Research Paper

Association of Increased Arterial Stiffness and P Wave Dispersion with Left Ventricular Diastolic Dysfunction

Wei–Chung Tsai[1,2], Kun–Tai Lee[1,3], Hsuan-Fu Kuo[1], Wei-Hua Tang[1], Shih-Jie Jhuo[1], Chih–Sheng Chu[1,3], Tsung–Hsien Lin[1,3], Po–Chao Hsu[1], Ming-Yen Lin[4], Feng-Hsien Lin[2], Ho–Ming Su[1,2,3 ✉], Wen-Chol Voon[1,3], Wen–Ter Lai[1,3], Sheng–Hsiung Sheu[1,3]

1. Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan;
2. Department of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan;
3. Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan;
4. Department of Public Health, Kaohsiung Medical University, Kaohsiung, Taiwan.

✉ Corresponding author: Ho–Ming Su, Division of Cardiology, Department of Internal Medicine; Kaohsiung Medical University Hospital, No.100, Ziyou 1st Rd., Kaohsiung City 807, Taiwan. Tel: (886)(7) 3121101 EXT. 7742 Fax: (886)(7) 3234845 E-mail: cobeshm@seed.net.tw.

Abstract

Background: The association between increased arterial stiffness and left ventricular diastolic dysfunction (LVDD) may be influenced by left ventricular performance. P wave dispersion is not only a significant determinant of left ventricular performance, but is also correlated with LVDD. This study is designed to compare left ventricular diastolic function among patients divided by brachial-ankle pulse wave velocity (baPWV) and corrected P wave dispersion (PWDC) and assess whether the combination of baPWV and PWDC can predict LVDD more accurately.

Methods: This cross-sectional study enrolled 270 patients and classified them into four groups according to the median values of baPWV and PWDC. LVDD was defined as impaired relaxation and pseudonormal/restrictive mitral inflow patterns.

Results: The ratio of transmitral E wave velocity to early diastolic mitral annulus velocity (E/Ea) was higher in group with higher baPWV and PWDC than in the other groups (all p <0.001). The prevalence of LVDD was higher in group with higher baPWV and PWDC than in the two groups with lower baPWV (p ≤ 0.001). The baPWV and PWDC were correlated with E/Ea and LVDD in multivariate analysis (p ≤ 0.030). The addition of baPWV and PWDC to a clinical mode could significantly improve the R square in prediction of E/Ea and C statistic and integrated discrimination index in prediction of LVDD (p ≤ 0.010).

Conclusions: This study showed increased baPWV and PWDC were correlated with high E/Ea and LVDD. The addition of baPWV and PWDC to a clinical model improved the prediction of high E/Ea and LVDD. Screening patients by means of baPWV and PWDC might help identify the high risk group of elevated left ventricular filling pressure and LVDD.

Key words: brachial-ankle pulse wave velocity; P wave dispersion; left ventricular diastolic dysfunction.

Introduction

Assessment of left ventricular diastolic function is useful in risk stratification for patients with cardiovascular disease and can provide a diagnostic clue for heart failure with preserved ejection fraction. The cardiac mortality and morbidity were increased in heart failure patients with left ventricular diastolic

dysfunction (LVDD) [1, 2].

Although there were several parameters using in the assessment of arterial stiffness, the gold standard of non-invasive arterial stiffness measurement is carotid-femoral pulse wave velocity [3]. The carotid-femoral pulse wave velocity directly reflected aortic pulse wave velocity [4, 5]. In contrast, brachial-ankle pulse wave velocity (baPWV) reflected a composite of several arterial segments, some of which were prone to arteriosclerosis alone (brachial and distal arteries) and some to both atherosclerosis and arteriosclerosis (aorta and femoral arteries). However, Tanaka et al. compared carotid-femoral pulse wave velocity and baPWV in 2287 patients and found a strong correlation between them [6]. Therefore, it is reasonable to use baPWV as a marker of arterial stiffness. In addition, increased baPWV is associated with LVDD [7, 8]. However, our group and others [9-12] recently found that left ventricular systolic performance also influenced the pulse wave velocity.

The 12-lead electrocardiogram (ECG) is a commonly using noninvasive tool to access cardiac electrophysiological properties. P wave dispersion in 12 lead ECG is a useful tool to assess the risk of atrial fibrillation and our recent study along with previous studies also demonstrated increased P wave dispersion had a significant correlation with LVDD [13-15]. P wave dispersion was also found to be related to some echocardiogrphic parameters, including left atrial diameter, interventricular septum thickness, left ventricular posterior wall thickness and left ventricular mass [16, 17]. Besides, increased P wave dispersion may be a significant determinant of impaired left ventricular performance [18-22]. Therefore, P wave dispersion may have a significant influence on the relationship between pulse wave velocity and left ventricular diastolic function. Accordingly, the aims of this study are to compare the left ventricular diastolic function among patients divided by the median values of baPWV and corrected P wave dispersion (PWDC) and to assess whether the combination of baPWV and PWDC can predict LVDD more accurately.

Methods

Study subjects

Study subjects were randomly included from a group of patients arranged for echocardiographic examinations in a local hospital because of suspecting coronary artery disease, heart failure, hypertension, abnormal cardiac physical examination, survey for dyspnea and the pre-operative cardiac function survey. We excluded the patients with significant aortic or mitral valve diseases, atrial fibrillation or inade-

quate image visualization. In total, 270 patients were included in this study. Study patients were further classified into four groups according to the median values of baPWV and PWDC. All patients were in sinus rhythm. The protocol was approved by our Institutional Review Board and all enrolled patients gave written, informed consent.

Collection of demographic, medical and laboratory data

Demographic and medical data including age, gender, smoking history, medication history and co-morbidity were obtained from chart review and interviews with patients. The body mass index was calculated as the ratio of weight in kilograms divided by square of height in meters. Coronary artery disease was defined as a history of typical angina with positive stress test, angiographically documented coronary artery disease, old myocardial infarction, or having undergone coronary artery bypass surgery or angioplasty. Clinical heart failure was defined as a history of symptoms such as fatigue, shortness of breath, dyspnea, tachypnea, diminished exercise capacity, orthopnea, paroxysmal nocturnal dyspnea, bilateral pitting edema, increasing abdominal girth and Cheyne-Stokes respiratory pattern during sleep. Laboratory data were measured from fasting blood samples using an autoanalyser (COBAS Integra 400; Roche Diagnostics GmbH, Mannheim, Germany). Blood samples were obtained within 1 month of enrollment.

Echocardiographic assessment

The echocardiographic examinations were performed by one experienced cardiologist using transthoracic echocardiography (Vivid 7, General Electric Medical Systems, Horten, Norway), with the participant respirating quietly in the left decubitus position. Two-dimensional and two-dimensionally guided M-mode images were recorded from the standardized views. The Doppler sample volume was placed at the tips of the mitral leaflets to obtain the left ventricular inflow waveforms from the apical 4-chamber view. All sample volumes were positioned with ultrasonic beam alignment to flow. Pulsed tissue Doppler imaging was obtained with the sample volume placed at the lateral corner of the mitral annulus from the apical 4-chamber view. The wall filter settings were adjusted to exclude high-frequency signals and the gain was minimized. A normal mitral inflow pattern was recognized if the ratio of transmitral E wave velocity (E) to transmitral A wave velocity (A) was ≥ 0.75, early diastolic mitral annulus velocity (Ea) ≥ 8 cm/s and E/Ea ≤ 10, impaired relaxation mitral inflow pattern if the E/A ratio was <0.75 and pseudonor-

mal/restrictive mitral inflow pattern if the E/A ratio was ≥ 0.75, Ea <8 cm/s or E/Ea>10 [23, 24]. In this study, LVDD was defined as impaired relaxation and pseudonormal/restrictive mitral inflow patterns. The left ventricular ejection fraction was measured by the modified Simpson's method. The left atrial volume (LAV) was measured by the biplane area–length method [25]. Apical 4- and 2-chamber views were obtained to determine the left atrial area and length (from the middle of the plane of the mitral annulus to the posterior wall). The maximal left atrial chamber area and length were measured before mitral valve opening, excluding the left atrial appendage and pulmonary veins. The LAV was calculated and indexed to the body surface area. The raw ultrasonic data were recorded and analyzed offline with software (EchoPAC, GE Medical Systems) by a cardiologist blinded to the other data.

Assessment of baPWV

Within 10 minutes after the completion of the echocardiographic examination, baPWV was assessed using an ABI-form device, which automatically and simultaneously measures blood pressure in both arms and ankles using an oscillometric method [26, 27]. For measuring baPWV, pulse waves that were obtained from the brachial and tibial arteries were recorded simultaneously and the transmission time, which was defined as the time interval between the initial increase in brachial and tibial waveforms, was determined. The transmission distance from the arm to each ankle was calculated according to body height. The value of baPWV was automatically computed as the transmission distance divided by the transmission time. After obtaining bilateral baPWV values, the average of two values was used for analysis. Systolic and diastolic blood pressures were measured by the same device. The averages of systolic and diastolic blood pressures of bilateral arms were used for analysis.

Assessment of PWDC

Within 10 minutes after the completion of echocardiographic examination, the standard 12-lead surface ECG (25-mm/s, 1-mV/cm, and 100-Hz) was recorded. ECGs were measured quantitatively for intervals and height and qualitatively for morphology. Quantitative assessments were performed by using image analysis software system (Image Tool 3.0). Qualitative assessments of ECG recordings were performed by 2 cardiologists with disagreement resolved by adjudication from a third cardiologist. The 2 cardiologists were blinded to the clinical details. The P wave dispersion was calculated by the difference between maximum and minimum P wave durations [28]. The P wave dispersion was corrected for heart rate by Bazett's formula [29].

Statistical analysis

SAS 9.1 statistics software was used for statistical analysis. Data were expressed as mean ± standard deviation or percentage. After we had determined normality using a Kolmogorov–Smirnov test for all continuous variables, appropriate parametric and nonparametric tests were used. One-way analysis of variance and the Kruskal-Wallis (nonparametric) tests were utilized for comparisons of more than two groups, and Bonferroni post hoc tests were performed. The relationships between normally and nonnormally distributed continuous variables were assessed by Pearson's and Spearman`s correlation, respectively. Categorical variables between groups were compared by chi-square analysis. The significant variables in the univariate analysis except medications were selected for multivariate analysis. The multivariate linear and logistic regression analyses were employed to identify the determinants of E/Ea and LVDD, respectively. To quantify discriminatory improvement for models with and without the baPWV and PWDC, we computed the adjusted R square, C statistic and integrated discrimination index according to the methods of Pencina et al. [30, 31]. All tests were 2-sided and the level of significance was established as $P < 0.05$.

Results

The comparison of clinical characteristics among the study groups was shown in Table 1. Patients were classified to four groups, lower baPWV and PWDC (n = 71), lower baPWV and higher PWDC (n = 64), higher baPWV and lower PWDC (n = 64), and higher baPWV and PWDC (n = 71). The median values of baPWV and PWDC were 1706 cm/s and 68 ms, respectively. There was no correlation between baPWV and PWDC (r = 0.002, p = 0.969). There were significant differences among the four groups in age, prevalence of diabetes mellitus and hypertension, using of angiotensin II receptor antagonists and calcium channel blockers, heart rate, systolic and diastolic blood pressures, hematocrit and albumin. The patients with higher baPWV were older and had higher prevalence of diabetes and hypertension, higher fasting glucose and systolic and diastolic blood pressure, and higher using rate of angiotensin II receptor antagonists and calcium channel blockers.

The echocardiographic characteristics, baPWV and PWDC were compared among the study groups (Table 2). There were significant differences among four groups in LAV index, left ventricular end-diastolic and end-systolic dimensions, left ven-

tricular ejection fraction, E, A, E/A, E-wave deceleration time, Ea, E/Ea, late diastolic mitral velocity, PWDC, baPWV, prevalence of normal mitral inflow, impaired relaxation mitral inflow and pseudonormal/restrictive mitral inflow patterns and LVDD.

When comparing the patients with lower baPWV, the baseline characteristics including age, prevalence of diabetes, hypertension and coronary artery disease, body mass index, medication use, blood pressure, pulse pressure, fasting glucose and lipid profiles were similar between patients with lower and higher PWDC. However, LAV index and left ventricular end-diastolic and end-systolic dimensions were larger and left ventricular ejection fraction, Ea, E/Ea and prevalence of LVDD were more impaired in patients with higher PWDC than with in patients with lower PWDC.

When comparing the patients with higher baPWV, the baseline characteristics including age, prevalence of diabetes and coronary artery disease, body mass index, medication use, heart rate, blood pressure, pulse pressure, fasting glucose and lipid profiles were comparable between patients with lower and higher PWDC. However, LAV index and left ventricular end-diastolic and end-systolic dimensions were larger and E/Ea was higher in patients with

higher PWDC than in patients with lower PWDC.

The determinants of E/Ea were showed in Table 3. Age, diabetes, hematocrit, baPWV and PWDC were significantly correlated to E/Ea in univariate analysis. After multivariate analysis, baPWV and PWDC were still significantly correlated with E/Ea.

Table 4 showed the determinants of LVDD in our study. The significant determinants in univariate analysis were age, diabetes, hypertension, baPWV and PWDC. After multivariate analysis, age, diabetes, baPWV and PWDC were still the major significant determinants of LVDD.

The adjusted R square in prediction of E/Ea was significantly improved after addition of baPWV and PWDC to a model including age, diabetes and hemocrit from 0.070 to 0.110 (p = 0.003). To assess the effect of addition of baPWV and PWDC to clinical model for predicting of LVDD, C statistic and integrated discrimination index were calculated. The addition of baPWV and PWDC to a clinical model including variables of age, diabetes and hypertension resulted in significant improvements in C statistic and integrated discrimination index for prediction of LVDD. The C statistic was improved from 0.76 to 0.81 (p = 0.010). The integrated discrimination index was 0.08 (p <0.001).

Table 1. Comparison of clinical characteristics among study groups.

	Lower baPWV		Higher baPWV		P value
	Lower PWDC	Higher PWDC	Lower PWDC	Higher PWDC	
Number	71	64	64	71	
Age (years)	51 ± 10	48 ± 13	65 ± 11*#	63 ± 12*#	< 0.001
Gender (M/F)	37/34	41/23	34/30	40/31	0.506
Diabetes	8 (11.3%)	15 (23.4%)	20 (31.3%)*	27 (38%)*	0.002
Hypertension	29 (40.8%)	29 (45.3%)	52(81.3%)*#	54 (76.1%)*#+	< 0.001
CAD	7 (10.4%)	9 (14.1%)	15 (24.6%)	14 (20.3%)	0.146
BMI (kg/m^2)	25.3 ± 4.2	26.0 ± 4.0	25.4 ± 3.8	25.1 ± 3.4	0.6
Medications					
ACEIs	11 (15.5%)	13 (20.3%)	12 (18.8%)	13 (18.3%)	0.907
ARBs	16 (22.5%)	12 (18.8%)	27 (42.2%)*#	30 (42.3%)*#	0.002
β Blockers	28 (39.4%)	29 (45.3%)	29 (45.3%)	28 (39.4%)	0.813
CCBs	11 (15.5%)	6 (9.4%)	22 (34.4%)*#	26 (36.6%)*#	< 0.001
Diuretics	14 (20.6%)	13 (20.3%)	10 (16.4%)	12 (17.1%)	0.898
Nitrate	16 (23.9%)	20 (31.3%)	27 (44.3%)	28 (40.0%)	0.068
HR (/min)	67 ± 10	74 ± 14*	69 ± 12	75 ± 15*	0.001
SBP (mmHg)	128 ± 16	126 ± 17	150 ± 20*#	148 ± 23*#	< 0.001
DBP (mmHg)	77 ± 10	77 ± 12	84 ± 12*#	84 ± 12*#	< 0.001
Hematocrit (%)	41.9 ± 5.3	42.5 ± 6.1	41.3 ± 4.9	39.5 ± 6.0*#	0.021
Fasting glucose (mg/dL)	101 ± 25	113 ± 41	120 ± 48*	132 ± 53*#	<0.001
Total cholesterol (mg/dL)	204 ± 58	206 ± 65	196 ± 45	189 ± 35	0.517
Triglyceride (mg/dL)	215 ± 399	194 ± 339	162 ± 86	178 ± 261	0.595

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CAD, coronary artery disease; CCBs, calcium channel blockers; DBP, diastolic blood pressure; F, female; HR, heart rate; M, male; PWDC, corrected P wave dispersion; PP, pulse pressure; SBP, systolic blood pressure. *P < 0.05 compared with lower PWDC and baPWV; #P < 0.05 compared with higher PWDC and lower baPWV; +P < 0.05 compared with lower PWDC and higher baPWV.

Table 2. Comparison of echocardiographic characteristics, baPWV and PWDC among study groups

1	Lower baPWV		Higher baPWV		P value
	Lower PWDC	Higher PWDC	Lower PWDC	Higher PWDC	
Number	71	64	64	71	
LAV index (ml/m²)	32 ± 15	37 ± 18*	35 ± 12	45 ± 17*#+	< 0.001
LVEDD (mm)	51 ± 7	56 ± 11*	51 ± 8#	56 ± 9*+	0.001
LVESD (mm)	33 ± 9	39 ± 15*	33 ± 11#	39 ± 12*+	0.002
EF (%)	62 ± 13	53 ± 20*	58 ± 16	52 ± 19*	0.014
E (cm/s)	85 ± 19	85 ± 22	73 ± 21*#	82 ± 30+	0.013
A (cm/s)	72 ± 19	70 ± 24	86 ± 16*#	82 ± 22*#	< 0.001
E/A	1.27 ± 0.48	1.45 ± 0.92	0.90 ± 0.3*#	1.13 ± 0.69#+	< 0.001
EDT (ms)	179 ± 36	169 ± 66	204 ± 52*#	192 ± 73#	0.001
Ea (cm/s)	11.6 ± 3.5	9.8 ± 3.8*	7.4 ± 2.6*#	7.1 ± 2.9*#	< 0.001
E/Ea	8.0 ± 3.2	10.7 ± 6.5*	11.1 ± 5.0*	13.8 ± 8.3*#+	< 0.001
Aa (cm/s)	9.3 ± 2.6	8.6 ± 3.3	10.2 ± 3.3#	9.1 ± 3.3+	0.057
PWDC (ms)	50 ± 11	85 ± 17*	49 ± 11#	89 ± 17*+	< 0.001
baPWV (cm/s)	1403 ± 137	1387 ± 135	2034 ± 478*#	2001 ± 333*#	< 0.001
LVDD	22(31.0%)	31(48.4%)*	47(73.4%)*#	59(83.1%)*#	<0.001
Diastolic function					
Normal mitral inflow pattern	49(69.0%)	33(51.6%)*	17(26.6%)*	12(16.9%)*#	< 0.001
Impaired relaxation mitral inflow pattern	7(9.9%)	8(12.5%)	28(43.7%)*#	27(38.0%)*#	
Pseudonormal/restrictive mitral inflow pattern	15(21.1%)	23(35.9%)*	19(29.7%)	32(45.1%)*	

A, transmitral A wave velocity; Aa, late diastolic mitral velocity; baPWV, brachial-ankle pulse wave velocity; E, transmitral E wave velocity; Ea, early diastolic mitral annulus velocity; EDT, E-wave deceleration time; EF, ejection fraction; LAV, left atrial volume; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PWDC, corrected P wave dispersion. *P < 0.05 compared with lower PWDC and baPWV; #P < 0.05 compared with higher PWDC and lower baPWV; +P < 0.05 compared with lower PWDC and higher baPWV.

Table 3. Determinants of E/Ea in study patients.

Parameters	Univariate		Multivariate	
	Unstandardized coefficient β	P	Unstandardized coefficient β	P
Age (years)	0.118 (0.064, 0.172)	<0.001	0.065 (-0.005, 0.136)	0.069
Female gender	-0.452 (-1.997, 1.093)	0.565		
Diabetes	1.903 (0.168, 3.638)	0.032	0.839 (-1.172, 2.850)	0.412
Hypertension	1.422 (-0.139, 2.983)	0.074		
CAD	1.904 (-0.166, 3.974)	0.071		
BMI	0.012 (-0.187, 0.212)	0.903		
Hematocrit (%)	-0.179 (-0.329, -0.028)	0.020	-0.079 (-0.231, 0.073)	0.309
Total cholesterol (mg/dL)	-0.009 (-0.026, 0.008)	0.318		
Triglyceride (mg/dL)	0.001 (-0.002, 0.004)	0.544		
baPWV (cm/s)	0.004 (0.003, 0.006)	<0.001	0.003 (0.001, 0.006)	0.019
PWDC (ms)	0.049 (0.017, 0.081)	0.003	0.042 (0.007, 0.077)	0.019

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CAD, coronary artery disease; CCBs, calcium channel blockers; E, transmitral E wave velocity; Ea, early diastolic mitral annulus velocity; PP, pulse pressure; PWDC, corrected P wave dispersion.

Table 4. Determinants of LVDD in study patients.

Parameters	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age (years)	1.063(1.041-1.086)	<0.001	1.036(1.010-1.063)	0.007
Female gender	0.711(0.436-1.159)	0.172		
Diabetes	3.385(1.794-6.385)	<0.001	2.422(1.200-4.886)	0.014
Hypertension	2.890(1.741-4.797)	<0.001	1.512(0.824-2.775)	0.182
CAD	1.154(0.596-2.235)	0.670		
BMI	1.048(0.982-1.118)	0.156		
Hematocrit (%)	0.953(0.908-1.000)	0.050		
Total cholesterol (mg/dL)	0.998(0.993-1.003)	0.432		
Triglyceride (mg/dL)	1.001(0.999-1.003)	0.312		
baPWV (cm/s)	1.003(1.002-1.004)	<0.001	1.002(1.001-1.003)	<0.001
PWDC (ms)	1.017(1.006-1.028)	0.002	1.023(1.009-1.036)	0.001

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CAD, coronary artery disease; CCBs, calcium channel blockers; CI, confidence interval; LVDD, left ventricular diastolic dysfunction; OR, odds ratio; PP, pulse pressure; PWDC, corrected P wave dispersion.

Subgroup analysis of the group with left ventricular ejection fraction >50% (n = 197) showed that the baPWV, but not PWDC, was significantly associated with LVDD in the multivariate analysis (p = 0.017). Subgroup analysis of patients without clinical heart failure (n = 235) showed that both the baPWV and PWDC were predictors of LVDD in the multivariate analysis (p ≤ 0.029).

Discussion

In the present study, we evaluated the association of baPWV and PWDC with LVDD and found both of them were independently associated with E/Ea and LVDD. Patients with higher PWDC and baPWV had the highest E/Ea and higher prevalence of LVDD. Dividing patients into four groups using baPWV and PWDC might be useful in identifying the high risk group of elevated E/Ea and LVDD. In addition, the addition of baPWV and PWDC to a clinical model could significantly improve the adjusted R square in prediction of E/Ea and C statistic and integrated discrimination index in prediction of LVDD. Hence, concurrent consideration of baPWV and PWDC may be helpful in improving the prediction of patients with high E/Ea and LVDD.

When comparing the patients with lower baPWV, the baseline clinical risk factors were not different, but many echocardiographic parameters such as LAV index, left ventricular end-diastolic and end-systolic dimensions, left ventricular ejection fraction, Ea, E/Ea and prevalence of LVDD were significantly different between patients with lower and higher PWDC. Hence, in patients with lower baPWV, the increased PWDC might be a useful parameter indicating large left atrial and left ventricular chambers and depressed left ventricular systolic and diastolic function.

When comparing the patients with higher baPWV, the baseline clinical risk factors were similar but many echocardiographic parameters such as LAV index, left ventricular end-diastolic and end-systolic dimensions were different between patients with lower and higher PWDC. Hence, in patients with higher baPWV, the increased PWDC was also a useful parameter suggesting large left atrial and left ventricular chambers and high left ventricular filling pressure.

The P wave dispersion measured by 12-lead ECG was found to be associated with the occurrence of atrial fibrillation [21, 28, 32-34], left atrial enlargement and increased LAV index [16, 35]. Higher P wave dispersion was associated with LVDD in previous studies [18, 20, 35]. After the multivariate analysis, our study consistently demonstrated that increased PWDC was significantly associated with increased E/Ea and LVDD.

The increased arterial stiffness was reported to be associated with increased LAV and LVDD [36-39]. The baPWV was also reported to be associated with mild LVDD in patients with hypertension [39]. Abhayaratna et al. evaluated the association between the aortic pulse wave velocity and left ventricular diastolic function in the elderly and found that the increased LAV and advanced LVDD were associated with increased arterial stiffness [38]. Roes et al. also reported the increased aortic pulse wave velocity was associated with LVDD in patients with metabolic syndrome regardless of hypertension [40]. Chung et al. found that quantification of aortic stiffness could predict the degree of LVDD [36]. Our result consistently found increased baPWV was correlated with high E/Ea and LVDD.

Subgroup analysis of the group with left ventricular ejection fraction >50% showed that the baPWV, but not PWDC, was significantly associated with LVDD in the multivariate analysis, which was compatible with previous studies [7, 8]. Hence, in patients with preserved left ventricular ejection fraction, in addition to clinical variables, additional consideration of baPWV might be useful in identifying patients with LVDD. However, in daily clinical practice, it was difficult to know the left ventricular ejection fraction without echocardiographic examination. Therefore, concurrent consideration of baPWV and PWDC might be helpful in improving the prediction value for LVDD in patients with unknown left ventricular systolic function.

There were several possible reasons for explaining the combination of increased baPWV and PWDC was associated with LVDD. Increased arterial stiffness could decrease diastolic blood pressure, impair the coronary blood supply, induce cardiac hypertrophy and increase cardiac stiffening [41, 42] and then cause LVDD. The increased PWDC represented the heterogeneous and different atrial conduction which might be secondary to the increased left atrium diameter, volume and strain caused by LVDD [19-21]. In the present study, although baPWV and PWDC had a significant correlation with E/Ea and LVDD, there was no correlation between them, which suggested these two parameters might be complementary in predicting increased E/Ea and LVDD. In fact, our patients with the coexistence of increased baPWV and PWDC had the highest E/Ea and higher prevalence of LVDD. Furthermore, the addition of baPWV and PWDC to a clinical model could significantly improve the adjusted R square in prediction of E/Ea and C statistic and integrated discrimination index in prediction of LVDD. Hence, concurrent consideration of baPWV and PWDC might be useful in identifying the

high risk group of elevated E/Ea and LVDD.

The majority of our patients were treated chronically with antihypertensive drugs. We did not withdraw these medications for ethical reasons. Therefore, we could not exclude the influence of antihypertensive agents on the present findings. The classification of LVDD was based on non-invasive echocardiographic parameters but not on invasive data. Hence, the result might be different if invasive data were used. In addition, this study only included patients referred for echocardiographic examination, so the prevalence of pseudonormal/restrictive mitral inflow pattern was relatively high. Therefore, the present findings were not necessarily applicable to the other population.

In conclusion, our study showed the increased baPWV and PWDC were significantly correlated with high E/Ea and LVDD. Patients with higher baPWV and PWDC had the highest level of E/Ea and relatively higher prevalence of LVDD. The addition of baPWV and PWDC to a clinical model could significantly improve the adjusted R square in prediction of E/Ea and C statistic and integrated discrimination index in prediction of LVDD. Therefore, screening patients by means of baPWV and PWDC may be helpful in identifying the high risk patients of elevated E/Ea and LVDD.

Competing Interests

There are no conflicts of interests in this study.

References

1. Shammas RL, Khan NUA, Nekkanti R, Movahed A. Diastolic heart failure and left ventricular diastolic dysfunction: What we know, and what we don't know! International Journal of Cardiology. 2007; 115: 284-92.
2. Hoit BD. Left ventricular diastolic function. Crit Care Med. 2007; 35: S340-7.
3. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac A-M, et al. Assessment of Arterial Distensibility by Automatic Pulse Wave Velocity Measurement: Validation and Clinical Application Studies. Hypertension. 1995; 26: 485-90.
4. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of Aortic Stiffness on Survival in End-Stage Renal Disease. Circulation. 1999; 99: 2434-39.
5. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial Calcifications, Arterial Stiffness, and Cardiovascular Risk in End-Stage Renal Disease. Hypertension. 2001; 38: 938-42.
6. Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, et al. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. Journal of Hypertension. 2009; 27: 2022-27.
7. Masugata H, Senda S, Yoshikawa K, Yoshihara Y, Daikuhara H, Ayada Y, et al. Relationships between Echocardiographic Findings, Pulse Wave Velocity, and Carotid Atherosclerosis in Type 2 Diabetic Patients. Hypertens Res. 2005; 28: 965-71.
8. Hsu PC, Tsai WC, Lin TH, Su HM, Voon WC, Lai WT, et al. Association of Arterial Stiffness and Electrocardiography-determined Left Ventricular Hypertrophy with Left Ventricular Diastolic Dysfunction. PLoS ONE, 2012; 7:e49100.
9. Weber T, Auer J, Lamm G, O'Rourke MF, Eber B. Arterial Stiffness, Central Blood Pressures, and Wave Reflections in Cardiomyopathy—Implications for Risk Stratification. Journal of Cardiac Failure. 2007; 13: 353-9.
10. Hsu PC, Lin TH, Lee CS, Chu CY, Su HM, Voon WC, et al. Impact of a systolic parameter, defined as the ratio of right brachial pre-ejection period to ejection time, on the relationship between brachial-ankle pulse wave velocity and left ventricular diastolic function. Hypertens Res. 2011; 34: 462-7.
11. Su HM, Lin TH, Hsu PC, Chu CY, Lee WH, Chen SC, et al. Impact of systolic time intervals on the relationship between arterial stiffness and left ventricular hypertrophy. Atherosclerosis. 2012; 223: 171-6.
12. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. European Heart Journal. 2006; 27: 2588-2605.
13. Tsai WC, Lee KT, Wu MT, Chu CS, Lin TH, Hsu PC, et al. Significant correlation of P wave parameters with left atrial volume index and left ventricular diastolic function. Am J Med Sci. 2013; 346: 45-51.
14. Tsioufis C, Syrseloudis D, Hatziyianni A, Tzamou V, Andrikou I, Tolis P, et al. Relationships of CRP and P wave dispersion with atrial fibrillation in hypertensive subjects. Am J Hypertens. 2010; 23: 202-7.
15. Yagmur J, Cansel M, Acikgoz N, Ermis N, Yagmur M, Atas H, et al. Assessment of Atrial Electromechanical Delay by Tissue Doppler Echocardiography in Obese Subjects. Obesity. 2011; 19: 779-83.
16. Kosar F, Aksoy Y, Ari F, Keskin L, Sahin I. P-wave duration and dispersion in obese subjects. Ann Noninvasive Electrocardiol. 2008; 13: 3-7.
17. Su HM, Tsai WC, Lin TH, Hsu PC, Lee WH, Lin MY, et al. P Wave Dispersion and Maximum P Wave Duration Are Independently Associated with Rapid Renal Function Decline. PloS One. 2012; 7: e42815.
18. Soliman RA, Battah AA, Hekaal A, Ashraf MDM, Wadei A. The Relationship between P Wave Dispersion and Diastolic Dysfunction in Patients with Significant and Insignificant Coronary Artery Disease. J Am Sci. 2010; 6:438-45.
19. Dagli N, Karaca I, Yavuzkir M, Balin M, Arslan N. Are maximum P wave duration and P wave dispersion a marker of target organ damage in the hypertensive population? Clin Res Cardiol. 2008; 97: 98-104.
20. Gunduz H, Binak E, Arinc H, Akdemir R, Ozhan H, Tamer A, et al. The relationship between P wave dispersion and diastolic dysfunction. Tex Heart Inst J. 2005; 32: 163-7.
21. Yilmaz R, Demirbag R, Durmus I, Kasap H, Baykan M, Kucukosmanoglu M, et al. Association of stage of left ventricular diastolic dysfunction with P wave dispersion and occurrence of atrial fibrillation after first acute anterior myocardial infarction. Ann Noninvasive Electrocardiol. 2004; 9: 330-8.
22. Senen K, Turhan H, Riza Erbay A, Basar N, Saatci Yasar A, Sahin O, et al. P-wave duration and P-wave dispersion in patients with dilated cardiomyopathy. European journal of heart failure. 2004; 6: 567-9.
23. 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.
24. Khouri SJ, Maly GT, Suh DD, Walsh TE. A practical approach to the echocardiographic evaluation of diastolic function. Journal of the American Society of Echocardiography. 2004; 17: 290-7.
25. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. Journal of the American Society of Echocardiography. 2005; 18: 1440-63.
26. Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, et al. Influences of age and gender on results of noninvasive brachial–ankle pulse wave velocity measurement—a survey of 12 517 subjects. Atherosclerosis. 2003; 166: 303-9.
27. Yokoyama H, Shoji T, Kimoto E, Shinohara K, Tanaka S, Koyama H, et al. Pulse Wave Velocity in Lower-Limb Arteries among Diabetic Patients with Peripheral Arterial Disease. Journal of Atherosclerosis and Thrombosis. 2003; 10: 253-8.
28. Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J. 1998; 135: 733-8.
29. Bazett HC. The time relations of the blood-pressure changes after excision of the adrenal glands, with some observations on blood volume changes. The Journal of Physiology. 1920; 53: 320-39.
30. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008; 27: 157-72.
31. Hosmer DW, Lemeshow S. Applied Logistic Regression (2nd Edition). New York, NY: John Wiley & Sons; 2000.
32. Dogan A, Kahraman H, Ozturk M, Avsar A. P wave dispersion and left atrial appendage function for predicting recurrence after conversion of

atrial fibrillation and relation of p wave dispersion to appendage function. Echocardiography. 2004; 21: 523-30.

33. Turhan H, Yetkin E, Sahin O, Yasar AS, Senen K, Atak R, et al. Comparison of P-wave duration and dispersion in patients aged > or =65 years with those aged < or =45 years. J Electrocardiol. 2003; 36: 321-6.

34. Dilaveris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol. 2001; 6: 159-65.

35. Guler H, Seyfeli E, Sahin G, Duru M, Akgul F, Saglam H, et al. P wave dispersion in patients with rheumatoid arthritis: its relation with clinical and echocardiographic parameters. Rheumatol Int. 2007; 27: 813-8.

36. Chung CM, Chu CM, Chang ST, Cheng HW, Yang TY, Wan PC, et al. Quantification of Aortic Stiffness to Predict the Degree of Left Ventricular Diastolic Function. The American Journal of the Medical Sciences. 2010; 340: 468-73.

37. Abhayaratna WP, Srikusalanukul W, Budge MM. Aortic stiffness for the detection of preclinical left ventricular diastolic dysfunction: pulse wave velocity versus pulse pressure. Journal of Hypertension. 2008; 26: 758-64.

38. Abhayaratna WP, Barnes ME, O'Rourke MF, Gersh BJ, Seward JB, Miyasaka Y, et al. Relation of Arterial Stiffness to Left Ventricular Diastolic Function and Cardiovascular Risk Prediction in Patients ≥65 Years of Age. The American journal of cardiology. 2006; 98: 1387-92.

39. Yambe M, Tomiyama H, Hirayama Y, Gulniza Z, Takata Y, Koji Y, et al. Arterial Stiffening as a Possible Risk Factor for Both Atherosclerosis and Diastolic Heart Failure. Hypertension Research. 2004; 27: 625-31.

40. Roes SD, Alizadeh Dehnavi R, Westenberg JJM, Lamb HJ, Mertens BJA, Tamsma JT, et al. Assessment of Aortic Pulse Wave Velocity and Cardiac Diastolic Function in Subjects With and Without the Metabolic Syndrome. Diabetes Care. 2008; 31: 1442-4.

41. Safar ME, Levy BI, Struijker-Boudier H. Current Perspectives on Arterial Stiffness and Pulse Pressure in Hypertension and Cardiovascular Diseases. Circulation. 2003; 107: 2864-9.

42. London GM, Cohn JN. Prognostic application of arterial stiffness: task forces. Am J Hypertens. 2002; 15: 754-8.