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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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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.

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) $\geq$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 * 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-

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