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ORIGINAL ARTICLE

Diastolic wall strain as a predictor of age-related cardiovascular events in patients with preserved left ventricular ejection fraction

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Abstract
Diastolic wall strain (DWS) was reported as a simple and feasible echocardiographic index in assessing left ventricular (LV) diastolic stiffness. We sought to evaluate whether DWS predicts age-related cardiovascular events. Patients referred for transthoracic echocardiogram, those with preserved LV ejection fraction and no clinical heart failure were studied. Cardiovascular events were ascertained using Framingham criteria (myocardial infarction, coronary insufficiency, stroke, transient ischemic attack, congestive heart failure, or cardiovascular death). DWS was calculated with a validated formula. Cox proportional hazards modeling was used to assess the risk of cardiovascular events. Of a total number of 962 patients (mean age 60.9 ± 14.9 years, 48.0% men), 69 (7.2%) developed at least 1 cardiovascular event during a mean follow-up of 43 ± 32 months. After adjusting for cardiovascular comorbidities in a multivariable model, low DWS (≦ 0.33) was a significant independent predictor of cardiovascular events [hazard ratio (HR): 1.87, 95% confidential interval (CI) 1.04–3.36, $P = 0.04$]. Echocardiographic assessment of DWS may help in identifying the patients at increased risk for future age-related cardiovascular events.

Keywords Cardiovascular events · Echocardiography · Risk factors

Introduction

It has been recognized that noninvasive echocardiographic identification of subclinical risk markers, such as left ventricular (LV) systolic or diastolic dysfunction, enhanced risk stratification for the development of adverse cardiovascular events [1–3]. However, the conventional echocardiographic Doppler indices, which reflect LV diastolic filling pressure, are influenced by loading conditions and require a high level of proficiency and equipment [4]. Recently, diastolic wall strain (DWS), a novel echocardiographic index using standard M-mode echocardiography, has been reported as a load-independent and direct measure of LV diastolic stiffness [5–7]. Further, lower DWS was reported to predict death or heart failure hospitalization in patients with heart failure [8, 9] as well as in patients without heart failure [10]. The findings of these recent studies support a potential role for DWS as part of an integrated approach to the assessment of myocardial function as well as the prognostic information. However, the utility of this new index as an age-related cardiovascular risk marker in clinically stable patients remains to be determined. The objective of our present study was to determine whether DWS predicts age-related cardiovascular events in stable patients with no clinical heart failure with preserved LV ejection fraction, and whether it is incremental to conventional risk factors for identifying patients at increased risk for future cardiovascular events.

Methods

Study subjects

Adult patients referred for a transthoracic echocardiography as a regular check-up between July 2007 and December 2007 were considered for inclusion in this study. Patients with

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clinical heart failure validated by Framingham criteria [11], impaired LV systolic function (i.e. ejection fraction < 50%), a history of atrial fibrillation/flutter, pacemaker/implantable cardioverter defibrillator implantation, significant valvular heart disease, congenital heart disease, hypertrophic cardiomyopathy, pericardial disease, or LV posterior wall motion abnormalities were excluded. Significant valvular heart disease was defined as ≧ moderate stenosis or regurgitation in the echocardiographic examination, or prior valve repair/replacement. Of a total of 1158 patients referred for a transthoracic echocardiography, 196 were excluded because of exclusion criteria. The study patients, thus, consisted of the remaining 962 patients, and were followed up from the baseline echocardiogram until the date of the occurrence of new events, death, or the last clinic visit.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Review Board of Kansai Medical University, Osaka, Japan, and informed consent was obtained from all patients.

Definition of outcome

Cardiovascular events during follow-up were defined as myocardial infarction, coronary insufficiency, stroke, transient ischemia attack, congestive heart failure, as well as cardiovascular death, according to the Framingham criteria [12, 13]. The same definitions and criteria for adjudication of outcome events were used for all patients throughout the study period.

Definition of covariates

Body mass index was calculated as weight in kilograms divided by square of height in meters. Pulse pressure was calculated as the mean systolic blood pressure minus the mean diastolic blood pressure on ≧ 2 separate measurements. Systemic hypertension was defined as systolic blood pressure ≧ 140 mmHg, or diastolic blood pressure ≧ 90 mmHg on ≧ 2 occasions that was not associated with acute illness or injury, or the use of antihypertensive therapy. Diabetes was defined as a fasting glucose level ≧ 126 mg/dl, a random glucose level ≧ 200 mg/dl, or the use of insulin or medications for diabetes mellitus. Coronary artery disease was defined by angiographic findings of lesions ≧ 50% in any of the 3 main arterial distributions, or history of myocardial infarction.

Echocardiographic data acquisition

All transthoracic echocardiograms were performed with patients in the left lateral decubitus position and interpreted by 1 echocardiologist who was masked to clinical data according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations [14]. LV dimensions and wall thickness were determined from 2-dimensional echocardiography (parasternal long-axis view). LV ejection fraction was calculated using the quantitative 2-dimensional biplane modified Simpson's method. LV mass was calculated with a validated formula [15] and was indexed to body surface area. Left atrial (LA) volume was measured using the biplane area–length formula: LA volume = (0.85 × 4-chamber area × 2-chamber area)/length, and was indexed to body surface area. Pulsed-wave Doppler examination was performed to obtain peak mitral inflow velocities at early (*E*) and late (*A*) diastole, E deceleration time, and *E*/*A* ratio. Tissue Doppler echocardiography was performed with the sample volume positioned at the septal mitral annulus to obtain the following parameters: peak early (*E*′) and late (*A*′) diastolic myocardial tissue velocities. The *E*/*E*′ ratio was calculated.

Measurements of DWS

As previously illustrated [5], DWS was calculated using a validated formula: DWS = (PWs − PWd)/PWs, where PWs is the posterior wall thickness at end-systole and PWd is the posterior wall thickness at end-diastole (Fig. 1). Because lower DWS (defines as ≦ 0.33) was reported as an index of more advanced diastolic stiffness [8], we categorized DWS ≦ 0.33 as "low DWS" and DWS > 0.33 as "high DWS". Echocardiographic measurements were obtained for 3 consecutive beats and averaged for all determinations.

Intra-observer and inter-observer variability

Inter-observer variability was assessed from 20 randomly selected patients by 2 independent observers, each blinded to the results obtained by the other. Intra-observer variability was assessed by repeated measurements from 20 patients by the same observer 1 week after the first analysis. Variability was expressed as the absolute difference between repeated measurements in terms of percentage of mean value. A coefficient of variation was also calculated.

Statistical analysis

Baseline characteristics were summarized in terms of means and SDs for continuous variables, or frequency numbers and % for categorical variables. Differences between the 2 groups were evaluated with chi-square analyzes (categorical variables), 2-sample *t* tests for variables with normal distributions, or Wilcoxon rank-sum tests for those with skewed distributions (continuous variables), as appropriate. Cox proportional hazards models were used to adjust for the effect of differences in baseline characteristics or pertinent covariates

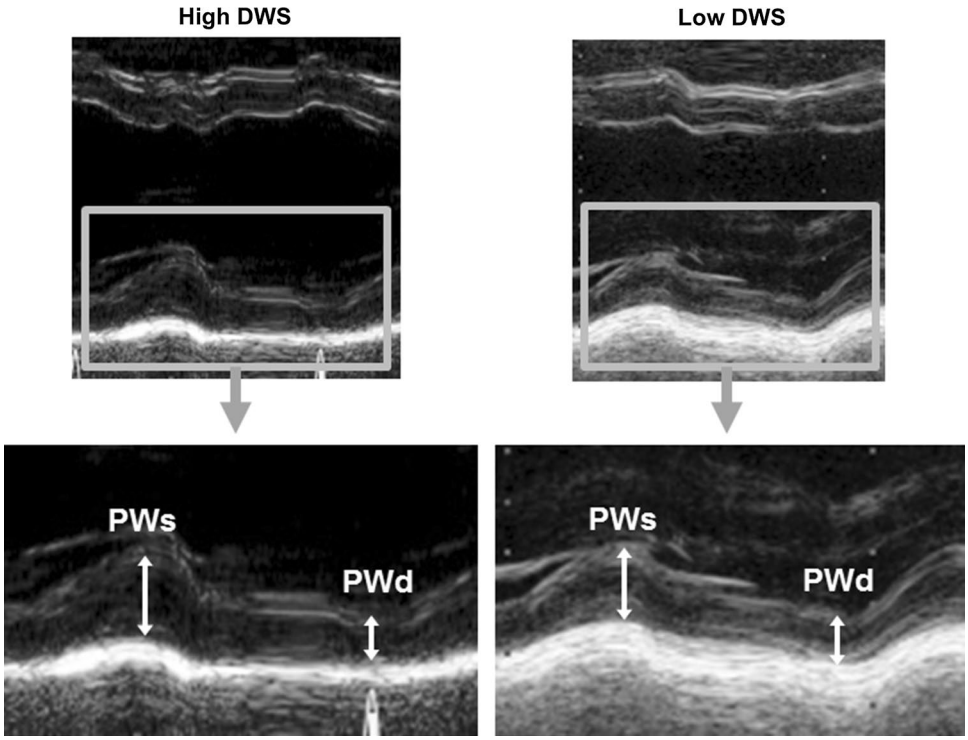

Fig. 1 Measurements and calculation of diastolic wall strain (DWS). Representative echocardiographic recordings in high DWS (left; DWS = 0.47) and low DWS (right; DWS = 0.31) are shown. The view of the M-mode echocardiography of left ventricular posterior wall is used to measure the posterior wall thickness at end-systole (PWs) and end-diastole (PWd). The DWS is calculated by the formula: DWS = (PWs − PWd)/PWs

on outcomes. We estimated univariable models as well as multivariable models, and hazard ratios (HR) and their relative 95% confidence intervals (CI) were derived. Covariates selected for multivariable models included significant variables at the univariable analysis. The Kaplan–Meier method tested for differences in the event-free rate between patients with low DWS and those with high DWS by the log-rank test, and the cumulative events-free survival curves were depicted graphically. To evaluate the incremental prognostic value, the global log-likelihood ratio chi-square statistics for models were determined by Cox proportional hazards regression using: (1) clinical risk factors alone; (2) clinical risk factors plus LV ejection fraction; (3) a combination of clinical risk factors, LV ejection fraction, and indexed LA volume; and (4) a combination of clinical risk factors, LV ejection fraction, indexed LA volume, and low DWS. The differences between these global chi-square statistics were used to test the significance of adding the echocardiographic parameters to the clinical variables and depicted graphically. All statistical analyzes were performed using the IBM SPSS Statistics software version 22.0 (SPSS Inc., IBM, Somers, New York, USA). All tests of significance were 2-tailed, and P value < 0.05 was considered as statistically significant.

Results

Baseline characteristics

Of 962 patients (mean age 60.9 ± 14.9 years, 48.0% men) who met all study criteria, 147 (15.3%) had a DWS ≦ 0.33 and, therefore, considered to have "low DWS". Table 1 shows the baseline characteristics of the study patients, stratified by DWS status. Patients with low DWS were older, tended to be male gender, and more likely to have systemic hypertension, prior coronary artery disease, had higher body mass index and LV mass, lower *E*/*A* ratio, *E*′ velocity and LV ejection fraction, when compared with those with high DWS. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and beta blockers were more common in patients with low DWS.

DWS and cardiovascular events

Of 962 study patients, 69 (7.2%) developed 81 new cardiovascular events (12 myocardial infarction, 19 coronary

Table 1 Baseline characteristics of study patients by DWS status

Variables	Overall ($N=962$)	High DWS ($N=815$)	Low DWS ($N=147$)
Clinical			
Age (years)	60.9 ± 14.9	60.4 ± 15.1	63.6 ± 13.5*
Men	462 (48.0%)	376 (46.1%)	86 (58.5%)*
Body mass index (kg/m^2)	23.6 ± 3.8	23.5 ± 3.9	24.2 ± 3.5*
Systolic blood pressure (mmHg)	135 ± 22	135 ± 23	135 ± 20
Diastolic blood pressure (mmHg)	78 ± 13	78 ± 13	78 ± 12
Pulse pressure (mmHg)	57 ± 15	57 ± 15	57 ± 14
1/creatinine (dl/mg)	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.5
Systemic hypertension	477 (49.6%)	390 (47.9%)	87 (59.2%)*
Diabetes mellitus	171 (17.8%)	137 (16.8%)	34 (23.1%)
Prior coronary artery disease	157 (16.3%)	114 (14.0%)	43 (29.3%)*
Echocardiographic			
LV end-diastolic dimension (mm)	48.6 ± 4.9	48.7 ± 4.8	48.2 ± 5.4
LV end-systolic dimension (mm)	28.7 ± 5.1	28.6 ± 5.0	29.5 ± 5.6*
LV end-diastolic septal wall thickness (mm)	8.7 ± 1.6	8.6 ± 1.5	9.4 ± 2.0*
LV end-diastolic posterior wall thickness (mm)	8.6 ± 1.3	8.5 ± 1.2	9.5 ± 1.4*
LV end-systolic posterior wall thickness (mm)	14.8 ± 2.4	15.1 ± 2.3	13.0 ± 2.0*
DWS	0.41 ± 0.09	0.44 ± 0.06	0.26 ± 0.05*
Mitral inflow Doppler induces			
E (cm/s)	69.2 ± 17.8	69.4 ± 17.7	67.8 ± 18.4
A (cm/s)	75.2 ± 20.0	74.4 ± 20.0	79.8 ± 19.6*
E/*A* ratio	0.99 ± 0.42	1.01 ± 0.43	0.90 ± 0.34*
E deceleration time (ms)	218 ± 57	217 ± 56	221 ± 63
Tissue Doppler imaging			
E′ (cm/s)	7.1 ± 2.7	7.1 ± 2.6	6.6 ± 2.8*
A′ (cm/s)	9.4 ± 4.2	9.3 ± 3.9	9.6 ± 5.4
E/*E*′ ratio	10.9 ± 5.0	10.8 ± 5.0	11.5 ± 4.8
Indexed LA volume (ml/m^2)	31.6 ± 11.2	31.5 ± 11.0	32.2 ± 12.0
Indexed LV mass (g/m^2)	92.2 ± 24.5	90.8 ± 22.8	99.7 ± 31.5*
LV ejection fraction (%)	73 ± 8	74 ± 8	71 ± 9*
Medication			
ACE-I or ARBs	240 (24.9%)	190 (23.3%)	50 (34.0%)*
Beta blockers	110 (11.4%)	81 (9.9%)	29 (19.7%)*
Diuretics	70 (7.3%)	56 (6.9%)	14 (9.5%)

Values are given as mean ± SD or number (%)

Differences were evaluated with chi-square analyzes (categorical variables), 2-sample *t* tests for variables with normal distributions, or Wilcoxon rank-sum tests for those with skewed distributions (continuous variables), as appropriate

ACE-I angiotensin-converting enzyme-inhibitors, *ARBs* angiotensin receptor blockers, *DWS* diastolic wall strain, *LA* left atrial, *LV* left ventricular

*$P<0.05$ versus high DWS

insufficiency, 18 stroke, 7 transient ischemic attack, 19 congestive heart failure, and 6 cardiovascular death) during a mean follow-up time of 43 ± 32 months. The follow-up rates at 1, 2, and 3 years were 88.5%, 80.9%, and 74.6%, respectively. The baseline characteristics of the study patients stratified by cardiovascular events (Table 2), and results of the univariable and multivariable Cox models for the prediction of cardiovascular events are shown (Table 3). Advancing age, male gender, higher systolic blood pressure, higher pulse pressure, lower 1/creatinine, systemic hypertension, diabetes mellitus, prior coronary artery disease, larger LV end-diastolic dimension, or end-systolic dimension, low DWS, higher A velocity, larger E deceleration time, lower *E*′ velocity, higher *E*/*E*′ ratio, larger indexed LA volume, higher indexed LV mass, and lower LV ejection fraction were associated with

Table 2 Baseline characteristics of study patients by event status

Variables	No CV events ($N=893$)	Had CV events ($N=69$)
Clinical		
Age (years)	60.4 ± 15.2	67.4 ± 9.6*
Men	414 (46.4%)	48 (69.6%)*
Body mass index (kg/m^2)	23.6 ± 3.9	23.5 ± 3.4
Systolic blood pressure (mmHg)	134 ± 22	142 ± 25*
Diastolic blood pressure (mmHg)	78 ± 13	78 ± 13
Pulse pressure (mmHg)	56 ± 14	65 ± 19*
1/creatinine (dl/mg)	1.3 ± 0.5	1.0 ± 0.5*
Systemic hypertension	424 (47.5%)	53 (76.8%)*
Diabetes mellitus	139 (15.6%)	32 (46.4%)*
Prior coronary artery disease	126 (14.1%)	31 (44.9%)*
Echocardiographic		
LV end-diastolic dimension (mm)	48.4 ± 4.8	51.0 ± 5.6*
LV end-systolic dimension (mm)	28.5 ± 4.9	31.8 ± 6.7*
LV end-diastolic septal wall thickness (mm)	8.7 ± 1.6	9.2 ± 1.6*
LV end-diastolic posterior wall thickness (mm)	8.6 ± 1.3	9.0 ± 1.3*
LV end-systolic posterior wall thickness (mm)	14.8 ± 2.4	15.1 ± 2.8
DWS	0.41 ± 0.09	0.39 ± 0.11
Low DWS (≦ 0.33)	128 (14.3%)	19 (27.5%)*
Mitral inflow Doppler induces		
E (cm/s)	69.1 ± 17.7	69.9 ± 18.8
A (cm/s)	74.7 ± 20.0	82.4 ± 19.3*
E/*A* ratio	1.00 ± 0.43	0.88 ± 0.30*
E deceleration time (ms)	217 ± 56	234 ± 68*
Tissue Doppler imaging		
E′ (cm/s)	7.2 ± 2.7	5.6 ± 1.5*
A′ (cm/s)	9.3 ± 3.8	9.7 ± 7.7
E/*E*′ ratio	10.7 ± 4.8	13.7 ± 6.0*
Indexed LA volume (ml/m^2)	31.1 ± 10.5	38.7 ± 16.4*
Indexed LV mass (g/m^2)	91.1 ± 23.8	106.0 ± 29.6*
LV ejection fraction (%)	73 ± 8	71 ± 10*
Medication		
ACE-I or ARBs	207 (23.2%)	33 (47.8%)*
Beta blockers	97 (10.9%)	13 (18.8%)*
Diuretics	54 (6.0%)	16 (23.2%)*

Values are given as mean ± SD or number (%)

Differences were evaluated with chi-square analyzes (categorical variables), 2-sample *t* tests for variables with normal distributions, or Wilcoxon rank-sum tests for those with skewed distributions (continuous variables), as appropriate

ACE-I angiotensin-converting enzyme-inhibitors, *ARBs* angiotensin receptor blockers, *CV* cardiovascular, *DWS* diastolic wall strain, *LA* left atrial, *LV* left ventricular

*$P<0.05$ versus patients with no CV events

cardiovascular events (Table 3). When adjusted in a multivariable model, higher pulse pressure, lower 1/creatinine, diabetes mellitus, prior coronary artery disease, larger indexed LA volume, and lower LV ejection fraction were independent predictors of cardiovascular events. Further, low DWS was a significant predictor of cardiovascular events independent of other comorbidities (HR: 1.87, 95% CI 1.04–3.36, $P=0.04$) (Table 3). Kaplan-Meier estimated cumulative cardiovascular events-free survivals according to DWS status are shown in Fig. 2 (Log-rank $P=0.027$).

The global log-likelihood ratio chi-square statistics for the models containing: (1) clinical risk factors only (i.e. pulse pressure, 1/creatinine, diabetes mellitus, and prior coronary artery disease); (2) clinical risk factors plus LV ejection fraction; and (3) a combination of clinical risk factors, LV ejection fraction, and indexed LA volume, (4) a combination of clinical

Table 3 Univariable and multivariable model for prediction of CV events

Variables	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age (per 10 years)	1.35 (1.09, 1.68)	< 0.01		
Men	2.38 (1.42, 3.97)	< 0.01		
Systolic blood pressure (per 10 mmHg)	1.16 (1.04, 1.29)	< 0.01		
Pulse pressure (per 10 mmHg)	1.42 (1.21, 1.66)	< 0.001	1.28 (1.07, 1.53)	< 0.01
1/creatinine (per 1 dl/mg)	0.23 (0.15, 0.38)	< 0.001	0.37 (0.22, 0.62)	< 0.001
Systemic hypertension	2.86 (1.64, 5.00)	< 0.001		
Diabetes mellitus	3.76 (2.34, 6.02)	< 0.001	2.16 (1.23, 3.81)	< 0.01
Prior coronary artery disease	3.26 (2.02, 5.23)	< 0.001	2.05 (1.18, 3.56)	0.01
LV end-diastolic dimension (per 1 mm)	1.08 (1.04, 1.13)	< 0.001		
LV end-systolic dimension (per 1 mm)	1.09 (1.06, 1.13)	< 0.001		
LV end-diastolic septal wall thickness (per 1 mm)	1.19 (1.04, 1.35)	< 0.05		
LV end-diastolic posterior wall thickness (per 1 mm)	1.20 (1.01, 1.42)	< 0.05		
DWS (per 0.1 decrease)	1.16 (0.90, 1.49)	0.25		
Low DWS (≦ 0.33)	1.80 (1.06, 3.05)	< 0.05	1.87 (1.04, 3.36)	0.04
A (per 10 cm/s)	1.18 (1.05, 1.33)	< 0.01		
E deceleration time (per 10 ms)	1.04 (1.01, 1.08)	< 0.05		
E′ (per 1 cm/s)	0.74 (0.65, 0.85)	< 0.001		
E/*E′* ratio (per 1.0 increase)	1.05 (1.03, 1.07)	< 0.001		
Indexed LA volume (per 10 ml/m^2)	1.45 (1.27, 1.65)	< 0.001	1.26 (1.03, 1.55)	0.03
Indexed LV mass (per 10 g/m^2)	1.20 (1.11, 1.29)	< 0.001		
LV ejection fraction (per 10%)	0.69 (0.52, 0.91)	< 0.01	0.73 (0.55, 0.97)	0.03

CI confidence interval, *CV* cardiovascular, *DWS* diastolic wall strain, *HR* hazard ratio, *LA* left atrial, *LV* left ventricular

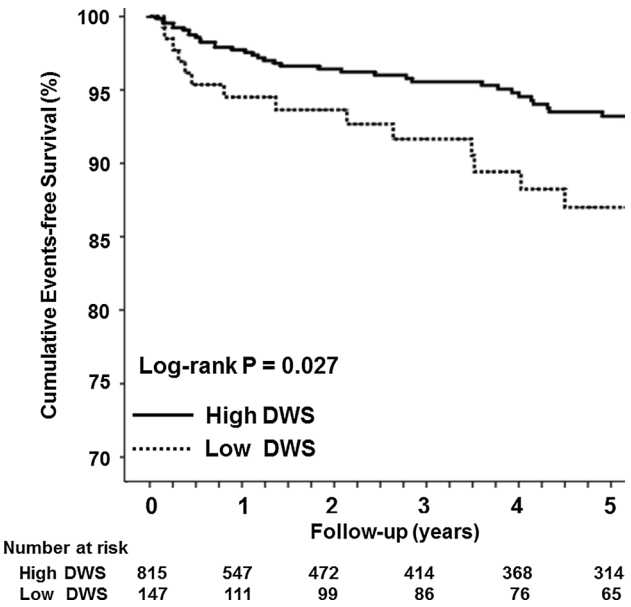

Fig. 2 Kaplan–Meier estimates of cumulative events-free survival in patients with low diastolic wall strain (DWS) compared with those with high DWS

risk factors, LV ejection fraction, indexed LA volume, and low DWS are shown in Fig. 3. The predictive power of the models showed that indexed LA volume added significantly to the clinical risk factors plus LV ejection fraction for cardiovascular outcome prediction ($P=0.02$). Addition of low DWS further strengthened ($P=0.04$) the predictive capability of the model.

Reproducibility

Intra-observer and inter-observer variability of DWS averaged $1.8 \pm 2.9\%$ and $2.6 \pm 2.8\%$, respectively. Intra-observer and inter-observer coefficient of variation of DWS were 2.6% and 2.4%, respectively.

Supplementary analysis: sub-population analysis without prior coronary artery disease

When analysis was restricted to the 805 patients without prior coronary artery disease at baseline, 38 (4.7%) developed new cardiovascular event, and DWS was a non-significant variable in a multivariable model (HR: 1.25, 95% CI 0.55–2.84).

Discussion

Our study showed that (1) low DWS was an echocardiographic predictor of age-related cardiovascular events in patients with no clinical heart failure with preserved LV

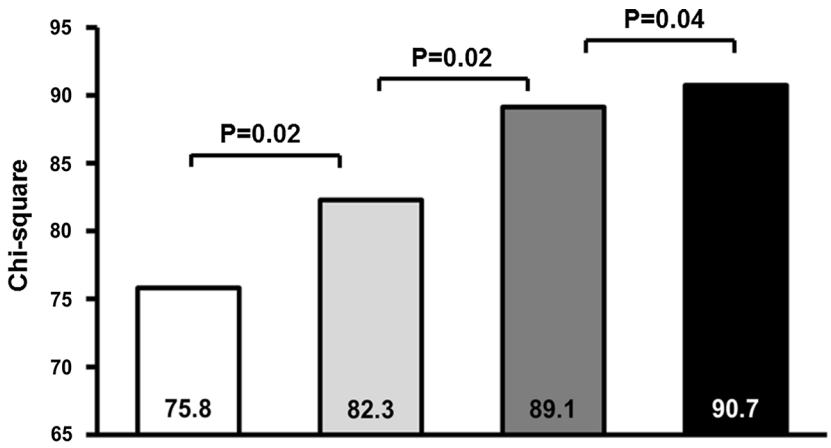

Fig. 3 Predictive power of 4 models for cardiovascular events. The global chi-square of sequential Cox models incorporating clinical risk factors (pulse pressure, 1/creatinine, diabetes mellitus, and prior coronary artery disease), left ventricular ejection fraction (LVEF), left atrial (LA) volume, and low diastolic wall strain (DWS) were illustrated

	Clinical	Clinical + LVEF	Clinical + LVEF, and LA volume	Clinical + LVEF, LA volume, and DWS
Pulse pressure	1.26 (1.07, 1.50), P<0.01	1.32 (1.11, 1.56), P<0.01	1.25 (1.05, 1.49), P=0.01	1.28 (1.07, 1.53), P<0.01
1/creatinine	0.35 (0.21, 0.59), P<0.001	0.35 (0.21, 0.59), P<0.001	0.39 (0.23, 0.65), P<0.001	0.37 (0.22, 0.62), P<0.001
Diabetes mellitus	2.18 (1.24, 3.82), P<0.01	2.05 (1.16, 3.63), P=0.01	2.01 (1.14, 3.54), P=0.02	2.16 (1.23, 3.81), P<0.01
Prior coronary artery disease	2.26 (1.32, 3.87), P<0.01	2.10 (1.21, 3.65), P<0.01	2.14 (1.23, 3.72), P<0.01	2.05 (1.18, 3.56), P=0.01
LVEF		0.70 (0.52, 0.94), P=0.02	0.71 (0.53, 0.95), P=0.02	0.73 (0.55, 0.97), P=0.03
LA volume			1.29 (1.05, 1.58), P=0.02	1.26 (1.03, 1.55), P=0.03
Low DWS				1.87 (1.04, 3.36), P=0.04

ejection fraction; and (2) the predictive value of low DWS was incremental to that of clinical and other echocardiographic risk factors.

Echocardiographic parameters as prognostic indicator

Identification of subclinical risk markers including LV systolic or diastolic dysfunction may enhance risk stratification for the development of adverse cardiovascular events [1–3]. A previous study suggested that even mild diastolic dysfunction is associated with increased risk of total mortality [2]. Historically, the invasive measurement of LV pressure has been regarded as the gold standard for assessment of LV diastolic function, but is not practical as a clinical tool. In contrast, the echocardiographic assessment has advantages of noninvasiveness, the simplicity in data acquisition, the absence of radiation exposure, cost-effectiveness, portability, and adaptability. However, current echocardiographic assessment of diastolic function, as an indirect estimation of LV diastolic filling pressure, is influenced by loading conditions [4], tends to be complex, involving Doppler evaluation of an array of hemodynamic data [2], and routine assessment of diastolic function remains a clinical challenge [16].

Echocardiographic assessment of DWS

Recently, DWS has been shown to represent a more direct measure of myocardial stiffness [5]. The easy and simple measurement of the DWS that can be assessed in the routine M-mode echocardiographic examination using commercially available machines is advantageous. The concept of DWS is based on the linear elastic theory, whereby distending forces exerted on the stiff myocardium in diastole produce less diastolic deformation (i.e., diastolic wall thinning) than forces applied to compliant or compressible myocardium [5, 8]. Therefore, impaired diastolic wall thinning theoretically reflects resistance to deformation in diastole and increased diastolic myocardial stiffness, rather than an abnormality of active relaxation [5, 8]. It was confirmed that DWS was significantly and inversely correlated with myocardial stiffness constant measured invasively in an animal model [5]. More recently, it was also reported that lower DWS was independently associated with increased rates of death or heart failure hospitalization in patients with heart failure [8, 9] as well as in patients without heart failure [10]. Present study demonstrates that DWS enhances the risk stratification for the development of age-related cardiovascular events, incrementally to clinical and other echocardiographic risk factors in stable patients. There are many asymptomatic patients with diastolic dysfunction [2], and identification of the patients at high risk for subsequent age-related cardiovascular events would be clinically important.

The exact mechanistic link between low DWS and age-related cardiovascular outcome remains to be unveiled. One possibility is that low DWS may represent a surrogate marker for cardiovascular risk burden. Decreased DWS was reported to be significantly associated with increased myocardial fibrosis [17]. At a subclinical level, atherosclerotic vascular risk factors may cause some myocardial damage that results in fibrous tissue replacement [18], leading to increased LV diastolic stiffness and reduced DWS. Because low DWS has been shown to be a barometer of diastolic dysfunction, which was often preclinical with no

recognized congestive heart failure diagnosis [2], and diastolic dysfunction has been linked to subsequent development of age-related cardiovascular outcomes [1–3], it is not very surprising that low DWS is a predictor of age-rerated cardiovascular events.

Patients with low DWS have a poorer prognosis, irrespective of a history of clinical heart failure. The measurement of DWS is simple and reproducible, allowing a rapid screening for abnormalities in diastolic stiffness. In conjunction with other risk factors, DWS may play an important role in risk assessment of the patients for future cardiovascular events. Whether effective treatment to increase DWS translates to the improvement in cardiovascular outcomes requires further investigations.

Limitations

We acknowledge the limitations of this study. First, because of the study design, data with respect to the medical therapy prior to cardiovascular events were not readily available, and how these factored into the events development is not known. Second, because both the number of study patients and outcome events were relatively small, we could not evaluate the contribution of heart failure events or cardiovascular death to adverse outcomes, significance of DWS in subpopulation without prior coronary artery disease, and the reasons for the high event rate amongst patients with lower DWS in the early period. Third, we did not attempt to address whether other deformation parameters, such as speckle-tracking measurements of myocardial radial strain, was more strongly related with adverse outcomes. Rather, we sought to determine whether a simple index easily derived from standard M-mode echocardiography might be useful. Further, limitation includes the lack of invasive gold standard measurement of diastolic stiffness. Finally, the study subjects were referral based, and the extent to which the findings can be generalized to other population groups is not known.

Conclusion

Low DWS provides simple and complementary prognostic information for the prediction of future age-related cardiovascular events in stable patients with no clinical heart failure with preserved LV ejection fraction, incrementally to other conventional risk factors. Future studies with larger number of community-based populations are warranted to investigate.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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