.07	12.30 ± 2.63	14.68 ± 2.64	< 0.001[*]
LAVi (mL/m²)	34.16 ± 0.38	38.05 ± 4.49	41.56 ± 7.21	< 0.001[*]
E velocity DT (msec)	191.58 ± 22.31	165.64 ± 23.33	136.12 ± 9.97	< 0.001[*]
TR jet velocity > 2.8 m/sec	1 (8.3)	15 (26.8)	6 (37.5)	0.552
H2FPEF score (mean ± SD)	1.83 ± 1.40	2.69 ± 1.40	4.06 ± 1.28	< 0.001[*]

Values are presented as number (%) or mean ± SD.
DT: deceleration time, LAVi: left atrial volume index, LV: left ventricular, LVEF: left ventricular ejection fraction, SD: standard deviation, TR jet: tricuspid regurgitation jet.
[*]Statistically significant p-value has been obtained by performing analysis of variance.

Table 5. Comparison of echocardiographic characteristics and H2FPEF scores between grades of diastolic dysfunction by 2016 guidelines

Parameters	2016 guidelines			
	Grade 1 (n = 2)	Grade 2 (n = 26)	Grade 3 (n = 16)	p-value
LVEF (%)	60 ± 1	62.58 ± 3.78	60.63 ± 6.44	0.030[*]
LV mass index (g/m²)	111 ± 1.41	91.51 ± 26.53	103.46 ± 32.64	0.032[*]
E velocity (cm/sec)	85 ± 2.82	94.13 ± 21.71	88.56 ± 23.31	< 0.001[*]
Trans mitral E/A ratio	0.65 ± 0.07	1.15 ± 0.307	1.90 ± 0.52	< 0.001[*]
Lateral e′ velocity (cm/sec)	10.5 ± 0.5	8.23 ± 0.69	7.49 ± 1.49	< 0.001[*]
Septal e′ velocity (cm/sec)	7.5 ± 0.5	5.61 ± 0.79	4.91 ± 1.40	< 0.001[*]
E/e′ (average)	11.75 ± 0.21	13.41 ± 3.07	14.92 ± 2.72	< 0.001[*]
LAVi (mL/m²)	35.5 ± 0.707	39.89 ± 4.38	41.56 ± 7.21	< 0.001[*]
E velocity DT (msec)	170 ± 0.05	161.31 ± 22.17	136.12 ± 9.97	< 0.001[*]
TR jet velocity > 2.8 m/sec	1 (50)	13 (50)	6 (37.5)	0.620[†]
H2FPEF score (mean ± SD)	3.50 ± 0.70	3.13 ± 1.30	4.06 ± 1.28	< 0.001[*]

Values are presented as number (%) or mean ± SD.
DT: deceleration time, LAVi: left atrial volume index, LV: left ventricular, LVEF: left ventricular ejection fraction, SD: standard deviation, TR jet: tricuspid regurgitation jet.
[*]Statistically significant p-value has been obtained by performing analysis of variance; [†]p-value has been obtained by performing Kruskal Wallis-H test.

with DD were categorized into Grade 2 and Grade 3. On the contrary, 74.2% of patients with DD were categorized into Grade 2 and Grade 3 by the 2009 guidelines (**Table 3**). The key echocardiographic variables (Lateral e′, Septal e′, Average E/e′, LAVi, TR jet velocity > 2.8 m/sec) between the DD grades by the 2009 and 2016 guidelines are shown in **Tables 4** and **5**.

The prevalence of elevated LVFP was significantly lower by the application of 2016 guidelines than the 2009 guidelines (8.4% [n = 42] vs. 12.8% [n = 64], p < 0.05). Of patients with DD by the

Table 6. DF, DD grades, and LV filling pressure according to 2009 and 2016 guidelines (n = 500)

DF & LV filling pressures	2009 guidelines	2016 guidelines	χ^2 value	p-value
Normal DF	403 (80.6)	404 (80.08)	0.043	0.836
DD	97 (19.4)	47 (9.4)	20.26	< 0.001[†]
ID*	0 (0)	49 (9.8)	51.47	< 0.001[†]
LV filling pressures				
Normal	447 (89.4)	458 (91.6)	1.40	0.235
Elevated	64 (12.8)	42 (8.4)	5.10	0.023[†]
DD grades				
Grade 1	12 (2.4)	2 (0.4)	7.23	0.007[†]
Grade 2	56 (11.2)	26 (5.2)	11.94	< 0.001[†]
Grade 3	16 (3.2)	16 (3.2)	0	1.000
Indeterminate DF/cannot determine DD grade*	13 (2.6)	52 (10.4)	25.0	< 0.001[†]

Values are presented as number (%).
DD: diastolic dysfunction, DF: diastolic function, ID: indeterminate diastolic function, LV: left ventricular.
*No specific category has been assigned in 2009 guidelines for patients in whom DF and DD grading was not possible because of discordant echocardiographic parameters; [†]Statistically significant p-value has been obtained by performing χ^2 test.

2009 guidelines, 61.9% had elevated LVFP. Based on the 2016 guidelines, this percentage was 89.4%. LVFP could not be determined in three patients with DD by the 2016 guidelines (**Table 6**).

Patients with indeterminate diastolic function were older, had more prevalent cardiometabolic risk factors like hypertension (59.2%) and diabetes mellitus (42.9%), and had higher LV mass index than those with normal diastolic function. The key echocardiographic parameters of indeterminate DF and the 'cannot be determined' category are depicted in **Figure 1**.

Patients with DD had significantly higher mean H2FPEF scores than those with normal DF as diagnosed by both 2009 and 2016 guidelines (p < 0.001). None of the patients with Grade1-3 DD diagnosed by the 2016 guidelines had H2FPEF scores < 2. Five patients (41.7%) with Grade 1 DD and 12 patients (21.4%) with Grade 2 DD diagnosed by the 2009 guidelines had H2FPEF scores < 2. H2FPEF scores across the DD grades by the 2009 and 2016 guidelines are shown in **Table 7**.
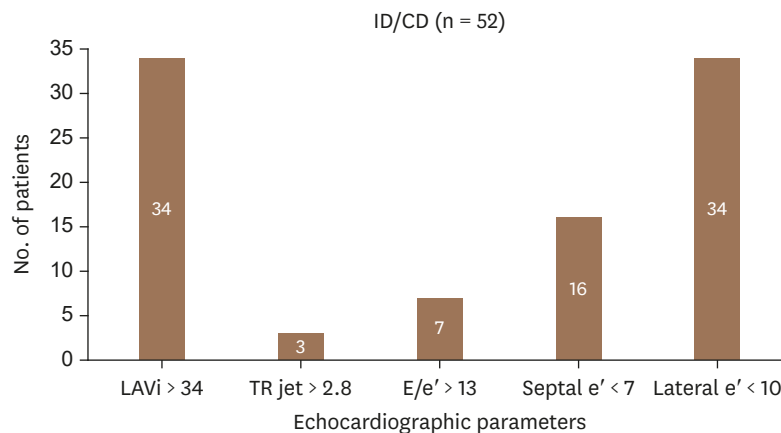

Figure 1. Key echocardiographic variables in ID/CD category.
LAVi: left atrial volume index, ID/CD: indeterminate diastolic function/cannot determine, TR jet: tricuspid regurgitation jet.

Table 7. H2FPEF scores and DD grades by 2009 and 2016 guidelines

	DD grades	H2FPEF score 0–1	H2FPEF score 2–5	H2FPEF score 6–9
2009 guidelines	Grade 1 (n = 12)	5 (41.7)	7 (58.3)	0
	Grade 2 (n = 56)	12 (21.4)	42 (75)	2 (3.6)
	Grade 3 (n = 16)	0	12 (75)	4 (25)
2016 guidelines	Grade 1 (n = 2)	0	2 (100)	0
	Grade 2 (n = 26)	0	24 (92.3)	2 (7.7)
	Grade 3 (n = 16)	0	12 (75)	4 (25)

Values are presented as number (%).
DD: diastolic dysfunction.

DISCUSSION

In the present study, the prevalence of DD and LVFP was assessed by the 2009 ASE and 2016 ASE/EACVI guidelines. We used a systematic 2-step approach of the 2016 recommendations to assess DF, DD grade, and LVFP. The "myocardial disease" entity, although proposed in the 2016 recommendations, was not considered for assessment of DF due to lack of clarity as to which diseases and their severity constituted myocardial disease. The principal findings were as follows. The prevalence of DD using the 2016 guidelines was significantly lower than the 2009 guidelines (9.4% vs. 19.4%). This occurred at the expense of an increase in the prevalence of indeterminate DF (9.8%). There was a moderate agreement between the 2009 and 2016 guidelines.

Almeida et al.,[15] in a community-based study, reported a DD prevalence of 1.4% according to the 2016 guidelines, which was much lower than the prevalence of 38.1% according to the 2009 guidelines. Huttin et al.,[16] in another population-based study, reported a DD prevalence of 1.3% according to the 2016 guidelines and 5.9% according to the 2009 guidelines. Sorrentino et al.[14] reported a DD prevalence of 42.6% and 30.0% according to the 2009 and 2016 guidelines, respectively. Other community-based studies have reported a prevalence of DD ranging from 11.1% to 36%, although obtained by applying criteria other than the 2009 and 2016 ASE guidelines.[20][21]

Our study findings partially agree with those from previous studies because our study was conducted in the hospital setting and we did not consider myocardial disease for DF assessment. Almeida et al.[15] and Huttin et al.[16] enrolled subjects from a population-based cohort and did not consider myocardial disease, thus reporting a very low prevalence of DD with the 2016 guidelines. Sorrentino et al.,[14] in a hospital-based study that did consider the myocardial disease entity, reported a higher prevalence of DD with the 2016 recommendations, although lower than with the 2009 recommendations. Hospital-based studies have always yielded a higher prevalence of DD compared with community-based studies.

Another key finding in our study was the reclassification of Grade 1 and 2 DD; albeit, Grade 3 DD remained in the same class by application of the 2016 guidelines. All patients with Grade 1 DD and a majority of patients with Grade 2 DD by the 2009 guidelines were reclassified to normal DF lower grades or indeterminate DF by the 2016 guidelines. By application of the 2016 guidelines, 4.3% of the subjects with DD were assigned as Grade 1 DD, 6.4% as 'cannot be determined' DD grade, and most as Grade 2 (55.3%) and Grade 3 (34%). In a study by Almeida et al.,[15] none of the patients with DD were assigned Grade 1; in a study by Sorrentino et al.,[14] 18.7% of the patients with DD were assigned Grade 1; and in a study by Sanchis et al.[22] 7% of the patients with DD were assigned Grade 1 by the 2016 guidelines. Sorrentino et al.[14] did

consider myocardial disease, and patients with myocardial disease were diagnosed with DD and thus bypassing the first step of DD assessment. The majority of these patients were categorized as Grade 1 DD with normal LVFP in the second step and hence prevalence of Grade 1 DD was high. The concordance rates are higher for advanced DD between the two guidelines.

Application of the 2016 guidelines resulted in a 9.8% prevalence of indeterminate DF. Sorrentino et al.[14] and Almeida et al.[15] reported 8% and 15.2% indeterminate DF prevalence, respectively. In our study, the majority of patients with indeterminate DF (61.2%) were considered to have DD according to the 2009 guidelines. The indeterminate DF group had only two of the three echocardiographic parameters (E/e′, TR velocity, and LAVi) and those two were discordant. Hence, DD grade could not be assigned as per the 2016 guidelines. These patients possible have a milder form of DD. Failure to reach a consensus in assigning distinct DD grade has been shown to increase risk of death when compared to individuals with normal diastolic function.[23]

In our study, 89.3% of patients with DD had elevated LVFP. The prevalence of elevated LVFP was significantly lower with the 2016 guidelines than with the 2009 guidelines (8.4% vs. 12.8%, respectively). In a study by Sorrentino et al.,[14] 35.74% of the patients with DD had elevated LVFP and the prevalence of elevated LVFP was significantly lower with the 2106 guidelines than the 2009 guidelines (10.7% vs. 21.6%, respectively). This striking difference was due to the consideration of myocardial disease for DF assessment, which contributed to an increased prevalence of DD, wherein the majority were categorized as Grade 1 DD and had normal LVFP. Assessment of LVFP is challenging in patients with normal LV function because of increased discordance of diastolic parameters, unlike in patients with depressed LV function.[24] Studies have reported a significant but modest relationship between individual abnormal 2D parameters, Doppler signals, and LV filling pressures.[17][25-27] Andersen et al.[25] validated the 2016 guidelines and reported that a comprehensive approach involving multiple echocardiographic parameters recommended in the 2016 guidelines significantly improved the diagnostic accuracy, which was 64% for clinical assessment alone and 84% by echocardiography. Obokata et al.[10] in a simultaneous invasive-echocardiographic study reported that the 2016 ASE/EACVI algorithm to diagnose DD was poorly sensitive but fairly specific when used to identify or exclude heart failure with preserved ejection fraction (HFpEF), with high positive predictive values but low negative predictive values. The low sensitivity for this algorithm was caused by a large number of subjects with indeterminate DF. The Euro-Filling study demonstrated that the 2016 guidelines for non-invasive assessment of LVFP are fairly reliable and clinically useful, as well as superior to the 2009 guidelines in estimating invasive LVEDP.[28]

We calculated H2FPEF score and examined its association with DD and DD grades diagnosed by the 2009 and 2016 guidelines. H2FPEF score is a validated tool to predict the probability of HFpEF and has been shown to discriminate HFpEF from non-cardiac causes of dyspnea. Studies have demonstrated the generalizability and prognostic value of the score.[29-32] All patients diagnosed with DD by the 2016 guidelines had H2FPEF scores > 2, suggestive of either intermediate or high probability of HFpEF. Of patients with DD by the 2009 guidelines, 20.2% had H2FPEF scores < 2, suggestive of low probability of HFpEF. This reinforces the fact that DD diagnosed by the 2016 guidelines can predict HFpEF better than the 2009 guidelines.

The addition of TR jet velocity in Algorithm A of the 2016 recommendations seems to be one of the main reasons for the reclassification. TR jet velocity is used to assess PASP which

is a surrogate measure of pulmonary venous hypertension (PVH). PVH is generally seen in patients with advanced DD with chronically elevated LV filling pressures. In our study, only 6.6% had TR jet velocity > 2.8 m/sec. This explains the finding of a significant number of patients with indeterminate DF and the lower prevalence of elevated LVFP.

The 2009 guidelines recommend multiple parameters, and a few of them are less feasible and poorly reproducible. Because of multiple parameters, several combinations of recorded parameters are possible, and they do not specify the hierarchy and the minimum number of parameters required to assign the grade. This makes DD assessment more difficult. In a meta-analysis of 60 studies where the 2009 consensus guidelines were applied, only 17 used a definition of e′ and LAVi to define DD, under which there was even greater heterogeneity within the definitions, as well as further classification. The resulting prevalence of DD in the studies ranged from 12% to 84%, depending upon the definition used.[33]

The 2016 update was published to address these ambiguities. The updated 2016 joint guidelines recommend a simplified 2-step approach with a focus on four key echocardiographic variables for the assessment of DF and LVFP in clinical practice. Echocardiographic indices with low feasibility and poor reproducibility are not recommended. LAVi reflects the chronic elevation of LV filling pressure and Doppler indices reflect filling pressure at the time of echocardiographic examination. Even though these individual parameters correlate with LV filling pressures, their relationship is modest. Hence, the 2016 update recommends a comprehensive approach combining these parameters to increase the diagnostic accuracy of LV filling pressures. Although this oversimplification has reduced the overall prevalence of DD and elevated filling pressures, the identified patients have advanced DD and elevated filling pressures more often than those identified by the 2009 recommendations. The downside of the 2016 criteria is possible underdiagnosis of milder grades of DD, especially if myocardial disease is not considered. Assessment of DF with or without considering myocardial disease in patients with preserved EF doesn't have a significant impact on Grade 2 and Grade 3 DD, or LVFP except for an increase in the prevalence of Grade 1 DD and a decrease in indeterminate DF.[14] This is of clinical concern because studies using various criteria have reported the influence of DD prevalence and grades on clinical outcomes.[34][35] Patients with higher grades of DD and progressive worsening of DD with preserved LVEF have been shown to have increased risk of mortality.[36] It is important and interesting to note that studies have shown that significant DD (Grade 2 or 3) and elevated filling pressures as assessed by the 2016 guidelines correlated with clinical outcomes better than the 2009 guidelines addressing the concerns.[22][37][38]

The updated 2016 joint guidelines also pose certain difficulties, such as 1) no clarity regarding which diseases and their severity constitute myocardial disease; 2) no guidance for use of additional parameters in patients with indeterminate DF and preserved LVEF; 3) TR jet velocity > 2.8 m/sec if present need not be due to elevated LVFP and could be due to precapillary causes; and 4) treated HFpEF patients with reductions in LAVi and peak tricuspid velocity may not meet the criteria for definitive background DD.

Future studies are required to address the implications of considering myocardial disease entity for DF assessment and the clinical significance of diagnosing indeterminate DF category.

Limitations

In our study, one of the main limitations is the lack of invasive assessment to validate the non-invasively assessed LV filling pressures. We have included patients with normal LV systolic function because of increased complexity in the assessment of DD and filling pressures in this subset and the same results cannot be extrapolated to patients with reduced LVEF. Myocardial disease entity was not considered for DF assessment because of lack of clarity regarding what disease and its severity constitute myocardial disease. Certain echocardiographic parameters like Valsalva maneuver-induced changes in transmitral E velocity and Doppler-derived pulmonary venous flow velocities were not acquired. These parameters are useful in specific cardiac diseases, such as atrial fibrillation, cardiomyopathies, and valvular heart disease, which were excluded in our study. Moreover, these parameters are cumbersome and poorly reproducible. Probably the prevalence of indeterminate DF could be lower in laboratories that record these parameters.

Conclusion

The prevalence of DD and elevated LVFP are significantly lower with the application of the 2016 ASE/EACVI guidelines in patients with normal LV systolic function. The concordance between the 2009 ASE and 2016 ASE/EACVI guidelines is moderate. The updated 2016 guidelines identify patients with advanced DD, which correlates better with H2FPEF score than the 2009 guidelines for prediction of HFpEF.

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