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Abstract—Exercise intolerance and heart failure with preserved ejection fraction are common in females. Recently, arterial stiffness has been suggested to be a significant contributor in the development of heart failure. How gender difference affects arterial stiffening and its response to exercise is not well known. We hypothesized that arterial elastance index during exercise would be more abnormal in females with hypertension than males. Arterial elastance index was estimated as arterial end systolic pressure/stroke volume controlled for body surface area and was measured at rest and during graded supine bicycle exercise (25 watts, 3-minute increments) in 298 patients with hypertension (149 males; 149 females; mean age, 59). The subjects were divided into 2 groups by gender. Exercise duration was significantly shorter in females compared to males (692±222 versus 483±128 seconds, $P<0.001$). Although arterial elastance index at baseline was significantly higher in males, the magnitude of increase was steeper in females with the magnitude of change at 75 W of exercise being significantly higher in females compared to males (0.69±0.83 versus 0.43±0.69, $P=0.018$). Arterial elastance index at each stage of exercise up to 75 W was independently associated with decreased exercise duration. In conclusion, despite lower arterial elastance index at rest, the increase during exercise was steeper in women with hypertension, suggesting a gender-related difference in dynamic arterial stiffness. The arterial elastance index during exercise was significantly associated with exercise duration in patients with hypertension. (***Hypertension*****. 2008;51:1163-1169.)**

Key Words: gender ■ arterial elastance index ■ exercise ■ hypertension ■ heart failure

In epidemiology studies, nearly 50% of patients with heart failure have preserved ejection fraction and hypertension is considered to be the most important cause of heart failure with preserved ejection fraction. Interestingly, advanced age and the female gender are known to be associated with development of heart failure with preserved ejection fraction because the prevalence of heart failure with ejection fraction increases sharply with age than systolic heart failure, especially in females.[1,2] Recently, arterial stiffness has been suggested to be a significant contributor in the development of heart failure.[3,4] Increased aortic stiffness in subjects contributed to increased afterload to the heart while reducing coronary perfusion pressure during diastole.[3,4] Greater aortic stiffness may increase myocardial stiffness and left ventricular (LV) diastolic filling pressure, which may be exaggerated during exercise.[5] How gender difference affects arterial stiffening and its response to exercise is not well known; therefore, we hypothesized that arterial elastance index (EaI) during exercise would be more abnormal in female patients with hypertension compared to males.

Methods

Study Population

Symptom-limited supine bicycle exercise (25 Watts, 3-minute increments) with simultaneous 2-dimensional and Doppler echocardiography was performed by 298 hypertension patients of 427 hypertensive subjects who performed diastolic stress echocardiography at Yonsei University College of Medicine (149 males, age, 58±9 years; 149 females, age, 59±8 years). Male subjects of similar age profiles as female subjects were selected by 1:1 matching. No patients had symptoms or signs of heart disease, were in sinus rhythm, or had a normal resting 12-lead ECG. Exclusion criteria were significant atrial or ventricular arrhythmia, significant valvular diseases (≥moderate severity), significant coronary artery disease, prior history of myocardial infarction, depressed LV systolic function (ejection fraction <50%, or any regional wall motion abnormality), pericardial disease, and inability to exercise. Subjects were divided into 2 groups according to gender. Study approval was obtained from the Institutional Review Board of Yonsei University College of Medicine.

Two-Dimensional and Exercise Doppler Echocardiography (Diastolic Stress Echocardiography)

Standard 2-dimensional measurements (LV diastolic and systolic dimensions, ventricular septum and posterior wall thickness [PWT], left atrial volume, and LV outflow tract diameter) were obtained with the patient in the left lateral position. LV ejection fraction (EF) was calculated by the modified Quinones method.[6] After obtaining rest images from standard parasternal and apical views, a multistage supine bicycle exercise test was performed with a variable load bicycle ergometer (Medical Positioning Inc) as described previously.[7] Patients pedaled at a constant speed beginning at a workload of

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Table 1. Clinical Characteristics and Baseline Echocardiographic Findings

Clinical and Echocardiographic Variables	Men (n=149)	Women (n=149)	*P* Value*
Age, y	58±9	59±8	0.161
Body mass index, kg/m^2	25.1±2.7	24.9±3.3	0.536
Treatment for hypertension, %	116/149 (77.9%)	127/149 (85.2%)	0.100
LVEDD, mm	49.6±3.8	47.9±3.9	<0.001
LVESD, mm	32.5±3.7	30.4±3.7	<0.001
Diabetes mellitus, %	31/149 (20.8%)	29/149 (19.5%)	0.773
LV ejection fraction, %	66.6±6.5	69.3±6.3	<0.001
IVS, mm	10.4±1.7	9.4±1.5	<0.001
PW, mm	10.3±1.6	9.2±1.4	<0.001
LV mass index, g/m^2	104.4±23.2	96.4±22.7	0.003
LV hypertrophy, %	28/149 (18.8%)	39/149 (26.2%)	0.127
LAVI, mL/m^2	21.9±6.9	23.7±7.2	0.084
E, cm/s	60.6±15.1	64.6±14.3	0.019
A, cm/s	67.5±15.9	70.6±15.6	0.095
E/A	0.9±0.3	0.9±0.3	0.594
DT, msec	204±41	200±37	0.381
Exercise duration, s	692±222	483±128	<0.001
Fasting blood sugar, mg/dL	105±32	104±31	0.759
Creatinine, mg/dL	1.0±0.2	0.8±0.2	<0.001
BUN, mg/dL	15.9±4.9	14.7±4.8	0.045
Triglyceride, mg/dL	155.5±88.7	146.7±106.1	0.465
HDL, mg/dL	50.5±13.3	54.4±13.7	0.021
LDL, mg/dL	120.6±30.3	122.2±32.4	0.711

LVEDD indicates left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; IVS, interventricular septal thickness; PW, posterior wall thickness; LAVI, left atrial volume index; E, peak velocity of early diastolic filling; A, peak velocity of diastolic filling during atrial contraction; DT, deceleration time; TR, tricuspid regurgitation; E′, early diastolic mitral annular velocity; S′, systolic mitral annular velocity.

*P<0.05 is considered significant.

25 W in increments of 25 W every 3 minute.Echocardiography was performed using a GE Vingmed System 7 ultrasound system with a 2.5-MHz transducer during rest, each stage of exercise, and recovery. The blood pressure was measured at the end of each stage of exercise on the left arm using an oscillometric blood pressure monitoring device (Solar 8000 mol/L patient monitoring device, GE Medical systems).

From the apical window, a 1- to 2-mm pulsed Doppler sample volume was placed at the mitral valve tip and mitral flow velocities from 5 to 10 cardiac cycles were recorded. Mitral inflow velocities were traced and the following variables were obtained: peak velocity of early (E) and late (A) filling, and deceleration time of E-wave velocity. SV was measured from LV outflow tract diameter and pulse wave Doppler signal as previously described.[8] Mitral annular velocity was measured by Doppler tissue imaging using pulse-wave Doppler mode. The filter was set to exclude high frequency signal, and the Nyquist limit was adjusted to a range of 15 to 20 cm/s. Gain and sample volume were minimized to allow for a clear tissue signal with minimal background noise. Early diastolic (E′) and systolic (S′) velocities of the mitral annulus were measured from the apical 4-chamber view with a 2- to 5-mm sample volume placed at the septal corner of the mitral annulus. Effective arterial elastance (Ea) was estimated as ESP/SV. End-systolic pressure (ESP) was estimated as systolic pressure ×0.9 as described previously.[9,10] The arterial elastance index (EaI) was estimated by normalizing the arterial elastance to body surface area as described previously.[9,11] These measurements were performed at baseline, each stage of exercise, and recovery in the same sequence. All data were stored digitally, and measurements were taken at the completion of each study. Two-dimensional echocardiographic images from apical views at rest and during exercise were acquired, digitized, recorded, and analyzed for the wall motion analysis.

Statistical Analysis

Continuous variables were summarized as a mean±SD. Categorical variables were summarized as a percentage of the group total. Unpaired Student t test and χ^2 analysis were used to compare continuous and categorical variables, respectively. Independent predictors for exercise duration were determined using multiple linear regression analysis. Four models entering arterial elastance index at baseline and each stage of exercise into the equation were assessed. Variables that showed significant association with exercise duration (age, gender, E/E′ at baseline, S′ at baseline, presence of diabetes, and left ventricular mass index [LVMI]) were entered into the equation. Statistical analysis was performed using SPSS 13.0 statistical program (SPSS Inc). Statistical significance was defined as <0.05.

Results

Clinical Characteristics

The comparison between 2 groups with regard to clinical variables is presented in Table 1. There was no significant difference in the proportion of patients being treated for hypertension at the time of study enrollment. Exercise duration (483±128 versus 692±222 s, P<0.001) was significantly shorter in females compared to males. There were no

Table 2. Hemodynamic Response to Exercise

Hemodynamic Variables During Exercise	Men (n=149)	Women (n=149)	*P* Value*
HR at rest, bpm	64±9	63±9	0.100
HR at 25 W, bpm	87±11	90±11	0.041
HR at 50 W, bpm	97±11	103±12	<0.001
HR at 75 W, bpm	107±13	117±17	<0.001
HR at peak exercise	117±17	114±18	0.070
Systolic BP at rest, mm Hg	133±16	134±17	0.809
Systolic BP at 25 W, mm Hg	153±19	154±24	0.365
Systolic BP at 50 W, mm Hg	164±21	166±25	0.459
Systolic BP at 75 W, mm Hg	174±21	179±29	0.188
Systolic BP at peak exercise, mm Hg	187±24	177±26	0.001
Pes, baseline	120±15	120±16	0.809
Pes at 25 W	138±17	139±22	0.824
Pes at 50 W	148±19	149±22	0.459
Pes at 75 W	157±19	161±26	0.188
Change of Pes from baseline to 25 W	18±13	18±17	0.964
Change of Pes from baseline to 50 W	28±16	29±18	0.505
Change of Pes from baseline to 75 W	38±17	40±22	0.325
Diastolic BP at rest, mm Hg	82±10	77±10	<0.001
Diastolic BP at 25 W, mm Hg	89±13	85±13	0.010
Diastolic BP at 50 W, mm Hg	90±13	89±14	0.605
Diastolic BP at 75 W, mm Hg	94±12	92±17	0.229
Diastolic BP at peak exercise, mm Hg	98±16	93±16	0.007
Maximal exercise load, W	91±24	66±18	<0.001

HR indicates heart rate; BP, blood pressure, Pes, end systolic pressure.
*$P<0.05$ is considered significant.

regional wall motion abnormalities either at rest or during exercise in both groups.

Baseline Echocardiographic Findings

Table 1 shows the comparison of echocardiographic findings between the 2 groups. Women had smaller LV cavity and LVMI compared to men. However, there was no significant gender difference in the proportion of subjects with LV hypertrophy, left atrial volume index, E velocity, A velocity, E/A ratio, and DT.

Hemodynamic Response to Exercise

The effect of supine bicycle exercise on heart rate and blood pressure is shown in Table 2. In both groups, heart rate, systolic blood pressure, and diastolic blood pressure were increased after exercise compared to those at rest. There were no significant differences in systolic blood pressure at rest or during exercise up to 75 W. However, peak systolic BP at peak exercise was significantly higher in males, most likely because of the higher maximal workload that was achieved in men (Table 2). Heart rate during exercise was significantly higher at 25 W, 50 W, and 75 W of exercise in females. Diastolic blood pressure was significantly lower in females at baseline, 25 W, and peak exercise.

The comparison of Doppler echocardiographic variables during exercise demonstrated significantly higher E velocity and A velocity at 25 W and 50 W of exercise in females. E′ was also significantly lower at 25 W in females. E/E′, an index of LV filling pressure, was significantly elevated at rest, 25 W, and 50 W of exercise in females. S′, an index of LV longitudinal contraction, was significantly decreased at rest and during all stages of exercise in females (Table 3).

EaI at Rest and Exercise

In females, SV was significantly lower than males at baseline and up to 75 W of exercise (Table 3). Despite lower EaI at rest, the increase of EaI during exercise was steeper in females (Figure 1) with the magnitude of change in EaI at 75 W of exercise being significantly higher in females compared to males (0.69±0.83 versus 0.43±0.69, $P=0.018$; Figure 2).

Arterial Elastance and Exercise Capacity

Multiple linear regression analysis was performed to determine the independent association of exercise duration with arterial elastance index while controlling for confounding factors such as age, female gender, diabetes, E/E′ at baseline, S′ at baseline, and LV mass index. The results demonstrated an independent association of arterial elastance index at each stage of exercise with exercise duration in hypertensive subjects (Table 4).

Discussion

The present study is, to our knowledge, the first to demonstrate the gender difference of arterial elastance during exercise in patients with hypertension. In addition, echocardiographically derived EaI was associated with exercise duration. These data may suggest that increase in arterial elastance during exercise in females may contribute to exercise-induced diastolic dysfunction and exercise intolerance in hypertensive subjects.

Gender Difference of EaI

After the onset of established clinical diseases, compensatory response differs between males and females. Previous investigations have shown higher rates of HF in females despite higher EF than males after myocardial infarction.[12,13] Females with HF tended to experience more symptoms and a higher number of hospitalizations than among males.[14] In addition, exercise intolerance and HF with preserved EF are more common in females; however, little is known about the mechanism underlying the gender difference in risk of HF in patients with hypertension. EaI is an index of pulsatile arterial load that correlates well with aortic impedance data as described previously.[9,11] Although EaI is determined by both systemic vascular resistance and pulsatile arterial load, the main determinant during exercise has been demonstrated to be systemic arterial compliance, which is increased during exercise.[15,16] Because age-adjusted EaI has been described to be higher in females compared to males, we hypothesized that there would be a greater increase of EaI during exercise in females, which may be a contributing factor for the gender difference in the prevalence of diastolic heart failure.[6] Females have been shown to demonstrate a greater age-related increase in proximal aortic stiffness and pulse pressure compared to males.[15,17] Arterial elastance at each stage of exercise was significantly higher in females, and the differ-

Table 3. Comparison of Doppler Echocardiographic Variables During Exercise

Doppler Echocardiographic Variables	Stages of Exercise	Male (n=149)	Women (n=149)	*P* Value*
E, cm/s	Rest	60.6±15.1	64.6±14.3	0.019
	25 W	89.2±18.0	94.5±21.7	0.022
	50 W	100.8±16.8	109.4±24.1	<0.001
A, cm/s	Rest	67.5±15.9	70.6±15.6	0.095
	25 W	84.1±18.9	91.6±20.8	0.001
	50 W	93.9±21.7	101.3±22.3	0.004
E′, cm/s	Rest	6.1±1.8	5.8±1.9	0.221
	25 W	8.5±2.3	7.9±2.2	0.021
	50 W	9.0±2.3	8.7±2.2	0.173
E/E′	Rest	10.7±3.5	12.0±4.1	0.003
	25 W	11.3±4.1	13.0±5.1	0.001
	50 W	12.0±4.0	13.3±4.2	0.006
Arterial elastance, mm Hg/mL	Rest	1.75±0.44	1.83±0.46	0.112
	25 W	1.83±0.46	1.97±0.50	0.021
	50 W	1.93±0.45	2.10±0.52	0.002
	75 W	1.97±0.49	2.29±0.67	<0.001
Arterial elastance index, mm Hg/mL per m^2	Rest	3.17±0.73	2.95±0.73	0.012
	25 W	3.33±0.79	3.16±0.78	0.076
	50 W	3.49±0.77	3.39±0.82	0.257
	75 W	3.60±0.82	3.71±1.03	0.404
Stroke volume, mL	Rest	71.7±15.9	68.3±13.3	0.044
	25 W	78.6±16.7	73.1±13.0	0.001
	50 W	79.5±15.9	73.6±13.7	0.001
	75 W	82.5±15.7	73.7±14.5	<0.001
Change of stroke volume from baseline to 25 W		6.9±10.7	4.8±9.6	0.069
Change of stroke volume from baseline to 50 W		7.8±11.2	5.3±10.9	0.051
Change of stroke volume from baseline to 75 W		10.8±11.6	5.9±10.6	0.003
Stroke volume index, mL/m^2	Rest	39.3±8.0	42.3±7.8	0.001
	25W	43.1±8.3	45.3±7.7	0.021
	50W	43.6±8.0	45.5±8.1	0.041
	75W	44.9±7.9	45.1±8.0	0.866
Change of stroke volume index from baseline to 25W		3.8±5.9	2.9±6.0	0.240
Change of stroke volume index from baseline to 50W		4.3±6.4	3.3±6.7	0.182
Change of stroke volume index from baseline to 75W		5.9±6.5	3.5±6.6	0.012
S′, cm/s	Rest	7.0±1.3	6.0±1.1	<0.001
	25 W	7.8±1.7	6.9±1.5	<0.001
	50 W	8.6±1.8	7.8±1.5	<0.001
	Peak exercise	10.0±2.4	8.2±1.9	<0.001
Change of S′, cm/s	Baseline to 25 W	0.8±1.4	0.9±1.2	0.408
	Baseline to 50 W	1.6±1.5	1.7±1.3	0.323
	Baseline to peak	3.0±2.2	2.2±1.7	<0.001
Change of E′, cm/s	Baseline to 25 W	2.4±1.8	2.1±1.6	0.081
	Baseline to 50 W	3.0±1.7	2.9±1.7	0.624
Change of E/E′	Baseline to 25 W	0.6±2.6	1.0±3.2	0.214
	Baseline to 50 W	1.3±2.9	1.3±3.2	0.923

E indicates early diastolic mitral inflow velocity; A, late diastolic mitral inflow velocity; S′, systolic mitral annular velocity deceleration time; E′, early diastolic mitral annular velocity.

* $P<0.05$ is considered significant.

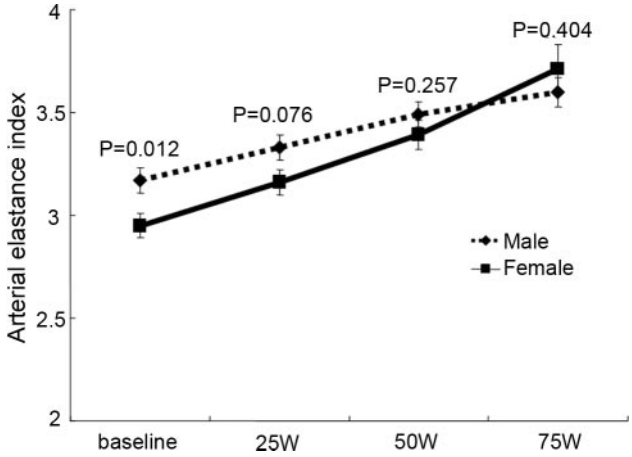

Figure 1. EaI at baseline and at 25 W, 50 W, and 75 W of exercise.

ence was driven by the fact that end systolic pressure at each stage of exercise was similar despite the significantly lower SV. This may be attributable to the lower arterial compliance in females compared to males. When arterial elastance was corrected for BSA to adjust for gender difference in body size, there was no significant gender difference for EaI at each stage of exercise because of the fact that SV corrected for BSA was higher in females compared to males at baseline, 25 W, and 50 W of exercise. However, the magnitude of increase of SV index at each stage of exercise was decreased in females despite similar levels of end systolic pressure. This was associated with the magnitude of increase of arterial elastance being steeper in females with the change in EaI at 75 W of exercise being significantly higher in females compared to males (0.69 ± 0.83 versus 0.43 ± 0.69, $P=0.018$; Figure 2). Because the main determinant of EaI during exercise is arterial compliance, the steeper rise of EaI during exercise may be attributable to gender difference in inherent arterial elasticity even when corrected for the discrepancy in body size. The steeper rise of arterial elastance may subsequently increase systolic pulsatile load to the heart and have a deleterious effect on myocardial function during exercise.

Association Between EaI and Exercise

We performed a multiple linear regression analysis to determine the relationship of EaI at each stage of exercise with exercise duration controlled for age, gender, presence of diabetes, E/E′ at baseline, S′ at baseline, and LVMI. The result demonstrated an independent association of EaI at each stage of exercise but not at baseline. This suggests that the increase in pusatile load, which is the determinant of EaI during exercise, may have an important role in determining exercise capacity. A recent study by Borlaug et al demonstrated the importance of pulsatile arterial afterload on cardiac function during exercise.[18] In this study, there was a significant correlation of the magnitude of change of EaI at 75 W of exercise with E/E′ at 50 W and S prime at peak exercise (Table 5), demonstrating that the increased pulsatile arterial load during exercise may have significant impact on myocardial relaxation and contractile function during exercise and have a significant impact on exercise capacity.

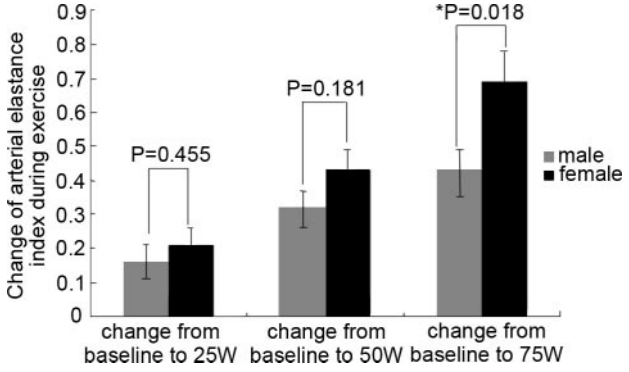

Figure 2. Magnitude of change of EaI at 25 W, 50 W, and 75 W compared to baseline.

In conclusion, despite lower EaI at rest, the increase in EaI during exercise was steeper in females with hypertension, suggesting a gender-related difference in dynamic arterial stiffness. EaI at rest as well as during exercise was significantly associated with exercise duration in patients with hypertension. Further studies to determine whether the steeper rise of EaI during exercise in females is associated with increased development of diastolic dysfunction and congestive heart failure are needed.

Study Limitations

The limitation of this study may be the relatively high proportion of treated hypertensive subjects at the time of enrollment; however, we believe that the effects of treatment were minimized by the similar proportion of treated patients and by the absence of significant differences in baseline systolic blood pressure between females and males. The second limitation is the use of brachial arterial pressure rather than the central aortic pressure measurements in determining the arterial elastance index. Because the heart rate at 75 W of exercise in females was significantly higher than that of males, the difference in heart rate and its effect on pressure amplification may impact the actual measurement of central aortic pressure during exercise. However, noninvasive calculation of end systolic pressure derived from brachial artery pressure has been shown to accurately predict end systolic pressure derived from direct measurement of central aortic pressure.[10,11] In addition, because the mean age of study population of the present study is relatively old, we believe that there would be a less effect of pressure amplification from the central to the peripheral arteries. In a study by Wilkinson IB et al, older subjects over the age of 50 showed significant decrease in pressure amplification compared to younger subjects.[19] Although it would be ideal to match heart rate and measure central blood pressure during exercise, it may not be practical to do in a large number of study subjects.

Perspectives

Heart failure with preserved ejection fraction is highly prevalent in hypertensive patients and is more prevalent in females. The main pathogenesis of heart failure with normal ejection fraction is explained by diastolic dysfunction. The increased diastolic dysfunction with aging is explained by steeper increase of arterial elastance (EaI) and LV end-sys-

Table 4. Independent Determinants of Exercise Duration

	Model 1			Model 2		
Clinical Variables	Beta	t	*P* Value*	Beta	t	*P* Value*
Female gender	−0.465	−9.13	<0.001	−0.472	−9.37	<0.001
Age	−0.346	−7.38	<0.001	−0.345	−7.43	<0.001
Diabetes mellitus	−0.109	−2.33	0.021	−0.112	−2.41	0.016
E/E′ at baseline	−0.076	−1.49	0.137	−0.062	−1.21	0.226
S′ at baseline	0.015	0.299	0.766	0.012	0.237	0.813
LVMI	−0.010	−0.204	0.838	−0.019	−0.388	0.698
Arterial elastance index at baseline	−0.053	−1.13	0.259	...	...	...
Arterial elastance index at 25 W	...	...	...	−0.102	−2.20	0.029
	Model 3			Model 4		
Clinical Variables	Beta	t	*P* Value*	Beta	t	*P* Value*
Female gender	−0.472	−9.53	<0.001	−0.384	−6.00	<0.001
Age	−0.346	−7.50	<0.001	−0.329	−5.51	<0.001
Diabetes mellitus	−0.097	−2.10	0.036	−0.096	−1.59	0.112
E/E′ at baseline	−0.064	−1.26	0.208	−0.045	−0.707	0.480
S′ at baseline	0.007	0.136	0.892	0.022	0.348	0.728
LVMI	−0.026	−0.535	0.593	0.063	1.002	0.318
Arterial elastance index at 50 W	−0.141	−3.09	0.002	...	...	...
Arterial elastance index at 75 W	...	...	...	−0.141	−2.36	0.019

*$P<0.05$ is considered significant.

tolic elastance (Ees) with age. Although the vascular-ventricular coupling is maintained despite steeper increase in arterial elastance because of the compensatory increase in LV elastance, the increase in LV elastance may increase the sensitivity of systolic pressure to changes in volume status, which may be exaggerated during exercise. However, the mechanism underlying the gender difference for the risk of heart failure in patients with hypertension has not been well defined. This study demonstrated that in hypertensive females, there was a steeper rise of EaI during exercise and EaI was an independent determinant of exercise duration. Because EaI during exercise is determined by the pulsatile arterial load, the steeper increase has a significant impact on myocardial relaxation and contractile function during exercise, which may result in decreased exercise capacity. The dynamic increase of arterial elastance, resulting in increase of dynamic pulsatile load during exercise, may be one of the mechanisms for the gender difference in the incidence of diastolic dysfunction and heart failure in hypertension.

Table 5. Relationship Between Magnitude of Change of Arterial Elastance at 75 W of Exercise (Delta of EaI at Baseline) With Indices of Diastolic and Systolic Function

Correlation With Change of EaI at 75 W From Baseline	Correlation Coefficient	*P* Value*
E/E′ at 50 W	0.166	0.017
Change of E/E′ from baseline to 50 W	0.010	0.889
S′ at peak	−0.156	0.025
Change of S′ from baseline to peak	−0.165	0.017

*$P<0.05$ is considered significant.

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Disclosures

None.

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