Arterial Stiffness and Left Ventricular Diastolic Function
Does Sex Matter?

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Diastolic heart failure with preserved systolic ejection fraction is becoming a major health burden and is responsible for >50% of heart failure hospital admissions.\(^1\) Arterial hypertension is one of the most important risk factors for diastolic dysfunction; however, systolic and diastolic blood pressures are the 2 extreme points of the arterial waveform. Arterial stiffness/elasticity derived from the continuous arterial waveform has been the focus of research to expand knowledge of blood pressure with diastolic (dys)function.\(^2\) Interestingly, women have a lower arterial elasticity (higher arterial stiffness) than men and tend to develop more diastolic dysfunction than men.\(^3\) A consistent finding among population studies is that women significantly outweigh men in this disease in a range of 2:1.

In this issue, Russo and coworkers reported their results about sex differences in relationship among arterial stiffness, wave reflections, and left ventricular diastolic function beyond the classical cardiovascular risk factors in the Cardiovascular Abnormalities and Brain Lesions (CABL) study cohort.\(^4\) They used applanation tonometry, considering the following hemodynamic parameters: central pulse pressure/stroke volume index, total arterial compliance, pulse pressure amplification, and augmentation index. These parameters of arterial stiffness and wave reflection were greater in women compared with men, independent of body size and heart rate, and showed inverse relationships with parameters of diastolic function in both sexes. Further adjustment for cardiovascular risk factors attenuated these relationships; however, the ratio central pulse pressure/stroke volume predicted left ventricular dysfunction both in women and men, independent of other risk factors. This study had several limitations. This was a cross-sectional design and did not allow demonstration of a cause-effect relationship. The majority of the central hemodynamic parameters provide only indirect information about arterial stiffness. Carotid-femoral pulse wave velocity, which is an important parameter for aortic stiffness, was not measured. Antihypertensive therapy was taken by 75.7% of the women and 68.5% of the men but was not stopped on the day of the measurement; however, there was an adjustment in the analysis for the use of antihypertensive therapy, and similar findings were confirmed.

Arterial wave reflections can be studied by wave analysis obtained by tonometry of the radial artery.\(^5\) The central aortic pressure waveform is composed by a forward-traveling wave-form and a backward wave reflection from the peripheral arteries to the aorta. The amplitude and timing of the reflected waves ultimately depend on the stiffness of the small and large arteries. Normally, the reflected pressure waves arrive in the aorta after the peak systolic pressure. When arterial stiffness increases, reflected waves arrive earlier and consequently augment the peak systolic pressure. These changes in central hemodynamics have a major impact on the left ventricle due to an increased afterload, enhancing the left ventricular remodeling process and also decreasing the coronary blood flow, leading to subendocardial ischemia.

There is a sex difference in arterial stiffness and arterial wave reflections. In the Multi-Ethnic Study of Atherosclerosis, we studied the large and small artery elasticity derived from the diastolic pulse contour analysis of the radial artery.\(^6\) Our results demonstrated that women had lower large and small artery elasticity than men. Height did explain much of the sex difference in both large and small artery elasticity in our data. Although frame size may be important in arterial elasticity, we did see a small difference in both large and small artery elasticity even for men and women of similar height. Height also played a role in ethnic differences in large and small artery elasticity, since Chinese and Hispanic men and women have both lower arterial elasticity and shorter height than white and black men. In a study where elderly hypertensive men and women were height-matched, Gatzka et al\(^7\) found that women still had earlier wave reflection. Moreover, women also had a smaller aortic diameter and a stiffer aortic arch than men.

The differences regarding increased arterial stiffness in women versus men may be the result of a difference in sex hormones, obesity, low-grade inflammation and fibrosis, and endothelial dysfunction, beyond height and advancing age (Figure). Increased arterial stiffness and wave reflections may accelerate the development of diastolic dysfunction and diastolic heart failure development in vulnerable subjects by increasing load and worsening the ventricular-vascular coupling. Beyond the sex differences of arterial stiffness and wave reflections, there is also a difference in ventricular remodeling due to increased vascular load to the heart.\(^8\) The female heart will tend to show a concentric hypertrophy, which is associated with an increase in wall thickness and initial preservation of cavity size and ejection fraction, while
the male heart tends more to develop an eccentric hypertrophy, which is associated with progressive left ventricle dilation and dysfunction. These differences between men and women are widely held to be related to sex hormones such as estrogen on the vasculature and the myocardium. Estrogen affects collagen synthesis and degradation and inhibits the renin-angiotensin system. Effects of estrogen may provide benefit to premenopausal women, and the loss of its protective mechanisms may render the heart of postmenopausal women more vulnerable to deleterious effects in diastolic ventricular-vascular coupling because of lack of estrogens with aging and menopause.

Obesity and diabetes affect myocardial and vascular stiffness differently and lead to different forms of myocardial hypertrophy in women and men. The Strong Heart Study demonstrated that left ventricular mass is actually greater in obese women than in obese men when normalized for measures of geometrically consistent body size that do not incorporate body weight (height or fat-free mass), even though absolute left ventricular mass is lower in women than in men.\(^9\) In particular, this difference was most evident when left ventricular mass was indexed for height.\(^2,7\)

The age-related abnormalities in the biomechanical properties of the arterial system and the myocardium are more pronounced in women than in men, leading to changes in the ventricular-vascular coupling.\(^10\) Therefore, elderly women have a higher prevalence of hypertension with aging and also higher blood pressure variability.

With the growing aging population in our society, especially among women, diastolic heart failure with preserved ejection fraction will become a major health problem. A strategy needs to be developed to detect early changes in arterial stiffness, arterial wave reflections, and ventricular-vascular coupling, with special attention to the elderly female. Noninvasive techniques for the examination of arterial stiffness and arterial wave reflections beyond the classical arterial blood pressure assessment need to be evaluated longitudinally. Moreover, clinical trials need to be done to examine the effect of novel medical therapies on the reduction of arterial stiffness, arterial wave reflections, and the improvement of ventricular-vascular coupling. Therapies that have these apparently beneficial effects need to be evaluated to see whether these novel therapies will also reduce the risk of morbidity and mortality due to diastolic heart failure with preserved ejection fraction.

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**Disclosures**

None.

**References**
