Verification of Echocardiographic Assessment of Left Ventricular Diastolic Dysfunction in Patients With Preserved Left Ventricular Ejection Fraction Using the American Society of Echocardiography and European Association of Cardiovascular Imaging 2016 Recommendations

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Background: Non-invasive evaluation of left ventricular (LV) diastolic dysfunction (DD) and elevated LV filling pressure are crucial for diagnosing heart failure. The 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) recommendations for evaluating elevated LV filling pressure (algorithm B) have acceptable diagnostic accuracy, including in patients with reduced LV ejection fraction (EF). No prior study, however, has assessed the diagnostic accuracy of algorithm A of the ASE/EACVI recommendations for evaluating LVDD in patients with normal LVEF.

Methods and Results: We evaluated the clinical relevance of algorithm A in 94 patients who underwent invasive LV pressure measurement. Algorithm A identified invasively defined LVDD (time constant $\tau \geq 48$ ms and/or LV end-diastolic pressure ≥ 16 mmHg) with low sensitivity (22.4%) but high specificity (90.7%). Algorithm A also identified elevated LV filling pressure with low sensitivity (41.7%) but high specificity (87.5%), and with a high negative predictive value (90.9%).

Conclusions: Algorithm A may not be useful for screening LVDD in patients with normal LVEF. Negative findings using algorithm A, however, may identify a patient with normal LVDD with high specificity, and most of such patients will have LV pre-A pressure in the normal range.

Key Words: Diastolic function; Guideline; Left ventricle; Non-invasive

Dyspnea at rest and on exercise can be caused by elevated left ventricular (LV) filling pressure.[1,2] Even when LV filling pressure remains within the normal range at rest, it may increase due to deteriorated LV relaxation and increased LV diastolic stiffness caused by exercise-induced hypertension. LV filling pressure may also increase due to the shortened LV filling time produced by increased heart rate and by myocardial ischemia and so on.[1,2]

In patients with heart failure with preserved LV ejection fraction (HFpEF), dyspnea upon exercise is recognized as a prime symptom of heart failure (HF), and abnormal LV relaxation has been emphasized as an important cause of this symptom in patients with HFpEF.[3-5] In patients with dyspnea upon exercise, it is important to assess the increased LV filling pressure during exercise, but it is difficult to determine the precise LV filling pressure without monitoring pulmonary capillary wedge pressure using a right-sided catheter.[6] Nonetheless, non-invasive evaluation of LV diastolic function at rest can provide substitutional and fundamental information about dyspnea upon exercise.[3-5]

Several investigators have reported the diagnostic validity of detecting increased LV filling pressure using algorithm B of the 2016 American Society of Echocardiography/ European Association of Cardiovascular Imaging (ASE/ EACVI) recommendations[7] for patients with decreased LVEF or with myocardial disease and normal LVEF.[8,9] Algorithm A from the 2016 ASE/EACVI recommendations,[7] however, has not been fully assessed regarding its diagnostic accuracy for evaluating LV diastolic dysfunction (LVDD) in patients with normal LVEF.

In the present study, we evaluated the clinical relevance of algorithm A in patients who underwent sophisticated LV pressure measurement and analysis.

Table 1. Clinical Characteristics, Cardiac Catheterization Data, and Medications

Variables	All subjects (n=94)	Algorithm A		
		Normal DF (n=77)	DD group (n=15)	P-value
Age (years)	69.5±8.4	68.8±8.6	73.3±7.0	0.067
Male gender	79.8	83.1	60.0	0.043
BMI (kg/m²)	23.5±3.0	23.4±2.9	24.4±3.9	0.257
Mean arterial BP (mmHg)	100.2±13.0	99.6±13.2	102.1±11.2	0.484
Heart rate (beats/min)	65.0±12.1	66.3±12.5	59.5±6.7	0.026
τ (ms)	46.3±9.5	45.4±9.4	50.6±9.9	0.054
LVEDP (mmHg)	14.6±5.6	13.6±5.0	18.9±6.6	0.001
LV pre-A (mmHg)	8.2±3.6	7.7±3.4	10.3±3.8	0.008
CAD	89.4	88.3	100	0.163
Prior MI	36.1	35.1	46.7	0.394
Prior PCI	48.9	49.4	53.3	0.881
Prior CABG	10.6	10.4	13.3	0.861
History of HF	4.3	3.9	6.7	0.373
Hypertension	71.2	70.1	80	0.703
Diabetes mellitus	46.8	50.6	33.3	0.400
Hyperlipidemia	74.5	70.1	73.3	0.971
eGFR (mL/min/1.73 m²)	70.2±15.1	70.3±15.6	69.4±13.0	0.830
Hemoglobin (g/dL)	13.2±1.5	13.4±1.4	12.5±1.8	0.097
BNP (pg/mL)	31.1 (14.1–75.8)	25.4 (12.3–58.8)	107.1 (47.4–143.8)	0.001
ACEI	12.8	11.7	20.0	0.628
ARB	38.3	37.7	46.7	0.748
RAS inhibitor	51.1	49.4	66.7	0.219
β-blockers	45.7	45.5	53.3	0.792
Aldosterone antagonists	0	0	0	0.818
Loop diuretics	8.5	9.1	6.7	0.861
Statins	61.7	62.3	66.7	0.876

Data given as mean±SD, %, or median (IQR). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; DD, diastolic dysfunction; DF, diastolic function; eGFR, estimated glomerular filtration rate; HF, heart failure; LV pre-A, left ventricular pre-atrial contraction pressure; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system; τ, time constant of left ventricular pressure decay during isovolumic relaxation.

Methods

Patients
We performed a retrospective cross-sectional study of the 730 patients who underwent cardiac catheterization for evaluation of coronary artery disease (CAD), and comprehensive assessment of LV function using a catheter-tipped micromanometer, at the present hospital between January 2006 and January 2013. All included patients gave their written informed consent for receiving cardiac catheterization at that time. We excluded patients with atrial fibrillation, acute decompensated HF, acute coronary syndrome, primary valvular heart disease, or serum creatinine >1.5 mg/dL, as well as patients lacking suitable Doppler echocardiography for evaluation of LV diastolic function.

Of the 730 patients, 389 underwent echocardiographic evaluation just prior to cardiac catheterization on the same day. Of the 94 patients with LVEF ≥50%, we retrospectively applied algorithm A of the 2016 ASE/EACVI recommendations[7] to evaluate LV diastolic function. Informed consent was again obtained by opt-out from the study participants, and the protocol of this study was approved by the Ethical Guidelines Committee of Nagoya City University Graduate School of Medical Sciences.

Cardiac Catheterization
LV pressure waves were obtained using a catheter-tipped micromanometer (SPC-454D; Millar Instrument, Houston, TX, USA) with a polygraph system (RMC-3000; Nihon Kohden, Tokyo, Japan) in the spine position, prior to using contrast media. From an LV pressure waveform, we calculated the time constant τ during isovolumic relaxation, following the method proposed by Weiss et al.[10] We then obtained the LV pressure at the phase just before left atrial (LA) contraction (pre-A) and the LV end-diastolic pressure (LVEDP). The LV filling pressure was estimated using the LV pre-A pressure, as proposed by Yamamoto et al.[11] After recording the LV pressure waves, we performed biplane contrast left ventriculography and selective coronary angiography.

Doppler Echocardiography
Before diagnostic cardiac catheterization, we performed transthoracic echocardiography using an Aplio 80™ (Toshiba, Japan). LVEF was determined using the biplane modified Simpson's method.[12] In pulsed Doppler studies, we obtained peak velocities of the transmitral inflow waveform during early (E) and late (A) diastole in the apical 4-chamber view. On the same plane, we obtained

Table 2. Echocardiography Parameters

Variables	All patients (n=94)	Algorithm A		
		Normal EF (n=77)	DD group (n=15)	P-value
LVEF (%)	66.0±88.9	66.4±8.7	65.3±9.9	0.623
E wave velocity (cm/s)	65.4±17.6	61.4±14.9	82.5±18.4	<0.001
A wave velocity (cm/s)	81.9±21.5	78.5±20.5	100.0±18.6	<0.001
E/A ratio	0.83±0.25	0.82±0.25	0.84±0.18	0.456
Septal e' (cm/s)	61±1.8	6.4±1.9	4.9±1.3	0.004
Lateral e' (cm/s)	8.1±2.2	8.4±2.3	6.7±1.3	0.007
E/averaged e' ratio	9.7±3.4	8.7±2.3	14.4±3.2	<0.001
TR velocity (m/s)	2.4±0.33	2.3±0.19	2.7±0.46	0.138
LAVI (mL/m²)	23.0±9.6	19.7±6.2	38.9±7.3	<0.001

Data given as mean±SD. A wave velocity, peak inflow velocity during late diastole; averaged e', average of septal e' and lateral e'; DD, diastolic dysfunction; E wave velocity, peak inflow velocity during early diastole; e', mitral annular velocity during early diastole on the septal or lateral side; EF, ejection fraction; LAVI, left atrial maximum volume at LV end-systole indexed by body surface area; LVEF, left ventricular ejection fraction; TR velocity, peak velocity of tricuspid regurgitation flow.

velocity waveforms of mitral annular movement at both the septal and lateral annular corners of the mitral annulus. From the recordings, we obtained each of the peak velocities at early diastole (septal e' and lateral e'), and averaged these values (averaged e'). We next calculated the averaged E/e' ratio. The peak velocity of tricuspid regurgitation flow (TR velocity) was determined using the continuous Doppler method in either the parasternal longitudinal or apical 4-chamber view. Inadequate recording – for example, with a vague TR velocity envelope around the peak during mid-systole – was excluded from analysis. LA maximum volume at LV end-systole (LAV) was computed using the biplane modified Simpson's method, and was indexed by body surface area (LAVI).[12]

Doppler Echocardiography Classification of LVDD According to the 2016 ASE/EACVI Algorithm A

The patients with LVEF ≥50% were classified into 2 groups: normal diastolic function and DD according to algorithm A. In patients with normal LVEF, LVDD was diagnosed using algorithm A, based on the combined presence of the following:[7] average E/e' >14; septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s; TR velocity >2.8 m/s; and LA volume index >34 mL/m². A patient with >50% of these findings would be diagnosed with LVDD, while a patient with <50% of these findings was considered to have normal LV diastolic function. The presence of 50% positive findings resulted in an intermediate decision. In all patients, we obtained septal and lateral e', E/e', and LAVI. However, a TR velocity waveform adequate for precise measurement was obtained in only 16 of 94 patients. When 3 parameters, but not the TR velocity, were available for a patient, algorithm A was applied to the 3 parameters.

Verification of Algorithm A Against the Invasive Parameters of LV Diastolic Function

To verify algorithm A, we used a time constant τ≥48 ms and/or LVEDP ≥16 mmHg as the gold standards of LVDD, in accordance with the consensus statement on how to diagnose diastolic HF from the Heart Failure and Echocardiography Associations of the European Society of Cardiology.[13] We also used an LV pre-A pressure ≥12 mmHg as a surrogate of increased LV filling pressure caused by

LVDD, in accordance with the consensus statement.[13]

Statistical Analysis

Continuous data are presented as mean±SD if normally distributed, and as median (IQR) if non-normally distributed. Categorical data are presented as percentage. To detect differences between 2 categories, we used Student's unpaired t-test for parametric data, and the Mann-Whitney U-test for non-parametric data. We used chi-squared test to evaluate the probability that each dichotomous variable would fall into the right category, as determined by the invasively obtained parameters. The relationship between 2 parameters was evaluated on linear regression analysis. We evaluated the accuracy of a non-invasive diagnosis of LVDD based on its sensitivity, specificity, positive and negative predictive values (PPV and NPV), and accuracy for detecting LVDD as defined using invasively obtained parameters.

Results

Clinical Characteristics

Table 1 lists the patient clinical characteristics overall, and according to group. A total of 84 patients (89.4%) had CAD, 34 (36.1%) had prior myocardial infarction, and 4 (4.3%) had a history of HF.

Assessment of LVDD Using the 2016 ASE/EACVI Algorithm A

According to ASE/EACVI algorithm A, 15 patients were classified as having LVDD, 77 patients were found to have normal LV diastolic function, and the remaining 2 patients were deemed indeterminate. LVEF did not significantly differ between the LVDD and normal LV diastolic function groups, as determined using algorithm A (65.3±9.9 vs. 66.4±8.7%, P=0.623). E wave velocity was faster in patients with LVDD than in those with normal LV diastolic function (82.5±18.4 vs. 61.4±14.9 cm/s, P<0.001), whereas the E/A ratio did not significantly differ between the 2 groups (0.84±0.18 vs. 0.82±0.25, P=0.456). Compared to the patients with normal LV diastolic function according to algorithm A, those with LVDD had significantly higher LVEDP (18.9±6.6 vs. 13.6±5.0 mmHg, P=0.001) and LV pre-A pressure (10.3±3.8 vs. 7.7±3.4 mmHg, P=0.008). The

Table 3. Identification of LVDD and Increased LV pre-A Pressure in Patients With Normal LVEF Using Algorithm A

	Algorithm A		
Available no. patients	n=92		n=2
Judgement	Positive	Negative	Indeterminate
Identification of LVDD			
τ≥48 ms and/or LVEDP ≥16 mmHg	11	38	2
τ<48 ms and LVEDP <16 mmHg	4	39	0
Sensitivity (%)	22.4		–
Specificity (%)	90.7		–
PPV (%)	73.3		–
NPV (%)	50.6		–
Accuracy (%)	54.3		–
Identification of increased LV pre-A pressure			
LV pre-A ≥12 mmHg	5	7	2
LV pre-A <12 mmHg	10	70	0
Sensitivity (%)	41.7		–
Specificity (%)	87.5		–
PPV (%)	33.3		–
NPV (%)	90.9		–
Accuracy (%)	81.5		–

LVDD, left ventricular diastolic dysfunction; NPV, negative predictive value; PPV, positive predictive value. Other abbreviations as in Tables 1,2.

Table 4. Accuracy in Detection of LVDD Using Algorithm A

	Averaged E/e' ratio >14		Septal e'<7 or lateral e'<10 cm/s		TR velocity >2.8 m/s		LAVI >34 mL/m²	
Available no. patients	n=94		n=94		n=16		n=94	
Judgement	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
τ≥48 ms	5	38	36	7	3	6	9	34
τ<48 ms	3	48	44	7	0	7	4	47
Sensitivity (%)	11.6		83.7		33.3		20.9	
Specificity (%)	94.1		13.7		100		92.2	
PPV (%)	62.5		45.0		100		69.2	
NPV (%)	55.8		50.0		53.8		58.0	
Accuracy (%)	56.4		45.7		62.5		59.6	

Abbreviations as in Tables 2,3.

patients with LVDD had a tendency to have a longer time constant τ compared with patients with normal LV diastolic function (50.6±9.9 vs. 45.4±9.4 ms, P=0.054). **Table 2** summarizes the echocardiography data.

Algorithm A identified invasively proven definite LVDD in 11 of 49 patients, and identified invasively proven definite normal LV diastolic function in 39 of 43 patients. Thus, for detecting definite LVDD, algorithm A had a sensitivity of 22.4% and a specificity of 90.7% (**Table 3**). Algorithm A identified elevated LV pre-A pressure in 5 of 12 patients, and identified an LV pre-A pressure in the normal range in 70 of 80 patients. Thus, for detecting an elevated LV pre-A pressure, algorithm A had a sensitivity of 41.7% and specificity of 87.5% (**Table 3**).

For detecting definite LVDD, algorithm A had a PPV of 73.3% and an NPV of 50.6%. For detecting an elevated LV pre-A pressure, algorithm A had a PPV of 33.3% and an NPV of 90.9% (**Table 3**).

Finally, decreased e' identified invasively defined LV abnormal relaxation (τ≥48 ms) with a sensitivity of 83.7%

but a low specificity of 13.7% (**Table 4**).

Correlations Between 2016 ASE/EACVI Recommendations and Invasively Obtained LV Diastolic Function Parameters

Each of the averaged values of E/e', TR velocity, and LAVI had significant correlations with LVEDP and LV pre-A pressure. Average E/e' and LAVI also had significant but weak correlations with τ. In contrast, the septal, lateral, and averaged e' velocities were not correlated with τ, LVEFP, or LV pre-A pressure (**Table 5**).

Discussion

The present results provide novel information regarding verification of algorithm A of the 2016 ASE/EACVI recommendations for diagnosing LVDD in patients with normal LVEF. We assessed the utility of algorithm A from 3 aspects: abnormal LV relaxation, increased LV diastolic stiffness, and elevated LV filling pressure. We found that algorithm A identified invasively defined LV diastolic func-

Table 5. Correlation of Each Parameter for Detecting LVDD in Algorithm A With τ, LVEDP, and LV pre-A

Available no. patients	Averaged E/e' ratio		Septal e'		Lateral e'		Averaged e'	
	n=94		n=94		n=94		n=94	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
τ	r=0.210	0.042	r=−0.172	0.097	r=−0.075	0.470	R=−0.130	0.212
LVEDP	r=0.289	0.005	r=−0.017	0.868	r=−0.042	0.688	R=−0.034	0.747
LV pre-A	r=0.304	0.003	r=−0.119	0.255	r=−0.085	0.417	R=−0.109	0.295

Available no. patients	TR velocity		LAVI	
	n=16		n=94	
	Correlation coefficient	P-value	Correlation coefficient	P-value
τ	r=0.314	0.237	r=0.220	0.033
LVEDP	r=0.598	0.014	r=0.365	<0.001
LV pre-A	r=0.652	0.006	r=0.212	0.040

Abbreviations as in Tables 1–4.

tion with low sensitivity but high specificity. Additionally, algorithm A identified elevated pre-A pressure with low sensitivity, high specificity, and a high NPV.

Prior studies have examined the diagnostic validity of algorithm B of the 2016 ASE/EACVI recommendations for detecting elevated LV pre-A pressure or LVEDP in patients with decreased LVEF, or with myocardial disease and normal LVEF, who underwent an invasive pressure study of the LV.[8,9] In their investigation of 159 patients (25% of whom had decreased LVEF), Lancellotti et al found that average LVEF was 53%, and 64% of patients had symptomatic HF (New York Heart Association category ≥II).[8] They reported that algorithm B identified patients with elevated LVEDP with moderate sensitivity (75%) and moderate specificity (74%).[8] In contrast, Andersen et al investigated 450 patients (including 209 patients with LVEF<50%) and reported that algorithm B identified elevated LV high filling pressure with high accuracy (sensitivity, 87%; specificity, 89%; PPV, 91%; NPV, 87%).[9] Both study cohorts, however, included many patients with reduced LVEF and with HF symptoms. It appears that algorithm B of the ASE/EACVI 2016 recommendations is useful to some extent in clinical settings, in the subjects to which this algorithm can be applied.

To our knowledge, few reports have examined the diagnostic validity of algorithm A of the 2016 ASE/EACVI recommendations for evaluating LVDD in the limited patients with LVEF ≥50%. Almeida et al reported the impact of the 2016 ASE/EACVI recommendations on the prevalence of DD in the general population, excluding those with previously known cardiac disease and LVEF <50%.[14] They found that algorithm A of the 2016 ASE/EACVI recommendations identified a much lower prevalence of LVDD (1.4%)[14] compared with the previously reported prevalence of 38.1% when using the 2009 ASE/EACVI recommendations for the diagnosis of LVDD in such a population.[15] The new 2016 recommendations detected only advanced grades of LVDD with elevated LV filling pressure, meaning that algorithm A has a low sensitivity for detecting LVDD.

No prior study has validated the accuracy of the proposed criteria in algorithm A against the invasively obtained gold standard of LVDD. Algorithm A recommends the diagnosis of LVDD using a combination of parameters with previously determined threshold values for diagnosing LV abnormal relaxation and elevated LV filling pressure. Therefore, here, the aim was to validate the accuracy of algorithm A for diagnosing LVDD relative to LVDD diagnosed using invasive methods based on a prior report from the European Society of Cardiology.[13] Patients were considered to have LVDD if they had a lengthened τ (≥48 ms) and/or an increased LVEDP (≥16 mmHg), reflecting increased LV diastolic stiffness and increased LV pre-A pressure.

We obtained LV pressure data using a high-fidelity catheter-tipped micromanometer, which enabled calculation of the time constant τ of LV pressure decay during isovolumic relaxation – a gold standard parameter for LV relaxation. Lengthening of τ reflects the early stage of LVDD – so-called abnormal relaxation – and is related to the deterioration of exercise intolerance.[2,3] In patients with abnormal relaxation, minimum LV pressure increases as the time constant τ lengthens.[2,16] These changes provoke a loss of blood suction from the LA to the LV during early diastole, causing the elevation of LV filling pressure upon exercise, and producing exercise intolerance.[2,17] Mitral annular motion velocity during early diastole e' is significantly and negatively correlated with the time constant τ in patients with LVEF <50%.[18] In the present study, the correlation between the τ of LV pressure decay and e' was not statistically significant. Septal e'<7 cm/s or lateral e'<10 cm/s, however, identified LV abnormal relaxation with relatively high sensitivity but low specificity. We previously reported that the correlation between τ and e' was significant but weak in patients with LVEF ≥50%.[19]

An increase in E/e', LA volume index, or TR velocity essentially reflects an elevation of LV filling pressure;[20–22] thus, we additionally examined whether algorithm A could identify patients with elevated LV pre-A pressure (a surrogate of LV filling pressure). As predicted, algorithm A detected an elevated LV pre-A pressure, even in this study cohort with preserved LVEF, with improved diagnostic accuracy compared with a lengthened τ and/or increased LVEDP. This finding is similar to that reported by Almeida et al.[14]

Study Limitations

First, the number of patients with adequate recording of the TR velocity envelope was small in the current study. The ASE/EACVI recommendations for evaluating LVDD,

however, already note that adequate recording of a full envelope is not always possible.[7] In the Lancellotti et al study, the percentage of patients in whom TR velocity could be recorded was <40%, although their study cohort included 25% of patients with LVEF <50%.[8] The recommendation itself might therefore be limited given that TR velocity is not necessarily recorded in most patients. Second, this retrospective and cross-sectional study was conducted at a single institute, with a relatively small number of patients. Additionally, algorithm A of the 2016 ASE/EACVI recommendations was applied only to our fixed cohort for whom precise LV pressure measurement and analysis were available. To our knowledge, no prior study has fully validated algorithm A, which is based on expert consensus. Thus, the present study provides useful information regarding the nature of algorithm A.

Conclusions

Algorithm A of the 2016 ASE/EACVI recommendations may not be useful for screening LVDD in patients with normal LVEF. Negative findings using algorithm A, however, may indicate with high specificity that a patient has normal LV diastolic function, and most of such patients may have LV pre-A pressure in the normal range. Additionally, septal e'<7cm/s or lateral e'<10cm/s may be useful in screening for LV abnormal relaxation.

Disclosures

Y.S. is a member of *Circulation Reports*' Editorial Team. The other authors declare no conflicts of interest.

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