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Age-related alterations in cardiac and arterial structure and function in hypertensive women and men

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Abstract

The study was to compare age-related alterations in cardiac and arterial structure and function by sex and to explore the impacts of achieved systolic blood pressure (SBP; <130 mm Hg vs. <140 mm Hg) level on age-related alterations in cardiac and arterial structure and function in hypertensive women and men. Community hypertensive individuals without cardiovascular disease who had echocardiographic examination were included. Age-related alterations in cardiac and arterial structure and function were compared by sex, and interplay between age and sex was analyzed according to achieved SBP level. The mean age of the cohort was 66.5 years, and women accounted for 62% (n = 602) of the cohort (n = 971). Compared to men, women had worse left ventricular (LV) diastolic function and greater LV and arterial stiffness. After adjusting for covariates, the magnitude of the associations between age with septal E/e′ ratio, septal S′ velocity, effective arterial elastance (Ea) and LV end-diastolic elastance (Eed) were greater in women. Sex differences in the magnitude of association between age with these four indices varied according to achieved SBP level. When achieved SBP <130 mm Hg, the magnitude of the associations between age with septal E/e′ ratio, septal S′ velocity, Ea and Eed did not differ by sex. Since age and sex are non-modifiable, achieving SBP target, especially at a lower level, might be beneficial to attenuate sex differences in age-related alterations in cardiac and arterial structure and function.

1 | INTRODUCTION

Among individuals with heart failure with preserved ejection fraction (HFpEF), the proportion of those older than 65 years is more than 60%.[1-3] Besides prevalent cardiac and noncardiac morbidities, age-related alterations in cardiac and arterial structure and function might also explain the HFpEF epidemic in the elderly.[4,5] For example, among community residents without cardiovascular disease (CVD)

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and hypertension, advancing age is associated with increases in left ventricular (LV) and arterial stiffness and decrease in LV relaxation,[6-8] which are purported to contribute to the pathogenesis of HFpEF.[9-11]

Women, especially elderly women, are more likely than men to have HFpEF.[12,13] Sex differences in the age-related cardiac and arterial alterations might partly explain the difference. For example, Redfield and colleagues[7] reported that LV end-systolic elastance (Ees), an index of LV stiffness, increased more steeply with age in women than in men. Among Japanese populations without CVD and hypertension, peak early diastolic mitral annular velocity (e′), an index of LV relaxation, deteriorated more greatly in women than in men in individuals older than 70 years.[6] One recent study from Chinese hypertensive individuals without CVD showed that the magnitude of the association between blood pressure (BP) with E/e′ ratio, an index of LV filling pressure, and effective arterial elastance (Ea), an index of arterial stiffness, were greater in women than in men.[14]

Blood pressure elevation is associated with increase in LV and arterial stiffness and decrease in LV relaxation. Reduction of systolic BP (SBP) is beneficial for the improvement of LV relaxation in hypertensive individuals with LV diastolic dysfunction,[15] and a lower achieved SBP level (<130 mm Hg vs. 130-140 mm Hg) is associated with a better achieved LV relaxation.[16] It is unknown whether these benefits differ by age and sex. Although studies have reported age- and sex-related cardiac and arterial alterations,[6-8,14,17] data from Chinese community populations and analyses of interplay between age and sex in hypertensive individuals without CVD are limited. Accordingly, the aims of the current study were as follows: (a) to compare age-related alterations in cardiac and arterial structure and function between hypertensive women and men; (b) to explore the impacts of the achieved SBP level on age-related alterations in cardiac and arterial structure and function in women and men.

2 | METHODS

2.1 | Study participants

This is a community-based study conducted in the Liaobu County, Dongguan, Guangdong Province, China. The current study was approved by the Clinical Research Ethic Committee of Guangdong Provincial People's Hospital and the Liaobu County Health Department. Written informed consent was obtained before enrollment. During the government-sponsored annual health examination in 2016, 1474 hypertensive individuals underwent echocardiographic examination. In specific, the definition of hypertension was based on prior physician's diagnosis and current antihypertensive therapy. Individuals who did not have data on tissue Doppler imaging (n = 464), had prior ischemic stroke (n = 23), and had coronary heart disease (n = 24) were excluded. Among these 47 individuals with prior CVD, 8 were also without data on tissue doppler imaging. Therefore, a total of 971 hypertensive individuals without CVD were included for the current analyses.

2.2 | Clinical characteristics and laboratory data

Clinical characteristics were collected using standardized questionnaire by trained healthcare staffs during the annual health examination. Body mass index (BMI) was calculated by weight in kilograms divided by height in squared meters, and BMI ≥28 kg/m^2 was defined as obesity based on the World Health Organization criteria for the Asian population.[18] Body surface area (BSA) was calculated as BSA = (Weight $^{0.425}$ × Height $^{0.725}$) × 0.007184. Waist circumference was measured at the level of the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the midaxillary line, and hip circumference was measured at the level of the widest portion of buttocks. Waist-hip ratio was calculated as waist circumference divided by hip circumference. Fasting venous blood was used to assess fasting plasma glucose, lipid profiles, serum uric acid, and serum creatinine, which was used to calculate estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula,[19] and eGFR <60 ml/min/1.73 m^2 was defined as chronic kidney disease. Hyperuricemia was defined as serum uric acid ≥420 μmol/L in men and ≥360 μmol/L in women, respectively. Current antihypertensive and other drugs use were collected.

2.3 | Blood pressure measurement

Prior to BP measurement, participants were required to stay at rest in a sitting position for 5 minutes. According to the China guideline's recommendation,[20] two BP measurements were performed with 1-minute interval with the arm positioned at the heart level using Omron HEM-7051 device (Omron HealthCare). Healthcare staff was attended during BP measurements. The average value of two BP readings was used. If the first two BP readings differed by >5 mm Hg, an additional measurement was required, and the mean value of three readings was used. Pulse pressure was calculated as SBP minus diastolic BP (DBP).

2.4 | Echocardiographic examination

Echocardiographic examination was performed according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging guideline's recommendation [21] using a Vivid S6 M4S-RS Probe (GE Ving-Med) interfaced with a 2.5- to 3.5-MHz phased-array probe. Left atrial (LA) volume was assessed using the modified biplane Simpson's rule from the apical 2- and 4-chamber view at end systole and was indexed to BSA. LV end-diastolic diameter (LVEDD), LV posterior wall and interventricular septum thickness in diastole were used to calculate left ventricular mass (LVM) and were indexed to BSA. LVM index ≥115 g/m^2 in men and ≥95 g/m^2 in women were defined as LV hypertrophy (LVH). Mitral inflow velocity (peak E- and A-wave) was assessed using pulsed-wave Doppler from the apical 4-chamber view. Peak early systolic tissue velocity (S′) and peak early diastolic tissue velocity (e′) were measured from the septal aspect of the mitral annulus.

According to the guideline recommendation,[22] septal e′ velocity <7 cm/s was defined as LV diastolic dysfunction and septal E/e′ ratio >15 was defined as an increased LV filling pressure. Stroke volume (SV) was calculated as LV end-diastolic volume (LVEDV) minus LV end-systolic volume (LVESV) and was indexed to BSA. Based on prior report,[23] effective arterial elastance (Ea) and Ees were calculated as Ea = 0.9 × SBP/SV and Ees = 0.9 × SBP/LVESV, and the Ea/Ees ratio was used to assess arterial-ventricular coupling. LV end-diastolic elastance (Eed) was calculated as Eed = (11.96 + 0.596 × E/e′)/LVEDV as previously validated.[24,25]

2.5 | Statistical analysis

Continuous variables were presented as mean ± standard deviation if normal distribution, otherwise were presented as median and interquartile range (IQR). Between-group differences were evaluated by *t* test or Mann-Whitney *U* test. Categorical variables were presented as number and proportion. Between-group differences were evaluated by Chi-square test or the Fisher exact test. We first compared cardiac and arterial indices by sex, and then we used linear regression analyses to evaluate the association between age (per 10 years increase) with cardiac and arterial indices in men and women, respectively, and the association was tested for potential interaction by sex. Participants were separated into two achieved SBP levels based on the 2017 AHA/ACC hypertension guideline (<130 mm Hg vs. ≥130 mm Hg)[26] and the 2018 China hypertension guideline (<140 mm Hg vs. ≥140 mm Hg).[20] We evaluated age-related alterations in selected cardiac and arterial indices with interaction by sex according to the achieved SBP level. The association between age (per 10 years increase) with selected cardiac and arterial indices was evaluated in women and men, respectively, and the association was tested for interaction by sex. β-coefficient and associated 95% confidence interval (CI) were reported. A *p*-value <.05 was considered as statistical significance. All the analyses were performed using R package (version 3.4 Vienna).

3 | RESULTS

3.1 | Baseline characteristics

The mean age of the cohort was 66.5 years, and women accounted for 62% (*n* = 602) of the study participants (Table 1). Age distribution was shown in Figure 1. Compared to men, women were older, more likely to be obese and dyslipidemia, and less likely to smoke. Women had a lower DBP and waist/hip ratio but had a higher BMI. Women were less likely than men to use diuretic.

3.2 | Comparisons of cardiac and arterial structure and function by sex

Women had a worse cardiac remodeling as reflected by a higher LA volume index and were more likely than men to have LA volume index >34 ml/m^2, and concentric and eccentric LVH (Table 2). Although women had a higher LVEF and SV index, septal S′ velocity was lower in women. Women had a worse LV diastolic function as reflected by a lower septal e′ velocity, a higher septal E/e′ ratio, and were more likely than men to have septal e′ velocity <7 cm/s and septal E/e′ ratio >15. LV and arterial stiffness were greater in women as reflected by a higher Ees, Eed, Ea, and pulse pressure in women. Arterial-ventricular coupling was worse in women as they had a lower Ea/Ees ratio.

3.3 | Age-related alterations in indices of LV diastolic function in women and men

Left atrial volume index and septal E/e′ ratio incrementally increased and septal e′ velocity incrementally decreased across increasing age group, and these trends were observed in both sexes (Figure 2, Panel A-C). After adjusting for covariates, increasing age remained associated with these indices in both sexes (Table 3). In the interaction analyses, septal E/e′ ratio increased more steeply with age in women than in men (*p*-interaction = .001), while the association between age with LA volume index and septal e′ velocity did not differ by sex.

3.4 | Age-related alterations in indices of LV and arterial stiffness in women and men

End-systolic elastance and Eed incrementally increased across increasing age group only in women (Figure 2, Panel D-E). After adjusting for covariates, increasing age remained associated with Ees and Eed in women (Table 3). The analysis of interaction suggested that the association between age with Eed was greater in women than in men (*p*-interaction = .002). Both Ea and pulse pressure increased with age in women, and pulse pressure increased with age in men (Figure 2, Panel F-G). After adjusting for covariates, increasing age remained associated with Ea and pulse pressure in women, while associated with pulse pressure in men. The analysis of interaction suggested that the association between age with Ea was greater in women than in men (*p*-interaction = .005). There was no association between age with Ea/Ees ratio in both sexes.

3.5 | Age-related alterations in indices of LV structure and systolic function in women and men

Left ventricular mass index increased across increasing age group in women (Figure 2, Panel I). After adjusting for covariates, increasing age remained associated with LVM index in women (Table 3). There was no association between age with LV mass-to-volume (LVMV) ratio in both sexes. Septal S′ velocity incrementally decreased across increasing age group in both sexes. After adjusting for covariates, increasing age remained associated with septal S′ velocity in both sexes (Figure 2, Panel M and Table 3). The analysis of interaction

TABLE 1 Baseline characteristics

Variables	Overall (*n* = 971)	Men (*n* = 369)	Women (*n* = 602)	*p*-Value
Age (years)	66.5 ± 11.4	64.2 ± 12.3	67.8 ± 10.7	<.001
SBP (mm Hg)	137.0 ± 16.7	136.9 ± 15.8	137.1 ± 17.2	.893
DBP (mm Hg)	81.9 ± 10.5	83.8 ± 10.7	80.8 ± 10.2	<.001
Heart rate (beat per minute)	71.7 ± 12.0	72.0 ± 12.3	71.5 ± 11.8	.572
Smoking, *n* (%)	208 (21.4)	203 (55.0)	5 (0.8)	<.001
Physical inactivity, *n* (%)	408 (42.0)	148 (40.1)	260 (43.2)	.38
Body surface area (m^2)	1.62 ± 0.18	1.73 ± 0.15	1.55 ± 0.15	<.001
Body mass index (kg/m^2)	25.3 ± 3.8	24.9 ± 3.5	25.5 ± 3.9	.024
Obesity, *n* (%)	205 (21.1)	61 (16.5)	144 (23.9)	.008
Waist/hip ratio	0.93 ± 0.06	0.94 ± 0.05	0.92 ± 0.06	<.001
Dyslipidemia, *n* (%)	597 (75.6)	209 (71.1)	388 (78.2)	.03
Diabetes mellitus, *n* (%)	216 (22.3)	75 (20.3)	141 (23.5)	.283
Hyperuricemia, *n* (%)	614 (64.7)	244 (67.4)	370 (63.0)	.194
CKD, *n* (%)	124 (13.3)	50 (14.0)	74 (12.8)	.684
FPG (mmol/L)	5.4 ± 1.5	5.3 ± 1.6	5.4 ± 1.5	.379
Total cholesterol (mg/dl)	211.1 ± 53.5	200.1 ± 49.6	217.9 ± 54.7	<.001
LDL cholesterol (mg/dl)	129.1 ± 38.4	125.3 ± 37.2	131.6 ± 39.0	.072
HDL cholesterol (mg/dl)	53.5 ± 14.4	50.2 ± 16.1	55.7 ± 12.7	<.001
Triglyceride (mg/dl)[a]	132.6 [96.2, 190.7]	128.5 [93.6, 190.1]	135.0 [97.5, 193.2]	.994
Creatinine (μmol/L)	79.3 ± 35.1	94.7 ± 46.0	69.7 ± 21.2	<.001
eGFR ($ml/min/1.73\ m^2$)	83.5 ± 24.0	82.4 ± 23.8	84.2 ± 24.1	.27
Uric acid (μmol/L)	429.2 ± 124.2	471.4 ± 121.9	403.2 ± 118.3	<.001
Aspirin, *n* (%)	167 (17.2)	73 (19.8)	94 (15.6)	.113
Statins, *n* (%)	272 (28.0)	112 (30.4)	160 (26.6)	.231
Oral antidiabetics, *n* (%)	175 (18.0)	64 (17.3)	111 (18.4)	.73
Insulin, *n* (%)	4 (0.4)	3 (0.8)	1 (0.2)	.312
Allopurinol, *n* (%)	22 (2.3)	12 (3.3)	10 (1.7)	.163
ACEI, *n* (%)	144 (14.8)	62 (16.8)	82 (13.6)	.207
ARB, *n* (%)	489 (50.4)	187 (50.7)	302 (50.2)	.929
CCB, *n* (%)	454 (46.8)	166 (45.0)	288 (47.8)	.424
Diuretic, *n* (%)	137 (14.1)	63 (17.1)	74 (12.3)	.047
Betablocker, *n* (%)	127 (13.1)	48 (13.0)	79 (13.1)	1
No. antihypertensive drugs[a]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	.302

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

[a]Presented as median [Q1, Q3].

indicated that the association between age with septal S′ velocity was greater in women than in men (*p*-interaction = .048). The association between age with LVEF and SV index did not differ by sex.

3.6 | Age-related alterations in selected cardiac and arterial indices according to the achieved SBP level

Among individuals with the achieved SBP <130 mm Hg, after adjusting for covariates, the magnitude of the association between age with septal S′ velocity, septal E/e′ ratio, Ea, and Eed did not differ by sex (Table 4). Nonetheless, among individuals with the achieved SBP ≥130 mm Hg, after adjusting for covariates, the magnitude of the association between age with these indices was greater in women. When the achieved SBP <140 mm Hg, similar findings were observed as SBP <130 mm Hg except that the magnitude of the association between age with septal E/e′ ratio was greater in women. Among individuals with the achieved SBP ≥140 mm Hg, similar findings were observed as SBP ≥130 mm Hg except that the magnitude of the association between age with septal S′ velocity did not differ by sex.

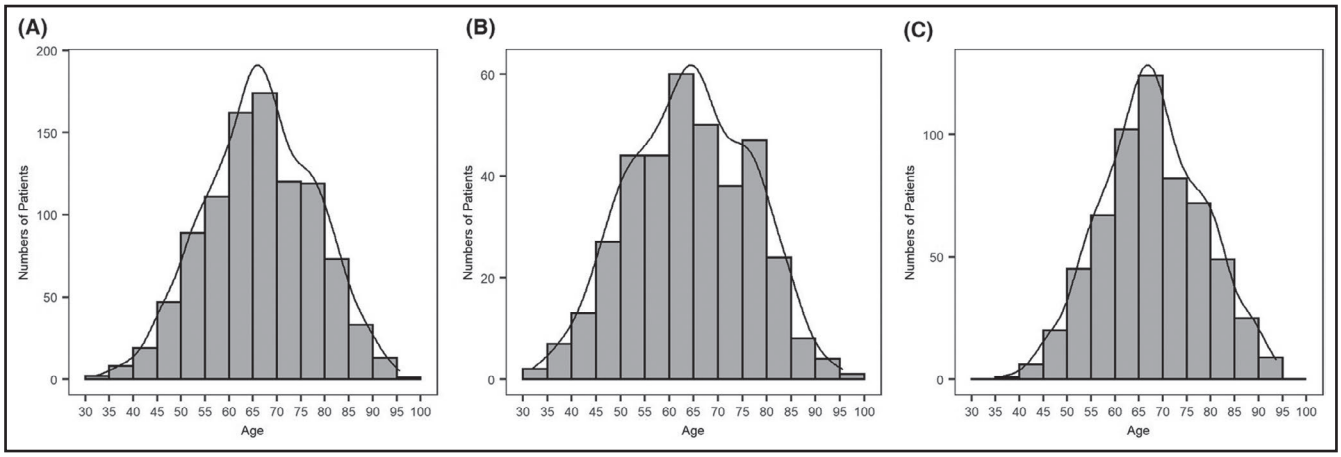

FIGURE 1 Age distributions in women and men. Panel A: overall participants; Panel B men; Panel C women

4 | DISCUSSION

This community-based study, which included 971 hypertensive individuals without CVD, shows that women had worse LV diastolic function and greater LV and arterial stiffness. Increasing age was associated with worse LV diastolic function and greater LV and arterial stiffness in women. Importantly, the sex differences in the association between age with selected cardiac and arterial indices varied according to the achieved SBP level. Since age and sex are non-modifiable, achieving SBP target, especially at a lower level (<130 mm Hg), might be beneficial to attenuate the sex differences in age-related alterations in cardiac and arterial structure and function.

4.1 | Association between age with LV diastolic function

Several indices from different pathophysiological aspects (eg, LV relaxation and LV stiffness) have been used to characterize LV diastolic function.[22,27] Septal e′ velocity, septal E/e′ ratio, and LA volume index are used commonly in clinical practices and researches.[22,27] Age is an important determinant of LV diastolic function, and several studies have assessed the association between age with LV diastolic function. For example, in individuals without CVD and hypertension, increasing age was associated with incremental impairment of LV diastolic function in both sexes.[6,7] We confirm prior studies by demonstrating that in hypertensive individuals without CVD, LV diastolic function, as indexed by septal e′ velocity, septal E/e′ ratio and LA volume index, incrementally reduced with increasing age in both women and men. Considering a higher burden of HFpEF in elderly women, it is of clinical importance to explore whether the magnitude of the associations between age with LV diastolic function differs by sex. We extend prior studies by showing that increasing age was associated with greater increase in septal E/e′ ratio and Eed (an index of LV diastolic stiffness) in women than in men. Mechanistically, LV stiffening causes impairment of LV diastolic function, resulting in elevation of LV filling pressure, which explain why age was associated with a higher septal E/e′ ratio in women than in men.

Results from Okura showed that in individuals younger than 50 years, e′ velocity was higher in women; while in those between 50 and 70 years, e′ velocity was similar between women and men; and in individuals older than 70 years, e′ velocity was lower in women.[6] We observe that in individuals younger than 55 years, septal e′ velocity was higher in women, while in those older than 55 years, septal e′ velocity was lower in women. Lack of cardioprotective effects of estrogen after menopause might contribute to impairment of LV relaxation in elderly women.[28,29] Indeed, prior studies have demonstrated that estrogen replacement therapy was beneficial for improvement of LV diastolic function.[30,31]

Left atrial volume index is an essential marker of long-term LV diastolic function.[32] Using cardiac magnetic resonance, Zemrak and colleagues[33] reported that age and female sex were positively associated with LA volume index. Using echocardiography, D'Andrea and colleagues[34] reported that in healthy individuals, LA volume index was correlated to age but not sex. Consistent to prior reports,[33,34] the current study demonstrates that age was positively associated with LA volume index. However, the magnitude of the association did not differ by sex. Taken together, the overall findings suggest that in hypertensive individuals without CVD, increasing age is associated with greater increases in LV filling pressure and LV stiffness in women, providing mechanistic evidence to explain the predisposition of elderly women to have HFpEF.

4.2 | Association between age with arterial and LV stiffness

Arterial stiffening is implicated in LV diastolic dysfunction and HFpEF development.[9,35] Age is a key determinant of arterial stiffness.[36] Elderly women usually have a greater arterial stiffness than elderly men.[37,38] We confirm prior studies by showing that increasing age was associated with increase in pulse pressure, and pulse pressure was higher in women than in men after

TABLE 2 Cardiac and arterial structure and function

Variables	Overall (*n* = 971)	Men (*n* = 369)	Women (*n* = 602)	*p*-Value
Left atrial volume (ml)	42.8 ± 21.0	42.7 ± 22.5	42.9 ± 20.0	.885
Left atrial volume index (ml/m^2)	26.5 ± 13.2	24.7 ± 13.4	27.6 ± 13.0	.001
Left atrial volume index >34 ml/m^2, *n* (%)	180 (18.5)	50 (13.6)	130 (21.6)	.004
Interventricular septum thickness (mm)	9.7 ± 1.3	10.0 ± 1.3	9.5 ± 1.3	<.001
Posterior wall thickness (mm)	9.5 ± 1.8	9.8 ± 1.9	9.3 ± 1.8	<.001
Relative wall thickness	0.43 ± 0.09	0.43 ± 0.09	0.43 ± 0.08	.245
Relative wall thickness >0.42, *n* (%)	493 (50.8)	197 (53.4)	296 (49.2)	.226
LVEDD (mm)	44.7 ± 4.4	45.8 ± 4.6	44.1 ± 4.1	<.001
LVESD (mm)	27.5 ± 4.2	28.6 ± 4.5	26.9 ± 3.8	<.001
LVEDV (ml)	92.4 ± 22.0	97.9 ± 24.0	89.1 ± 19.9	<.001
LVEDV index (ml/m^2)	57.1 ± 12.6	56.5 ± 13.0	57.5 ± 12.3	.246
LVESV (ml)	29.4 ± 12.4	32.4 ± 14.5	27.6 ± 10.4	<.001
LVESV index (ml/m^2)	18.1 ± 7.3	18.7 ± 8.1	17.8 ± 6.8	.067
Left ventricular mass (g)	146.2 ± 42.1	159.0 ± 45.5	138.4 ± 37.9	<.001
Left ventricular mass index (g/m^2)	90.1 ± 23.8	91.7 ± 25.0	89.1 ± 23.0	.105
Left ventricular hypertrophy, *n* (%)	242 (24.9)	53 (14.4)	189 (31.4)	<.001
LVMV ratio (g/ml)	1.59 ± 0.32	1.64 ± 0.33	1.57 ± 0.32	.001
Left ventricular geometry				
Normal, *n* (%)	375 (38.6)	150 (40.7)	225 (37.4)	.342
Concentric remodeling, *n* (%)	354 (36.5)	166 (45.0)	188 (31.2)	<.001
Concentric hypertrophy, *n* (%)	103 (10.6)	22 (6.0)	81 (13.5)	<.001
Eccentric hypertrophy, *n* (%)	139 (14.3)	31 (8.4)	108 (17.9)	<.001
Septal S′ velocity (cm/s)	6.4 ± 1.5	6.8 ± 1.4	6.2 ± 1.6	<.001
Left ventricular ejection fraction (%)	67.6 ± 7.1	66.7 ± 7.0	68.2 ± 7.0	.001
Stroke volume (ml)	65.0 ± 14.9	68.0 ± 15.9	63.1 ± 13.9	<.001
Stroke volume index (ml/m^2)	40.3 ± 8.5	39.4 ± 8.4	41.0 ± 8.5	.041
Peak E-wave velocity (m/s)	0.68 ± 0.21	0.67 ± 0.21	0.69 ± 0.21	.05
Peak A-wave velocity (m/s)	0.87 ± 0.19	0.82 ± 0.20	0.90 ± 0.18	<.001
E/A ratio	0.80 ± 0.25	0.85 ± 0.30	0.77 ± 0.22	<.001
Septal e′ velocity (cm/s)	5.5 ± 1.8	5.9 ± 1.8	5.2 ± 1.7	<.001
Septal e′ velocity <7 cm/s, *n* (%)	728 (75.0)	239 (64.8)	489 (81.2)	<.001
Septal E/e′ ratio	13.4 ± 5.4	12.0 ± 5.3	14.3 ± 5.2	<.001
Septal E/e′ ratio >15, *n* (%)	273 (28.1)	57 (15.4)	216 (35.9)	<.001
Ees (mm Hg/ml)	4.74 ± 1.80	4.35 ± 1.88	4.98 ± 1.71	<.001
Eed (mm Hg/ml)	0.23 ± 0.06	0.21 ± 0.06	0.24 ± 0.06	<.001
Ea (mm Hg/ml)	1.99 ± 0.52	1.93 ± 0.52	2.03 ± 0.52	.03
Ea/Ees ratio	0.47 ± 0.17	0.50 ± 0.19	0.45 ± 0.15	<.001
Pulse pressure (mm Hg)	55.2 ± 14.4	53.2 ± 14.0	56.4 ± 14.5	.001

Abbreviations: Ea, effective arterial elastance; Eed, left ventricular end-diastolic elastance; Ees, left ventricular end-systolic elastance; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVMV, left ventricular mass-to-volume.

65 years. We additionally assessed the association between age with Ea, which is a reliable marker of arterial stiffness that captures peripheral vascular resistance, pulsatile load, and systolic and diastolic time intervals.[39,40] The current study suggests that age was associated with Ea only in women, and the magnitude of the association was greater in women. Elevated vascular oxidative stress and inflammation after menopause might contribute to a steep increase in arterial stiffness in elderly women.[38,41] Indeed, in the current study, we observe that both Ea and pulse pressure increased significantly after 55 years in women. Improvement of arterial stiffness with estrogen replacement therapy also supports this hypothesis.[42,43]

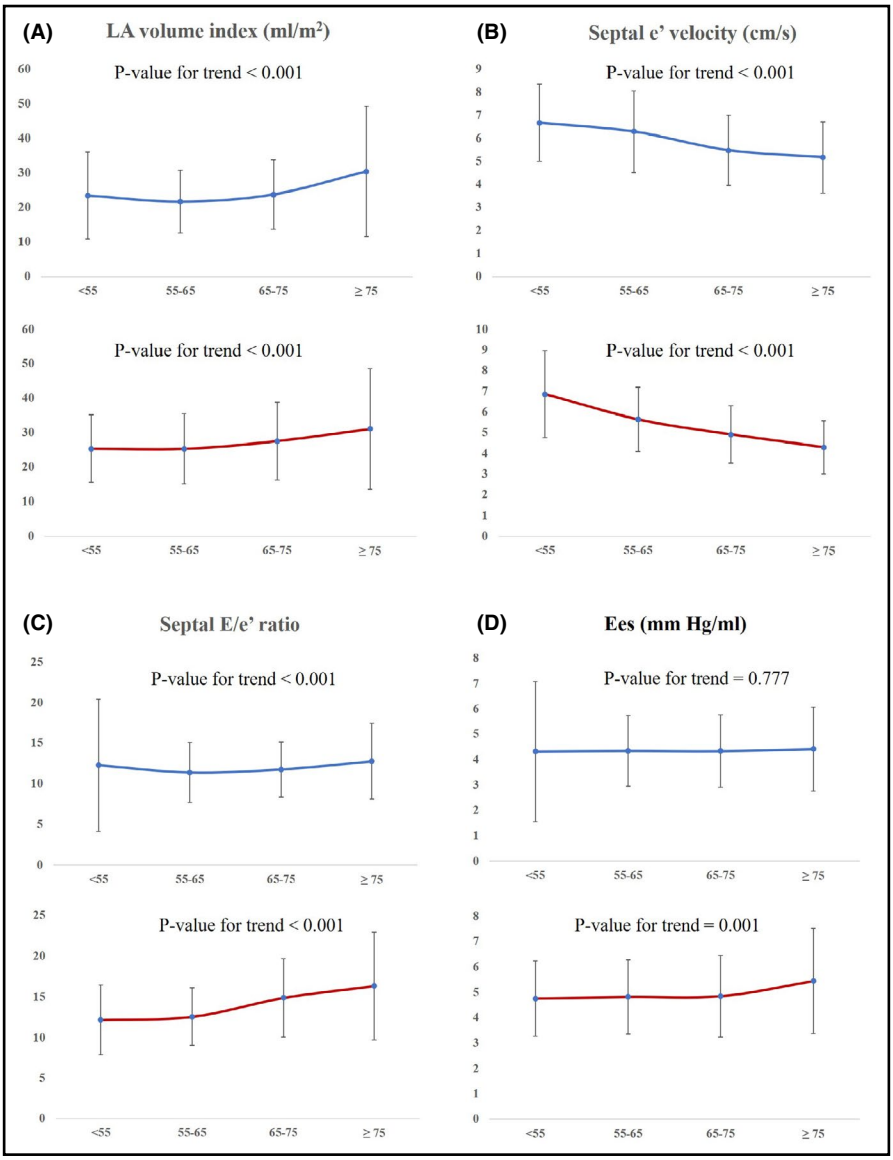

FIGURE 2 Alterations in cardiac and arterial structure and function across increasing age groups in women and men. Across increasing age groups, there was a trend of increase in LA volume index (Panel A), septal E/e′ ratio (Panel C) and pulse pressure (Panel G) and a trend of decrease in septal e′ velocity (Panel B) and septal S′ velocity (Panel M) in women and men. There was a trend of increase in Ees (Panel E), Eed (Panel D), Ea (Panel F), and LVM index (Panel I) with increasing age only in women, and no significant trend of alterations in Ea/Ees (Panel H), LVMV ratio (Panel J), LVEF (Panel K), and SV index (Panel L) with increasing age in both sexes. Blue line indicates men and red line indicates women. Ea, effective arterial elastance; Eed, left ventricular end-diastolic elastance; Ees, left ventricular end-systolic elastance; LA, left atrial; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMV, left ventricular mass-to-volume; SV, stroke volume

End-systolic elastance is an index of LV systolic stiffness. Prior study reported that age was associated with Ees in both sexes, and the magnitude of the association was greater in women.[7] In the current study, age was associated with Ees only in women and the magnitude of the association did not differ by sex. Differences in the findings are not surprising given that multiple determinants (eg, age and arterial load) might influence Ees. Ees normally matches with arterial load to achieve near optimal mechanical and metabolic function.[44] Therefore, an increase in Ees with age is served as a corresponding alteration to match with Ea increase with age. Notwithstanding, higher Ea and Ees indicate that arterial and LV stiffness become more sensitive to LV volume alteration, resulting in abnormalities of LV diastolic filling.[45] The important role of arterial-ventricular coupling in the pathophysiology of LV diastolic dysfunction and HFpEF has long been recognized.[46] Ea/Ees ratio is an index of arterial-ventricular coupling, and maximal cardiac efficiency is achieved when Ea/Ees ratio equals 0.5.[47] In the current study, women had a lower mean Ea/Ees ratio than men (0.45 mm Hg/ml vs. 0.50 mm Hg/ml), suggesting a lower cardiac efficiency and worse cardiac performance. These findings together provide additional mechanistic evidence to explain the HFpEF epidemic in the elderly women.

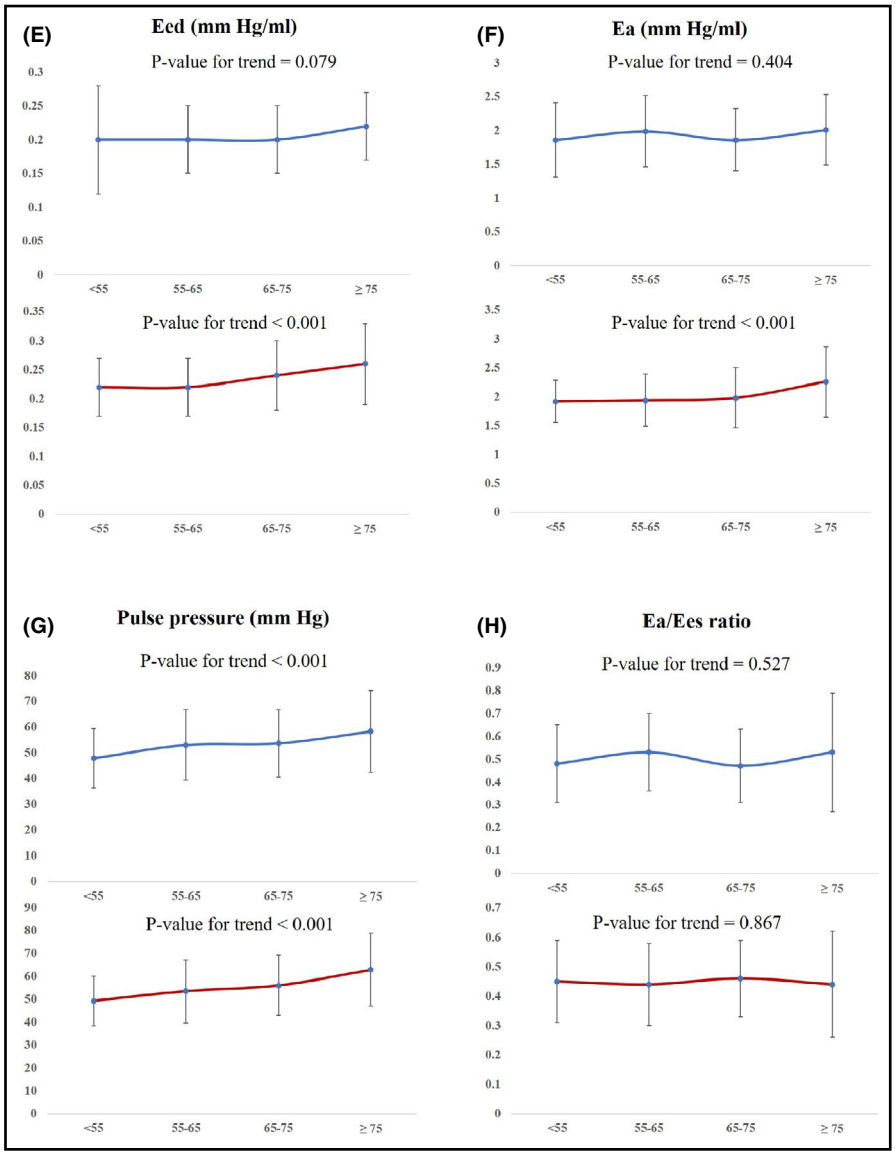

FIGURE 2 (Continued)

4.3 | Association between age with LV structure and systolic function

Among community populations without CVD, findings regarding the association between age with LVM index are inconsistent. Cheng and colleagues reported that increasing age was associated with a reduction in LVM index in both sexes,[8] which was opposite to the findings from the other study.[7] Results from Japanese populations suggested no significant association between age with LVM index in both sexes.[6] Interestingly, in the current study, age was positively associated with LVM index in women only. LVM index has multiple determinants and differences in the determinants such as ethnicity, age, clinical characteristics, and measurements might explain these differences. In individuals without CVD, age was associated with increase in LVEF and decrease in SV index.[8] The other study reported a poor correlation between age with LVEF and S′ velocity.[6] In the current study, only significant association between age with septal S′ velocity was observed, and the association was greater in women than in men. Septal S′ velocity measures longitudinal LV contraction and is a surrogate of clinical LV systolic function. Results of the current study suggest that in hypertensive individuals without CVD, despite with a normal range of LVEF, a greater reduction of septal S′ velocity with age in women further supports that women had a lower cardiac efficiency and worse cardiac performance.

4.4 | Achieving SBP target attenuates the sex differences in age-related alterations in selected cardiac and arterial indices

Novel to this study is our observation that achieving a lower SBP target (<130 mm Hg vs. <140 mm Hg) might be more helpful to attenuate the sex differences in age-related alterations in selected

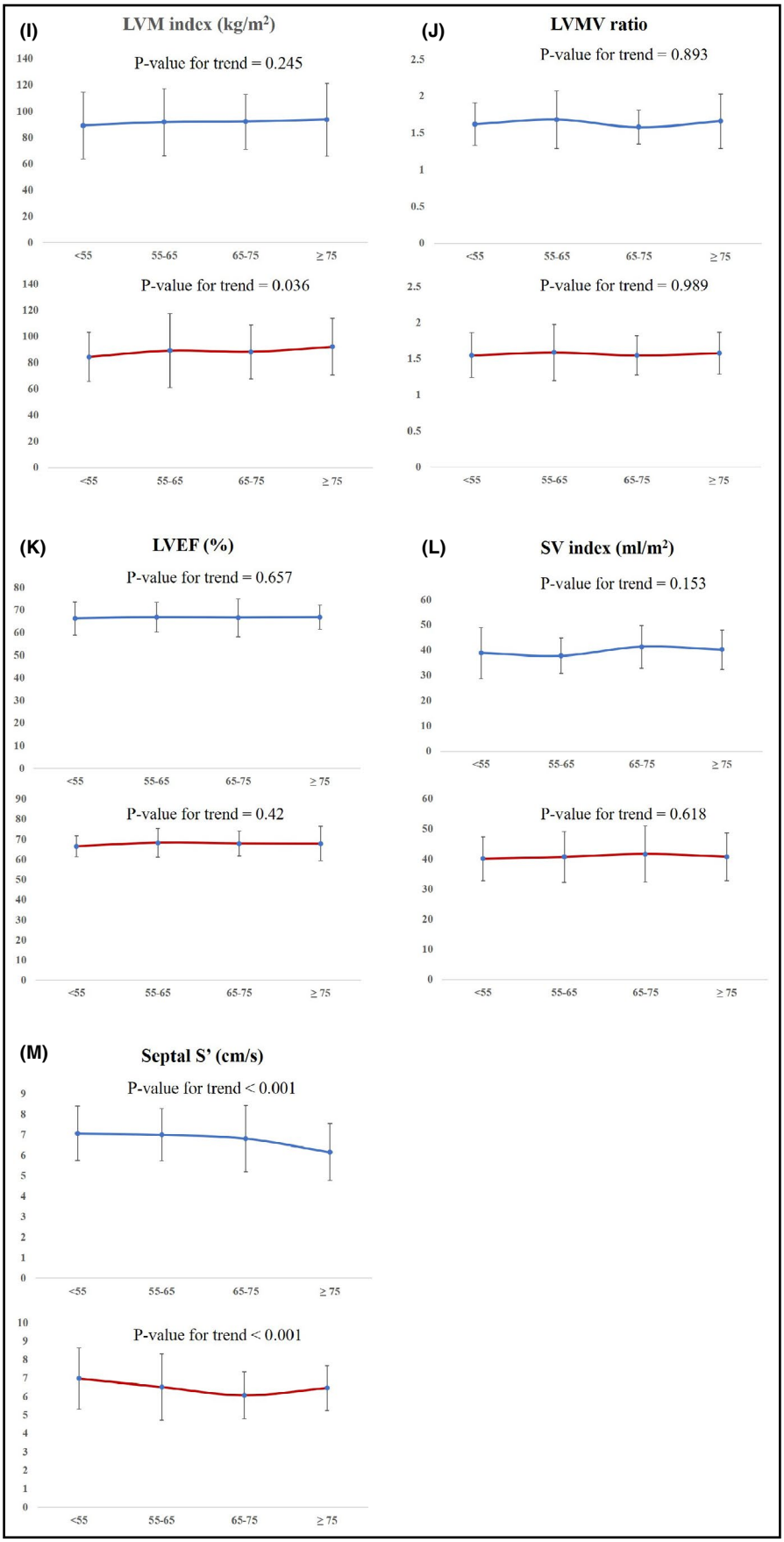

FIGURE 2 (Continued)

TABLE 3 Association between age with indices of cardiac and arterial structure and function

	β-coefficient (95% confidence interval)		
Per 10 years increase in age	**Men**	**Women**	***p*-Interaction**
Left atrial volume index (ml/m^2)	1.53 (−0.34, 3.40)	0.97 (−0.55, 2.48)	.637
Septal e′ velocity (cm/s)	−0.55 (−0.68, −0.41)	−0.74 (−0.85, −0.63)	.029
Septal E/e′ ratio	0.36 (−0.08, 0.80)	1.39 (1.01, 1.77)	<.001
Left ventricular mass index (g/m^2)	1.64 (−0.44, 3.71)	2.04 (0.31, 3.76)	.768
LVMV ratio (g/ml)	0.004 (−0.020, 0.028)	0.004 (−0.024, 0.031)	.988
LVEF (%)	0.06 (−0.53, 0.64)	−0.31 (−0.84, 0.22)	.36
SV index (ml/m^2)	0.60 (−0.37, 1.57)	−0.01 (−0.91, 0.89)	.364
Septal S′ (m/s)	−0.30 (−0.42, −0.19)	−0.47 (−0.58, −0.36)	.038
Ees (mm Hg/ml)	0.06 (−0.10, 0.21)	0.24 (0.11, 0.36)	.071
Eed (mm Hg/ml)	0.006 (0.001, 0.010)	0.016 (0.01, 0.020)	.004
Ea (mm Hg/ml)	0.04 (−0.02, 0.10)	0.13 (0.07, 0.18)	.038
Ea/Ees ratio	0.010 (−0.012, 0.032)	0.001 (−0.014, 0.017)	.501
Pulse pressure (mm Hg)	3.10 (1.98, 4.23)	3.91 (2.87, 4.95)	.303
	Adjusted β-coefficient (95% confidence interval)		
Per 10 years increase in age	**Men**	**Women**	***p*-interaction**
Left atrial volume index (ml/m^2)	3.29 (1.02, 5.57)	2.30 (0.61, 4.00)	.358
Septal e′ velocity (cm/s)	−0.64 (−0.80, −0.49)	−0.74 (−0.87, −0.61)	.115
Septal E/e′ ratio	0.66 (0.14, 1.18)	1.45 (1.00, 1.89)	.001
Left ventricular mass index (g/m^2)	1.61 (−0.91, 4.13)	2.14 (0.13, 4.14)	.805
LVMV ratio (g/ml)	0.004 (−0.023, 0.032)	0.007 (−0.026, 0.040)	.603
LVEF (%)	−0.26 (−0.99, 0.47)	−0.39 (−1.02, 0.24)	.225
SV index (ml/m^2)	0.27 (−0.95, 1.49)	−0.15 (−1.22, 0.92)	.219
Septal S′ (m/s)	−0.27 (−0.41, −0.13)	−0.45 (−0.58, −0.32)	.048
Ees (mm Hg/ml)	−0.02 (−0.22, 0.17)	0.18 (0.04, 0.33)	.064
Eed (mm Hg/ml)	0.006 (0, 0.012)	0.014 (0.009, 0.019)	.002
Ea (mm Hg/ml)	0.03 (−0.04, 0.11)	0.12 (0.06, 0.18)	.005
Ea/Ees ratio	0.020 (−0.010, 0.040)	0.002 (−0.020, 0.020)	.634
Pulse pressure (mm Hg)	3.23 (1.85, 4.62)	4.06 (2.83, 5.30)	.274

Note: Adjusting for smoking, body mass index, waist/hip ratio, diabetes mellitus, eGFR, uric acid and antihypertensive drugs.

Abbreviations: Ea, effective arterial elastance; Eed, left ventricular end-diastolic elastance; Ees, left ventricular end-systolic elastance; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVMV, left ventricular mass-to-volume; SV, stroke volume.

cardiac and arterial indices. Indeed, when the achieved SBP <130 mm Hg, the magnitude of the associations between age with septal S′ velocity, septal E/e′ ratio, Ea, and Eed did not differ by sex. Similar but less consistent findings were also observed when SBP <140 mm Hg. Solomon and colleagues reported that in uncontrolled hypertensive individuals with LV diastolic dysfunction, a lower achieved SBP level was associated with a better achieved LV diastolic relaxation.[16] Li and colleagues[14] recently reported that cardiac and vascular responses to BP elevation were greater in women than in men. Considering the non-modifiable nature of age, achieving a lower SBP target might be more beneficial to improve age-related alterations in cardiac and arterial structure and function in women.

4.5 | Limitations

There are some limitations of the current study, first, the cross-sectional nature of the data, which limits conclusions about causality. Second, although we discussed possible relationship between estrogen and arterial and LV stiffness, the exact menstrual status as well as estrogen concentration of the study participants is unknown. Third, the current study only measured septal e′ velocity and the findings might not be generalized to the e′ velocity obtained from lateral mitral annulus. Fourth, the mean age of participants in the study approached 65 years and the findings might not be generalized to the young populations. Fifth, although statistical differences were observed in several parameters according to age by sex (eg, septal e′ velocity), considering the relatively small sample size, the

TABLE 4 Impacts of the achieved SBP level on age-related changes in selected indices of cardiac and arterial structure and function

Per 10 years increase in age	Adjusted β-coefficient (95% confidence interval)		
SBP <130 mm Hg	**Men (*n* = 110)**	**Women (*n* = 195)**	***p*-Interaction**
Septal S′ (m/s)	−0.58 (−0.82, −0.34)	−0.39 (−0.60, −0.18)	.569
Septal E/e′ ratio	1.01 (0.39, 1.62)	1.27 (0.40, 2.15)	.325
Ea (mm Hg/ml)	−0.02 (−0.13, 0.08)	0.12 (0.06, 0.18)	.488
Eed (mm Hg/ml)	0.006 (−0.003, 0.015)	0.011 (0.001, 0.021)	.286
SBP ≥130 mm Hg	**Men (*n* = 259)**	**Women (*n* = 407)**	***p*-Interaction**
Septal S′ (m/s)	−0.13 (−0.31, 0.05)	−0.45 (−0.62, −0.29)	.014
Septal E/e′ ratio	0.48 (−0.23, 1.18)	1.42 (0.89, 1.94)	.003
Ea (mm Hg/ml)	0.05 (−0.04, 0.14)	0.14 (0.07, 0.22)	.019
Eed (mm Hg/ml)	0.005 (−0.003, 0.012)	0.016 (0.009, 0.022)	.002
SBP <140 mm Hg	**Men (*n* = 220)**	**Women (*n* = 354)**	***p*-Interaction**
Septal S′ (m/s)	−0.30 (−0.48, −0.12)	−0.50 (−0.69, −0.32)	.197
Septal E/e′ ratio	0.38 (−0.36, 1.12)	1.26 (0.67, 1.85)	.026
Ea (mm Hg/ml)	0.01 (−0.06, 0.09)	0.06 (−0.01, 0.13)	.184
Eed (mm Hg/ml)	0.004 (−0.004, 0.012)	0.011 (0.004, 0.018)	.067
SBP ≥140 mm Hg	**Men (*n* = 149)**	**Women (*n* = 248)**	***p*-Interaction**
Septal S′ (m/s)	−0.21 (−0.45, 0.04)	−0.36 (−0.54, −0.17)	.082
Septal E/e′ ratio	1.22 (0.59, 1.85)	1.65 (0.96, 2.34)	.049
Ea (mm Hg/ml)	0.08 (−0.06, 0.21)	0.16 (0.06, 0.26)	.034
Eed (mm Hg/ml)	0.011 (0.003, 0.019)	0.018 (0.009, 0.026)	.016

Note: Adjusting for smoking, body mass index, waist/hip ratio, diabetes mellitus, eGFR, uric acid and antihypertensive drugs.

Abbreviations: Ea, effective arterial elastance; Eed, left ventricular end-diastolic elastance; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

clinical implications of these differences were unclear and deserve further investigation. Last but not the least, no sex difference in the selected parameters among the subgroup of SBP <130 mm Hg might be partly due to the lack of statistical power. However, the current study provided preliminary findings based on which future studies can investigate whether achieving a lower SBP level can mitigate the sex differences in cardiac and vascular remodeling.

5 | CONCLUSION

In conclusion, results of the current study provide additional mechanical evidence to explain the predisposition of elderly women to have HFpEF. The novelty of the current study is that achieving SBP target, especially at a lower level, might be more beneficial to mitigate the age-related alterations in cardiac and arterial structure and function in women.

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CONFLICT OF INTEREST

The authors disclose that they do not have conflict of interest.

AUTHOR CONTRIBUTIONS

Anping Cai wrote the paper; Dan Zhou performed echocardiogram examination; Lin Liu conducted statistical analysis; Yingling Zhou helped conduct the current study; Songtao Tang and Yingqing Feng conceived, designed, and conducted this cohort study.

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