Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 61, No. 1, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.08.997

Sex Differences in Arterial Stiffness and Ventricular-Arterial Interactions

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Objectives This study sought to assess sex differences in ventricular-arterial interactions.

Background Heart failure with preserved ejection fraction is more prevalent in women than in men, but the basis for this difference remains unclear.

Methods Echocardiography and arterial tonometry were performed to quantify arterial and ventricular stiffening and interaction in 461 participants without heart failure (189 men, age 67 ± 9 years; 272 women, age 65 ± 10 years). Aortic characteristic impedance (Z_c), total arterial compliance (pulsatile load), and systemic vascular resistance index (steady load) were compared between men and women, and sex-specific multivariable regression analyses were performed to assess associations of these arterial parameters with diastolic dysfunction and ventricular-arterial coupling (effective arterial elastance/left ventricular end-systolic elastance [Ea/Ees]) after adjustment for potential confounders.

Results Z_c was higher and total arterial compliance was lower in women, whereas systemic vascular resistance index was similar between sexes. In women but not men, higher log Z_c was associated with mitral inflow E/A ratio ($\beta \pm$ SE: -0.17 ± 0.07), diastolic dysfunction (odds ratio: 7.8; 95% confidence interval: 2.0 to 30.2) and Ea/Ees ($\beta \pm$ SE: 0.13 ± 0.04) ($p \leq 0.01$ for all). Similarly, total arterial compliance was associated with E/A ratio ($\beta \pm$ SE: 0.12 ± 0.04), diastolic dysfunction (odds ratio: 0.33; 95% confidence interval: 0.12 to 0.89), and Ea/Ees ($\beta \pm$ SE: -0.09 ± 0.03) in women only ($p \leq 0.03$ for all). Systemic vascular resistance index was not associated with diastolic dysfunction or Ea/Ees.

Conclusions Proximal aortic stiffness (Z_c) is greater in women than men, and women may be more susceptible to the deleterious effects of greater pulsatile and early arterial load on diastolic function and ventricular-arterial interaction. This may contribute to the greater risk of heart failure with preserved ejection fraction in women. (J Am Coll Cardiol 2013;61:96–103) © 2013 by the American College of Cardiology Foundation

Heart failure with preserved ejection fraction (HFpEF) is associated with high morbidity and mortality, and its prevalence is increasing (1). Women outnumber men with HFpEF by a 2:1 ratio (1–4). One hypothesis proposed for this discrepancy is based on sex differences in ventricular-arterial mechanics; women display increased arterial and ventricular stiffening and deranged ventricular-arterial coupling compared with men, particularly with aging (5). This may impair cardiac performance by increasing blood pressure lability, reducing cardiac efficiency, prolonging diastolic relaxation (6), and increasing diastolic chamber stiffness (7). In addition, the association of increased arterial stiffness with mortality is almost 2-fold higher in women than in men (8). Thus, investigation of sex differences in arterial stiffness and its association with cardiac function is needed to better understand the pathophysiology of HFpEF and the sequelae of arterial aging.

The hemodynamic (arterial) load on the left ventricle can be divided into steady (systemic vascular resistance) and pulsatile components (total arterial compliance [TAC], aortic characteristic impedance [Z_c]). Given the increase in aortic stiffening with aging and the potential impact of proximal aortic properties on left ventricular loading and performance, we hypothesized that increased Z_c (and therefore greater pulsatile hemodynamic load on the left ventricle) would be more strongly associated with diastolic dysfunction and with altered ventricular-arterial coupling in women than in men.

To this end, in a large, well-characterized cohort of community-dwelling subjects without heart failure, we eval-

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Manuscript received July 13, 2012; accepted August 14, 2012.

uated sex differences in Z_c and investigated whether the associations of Z_c with diastolic dysfunction and systolic ventricular-arterial coupling were different in men and women. Our secondary objectives were to: 1) determine whether the pulsatile (Z_c, TAC) versus the steady (systemic vascular resistance index [SVRI]) components of hemodynamic load were more strongly associated with diastolic dysfunction and systolic ventricular-arterial coupling in men and women and 2) assess whether the associations of central pulse pressure (PP), PP amplification, carotid-femoral pulse wave velocity (cfPWV), and augmentation index (AIx) with diastolic dysfunction and systolic ventricular-arterial coupling differed by sex.

Methods

Study participants and assessment of baseline characteristics. The study participants consisted of non-Hispanic whites from the GENOA (Genetic Epidemiology Network of Arteriopathy) study (9) and belonged to sibships with at least 2 family members with a diagnosis of hypertension before 60 years of age. Hypertension was defined based on a previous diagnosis of hypertension and/or current treatment with medications for hypertension. The study was approved by the Mayo Clinic's Institutional Review Board, and participants gave informed consent. Between October 2009 and December 2010, 493 participants completed the study protocol. We excluded 16 participants with inadequate tonometry or echocardiographic data, 3 with a history of heart failure, 2 with low ejection fraction, 8 with history of valve surgery or more than mild aortic stenosis, and 3 with atrial fibrillation, leaving 461 participants for the final analyses. The methods for assessing baseline characteristics of the participants are outlined in the Online Appendix.

Noninvasive assessment of Z_c and other hemodynamic parameters. A comprehensive noninvasive hemodynamic evaluation including arterial tonometry and transthoracic echocardiography, with simultaneous electrocardiographic recording, was performed during a single visit to the Echocardiography Laboratory at the Mayo Clinic. Characteristic impedance (Z_c) is a major property of the aorta, representing aortic opposition to pulsatile inflow from the contracting left ventricle, and is calculated as the ratio of aortic pulsatile pressure to flow. To estimate Z_c, arterial tonometry (NIHem, Cardiovascular Engineering Inc., Norwood, Massachusetts) of the right carotid artery was performed to obtain a surrogate of central aortic pressure, followed immediately by 2-dimensional Doppler echocardiography to measure the left ventricular outflow tract diameter (parasternal long-axis view) and time velocity integral (apical long-axis view). Left ventricular outflow tract area was multiplied by left ventricular outflow tract velocity time integral to calculate aortic flow. Z_c was then calculated in the time domain as the ratio of increase in central pressure to the corresponding increase in aortic flow in early systole, using software capable of Fourier analysis of the pressure and flow data obtained (NIHem, Cardiovascular Engineering Inc.) (10). When obtained in this manner, Z_c has been shown to correlate well with invasively obtained aortic impedance ($r = 0.92$) (11).

Arterial load can be divided into steady (systemic vascular resistance) and pulsatile (TAC) components. Systemic vascular resistance is the resistance to blood flow offered by all of the systemic vasculature, excluding the pulmonary vasculature, and is mainly determined by the resistance of the small peripheral arteries, arterioles, and capillaries. TAC is the change in arterial blood volume due to a given change in pulsatile arterial blood pressure. Because most of the compliance of the arterial tree resides in the aorta, TAC mostly represents aortic compliance, although smaller arteries also contribute. The techniques used to obtain TAC, SVRI, cfPWV, and AIx are described in the Online Appendix.

Abbreviations and Acronyms

- **AIx** = augmentation index
- **cfPWV** = carotid-femoral pulse wave velocity
- **CI** = confidence interval
- **DBP** = diastolic blood pressure
- **Ea** = effective arterial elastance
- **Ees** = left ventricular end-systolic elastance
- **Ea/Ees** = ventricular-arterial coupling ratio
- **HFpEF** = heart failure with preserved ejection fraction
- **LAVI** = left atrial volume index
- **OR** = odds ratio
- **PP** = pulse pressure
- **SBP** = systolic blood pressure
- **SVRI** = systemic vascular resistance index
- **TAC** = total arterial compliance
- **Z_c** = aortic characteristic impedance

Assessment of diastolic function. Transthoracic 2-dimensional and Doppler echocardiography (ACUSON Sequoia c512, Siemens Medical Solutions USA Inc., Malvern, Pennsylvania) was performed during the same visit to assess diastolic function according to American Society of Echocardiography recommendations (12). Methods for assessing diastolic function and cardiac structure are detailed in the Online Appendix. Diastolic function was categorized based on the algorithm proposed by Kane et al. (13), except that left atrial volume index (LAVI) ≥ 32 ml/m^2 was used as the second measure of increased filling pressures because it has been shown to be a marker of diastolic dysfunction (14) (Online Table S1). We then grouped the patients with grades 1 to 4 diastolic dysfunction into 1 unifying variable called diastolic dysfunction.

Systolic ventricular-arterial coupling assessment. Left ventricular end-systolic pressure was calculated as $0.9 * \text{SBP}$ (15). Effective arterial elastance (Ea), a global marker of arterial stiffness that encompasses both steady and pulsatile arterial load, was calculated as end-systolic pressure divided by stroke volume (15). The left ventricular end-systolic elastance (Ees) describes the slope and volume intercept of the left ventricular end-systolic pressure volume relationship. Ees is sensitive to contractility, chamber geometry, and passive ventricular stiffening and was determined using the single-beat technique (16) based on measured arterial pres-

sure, left ventricular stroke volume, ejection fraction, and systolic time intervals.

As arterial stiffening and Ea increase, the elastance of the left ventricle (Ees) increases to match it to ensure adequate systolic ventricular-arterial coupling and to optimize the transfer of blood from the heart to the arteries. We quantified systolic ventricular-arterial coupling by calculating the coupling ratio Ea/Ees (6).

Statistical analyses. Continuous variables are reported as mean ± SD. Differences between sexes were compared by a *t* test (normally distributed variables) or by a Wilcoxon rank sum test (skewed variables). Categorical variables were reported as number and percentage, and differences across groups were assessed with the chi-square test. Sex differences in Z_c were further assessed by linear regression with hierarchical adjustment for potential confounders. All regression analyses were performed using generalized estimating equations to account for the presence of sibships in the cohort. First, we adjusted for age (model 1). Next, we adjusted for potential confounders that have been shown to influence arterial stiffness and/or diastolic dysfunction: body mass index; systolic blood pressure (SBP); diastolic blood pressure (DBP); history of hypertension, diabetes, and smoking; and estimated glomerular filtration rate (model 2). In addition, because aortic size influences Z_c, models were further adjusted for ascending aorta diameter.

To reduce skewness, Z_c, LAVI, and the mitral inflow E/A ratio were log-transformed. Sex-specific linear and logistic regression analyses were then performed to assess the associations of log Z_c with diastolic function parameters (log LAVI, log E/A ratio, medial and lateral e′ velocities), ventricular-arterial coupling parameters (Ea, Ees, Ea/Ees), and the presence of diastolic dysfunction, respectively, after adjustment for the variables in models 1 and 2. In addition, to assess whether the associations of Z_c with diastolic dysfunction and ventricular-arterial coupling were independent of left ventricular remodeling, we repeated the multivariable regression analyses to include relative wall thickness as an independent variable. We also constructed sex-specific receiver-operating characteristic curves and calculated the c-statistics for the models described. To assess whether sex modified the associations of Z_c with diastolic dysfunction and ventricular-arterial coupling, we included the interaction term sex *Z_c in the models.

To determine whether the pulsatile (Z_c and TAC) versus steady (SVRI) components of hemodynamic load were associated with diastolic dysfunction and ventricular-arterial coupling in men and women, we performed additional sex-specific multivariable linear and logistic regression analyses to predict diastolic function parameters, the presence of diastolic dysfunction, and Ea/Ees, respectively, using TAC and SVRI as independent variables. Models were adjusted as for the Z_c models described previously, except that blood pressure was not included in SVRI models to avoid collinearity.

Lastly, cfPWV was log-transformed to reduce skewness, and multivariate linear and logistic regression analyses were used to assess the associations of additional measures of arterial stiffness (central PP, PP amplification, log cfPWV, AIx) with diastolic and ventricular-arterial coupling variables as described in the models above. Because heart rate can influence PP and AIx, central PP, PP amplification, and AIx models were additionally adjusted for heart rate.

Statistical analyses were performed with SPSS version 20.0 (IBM Corporation, Armonk, New York). A p value ≤0.05 was considered to be statistically significant.

Results

Background characteristics. The mean age was 65 years in women and 67 years in men (Table 1). Seventy-six percent of women and 83% of men were hypertensive; the means for SBP and DBP did not differ between the 2 sexes. The prevalence of diabetes and smoking was higher in men. Although the mean arterial pressure did not differ between sexes, brachial and central PPs were significantly higher in women. PP amplification was attenuated in women, with greater central PP, amplitude of forward and reflected pressure waves, higher AIx, and lower TAC, all consistent with greater vascular stiffness in women than in men. Both Ea and Ees were significantly higher in women, but the Ea/Ees ratio was similar between sexes (Table 1).

The higher Ea in women was due to the increased pulsatile components of arterial load (higher Z_c, lower TAC) and slightly higher heart rate (63 vs. 60 beats/min) and not due to the steady component of arterial load because SVRI was similar between sexes (Table 1).

Sex differences in Z_c and its association with diastolic dysfunction and ventricular-arterial coupling. Z_c was significantly higher in women than in men (Table 1). In a multivariable linear regression model that adjusted for age, body mass index, SBP, DBP, estimated glomerular filtration rate, ascending aorta diameter, and history of hypertension, diabetes, and smoking, women remained independently associated with higher Z_c, ($p \leq 0.0001$).

Z_c was higher in women with diastolic dysfunction than men with diastolic dysfunction (237.4 ± 80.5 vs. 181.2 ± 60.3 dyne × s/cm^5, $p < 0.0001$). The sex-specific associations of Z_c with LAVI, E/A ratio, medial and lateral e′ velocities, the presence of diastolic dysfunction, Ea, Ees, and Ea/Ees are summarized in Table 2. The unadjusted associations of Z_c with E/A ratio and Ea/Ees in men and women are represented graphically in Figure 1. After adjustment for age, higher Z_c was associated with lower mitral inflow E/A ratio, higher medial and lateral e′ velocities, higher Ea/Ees, and greater odds of diastolic dysfunction in women but not in men. After further adjustment for confounders, greater Z_c remained significantly associated with a lower mitral inflow E/A ratio, higher Ea/Ees, and greater odds of diastolic dysfunction in women only (Table 2). Inferences remained unchanged

Table 1 Baseline Characteristics of the Participants

Variable	Men (n = 189)	Women (n = 272)	p Value
Age, yrs	67.2 ± 9.3	65.0 ± 9.5	0.99
Hypertension	154 (82)	197 (72)	0.07
Diabetes	46 (24)	35 (13)	0.02
Smoking	108 (57)	95 (35)	<0.0001
SBP, mm Hg	136 ± 17	138 ± 19	0.10
DBP, mm Hg	71 ± 9	69 ± 8	0.97
Heart rate, beats/min	60 ± 9	63 ± 10	0.003
Fasting glucose, mmol/l	5.9 ± 1.5	5.3 ± 1.1	<0.0001
Total cholesterol, mmol/l	4.3 ± 0.9	4.8 ± 1.0	<0.0001
HDL cholesterol, mmol/l	1.1 ± 0.3	1.5 ± 0.5	<0.0001
Triglycerides, mmol/l	1.5 ± 0.7	1.5 ± 0.8	0.63
Serum creatinine, μmol/l	92.0 ± 20.0	73.0 ± 18.0	<0.0001
eGFR, ml/min/1.73 m^2	80.3 ± 18.3	78.0 ± 17.5	0.90
Body mass index, kg/m^2	31.0 ± 4.9	30.4 ± 9.6	0.81
Arterial stiffness variables			
Mean arterial pressure, mm Hg	97 ± 11	98 ± 12	0.10
Brachial PP, mm Hg	66 ± 16	70 ± 18	0.007
Central SBP, mm Hg	134 ± 21	140 ± 23	0.01
Central DBP, mm Hg	71 ± 9	69 ± 8	0.97
Central PP, mm Hg	64 ± 20	71 ± 21	0.0006
PP amplification	1.05 ± 0.13	1.00 ± 0.14	0.99
cfPWV, m/s	11.9 ± 3.8	10.5 ± 3.4	0.0001
Z_c, dyne × s/cm^5	172 ± 64	211 ± 75	<0.0001
Total arterial compliance, ml/mm Hg	1.9 ± 0.7	1.4 ± 0.5	<0.0001
SVRI, dyne·m^2/s·cm^{-5}	2,941 ± 598	2,921 ± 561	0.62
Forward pressure wave, mm Hg	52 ± 15	56 ± 16	0.02
Reflected pressure wave, mm Hg	19 ± 6	21 ± 7	0.005
Augmentation index, %	11.7 ± 10.8	18.2 ± 11.0	<0.0001
Reflected wave arrival time, ms	147.5 ± 22.4	128.6 ± 24.7	<0.0001
Echocardiographic variables			
LV septal thickness, mm	12 ± 2	10 ± 1	<0.0001
LV posterior wall thickness, mm	11 ± 2	10 ± 1	<0.0001
LV end-diastolic diameter, mm	49 ± 5	45 ± 4	<0.0001
LV end-systolic diameter, mm	31 ± 5	27 ± 4	<0.0001
LV mass index, g/m^2	99.9 ± 24.4	86.7 ± 19.0	<0.0001
LV relative wall thickness	0.48 ± 0.07	0.46 ± 0.07	0.99
LV ejection fraction, %	61 ± 7	65 ± 5	<0.0001
LAVI, ml/m^2	30 ± 9	29 ± 8	0.51
Mitral inflow E/A ratio	0.91 ± 0.27	0.96 ± 0.29	0.07
Deceleration time, ms	227 ± 48	216 ± 42	0.99
Tissue Doppler medial E′ velocity, m/s	0.08 ± 0.02	0.09 ± 0.03	0.01
Tissue Doppler lateral E′ velocity, m/s	0.10 ± 0.03	0.10 ± 0.03	0.11
Medial E/e′ ratio	8.0 ± 2.3	8.8 ± 3.4	0.05
Lateral E/e′ ratio	6.7 ± 2.3	7.4 ± 2.7	0.01
Normal diastolic function	59 (31)	95 (35)	0.43
Diastolic dysfunction			
Grade 1	61 (33)	77 (29)	0.37
Grade 2	13 (7)	28 (10)	0.23
Grades 3–4	0	0	N/A
Any	74 (39)	105 (39)	0.86
Indeterminate diastolic function*	49 (26)	67 (25)	0.66
RVSP, mm Hg	29.7 ± 6.8	29.7 ± 5.9	0.66
Ascending aorta diameter, mm	35.6 ± 3.7	32.6 ± 3.7	<0.0001
LV outflow tract diameter, mm	2.3 ± 0.2	2.0 ± 0.2	<0.0001
Ventricular-arterial coupling variables (n = 380)†			
Ea, mm Hg/ml	1.30 ± 0.28	1.57 ± 0.36	<0.0001
Ees, mm Hg/ml	1.42 ± 0.38	1.73 ± 0.47	<0.0001
Ea/Ees	0.94 ± 0.17	0.93 ± 0.19	0.71

Values are mean ± SD or n (%). *Includes participants with missing diastolic function variables or those whose diastolic function did not meet criteria for normal diastolic function or for diastolic dysfunction. †Available for 380 participants.

cfPWV = carotid-femoral pulse wave velocity; DBP = diastolic blood pressure; Ea = effective arterial elastance; Ees = end-systolic elastance; Ea/Ees = ventricular-arterial coupling ratio; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LAVI = left atrial volume index; LV = left ventricular; N/A = not available; PP = pulse pressure; RVSP = right ventricular systolic pressure; SBP = systolic blood pressure; SVRI = systemic vascular resistance index; Z_c = aortic characteristic impedance.

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Table 2 Sex-Specific Associations of log Z_c With Measures of Diastolic Function and Ventricular-Arterial Coupling

	Men	Women
Age-adjusted model		
Log LAVI, ml/m^2	0.09 ± 0.08	0.06 ± 0.06
Log E/A ratio	0.05 ± 0.05	−0.14 ± 0.06*
Medial e′, m/s	0.002 ± 0.004	−0.009 ± 0.005*
Lateral e′, m/s	−0.008 ± 0.006	−0.010 ± 0.005*
Diastolic dysfunction, OR (95% CI)	0.92 (0.34–2.48)	2.94 (1.21–7.14)*
Ea, mm Hg/ml	0.34 ± 0.07†	0.42 ± 0.07†
Ees, mm Hg/ml	0.46 ± 0.11†	0.26 ± 0.09‡
Ea/Ees	−0.05 ± 0.04	0.13 ± 0.04†
Multivariable model§		
log LAVI, ml/m^2	−0.02 ± 0.12	−0.09 ± 0.07
log E/A ratio	0.04 ± 0.07	−0.17 ± 0.07‡
Medial e′, m/s	0.009 ± 0.007	−0.008 ± 0.006
Lateral e′, m/s	−0.001 ± 0.008	−0.009 ± 0.006
Diastolic dysfunction, OR (95% CI)	0.55 (0.10–3.11)	7.76 (1.99–30.24)‡
Ea	0.30 ± 0.08†	0.38 ± 0.07†
Ees	0.39 ± 0.11†	0.23 ± 0.10*
Ea/Ees	−0.04 ± 0.04	0.13 ± 0.04‡

Values are $\beta \pm$ SE unless otherwise specified. *p ≤ 0.05. †p ≤ 0.001. ‡p ≤ 0.01. §Multivariable models were adjusted for age, body mass index, estimated glomerular filtration rate, ascending aorta diameter, systolic and diastolic blood pressure, and history of hypertension, diabetes, and smoking.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

when models were adjusted for mean arterial pressure rather than SBP and DBP (analyses not shown). The associations of Z_c with E/A ratio ($\beta \pm$ SE: −0.23 ± 0.07, p = 0.002), diastolic dysfunction (odds ratio [OR]: 11.43; 95% confidence interval [CI]: 2.23 to 58.46; p = 0.003), and Ea/Ees ($\beta \pm$ SE: 0.14 ± 0.04, p = 0.001) in women remained significant after adjustment for relative wall thickness, indicating that left ventricular remodeling alone was not responsible for the sex differences. In the pooled sample, interaction term analyses confirmed that sex was a significant effect modifier of the associations of Z_c with E/A ratio, diastolic dysfunction, and Ea/Ees (p ≤ 0.01 for all interactions).

Results of the receiver-operating characteristic curves to predict the presence of diastolic dysfunction are summarized in Online Table S2. Age was the main predictor of diastolic dysfunction in both sexes. Addition of Z_c to a model that included relevant clinical variables increased the c-statistic from 0.81 to 0.84 in women (p = 0.01), whereas no significant increase in the c-statistic was noted in men (0.83 to 0.83, p = 0.35) once Z_c was added to the model.

Associations of different components of hemodynamic load with diastolic dysfunction and ventricular-arterial coupling. Although SVRI was similar between the sexes, TAC was lower in women than in men (Table 1). In multivariable analyses, SVRI was not associated with any of the diastolic parameters in men or women (p > 0.05 for all). However, TAC was independently associated with E/A ratio ($\beta \pm$ SE: 0.12 ± 0.04, p = 0.004) and Ea/Ees ($\beta \pm$ SE: −0.09 ± 0.03, p = 0.002) in women. The unadjusted associations of TAC with E/A ratio and Ea/Ees in men and women are represented graphically in Figure 1. Interestingly, the association of higher TAC with the presence of diastolic dysfunction differed based on sex, being inverse in women (OR: 0.33, 95% CI: 0.12 to 0.89, p = 0.03 and direct in men (OR: 2.79, 95% CI: 1.09 to 7.13, p = 0.03). Inferences remained unchanged when models were adjusted for mean arterial pressure rather than SBP and DBP (analyses not shown). The association of higher TAC with E/A ratio ($\beta \pm$ SE: 0.17 ± 0.04, p ≤ 0.001), diastolic dysfunction (OR: 0.33, 95% CI: 0.12 to 0.90, p = 0.03), and Ea/Ees ($\beta \pm$ SE: −0.09 ± 0.03, p = 0.002) in women remained significant despite further adjustment for relative wall thickness. There was a significant interaction between sex and TAC in the prediction of the E/A ratio, diastolic dysfunction, and Ea/Ees (p ≤ 0.05 for all).

Sex differences in the associations of additional arterial stiffness parameters with diastolic dysfunction and ventricular-arterial coupling. Central PP was associated with higher log LAVI in men ($\beta \pm$ SE: 0.002 ± 0.001, p = 0.04) and women ($\beta \pm$ SE: 0.004 ± 0.001, p = 0.01) and with lower Ea/Ees in women ($\beta \pm$ SE: −0.001 ± 0.0007, p = 0.04), independent of age and other potential confounders. However, there was no interaction between central PP and sex in the prediction of LAVI or Ea/Ees (p > 0.05 for both). Higher PP amplification was associated with lower Ea/Ees in women ($\beta \pm$ SE: −0.24 ± 0.12, p = 0.05), and there was a trend toward an interaction between sex and PP amplification in the prediction of Ea/Ees (p = 0.08). Log cfPWV was associated with higher medial e′ velocity in men but not in women ($\beta \pm$ SE: 0.02 ± 0.009, p = 0.02), but the interaction term cfPWV * sex was not significant (p = 0.37). The remainder of the associations between central PP, PP amplification, and cfPWV with diastolic function and ventricular-arterial coupling were not statistically significant (analyses not shown). AIx was not associated with any of the diastolic function or ventricular-arterial coupling variables in men or women (p > 0.05 for all).

Discussion

To better understand how sex differences in ventricular and arterial stiffness and ventricular-arterial coupling might contribute to the greater risk of HFpEF in women, we performed a comprehensive noninvasive hemodynamic evaluation of arterial stiffness and cardiac function in a large, well-characterized sample of community-dwelling subjects without heart failure but with multiple risk factors for HFpEF. To our knowledge, this is the first study focused on the assessment of the sex-specific associations of Z_c with diastolic dysfunction and altered ventricular-arterial coupling. Our findings confirm the hypothesis that pulsatile hemodynamic load on the left ventricle is significantly associated with diastolic dysfunction and altered systolic ventricular-arterial coupling in women, but not men. These findings provide novel insights into the relationship between arterial and ventricular function in women and men without

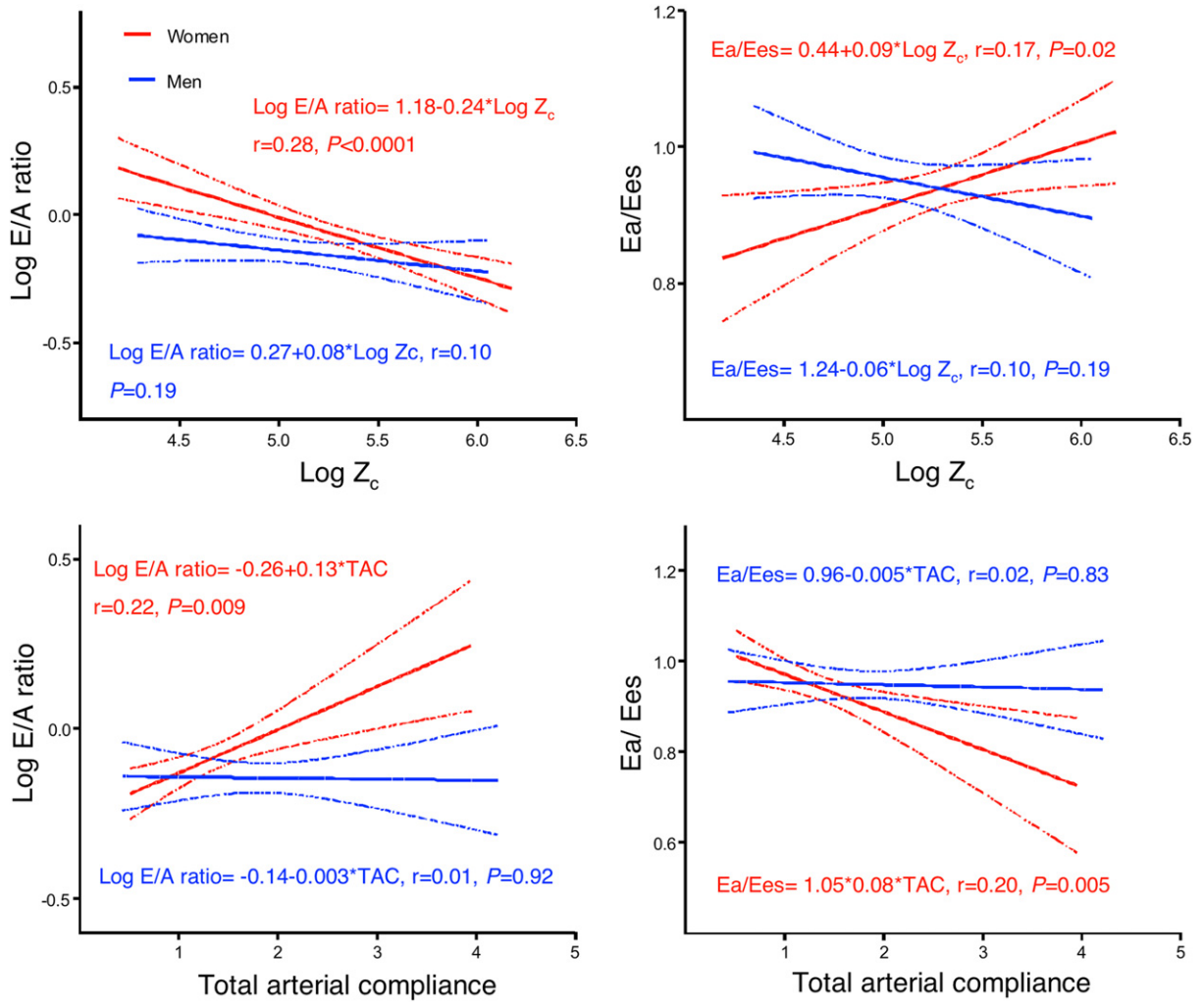

Figure 1 **Unadjusted Associations of Z_c and Total Arterial Compliance With Mitral Inflow E/A Ratio and Ventricular-Arterial Coupling**

Aortic characteristic impedance (Z_c) and total arterial compliance are associated with E/A ratio and with ventricular-arterial coupling in women, but not in men. Ea/Ees = ventricular-arterial coupling ratio; TAC = total arterial compliance.

heart failure, while also highlighting differences in aortic impedance to flow and arterial compliance as potential explanations for the higher prevalence of HFpEF in women.

Sex differences in arterial stiffness are also relevant for prognosis because greater central arterial stiffness (defined as an attenuation of the natural carotid-brachial pressure augmentation) has been shown to be associated with mortality, and this association was almost 2-fold stronger in women than in men (8). In our study, women had greater proximal aortic stiffness (Z_c) than men, consistent with the findings of 3 previous studies in the general population (17–19). Z_c varies inversely with aortic size, but women remained associated with higher Z_c after adjusting for ascending aorta diameter, suggesting that greater aortic stiffening in women may be due to differences in the material properties of the aorta. Waddell et al. (20) demonstrated that age-related increases in aortic impedance are more pronounced in women than in men and that circulating levels of estradiol were inversely correlated with aortic impedance, suggesting a hormonal basis for the sex differences in proximal aortic stiffness.

Our results indicate that Z_c is associated with diastolic dysfunction and deranged ventricular-arterial coupling (relative afterload mismatch) in women but not in men. Increased concentric remodeling in women is thought to contribute to sex differences in HFpEF (4). However, the associations of Z_c with diastolic dysfunction and ventricular-arterial coupling in women were independent of left ventricular remodeling, suggesting an additional contribution of aortic impedance to the pathophysiology of diastolic dysfunction in women. Further, the addition of Z_c to age, conventional risk factors, and relative wall thickness leads to a slight improvement in the prediction of diastolic dysfunction in women but not in

men. The current data confirm and extend observations from previous studies (21) showing that pulsatile arterial load (Z_c, TAC) rather than the nonoscillatory load has the greatest impact on diastolic dysfunction and deranged ventricular-arterial coupling. Z_c is also considered to be the major determinant of early systolic load, highlighting a possible contribution of early hemodynamic load on the left ventricle to diastolic dysfunction and altered ventricular-arterial coupling in women. In contrast to earlier studies (21,22), we did not observe a relationship between diastolic dysfunction and measures of late systolic loading (AIx), likely due to the older age of our participants. In the Framingham Heart Study, the AIx was shown to plateau and subsequently decrease starting at age 50 (23). This pattern was also observed in our cohort (analyses not shown). Thus, the decrease in the AIx with age in older adults may explain the differences between previous studies and ours. In addition, although both cfPWV and Z_c are measures of arterial stiffness, we found them to be only modestly correlated ($r = 0.36$). Given the parallel transmission of flow to the carotid arteries and the aortic arch, cfPWV does not fully represent stiffness of the proximal ascending aorta, which is the site of determination of Z_c and where ventricular-arterial interaction initially occurs. This may explain why Z_c was associated with diastolic dysfunction and altered ventricular-arterial coupling in women, whereas cfPWV was not.

In the normal state, the elastance (stiffness) achieved by the left ventricle during systole is closely coupled to the elastance of the arterial system (i.e., normal coupling ratio, Ea/Ees), and in the setting of a compliant aorta and left ventricle, forward blood flow during ejection occurs with only minimal increases in blood pressure. The majority of the compliance of the arterial system resides in the proximal thoracic aorta, which serves as an elastic reservoir that not only conducts blood to the periphery but also buffers the ample pulsatile energy generated by the heart with each beat. As such, increasing Z_c represents the pressure-flow relationship at the level of the proximal aorta, precisely at the site of its interaction with the heart. Increased Z_c translates into a greater increase in pressure due to the increase in flow during left ventricular ejection. The rate of left ventricular diastolic pressure decay during diastole is directly related to the peak aortic pressure generated by the preceding systole (24). Thus, it is possible that lower aortic compliance in women leads to greater impedance of flow during early ejection, greater pulsatile hemodynamic load on the left ventricle, relative afterload mismatch, and impaired left ventricular diastolic relaxation, which may promote progression from asymptomatic hypertensive heart disease (American College of Cardiology/American Heart Association stage A/B) to symptomatic HFpEF (American College of Cardiology/American Heart Association stage C). Results of drug trials in stage C HFpEF to date have been uniformly disappointing (25), and intervention at an earlier stage may be needed to prevent disease progression. Identification of women at risk of HFpEF using novel risk markers such as Z_c might be useful to test preventive strategies moving forward.

Shim et al. (26) assessed sex-specific associations of central hemodynamics with diastolic function and found that lower PP amplification was associated with lower tissue Doppler e′ velocity in women only. In contrast, we did not find PP amplification to be associated with diastolic dysfunction in either sex. There are several differences between the present study and that of Shim et al.; the latter study (26) did not measure Z_c, did not assess the impact of different components of load on cardiac function, included a referral population (referred for echocardiography due to dyspnea) of a relatively small sample size ($n = 158$). Their subjects were younger (mean age, 58 years compared with 66 years in our study), less obese (mean body mass index 25 kg/m^2, compared with 31 kg/m^2 in our study), less often hypertensive (71% vs. 78%), and, importantly, displayed less aortic stiffening (mean cfPWV was 8 m/s, normal for the age enrolled [27] than participants in the current study).

Study limitations. We did not have invasive hemodynamic data to corroborate the diagnosis of diastolic dysfunction or to invasively estimate arterial parameters. However, the noninvasive arterial measures that we used have been validated and are well accepted by the scientific community. Because our study was restricted to hypertensive sibships of non-Hispanic whites, further studies will be necessary to determine whether the associations found are also present in other ethnic groups and in normotensive individuals. Lastly, the cross-sectional nature of our study does not allow us to make inferences about the causality or temporality of the associations found.

Conclusions

In a cohort of subjects from the community with multiple risk factors for HFpEF, women had greater aortic stiffening as evidenced by higher Z_c and lower total arterial compliance than men. Furthermore, these measures were independently associated with diastolic dysfunction and relative afterload mismatch in women but not in men, suggesting that greater aortic stiffness and pulsatile load during early systole may decrease the efficiency of the cardiovascular system in women and therefore predispose to HFpEF. These results motivate further investigation of the impact of proximal aortic stiffness as a risk factor for HFpEF in women. Longitudinal studies will help clarify whether increased Z_c at baseline is associated with future development of HFpEF and whether Z_c is a suitable therapeutic target for preventing the onset of HFpEF in women.

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Key Words: aortic stiffness ■ diastolic dysfunction ■ echocardiography ■ sex specific ■ ventricular-arterial interaction.

APPENDIX

For supplemental material and tables, please see the online version of this article.