Relationship Between Effective Arterial Elastance, Total Vascular Resistance, and Augmentation Index at the Ascending Aorta and Left Ventricular Diastolic Function in Older Women

Toshihiko Goto, MD; Nobuyuki Ohte, MD; Hidekatsu Fukuta, MD;
Kazuaki Wakami, MD; Tomomitsu Tani, MD; Genjiro Kimura, MD

Background: Heart failure with preserved ejection fraction (HFpEF) is frequently observed in older women. Increased arterial stiffness in this population may be a cause of HFpEF.

Methods and Results: In 75 patients who underwent cardiac catheterization and who had no significant coronary artery stenosis or left ventricular (LV) wall motion abnormalities, the LV relaxation time constant (T_p) was calculated. The LVEF was obtained from left ventriculography, and plasma brain natriuretic peptide (BNP) level was measured. From the pressure waveforms at the ascending aorta, the augmentation index (AIx) was calculated. Effective arterial elastance (Ea) and total vascular resistance (TVR) were also determined. No significant differences were found between genders for age, heart rate, central blood pressure, or LVEF. Ea, TVR, AIx, and BNP level were significantly greater in women than in men, but only AIx was significantly correlated with T_p ($r=0.25$, $P=0.04$) and BNP level ($r=0.33$, $P=0.005$).

Conclusions: The arterial system is stiffer in women than in men of the same age. Among the parameters of arterial stiffness, only AIx is related to abnormal LV relaxation and increased BNP level. Elevated AIx is a factor that causes LV diastolic dysfunction and may be associated with the development of HFpEF in this gender. (*Circ J* 2013; **77**: 123–129)

Key Words: Augmentation index; Brain natriuretic peptide; Relaxation; Women

Heart failure with preserved ejection fraction (HFpEF) accounts for more than 50% of all HF cases and is more commonly seen in women and the elderly.¹ The mechanisms of HFpEF are still controversial, although left ventricular (LV) diastolic dysfunction is known to play a central role in its pathogenesis.^{2,3} Most patients with isolated LV diastolic dysfunction, however, do not have clinical features of HF.⁴ Recent studies have suggested that arterial stiffening might contribute to the pathogenesis of HFpEF.^{5–8} As arterial stiffness increases, the pulse wave velocity along the aorta increases, so that the reflected pulse wave arrives earlier at the ascending aorta and augments the late-systolic ascending aortic pressure waveform.⁹ Thus, the augmentation index (AIx) is a surrogate indicator of arterial stiffness^{10,11} and late-systolic arterial load to the left ventricle, which results in deteriorated LV relaxation.^{12–14} This story has not been fully clarified in clinical setting, however, because left-sided cardiac catheterization using a catheter-tipped micromanometer is need-

ed for the measurement of an LV relaxation constant. In addition, the reason why HFpEF is observed at a higher incidence in older women also has not been adequately elucidated. Accordingly, we investigated gender differences in clinical and hemodynamic indices, including AIx, effective arterial elastance (Ea), and total vascular resistance (TVR) in the invasive setting, in patients with normal coronary arteries and normal LV wall motion.

Methods

Subjects

Study participants were enrolled from a pool of 763 consecutive patients who underwent diagnostic cardiac catheterization for the evaluation of coronary artery disease and from whom blood samples for measuring plasma brain natriuretic peptide (BNP) level were obtained. All enrolled patients had symptoms suggestive of angina pectoris and/or clinical signs of coronary

Received June 3, 2012; revised manuscript received July 30, 2012; accepted August 29, 2012; released online September 29, 2012 Time for primary review: 24 days

Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
Mailing address: Nobuyuki Ohte, MD, Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. E-mail: ohite@med.nagoya-cu.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-12-0733

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

artery disease, including positive exercise electrocardiographic changes, abnormal myocardial perfusion scintigraphic findings, or a history of myocardial infarction or coronary revascularization. Exclusion criteria were renal insufficiency (serum creatinine ≥ 1.5 mg/dl), atrial fibrillation or flutter, artificial pacemaker, hemodynamically significant valvular heart disease, or peripheral arterial disease. Based on coronary angiographic and left ventriculographic findings, a total of 75 patients (32 men and 43 women) who did not have significant coronary stenosis or abnormal LV wall motion were eligible for enrollment. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or on treatment with antihypertensive drugs. Diabetes mellitus was diagnosed when the fasting blood glucose level was >126 mg/dl or when the patient was treated with blood glucose-lowering medicine. Hypercholesterolemia was defined as low-density lipoprotein-cholesterol level >140 mg/dl or on treatment with cholesterol-lowering medicine. All patients provided written informed consent for study participation. The study protocol was reviewed by the Ethics Guidelines Committee of Nagoya City University Graduate School of Medical Sciences.

Pressure Measurements

The LV pressure waves were obtained using a catheter-tipped micromanometer (SPC-454D, Millar Instrument, Houston, TX, USA) and recorded on a polygraph system (RMC-3000, Nihon Kohden, Tokyo, Japan) and also on a digital data recorder (NR-2000, Keyence, Osaka, Japan) as previously described.¹⁴⁻¹⁶ From the recorded ascending aortic (central) pressure waveforms, central systolic, diastolic, and pulse pressures were measured as shown in Figure 1. The augmented pressure produced by pulse wave reflection from the lower body was also calculated as the difference between P2 and P1 (ΔP ; Figure 1). The

AIx was calculated as the augmented pressure divided by the central pulse pressure and expressed as a percentage.¹⁴ From the recorded LV pressure waves, a time constant of the decrease in LV pressure (T_w) was calculated by applying mono-exponential fitting with zero asymptote to the pressure decay.¹⁷ We also computed another time constant of LV relaxation, T_p , which is relatively independent of LV systolic function, from the LV pressure (P)-dP/dt relationship (phase loop) as previously reported.^{18,19} LV end-diastolic pressure was then determined. LV end-systolic and end-diastolic volumes were obtained from biplane left ventriculography using the method proposed by Chapman et al.²⁰ Stroke volume was obtained by subtracting LV end-systolic volume from LV end-diastolic volume; Ea was calculated as LV end-systolic pressure divided by stroke volume,²¹ and TVR was also calculated as mean central aortic pressure divided by cardiac output, which was stroke volume multiplied by heart rate. Stroke volume was divided by the body surface area (BSA) of each individual and expressed as stroke volume index to normalize body size.

BNP Assay

The venous blood sample (6 ml) for plasma BNP assay was collected from the right femoral vein or median cubital vein of each patient at the time of cardiac catheterization and kept in chilled disposable tubes containing aprotinin (500 kallikrein inactivator units/ml) and EDTA (1 mg/ml). Blood samples were centrifuged (1,000 g for 10 min at 4°C) and stored at -70°C. The plasma BNP concentration was measured using an immunoradiometric assay kit specific for human BNP (Shionoria™; Shionogi, Osaka, Japan). The minimum detectable quantity of human plasma BNP was 2 pg/ml.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). BNP and triglyceride levels are given as median and interquartile range (IQR). Other data are presented as mean $\pm$ SD or frequency (%). Parameters between 2 groups were compared using unpaired Student t-tests or Wilcoxon signed-rank test appropriately. Differences in prevalence between 2 groups were also compared using the chi-squared test. Hemodynamic parameters were then compared using analysis of covariance (ANCOVA) to adjust for the effect of age on differences between genders. When there was no significant interaction between the independent variable and the covariate (age), this analysis was performed in such parameters. Relationships between 2 parameters were evaluated on univariate linear regression analysis. In addition, stepwise multivariate regression analysis was performed to determine which independent variables would significantly affect the T_p and log BNP. Because BNP level was not normally distributed, logarithmic transformation was applied. The possible independent variables for determining T_p were age, female gender, heart rate, central mean pressure, AIx, LVEF, and LV end-systolic and diastolic volumes. Female gender was treated as a binary categorical parameter. The possible independent variables for determining log BNP were these and T_p . Significance was set at $P < 0.05$.

Results

Demographic Data

Table 1 lists the baseline patient characteristics. No significant differences were found between genders for age, body mass index, and the incidence of morbidities including diabetes mellitus, hypertension, and hypercholesterolemia. Medication

Table 1. Baseline Characteristics vs. Gender

Characteristic	Men	Women	P-value
Patient number	32	43	
Age (years)	64.6±8.6	67.6±9.8	0.19
Height (cm)	165.9±5.0	151.0±7.2	<0.001
Weight (kg)	67.5±8.1	56.5±9.6	<0.001
Body surface area (m ²)	1.76±0.11	1.53±0.14	<0.001
Body mass index (kg/m ²)	24.5±3.0	24.8±4.3	0.82
Triglycerides (mg/dl)	156 (IQR, 115–197)	129 (IQR, 85–179)	0.05
HDL-C (mg/dl)	46.2±13.6	55.6±12.7	0.003
LDL-C (mg/dl)	130.8±44.0	122.6±30.3	0.40
Glucose (mg/dl)	113.5±41.3	116.7±44.9	0.77
HbA _{1c} (%)	5.4±0.7	5.7±1.2	0.35
Hypertension (%)	43.8	53.5	0.40
Hypercholesterolemia (%)	50	53.5	0.77
Diabetes (%)	15.6	18.6	0.74
Statin treatment (%)	21.9	39.5	0.11
ACEI treatment (%)	6.3	7.0	0.90
ARB treatment (%)	12.5	27.9	0.11
β-blocker treatment (%)	6.3	16.3	0.19
Calcium channel blocker treatment (%)	31.3	34.9	0.74
Current smoker (%)	6.3	7.0	0.90

Data given as mean ± SD, frequency, or median (IQR).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HDL-C, high-density lipoprotein-cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol.

Table 2. Baseline Hemodynamics vs. Gender

Characteristics	Men	Women	P-value	P-value (ANCOVA)
Heart rate (beats/min)	68.9±13.4	67.4±12.5	0.60	
Central systolic BP (mmHg)	139.2±23.9	143.0±21.7	0.47	
Central diastolic BP (mmHg)	72.1±10.6	70.2±11.8	0.42	
Central mean BP (mmHg)	100.7±14.8	100.1±14.4	0.86	
Central pulse pressure (mmHg)	67.0±18.0	73.0±17.2	0.15	0.31
Augmentation pressure (mmHg)	26.6±15.4	33.9±15.2	0.05	0.16
Alx (%)	37.9±13.9	45.7±14.0	0.02	0.048
Ea (mmHg/ml)	1.21±0.23	1.55±0.63	0.008	
TVR (dyne · s · cm ⁻⁵)	1,343.2±587.3	1,642.1±622.7	0.04	
Tw (ms)	40.9±7.6	41.3±5.9	0.80	
Tp (ms)	62.2±14.4	73.6±28.0	0.04	
LVEF (%)	72.1±4.9	72.3±4.7	0.82	0.88
LV end-diastolic volume (ml)	136.3±27.6	111.5±29.3	<0.001	0.001
LV end-systolic volume (ml)	37.8±11.1	30.5±12.0	0.009	0.02
Stroke volume (ml)	98.4±20.4	81.0±19.8	<0.001	
Stroke volume index (ml/m ²)	53.0±11.3	55.6±10.0	0.32	
LV end-diastolic pressure (mmHg)	13.4±4.2	13.0±4.3	0.69	
LV end-systolic pressure (mmHg)	113.6±18.3	115.9±16.5	0.63	

Data given as mean ± SD. ANCOVA P-values given only when there was no significant interaction between the independent variable and the covariate (age).

Alx, augmentation index; ANCOVA, analysis of covariance; BP, blood pressure; Ea, effective arterial elastance; EF, ejection fraction; LV, left ventricular; Tp, LV relaxation time constant calculated from the phase loop; TVR, total vascular resistance; Tw, LV relaxation time constant calculated by Weiss's method.

use did not differ significantly between genders.

Hemodynamic Data

Data concerned with the hemodynamic indices are given in [Table 2](#). No significant differences were observed between

genders for heart rate, central systolic and diastolic pressure, central mean pressure, central pulse pressure, LV end-systolic pressure, LVEF, Tw, LV end-diastolic pressure, or stroke volume index. In contrast, Tp, which is considered to be more sensitive to the change in LV relaxation, was significantly

Figure 2. Comparison of (A) body surface area (BSA), (B) augmentation index (AIx), and (C) the time constant of left ventricular relaxation (Tp) between genders. Women had significantly smaller BSA, significantly greater AIx, and significantly longer Tp than men (data given as mean±SD).

Table 3. Correlations Between AIx, Ea and TVR: Univariate and Multivariate Regression Analysis

	AIx		Ea		TVR	
	r	P-value	r	P-value	r	P-value
Age	0.34	0.003	0.20	0.10	0.07	0.57
Height	−0.35	0.003	−0.38	0.001	−0.30	0.008
Weight	−0.35	0.003	−0.51	<0.001	−0.42	<0.001
Body surface area	−0.40	<0.001	−0.51	<0.001	−0.42	<0.001
Stroke volume	−0.01	0.91	−0.73	<0.001	−0.68	<0.001
Heart rate	−0.39	0.001	0.22	0.07	−0.17	0.15
Tp	0.25	0.04	0.01	0.93	0.13	0.28
AIx			0.28	0.02	0.44	<0.001
Ea	0.28	0.02			0.92	<0.001
TVR	0.41	<0.001	0.92	<0.001		
LVEF	0.18	0.14	0.03	0.82	−0.05	0.69
LV end-diastolic pressure (mmHg)	0.03	0.79	−0.15	0.23	0.11	0.35
Log BNP (pg/ml)	0.33	0.005	0.23	0.06	0.13	0.29

BNP, brain natriuretic peptide. Other abbreviations as in Table 2.

longer in women compared to men. As expected, women were significantly smaller with regard to height, weight, and BSA than men (Table 1; Figure 2). Stroke volume index was not different between genders, but stroke volume was significantly smaller in women compared to men, resulting in significantly higher Ea and TVR in women than in men. The smaller stroke volume was a crucial factor for stiffer arterial systems in women. The AIx was also significantly greater in women compared to men, even when the effect of age was adjusted for (Figure 2). The AIx positively correlated with age and Tp ($P<0.05$ for each), but it negatively correlated with height, weight, and BSA ($P<0.05$ for each). In contrast, Ea and TVR did not correlate

with age or Tp (Table 3). The central pulse pressure also did not correlate with Tw ($r=-0.09$, $P=0.44$) or Tp ($r=-0.10$, $P=0.38$). In multivariate regression analysis for Tp, only AIx was selected as a determinant ($r=0.30$, $P=0.02$; Table 4).

Plasma BNP level was significantly higher in women than in men (21.1 pg/ml, IQR: 8.2–40.1 pg/ml vs. 14.6 pg/ml, IQR: 8.1–23.7 pg/ml, $P=0.03$; Figure 3). AIx was significantly correlated with log BNP ($r=0.33$, $P=0.005$), but Ea and TVR were not (Table 4). On multivariate regression analysis for log BNP, age and AIx were selected as determinants ($r=0.54$, $P<0.001$; Table 4), but female gender was not selected as a significant covariant ($P=0.18$).

Table 4. Correlations Between Tp and Log Plasma BNP

	Tp				Log BNP			
	Univariate		Multivariate		Univariate		Multivariate	
	r	P-value	β	P-value	r	P-value	β	P-value
Age (years)	0.12	0.30			0.50	<0.001	0.42	<0.001
Heart rate (beats/min)	-0.23	0.047			-0.12	0.30		
Central mean BP (mmHg)	-0.08	0.52			0.094	0.42		
Tp (ms)					0.24	0.04		
AIx (%)	0.24	0.04	0.30	0.02	0.33	0.005	0.23	0.03
LVEF (%)	0.10	0.39			0.09	0.47		
LV end-diastolic volume (ml)	-0.41	0.73			-0.13	0.28		
LV end-systolic volume (ml)	-0.08	0.50			-0.11	0.35		
Log BNP (pg/ml)	0.24	0.04						

Abbreviations as in Tables 2,3.

Discussion

The aim of this study was to clarify the baseline cardiovascular characteristics in older women, in whom HFpEF is often seen. Elevated Ea, TVR, and increasing aortic AIx were observed in women in relation to smaller BSA. In these parameters of arterial stiffness, only AIx was significantly correlated with Tp. Furthermore, age, Tp, and AIx were significantly correlated with plasma BNP level.

Both Ea, a component of lumped mean and pulsatile load to the left ventricle, and TVR, a component of non-pulsatile load to the left ventricle, were higher in women than in men due to smaller stroke volume in women. Chen et al showed that an increase in Ea in normal, older individuals causes augmented LV end-systolic elastance in order to maintain arterio-LV coupling and the mechanical efficiency of the left ventricle.⁵ In older subjects, the mechanism of arterio-LV coupling is sensitive to increased LV end-diastolic volume, which is caused by increased venous return due to muscle contraction in the lower extremities during exercise, and easily augments LV end-systolic pressure. This increase in LV end-systolic pressure should result in the deterioration of LV relaxation and exercise intolerance. Kawaguchi et al also reported that Ea and LV end-systolic elastance are significantly greater in patients with HFpEF than in age-matched asymptomatic controls.⁶ This mechanism is thought to be one of the causes of HFpEF. But Kawaguchi et al also reported that a time constant of LV relaxation obtained using an exponential model with non-zero asymptote was not prolonged in this category of patients.⁶ In the present study, Ea and TVR were significantly higher in women than in men. Similar to the findings of Kawaguchi et al,⁶ however, these parameters did not correlate with LV relaxation time constants Tw or Tp.

AIx is a surrogate indicator of arterial stiffness^{10,11} and has been reported to be different between men and women based on applanation tonometric radial pulse wave measurements with the use of generalized transfer function.^{22–25} In the present study, however, we directly measured AIx from the ascending aortic pressure waveform obtained using a catheter-tipped micromanometer. This methodology without any assumption provided more precise measurements of the AIx than the non-invasive method and should represent accurate results. The AIx was significantly higher in women than in men and it is similar to the previous reports.^{22–26} Although whether the AIx is influenced by gender itself remains unclear,^{26–28} height should play an important role in the higher AIx in women because

aortic length is a substantial factor influencing AIx.^{22–26} In the present study, height negatively correlated with AIx, as observed in previous studies.^{22–26} Body weight also negatively correlated with AIx. Generally, individuals who are shorter weigh less. In this study, a more prominent correlation was observed between BSA and the AIx. BSA is calculated from the height and weight of each individual and it may have a stronger effect on the AIx than either height or weight. In addition, smaller BSA may be related to greater tapering of arteries between the aorta and periphery, forming a more proximal reflecting site of pulse wave.²⁵ Thus, BSA measurements are important for estimating AIx based on the body size of individual patients. In addition, it has been reported that central pulse wave velocity increases more rapidly with age in women than in men, crossing over at around the age of 45 years.^{26–28} Thus, we consider that the present female subjects, whose mean

age was 67.6 years, should have a stiffer aorta than the male subjects from the viewpoint of pulse wave velocity analysis.^{26–28} Therefore, the increased AIx observed in women compared with age-matched men in the present study was associated with the stiffer aorta in the older women as well as the smaller body size in women.^{22–28}

In this study, the increased AIx in women resulted in prolonged Tp compared to age-matched men. The increased AIx, however, did not lengthen Tw. The time constant Tp is relatively independent of LV systolic function or LV elastic recoil, and it can sensitively detect abnormal LV relaxation.^{18,19} In contrast, Tw is calculated by applying monoexponential fitting with zero asymptote to the LV pressure decay, starting at the phase of $-\max.dP/dt$.¹⁷ Because LV pressure decay is not necessarily fitted by a monoexponential curve with zero asymptote, Tw is less sensitive for detecting abnormal LV relaxation compared to Tp. In addition, Tw theoretically depends on LV elastic recoil because the recoil strongly affects LV pressure decreasing speed around the phase of $-\max.dP/dt$.^{18,19} Thus, in the present subjects, who lacked significant coronary stenosis and LV wall motion abnormality, LV elastic recoil, which is generated by normal LV systolic function, may have compensated for Tw, which should be prolonged due to the increased afterload in women. The time constant that Kawaguchi et al used was obtained by applying a monoexponential fitting with non-zero asymptote,⁶ and may be much more sensitive to the deterioration of LV relaxation than the time constant Tw; but it is also dependent on LV elastic recoil because the monoexponential fitting starts at the timing of $-\max.dP/dt$, similar to Tw. Thus, for detecting abnormal LV relaxation in patients with normal LV systolic function without LV wall motion abnormalities, a sensitive and systolic function-independent time constant, such as Tp, should be used.

In the present study, plasma BNP level was slightly, but significantly, elevated in women compared to men. Plasma BNP level is recognized as one of the markers of LV diastolic function.^{29,30} We previously reported that, in patients with coronary artery disease who underwent cardiac catheterization and who had preserved LVEF ($\geq 50\%$), the threshold plasma BNP value to distinguish abnormal LV relaxation ($Tw \geq 48$ ms) was 22.4 pg/ml.¹⁵ In the present study, when considering the median and IQRs, more women than men exceeded this threshold value, showing isolated LV diastolic dysfunction. Previous reports showed that plasma BNP level was significantly higher in women than in men in healthy subjects.^{31,32} Redfield et al suggested that the association of female gender and plasma BNP level appeared to be in part related to estrogen status, because plasma BNP level was higher in women using hormone replacement treatment.³² In the current study, significantly prolonged Tp in women than in men was observed in relation to the elevated AIx. This finding may suggest that higher arterial load to the left ventricle and worse LV relaxation in women partly affected the elevated plasma BNP level in women through the hemodynamic mechanism. In multivariate regression analysis for the determinants of BNP level, female gender was not selected as an explanatory parameter in the current study. Thus, we consider that a higher plasma BNP level was observed in relation to hemodynamic characteristics in older women, although the extent of elevation was not so remarkable.

AIx is known to be influenced by numerous factors besides gender and age, including smoking, hypertension, diabetes mellitus, and hypercholesterolemia.^{13,33–36} In the present study, we found no significant differences in these clinical factors between genders.

Shim et al recently reported on sex differences in central hemodynamics and their relationship to LV diastolic function.³⁷ They showed that the central hemodynamics reflecting arterial stiffness were different between men and women. It is similar to the present result. They also indicated that LV relaxation, which was assessed using the mitral annular velocity during early diastole (Em), was not different between men and women. This finding may be similar to the present finding that Tw was not different between genders due to being less sensitive to deterioration in LV relaxation. There were also several differences between the studies. The age of study subjects was higher in the present study. In elderly women, HFpEF is more often observed. Subject age range may be an important issue for study design when dealing with HFpEF. Arterial stiffness and LV function parameters were obtained invasively in the present study and this methodology is considered to be more precise than the non-invasive method. They also indicated a significant positive correlation between the Em and the pulse pressure amplification ratio from periphery to central in women but not in men. Measurement of central and radial pressures at the same time for the calculation of pulse pressure amplification ratio was difficult in the present invasive setting. The physiological meaning of pulse pressure amplification ratio is somewhat different from AIx, and the difference should be investigated in future.

To our knowledge, we have demonstrated for the first time that invasively obtained LV relaxation time constant Tp, which is relatively independent of LV systolic function, is worse in women than in men of the same age, and we have also found significant relationships among AIx, the time constant Tp, and plasma BNP level. We believe that these findings are important to appreciate particular hemodynamics in older women.

Study Limitations

The low number and the selected category of patients may have affected the present results, but the gold standard parameter of LV relaxation, such as the time constant Tp, could not have been obtained in another setting of patients using an invasive method. We believe that the obtained data are important for deducing the gender differences in hemodynamics in the general population despite such a limitation.

Conclusions

The arterial system is stiffer and LV relaxation is worse in women than in men of the same age. Among elevated Ea, TVR, and AIx observed in older women, only AIx, which is an index of late-systolic arterial load to the left ventricle, is significantly related to abnormal LV relaxation and increased plasma BNP level. Elevated AIx may be a factor of LV diastolic dysfunction in older women and may be associated with the development of HFpEF in this gender.

References

- 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**: 251–259.
- 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**: 1953–1959.
- Aizawa Y, Sakata Y, Mano T, Takeda Y, Ohtani T, Tamaki S, et al. Transition from asymptomatic diastolic dysfunction to heart failure with preserved ejection fraction: Roles of systolic function and ventricular distensibility. *Circ J* 2011; **75**: 596–602.
- Kitzman DW. Diastolic dysfunction in the elderly: Genesis and diagnostic and therapeutic implications. *Cardiol Clin* 2000; **18**: 597–617.

5. Chen CH, Nakayama M, Nevo E, Fetis BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: Implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol* 1998; **32**: 1221–1227.
6. Kawaguchi M, Hay I, Fetis 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**: 714–720.
7. Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001; **38**: 796–802.
8. Odaira M, Tomiyama H, Matsumoto C, Yoshida M, Shiina K, Nagata M, et al. Strength of relationships of the pulse wave velocity and central hemodynamic indices with the serum N-terminal fragment B-type natriuretic peptide levels in men. *Circ J* 2012; **76**: 1928–1933.
9. O'Rourke MF, Mancia G. Arterial stiffness. *J Hypertens* 1999; **17**: 1–4.
10. Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, et al. Central blood pressure measurements and antihypertensive therapy: A consensus document. *Hypertension* 2007; **50**: 154–160.
11. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *Eur Heart J* 2006; **27**: 2588–2605.
12. Hori M, Inoue M, Kitakaze M, Tsujioka K, Ishida Y, Fukunami M, et al. Loading sequence is a major determinant of afterload-dependent relaxation in intact canine heart. *Am J Physiol* 1985; **249**: H747–H754.
13. Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989; **80**: 1652–1659.
14. Fukuta H, Ohte N, Wakami K, Asada K, Goto T, Mukai S, et al. Impact of arterial load on left ventricular diastolic function in patients undergoing cardiac catheterization for coronary artery disease. *Circ J* 2010; **74**: 1900–1905.
15. Goto T, Ohte N, Wakami K, Asada K, Fukuta H, Mukai S, et al. Usefulness of plasma brain natriuretic peptide measurement and tissue Doppler imaging in identifying isolated left ventricular diastolic dysfunction without heart failure. *Am J Cardiol* 2010; **106**: 87–91.
16. Ohte N, Saeki T, Miyabe H, Sakata S, Mukai S, Hayano J, et al. Relationship between blood pressure obtained from the upper arm with a cuff-type sphygmomanometer and central blood pressure measured with a catheter-tipped micromanometer. *Heart Vessels* 2007; **22**: 410–415.
17. Weiss JL, Frederiksen JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. *J Clin Invest* 1976; **58**: 751–760.
18. Sugawara M, Uchida K, Kondoh Y, Magosaki N, Niki K, Jones CJ, et al. Aortic blood momentum: The more the better for the ejecting heart in vivo? *Cardiovasc Res* 1997; **33**: 433–446.
19. Yoshida T, Ohte N, Narita H, Sakata S, Wakami K, Asada K, et al. Lack of inertia force of late systolic aortic flow is a cause of left ventricular isolated diastolic dysfunction in patients with coronary artery disease. *J Am Coll Cardiol* 2006; **48**: 983–991.
20. Chapman CB, Baker O, Reynolds J, Bonte FJ. Use of biplane cine-fluorography for measurement of ventricle volume. *Circulation* 1958; **18**: 1105–1117.
21. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol* 1983; **245**: H773–H780.
22. Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. *J Am Coll Cardiol* 1997; **30**: 1863–1871.
23. Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME, London GM. Influence of body height on pulsatile arterial hemodynamic data. *J Am Coll Cardiol* 1998; **31**: 1103–1109.
24. London GM, Guerin AP, Pannier B, Marchais SJ, Stimpel M. Influence of sex on arterial hemodynamics and blood pressure: Role of body height. *Hypertension* 1995; **26**: 514–519.
25. Cecelja M, Jiang B, McNeill K, Kato B, Ritter J, Spector T, et al. Increased wave reflection rather than central arterial stiffness is the main determinant of raised pulse pressure in women and relates to mismatch in arterial dimensions. *J Am Coll Cardiol* 2009; **54**: 695–703.
26. Gatzka CD, Kingwell BA, Cameron JD, Berry KL, Liang YL, Dewar EM, et al. Australian comparative outcome trial of angiotensin-converting enzyme inhibitor- and diuretic-based treatment of hypertension in the elderly: Gender differences in the timing of arterial wave reflection beyond differences in body height. *J Hypertens* 2001; **19**: 2197–2203.
27. Vermeersch SJ, Rietzschel ER, De Buyzere ML, De Bacquer D, De Backer G, Van Bortel LM, et al. Age and gender related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population. *J Hypertens* 2008; **26**: 1411–1419.
28. Lee HY, Oh BH. Aging and arterial stiffness. *Circ J* 2010; **74**: 2257–2262.
29. Mottram PM, Leano R, Marwick TH. Usefulness of B-type natriuretic peptide in hypertensive patients with exertional dyspnea and normal left ventricular ejection fraction and correlation with new echocardiographic indexes of systolic and diastolic function. *Am J Cardiol* 2003; **92**: 1434–1438.
30. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: Comparison with Doppler velocity recordings. *Circulation* 2002; **105**: 595–601.
31. Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PW, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol* 2002; **90**: 254–258.
32. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: Impact of age and gender. *J Am Coll Cardiol* 2002; **40**: 976–982.
33. Murgu JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: Relationship to pressure wave forms. *Circulation* 1980; **62**: 105–116.
34. Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, et al. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: The Hoorn Study. *Hypertension* 2004; **43**: 176–181.
35. Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, et al. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *J Am Coll Cardiol* 2002; **39**: 1005–1011.
36. Kubozono T, Miyata M, Ueyama K, Hamasaki S, Kusano K, Kubozono O, et al. Acute and chronic effects of smoking on arterial stiffness. *Circ J* 2011; **75**: 698–702.
37. Shim CY, Park S, Choi D, Yang WI, Cho IJ, Choi EY, et al. Sex differences in central hemodynamics and their relationship to left ventricular diastolic function. *J Am Coll Cardiol* 2011; **57**: 1226–1233.