The relationship between ambulatory arterial stiffness index and left ventricular diastolic dysfunction in HFpEF: a prospective observational study

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Abstract

Background The relationship between ambulatory arterial stiffness index (AASI) and left ventricular diastolic dysfunction in patients with heart failure with preserved ejection fraction (HFpEF) is unknown. We aimed to investigate whether increased AASI was related to left ventricular diastolic dysfunction in patients with HFpEF.

Methods We prospective enrolled consecutive patients with HFpEF in Chongqing, China. Twenty-four-hour ambulatory blood pressure monitoring (24h-ABPM) and echocardiography were performed in each patient. AASI was obtained through individual 24h-ABPM. The relationship between AASI and left ventricular diastolic function was analyzed.

Results A total of 91 patients with HFpEF were included. The mean age was 68.7 ± 13.9 years and 54 (59%) were women. The patients were divided into two groups according to the upper normal border of AASI (0.55). AASI > 0.55 group were more likely to be older, to have higher mean systolic blood pressure and worsen left ventricular diastolic function than AASI group ≤ 0.55 . AASI was closely positive related to the diastolic function parameters, including mean E/e' ($r = 0.290$, $P = 0.005$), septal E/e' ($r = 0.237$, $P = 0.024$), lateral E/e' ($r = 0.295$, $P = 0.004$) and E ($r = 0.262$, $P = 0.012$). After adjusting for conventional risk factors, AASI was still an independent risk factors of left ventricular diastolic dysfunction in patients with HFpEF (odds ratio: 3.261, 95%CI: 1.099-9.673, $P=0.033$).

Conclusion Increased AASI was independent associated with left ventricular diastolic dysfunction in patients with HFpEF.

Introduction

Ambulatory arterial stiffness index (AASI) is defined as 1 minus the regression slope of diastolic on systolic blood pressure (BP) values obtained from the 24-hour ambulatory blood pressure monitoring (ABPM) recordings^{1,2}. It has been proposed as a novel indicator of arterial stiffness and has advantages by the low cost and noninvasive. Substantial reports revealed that increased arterial stiffness was associated with preclinical target organ damage and increased risk of cardiovascular mortality and morbidity in hypertension^{3,4,5}.

Heart failure with preserved ejection fraction (HFpEF) is characterized by diastolic dysfunction and cardiac remodeling (fibrosis, inflammation, and hypertrophy), which has become a major cause of hospitalization for the elders^{6,7,8}. Hypertension, diabetes and obesity were risk factors for HFpEF and were associated with arterial stiffness raise^{9,10}. It was reported that microvascular dysfunction and chronic low-grade inflammation have been proposed to participate in HFpEF development¹¹. Other parameters reflecting arterial stiffness such as cardio-ankle vascular index (CAVI), has been reported associated with the hospitalization of HFpEF patients¹², but the role of AASI in HFpEF is still unknown.

The objective of the present study was to investigate the relationship between ambulatory arterial stiffness index (AASI) and left ventricular diastolic dysfunction in patients with HFpEF.

Methods

Study design and participants

From November 2020 to February 2021, we conducted a prospective observational study registry with clinicaltrials.gov identifier NCT05059769. This study finally enrolled 91 patients with HFpEF in the First Affiliated Hospital of Chongqing Medical University (Fig. 1). Inclusion criteria included age > 18 years and conform to HFpEF diagnostic criteria (Left ventricular ejection fraction $\geq 50\%$, typical symptoms and signs of heart failure, HFA-PEFF score ≥ 5)¹³, whereas the exclusion criteria were secondary hypertension, severe valvular heart disease and persistent atrial fibrillation. Informed consent was obtained from the patients, and the study was approved by the institutional ethics board of the First Affiliated Hospital of Chongqing Medical University (approval NO.2020-606). Baseline clinical and demographic information was obtained from all patients. Body mass index (BMI) was calculated as weight (kg)/height (m²). 24-hour ABPM and echocardiography were carried out in all patients during hospitalization.

24-hour ABPM

24-hour ABPM was performed using the Mobil-O-Graph NG (Z02505), a non-invasive ambulatory BP monitoring instrument. BP readings were obtained at 15-min intervals during the day and at 30-min intervals during the night. Of the total readings, $\geq 80\%$ was considered valid. Furthermore, for the records valuable, at least 14 measurements during the daytime period or at least 7 measurements during the night or rest period were required¹⁴.

Ambulatory arterial stiffness index (AASI)

AASI is a more physiologically significant marker of arterial stiffness than a simple snapshot of pulse wave velocity or pulse pressure, which is derived from the regression slope of diastolic BP and systolic BP recorded in unedited 24 hours. Based on the 24-hour ABPM records, we calculated the regression slopes of individual patients' diastolic BP and systolic BP. The stiffer the arterial tree, the closer the regression slope and AASI are to 0 and 1, respectively^{1,2}. AASI was obtained as follows:

AASI = 1-slope (diastolic BP/systolic BP)

Echocardiography

The cardiac diastolic function of HFpEF was assessed by transthoracic echocardiography (Vivid E95, AU11403, GE Vingmed Ultrasound AS). Using the parasternal short-axis two-dimensional view to image the heart and record an M-mode echocardiogram at the level of the papillary muscles. Cardiac function parameters, such as left ventricular ejection fraction (LVEF), diastolic interventricular septum thickness (IVSd), diastolic left ventricular posterior wall thickness (LVPWd), left atrium volume index (LAVI), left ventricle mass index (LVMI), the peak velocity of the filling peak in the early diastolic period (E), the peak velocity of the filling peak in the late diastolic period (A), the E/A ratio (E/A), the ratio of the early diastolic transmitral filling velocity to the early diastolic septal tissue velocity (Septal E/e') and the ratio of early diastolic transmitral flow velocity to mitral annular velocity at the lateral wall (Lateral E/e') were measured by the same investigator. At the same time, tricuspid annular plane systolic excursion (TAPSE) and plane contraction offset velocity of tricuspid annulus (TAPSE-S) reflecting right ventricular function were measured as well¹⁵.

Data collection

Data on epidemiological information, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory, and radiological characteristics were obtained from electronic medical records. All the data were collected by two investigators independently and double checked by other investigators.

Definition

Not all patients had severe diastolic dysfunction, so in the logistic regression, we set mean E/e' = 10 rather than 14 as the critical value. AASI = 0.52 was the cut-off point of receiver operating characteristic (ROC) curves (Fig 3). It was close to the upper normal border of AASI = 0.55^{1,2}, so we pre-specified that the patients would be divided into two groups according to the upper normal border: AASI group ≤ 0.55 group and AASI > 0.55 group.

Statistical analysis

Categorical variables were described as frequency rates and percentages, and continuous measurements as mean (standard deviation: [SD]) if they are normally distributed or median (interquartile range: [IQR]) if they are not. χ^2 test was used to test for differences in categorical variables among the two groups. T test or Mann-Whitney test was used to compare continuous variables according to the normal distribution or not. Spearman correlation analysis was used for assessing the correlates of left ventricular diastolic function. logistic regression analysis was used to test independent factors of left ventricular diastolic dysfunction. To explore whether AASI provides additional value in predicting impaired left ventricular diastolic function in patients with HFpEF, we performed ROC curves and tested for equality of the areas

under the curves (AUC). All P values were two-tailed, and significance was set at $P < 0.05$. Statistical analyses were performed using SPSS software (version 22.0).

Results

Baseline characteristics

The study initially enrolled 129 consecutive patients with HFpEF. Patients who had secondary hypertension ($n = 8$), severe valvular heart disease ($n = 10$) and persistent atrial fibrillation ($n = 20$) were excluded (Fig. 1). Finally, a total of 91 HFpEF patients were included. The patients were divided into two groups according to the upper normal border of AASI (0.55). Table 1 showed the overall baseline clinical and demographic data in two groups. The mean age of the patients was 68.73 ± 13.93 years. More than half had comorbidities including hypertension (60, 66%), diabetes (30, 33%) and coronary artery disease (41, 45%). Age, ave-systolic BP, LAVI, E, septal E/e', lateral E/e' and mean E/e' in the AASI > 0.55 group were significantly higher than the AASI group ≤ 0.55 . There was no significant difference in the other clinical parameters between the two groups, including comorbidities, height, weight, BMI and LVEF. We also focused on the right ventricular systolic function, in which the TAPSE and TAPSE-S did not differ between the two groups.

Spearman correlations between clinical characteristics and left ventricular diastolic function

The relationships for AASI and other clinical parameters between left ventricular diastolic function, including E, septal E/e', lateral E/e' and mean E/e' were conducted by spearman correlations analysis. The results were shown in Table 2. We found that AASI was closely positive related to the diastolic function parameters, including mean E/e' ($r = 0.290$, $P = 0.005$; Fig.2a), septal E/e' ($r = 0.237$, $P = 0.024$; Fig.2b), lateral E/e' ($r = 0.295$, $P = 0.004$; Fig.2c) and E ($r = 0.262$, $P = 0.012$; Fig.2d). The proportion of patients with E/e' > 10 was 35 (76%) in the AASI > 0.55 group, which was higher than that in the AASI ≤ 0.55 group (25, 53%, $P = 0.023$). Age and ave-systolic BP were also related to mean E/e', septal E/e' and lateral E/e'. BMI was related to lateral E/e'. We studied the relationships for AASI between right ventricular systolic function, but spearman correlation analysis indicated that AASI was related to TAPSE-S rather than TAPSE (Supplemental table 1).

Logistic regression demonstrating the risk factors of left ventricular diastolic dysfunction

Univariate regression analysis showed that AASI was associated with increased risk of left ventricular diastolic dysfunction [OR: 2.784, 95% Confidence interval (CI) 1.137-6.817, $P = 0.025$] (Data not show). To identify factors that would be independently associated with left ventricular diastolic dysfunction, we

adjusted for conventional risk factors including age, gender, hypertension, diabetes, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), smoking, drinking, average systolic BP and BMI. We found that AASI was still an independent risk factor of left ventricular diastolic dysfunction in patients with HFpEF [OR: 3.261, 95% Confidence interval (CI) 1.099-9.673, $P = 0.033$] (Table 3).

ROC curve for AASI to predict left ventricular diastolic dysfunction

To explore whether AASI provides additional value in predicting impaired left ventricular diastolic function in patients with HFpEF, we conducted ROC curve analysis and found that the AASI had a favorable predictive value for mean $E/e' > 10$ in patients with HFpEF (AUC = 0.6491, $P = 0.010$, Fig. 3), with sensitivity and specificity values of 67.8% and 65.6%, respectively. According to ROC curve analysis, baseline AASI was identified at 0.5248 as the optimal cut-off point to predict left ventricular diastolic dysfunction (Fig. 3).

Discussion

The major findings of this study were the following: (i) HFpEF with high AASI were more likely to be older, to have higher mean systolic blood pressure and worsen left ventricular diastolic function; (ii) AASI was positively correlated with left ventricular diastolic dysfunction parameters; (iii) AASI might be an independent predictor of left ventricular diastolic dysfunction in patients with HFpEF.

HFpEF is a group of syndromes with left ventricular diastolic dysfunction as the main clinical manifestation, often accompanied by risk factors such as advanced age, hypertension and diabetes^{16,17}, which was consistent with the characteristics of our cohort study. AASI was determined from the records of ABPM has been proposed as a surrogate indicator of arterial stiffness^{1,2}. Several studies reported that AASI may be related to diastolic function and prognosis in hypertension and diabetes^{3,4,18}. Nevertheless, the role of AASI in patients with HFpEF has not been reported.

In the present study, we found that HFpEF with high AASI were more likely to be older, to have higher systolic blood pressure. This can be explained by the reason that the elderly and high sBP were major factors contributed to arterial stiffness^{19,20}. The septal E/e' , lateral E/e' and mean E/e' are representative parameters that reflect ventricular diastolic dysfunction²¹. As we expected, above mentioned parameters were significantly higher in the AASI > 0.55 group than the AASI ≤ 0.55 group. Spearman correlation also indicated that AASI was closely positive related to the parameters of diastolic dysfunction. Although E/A value is often regarded as a parameter of diastolic dysfunction, we did not observe the correlation between AASI and E/A in HFpEF. The possible reason was that E/A may have similar values in different stages of diastolic dysfunction²².

Univariate logistic regression analysis found that AASI was associated with increased risk of left ventricular diastolic dysfunction. Previous studies reported that conventional risk factors such as age, hypertension, diabetes, BMI and so on were closely positive related to cardiac dysfunction^{23,24,25}. In our study, spearman correlation analysis confirmed that the age and ave-sBP were related to E/e'. These confounding factors may affect the predictive value of AASI in diastolic dysfunction. However, after adjusting for above mentioned risk factors, an independent correlation between AASI and E/e' was still observed in HFpEF. Additionally, we also focused on the right ventricular systolic function, in which the TAPSE and TAPSE-S did not differ between the two groups, indicating that AASI may be a risk factor for left ventricular diastolic dysfunction rather than right ventricular in patients with HFpEF.

Our data showed that the incidence rate of diastolic dysfunction was marked higher in AASI > 0.55 group than AASI ≤ 0.55 group. ROC curve analysis indicated that the AASI had a favorable predictive value for diastolic dysfunction in patients with HFpEF (sensitivity 67.8% and specificity 65.6%). AASI is one of the major indicators of arterial stiffness. Our finding supported the view that arterial stiffness may serve as risk factors for the development of HFpEF^{26,27}. Severe diastolic dysfunction was associated with an increased risk of major adverse cardiovascular event²⁸. Therefore, AASI might be a predictor of adverse events in patients with HFpEF, which needs to be confirmed in the future.

The present study has several limitations that should be considered. First, because this is an observational study, we cannot determine the causality of the results of the study. Second, the sample of this study was small and our findings still need to be further confirmed. Third, because of the small sample, whether AASI was associated with major cardiovascular adverse events in HFpEF could not be determined. Fourth, although we adjusted several risk factors, the effect of potentially unrecognized confounders on the predictive value of AASI in diastolic dysfunction cannot be entirely rule out.

Conclusion

Increased AASI might be independent associated with left ventricular diastolic dysfunction in patients with HFpEF.

Abbreviations

AASI: Ambulatory arterial stiffness index; Ave-sBP: Averaged systolic blood pressure; Ave-dBP: Averaged diastolic blood pressure; BMI: Body mass index; CAD: Coronary artery disease; CAVI: Cardio-ankle vascular index; COPD: Chronic obstructive pulmonary disease; E: The peak velocity of the filling peak in the early diastolic period; E/A: The E/A ratio; HFpEF: Heart failure with preserved ejection fraction; GM: General measurement; IVSd: Ventricular septal end diastolic thickness; LAVI: Left atrium volume index; LVEF: Left ventricular ejection fraction; LVMI: Left ventricle mass index; LVPWd: Left ventricular posterior wall end diastolic thickness; Lateral E/e': The ratio of early diastolic transmitral flow velocity to mitral annular velocity at the lateral wall; Septal E/e': The ratio of the early diastolic transmitral filling velocity to

the early diastolic septal tissue velocity; TAPSE: Tricuspid annular plane systolic excursion; TAPSE-S: Tricuspid annular plane systolic excursion velocity.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional ethics board of the First Affiliated Hospital of Chongqing Medical University (approval NO.2020-606) and informed consent was obtained from the patients.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZQL, XCC, DYZ: study design. DYZ, GLC: financial support. HWZ, WWH, ZQL, LNY: data acquisition. HWZ, YW, JL: data analysis. DJ: technical support. All authors contributed to writing, revising and approved the manuscript.

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Tables

Table 1

Baseline clinical characteristics of included patients with HFpEF.

	All	AASI≤0.55	AASI>0.55	<i>P</i>
Characteristics	(N=91)	(N=45)	(N=46)	
Age(years)	68.73±13.93	63.78±14.64	73.57±11.41	<0.001
Female	54(59%)	26(58%)	28(61%)	0.764
History				
Smoking	14(15%)	5(11%)	9(20%)	0.264
Drinking	23(25%)	11(24%)	12(26%)	0.857
Hypertension	60(66%)	26(58%)	34(74%)	0.104
CAD	41(45%)	18(40%)	23(50%)	0.338
Diabetes	30(33%)	12(27%)	18(39%)	0.206
COPD	10(11%)	6(13%)	4(9%)	0.479
GM				
Height(m)	1.59±0.08	1.59±0.08	1.59±0.08	0.905
Weight(kg)	59.73±9.88	59.64±10.29	59.82±9.58	0.931
BMI	23.60±3.35	23.62±3.76	23.57±2.92	0.941
Ave-sBP(mmHg)	121.20±17.04	116.29±15.10	126.00±17.60	0.006
Ave-dBP(mmHg)	68.77±8.24	69.40±7.10	68.15±9.26	0.473
AASI	0.54±0.19	0.39±0.14	0.69±0.10	<0.001
Echo data				
IVSd(mm)	11.08±1.87	10.93±1.77	11.22±1.98	0.468
LVPWd(mm)	10.55±1.44	10.52±1.50	10.58±1.39	0.858
LAVI(ml/m ²)	35.32±13.73	32.21±12.51	38.15±14.30	0.047
LVMI(g/m ²)	118.62±37.68	114.86±34.03	122.20±40.92	0.364
LVEF(%)	62.29±5.453	62.84±5.94	61.74±4.94	0.337
E	69.62±23.55	64.02±20.05	75.10±25.58	0.024
E/A	0.82±0.36	0.83±0.36	0.82±0.36	0.865
Mean E/e'	12.68±4.73	11.34±4.22	13.99±4.88	0.007
Septal E/e'	14.63±5.90	13.29±5.89	15.95±5.67	0.031
Lateral E/e'	10.73±4.25	9.39±3.26	12.04±4.72	0.003

TAPSE	19.17±3.91	18.73±4.15	19.59±3.66	0.302
TAPSE-S	11.73±2.70	11.62±3.10	11.84±2.29	0.704
AASI: Ambulatory arterial stiffness index, Ave-sBP: Averaged systolic blood pressure, Ave-dBP: Averaged diastolic blood pressure, BMI: Body mass index, CAD: Coronary artery disease, COPD: chronic obstructive pulmonary disease, E: the peak velocity of the filling peak in the early diastolic period, E/A: the E/A ratio, GM: General measurement, IVSd: Ventricular septal end diastolic thickness, LAVI: left atrium volume index, LVEF: left ventricular ejection fraction, LVMI: left ventricle mass index, LVPWd: Left ventricular posterior wall end diastolic thickness, Lateral E/e': the ratio of early diastolic transmitral flow velocity to mitral annular velocity at the lateral wall, Septal E/e': the ratio of the early diastolic transmitral filling velocity to the early diastolic septal tissue velocity, TAPSE: tricuspid annular plane systolic excursion, TAPSE-S: tricuspid annular plane systolic excursion velocity.				

Table 2

Spearman correlations between clinical characteristics and left ventricular diastolic function

	Mean E/e'		Septal E/e'		Lateral E/e'		E	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	0.285	0.006	0.270	0.010	0.274	0.009	0.192	0.068
Height	-0.108	0.306	-0.111	0.296	-0.123	0.245	-0.094	0.252
Weight	0.042	0.690	-0.024	0.823	0.144	0.174	-0.085	0.424
BMI	0.133	0.208	0.055	0.605	0.259	0.013	0.010	0.924
Ave-sBP	0.316	0.002	0.280	0.007	0.330	0.001	0.131	0.214
Ave-dBP	0.036	0.734	-0.014	0.895	0.109	0.303	-0.096	0.366
AASI	0.290	0.005	0.237	0.024	0.295	0.004	0.262	0.012
AASI: Ambulatory arterial stiffness index, Ave-sBP: Averaged systolic blood pressure, Ave-dBP: Averaged diastolic blood pressure, BMI: Body mass index.								

Table 3

Multivariate logistic regression demonstrating the risk factors of diastolic dysfunction.

Risk factors	Mean E/e'>10		
	OR	95%CI	<i>P</i>
AASI>0.55	3.261	1.099-9.673	0.033
Age>65	1.046	0.292-3.745	0.945
Female	1.429	0.355-5.746	0.615
Hypertension	1.137	0.292-4.427	0.853
Diabetes	1.278	0.413-3.951	0.671
CAD	1.807	0.595-5.490	0.296
COPD	4.905	0.686-35.084	0.113
Smoking	0.969	0.207-4.542	0.968
Drinking	0.316	0.075-1.336	0.117
Ave-sBP >135	1.552	0.348-6.931	0.565
BMI>25	2.018	0.670-6.077	0.212
AASI: Ambulatory arterial stiffness index, Ave-sBP: Averaged systolic blood pressure, BMI: Body mass index, CAD: Coronary atherosclerotic heart disease, COPD: chronic obstructive pulmonary disease.			

Figures

Figure 1

Flow diagram for the study population.

Figure 2

Correlation of the AASI with left ventricular diastolic function.

Figure 3

ROC curves of AASI for left ventricular diastolic dysfunction.

Supplementary Files

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