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

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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 (Tp) 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 Tp (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
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. 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). The augmentation index was obtained as the ΔP divided by the pulse pressure and expressed as a percentage.

**Figure 1.** Representative pressure waveform obtained in the ascending aorta using a catheter-tipped micromanometer. The augmented pressure was calculated as the difference between P2 and P1 (ΔP). The augmentation index was obtained as the ΔP divided by the pulse pressure and expressed as a percentage.

Alx was calculated as the augmented pressure divided by the central pulse pressure and expressed as a percentage. From the recorded LV pressure waves, a time constant of the decrease in LV pressure (Tw) was calculated by applying monoexponential fitting with zero asymptote to the pressure decay. We also computed another time constant of LV relaxation, Tp, which is relatively independent of LV systolic function, from the LV pressure (P)-dP/dt relationship (phase loop) as previously reported. 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. 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, 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±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 Tp and log BNP. Because BNP level was not normally distributed, logarithmic transformation was applied. The possible independent variables for determining log BNP were these and Tp. 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
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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 higher in women than in men.

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Table 1. Baseline Characteristics vs. Gender

| Characteristic                             | Men       | Women     | P-value |
|--------------------------------------------|-----------|-----------|---------|
| Patient number                             | 32        | 43        | 0.19    |
| Age (years)                                | 64.6±8.6  | 67.6±9.8  | <0.001  |
| Height (cm)                                | 165.9±5.0 | 151.0±7.2 | <0.001  |
| Weight (kg)                                | 67.9±8.1  | 56.5±9.6  | <0.001  |
| Body surface area (m²)                     | 1.76±0.11 | 1.53±0.14 | <0.001  |
| Body mass index (kg/m²)                    | 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    |

Table 2. Baseline Hemodynamics vs. Gender

| Characteristics                             | Men       | Women     | P-value (ANOVA) |
|---------------------------------------------|-----------|-----------|-----------------|
| 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            |
| Augmentation pressure (mmHg)                | 26.6±15.4 | 33.9±15.2 | 0.05            |
| Aix (%)                                     | 37.9±13.9 | 45.7±14.0 | 0.02            |
| Ea (mmHg/ml)                                | 1.21±0.23 | 1.55±0.63 | 0.008           |
| TVR (dyne·s·cm⁻²)                           | 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            |
| LV end-diastolic volume (ml)                | 156.3±27.6| 111.5±29.3| <0.001          |
| LV end-systolic volume (ml)                 | 37.8±11.1 | 30.5±12.0 | 0.009           |
| Stroke volume (ml)                          | 98.4±20.4 | 81.0±19.8 | <0.001          |
| Stroke volume index (ml/m²)                 | 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. ANOVA P-values given only when there was no significant interaction between the independent variable and the covariate (age).

Aix, augmentation index; ANOVA, 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.
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).

**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 |
| Alx     | 0.28 | 0.02 | 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.
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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. 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. 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. In the present study, Ea and TVR were significantly higher in women than in men. Similar to the findings of Kawaguchi et al, however, these parameters did not correlate with LV relaxation time constants Tw or Tp.

AIx is a surrogate indicator of arterial stiffness 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. 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.

Aortic length is a substantial factor influencing AIx. In the present study, height negatively correlated with AIx, as observed in previous studies. 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. 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. Thus, we consider that the present female subjects, whose mean

| Table 4. Correlations Between Tp and Log Plasma BNP |
|-----------------------------------------------|
|                                | Tp        | Log BNP                      |
|                                | Univariate | Multivariate | Univariate | Multivariate |
| Age (years)        | 0.12      | 0.30          | 0.50       | <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         |
| 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.
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.21–28

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.19,39 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.37 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, 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.35,30 We previously reported that, in patients with coronary artery disease who underwent cardiac catheterization and who had preserved LVEF (≥50%), the threshold plasma BNP value to distinguish abnormal LV relaxation (Tw ≥48 ms) was 22.4 µg/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.15,33–36 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.35 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, HFP EF is more often observed. Subject age range may be an important issue for study design when dealing with HFP EF. 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 HFP EF in this gender.

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