ORIGINAL RESEARCH ARTICLE

Age- and sex-related differences in diastolic function and cardiac dimensions in a hypertensive population

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Abstract

Aims   The prevalence of left ventricular diastolic dysfunction increases with age, particularly in hypertensive women. We aimed to determine the age- and sex-related differences in diastolic function, and its relation to alterations of cardiac dimensions in a hypertensive population.

Methods and results   We enrolled 479 hypertensive patients with a left ventricular ejection fraction (LVEF) $\geq$50% (men/women, 267/212) and their echocardiographic parameters regarding LV performance and vascular function were measured. Left atrial volume index (LAVI) and operant diastolic elastance (EdI: E/e'/stroke volume index), but not LV mass index (LVMI), correlated weakly with age in both sexes. The arterial elastance index (EaI) and EdI did not differ significantly between sexes in any of the three age groups (A, <65 years; B, $\geq$65 years but <75 years; C, age $\geq$75 years). The EdI indexed to EaI, EdI/EaI = E/e'/(0.9 × systolic blood pressure), was significantly more impaired in women than in men only in group C. There were significant differences in LAVI, LVMI, and EdI/EaI between groups B and C only in women.

Conclusions   Impairment of diastolic function relative to arterial elasticity, EdI/EaI, occurred in elderly hypertensive women and was coincident with the alteration of cardiac dimensions. The coincidence with the changes in diastolic function and the alterations of cardiac dimensions occurred in a different time point between the sexes.

Introduction

Heart failure with a preserved ejection fraction (HFpEF) is an important clinical condition, observed mainly in elderly women. Diastolic dysfunction alone is not pathognomonic of HFpEF, which involves multiple cardiovascular abnormalities.[1] In patients with HFpEF, structural or functional alterations contribute to the transition to, and progression of overt heart failure, thus acting as prognostic indicators.[2,3] Patients with HFpEF present a particularly high frequency of concentric left ventricular hypertrophy (LVH), left atrial remodelling, and epicardial volume enlargement. Regression modelling has identified the changes in left heart size, such as greater LVH and atrial dilation, as the parameters that best distinguish HFpEF from hypertensive LVH without heart failure.[4] These parameters may be useful in the identification of patients at increased risk of developing incidental heart failure at a preclinical level. However, the difference in diastolic function relative to vascular function between elderly men and women, and its relation to the alteration of cardiac dimensions in hypertensive patients before the onset of heart failure, remain unclear. Accordingly, we aimed to determine the age- and sex-related differences in diastolic function relative to arterial elasticity, a new marker for the diastolic function assessment, amongst a hypertensive population with a preserved left ventricular ejection fraction (LVEF) and no history of heart failure. Furthermore, we tested the hypothesis that impaired diastolic function is coincident with altered cardiac dimension, and that the coincidence occurs in a different time point between the sexes.

Methods

The study population consisted of hypertensive patients referred for clinical assessment in the echo lab of our hospital. The inclusion criteria for this study were as follows: LVEF ≥50% without a history of heart failure and regional abnormality of LV wall motion; normal sinus rhythm at the time of enrollment; an echocardiogram of adequate quality; accurate baseline data on medical history, medications, and biochemical markers; and measurement of blood pressure and heart rate at the time of cardiac echocardiographic examination. Blood pressure was measured by a sphygmomanometer. Patients using antihypertensive drugs or with a clinical history of hypertension were classified as hypertensive. Those with hemodynamically significant valve disease (more-than-moderate regurgitation or more-than-mild stenosis), history of myocardial infarction, asymmetric hypertrophy of the LV wall (septal/posterior wall thickness ratio ≥1.5), and renal failure [estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2] were excluded. Of 745 consecutive patients examined, 479 patients [267 men, 212 women; mean age, 70 years (range 35–96 years)] were included in the final sample.

The entire investigation conforms with the principles outlined in the *Declaration of Helsinki*. The study protocol was approved by the institutional review board at our hospital.

Echocardiographic study

All echocardiograms were taken by registered diagnostic cardiac sonographers using the same echocardiographic instrument (Aplio XG, Toshiba, Tokyo, Japan) according to a standardized protocol. All parameters were measured in duplicate and averaged. All echocardiographic measurements were interpreted by the attending physician (T. W.).

End-systolic pressure (Pes) was calculated as systolic pressure × 0.90.[5,6] Stroke volume (SV), calculated from the LV outflow tract diameter and pulsed-wave Doppler measurement of the blood flow through the tract,[7] was indexed to body surface area (BSA) (stroke volume index, SVI = SV/BSA). Effective arterial elastance (Ea) was calculated as Pes/SV and was indexed to the BSA to obtain the effective arterial elastance index (EaI).[5] Ea correlates very well with measures of arterial load derived from aortic input impedance data.[5] Systemic vascular resistance index (SVRI) was calculated as mean blood pressure/cardiac index × 80.

Measurement of LVEF was performed by the method reported previously.[8] Fractional shortening (FS, %) was calculated as [(LVEDD − LVESD)/LVEDD], where LVEDD is the LV end-diastolic dimension and LVESD is the end-systolic LV dimension. End-systolic wall stress (σes, g/cm^2) was estimated as (Pes × LVESD × 1.35)/[4 × hes × (1 + hes/LVESD)], where hes is the average of the end-systolic thicknesses of the septal and posterior walls.[9] Instead of end-systolic elastance, the ratio of FS to σes (stress-corrected FS) was used as a load-independent measure of systolic performance.

LV end-diastolic volume (LVEDV) was calculated by the previously reported method[7] and was indexed to the BSA to determine the LVEDV index (LVEDVI). Left atrial volume was measured using the prolate ellipse method and was indexed to the BSA to obtain the left atrial volume index (LAVI). LV mass was measured by the method reported previously[8] and was indexed to the BSA to obtain the LV mass index (LVMI). Relative wall thickness was calculated as (2 × posterior wall thickness)/LVEDD. Pulsed-wave Doppler examination of mitral inflow and Doppler tissue imaging of the mitral annulus were performed in each patient.[10,11] To provide a continuous variable that would reflect diastolic elastance (Ed), E/e′ was examined, where E is the early diastolic mitral inflow velocity and e′ is the early diastolic mitral annular velocity.[12,13] We measured e′ averaged from septal and lateral part of the mitral annulus. Operant Ed was then calculated as E/e′ divided by SV, assuming the absence of significant aortic regurgitation, and was indexed to the BSA to obtain the diastolic elastance index (EdI = E/e′/SVI).

To clarify the age- and sex-related differences in all parameters, our subjects were divided into three age groups (A, age <65 years, n = 133; B, age ≥65 to <75 years, n = 170; C, age ≥75 years, n = 176) in both men and women.

Statistical analysis

Data are reported as mean ± SD. *P* values are two-sided, and *P* < 0.05 was considered statistically significant. Correlations were tested using the Pearson or Spearman coefficient. Between-sex differences in all participants or each age-based group were assessed by unpaired *t*-test, Wilcoxon rank-sum test, or χ^2 test as appropriate. Differences amongst all three age groups in each sex were assessed by one-way analysis of variance or Kruskal–Wallis analysis, and differences between pairs of age groups were assessed by post hoc Bonferroni test. We also performed multivariate regression analysis to identify factors associated with diastolic function indexed to arterial elastance by using significant parameters in univariate analysis. All statistical analyses were performed using StatFlex for Windows Version 6 (Artech Co. Ltd., Osaka, Japan).

Results

Demographics and comorbidities

The baseline characteristics of the study participants are provided in *Table 1*. The haemoglobin level, but not eGFR, was significantly lower in women than in men. The difference in haemoglobin level was also observed for each age group (*Table 1*). The eGFR and haemoglobin levels decreased with

Table 1 Clinical characteristics, laboratory data, comorbidities, and medications in all participants and the three age-based groups

	All			Group A: <65 years			Group B: 65 years ≤ age < 75 years			Group C: >75 years		
	Men (n = 267)	Women (n = 212)	P value	Men (n = 85)	Women (n = 48)	P value	Men (n = 89)	Women (n = 81)	P value	Men (n = 93)	Women (n = 83)	P value
Age, years	69.4 ± 10.1	70.9 ± 10.0	0.099	57.8 ± 6.4	57.1 ± 7.2	0.554	69.6 ± 2.7	69.6 ± 3.0	0.956	79.8 ± 4.1	80.2 ± 4.3	0.472
Body mass index, kg/m^2	23.3 ± 3.5	23.5 ± 3.7	0.435	24.7 ± 2.9	24.8 ± 4.2	0.917	22.7 ± 4.0	23.4 ± 3.5	0.223	22.5 ± 3.0	22.9 ± 3.4	0.387
eGFR, mL/min/1.73 m^2	64.7 ± 19.8	66.1 ± 21.0	0.447	73.6 ± 19.6	81.0 ± 22.9	0.051	64.9 ± 19.8	66.2 ± 16.2	0.627	56.3 ± 16.3	57.3 ± 19.3	0.704
Haemoglobin, g/dL	13.7 ± 1.8	12.6 ± 1.5	<0.001	14.8 ± 1.3	12.7 ± 1.7	<0.001	13.7 ± 1.7	13.0 ± 1.1	0.003	12.8 ± 1.8	12.1 ± 1.5	0.003
Comorbidity, n (%)												
Diabetes mellitus	60 (22)	43 (20)	0.320	20 (24)	13 (27)	0.403	21 (24)	15 (19)	0.267	19 (20)	15 (18)	0.419
Hypercholesterolemia	104 (39)	99 (47)	0.054	39 (46)	20 (42)	0.387	32 (36)	40 (49)	0.053	33 (35)	39 (47)	0.081
Medication, n (%)												
ACEI/ARB	164 (61)	119 (56)	0.141	51 (60)	32 (67)	0.282	52 (58)	42 (52)	0.239	61 (65)	45 (54)	0.083
BB	57 (21)	33 (16)	0.068	21 (25)	9 (19)	0.283	21 (24)	12 (15)	0.105	15 (16)	12 (14)	0.461
CCB	153 (57)	131 (62)	0.184	46 (54)	26 (54)	0.570	49 (55)	50 (62)	0.234	58 (62)	55 (66)	0.351
Diuretics	33 (12)	28 (13)	0.445	8 (9)	9 (19)	0.101	13 (15)	5 (6)	0.062	12 (13)	14 (17)	0.299

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor, blocker; BB, beta blocker; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate.

age in both men ($r = -0.349$, $P < 0.001$, and $r = -0.469$, $P < 0.001$, respectively) and women ($r = -0.418$, $P < 0.001$, and $r = -0.214$, $P = 0.002$, respectively). No significant differences in any hypertensive medications were observed between men and women in any age group.

Age- and sex-related alterations

No differences between sexes in diastolic or systolic blood pressure (SBP) were observed in any age group (*Table 2*). The correlation between age and EaI was not significant in either men ($r = 0.051$, $P = 0.404$) or women ($r = -0.014$, $P = 0.829$). There was no difference in EaI between men and women in any age group (*Table 2*). However, SVRI was significantly lower in women than in men in groups B and C.

There was no correlation between age and LVEF ($r = -0.030$, $P = 0.614$ and $r = 0.074$, $P = 0.280$, respectively) in either men or women. However, the stress-corrected FS (the ratio of FS to σes) was positively but weakly correlated with age in women ($r = 0.187$, $P = 0.006$); there was no correlation in men. Stress-corrected FS was not different between men and women in any age group.

LAVI, but not LVMI and LVEDVI, weakly correlated with age in both men ($r = 0.182$, $P = 0.002$) and women ($r = 0.190$, $P = 0.005$). No differences were observed in relative wall thickness, LVEDVI, or LAVI between men and women, in any age group (*Table 2*, *Figure 1A*). The LVMI was significantly lower in women than in men only in group B (*Figure 1B*). In women there were significant differences between groups B and C, in terms of LAVI (*Figure 1A*, $P = 0.002$) and LVMI (*Figure 1B*, $P = 0.008$), but not LVEDVI. In contrast, in men there were no significant differences amongst the three age groups in terms of LAVI, LVEDVI, or LVMI.

Diastolic function indexed to vascular function

The E/e′ and operant diastolic elastance index (EdI = E/e′/SVI, used to reflect diastolic function) were positively but weakly correlated with age in both men ($r = 0.260$, $P < 0.001$, and $r = 0.230$, $P = 0.001$, respectively) and women ($r = 0.280$, $P < 0.001$, and $r = 0.222$, $P = 0.001$, respectively). No difference was observed in chamber stiffness (E/e′/LVEDDI, data not shown) or EdI (*Figure 1C*) between men and women in any age group, although E/e′ was significantly higher in women than in men in group C only ($P = 0.004$, *Table 2*). The operant diastolic elastance indexed to arterial elastance, EdI/EaI = E/e′/0.9SBP, increased with age in both sexes (men, $r = 0.251$, $P < 0.001$; women, $r = 0.264$, $P < 0.001$), and was significantly higher in women than in men only in group C ($P = 0.025$) (*Figure 1D*). Similar results with regard to EdI/EaI were obtained when we analysed the data in untreated hypertensive patients of group C (data not shown). Similar to the

Table 2 Between-sex differences in vascular and ventricular indexes in the three age-based groups

	Group A: <65 years			Group B: 65 years ≤ age < 75 years			Group C: ≥75 years		
	Men (n = 85)	Women (n = 48)	P value	Men (n = 89)	Women (n = 81)	P value	Men (n = 93)	Women (n = 83)	P value
Heart rate	71 ± 12	72 ± 12	0.729	67 ± 13	72 ± 10	0.006	69 ± 11	71 ± 11	0.239
Systolic blood pressure	135 ± 18	134 ± 15	0.705	136 ± 17	140 ± 18	0.117	134 ± 17	136 ± 16	0.307
Diastolic blood pressure	82 ± 11	80 ± 12	0.411	77 ± 11	78 ± 10	0.465	73 ± 10	72 ± 11	0.505
SVI	38.4 ± 8.0	39.5 ± 9.3	0.484	39.8 ± 8.9	41.4 ± 9.1	0.243	38.5 ± 8.5	41.9 ± 9.8	0.015
SVRI	3.10 ± 0.82	2.95 ± 0.71	0.281	3.11 ± 0.83	2.81 ± 0.74	0.014	2.97 ± 0.76	2.70 ± 0.87	0.030
EaI = Pes/SVI	3.31 ± 0.86	3.21 ± 0.78	0.527	3.23 ± 0.83	3.21 ± 0.89	0.887	3.27 ± 0.77	3.12 ± 0.96	0.249
LVEF, %	66 ± 7	66 ± 5	0.941	65 ± 6	68 ± 5	0.002	66 ± 6	68 ± 5	0.135
FS/sigma ES	4.2 ± 1.4	4.2 ± 1.3	0.833	4.2 ± 1.3	4.3 ± 1.6	0.574	4.5 ± 1.4	4.7 ± 1.9	0.250
RWT	0.42 ± 0.07	0.42 ± 0.09	0.976	0.43 ± 0.07	0.42 ± 0.07	0.511	0.45 ± 0.07	0.45 ± 0.09	0.895
LVEDVI	58 ± 11	61 ± 19	0.351	62 ± 13	61 ± 12	0.672	59 ± 12	62 ± 14	0.102
E/e'	10.0 ± 2.9	10.5 ± 2.9	0.369	10.8 ± 3.3	10.5 ± 3.0	0.473	11.7 ± 3.2	13.2 ± 4.4	0.009

EaI, arterial elastance index; FS, fractional shortening; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; Pes, end-systolic pressure; RWT, relative wall thickness; Sigma ES, end-systolic wall stress; SVI, stroke volume index; SVRI, systemic vascular resistance index.

differences observed in cardiac dimensions such as LAVI and LVMI (*Figure 1A, 1B*), in women, this diastolic index differed significantly between groups B and C (*Figure 1D*). The age-linked change in EdI/EaI occurred over a different time point between sexes, similar to the alteration of cardiac dimension, LAVI or LVMI, in each sex. There was no significant difference in the slopes of regression lines for the relationship with age and LAVI, LVMI, or EdI/EaI between sexes. However, in patients aged over 65 years (groups B and C), the slopes were different in the relationship with age and LVMI ($P = 0.039$) or EdI/EaI ($P = 0.090$) between the sexes (*Figures 2A,B*).

When multivariate regression analysis was performed by using significant parameters in univariate analysis, EdI/EaI was independently associated with age ($P = 0.002$) and LAVI ($P < 0.001$) in men, but with age ($P = 0.036$), eGFR ($P = 0.035$), heart rate ($P = 0.003$), and LAVI ($P < 0.001$) in women (*Table 3*). In both men and women, the correlation between EdI/EaI and LAVI was moderate ($r = 0.336$, $P < 0.001$ and $r = 0.398$, $P < 0.001$, respectively) and that between EdI/EaI and LVMI was weak ($r = 0.162$, $P = 0.007$ and $r = 0.199$, $P = 0.003$, respectively).

Discussion

Diastolic function indexed to arterial elastance

It has been reported that the Ea increases with age[14] and is higher in women than in men.[14,15] In the present study, however, no differences were observed in the Ea when indexed to BSA (EaI) between sexes in any age group.

As an index for diastolic function, the diagnostic value of deceleration time or E/A ratio, is limited. The correlation of E/e' with pulmonary capillary wedge pressure is well established in patients with systolic dysfunction,[12,13] but is very sensitive to changes in LV load. There is insufficient evidence to support that E/e' can reliably estimate LV diastolic dysfunction in preserved EF.[16] It is also well known that pulmonary capillary wedge pressure and diastolic function are not same. A recent longitudinal study showed that LV diastolic stiffness increases over time in humans, particularly in women.[17] A previous report using E/e'/SV to calculate Ed found that Ed increased with age and that it was higher in women than in men,[18] although the study did not index Ed to BSA. In agreement with that study, the operant Ed indexed to BSA (EdI = E/e'/SVI) increased with age in both men and women in the present study. However, there was no difference in the EdI between men and women in any age group, indicating that the EdI may not be a suitable index for differentiation of diastolic function between sexes.

Given that EdI may increase because of vascular changes, we examined the relationships amongst diastolic function,

Figure 1 Age- and sex-related differences in cardiac dimensions (left atrial volume index, LAVI, 1A; left ventricular mass index, LVMI, 1B) and diastolic function [EdI = E/e'/stroke volume index (E/e'/SVI) 1C; EdI/EaI = E/e'/(SVI*EaI), 1D]. Data are mean ± SD. Between-sex differences in each age-based group were assessed by unpaired *t*-test or Wilcoxon rank-sum test. Differences between pairs of age groups were assessed by post hoc Bonferroni test following the assessment of differences amongst all three age groups in each sex by one-way analysis of variance or Kruskal–Wallis analysis.
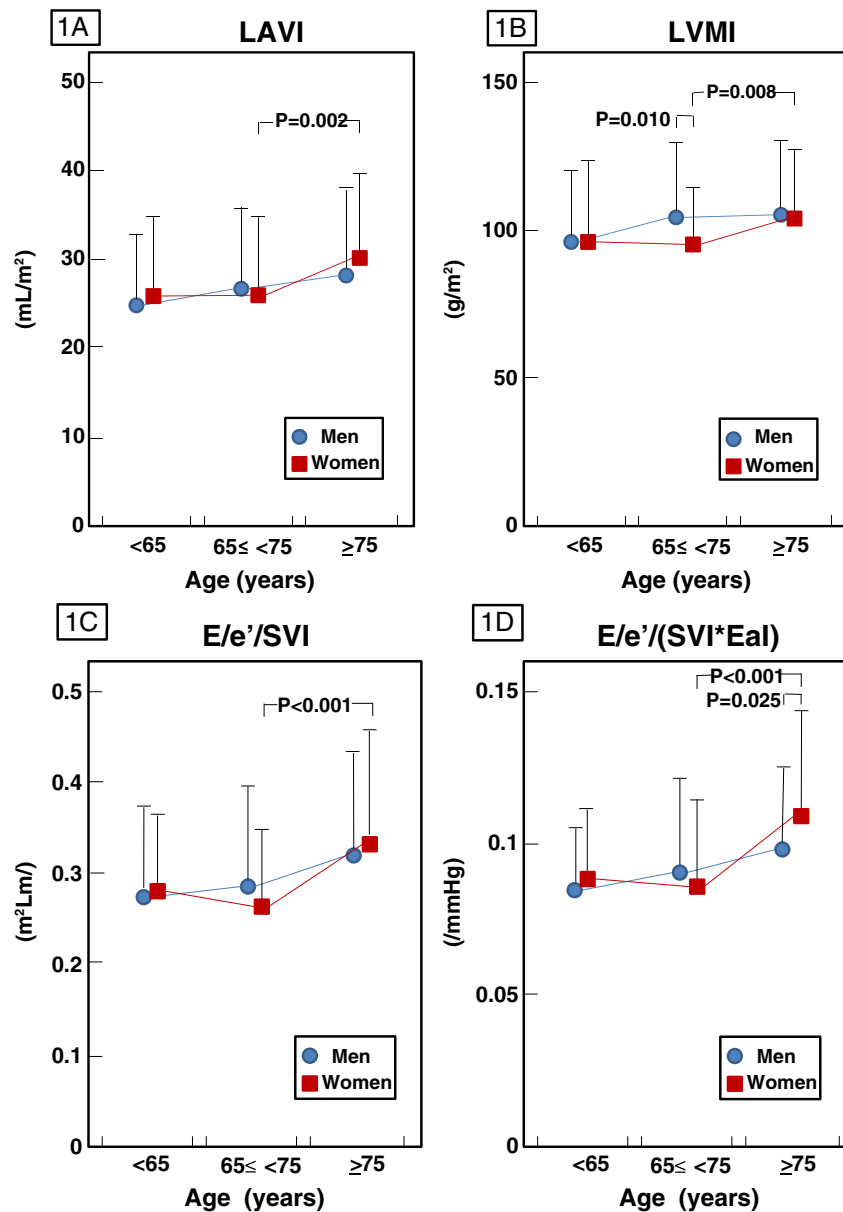
age, sex, and vascular function. Diastolic elastance indexed to arterial elastance, calculated as EdI/EaI = E/e'/0.9SBP, may be a suitable index to determine between-sex differences with alterations in diastolic function with age. Furthermore, it is important to note that impaired diastolic function independent of arterial elasticity occurred over a different time point in men and women; only in women, this diastolic index differed significantly between groups B and C. In patients aged over 65 years (groups B and C), the slopes were insignificantly different in the relationship with age and EdI/EaI between

sexes ($P = 0.090$). The reason for the insignificance may be because of small number of patients and/or a relatively larger standard deviation in the slopes.

Relationship between diastolic function and cardiac dimensions

The index of cardiac dimension may help identify preclinical patients at increased risk of developing incidental heart failure.[4] It

Figure 2 Correlation between age and left ventricular mass index (LVMI, 2A, men, $y = 96.0 + 0.113x$, $r = 0.027$, $P = 0.710$; women, $y = 27.1 + 0.945x$, $r = 0.276$, $P < 0.001$) or EdI/EaI = E/e'/(SVI*EaI) (2B, men, $y = 0.0322 + 0.00082x$, $r = 0.173$, $P = 0.019$; women, $y = -0.0322 + 0.00172x$, $r = 0.322$, $P < 0.001$) in men (blue) and women (red) of patients aged over 65 years. The slopes of the regression lines were different between sexes in both correlations ($P = 0.039$ and $P = 0.090$, respectively).
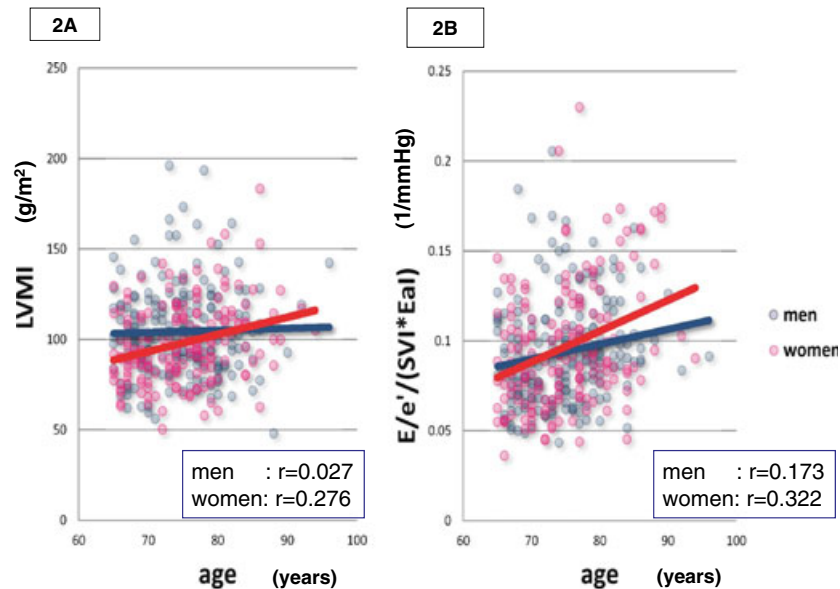

Table 3 Regression analysis for diastolic elastance indexed to arterial elastance, EdI/EaI, in men and women

	Men			Women		
		P value			P value	
	r value	Univariate	Multivariate	r value	Univariate	Multivariate
Age	0.251	<0.001	0.002	0.264	<0.001	0.036
Body mass index	−0.076	0.212	—	0.038	0.580	—
eGFR	−0.159	0.008	0.740	−0.286	<0.001	0.035
Haemoglobin	−0.118	0.054	—	−0.212	0.001	0.935
Diabetes mellitus	−0.018	0.768	—	0.042	0.536	—
Hypercholesterolemia	0.028	0.647	—	0.140	0.040	0.133
Heart rate	−0.095	0.117	—	−0.283	<0.001	0.003
LVEF	−0.123	0.043	0.083	0.063	0.357	—
RWT	0.102	0.096	—	0.124	0.070	—
LAVI	0.336	<0.001	<0.001	0.398	<0.001	<0.001
LVEDVI	−0.047	0.438	—	0.100	0.145	—
LVMI	0.162	0.007	0.864	0.199	0.003	0.426

eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RWT, relative wall thickness.

has previously been reported that LV diastolic dysfunction does not negatively affect clinical parameters when it is not associated with changes in the index of left cardiac structural remodelling, based on LVH magnitude and atrial dilation.[19] Increased LA volume is an independent predictor of heart failure and worsened mortality in previously asymptomatic elderly subjects with a preserved ejection fraction.[20]

In the present study, LAVI and LVMI were significantly higher amongst the oldest age group than amongst younger age groups in women, but not in men. Importantly, the changes in the two indexes, EdI/EaI and LAVI or LVMI, coincidently occurred in a different time point between sexes. In women, alteration in cardiac dimensions leading to hemodynamic changes occurs very late in life; in men, on the other hand, such alteration gradually occurs, resulting in the gradual impairment of diastolic function. EdI/EaI was independently associated with heart rate and renal function in addition to age and LAVI in women, but not in men, by multivariate analysis. The reduction of heart rate and/or renal function may be a possible mechanism for the exacerbation

of diastolic function, leading to the occurrence of incidental heart failure in elderly women. Clarification of renal function- and heart rate-related roles for the impaired diastolic function may imply a novel clue to identify the mechanism by which elderly hypertensive women are prone to exhibit HFpEF. It is plausible that the change in diastolic function independent of arterial elasticity is because of cardiac response for the alteration of cardiac structure, and that the imbalance between these changes in the elderly women may contribute to the occurrence of HFpEF. A large-scale prospective study is needed to clarify the differences in the manner in which dynamic and static parameters of vascular and ventricular function including EdI/EaI and heart rate change with age, and the differences in the course of age-linked alterations of cardiac dimensions and renal function between sexes.

Study limitations

Our statistical analysis may have been biassed because of the modest sample size; a larger data set might reveal differences where we were unable to find any. Our study is also limited by its referral nature as a retrospective database study. Treated and hypertensives receiving no treatment may be different in the evolution of cardiac and vascular function and anatomy with age. We did not evaluate the duration of hypertension or the extent of medication usage, all of which may affect left cardiac performance and diastolic dysfunction, and we did not evaluate right cardiac performance or the effects of exercise or stress. In addition, we did not obtain data on clinical symptoms. Participation bias may also have affected the observed results. Patients with coronary artery disease were not excluded unless they had a history of myocardial infarction, and our participants were not representative of patients with HFpEF because they had not experienced heart failure. These issues limited the applicability of our results with regard to assessing the contribution of altered vascular and ventricular function and changes in cardiac dimensions to the pathogenesis of HFpEF in very elderly women, although increases in vascular and ventricular stiffness may predispose to heart failure.

Conclusions

In an elderly hypertensive population, LV diastolic function indexed to the arterial elastance, EdI/EaI = E/e'/0.9SBP, was impaired in women compared with that in men, whereas there were no differences in systolic function and relative wall thickness. The age-linked change in LV diastolic function independent of arterial elasticity was coincident with the alteration of cardiac dimensions in each sex and the coincidence occurred over a different time point between men and women.

Conflict of interest

None declared.

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