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ORIGINAL RESEARCH

Redefining Diastolic Dysfunction Grading

Combination of E/A ≤0.75 and Deceleration Time >140 ms and E/ε′ ≥10

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ABSTRACT

OBJECTIVES This study sought to examine left atrial (LA) mechanics and the prognostic impact of patients with echocardiographic findings of E/A ratio ≤0.75, deceleration time (DcT) of mitral E-wave >140 ms, but E/ε′ ≥10.

BACKGROUND Traditional diastolic dysfunction (DD) grading system could not classify every patient into a specific group. We considered the group of patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 (proposed new DD grade) as a new group in the DD grading system.

METHODS A total of 1,362 consecutive patients were stratified according to the new DD grading system, and the LA volumes, strain, and strain rates were measured by 2-dimensional speckle-tracking analysis. All patients were followed up to determine cardiac death and major adverse cardiac events.

RESULTS An E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 was observed in 227 patients (17%). LA volumes in patients with the new DD grade were between those of the impaired relaxation group and the pseudonormal group. LA strain of the new DD grade was similar to that of the pseudonormal group, whereas LA booster function was preserved as in the impaired relaxation group. During a mean follow-up of 3.0 ± 1.1 years, 25 patients had cardiac death and 61 had major adverse cardiac events. Event-free survival for major adverse cardiac events of the new DD grade was worse than that of the impaired relaxation group but similar to that of the pseudonormal group.

CONCLUSIONS The new DD grade is frequently observed and has a prognosis similar to that of the pseudonormal group but significantly worse than that of the impaired relaxation group. However, LA booster function was maintained at the expense of LA volume enlargement. Thus, the new grade should be a distinct entity for routine DD grading. (J Am Coll Cardiol Img 2014;7:749–58) © 2014 by the American College of Cardiology Foundation.

Determination of diastolic dysfunction (DD) grade using Doppler ultrasound is fundamental and has been routinely practiced in the echocardiography laboratory (1,2). However, current DD grading systems could not classify every patient into 1 of 4 or 5 categories of DD grade, depending on the definition used, and left a substantial portion of patients as indeterminate (3,4). We found that the majority of subjects classified as indeterminate had an E/A ratio ≤0.75, deceleration time (DcT) of the mitral E-wave velocity >140 ms, but an E/ε′ ratio ≥10. Although a main echocardiography textbook labeled this entity as DD grade Ia (5), little is known regarding the left atrial (LA) mechanical properties and the prognosis in this subset of patients.

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

DD = diastolic dysfunction

DcT = deceleration time

ε′ = peak diastolic annular velocity during early diastolic rapid filling

ICC = intraclass correlation coefficient

LA = left atrium

LAV = left atrial volume

LAVI = left atrial volume index

LAVIn = minimal left atrial volume index

LAVIprea = left atrial volume index before the atrial contraction

LAVIx = maximal left atrial volume index

LV = left ventricle

LVEF = left ventricular ejection fraction

MACE = major adverse cardiac events

SRa = late diastolic peak negative strain rate

SRe = early diastolic peak negative strain rate

SRs = peak positive strain rate during systole

Two-dimensional (2D) speckle-tracking echocardiography has been a reliable technique for the assessment of LA mechanics (6–12). We hypothesized that the group with E/A ratio ≤0.75, DcT of mitral E-wave velocity >140 ms, but E/ε′ ≥10 may be a distinct, new entity for the purposes of grading DD. Accordingly, the aims of this study were the following: 1) to determine LA mechanical properties in patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 compared with patients with other traditional DD grades; and 2) to compare the prognosis in this subset of patients to those with other DD grades in a large number of patients.

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METHODS

STUDY SUBJECTS. The study group consisted of 2,015 consecutive patients who had undergone clinically indicated routine transthoracic echocardiography during the period from January 1, 2009 to May 31, 2009 in our echocardiography laboratory. Exclusion criteria included repeated examinations, presence of irregular heart rhythm, rapid heart rates (usually >90 beats/min) causing fusion of the E and A waves, mitral valvular disease, ventricular pacing, and inadequate 2D image quality. The indications for transthoracic echocardiography were categorized as valvular function assessment, ventricular function assessment, chest pain with or without previous history of coronary artery disease, abnormal electrocardiographic findings, and arrhythmia. The institutional review board of the hospital approved the study, and all subjects provided written informed consent prior to participation.

ECHOCARDIOGRAPHY. 2D echocardiographic examinations were performed using commercially available ultrasound machines (Vivid 7, GE Healthcare, Holten, Norway; or Aloka SSD-5500, Hitachi Aloka Medical, Tokyo, Japan). Each subject underwent comprehensive 2D echocardiography, pulsed- and continuous-wave Doppler examination, and tissue Doppler imaging.

ASSESSMENT OF LV DIASTOLIC FUNCTION GRADE. From mitral inflow velocities, the E- and A-wave velocities, DcT of the E-wave, and E/A velocity ratio were measured. The peak diastolic annular velocity during early diastolic rapid filling (ε′) at the lateral corner of the mitral annulus was also measured for the calculation of E/ε′ ratio in all subjects. All Doppler measurements were averaged over 3 consecutive beats. LV diastolic function was categorized into 4 groups: normal, impaired relaxation, pseudonormal, and restrictive physiology, as previously described by Redfield (13) (**Table 1**) and E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10. Subjects were required to have at least 2 Doppler criteria consistent with a DD grade to be so classified. Subjects with 1 criterion for DD or those whose parameters were borderline and suggestive of, but not definite for DD, were classified as indeterminate.

2D SPECKLE TRACKING ANALYSIS OF THE LA WALL. Three consecutive beats were acquired in the apical 4-chamber view (62 ± 6 frames/s) using the second harmonic mode. 2D speckle tracking of the LA wall was performed using vendor-independent speckle tracking software (2D Cardiac Performance Analysis, TomTec Imaging Systems GmbH, Unterschleissheim, Germany). After importing datasets as digital imaging and communication in medicine data, the endocardial border of the LA wall was manually traced at the end-systolic frame (just before the mitral valve opening). Software subsequently performed speckle tracking on the LA wall and generated left atrial volume (LAV) curves according to time, from which maximum left atrial volume index (LAVIx) and minimum left atrial volume index (LAVIn) and left atrial volume index prior to atrial contraction (LAVIprea) were measured. LA reservoir volume (LAVIx - LAVIn) and LA active emptying volume (LAVIprea - LAVIn) were calculated. All volume data were indexed to body surface area. The software also provided the LA strain and strain rate. We used the onset of the R-wave as the reference point to calculate the LA strain and strain rate (8,10). The software divided the tracking line into 6 segments and generated regional longitudinal strain curves in each segment and averaged longitudinal strain curve from 6 segmental strain curves. Global LA longitudinal strain was determined as a peak positive strain value from averaged longitudinal strain curve. We also determined the peak positive strain rate during systole (SRs), early diastolic peak negative strain rate (SRe), and late diastolic peak negative strain rate (SRa) from averaged LA longitudinal strain rate curve in each patient.

LA reservoir function was assessed by the expansion index, defined as (LAVIx - LAVIn)/LAVIn and global LA longitudinal strain. LA booster function was assessed by the active emptying index, defined as (LAVIprea - LAVIn)/(LAVIx - LAVIn) (11) and

TABLE 1 Doppler Criteria for Classification of Diastolic Function

	Normal	Impaired Relaxation	Pseudonormal	Restrictive
Mitral inflow	$0.75 < E/A < 1.5$ $DcT > 140$ ms	$E/A \le 0.75$ $DcT > 140$ ms	$0.75 < E/A < 1.5$ $DcT > 140$ ms	$E/A > 1.5$ $DcT < 140$ ms
Mitral inflow at peak Valsalva maneuver	$\Delta E/A < 0.5$	$\Delta E/A < 0.5$	$\Delta E/A \ge 0.5$	$\Delta E/A \ge 0.5$
TDI	$E/\varepsilon' < 10$	$E/\varepsilon' < 10$	$E/\varepsilon' \ge 10$	$E/\varepsilon' \ge 10$
PV flow	$S \ge D$ $ARdur < Adur$	$S > D$ $ARdur < Adur$	$S < D$ or $ARdur > Adur + 30$ ms	$S < D$ or $ARdur > Adur + 30$ ms

Adur = duration of mitral inflow at atrial contraction; ARdur = duration of pulmonary venous atrial reversal flow; D = diastolic forward flow; DcT = deceleration time; ε′ = peak diastolic annular velocity during early diastolic rapid filling; PV = pulmonary venous; S = systolic forward flow; TDI = tissue Doppler imaging.

global SRa. To determine the Frank-Starling law, LAVIprea and LAVprea - LAVIn were plotted for each DD group.

FOLLOW-UP STUDY. Follow-up information was obtained regularly in the outpatient clinic. Telephone contacts with patients, physicians, and next of kin were performed if the patient had been treated in another hospital. The final follow-up date was determined as of October 1, 2012. The primary endpoint was cardiac death. The secondary endpoint was major adverse cardiac events (MACE), including cardiac death, nonfatal myocardial infarction, and congestive heart failure or major vascular disorder requiring admission.

STATISTICAL ANALYSIS. Continuous data were expressed as mean ± SD. Categorical data are presented as a number or percentage. Data points describing LAV according to time were exported to a spreadsheet program (Microsoft Excel, Microsoft Corp., Redmond, Washington) to calculate LAV waveforms in each subject. To adjust for intersubject differences in heart rate and frame rate, time sequences were normalized as a percentage of systolic duration (i.e., at end systole, t was 100%) as well as diastolic duration (i.e., at end diastole, t was 100%). All statistical analysis was carried out using commercial software (JMP, version 11.0, SAS Institute Inc., Cary, North Carolina; or SPSS, version 21.0, SPSS Inc., Chicago, Illinois). Categorical variables were compared using the chi-square test. Continuous data were analyzed using analysis of variance with post-hoc analysis of the Bonferroni correction between DD grades. Kaplan-Meier survival analysis was used to plot cardiac death and MACE. Differences between survival curves were obtained using the log-rank test. Incremental value of DD grade was assessed in levels using the nested Cox regression model. Level I consisted of age and sex. In level II, left ventricular ejection fraction (LVEF) was added to the variables in level I. In level III, ε′ or LAVIx were fitted on top of the level II variables. And in level IV, the new DD grading system was included in the final step of the evaluation. Harrell C of each level was used as an analogous overall measure of discrimination for predicting survival time. A p value of <0.05 was considered significant. Intraobserver and interobserver variabilities for the LAV and strain/strain rate measurements using 2D speckle tracking echocardiography were determined in 20 randomly selected patients and reported as the percentage of variability defined as absolute difference in percentage of the mean of repeated measurements and intraclass correlation coefficient (ICC). Observer variability for DD grade including new DD grade ($E/A \le 0.75$, $DcT > 140$ ms, but $E/\varepsilon' \ge 10$) was assessed by kappa statistics in 100 randomly selected patients.

RESULTS

Among 2,015 patient reports, 653 were excluded from analysis, mainly because of repeat examinations or arrhythmias, leaving 1,362 patients in the final group for analysis (Fig. 1). Traditional DD grade could not classify 318 patients (23.4%). Among them, the number of patients who satisfied the composite criterion $E/A \le 0.75$, $DcT > 140$ ms, but $E/\varepsilon' \ge 10$ was 227 (16.7%). Thus, a total of 91 patients (6.7%) could not be classified according to the new DD grade criteria. The baseline clinical characteristics and fundamental echo parameters of the study patients in the 5 DD groups are shown in Tables 2 and 3. The group of patients with $E/A \le 0.75$, $DcT > 140$ ms, but $E/\varepsilon' \ge 10$ was characterized by more advanced age, higher A velocity, and lower ε′ compared with the other traditional DD group. The prevalence of mitral annular calcification was also highest (19.3%) in the group with $E/A \le 0.75$, $DcT > 140$ ms, but $E/\varepsilon' \ge 10$.

LEFT ATRIAL MECHANICAL PROPERTIES. 2D speckle tracking analysis of the LA wall could not be performed in 155 patients due to missing image data in 9 patients and poor LA wall tracking due to inadequate image quality in 146 patients. Thus, the feasibility for LA speckle tracking analysis was 89%. Representative

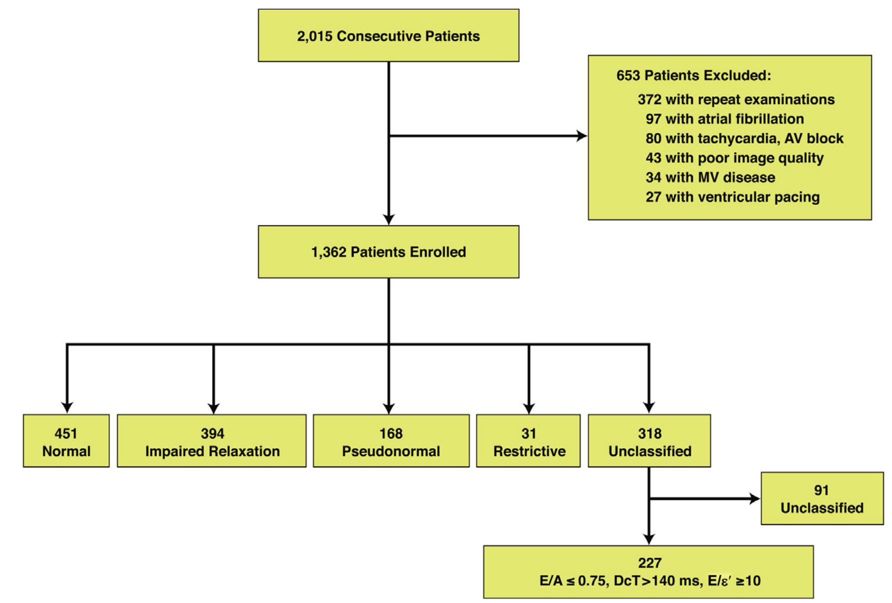

FIGURE 1 Study Population

We enrolled 2,015 consecutive patients who underwent transthoracic echocardiography in our laboratory where 653 patients were excluded. A total of 1,362 patients were classified into the following groups: normal; impaired relaxation; pseudonormal; restrictive; E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10. Or they were unclassified. AV = atrioventricular; DcT = deceleration time; ε′ = peak diastolic annular velocity during early diastolic rapid filling; MV = mitral valve.

cases are shown in Online Figures 1 and 2. **Figure 2** shows the LAV curves in the 5 DD groups. As expected, LAVIx, LAVIprea, and LAVIn increased parallel with the traditional DD grade. The absolute values of the LAVI curves in the group of patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 were between those of the impaired relaxation group and the pseudonormal group. However, the percentage contribution of LA contraction was similar to that in the impaired relaxation group. Scatter plots between LAVIprea and LAVIprea - LAVIn, reflecting the Frank-Starling relationship of the LA, revealed that there was significant correlation between them in the normal (r^2 = 0.48) and impaired relaxation groups (r^2 = 0.49); however, this relation became weak in the group of patients who showed E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 (r^2 = 0.29) and the pseudonormal group (r^2 = 0.24), and the relation was lost in the restrictive physiology group (r^2 = 0.09). **Table 4** summarizes the LA mechanical properties among the 5 DD groups. LA strain and strain rates impaired in accordance with the traditional DD grade. LA strain, SRs, and SRe in the group of patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 were similar to those of the pseudonormal group, and the values were significantly reduced compared with those of the impaired relaxation group. Regarding booster function, active emptying index and SRa in the group of patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 were significantly higher compared with those of the pseudonormal group.

PROGNOSTIC VALUE. During a mean follow-up period of 3.0 ± 1.1 years, 25 patients suffered cardiac death and 61 had MACE. **Figure 3** depicts the Kaplan-Meier survival analysis regarding cardiac death and MACE among the 5 DD groups. For both cardiac death and MACE, patients with restrictive physiology showed significantly worse prognosis than did patients in the other 4 groups. For cardiac death, the new DD group was nearly the same as the pseudonormal group. For MACE, the prognosis in patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 was again nearly identical to those in the pseudonormal group, but significantly worse than for the prognosis of the impaired relaxation group or normal group (**Table 5**).

Electronic medical records searches revealed that 148 patients had heart failure symptoms. The prevalence of heart failure symptoms increased according

TABLE 2 Clinical Characteristics of Study Subjects (n = 1,362)

Age, yrs	65 ± 16
Male	623 (46)
Body surface area, m^2	1.57 ± 0.21
Heart rate, beats/min	71 ± 13
Systolic blood pressure, mm Hg	139 ± 23
Diastolic blood pressure, mm Hg	77 ± 14
Medical history	
Hypertension	878 (65)
Diabetes	516 (38)
Hypercholesterolemia	492 (36)
Hemodialysis	78 (5)
Medical diagnosis	
Coronary artery disease	119 (9)
Prior myocardial infarction	81 (6)
Aortic valve disease	64 (5)
Cardiomyopathy	17 (1)
Cancer	346 (25)
Indication of echocardiography	
Assessment of ventricular functions	517 (38)
Symptom evaluations	389 (29)
Suspected or known CAD	218 (16)
Arrhythmia or abnormal ECG	153 (11)
Assessment of valvular functions	85 (6)

Values are mean ± SD or n (%).
CAD = coronary artery disease; ECG = electrocardiogram.

to the advanced stage of DD grades (normal: 4.4%, impaired relaxation: 10.9%, E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10: 11.9%, pseudonormal: 23.8%, restrictive: 58.1%; $p < 0.0001$). In symptomatic patients, only the restrictive group had a significantly worse prognosis for future cardiac death and MACE due to limited sample size (Online Figs. 3A and 3B). Interestingly, in asymptomatic patients, prognosis in the group of patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 was significantly worse than the prognosis in the normal group and the pseudonormal group for cardiac death. Regarding MACE, this new DD group had significantly worse prognosis than did the normal, impaired relaxation, and pseudonormal groups (Online Figs. 3C and 3D, Online Table 1).

Nested regression models showed that the new DD grading system had incremental value in addition to age, sex, LVEF, and diastolic function parameters either ε′ or LAVIx (**Fig. 4**). In these models, the predictive power was first significantly strengthened by the addition of LVEF. However, the prognostic power of these models was further improved by the addition of the new DD grading system.

TABLE 3 Clinical and Echocardiographic Characteristics of Study Population (n = 1,271)

	Normal (n = 451)	Impaired Relaxation (n = 394)	E/A ≤0.75, DcT >140 ms, E/ε′ ≥10 (n = 227)	Pseudonormal (n = 168)	Restrictive (n = 31)	p Value
Age, yrs	58 ± 15*	71 ± 9*	75 ± 9	70 ± 11*	67 ± 11*	<0.001
Men/women	211/240	176/218	98/129	82/86	16/15	0.7279
HR, beats/min	70 ± 12	73 ± 14	72 ± 12	68 ± 12*	72 ± 14	<0.001
SBP, mm Hg	134 ± 20*	143 ± 23*	149 ± 24	145 ± 23	135 ± 30*	<0.001
DBP, mm Hg	78 ± 13	78 ± 13	80 ± 14	76 ± 14	70 ± 16*	0.0014
LVEDVI, ml/m^2	60 ± 13*	58 ± 16*	66 ± 26	72 ± 28*	102 ± 45*	<0.001
LVESVI, ml/m^2	21 ± 8*	20 ± 9*	28 ± 22	30 ± 25	62 ± 45*	<0.001
LVEF, %	66 ± 9*	66 ± 10*	62 ± 15	62 ± 16	45 ± 19*	<0.001
E velocity, cm/s	67 ± 14	53 ± 11*	68 ± 17	87 ± 21*	113 ± 28*	<0.001
A velocity, cm/s	68 ± 15*	86 ± 17*	109 ± 24	89 ± 23*	53 ± 27*	<0.001
E/A ratio	1.01 ± 0.24*	0.63 ± 0.11	0.63 ± 0.11	1.02 ± 0.26*	2.62 ± 1.22*	<0.001
DcT, ms	215 ± 53*	257 ± 67	254 ± 83	215 ± 65*	128 ± 20*	<0.001
ε′, cm/s						
IVS	6.8 ± 1.9*	5.2 ± 1.4	4.0 ± 1.2	5.1 ± 1.5*	4.8 ± 1.7	<0.001
Lateral	9.4 ± 2.5*	7.5 ± 1.8*	4.9 ± 1.5	6.1 ± 1.7*	6.7 ± 2.4*	<0.001
Average	8.1 ± 2.0*	6.3 ± 1.4*	4.4 ± 1.2	5.6 ± 1.4*	5.7 ± 1.9*	<0.001
E/ε′						
Lateral	7.4 ± 1.7*	7.4 ± 1.8*	14.8 ± 5.2	15.2 ± 5.5	19.5 ± 9.6	<0.001
Average	8.6 ± 1.9*	8.7 ± 2.0*	16.0 ± 4.9	16.3 ± 5.4	22.0 ± 8.9	<0.0001
MAC	10 (2.2)	33 (8.3)	44 (19.3)	26 (15.4)	1 (3.2)	<0.001

Values are mean ± SD, n, or n (%). *p <0.05 compared with value for the E/A ≤0.75, DcT > 140 ms, but E/e′ ≥10 group.
DBP = diastolic blood pressure; DcT = deceleration time; e′ = peak diastolic lateral annular velocity during early diastole; HR = heart rate; IVS = interventricular septum; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MAC = mitral annular calcification; SBP = systolic blood pressure.

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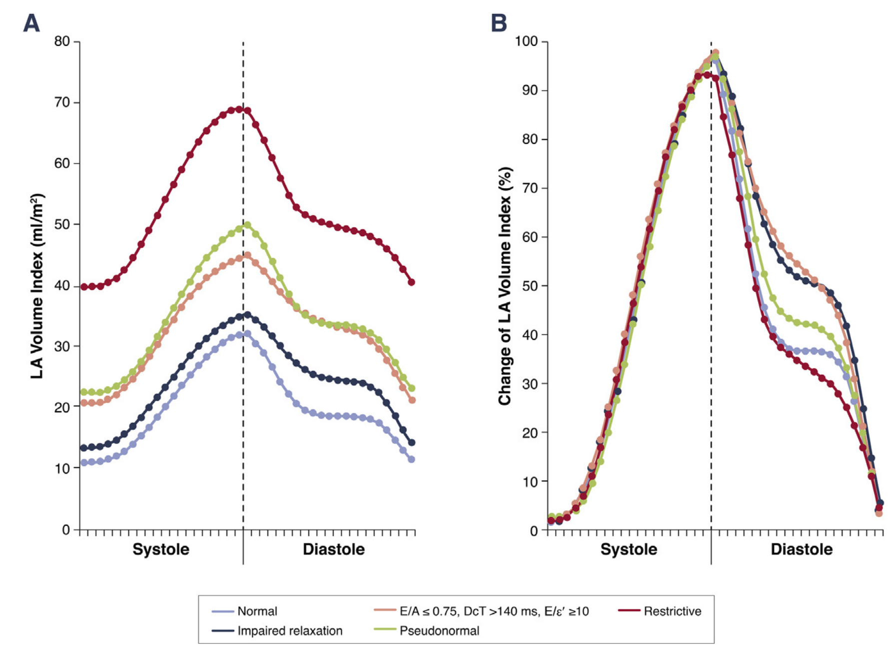

FIGURE 2 LA Volumes Among 5 DD Grades

(A) Left atrial (LA) volumetric change in each diastolic dysfunction (DD) group over 1 cardiac cycle. The y axis denotes the absolute value of LA volumes. The dotted vertical line represents the boundary between systole and diastole. **(B)** Percentage of change of LA volume in each DD group in 1 cardiac cycle. The percentage contribution of LA volume index before the atrial contraction is large in the impaired relaxation group and E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group. This contribution decreased in the pseudonormal and restrictive physiology groups. Abbreviations as in Figure 1.

OBSERVER VARIABILITIES. Intraobserver variability of LAV, strain, and strain rates were 8 ± 7%, 11 ± 7%, and 13 ± 10%, respectively. The corresponding values of interobserver variability were 12 ± 13%, 13 ± 13%, and 13 ± 13%, respectively. Intraobserver ICC for LAV, strain, and strain rates were 0.994, 0.977, and 0.959, respectively. The corresponding values of interobserver ICC were 0.995, 0.936, and 0.944, respectively. The levels of intraobserver and interobserver agreement for categorizing DD groups using the kappa statistic were 93% and 86%, respectively.

DISCUSSION

The major findings in this study were as follows: 1) the majority of patients who could not be classified by the current DD grading system satisfied the new DD grade with composite criteria of E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10; 2) the absolute values of LAVI in this group were between impaired relaxation group and pseudonormal group; 3) although LA strain, SRs and SRe in this group was similar to pseudonormal group, the active emptying index and SRa were preserved and better than those for the pseudonormal group; 4) the prognosis of this group was identical to that of the pseudonormal group, but significantly worse than that of the impaired relaxation group; and 5) the new DD grading system provided significant, incremental power over age/sex, LVEF, and traditional diastolic function parameters for predicting future cardiovascular events.

LA MECHANICAL PROPERTIES. 2D speckle-tracking echocardiography is useful for quantifying LA mechanical properties, including LAV (11), strain, and strain rates (7,8,10,12,14). Interestingly, the absolute LAV curve in the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group was clearly different from that in both the impaired relaxation group and the pseudonormal group (Fig. 2A). However, regarding the percentage contribution of active LA function (booster function), the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group was similar to the impaired relaxation group but different from the pseudonormal group (Fig. 2B). Global LA strain and SRs and SRe in this group were similar to those in the pseudonormal

TABLE 4 LA Mechanical Parameters of Each DD Grade

	Normal	Impaired Relaxation	E/A ≤0.75, DcT >140 ms, E/ε′ ≥10	Pseudonormal	Restrictive	p Value
LAVIx, ml/m^2	32.5 ± 10.2*	35.7 ± 12.3*	44.7 ± 16.5	52.4 ± 17.7*	67.5 ± 22.4*	<0.0001
LAVIprea	18.7 ± 7.3*	24.8 ± 10.5*	33.2 ± 14.6	35.0 ± 14.5	48.9 ± 21.8*	<0.0001
LAVIn	10.5 ± 5.6*	13.2 ± 7.9*	20.2 ± 12.3	23.6 ± 12.8	46.1 ± 44.4*	<0.0001
LAVIprea - LAVIn	8.1 ± 3.1*	11.3 ± 4.4*	12.9 ± 4.7	11.5 ± 4.9*	9.5 ± 5.1*	<0.0001
EI, %	267 ± 186*	231 ± 158*	173 ± 132	162 ± 108	89 ± 64	<0.0001
AEI, %	37 ± 12*	50 ± 13	52 ± 14	41 ± 14*	31 ± 13*	<0.0001
LA strain, %	46.5 ± 18.0*	40.2 ± 15.9*	31.1 ± 13.0	32.9 ± 16.2	22.4 ± 14.1	<0.0001
LA SRs, s-1	1.71 ± 0.63*	1.52 ± 0.59*	1.23 ± 0.50	1.30 ± 0.55	0.94 ± 0.57	<0.0001
LA SRe	-0.94 ± 0.45*	-0.66 ± 0.39*	-0.53 ± 0.39	-0.61 ± 0.39	-0.49 ± 0.25	<0.0001
LA SRa	-1.23 ± 0.49*	-1.29 ± 0.48*	-1.09 ± 0.43	-0.89 ± 0.44*	-0.54 ± 0.39*	<0.0001

Values are mean ± SD. *p < 0.05 compared with the value for the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group.

AEI = active emptying index; DcT = deceleration time; DD = diastolic dysfunction; EI = expansion index; LA = left atrial; LAVIprea = left atrial volume index before atrial contraction; LAVIn = minimal left atrial volume index; LAVIx = maximal left atrial volume index; SRa = late diastolic peak negative strain rate; SRe = early diastolic peak negative strain rate; SRs = peak positive strain rate during systole.

group. However, SRa were more preserved compared with those of the pseudonormal group. These results suggested that the group of patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 were in transition from impaired relaxation to pseudonormal demonstrated by LA mechanical properties. In patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10, LA booster function still maintained at the expense of LAV enlargement. However, further diastolic dysfunction deterioration and LA dilation triggered the obvious decline in the active LA function and failure of Frank-Starling law associated with poor prognosis. We suspect that this is a reason why the prognosis was similar between the pseudonormal group and E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group.

PROGNOSTIC VALUE. Proper assessment of DD grade can offer prognostic information in various

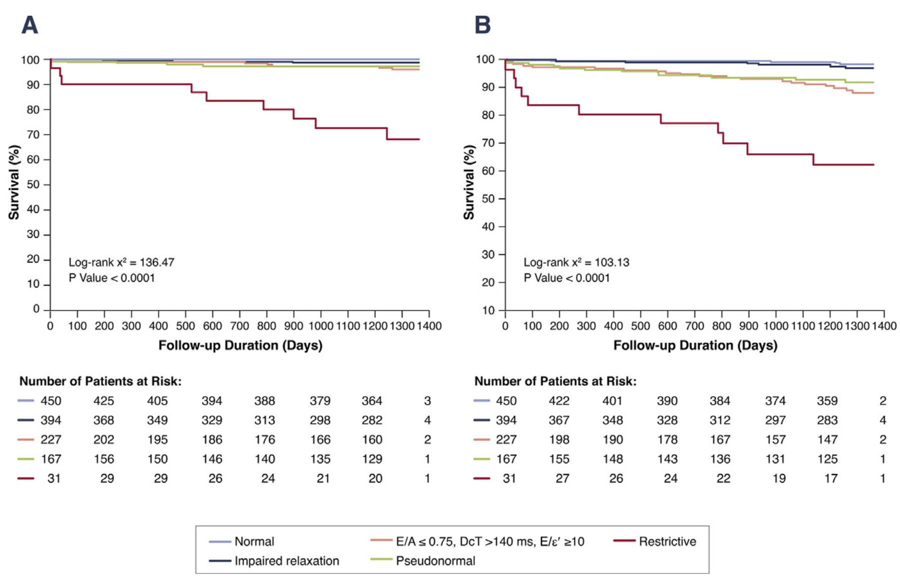

FIGURE 3 Survival Analysis of Cardiac Death and MACE

(A) Kaplan-Meier survival analysis of cardiac death. Restrictive physiology showed the worst prognosis compared with that of the other 4 groups. **(B)** Kaplan-Meier survival analysis of major adverse cardiac events (MACE). The prognosis of the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group appeared to be nearly identical to that of the pseudonormal group, though significantly worse than those of the normal and impaired relaxation groups. Abbreviations as in Figure 1.

TABLE 5 Pairwise Comparison of DD Groups Between New DD Grade (E/A ≤0.75, DcT >140 ms, E/ε′ ≥10) and Other DD Grades

	Cardiac Death		MACE	
	Log-Rank Chi-Square	p Value	Log-Rank Chi-Square	p Value
New DD grade vs. normal	14.9840	<0.0001*	24.8223	<0.0001*
New DD grade vs. impaired relaxation	3.6272	0.0568	15.9199	<0.0001*
New DD grade vs. pseudonormal	0.0157	0.9004	0.4371	0.4916
New DD grade vs. restrictive	31.3695	<0.0001*	17.4785	<0.0001*

*$p < 0.05$.
MACE = major adverse cardiac events; other abbreviations as in Tables 1 and 4.

clinical scenarios. Although several criteria for the classification of DD have been reported (15,16), up to 40% of those patients could not be classified into a specific DD grade, resulting in no prognostic information (3,13,17,18). In this series of consecutive patients who underwent routine echocardiography in our laboratory, we found that 23% of patients were unclassified using the Redfield criteria. However, the majority of patients (71%) not classified in the current DD grading system could satisfy the composite criteria E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10. However, there was a paucity of data regarding the prognostic value of this criteria. In the community-based study by Redfield (13) on assessing systolic and diastolic ventricular dysfunction, patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 were reported as impaired relaxation with moderate elevation of LV filling pressures. The investigators determined all-cause mortality in 3 DD categories: 1) impaired relaxation without evidence of increased filling pressures; 2) E/A ≤0.75 and DcT >140 ms, but E/ε′ ≥10 grouped with pseudonormal; and 3) restrictive physiology. Thus, there was no separate survival analysis performed for the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group. Although the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group was termed the Ia grade in a major echocardiography text (5), no outcome data were reported. Another study published recently from the Mayo Clinic also described E/A ≤0.75, DcT >140 ms but E/ε′ ≥10 as grade Ia (19). However, they also did not report the prevalence and prognostic value of this grade Ia for patients who would develop heart failure and/or atrial fibrillation in their population-based study. We observed that

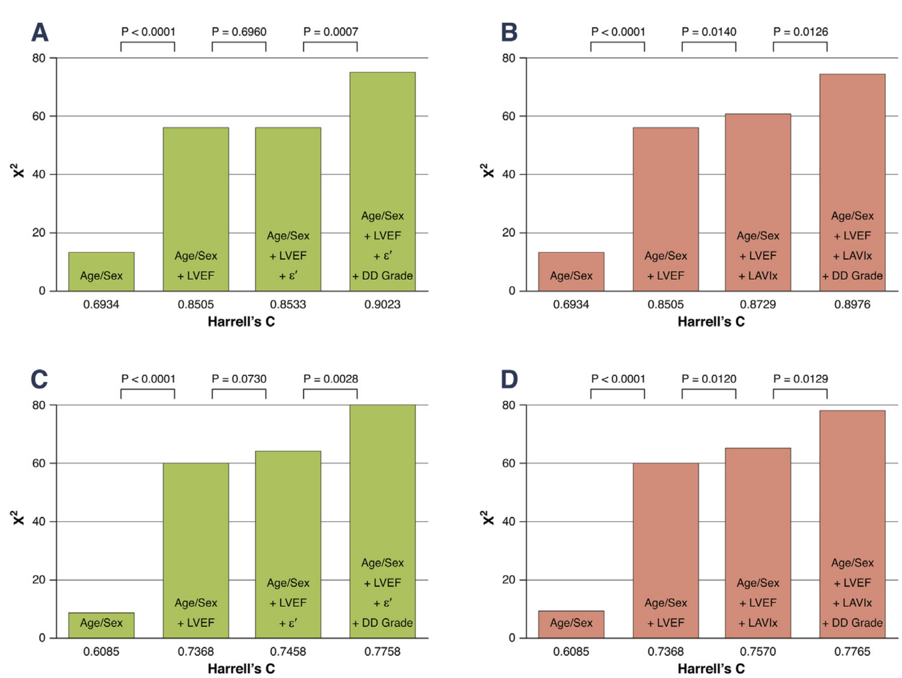

FIGURE 4 Nested Regression Model

In level I, the Cox proportional hazards were calculated for cardiac death **(A and B)** and MACE **(C and D)** with independent variables age and sex. In level II, left ventricular ejection fraction (LVEF) was fitted on top of level I. In level III, the diastolic parameters of either ε′ **(A** and **C)** or maximum left atrial volume index (LAVIx) **(B and D)** were fitted on top of level II. And in level IV, the new DD grading system was fitted on top of level IV. Significance for incremental values was assessed in between each 2 consecutive levels. Abbreviations as in Figures 2 and 3.

the prognostic value of the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group was similar to that of the pseudonormal group but significantly worse than that of the impaired relaxation group for predicting future MACE. Although the LV inflow pattern appeared similarly in the impaired relaxation group and the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group, our findings in this study indicated that those patients' prognosis was distinctly different.

CLINICAL IMPLICATIONS. Although discrimination of the E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 group from the traditional impaired relaxation group is relatively straightforward, we often ascribe these patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 into the impaired relaxation group rather than the pseudonormal group. However, our results showed that patients with E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 have already had an advanced stage of DD. Therefore, these patients should be managed differently and aggressive treatment instituted while the LA booster function is still preserved. Serial follow-up of echocardiography using the proposed classification would offer us clues as to how successful the medical treatment has been.

STUDY LIMITATIONS. First, this was a retrospective single-center study. Therefore, there may be recall bias. Second, there was no gold standard to verify the accuracy of strain measurements. However, the strain value in patients with normal diastolic function was nearly identical to the values of healthy subjects in previous publications (6,14,20). We also believe that study population was large enough to establish the range of strain/strain rates in each DD grade compared with those of the previous studies (7,9). Third, the low event number of cardiac death and MACE in multivariate regression models incurs the risk of overfitting. Thus, interpretation is cautioned. Last, there was always potential error in interpreting diastolic function. However, the levels of interobserver and intraobserver agreement in this new DD grading system were 86% and 93%, respectively, and the values were better than those of the previously published study (21).

CONCLUSIONS

This study revealed that the composite criteria E/A ≤0.75, DcT >140 ms, but E/ε′ ≥10 represented a distinct, new entity within the DD grading system. The new group occupies an important transitional position from a mild to a more advanced stage of DD. Although LA booster function was still preserved, it was associated with a poor outcome that was similar to that of the pseudonormal group.

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REFERENCES

1. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.

2. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.

3. Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality rate in patients with diastolic dysfunction and normal systolic function. Arch Intern Med 2011;171:1082–7.

4. Møller JE, Pellikka PA, Hillis GS, Oh JK. Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. Circulation 2006;114:438–44.

5. Oh JK, Seward J, Tajik A. The Echo Manual. Philadelphia, PA: Lippincott Williams & Wilkins, 2006.

6. Cameli M, Caputo M, Mondillo S, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. Cardiovasc Ultrasound 2009;7:6.

7. Khan U, de Simone G, Hill J, Tighe D, Aurigemma G. Depressed atrial function in diastolic dysfunction: a speckle tracking imaging study. Echocardiography 2013;30:309–16.

8. Kurt M, Tanboga IH, Aksakal E, et al. Relation of left ventricular end-diastolic pressure and N-terminal pro-brain natriuretic peptide level with left atrial deformation parameters. Eur Heart J Cardiovasc Imaging 2012;13:524–30.

9. Motoki H, Borowski A, Shrestha K, et al. Impact of left ventricular diastolic function on left atrial mechanics in systolic heart failure. Am J Cardiol 2013;112:821–6.

10. Obokata M, Negishi K, Kurosawa K, et al. Incremental diagnostic value of LA strain with leg lifts in heart failure with preserved ejection fraction. J Am Coll Cardiol Img 2013;6:749–58.

11. Okamatsu K, Takeuchi M, Nakai H, et al. Effects of aging on left atrial function assessed by two-dimensional speckle tracking echocardiography. J Am Soc Echocardiogr 2009;22:70–5.

12. Vianna-Pinton R, Moreno CA, Baxter CM, Lee KS, Tsang TSM, Appleton CP. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. J Am Soc Echocardiogr 2009;22:299–305.

13. Redfield MM. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

14. Saraiva RM, Demirkol S, Buakhamsri A, et al. Left atrial strain measured by two-dimensional speckle tracking represents a new tool to evaluate left atrial function. J Am Soc Echocardiogr 2010;23:172–80.

15. Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. Circulation 2009;120:802–9.

16. Tschöpe C, Paulus WJ. Is echocardiographic evaluation of diastolic function useful in determining clinical care? Doppler echocardiography yields dubious estimates of left ventricular diastolic pressures. Circulation 2009;120:810–20, discussion 820.

17. Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. Heart 2006;92:1259–64.

18. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.

19. Vogel MW, Slusser JP, Hodge DO, Chen HH. The natural history of preclinical diastolic dysfunction: a population-based study. Circulation: Heart Fail 2012;5:144–51.

20. Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. Circ Cardiovasc Imaging 2009;2:10–5.

21. Unzek S, Popovic ZB, Marwick TH, for the Diastolic Guidelines Concordance Investigators. Effect of recommendations on interobserver consistency of diastolic function evaluation. J Am Coll Cardiol Img 2011;4:460–7.

KEY WORDS diastolic dysfunction, echocardiography, left atrium, prognosis, speckle tracking

APPENDIX For a supplemental table and figures, please see the online version of this article.