ORIGINAL ARTICLE

Relationship Between Augmentation Index and Left Ventricular Diastolic Function in Healthy Women and Men

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BACKGROUND
The aim of this study was to investigate the effect of sex on the correlation between arterial stiffness and left ventricular (LV) diastolic function in a healthy population without significant atherosclerosis.

METHODS
Subjects (n = 446) who had simultaneous echocardiography and arterial stiffness recordings were enrolled. From these subjects, 95 men and 72 age-matched women without atherosclerotic risk factors (hypertension, dyslipidemia, and diabetes mellitus) were included in the analysis. We measured brachial–ankle pulse wave velocity (baPWV) and carotid augmentation index (AIx) as arterial stiffness parameters.

RESULTS
Peak early diastolic mitral annular velocity (e′) was significantly correlated with baPWV (men: $r = -0.428$, $P < 0.001$; women: $r = -0.515$, $P < 0.001$) and carotid AIx (men: $r = -0.295$, $P = 0.004$; women: $r = -0.558$, $P < 0.001$). The ratio of early diastolic mitral flow velocity to e′ (E/e′) was significantly correlated with both arterial stiffness parameters in women but not men. Multivariable regression analysis revealed carotid AIx ($\beta = -0.257$; $P = 0.02$) was a significant independent predictor of e′ in women but not men.

CONCLUSIONS
These results suggest that the correlation between AIx and LV diastolic function is stronger in women than men in a healthy population.

Keywords: arterial stiffness; augmentation index; blood pressure; diastolic function; hypertension; sex difference.

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Heart failure remains one of the most important causes of morbidity and mortality in developed countries. Diastolic heart failure, which is known as heart failure with preserved ejection fraction, accounts for almost half of all heart failure patients, and these patients are more likely to be older, female, and have atherosclerotic disease.[1–3] Many reports have demonstrated that aging or atherosclerotic diseases including hypertension are associated with left ventricular (LV) diastolic function.[1,3,4] However, it is not clear why heart failure with preserved ejection fraction is more common among women than men.

Arterial stiffness has been reported to play a potential role in the pathophysiology of heart failure with preserved ejection fraction.[5] A few previous studies have shown that sex influences the relationship between arterial stiffness and LV diastolic function.[6–8] However, the participants in these studies included many patients with atherosclerotic disease, which may have affected LV diastolic function. There are no clinical data on just the effect of sex on the relation between arterial stiffness and LV diastolic function in healthy subjects. Therefore, the aim of this study was to investigate the effect of sex on the correlation between arterial stiffness and LV diastolic function in a healthy population without atherosclerotic disease.

METHODS

Study population

Between December 2008 and August 2010, 446 consecutive subjects were enrolled based on a periodic group examination. All subjects underwent echocardiography and nearly simultaneous assessment of arterial stiffness as part of an annual health check in our hospital. Among them, subjects with atherosclerotic risk factors (hypertension, dyslipidemia, and diabetes mellitus) were excluded. Hypertension was defined as either systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medication. Dyslipidemia was defined as either a fasting low-density lipoprotein cholesterol > 140 mg/dl,

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high-density lipoprotein cholesterol < 40 mg/dL in men and < 50 mg/dl in women, triglycerides > 150 mg/dl, or treatment with a prescribed diet or medication. Diabetes mellitus was defined as either fasting blood glucose ≥ 126 mg/dl or HbA_1c ≥ 6.5%. We excluded participants that were under medical treatment or had atrial fibrillation and LV wall motion abnormality or significant valvular disease and overt heart failure. Participants with angina were excluded based on the detailed medical questionnaire or the medical examination by interview, and subjects with abnormal electrocardiograms were also excluded. As a result, 133 male and 72 female subjects were selected. Each male subject was age-matched to each female subject. If an exact age match could not be found, then the male subject closest to the age of the female subject (within the same 2-year age group) was selected. Finally, among 133 male subjects, 38 subjects were eliminated after age matching between the sexes, and 95 male and 72 female subjects were analyzed. The protocol was approved by the institutional review board of our hospital, and informed consent was obtained from all subjects before participation.

Echocardiographic examination

Subjects were examined in the morning (8:30–9:00 AM) after a 12-hour overnight fast in a quiet, temperature-controlled laboratory (22 °C). All echocardiographic examinations were performed with Vivid-7 ultrasound machine (GE Healthcare, Milwaukee, WI) by trained, registered sonographers. Conventional parameters, such as LV dimensions and wall thickness, were measured according to the American Society of Echocardiography's recommendations,[9] and LV ejection fraction (EF) was calculated using the biplane Simpson's method. As parameters of LV diastolic function, the ratio of early (E) to late (A) diastolic mitral flow velocity and deceleration time were measured using pulsed-wave Doppler imaging of the mitral valve inflow from the apical 4-chamber view. Peak early diastolic mitral annular velocity (e′) was also measured in the septal position using tissue Doppler imaging. E/e′ was used as a surrogate of LV filling pressure.[10]

Measurements of arterial stiffness parameters

As arterial stiffness parameters, we simultaneously measured brachial–ankle pulse wave velocity (baPWV) and carotid augmentation index (AIx) using the same machine immediately after the echocardiographic examination. The volume-plethysmographic method was employed to measure baPWV noninvasively using previously validated equipment (form PWV/ABI; Colin Medical Technology, Komaki, Japan). A detailed description of this device has been reported previously.[11] The average of the right and left baPWV values was used in the final analysis.

The AIx was defined as the increment in pressure from the first systolic shoulder (inflection point) to the peak pressure of the aortic pressure waveform and was expressed as a percentage of the peak pressure. Carotid AIx was measured using a multielement applanation tonometry sensor for the left common carotid artery.[11]

The inter- and intraobserver variabilities were assessed for measuring the baPWV and AIx in 10 randomly selected subjects. The interobserver variability was calculated as the coefficient of variation of the differences between the measurements of 2 independent observers and expressed as a percentage of the average. The intraobserver variability was calculated as the coefficient of variation of the differences between the first and second determination (2-week interval) for a single observer and expressed as a percentage of the average. The inter- and intraobserver variabilities were 3.6% and 2.8% for baPWV and 9.3% and 8.9% for carotid AIx, respectively.

Blood testing

Blood samples were obtained during the early morning after an overnight fast. Metabolic factors related to atherosclerosis, including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting blood glucose, and HbA_1c, were analyzed.

Statistical analysis

Continuous variables are presented as the mean±SD. The significance of differences between the groups was assessed using an unpaired *t* test when the distributions were normal. A nonparametric test (Mann–Whitney *U* test) was used whenever there was an abnormal distribution. Spearman simple correlation analysis was performed to determine the association between indices reflecting arterial stiffness and parameters of diastolic function (e′ and E/e′) in both sexes. To determine the independent predictors of e′, stepwise multivariable regression analysis was performed with age, body height, body weight, heart rate, mean blood pressure, HbA1c, LV mass index, EF, and carotid AIx. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS 11.0 (SPSS, Chicago, IL).

RESULTS

The baseline characteristics in men and women are shown in Table 1. The mean age was 47 ± 11 years (range = 17–74 years) in men and 47 ± 10 years (range = 17–72 years) in women. Compared with men, women weighed less and were shorter, and they had a lower body mass index. Women had higher high-density lipoprotein cholesterol ($P < 0.001$) and lower triglycerides ($P = 0.001$) than men. Systolic blood pressure ($P = 0.499$), diastolic blood pressure ($P = 0.26$), and heart rate ($P = 0.10$) were not significantly different between sexes.

Echocardiographic measurements

Comparisons of echocardiographic findings between the groups are demonstrated in Table 1. Women had smaller LV end-diastolic ($P < 0.001$) and end-systolic dimensions ($P < 0.001$), smaller LV mass index ($P < 0.001$), higher EF ($P < 0.001$), and prolonged ejection time ($P = 0.03$) than men. However, there were no

Table 1. Clinical characteristics, echocardiographic data, and arterial stiffness parameters in all subjects

Variable	Men (n = 95)	Women (n = 72)	*P* value
Age, y	47 ± 11	47 ± 10	0.82
Height, cm	167 ± 8	157 ± 6	<0.001
Weight, kg	68 ± 11	56 ± 9	<0.001
Body mass index, kg/m^2	24 ± 3	23 ± 3	0.001
Systolic blood pressure, mm Hg	123 ± 13	122 ± 16	0.499
Diastolic blood pressure, mm Hg	75 ± 11	73 ± 10	0.26
Mean blood pressure, mm Hg	94 ± 14	92 ± 11	0.33
Pulse pressure, mm Hg	47 ± 7	49 ± 11	0.95
Heart rate, beats/min	65 ± 8	67 ± 9	0.10
Fasting blood glucose, mg/dl	97 ± 11	96 ± 10	0.20
HbA1c, %	5.2 ± 0.3	5.2 ± 0.3	0.56
High-density lipoprotein cholesterol, mg/dl	54 ± 14	65 ± 17	<0.001
Low-density lipoprotein cholesterol, mg/dl	111 ± 29	116 ± 33	0.37
Triglycerides, mg/dl	129 ± 74	92 ± 62	0.001
LVDd, mm	51 ± 6	46 ± 4	<0.001
LVDs, mm	34 ± 7	29 ± 4	<0.001
IVSTd, mm	8 ± 1	7 ± 2	<0.001
PWTd, mm	8 ± 1	7 ± 1	<0.001
EDVI, ml/m^2	47 ± 19	40 ± 12	0.008
ESVI, ml/m^2	26 ± 10	26 ± 8	0.72
LVMI, g/m^2	92 ± 23	75 ± 20	<0.001
LVEF, %	63 ± 9	67 ± 7	<0.001
E, cm/sec	65 ± 14	74 ± 17	<0.001
A, cm/sec	53 ± 13	56 ± 19	0.23
E/A	1.33 ± 0.49	1.48 ± 0.66	0.11
Deceleration time, msec	214 ± 50	215 ± 50	0.94
e′, cm/sec	8.6 ± 2.2	9.2 ± 2.7	0.11
E/e′	8.0 ± 2.7	8.6 ± 2.9	0.21
Ejection time, msec	295 ± 22	303 ± 23	0.03
baPWV, cm/sec	1,360 ± 194	1,309 ± 216	0.11
Carotid AIx, %	14 ± 21	24 ± 12	<0.001

Data are presented as mean ± SD.
Abbreviations: A, late diastolic mitral flow velocity; AIx, augmentation index; baPWV, brachial-ankle pulse wave velocity; E, early diastolic mitral flow velocity; e′, early diastolic mitral annular velocity; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; IVSTd, end-diastolic thickness of the interventricular septum; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PWTd, end-diastolic thickness of the posterior wall.

significant differences in e′ ($P = 0.11$) and E/e′ ($P = 0.21$) between the 2 groups.

Arterial stiffness parameters

There was no significant difference in baPWV between men and women (1,360 ± 194 cm/sec vs. 1,309 ± 216 cm/sec; $P = 0.11$). However, carotid AIx was higher in women than men (24% ± 12% vs. 14% ± 21%; $P < 0.001$) (Table 1).

Correlation of LV diastolic function and arterial stiffness

Table 2 shows the associations between arterial stiffness parameters and e′ or E/e′. baPWV and carotid AIx were significantly correlated with e′ in both sexes. These correlations in women were stronger than the corresponding correlations in men (Figure 1a,b). Neither baPWV nor carotid AIx was significantly correlated with E/e′ in men; however, both arterial stiffness parameters were significantly correlated with E/e′ in women (Figure 1c,d). Multivariable regression analysis revealed that carotid AIx had an independent correlation with e′ only in women, even after controlling for confounding factors such as age, height, weight, heart rate, mean blood pressure, LV mass index, and EF as dependent variables (Table 3).

Table 2. Simple correlations between arterial stiffness parameters and diastolic function in men and women

	Men		Women	
Variable	*r*	*P* value	*r*	*P* value
e′				
baPWV	−0.428	<0.001	−0.515	<0.001
Carotid AIx	−0.295	0.004	−0.558	<0.001
E/e′				
baPWV	0.079	0.46	0.306	0.01
Carotid AIx	0.105	0.32	0.375	0.002

Abbreviations: AIx, augmentation index; baPWV, brachial-ankle pulse wave velocity; E, early diastolic mitral flow velocity; e′, early diastolic mitral annular velocity.

DISCUSSION

The major finding of this study was that LV diastolic function had a stronger association with the arterial stiffness parameters (particularly AIx) in healthy women than men. This might partially account for a higher incidence of heart failure with preserved ejection fraction in women than men.

In this study, the associations between arterial stiffness parameters and e′ were stronger in women than men. Moreover, multivariable analysis revealed that carotid AIx was an independent predictor of e′ only in women. It is well known that e′ has a good correlation with the time constant of isovolumic relaxation.[12] The precise mechanism for the sex effect on this relationship is unknown. In general, because women are not as tall as men and have a shorter aorta and smaller aortic diameter, the reflected pressure wave in women returns earlier and augments the first forward wave during late systole.[13] This phenomenon was suggested by a higher value of AIx in women than men. The intrinsic characteristics of vascular networks in woman might have a similar effect as increased arterial stiffness. This could be the cause of augmentation of systolic blood pressure, late peaking of blood pressure

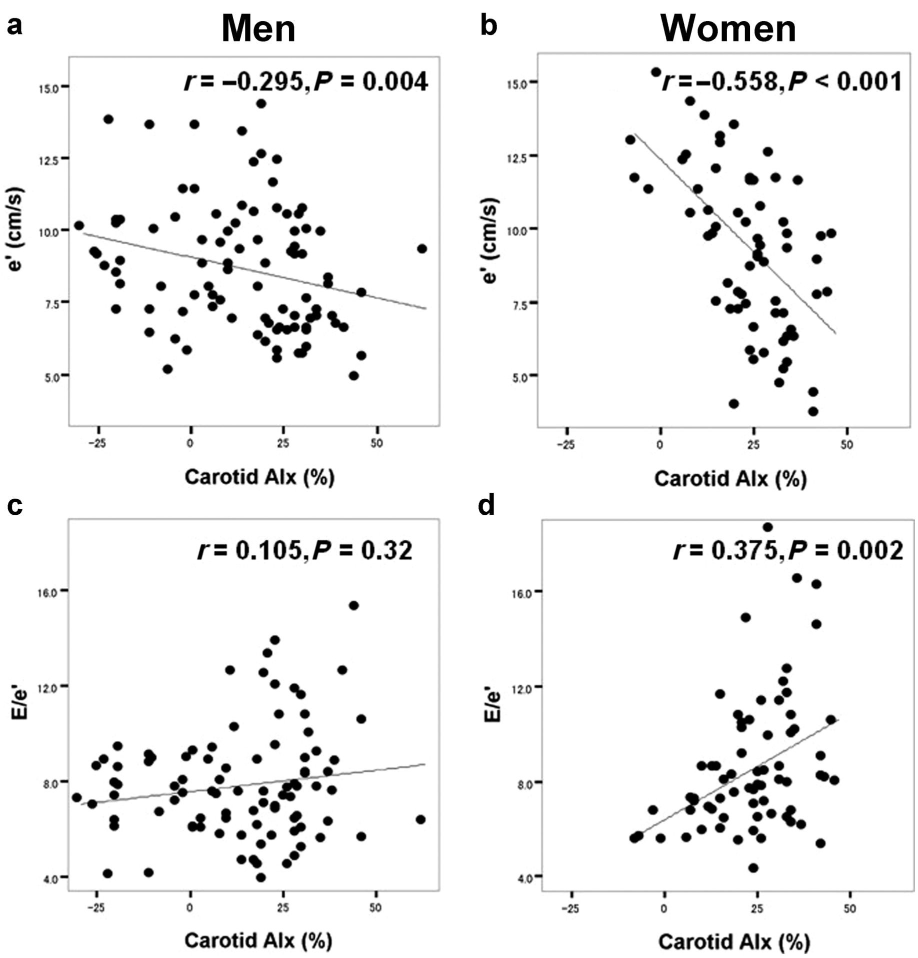

Figure 1. Correlation between carotid augmentation index (AIx) and early diastolic mitral annular velocity (e′) in men (a) and women (b). Correlation between carotid AIx and early diastolic mitral flow velocity (E)/e′ in men (c) and women (d). Carotid AIx was correlated with e′ in both sexes. The relation was stronger in women than men. Moreover, carotid AIx was correlated with E/e′ only in women.

Table 3. Multivariable regression of early diastolic mitral annular velocity with various parameters in men and women

Variable	Men (r^2 = 0.511)			Women (r^2 = 0.635)		
	β	τ	*P* value	β	τ	*P* value
Age	−0.548	−5.133	<0.001	−0.314	−2.879	0.006
Body height	0.111	1.061	0.29	0.148	1.443	0.15
Body weight	−0.252	−2.334	0.02	−0.13	−1.264	0.21
Heart rate	−0.096	−1.077	0.29	−0.217	−2.398	0.02
Mean blood pressure	−0.101	−1.014	0.31	−0.122	−1.311	0.20
LVMI	−0.159	−1.777	0.08	−0.314	−3.516	0.001
EF	0.194	2.237	0.03	0.143	1.627	0.11
Carotid AIx	0.118	1.124	0.26	−0.257	−2.307	0.02

Abbreviations: AIx, augmentation index; EF, ejection fraction; LVMI, left ventricular mass index.

(loading sequence: increase in late-systolic load), and a subsequent decreased diastolic blood pressure, resulting in an increase in cardiac afterload and myocardial oxygen demand and impairment of myocardial blood flow.[11,14,15] Eventually, these phenomena could influence LV diastolic function. This hypothesis might explain the stronger relationship between AIx and LV relaxation in women than men.

In addition to AIx, several determinants of e′ were different between men and women, as shown in Table 3. Burns *et al.*[16] demonstrated that e′ decreased as heart rate increased. On the other hand, some previous studies showed no correlation between heart rate and e′.[17,18] In our study, heart rate was an independent predictor of e′ only in women. In addition to heart rate, LV mass index was an independent predictor of e′ only in women. However, body weight and EF were independent predictors of e′ only in men. In general, LV hypertrophy, obesity, and LV systolic function have been shown to be closely correlated with e′.[17,19–21] Although these parameters were associated with e′ in our study, there were significant sex differences, and the precise mechanisms responsible for these differences will require further investigation.

Although Shim *et al.*[7] showed significant correlations between some arterial stiffness parameters and e′ only in women, these correlations were observed in both sexes in our study. In contrast with the previous study, the subjects in our study were younger, healthier, did not have conventional atherosclerotic risk factors, and were not on any medications. In addition, we measured carotid AIx and baPWV as surrogate parameters of arterial stiffness, whereas they used radial AIx determined from pulse pressure amplification (the ratio of the peripheral to central pulse pressure) and carotid–femoral PWV as arterial stiffness parameters. Radial AIx is more commonly used and easily measured than carotid AIx. However, because radial AIx is highly subject specific in the transfer equation compared with carotid AIx, the interpretation of AIx data may be complicated. These differences in subject characteristics and arterial stiffness parameters might account for the difference in the correlations. Nonetheless, in our study, the correlations in men were weaker than in women. Therefore, our results tend to confirm the main results of their study.

In our study, there were no significant differences in the diastolic function parameters between men and women. Generally, women have a higher EF, a smaller LV end-diastolic volume (even after adjusting for body size), and a steeper slope of the stroke work–end-diastolic volume relationship, suggesting enhanced LV systolic performance.[22,23]

E/e′ was significantly correlated with the arterial stiffness parameters only in women in our study. Generally, E/e′ has been shown to be the most accurate noninvasive predictor of elevated LV filling pressure under most conditions, except for valvular disease and the presence of wall motion abnormalities.[10] The deterioration of LV relaxation results in an increase of LV filling pressure.[24] Because it is thought that elevated arterial stiffness intrinsically affects LV relaxation, the impact of arterial stiffness on LV filling pressure might be secondary. Therefore, this might account for the significant relationships between the arterial stiffness parameters and E/e′ only in women. In addition, a recent report has shown that E/e′ was not accurate enough to reliably estimate LV filling pressure in subjects with normal LV ejection fraction, which might also explain our results.[25]

In our study, there was no significant difference in baPWV between men and women. However, carotid AIx was higher in women than men. This phenomenon would mainly depend on stature because the value of baPWV was corrected by stature, unlike AIx. However, because several papers have shown that AIx was independent of differences in height, the higher AIx in women than men might be not only because of shorter stature but also because of the intrinsic characteristics of vascular networks in women and arterial stiffness.[26,27]

In our study, LV diastolic functional parameters were significantly correlated with not only AIx but also PWV in both sexes. The increment of PWV could cause the acceleration of the reflection of the pulse wave. Consequently, LV afterload theoretically could be increased. In fact, several studies have shown that PWV was significantly correlated with not only AIx but also LV diastolic function.[28–30] Therefore, the results of our study might be consistent with previous studies. On the other hand, there was no significant correlation between PWV and LV diastolic functional parameters in both sexes in a report by Shim *et al.*[7] In our study, we measured baPWV, whereas they measured carotid–femoral PWV. It has been reported that baPWV reflects not only elastic arterial stiffness but also muscular arterial stiffness.[31] Because baPWV is influenced by microvascular function, it might be better correlated with the reflection of pulse wave and LV afterload compared with carotid–femoral PWV.

Our study has several limitations. First, we used noninvasive parameters as surrogate parameters of arterial stiffness and LV diastolic function. However, it has been reported that those parameters have been well validated in comparison with each of the invasive parameters.[10,12,32] Second, the absence of coronary artery disease or subclinical myocardial ischemia was not investigated completely. In our study, it was difficult ethically to justify invasive tests in healthy subjects undergoing a routine physical examination. Finally, the number of patients in this study was small. Therefore, more clinical prospective studies in larger populations must be performed to confirm the sex influence on the relation between arterial stiffness and left ventricular diastolic function.

Our study showed that the correlation between arterial stiffness parameters (particularly AIx) and LV diastolic function was stronger in women than in men in a healthy population.

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DISCLOSURE

The authors declared no conflict of interest.

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