Influence of Comorbid Cardiovascular Risk Factors on Left Atrial-Left Ventricular Interaction in Asymptomatic Patients

Clinical Application of Two-Dimensional Speckle-Tracking Echocardiography

Hirokazu MIYOSHI,¹ MD, Yoshifumi OISHI,¹ MD, Yukio MIZUGUCHI,¹ MD, Arata IUCHI,¹ MD, Norio NAGASE,¹ MD, Nusrat ARA,² MD, and Takashi OKI,¹ MD

SUMMARY

Previous studies have examined the negative impacts of individual cardiovascular risk (CVR) factors on left atrial (LA)-left ventricular (LV) interaction, whereas the combined effects of these risk factors are insufficiently elucidated. We studied 176 asymptomatic patients with CVR factors and age-matched 50 healthy individuals by conventional and 2-dimensional speckle-tracking echocardiography. The patients were classified into 2 groups according to the number of CVR factors: one risk factor (single) group ($n = 79$) and 2 or more risk factors (comorbid) group ($n = 97$). The peak early diastolic transmitral flow velocity (E)/peak early diastolic mitral annular motion velocity (e')/peak systolic LA strain (S-LAs) was used as a surrogate for LA stiffness during ventricular systole. The E/e'/S-LAs was greatest in the comorbid group. The peak systolic LV circumferential and radial strains, peak early diastolic LV radial strain rate, and peak early diastolic LA strain and strain rate were lower in the comorbid group than in the single group. Multivariate regression analysis identified age, body mass index, systolic blood pressure, end-systolic LV diameter, peak systolic mitral annular motion velocity (s'), and peak systolic LV radial strain in the comorbid group, and peak atrial systolic transmitral flow velocity and s' in the single group, as independent predictors of E/e'/S-LAs. Subtle LA and LV dysfunction with individual CVR factors were more aggravated with the comorbid conditions in asymptomatic patients. (Int Heart J 2014; 55: 138-145)

Key words: LA diastolic stiffness, LA-LV interaction, 2-D speckle-tracking echocardiography

It is now recognized that approximately one-half of patients with the clinical syndrome of congestive heart failure (HF) have preserved systolic function, a condition referred to as HF with preserved ejection fraction (HFPEF).^{1,2} The prevalence of this disease condition is anticipated to increase in elderly patients with cardiovascular risk (CVR) factors such as hypertension, diabetes, dyslipidemia, obesity, and smoking.^{2,3} Therefore, it is expected that a higher comorbid burden of the CVR factors is an important contributor to the development of HFPEF. Assessment of left atrial (LA) and left ventricular (LV) function, which we named as LA-LV interaction,⁴ seems to have a clinical impact, because an abnormal LA-LV interaction is a mechanism responsible for producing congestion symptom.^{4,5} However, few data are available on use and outcome studied with conventional echocardiography in the evaluation of LA-LV interaction in asymptomatic patients in the community. Angle-independent two-dimensional speckle-tracking echocardiography (2DSTE) has recently been introduced into clinical practice because it offers early detec-

tion of impaired LA reservoir function^{6,7} and LV contraction and relaxation^{8,9} in subclinical patients with CVR factors. We hypothesized that comorbid conditions of CVR factors would be associated with worse LA-LV interaction, probably providing a potential explanation for the development to HFPEF in future. To test this hypothesis, we performed 2DSTE in asymptomatic patients with CVR factors, and evaluated the influence of comorbid conditions on LA and LV function.

METHODS

Study population: A total of 360 patients from routine health checkups and outpatient facilities at Higashi Tokushima Medical Center between 2009 and 2012 were recruited to participate in the present study. The study protocol was approved by the ethics committee. The purpose of the study was explained and informed consent to participate was obtained from each patient. Each patient underwent an interview, electrocardio-

From the ¹ Cardiovascular Section, Higashi Tokushima Medical Center, National Hospital Organization, Tokushima, Japan and ² Department of Cardiology, Rawalpindi Medical College, Rawalpindi, Pakistan.

Address for correspondence: Hirokazu Miyoshi, MD, Cardiovascular Section, Higashi Tokushima Medical Center, National Hospital Organization, 1-1 Ohmukai-kita, Ohtera, Itano, Tokushima 779-0193, Japan. E-mail: hmiyoshi@higashitokushima.hosp.go.jp

Received for publication July 30, 2013. Revised and accepted September 4, 2013.

Released advance online J-STAGE March 14, 2014.

All rights are reserved to the International Heart Journal Association.

gram (ECG), physical examination, and conventional echocardiography. As a result, 116 of the 360 patients were excluded for the following reasons: poor image quality, history of heart failure, atrial fibrillation, clinically significant valvular heart disease, known coronary artery disease, previous stroke, chronic obstructive pulmonary disease, liver dysfunction, renal disease, aortic disease, or LV ejection fraction < 60%. The remaining 244 asymptomatic patients were included in the study sample.

The 244 patients were divided into 2 groups; clinically healthy individuals reported as having normal echocardiography, no major illness, and being free of CVR factors ($n = 68$), and patients with CVR factors ($n = 176$). Of the former group, 50 age-matched patients were used as the control group (17 men, 33 women; mean age, 60 ± 12 years) in the present study. The latter group included patients with hypertension with systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg ($n = 138$), obesity with a body mass index (BMI) ≥ 25 kg/m² ($n = 71$), hyperlipidemia with total cholesterol > 220 mg/dL and/or triglycerides > 150 mg/dL ($n = 80$), hyperglycemia with fasting glucose concentration ≥ 110 mg/dL with no retinopathy, nephropathy, or neuropathy ($n = 13$), and/or current smoker ($n = 14$). In 176 patients with CVR factors, one risk factor was observed in 79 patients, 2 risk factors in 56 patients, 3 risk factors in 39 patients, and 4 risk factors in 2 patients. Furthermore, these 176 patients were subdivided into the 2 groups according to the number of CVR factors: one risk factor (single) group ($n = 79$; 35 men, 44 women; mean age 61 ± 12 years), and 2 or more risk factors (comorbid) group ($n = 97$; 58 men, 39 women; mean age 62 ± 11 years).

Conventional, pulsed Doppler, and tissue Doppler echocardiography: All echocardiographic measurements were performed using a commercially available ultrasound system (Vivid 7, General Electric Healthcare, Milwaukee, WI, USA) equipped with a harmonic 4.0-MHz variable-frequency phased-array transducer. The end-diastolic LV diameter (Dd), end-systolic LV diameter (Ds), end-diastolic thickness of the ventricular septum (VSth), and end-diastolic thickness of the LV posterior wall (PWth) were measured by M-mode echocardiography. By using these parameters, we calculated the LV mass⁽¹⁰⁾ and relative LV wall thickness as follows:

$$\text{LV mass (g)} = 0.8 \times 1.04 \times [(Dd + PWth + VSth)^3 - Dd^3] + 0.6$$

$$\text{Relative LV wall thickness} = 2 \times PWth/Dd$$

The LV mass index (g/m²) was determined by dividing the LV mass measurement by the body surface area.

The LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated from the apical 2- and 4-chamber views using a modified Simpson's method. The LV ejection fraction (EF) was calculated as ejection fraction (%) = $[(EDV - ESV) / EDV] \times 100$. The LA volume was measured offline using the biplane area-length method, and was indexed to the body surface area.

The transmitral flow (TMF) velocity was obtained from the apical long-axis view with the pulsed Doppler method. The peak early diastolic velocity (E), deceleration time from the peak of the early diastolic wave to baseline (E-DT), peak atrial systolic velocity (A), and E/A ratio were assessed from the TMF velocity pattern.

The mitral annular motion velocity was recorded at the

LV lateral and septal wall sites in the apical 4-chamber view by pulsed tissue Doppler echocardiography. The means of peak systolic motion velocity (s'), peak early diastolic motion velocity (e'), and peak motion velocity during atrial systole (a') at both sites, and the ratio of E to e' (E/e') were determined.⁽¹¹⁾

Two-dimensional speckle-tracking echocardiography (2DSTE): LV wall strain

We acquired LV short-axis views at the apical, mid and basal levels, and LV apical 2- and 4-chamber views using a frame rate (60-100 frames/sec).^(8,9) The basal short-axis view contained the mitral valve, the mid short-axis view contained the chordae tendineae, and the apical short-axis view was acquired distal to the papillary muscles. At each plane, 3 consecutive cardiac cycles were acquired at end-expiration breath holding and stored digitally on a hard disk for offline analysis. Image analysis was performed offline on a PC workstation using custom analysis software (EchoPAC PC, Version 6.0.X, GE Healthcare, Fairfield, CT, USA). The LV endocardial border of the end-systolic frame was manually traced. On the basis of this line, the computer automatically created a region of interest including the entire transmural wall in all patients, and the software selected natural acoustic markers moving with the tissue. Automatic frame-by-frame tracking of these markers during the cardiac cycle (2D systolic time interval method) yielded a measure of strain, and strain rate at any point of myocardium. The LV was divided into 18 segments, and each segment was individually analyzed.

In the present study, longitudinal strain and strain rate were assessed in the 6 LV wall segments on the apical 2-chamber view and in the 6 LV wall segments on the apical 4-chamber view, and their average values were used. Circumferential and radial strains and strain rates were assessed in the 6 LV wall segments on the parasternal LV short-axis view at the level of the chordae tendineae, and their average values were used.

LA wall strain:

Two-dimensional grayscale images of the septal and lateral LA walls were acquired in the standard apical 4-chamber view (Figure, left). We used an offline EchoPAC workstation to calculate LA strain and strain rate.⁽⁶⁾ A line was manually dragged along the LA endocardium when the LA was at its minimum volume after contraction. The software automatically generates additional lines near the LA epicardium and mid-myocardial line. If tracking of the LA endocardium is inadequate, manual adjustments or changing software parameters can be performed.

Global LA strain and strain rate parameters were assessed as the average of 6 segmental values. Zero strain of the LA wall was set at LV end-diastole. Peak LA strains during ventricular systole, early diastole, and atrial contraction (S-LAs, S-LAe, and S-LAa, respectively) were measured as LA function parameters (Figure, right and top). Also, peak strain rate was measured during ventricular systole, early diastole, and atrial contraction (SR-LAs, SR-LAe, and SR-LAa, respectively) (Figure, right and bottom).

Derived measurements: The following parameters were derived from the primary measurements: 1) E/e' used as a surrogate for LV filling pressure or LV diastolic stiffness, as indicated by Nagueh, *et al.*⁽¹¹⁾; 2) LA stiffness index calculated as E/e' / S-LAs (%), as described by Kurt, *et al.*⁽¹²⁾

Statistical analysis: Measurements are presented as the mean

Figure. Left atrial strain (top) and strain rate (bottom) curves obtained from the apical 4-chamber view in a healthy patient and measurement method of the parameters. S-LAs indicates peak left atrial strain during ventricular systole; S-LAe, peak left atrial strain during early diastole; S-LAa, peak left atrial strain during atrial systole; SR-LAs, peak left atrial strain rate during ventricular systole; SR-LAe, peak left atrial strain rate during early diastole; and SR-LAa, peak left atrial strain rate during atrial systole.

± standard deviation. Differences in the parameters between the control and 2 groups with CVR factors were compared using one-way analysis of variance (ANOVA). Post-hoc analysis was performed using the Bonferroni method. The relationships between different parameters in the 2 groups with CVR factors and E/e'/S-LAs were determined by linear regression analysis. Multivariate regression analysis was applied to evaluate the relationships between E/e'/S-LAs and other continuous variables. Variables with a significant level of $P < 0.05$ on univariate analysis were included in the multivariate analyses to determine independent LA and LV predictors related to E/e'/S-LAs. $P < 0.05$ was considered statistically significant.

RESULTS

Control group versus patient groups:

Clinical, M-mode, 2-dimensional, and pulsed Doppler

echocardiographic variables

There were no differences in age, heart rate, left atrial volume index (LAVI), relative LV wall thickness, LV ejection fraction (EF), or E among the control, one risk factor (single), and ≥ 2 risk factors (comorbid) groups (Table I). Body mass index (BMI), end-diastolic LV diameter, and A were greatest in the comorbid group among the 3 groups. Systolic and diastolic blood pressure (SBP and DBP, respectively), end-diastolic LV thicknesses, and LV mass index were greater in the 2 patient groups than in the control group. The end-systolic LV diameter and deceleration time of the early diastolic TMF velocity (E-DT) were greater in the comorbid group than in the control group. The E/A was lower in the comorbid group than in the control group.

LV wall variables measured by tissue Doppler velocity and 2DSTE

The peak early diastolic mitral annular motion velocity (e') was lower in the comorbid group than in the control group (Table II). In contrast, peak mitral annular motion velocity during atrial systole (a') and E/ e' were greater in the comorbid group than in the control group.

The peak systolic LV circumferential strain was lower in the comorbid group than in the single group. The peak systolic LV radial strain and early diastolic LV radial strain rate were lowest in the comorbid group among the 3 groups. The peak atrial systolic LV longitudinal and circumferential strain rates were greater in the comorbid group than in the control group.

LA wall variables measured by 2DSTE

The peak systolic LA strain (S-LAs) and strain rate (SR-LAs) were lower in the comorbid group than in the control group (Table III). The peak early diastolic LA strain (S-LAe) and strain rate (SR-LAe) were lowest in the comorbid group among the 3 groups. The S-LAe, SR-LAs, and SR-LAe were lower in the single group than in the control group. The E/ e' /S-LAs was greatest in the comorbid group among the 3 groups.

Relations of E/ e' /S-LAs to concerned variables in the patient groups: Among the clinical, M-mode, 2D, and pulsed Doppler parameters, significant correlations were found between E/ e' /S-LAs and age, LAVI, and A in the single group, and between E/ e' /S-LAs and all parameters, except DBP, LV mass index, and E-DT, in the comorbid group (Table IV). In the tissue Doppler velocity and 2DSTE LV variables, s' , peak systolic LV longitudinal strain and strain rates, and peak early diastolic LV longitudinal strain rate significantly correlated with E/ e' /S-LAs in the single group, and s' , peak systolic LV radial strain, peak systolic LV circumferential strain rate, peak early diastolic LV longitudinal, circumferential, and radial strain rates, and peak atrial systolic LV circumferential strain rate significantly correlated with E/ e' /S-LAs in the comorbid group (Table V). Multivariate regression analysis identified A and s' in the single group, and age, BMI, SBP, end-systolic LV diameter, LVEF, s' , and peak systolic LV radial strain in the comorbid group, as independent predictors of E/ e' /S-LAs (Table VI).

Measurement variability: Images for LA and LV strain and strain rate values were interpreted by 2 experienced investigators in 15 randomly selected patients. To assess the variability of LA and LV strain analysis, measurements were repeated from the 15 patients either by the same investigator or by 2 independent investigators. Intraobserver and interobserver variabilities were 4.6% to 5.8% and 6.1% to 7.9% for LA strain values, respectively, and 4.2% to 5.6% and 5.9% to 7.2% for

Table I. Comparisons of Clinical, M-mode, 2-Dimensional, and Pulsed Doppler Echocardiographic Parameters Between Controls and Patients With Cardiovascular Risk Factors

	Controls (n = 50)	Patients with cardiovascular risk factors (n = 176)	
		Single (1 risk factor) (n = 79)	Comorbid (≥ 2 risk factors) (n = 97)
Age (years)	60 $\pm$ 12	61 $\pm$ 12	62 $\pm$ 11
Body mass index (kg/m ²)	21.3 $\pm$ 1.8	22.5 $\pm$ 2.6 ^{§§}	25.0 $\pm$ 2.9 ^{§§**}
Systolic blood pressure (mmHg)	117 $\pm$ 11	135 $\pm$ 20 ^{§§}	136 $\pm$ 19 ^{§§}
Diastolic blood pressure (mmHg)	69 $\pm$ 6	79 $\pm$ 10 ^{§§}	78 $\pm$ 10 ^{§§}
Heart rate (beats per minute)	63 $\pm$ 10	63 $\pm$ 10	65 $\pm$ 10
End-diastolic LV diameter (cm)	4.6 $\pm$ 0.4	4.7 $\pm$ 0.5	4.9 $\pm$ 0.5 ^{§§*}
End-systolic LV diameter (cm)	2.6 $\pm$ 0.4	2.8 $\pm$ 0.4	2.8 $\pm$ 0.4 [§]
Left atrial volume index (mL/m ²)	27.4 $\pm$ 7.0	29.9 $\pm$ 9.0	29.7 $\pm$ 9.9
End-diastolic ventricular septal thickness (mm)	8.3 $\pm$ 1.4	9.1 $\pm$ 1.5 ^{§§}	9.3 $\pm$ 1.7 ^{§§}
End-diastolic LV posterior wall thickness (mm)	8.2 $\pm$ 1.4	8.9 $\pm$ 1.5 [§]	9.2 $\pm$ 1.7 ^{§§}
Relative LV wall thickness	0.36 $\pm$ 0.08	0.38 $\pm$ 0.07	0.38 $\pm$ 0.08
LV mass index (g/m ²)	80.1 $\pm$ 18.5	95.6 $\pm$ 23.2 ^{§§}	97.6 $\pm$ 24.4 ^{§§}
LV ejection fraction (%)	73.4 $\pm$ 6.6	72.7 $\pm$ 6.9	73.3 $\pm$ 6.6
E (m/s)	0.75 $\pm$ 0.16	0.73 $\pm$ 0.16	0.72 $\pm$ 0.15
A (m/s)	0.70 $\pm$ 0.18	0.74 $\pm$ 0.18	0.80 $\pm$ 0.18 ^{§§*}
E/A	1.15 $\pm$ 0.41	1.03 $\pm$ 0.34	0.94 $\pm$ 0.28 ^{§§}
E-DT (ms)	186 $\pm$ 35	200 $\pm$ 45	207 $\pm$ 52 [§]
Risk factors			
Hypertension		49 (62%)	89 (92%)
Obesity		12 (15%)	59 (61%)
Hyperlipidemia		15 (19%)	65 (67%)
Hyperglycemia		1 (1%)	12 (12%)
Smoking		2 (3%)	12 (12%)

Values are mean $\pm$ standard deviation or number (%) of patients. [§] $P < 0.05$, ^{§§} $P < 0.01$, comparison with control group, ^{*} $P < 0.05$, ^{**} $P < 0.01$, comparison with 1 risk factor group. A indicates peak atrial systolic velocity of transmitral flow; E, peak early diastolic velocity of transmitral flow; E-DT, deceleration time from the peak to baseline of the early diastolic transmitral flow velocity; and LV, left ventricular.

Table II. Comparisons of LV Tissue Doppler Velocity and 2DSTE Parameters Between Controls and Patients With Cardiovascular Risk Factors

	Controls (n = 50)	Patients with cardiovascular risk factors (n = 176)	
		Single (1 risk factor) (n = 79)	Comorbid (≥ 2 risk factors) (n = 97)
Mitral annular motion velocity			
s' (cm/s)	9.6 $\pm$ 2.2	9.3 $\pm$ 2.1	9.1 $\pm$ 2.2
e' (cm/s)	11.0 $\pm$ 3.4	10.1 $\pm$ 3.4	9.4 $\pm$ 2.9 ^{§§}
a' (cm/s)	9.9 $\pm$ 1.8	10.4 $\pm$ 2.4	10.9 $\pm$ 2.2 [§]
E/e'	8.0 $\pm$ 2.2	8.3 $\pm$ 2.3	9.0 $\pm$ 2.8 [§]
LV wall strain and strain rate			
Peak systolic strain (%)			
Longitudinal	-21.0 $\pm$ 2.8	-20.4 $\pm$ 2.7	-20.1 $\pm$ 2.8
Circumferential	-18.6 $\pm$ 3.5	-18.8 $\pm$ 4.3	-18.0 $\pm$ 3.9 [*]
Radial	69.0 $\pm$ 18.6	65.3 $\pm$ 17.4 [§]	64.2 $\pm$ 18.0 ^{§*}
Systolic strain rate (s ⁻¹)			
Longitudinal	-1.1 $\pm$ 0.2	-1.1 $\pm$ 0.2	-1.1 $\pm$ 0.2
Circumferential	-1.1 $\pm$ 0.3	-1.2 $\pm$ 0.4	-1.2 $\pm$ 0.4
Radial	2.2 $\pm$ 0.5	2.2 $\pm$ 0.5	2.1 $\pm$ 0.5
Early diastolic strain rate (s ⁻¹)			
Longitudinal	1.4 $\pm$ 0.4	1.3 $\pm$ 0.3	1.3 $\pm$ 0.3
Circumferential	1.3 $\pm$ 0.4	1.3 $\pm$ 0.5	1.3 $\pm$ 0.5
Radial	-2.5 $\pm$ 0.8	-2.4 $\pm$ 0.7	-2.1 $\pm$ 0.6 ^{§§*}
Atrial systolic strain rate (s ⁻¹)			
Longitudinal	1.1 $\pm$ 0.2	1.1 $\pm$ 0.3	1.2 $\pm$ 0.2 [§]
Circumferential	0.7 $\pm$ 0.3	0.8 $\pm$ 0.4	0.8 $\pm$ 0.4 [§]
Radial	-1.8 $\pm$ 0.7	-1.8 $\pm$ 0.7	-1.9 $\pm$ 0.8

Values are mean $\pm$ standard deviation. [§] $P < 0.05$, ^{§§} $P < 0.01$, comparison with control group, ^{*} $P < 0.05$, comparison with 1 risk factor group. a' indicates peak mitral annular motion velocity during atrial systole; E, peak early diastolic velocity of transmitral flow; e', peak early diastolic mitral annular motion velocity; LV, left ventricular; s', peak systolic mitral annular motion velocity; and 2DSTE, 2-dimensional speckle-tracking echocardiography.

Table III. Comparisons of LA 2DSTE Parameters Between Controls and Patients With Cardiovascular Risk Factors

	Controls (n = 50)	Patients with cardiovascular risk factors (n = 176)	
		Single (1 risk factor) (n = 79)	Comorbid (≥ 2 risk factors) (n = 97)
S-LAs (%)	36.4 $\pm$ 8.2	33.7 $\pm$ 9.0	31.6 $\pm$ 8.3 ^{§§}
S-LAe (%)	21.1 $\pm$ 6.6	18.7 $\pm$ 6.6 [§]	16.8 $\pm$ 5.6 ^{§§*}
S-LAa (%)	15.4 $\pm$ 4.1	15.1 $\pm$ 4.5	14.9 $\pm$ 4.7
SR-LAs (s ⁻¹)	1.7 $\pm$ 0.4	1.4 $\pm$ 0.4 ^{§§}	1.4 $\pm$ 0.4 ^{§§}
SR-LAe (s ⁻¹)	-1.7 $\pm$ 0.5	-1.4 $\pm$ 0.5 ^{§§}	-1.2 $\pm$ 0.4 ^{§§**}
SR-LAa (s ⁻¹)	-2.0 $\pm$ 0.6	-1.8 $\pm$ 0.5	-1.7 $\pm$ 0.5 [§]
E/e'/S-LAs	0.23 $\pm$ 0.09	0.26 $\pm$ 0.11	0.31 $\pm$ 0.14 ^{§§*}

Values are mean $\pm$ standard deviation. [§] $P < 0.05$, ^{§§} $P < 0.01$, comparison with control group, * $P < 0.05$, ** $P < 0.01$, comparison with 1 risk factor group. E/e' indicates ratio of peak early diastolic transmitral flow velocity (E) to peak early diastolic mitral annular motion velocity (e'); LA, left atrial; S-LAa, peak left atrial strain at atrial systole; S-LAe, peak left atrial strain at early diastole; S-LAs, peak left atrial strain during ventricular systole; SR-LAa, peak left atrial strain rate at atrial systole; SR-LAe, peak left atrial strain rate at early diastole; SR-LAs, peak left atrial strain rate during ventricular systole; and 2DSTE, 2-dimensional speckle-tracking echocardiography.

Table IV. Correlations Between Clinical, M-mode, 2-Dimensional, and Pulsed Doppler Echocardiographic Parameters and E/e'/S-LAs in the 2 Groups With Cardiovascular Risk Factors

	Single (1 risk factor)		Comorbid (≥ 2 risk factors)	
	r	P	r	P
Age (years)	0.41	< 0.001	0.49	< 0.001
Body mass index (kg/m ²)	-0.01	NS	0.23	< 0.05
Systolic blood pressure (mmHg)	0.21	NS	0.34	< 0.001
Diastolic blood pressure (mmHg)	0.08	NS	-0.11	NS
Heart rate (beats per minute)	-0.05	NS	-0.21	< 0.05
End-diastolic LV diameter (cm)	-0.10	NS	-0.34	< 0.001
End-systolic LV diameter (cm)	-0.10	NS	-0.40	< 0.001
Left atrial volume index (mL/m ²)	0.30	< 0.01	0.36	< 0.001
End-diastolic ventricular septal thickness (mm)	0.21	NS	0.36	< 0.001
End-diastolic LV posterior wall thickness (mm)	0.08	NS	0.26	< 0.01
Relative LV wall thickness	0.13	NS	0.39	< 0.001
LV mass index (g/m ²)	0.17	NS	0.12	NS
LV ejection fraction (%)	0.05	NS	0.24	< 0.05
A (m/s)	0.28	< 0.05	0.40	< 0.001
E-DT (ms)	0.08	NS	0.15	NS

NS indicates not statistically significant. A indicates peak atrial systolic velocity of transmitral flow; E-DT, deceleration time from the peak to baseline of the early diastolic transmitral flow velocity; E/e', ratio of peak early diastolic transmitral flow velocity (E) to peak early diastolic mitral annular motion velocity (e'); LV, left ventricular; and S-LAs, peak left atrial strain during ventricular systole.

LV strain values, respectively.

DISCUSSION

The key finding of the present study is that combination of 2 or more cardiovascular risk (CVR) factors led to worse left atrial (LA)-left ventricular (LV) interaction, particularly impaired LA reservoir and conduit function related to LV systolic and diastolic dysfunction, respectively, compared to the condition of one CVR factor, probably accounting for the risk associated with development of heart failure with preserved ejection fraction (HFPEF) in future.

HFPEF frequently occurs in the context of CVR factors, such as hypertension, diabetes, dyslipidemia, obesity, and smoking.^{2,3)} HF symptoms under the disease conditions link 2 different underlying pathophysiologic mechanisms responsible for elevated LV filling pressures: 1) an elevation in LA pres-

sure related to the diastolic LV dysfunction, particularly increased myocardial stiffness⁵⁾ (which we named as LA-LV interaction⁴⁾); and 2) increased LV-arterial stiffening during systole, resulting in systolic and diastolic LA functional reserve limitations^{13,14)} (which we named as LA-LV-arterial interaction^{6,15)}). Generally, abnormal LV relaxation is often the main problem, and with no or only a minor increase in passive stiffness,¹⁶⁾ whereas arterial stiffness tends to increase with aging in asymptomatic patients with CVR factors.¹⁷⁾ A recent study also indicated a close relationship between combination of CVR factors and risk of peripheral artery disease.¹⁸⁾ Therefore, early detection of the negative effect of CVR factors on LA and LV dysfunction related to arterial stiffness is clinically important in subclinical patients.^{6,19)}

The new angle-independent 2-dimensional speckle-tracking echocardiography (2DSTE) permits the evaluation of not only LA and LV myocardial deformation⁶⁻⁹⁾ but also aortic and carotid arterial circumferential deformation.^{17,19)} This new mo-

Table V. Correlations Between LV Tissue Doppler Velocity and 2DSTE Parameters and E/e⁺/S-LAs in the 2 Groups

	Single (1 risk factor)		Comorbid (≥ 2 risk factors)	
	r	P	r	P
Mitral annular motion velocity				
s' (cm/s)	-0.40	< 0.001	-0.36	< 0.001
a' (cm/s)	0.00	NS	-0.14	NS
LV wall strain and strain rate				
Peak systolic strain (%)				
Longitudinal	0.27	< 0.05	-0.11	NS
Circumferential	0.09	NS	-0.03	NS
Radial	-0.12	NS	-0.25	< 0.05
Systolic strain rate (s ⁻¹)				
Longitudinal	0.22	< 0.05	0.15	NS
Circumferential	0.08	NS	0.24	< 0.05
Radial	0.07	NS	-0.19	NS
Early diastolic strain rate (s ⁻¹)				
Longitudinal	-0.37	< 0.001	-0.25	< 0.05
Circumferential	-0.09	NS	-0.21	< 0.05
Radial	-0.04	NS	0.27	< 0.01
Atrial systolic strain rate (s ⁻¹)				
Longitudinal	0.09	NS	0.08	NS
Circumferential	0.12	NS	-0.24	< 0.05
Radial	-0.12	NS	0.14	NS

NS indicates not statistically significant. a' indicates peak mitral annular motion velocity during atrial systole; E/e⁺, ratio of peak early diastolic transmitral flow velocity (E) to peak early diastolic mitral annular motion velocity (e⁺); LV, left ventricular; s', peak systolic mitral annular motion velocity; S-LAs, peak left atrial strain during ventricular systole; and 2DSTE, 2-dimensional speckle-tracking echocardiography.

Table VI. Multivariate Regression Analyses to Determine the Best Predictor of E/e⁺/S-LAs in the 2 Groups With Cardiovascular Risk Factors

	Single (1 risk factor)		Comorbid (≥ 2 risk factors)	
	β	P	β	P
Age (years)	0.207	0.0901	0.351	0.0037
Body mass index (kg/m ²)			0.222	0.0094
Systolic blood pressure (mmHg)			0.224	0.0058
Heart rate (beats per minute)			-0.178	0.0585
End-diastolic LV diameter (cm)			0.063	0.8443
End-systolic LV diameter (cm)			-0.598	0.0158
Left atrial volume index (mL/m ²)	0.155	0.1235	0.137	0.1377
End-diastolic ventricular septal thickness (mm)			0.237	0.1234
End-diastolic LV posterior wall thickness (mm)			0.171	0.7395
Relative LV wall thickness			-0.350	0.5637
LV ejection fraction (%)			-0.325	0.0488
A (m/s)	0.232	0.0498	0.083	0.4660
s' (cm/s)	-0.230	0.0286	-0.249	0.0016
Peak systolic LV longitudinal strain (%)	0.164	0.2279		
Peak systolic LV radial strain (%)			-0.398	< 0.0001
Peak systolic LV longitudinal strain rate (s ⁻¹)	0.182	0.2564		
Peak systolic LV circumferential strain rate (s ⁻¹)			-0.005	0.9747
Peak early diastolic LV longitudinal strain rate (s ⁻¹)	-0.008	0.9589	0.175	0.0967
Peak early diastolic LV circumferential strain rate (s ⁻¹)			0.057	0.6583
Peak early diastolic LV radial strain rate (s ⁻¹)			-0.096	0.2560
Peak atrial systolic LV circumferential strain rate (s ⁻¹)			-0.077	0.5164

A indicates peak atrial systolic velocity of transmitral flow; E/e⁺, ratio of peak early diastolic transmitral flow velocity (E) to peak early diastolic mitral annular motion velocity (e⁺); LV, left ventricular; s', peak systolic mitral annular motion velocity; and S-LAs, peak left atrial strain during ventricular systole.

dality has demonstrated that LV myocardial contraction and relaxation are first and simultaneously impaired in the longitudinal direction,⁸⁾ and radial thickening is preserved with an increase in circumferential shortening⁸⁾ and "sheet" reorientation in the cross-fiber direction,²⁰⁾ resulting in maintenance of LVEF, in subclinical patients with CVR factors, and that concentric LV hypertrophy in hypertensive patients brings deterioration of systolic longitudinal, circumferential, and radial myo-

cardial deformation even in the presence of preserved LVEF.⁹⁾

In the present study, LV contraction (peak systolic circumferential and radial strains) and relaxation (peak early diastolic radial strain rate) were significantly impaired in the comorbid group compared to in the single group. In systole, radial thickening is generally preserved with an increase in circumferential shortening accompanying the decrease in longitudinal shortening, resulting in maintenance of LVEF at the early

stage of subclinical patients with $E/A \geq 1$ (normal TMF pattern).^{8,9)} The more impaired LV contraction in the comorbid group may be explained by the results of previous studies.^{8,9)} It is well known that the level of circumferential shortening in the subendocardial layer is approximately two times greater than that in the subepicardial layer in normal LV,²¹⁾ and that myocardial ischemia or fibrosis caused by CVR factors extends from the subendocardium to the subepicardium.²²⁻²⁴⁾ Therefore, it is reasonable to speculate the possibility that LV contraction and relaxation in the subendocardial layer are easily impaired in the comorbid group compared to the single group even in the presence of preserved LVEF.

The principal role of the LA is to modulate LV filling through the interaction of atrial reservoir, conduit, and booster pump functions.²⁵⁾ During ventricular systole, the LA functions as a reservoir for blood returning to the pulmonary veins due to active myocardial relaxation and passive expansion of the LA. Therefore, LA reservoir function has been shown to be related to LA myocardial relaxation, descent of the LV base during systole (LV systolic function), and LA contraction (Frank-Starling mechanism). LA myocardium consists of two layers, with longitudinal and circumferential fibers predominantly arranged in the deep and superficial layers, respectively.²⁶⁾ Therefore, SR-LAs measured by 2DSTE mainly reflects LA myocardial relaxation in the longitudinal direction. Also, systolic descent of the mitral annulus due to LV contraction, which decreases LA pressure, contributes to LA filling.^{27,28)} In the present study, LA reservoir (S-LAs, SR-LAs, and E/e' /S-LAs) and conduit (S-LAe and SR-LAe) function, LV relaxation (early diastolic LV radial strain rate), and systolic LV function (end-systolic LV diameter, and peak systolic LV circumferential and radial strains) were impaired, whereas an augmented LA booster pump function (A of the TMF) was an important compensatory mechanism that facilitated LV filling in the comorbid group compared to the control and single groups.

Interestingly, it has been clarified that 1) impaired LA and LV relaxation in the longitudinal direction are early signs of abnormal LA-LV interaction related to increased arterial stiffness in subclinical patients with CVR factors and $E/A \geq 1$ (normal TMF pattern),⁶⁾ 2) LA strain and strain rate during ventricular systole and early diastole are already impaired in patients with hypertension or diabetes with normal LA size,⁷⁾ 3) impairment of LA longitudinal systolic and diastolic strain rates is common and possibly associated with the same fibrotic processes that affect the LV subendocardial fibers and to a lesser extent with elevated LV filling pressure in patients with HFPEF,²⁹⁾ and 4) an increase in aortic stiffness is associated with increased LA stiffness during ventricular systole and impaired LV relaxation in asymptomatic patients with CVR factors and $E/A < 1$ (impaired LV relaxation).¹⁹⁾

In the present study, multivariate regression analysis identified age, BMI, SBP, and LV systolic parameters (end-systolic diameter, LVEF, s' , and peak systolic radial strain) as independent predictors of LA diastolic stiffness in the comorbid group. Recent studies have demonstrated that subendocardial LA and LV layers along the longitudinal direction and intima and media of large arteries are first and simultaneously impaired by physiologic aging and by CVR factors through various mechanisms,^{6,8)} and subsequently, a combination of CVR factors leads to a significant and additive negative impact on LA diastolic stiffness related to LV dysfunction and arterial

stiffening.^{15,19)} Therefore, inappropriate increases in the number of CVR factors seem to cause more deteriorated LA-LV-arterial interaction, and may predispose the patient to HFPEF.

Study limitations: First of all, the principal limitation was the comparatively small number of patients available for analysis. Second, it may be useful to reanalyze the present data using patients with individual CVR factors, in order to study a more uniform disease process. Finally, no data were available for hemodynamic measurement of the LA and LV function in the present study, because we used asymptomatic patients who visited for routine checkups and were from outpatient facilities.

Conclusions: In asymptomatic patients, combination of the CVR factors was strongly associated with more severe LA and LV dysfunction, and probably with evolving changes in abnormal LA-LV interaction until HFPEF occurs.

REFERENCES

1. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004; 43: 317-27. (Review)
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; 355: 251-9.
3. Fischer M, Baessler A, Hense HW, *et al.* Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. *Eur Heart J* 2003; 24: 320-8.
4. Oki T, Oishi Y, Tanaka H, *et al.* Renewed interest in left atrial function: what do we need to evaluate clinically? *J Echocardiogr* 2005; 3: 60-76.
5. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure – abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004; 350: 1953-9.
6. Miyoshi H, Mizuguchi Y, Oishi Y, *et al.* Early detection of abnormal left atrial-left ventricular-arterial coupling in preclinical patients with cardiovascular risk factors: evaluation by two-dimensional speckle-tracking echocardiography. *Eur J Echocardiogr* 2011; 12: 431-9.
7. Mondillo S, Cameli M, Caputo ML, *et al.* Early detection of left atrial strain abnormalities by speckle tracking in hypertensive and diabetic patients with normal left atrial size. *J Am Soc Echocardiogr* 2011; 24: 898-908.
8. Mizuguchi Y, Oishi Y, Miyoshi H, Iuchi A, Nagase N, Oki T. The functional role of longitudinal, circumferential, and radial myocardial deformation for regulating the early impairment of left ventricular contraction and relaxation in patients with cardiovascular risk factors: a study with two-dimensional strain imaging. *J Am Soc Echocardiogr* 2008; 21: 1138-44.
9. Mizuguchi Y, Oishi Y, Miyoshi H, Iuchi A, Nagase N, Oki T. Concentric left ventricular hypertrophy brings deterioration of systolic longitudinal, circumferential, and radial myocardial deformation in hypertensive patients with preserved left ventricular pump function. *J Cardiol* 2010; 55: 23-33.
10. Lang RM, Bierig M, Devereux RB, *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. *J Am Soc Echocardiogr* 2005; 18: 1440-63.
11. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a non-invasive technique for evaluation of left ventricular relaxation and estimation of filling pres-

- sures. *J Am Coll Cardiol* 1997; 30: 1527-33.
12. Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging* 2009; 2: 10-5.
13. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003; 107: 714-20.
14. Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2009; 54: 410-8.
15. Oki T, Miyoshi H, Oishi Y. Left atrial-left ventricular-arterial coupling: a new concept for evaluating the mechanisms of left ventricular dysfunction using 2D speckle-tracking echocardiography. *Cardiac Ultrasound Today* 2012; 18: 193-224.
16. Hatle L. How to diagnose diastolic heart failure a consensus statement. *Eur Heart J* 2007; 28: 2421-3.
17. Oishi Y, Miyoshi H, Iuchi A, Nagase N, Ara N, Oki T. Vascular aging of common carotid artery and abdominal aorta in clinically normal individuals and preclinical patients with cardiovascular risk factors: diagnostic value of two-dimensional speckle-tracking echocardiography. *Heart Vessels* 2013; 28: 222-8.
18. Joosten MM, Pai JK, Bertoia ML, *et al.* Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA* 2012; 308: 1660-7.
19. Oishi Y, Miyoshi H, Iuchi A, Nagase N, Ara N, Oki T. Negative impact of cardiovascular risk factors on left atrial and left ventricular function related to aortic stiffness -- new application of 2-dimensional speckle-tracking echocardiography. *Circ J* 2013; 77: 1490-8.
20. Costa KD, Takayama Y, McCulloch AD, Covell JW. Laminar fiber architecture and three-dimensional systolic mechanics in canine ventricular myocardium. *Am J Physiol* 1999; 276: H595-607.
21. Clark NR, Reichek N, Bergey P, *et al.* Circumferential myocardial shortening in the normal human left ventricle. Assessment by magnetic resonance imaging using spatial modulation of magnetization. *Circulation* 1991; 84: 67-74.
22. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wave-front phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977; 56: 786-94.
23. Gallagher KP, Osakada G, Matsuzaki M, Miller M, Kemper WS, Ross J Jr. Nonuniformity of inner and outer systolic wall thickening in conscious dogs. *Am J Physiol* 1985; 249: H241-8.
24. Mizuguchi Y, Oishi Y, Miyoshi H, *et al.* Possible mechanisms of left ventricular torsion evaluated by cardioreparative effects of telmisartan in patients with hypertension. *Eur J Echocardiogr* 2010; 11: 690-7.
25. Prioli A, Marino P, Lanzoni L, Zardini P. Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. *Am J Cardiol* 1998; 82: 756-61.
26. Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 1999; 10: 1525-33.
27. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation* 1999; 100: 427-36.
28. Miyoshi H, Oishi Y, Mizuguchi Y, *et al.* Early predictors of alterations in left atrial structure and function related to left ventricular dysfunction in asymptomatic patients with hypertension. *J Am Soc Hypertens* 2013; 7: 206-15.
29. Morris DA, Gailani M, Vaz Pérez A, *et al.* Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. *J Am Soc Echocardiogr* 2011; 24: 651-62.