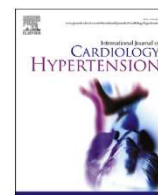




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Research Paper

Arterial stiffening is a crucial factor for left ventricular diastolic dysfunction in a community-based normotensive population



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ABSTRACT

Background: Left ventricular (LV) diastolic dysfunction is an important underlying hemodynamic mechanism for heart failure. Hypertension reportedly increases aortic stiffness with histological changes in the aorta assessed using aortic pulse wave velocity (PWV) that is associated with LV diastolic dysfunction. The role of hypertension *per se* in the relationship between aortic stiffness and LV diastolic dysfunction has not been clarified; therefore, we investigated whether this relation works for normotensive subjects.

Methods: Of the 502 subjects who underwent both echocardiography and PWV measurement in a medical check-up conducted in Arita, Japan, we enrolled 262 consecutive normotensive subjects (age 52 ± 13 years). LV diastolic dysfunction was defined as abnormal relaxation and pseudonormal or restrictive patterns determined with both transmitral flow velocity and mitral annular velocity. Aortic stiffness was assessed via non-invasive brachial-ankle PWV measurement.

Results: LV diastolic dysfunction was detected in 67 of the 262 (26%) normotensive subjects, and PWV was higher in subjects with LV diastolic dysfunction (15.4 ± 3.6 vs. 13.0 ± 2.7 m/s, $p < 0.01$). Multivariate logistic regression analyses revealed that PWV was independently associated with LV diastolic dysfunction ($p = 0.02$) after the adjustment for age; body mass index; blood pressure; eGFR; blood levels of BNP, glucose, and HDL cholesterol; LV mass index; and LA dimension.

Conclusions: Both aortic stiffness and LV diastolic function are mutually related even in normotensive subjects, independent of the potential confounding factors. The increase in aortic stiffness may be a risk factor for LV diastolic dysfunction, irrespective of blood pressure.

1. Introduction

Left ventricular (LV) diastolic dysfunction is an important underlying hemodynamic mechanism of heart failure (HF) with preserved LV ejection fraction (HFpEF) that accounts for up to 50% of HF cases that are often observed in elderly women, particularly in those with a history of hypertension, LV hypertrophy, or diabetes mellitus [1]. HFpEF is reported to be attributable to the abnormalities of the myocardium; stiff ventricle attributable to myocardial fibrosis and hypertrophy may not allow the blood to fill completely during diastole despite preserved

ventricular contractility. However, the systemic large artery acts not only as a conduit, but also as an elastic buffering chamber; further, the less elastic large artery is reported to cause excess rise in pressure during systole and impair LV relaxation [2–4], thus contributing to HFpEF. Hypertension is a primary cause of HFpEF [5,6], and pulse wave velocity (PWV), a measure of aortic stiffness, is related to LV diastolic dysfunction in patients with hypertension [7,8]. However, the critical question is whether hypertension *per se* is essential to constitute the relationship between PWV and LV diastolic dysfunction because this question implies that we simply need to treat hypertension or that we need to improve the

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vascular function to improve the pathophysiology of HFpEF.

In order to resolve this issue, we sought to find that LV diastolic dysfunction is the function of systemic artery stiffness in normotensive subjects. We investigated various parameters, including medical data, echocardiography, blood analysis, and PWV in a community-based normotensive population.

2. Methods

2.1. Study design

In 2007, an annual health examination was conducted in Arita, located in the west of the Saga Prefecture on the island of Kyusyu, southern Japan, to investigate the pathophysiology of the early phase of lifestyle-oriented diseases. The population of this town was approximately 22,000; 48% of the residents were male and 52% were females. The Arita-cho study is a community-based and baseline survey that included a formal medical history interview, ECG, and physical as well as laboratory examinations. The study was approved by the Ethics Committees of the National Cerebral and Cardiovascular Center, the Arita city, HuBit genomics, Inc., CRO. The study was performed as per the ethical principles of the Helsinki Declaration, and written informed consent was obtained from all the participants. We retrospectively reviewed the charts of 3133 subjects aged >30 years who visited for a check-up at Arita, Saga, Japan in 2007, and underwent both echocardiography and ba-PWV.

2.2. Study population

Fig. 1 shows the patient characteristics. Both two-dimensional echocardiography data with optimal quality and the value of ba-PWV were obtained in 502 of the 3133 subjects. Subjects with 1) left ventricular (LV) ejection fraction < 50%; 2) LV end-diastolic volume index > 97 mL/m²; 3) ankle-brachial pressure index (ABI) < 0.9 [9]; 4) no available data of transmitral flow, tissue Doppler imaging (TDI), or LV dimension; or 5) no hematological examination were excluded. In addition to those with hypertension, we also excluded those with diabetes mellitus, atrial fibrillation, or age >75 years [10] because these conditions are linked to LV diastolic dysfunction. Finally, both Doppler mitral profiles and TDI of sufficient quality were obtained for 262 subjects (age 52 ± 13 years, 75 men) for determination of LV diastolic property. All of the data were obtained from the medical records, echocardiography and the

investigation of ba-PWV in all of the subjects.

2.3. Medical records of the enrolled subjects

We obtained the medical records regarding age, sex, height, smoking habits, current medication, previous history of myocardial infarction, diabetes mellitus, hypertension, and dyslipidemia. The patients were asked about their lifestyle and physical factors; the answers were reviewed by trained nurse abstractors. In addition, a clinical diagnosis of coronary artery disease, atrial fibrillation, or valvular heart disease was recorded. Hypertension was defined as systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg or receiving medications from outpatient clinics in the past and the present [11]. The patient was considered to have dyslipidemia or diabetes mellitus if he/she was receiving cholesterol or glucose-lowering agents, respectively, or if so reported in the clinical questionnaire. In addition, high low-density lipoprotein (LDL) cholesterol levels, low high-density lipoprotein (HDL) cholesterol levels, and high triglyceride (TG) levels were defined as LDL cholesterol levels > 140 mmHg, HDL-cholesterol levels < 40 mmHg, and TG > 150 mmHg, respectively. Metabolic syndrome (MetS) was defined as per the established criteria for MetS [12, 13]. Body mass index (BMI) was calculated as kg/m². Estimated-glomerular filtration rate (eGFR) was calculated based on the sex, serum creatinine level, and age (Male = $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$. Female = $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$) [14].

2.4. Measurements

2.4.1. Clinical measurements

Systemic BP was defined as a mean of two readings on the right arm with the random zero method, measured under standardized conditions with the participant seated (after 5 min of rest). The mean BP (MBP) and pulse pressure were calculated as [systolic BP (SBP) + 2/diastolic BP (DBP)]/3, and SBP-DBP, respectively. Waist circumference was measured with a flexible tape, at the mid-point between the lowest rib and the iliac crest.

2.4.2. Brachial-ankle pulse wave velocity

PWV was determined using the form PWV/ABI (Colin, Tokyo, Japan) that records blood pressure, PWV, ABI, heart sounds, and performs electrocardiography (ECG) simultaneously. The subject was examined in

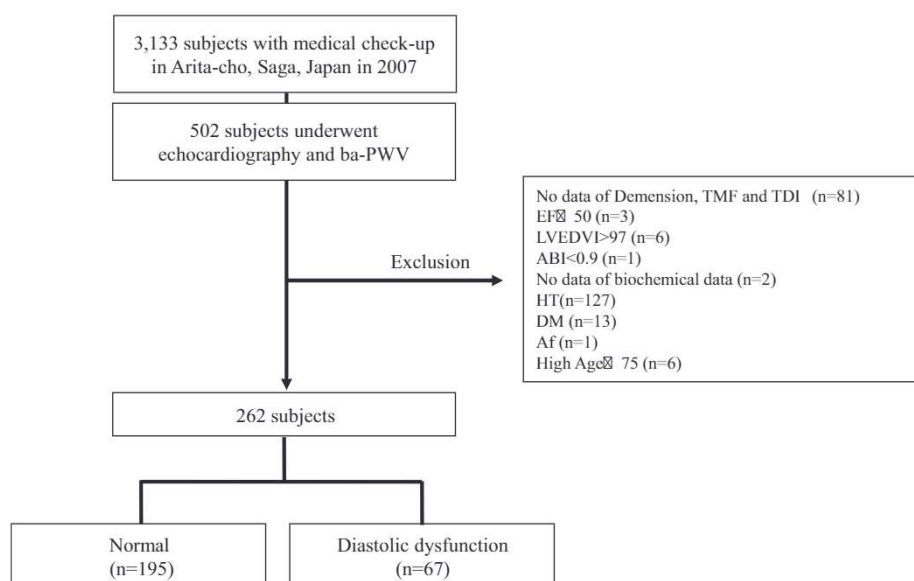


Fig. 1. Schematic presentation of the study profiles. EF: ejection fraction, EDVI: end-diastolic volume index, HT: hypertension, DM: diabetes mellitus, Af: atrial fibrillation.

the supine position, with ECG electrodes placed on both the wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and cuffs wrapped on both the brachia and ankles. The cuffs were connected to a plethysmographic sensor that determines the volume pulse form and an oscillometric pressure sensor that measures the blood pressure. The characteristic points of the waveforms were automatically determined.

Brachial-ankle PWV (ba-PWV) was calculated using the standard method [8]. In sum, the time interval between the wave front of the brachial waveform and that of the ankle waveform was defined as the time interval between the brachium and ankle (ΔT). The distance between the suprasternal notch to the brachium (Lb) was obtained from superficial measurements and between the length from the suprasternal notch to the ankle (La) were estimated. Then, the following equation was used: $ba-PWV = (La - Lb)/\Delta T$. The device has been validated and provides accurate automatic measurement of ba-PWV [8,15]. The ba-PWV was measured after at least 5 min of rest.

2.4.3. Echocardiography

Comprehensive transthoracic echocardiography was performed by seven cardiologists who were blinded to all clinical data using commercially available Vivid I (GE Healthcare, Milwaukee, WI) and Aplio XG (Toshiba Medical Systems, Tokyo, Japan) machines. Two-dimensional and color Doppler imaging was performed in standard parasternal and apical views according to the guidelines of the American Society of Echocardiography [16]. A sample volume of the pulsed-wave Doppler was placed between the tips of the mitral leaflets in the apical long axis view. Early (E) and late (A) transmitral flow velocities, the ratio of early to late peak velocities (E/A), and deceleration time of E velocity were measured. The LV ejection fraction was calculated using Teichholz equations [17], and LV mass index to BSA (LVMI) was calculated with the M-mode method [18]. LV hypertrophy was defined LVMI $>131 \text{ g m}^{-2}$ in men and $>100 \text{ g m}^{-2}$ in women [19]. The relative wall thickness (RMT) was calculated as the ratio of wall thickness to end-diameter in diastole [20]. Tissue Doppler imaging were records using a sample volume of 10 mm placed at the lateral side of the annulus from apical 4-chamber view [21,22]. Analysis was performed for the early (e') and late (a') diastolic velocity. All the subjects were categorized using transmitral flow velocity and mitral annular velocity: normal (E-DcT 160–240 ms and $E/e' \leq 8$), abnormal relaxation ($E/A < 1.0$ and $E-DcT > 240$ ms), pseudonormal (E-DcT 160–200 ms and $E/e' > 8$); restrictive ($E/A > 1.5$ and $E-DcT < 160$ ms) patterns [21,23,24]. LV diastolic dysfunction was defined as abnormal relaxation as well as pseudonormal and restrictive patterns.

2.5. Statistical methods

Continuous data are presented as mean \pm SD values, and categorical data are shown as numbers (percentages). Comparisons of the data of the two groups were performed using Pearson correlation coefficients. A P -value < 0.05 was considered statistically significant. In the univariate logistic regression analysis, categorical variables were reported as independent predictors of LV diastolic dysfunction [25] and were analyzed using a likelihood ratio test. We defined that LVMI was a marker of LV hypertrophy, BMI was a maker of obesity, and systolic blood pressure was a marker of blood pressure. We also developed a multivariate logistic regression model using a significance level of $p < 0.1$ for entry and $p > 0.20$ for removal. All the statistical analyses were performed using JMP 8 (SAS Institute, Cary, NC).

3. Results

3.1. Participant characteristics

The baseline characteristics of the enrolled subjects are presented in Table 1. Of the 262 subjects, LV diastolic dysfunction was detected in 67

Table 1

Comparison between the with diastolic dysfunction group and the without diastolic dysfunction group in normotensive subjects at the baseline.

	Normal Diastolic function (n = 195)	Diastolic Dysfunction (n = 67)	p Value
Age, yrs	50 \pm 12	59 \pm 13	<0.001
Male, n (%)	55 (28)	20 (30)	0.798
BMI, kg/m ²	21.5 \pm 2.8	22.5 \pm 2.8	0.014
Heart rate, /min	64 \pm 9	63 \pm 9	0.468
Systolic BP, mmHg	95 \pm 11	100 \pm 12	0.001
Diastolic BP, mmHg	73 \pm 8	76 \pm 9	0.022
Pulse pressure, mmHg	22 \pm 5	24 \pm 6	0.002
ba PWV, m/sec	13.0 \pm 2.7	15.4 \pm 3.6	<0.001
Systolic BP at ba PWV, mmHg	117 \pm 16	127 \pm 18	<0.001
Diastolic BP at ba PWV, mmHg	68 \pm 10	72 \pm 10	<0.002
Low-HDL, n (%)	4 (2)	1 (1)	0.774
High-LDL, n (%)	45 (23)	24 (36)	0.044
High-TG, n (%)	12 (6)	6 (9)	0.436
Metabolic syndrome, n (%)	3 (2)	1 (1)	0.979
Coronary artery disease, n (%)	0 (0)	0 (0)	–
Smoker, n (%)	50 (26)	13 (19)	0.304
Hemoglobin Ale, %	5.1 \pm 0.3	5.2 \pm 0.3	0.618
Blood sugar, mg/dl	88 \pm 10	91 \pm 13	0.015
Hemoglobin, g/dl	13.2 \pm 1.5	13.6 \pm 1.3	0.061
HDL, mg/dl	65 \pm 14	60 \pm 13	0.013
LDL, mg/dl	122 \pm 35	130 \pm 29	0.084
TG, mg/dl	88 \pm 51	95 \pm 41	0.307
Creatinine, mg/dl	0.60 \pm 0.13	0.64 \pm 0.21	0.061
eGFR, ml/min/1.73m ²	93 \pm 17	85 \pm 18	0.001
BNP, pg/ml	16.4 \pm 17.5	24.8 \pm 24.7	0.003
LV dimensions, mm			
Diastole, mm	45.7 \pm 3.6	45.5 \pm 4.3	0.580
Systole, mm	27.8 \pm 3.7	27.2 \pm 4.1	0.273
%fractional shortening, %	39 \pm 6	40 \pm 7	0.363
Ejection fraction, %	69 \pm 7	70 \pm 9	0.445
LV end-diastolic volume index, ml/m ²	63 \pm 10	63 \pm 13	0.701
LV mass index*, g/m ²	77 \pm 19	88 \pm 23	<0.001
Relative wall thickness	0.36 \pm 0.06	0.39 \pm 0.07	<0.001
LA dimension, mm	34 \pm 5	36 \pm 5	0.027
Trans Mitral Velocity			
E velocity, cm/s	69 \pm 16	63 \pm 16	0.011
A velocity, cm/s	55 \pm 16	73 \pm 25	<0.001
E/A ratio	1.4 \pm 0.5	1.0 \pm 0.4	<0.001
E-DcT, ms	192 \pm 38	224 \pm 67	<0.001
e'			<0.001
Septal	9.6 \pm 2.4	7.1 \pm 2.8	
Lateral	13.0 \pm 3.4	9.8 \pm 3.9	<0.001
E/e'			
Septal	7.5 \pm 2.0	9.9 \pm 3.6	<0.001
Lateral	5.5 \pm 1.5	7.4 \pm 3.3	<0.001

Values expressed as mean \pm SD. Values in parentheses are percentages.

BMI, body mass index; BP, blood pressure; ba-PWV, brachial-ankle pulse wave velocity; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LA, left atrial; E/A velocity, early and late left ventricular filling.

(26%) subjects (age 59 \pm 13 years, 20 men). Of the 67 subjects with LV diastolic dysfunction, 36, 16 and 15 subjects belonged to the categories of abnormal pattern, pseudo-normal pattern and restrictive pattern, respectively. They were older, and their BMI, BP, pulse pressure, ba-PWV, BNP, and bloodsugar levels were higher than those of subjects with normal LV diastolic function; the mean HDL and eGFR levels were lower in this group. Prevalence of MetS was comparable in both groups (Table 1).

3.2. Echocardiographic data

The echocardiographic parameters of the normotensive subjects are presented in Table 1. LV mass index, relative wall thickness, and LA

dimension were higher in those with LV diastolic function than in those without LV diastolic function. LV dimension, %FS, LV ejection fraction, and LV diastolic volume were similar in the two groups. With respect to transmitral flow and tissue Doppler velocities, A velocity, E-DcT, and E/e' were higher, while the E/A ratio and e' were lower in subjects with LV diastolic dysfunction.

3.3. Aortic stiffness and LV diastolic dysfunction

In the enrolled subjects, there was a moderate correlation between ba-PWV and E/e' as a diastolic dysfunction (r = 0.45, p < 0.001). The factors that independently E/e' as a diastolic dysfunction are shown in Table 2 in the univariate and multivariate regression analyses. The multivariable-adjusted model showed that both aging and ba-PWV were independent factors for E/e' in normotensive subjects. The independent predictors of LV diastolic dysfunction are shown in Table 3 in the multivariate logistic regression analysis. The multivariable-adjusted model found that only ba-PWV was an independent factor for LV diastolic dysfunction in normotensive subjects.

4. Discussion

This study validated the evidence for an association between aortic stiffness measured using ba-PWV and LV diastolic dysfunction even in the normotensive population. Further, we found that ba-PWV is the predictive factor for the LV diastolic dysfunction even in the normotensive subjects. Before reaching this conclusion, we need to consider and discuss several issues appeared in the present study.

4.1. Validation of the assessment of aortic stiffness

First of all, we employed ba-PWV as an index of the aortic stiffness in the present study; however, carotid-Femoral PWV (cf-PWV) is the standard method for assessing aortic stiffness recommended in the ESC guideline and has been used to predict cardiovascular events in many studies [26]. In the Framingham studies, the elevation of aortic stiffness is reportedly linked to cardiovascular events, including myocardial infarction, unstable angina, HF, and cerebral infarction in community-based populations. Total 151 patients (6.8%) experienced cardiovascular events during a mean follow-up period of 7.8 years, suggesting that the aortic stiffness assessed using cf-PWV was an independent risk factor for cardiovascular events [27], although cf-PWV can be obtained only using an invasive and costly method. Recently, aortic stiffness using ba-PWV has been shown as an easier and non-invasiveness method that provides good correlation with cf-PWV using a catheter method [8]. In fact, Tanaka et al. reported a good correlation between cf-PWV and ba-PWV in 2287 subjects, and ba-PWV was a crucial predictor for cardiovascular events as well as cf-PWV [28], indicating that ba-PWV can be used as a better tool for assessing aortic stiffness in several

Table 2

Factors that independently E/e' as a marker of diastolic dysfunction in normotensive subjects from univariate and multivariate regression model.

	Univariate				Multivariate				
	B	α	R ²	P	β	α	R ²	P	
baPWV, m/sec	2.27	0.35	0.236	<0.001	baPWV, m/sec	-1.06	0.19	0.37	<0.001
Age, yrs	2.66	0.08	0.246	<0.001	Age, yrs		0.04		0.009
BMI, kg/m ²	5.14	0.09	0.012	0.073	BNP, pg/dl		0.01		0.129
HR, /min	7.95	-0.01	0.003	0.380	eGFR, ml/min/1.73m ²		0.01		0.391
BNP, pg/dl	6.41	0.04	0.101	<0.001	LV mass index, g/m ²		0.01		0.458
eGFR, ml/min/1.73m ²	9.18	-0.02	0.032	0.003	LA dimension, mm		0.07		0.001
Glu, mg/dl	4.72	0.03	0.016	0.434					
HDL-cho, mg/dl	7.08	<0.01	<0.001	0.990					
LV mass index, g/m ²	4.42	0.04	0.089	<0.001					
LA dimension, mm	2.29	0.14	0.094	<0.001					

Ba-PWV, brachial-ankle pulse wave velocity; BMI, body mass index; HR, heart rate; BNP, brain natriuretic peptide;; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LA, left atrial; OR, odds ratio; CI, 95% confidence interval.

Table 3

Factors that independently diastolic dysfunction in normotensive subjects from univariate and multivariate logistic regression model.

	Univariate			Multivariate		
	OR	95%CI	P	OR	95%CI	P
ba PWV, m/sec	1.26	(1.15–1.38)	<0.001	1.29	(1.06–1.56)	0.008
Age, yrs	1.06	(1.04–1.09)	<0.001	1.01	(0.97–1.05)	0.552
Female	0.92	(0.50–1.70)	0.797	1.63	(0.73–3.64)	0.221
BMI, kg/m ²	1.13	(1.02–1.24)	0.016	1.12	(0.98–1.27)	0.087
Systolic BP at ba PWV, mmHg	1.04	(1.02–1.07)	0.001	0.99	(0.95–1.02)	0.520
Diastolic BP at ba PWV, mmHg	1.04	(1.01–1.08)	0.023	0.99	(0.94–1.04)	0.647
HR, /min	0.99	(0.96–1.02)	0.518	0.98	(0.94–1.02)	0.252
BNP, pg/dl	1.02	(1.00–1.03)	0.005	1.00	(0.99–1.02)	0.594
eGFR, ml/min/ 1.73m ²	0.97	(0.95–0.99)	0.002	0.99	(0.97–1.01)	0.491
Glu, mg/dl	1.03	(1.00–1.06)	0.027	1.02	(0.99–1.05)	0.285
HDL-cho, mg/ dl	0.97	(0.95–1.00)	0.014	0.98	(0.95–1.00)	0.072
LV mass index, g/m ²	1.03	(1.01–1.04)	<0.001	1.02	(1.00–1.03)	0.080
LA dimension	1.07	(1.01–1.13)	0.028	0.96	(0.90–1.04)	0.304

Ba-PWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; BNP, brain natriuretic peptide;; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LA, left atrial; OR, odds ratio; CI, 95% confidence interval.

community-based studies [7].

4.2. Association aging and diastolic dysfunction

Secondly, normal aging is associated with a number of changes in the heart and vascular system, especially slowing of LV relaxation which may lead to diastolic dysfunction. LV diastolic dysfunction is usually the result of impaired LV relaxation and LV chamber stiffness, which increase cardiac filling pressure. The mechanisms of diastolic dysfunction in healthy elderly appear to be due to in part to increased LV stiffness compared with younger individuals [29]. Yamakado et al. reported the filling abnormality was showed by Doppler parameters even in the normal subjects (over 60 years), but the data on aging and relaxation are not entirely consist across the studies [30]. Age should be considered when LV diastolic function is evaluated, however E/e' is the less age-dependent marker [31].

4.3. How does stiff aorta induce LV diastolic dysfunction?

Thirdly, we need to consider how aortic property influences the LV diastolic function. It is reported that increasing aortic stiffness impairs Windkessel function and increases/decrease systolic/diastolic pressure

[32]. Reduction in the diastolic pressure decreases the coronary flow, resulting in low myocardial perfusion, thus causing diastolic dysfunction due to impairment of myocardial microcirculation [33]. In addition, secondary wave reflection from the peripheral artery, which is ordinarily reached at diastole, was apparent in late systole, resulting in increased systolic pressure and pulse pressure. In a similar manner, increased aortic stiffness induces pulsatile load on the LV and LV wall stress [2,3,34] that raises myocardial cell hypertrophy and myocardial collagen, resulting in LV diastolic dysfunction [34–36]. In addition, increasing aortic stiffness changed the LV ejection phase and prolonged LV relaxation [37], affecting LV systolic pressure and systolic loading condition, and causing degenerative changes in the aorta [38–40]. Furthermore, arterial stiffness further increases with age, cardiometabolic abnormalities, and increased sodium intake, as seen in the pathophysiology of HFpEF [41]. In sum, ventricular-vascular uncoupling may lead to diastolic dysfunction [42]. Although this study did not include central aortic blood pressure, ba-PWV, as a marker of aortic stiffness, was associated with LV mass index in the normotensive population. Thus, increasing aortic stiffness caused LV hypertrophy and LV diastolic dysfunction even in a normotensive population.

4.4. What is the worsening of HFpEF?

The final issue is whether vascular abnormality *per se* causes HF. Milo-Cotter O et al. considered vascular disorder, which increasing systematic vascular resistance and systematic blood pressure caused by activation of neurohumoral factors and cytokine, increased LV after load and led flash pulmonary edema especially in LV diastolic dysfunction [41]. This study indicated that increasing aortic stiffness was an important mechanism in worsening of HFpEF. Meguro et al. reported that ba-PWV, as a marker of aortic stiffness, predicted HF re-admission and mortality [7]. In a similar manner, Kawaguchi et al. concluded that deteriorated aortic stiffness and LV diastolic dysfunction led to worsening HFpEF, especially in elderly patients [42,44].

In fact, increasing aortic stiffness was the crucial factor for hypertension and LV diastolic dysfunction, resulting in heart failure. In this study, we reported a clinical association between aortic stiffness and LV diastolic dysfunction, irrespective of blood pressure. We believe that early detection of increased aortic stiffness and prevention of worsening HF are crucial for improving the prognosis of HF patients with LV diastolic dysfunction.

4.5. Limitation

First, the number of enrolled subjects was relatively smaller than that in studies on the general population [45–47] as well as those conducted on subjects with LV diastolic dysfunction as per the criterion defined by Redfield et al. [43] and Walter et al. [46,48]. The smaller sample size may have led to the overlooking of important factors for LV diastolic dysfunction other than PWV. However, we found that PWV is an important determinant of LV dysfunction, suggesting that we are able to test the working hypothesis.

Secondly, the occurrence of masked hypertension in subjects is unclear based on medical records. Masked hypertension is defined as abnormal BP in the clinic, but high BP out of the clinic. In normotensive healthy workers in Japan, the prevalence was 7.2% (systolic) and 8.7% (diastolic) [49]. The subjects with masked hypertension had a higher LV mass and more carotid atherosclerosis than true normotensives, in the SHEAF study, which recruited elderly hypertensive on treatment, the hazard ratio for cardiovascular events was 2.06 in patients with masked hypertension [50]. Future studies are needed to investigate the association among masked hypertension, the increases in aortic stiffness and LV diastolic dysfunction.

Thirdly, the definition of LV diastolic dysfunction is critical. This study intended community-based healthy population without history of HF, and the subjects with LV diastolic dysfunction using the same

criterion was a mere 2%. When we defined LV diastolic dysfunction using a simple approach with echocardiographic assessment including mitral inflow [23] and Tissue Doppler imaging as reported previously [24], 35% subjects had LV diastolic dysfunction; this prevalence was higher than that reported in other studies. Considering that the number of comorbidities of LV diastolic dysfunction, such as hypertension, coronary artery disease, and cardiac hypertrophy was larger than in other studies, the differences in the prevalence of LV dysfunction may be attributable to the difference in the study population.

5. Conclusion

Both aortic stiffness and LV diastolic function are closely associated in normotensive subjects, irrespective of the presence of the potential confounding factors. Hence, we need to pay special attention to patients with increased aortic stiffness with respect to the occurrence of HF even in the absence of hypertension.

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Nothing to disclose

Declaration of competing interest

All co-authors of this manuscript have read and approved the submission of the manuscript. All of the authors have made an important contribution to the study and are thoroughly familiar with the original data.

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