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ORIGINAL RESEARCH

Association Between Visceral Fat, Blood Pressure and Arterial Stiffness in Patients with HFpEF: A Mediation Analysis

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Purpose: To investigate the association of visceral fat with arterial stiffness of heart failure patients with preserved ejection fraction (HFpEF) and to evaluate the extent to which this association is mediated by blood pressure (BP).

Patients and Methods: This cross-sectional descriptive study (clinicaltrials.gov identifier: NCT04535726) recruited 94 patients with HFpEF totally from October to December 2020. The obesity-related measurements included visceral fat area (VFA), body mass index (BMI), waist circumference (WC), hip circumference (HC), waist–hip ratio (WC/HC), abdominal circumference (AC), body fat mass and fat percentage. Brachial-ankle pulse wave velocity (baPWV) was used to estimate the degree of arterial stiffness. Mediation analysis was performed to reveal whether the effect of visceral fat area on arterial stiffness can be mediated by BP in patients with HFpEF and the extent to which this association was mediated by BP.

Results: About 93.6% of HFpEF patients were accompanied with abdominal obesity. Patients in baPWV ≥1800cm/s group were older, with a higher incidence of type 2 diabetes mellitus (T2DM), hypertension and abdominal obesity. VFA, systolic BP (SBP), diastolic BP (DBP) and pulse pressure (PP) were correlated with baPWV in total group. Adjusted for age ≥75 years old, gender, smoking, T2DM, calcium channel blocker and statins, the mediation effect of systolic SBP and PP on the VFA-baPWV association were 53.3% (indirect effect was 2.28, 95% CI 0.62–4.73) and 48.4% (indirect effect was 2.07, 95% CI 0.51–4.38), respectively. DBP failed to mediate the association between VFA and baPWV (indirect effect was 0.50, 95% CI −0.41–2.14).

Conclusion: The association of visceral fat with baPWV in HFpEF patients may be partly accounted for SBP or PP. Elevated SBP and PP might be important potential targets for preventing arterial stiffness in HFpEF patients.

Keywords: mediation analysis, blood pressure, visceral fat area, brachial-ankle pulse wave velocity, HFpEF

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disease with typical diastolic dysfunction of the left ventricle (LV).[1,2] Studies had proven that arterial stiffness, which means the decrement of arterial compliance, was an important harmful factor for LV diastolic function and HFpEF.[3,4] Brachial-ankle pulse wave velocity (baPWV) is a widely used measure for arterial stiffness, and numerous studies had found baPWV to be associated with visceral fat, waist circumference (WC), and body mass index (BMI),[5–7] while the underlying mechanism of these observations is not fully understood. Blood pressure (BP) as a leading promoter of arterial stiffness might mediate the association of BMI with baPWV.[8–10] Compared with systemic obesity evaluated by BMI, abdominal obesity was the main form of Chinese HFpEF patients[11–13] and may cause more serious adverse consequences in obese HFpEF patients.[14] Thus, a key unsolved mystery for HFpEF-patient health is the extent to which the effect of abdominal obesity on baPWV might be mediated by

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BP. To address this concern, we applied a mediation analysis to investigate the extent of blood pressure mediated the association of visceral fat area (VFA, a method to measure abdominal obesity)[15] with baPWV within HFpEF.

Materials and Methods

Participants and Study Design

A total of 131 patients with HFpEF were recruited to the study from October to December 2020. The eligible subjects at screening required an age over 50 years, signs and symptoms of heart failure, an ejection fraction of 50% or higher, elevated level of natriuretic peptides or B-type natriuretic peptide (with different cutoffs depending on whether the rhythm was sinus or atrial fibrillation and/or flutter: sinus rhythm at least higher than 125 pg/mL, fibrillation and/or flutter rhythm at least higher than 365 pg/mL), changes in the structure and/or function of the heart and the HFA-PEFF score ≥5 points (details see the consensus recommendation from the Heart Failure Association of the European Society of Cardiology).[16] Patients with malignant tumor, severe valvular disease, severe liver or kidney insufficiency (severe liver insufficiency defined as the level of aspartate transaminase or alanine transaminase higher than 3 × ULN or the level of total bilirubin higher than 2 × ULN at admission. Severe kidney insufficiency was defined as the level of estimated glomerular filtration rate lower than 30 mL/min/1.73 m^2), and missing brachial-ankle pulse wave velocity (baPWV) or VFA data were excluded. Finally, 94 HFpEF patients were included (Figure 1), and all patients agreed to participate with a written informed consent. The study was a cross-sectional study with *clinicaltrials.gov* identifier of NCT04535726. All procedures were complied with the *Declaration of Helsinki* and followed the instructions of local ethic committee of *the First Affiliated Hospital of Chongqing Medical University* (approval NO. 2020-606).

Baseline Data

Clinical features and medical history were collected by the investigator. Laboratory results and echocardiogram data were defined using the first-time examination after admission. All the laboratory data were tested in the same laboratory with the same standard. All the echocardiographic data were collected by the same echocardiologist using the same ultrasound machine (Vivid E95, AU11403, GE Vingmed Ultrasound AS).

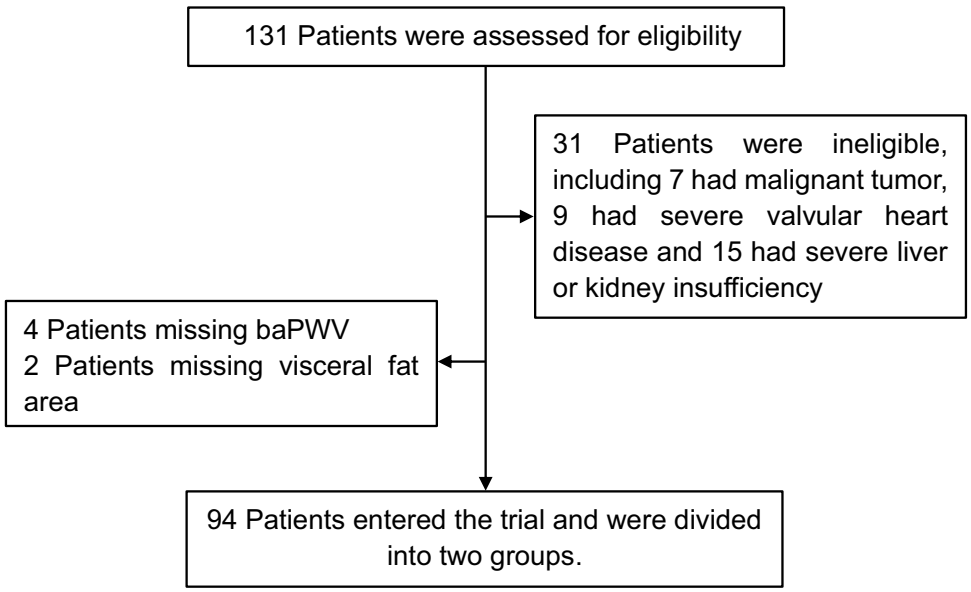


Figure 1 Population screening flow diagram.
Abbreviation: baPWV, brachial-ankle pulse wave velocity.

Body Measurements

Body weight and height were recorded without shoes using a Detecto balance beam scale and a wall-mounted stadiometer to the nearest 0.1 kg and 0.1 cm, respectively. BMI, WC, hip circumference (HC) and AC were measured by a standard procedure described before.[17] Systemic obesity is defined as BMI ≥ 28.0kg/m^2.[18] Abdominal obesity was defined as WC ≥ 90.0 cm (male) or 85.0 cm (female), or WC/HC ≥1.0, or VFA ≥80 cm^2.[19] Bioelectrical impedance analysis, emerged as an assessment tool of body composition,[20] was used to identify and measure VFA, body fat mass and fat percentage in the present study as reported.[21]

BP and Arterial Stiffness Measurement

BP and arterial stiffness evaluated by baPWV were detected twice by a BP-203 RPE III networked arteriosclerosis detection device (Omron Health Medical [China], Co, Ltd) at the same time as possible in a comfortable environment. All participants were asked to rest peacefully at least 30 minutes on sitting before the test without smoking, drinking or moving. Observer was asked to do not talk with participant during the test. The cuffs were evenly and tightly wrapped around the bilateral upper arms and the lower edges of cuffs were 2.5cm from the elbows. The center of the cuff was located above the brachial arteries. Systolic BP (SBP) and diastolic BP (DBP) were the average values of upper limbs. Pulse pressure (PP) was calculated by SBP minus DBP.

Statistical Analysis

Categorical parameters were displayed by number (%), and continuous parameters were expressed as mean ± standard deviation (SD) or median (quartiles). X^2-test or *Fisher's* exact test was used to check the difference between groups for categorical variables. *t*-test or *Mann–Whitney U*-test was performed for continuous variables. Linear regression analysis was carried out to show the associations of body measurements with baPWV, with baPWV used as the dependent variable, body measurements (VFA, BMI, WC, HC, WC/HC, AC, body fat mass, fat percent, SBP, DBP, PP, age, fasting plasma glucose (FBG) and glycosylated hemoglobin (HbA1c)) used as independent variables. *SPSS* software (Version 25.0, IBM) was used for statistical analyses. A *P*-value <0.05 was considered to be statistically significant in two-tailed.

The PROCESS macro developed by Hayes[22] was used to calculate the total effect, indirect effect (the effect of VFA on baPWV through BP) and direct effect (BP-independent effect of VFA on baPWV) of VFA on baPWV mediated by BP. The proportion of the mediation is the outcome of indirect effect divided by total effect. In mediation analysis models, predictor variable (X) was VFA; mediator variables (M) were SBP, DBP or PP; the outcome variable (Y) was baPWV. In multiple mediation analysis, age ≥75 years old, gender, smoking, type 2 diabetes mellitus (T2DM), calcium channel blocker (CCB) and statins were considered to be covariates. The differences were considered to be statistically significant if the 95% bootstrap confidence interval (CI) did not cross 0.

Results

Baseline Characteristics

All patients were divided into two groups, baPWV <1800 cm/s group (n = 40) and ≥1800 cm/s group (n = 54). Patients in baPWV ≥1800cm/s group were older, with a higher incidence of T2DM, hypertension and abdominal obesity, a lower possibility to take CCB and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II type 1 receptor blocker (ARB), a higher level of SBP, PP, WC, AC, VFA, high-density lipoprotein cholesterol (HDL-C), FBG and mean E/e', and a thicker posterior wall of left ventricle (LVPW), compared with the patients in baPWV <1800 cm/s group. There were no significant differences in other characteristics between two groups (Table 1).

Linear Regression Analysis Between Body Measurements and baPWV

VFA, SBP, DBP, PP, age and FBG were significantly correlated with baPWV (Table 2); the values were β=5.898 for VFA (95% CI 2.226–9.569, *P*=0.002), β=10.049 for SBP (95% CI 5.935–14.706, *P*<0.001), β=10.753 for DBP (95% CI 2.657–18.849, *P*=0.010), β=13.645 for PP (95% CI 7.347–20.114, *P*<0.001), β=19.730 for age (95% CI 11.258–28.203, *P*<0.001), β=55.437 for FBG (95% CI 3.294–107.580, *P*=0.037).

Table 1 Characteristic Distribution of Participants in This Study

	Total (N=94)	baPWV		*P* value
		<1800cm/s (N = 40)	≥1800cm/s (N = 54)	
Age (years)	72±12	66±13	76±8	<0.001
Age ≥75 years old	40(42.6%)	10(25.0%)	30(55.6%)	0.003
Female (%)	51(54.3%)	21(52.5%)	30(55.6%)	0.769
Smoke (%)	24(25.5%)	9(22.5%)	15(27.8%)	0.562
Past	15(16.0%)	4(10.0%)	11(20.4%)	0.175
Current	9(9.6%)	5(12.5%)	4(7.4%)	0.635
History				
T2DM (%)	27(28.7%)	6(15.0%)	21(38.9%)	0.011
Hypertension (%)	46(48.9%)	14(35.0%)	32(59.3%)	0.020
CHD (%)	48(51.1%)	17(42.5%)	31(57.4%)	0.153
AF (%)	35(37.2%)	13(32.5%)	22(40.7%)	0.414
COPD (%)	5(12.5%)	5(9.3%)	10(10.6%)	0.869
Therapies				
CCB	41(43.6%)	12(30.0%)	29(53.7%)	0.022
Beta-blocker	43(45.7%)	15(37.5%)	28(51.9%)	0.167
ACEI/ARB	44(46.8%)	14(35.0%)	30(55.6%)	0.048
Diuretics	70(74.5%)	27(67.5%)	43(79.6%)	0.182
ARNI	40(42.6%)	18(45.0%)	22(40.7%)	0.680
SGLT2i	18(19.1%)	5(12.5%)	13(24.1%)	0.159
Statins	69(73.4%)	26(65.0%)	43(79.6%)	0.112
Blood pressure (mmHg)				
SBP	135±22	127±16	141±24	0.001
DBP	72±13	69±14	74±12	0.070
PP	64(51–74)	59(47–66)	67(53–78)	0.003
Anthropometry				
VFA (cm^2)	131.6±28.0	121.8±32.5	138.8±21.8	0.005
BMI (kg/m^2)	24.3±3.8	24.1±3.9	24.5±3.7	0.600
WC (cm)	88.0(83.0–93.0)	83.0(81.0–91.3)	89.0(83.8–95.0)	0.012
HC (cm)	95.5(92.0–100.0)	94.0(90.3–100.0)	97.0(93.0–100.0)	0.185
WC/HC	0.92±0.06	0.91±0.06	0.92±0.06	0.141
AC (cm)	92.0(86.8–95.5)	88.0(86.0–94.0)	92.0(88.0–97.3)	0.031
Body fat mass (kg)	18.4(12.8–21.6)	16.5(11.8–21.5)	19.4(14.2–22.2)	0.172
Fat (%)	27.6±9.8	26.4±9.6	28.6±9.9	0.287
Abdominal obesity	88(93.6%)	34(85.0)	54(100.0%)	0.005
Systemic obesity	13(13.8%)	5(12.5%)	8(14.8%)	0.748
Laboratory data				
TC (mmol/L)	3.83±1.11	3.7±1.2	3.9±1.1	0.537
TG (mmol/L)	1.15(0.78–1.84)	1.02(0.76–1.95)	1.18(0.87–1.75)	0.284
HDL-C (mmol/L)	1.13(0.95–1.42)	1.08(0.84–1.37)	1.18(0.99–1.50)	0.026
LDL-C (mmol/L)	2.14(1.54–2.63)	2.26(1.45–2.60)	2.06(1.57–2.84)	0.810
FBG (mmol/l)	5.7(5.0–6.7)	5.3(4.8–5.9)	6.0(5.3–6.9)	0.001
HbA1c (%)	6.0(5.6–6.4)	5.9(5.5–6.1)	6.0(5.7–6.7)	0.070
NT-proBNP (pg/mL)	990(495–2036)	840(457–1619)	1010(499–2120)	0.851
Echocardiographic measures				
LA (mm)	38±8	37±8	39±8	0.323
LV (mm)	48±6	48±7	48±5	0.871
RA (mm)	39(35–45)	39(35–46)	39(34–45)	0.402
RV (mm)	21(20–22)	21(20–24)	20(20–22)	0.221
LVPW (mm)	11±1	10±1	11±1	0.002
EF (%)	61±5	61±6	61±4	0.918

(*Continued*)

Table 1 (Continued).

	Total (N=94)	baPWV		*P* value
		<1800cm/s (N = 40)	≥1800cm/s (N = 54)	
Septal e' (cm/s)	4.7(4.0–6.1)	4.7(4.1–6.2)	4.7(3.9–5.8)	0.557
Lateral e' (cm/s)	6.9±2.4	7.4±2.4	6.4±2.3	0.121
Mean E/e'	12.6(9.4–16.8)	10.5(7.6–14.2)	13.3(11.0–17.8)	0.018
TR velocity (cm/s)	263(240–310)	264(238–309)	259(240–312)	0.888
PASP (mmHg)	40(32–54)	36(32–63)	42(32–54)	0.814
LAVI (mL/m^2)	41(30–64)	37(30–52)	48(31–70)	0.160
LVMI (g/m^2)	117(100–145)	115(98–138)	123(100–156)	0.179

Abbreviations: baPWV, brachial-ankle pulse wave velocity; T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type I receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; SGLT2i, sodium glucose cotransporter-2 inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index; WC, waist circumference; HC, hip circumference; AC, abdominal circumference; VFA, visceral fat area; TC, total cholesterol; TG, total triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; N%, neutrophil percentage; FBG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; NT-proBNP, type B brain natriuretic peptide precursor; LA, left atria; LV, left ventricle; RA, right atria; RV, right ventricle; LVPW, posterior wall thickness of left ventricle; EF, ejection fraction; TR, tricuspid regurgitant; PSAP, pulmonary artery systolic pressure; LAVI, left atrial volume index; LVMI, left ventricular mass index.

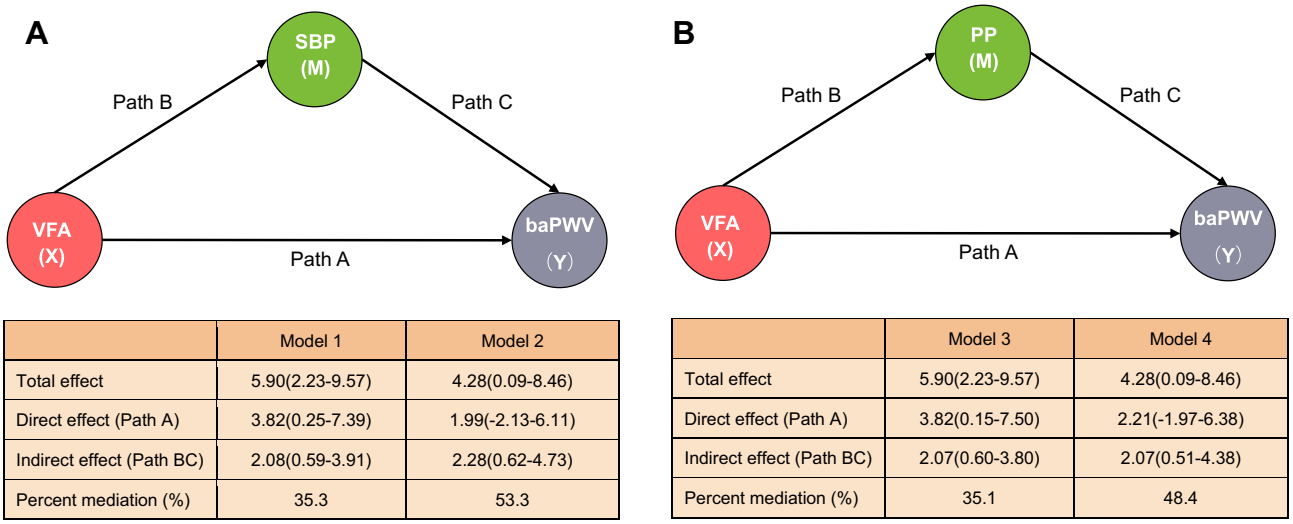
Table 2 Linear Regression Analysis Between Independent Variables and baPWV

Parameters	β	*P* value	95% CI
VFA	5.898	0.002	2.226–9.569
BMI	−3.645	0.803	−32.536–25.246
WC	6.823	0.232	−4.429–18.076
HC	8.069	0.284	−6.816–22.954
WC/HC	517.144	0.579	−1328.146–2362.434
AC	5.085	0.387	−6.525–16.696
Body fat mass	4.740	0.501	−9.186–18.666
Fat (%)	6.725	0.226	−4.243–17.694
SBP	10.049	<0.001	5.935–14.706
DBP	10.753	0.010	2.657–18.849
PP	13.645	<0.001	7.347–20.114
Age	19.730	<0.001	11.258–28.203
FBG	55.437	0.037	3.294–107.580
HbA1c	92.375	0.073	−8.758–193.471

Abbreviations: baPWV, brachial-ankle pulse wave velocity; 95% CI, 95% confidence interval; FBG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index; WC, waist circumference; HC, hip circumference; AC, abdominal circumference; VFA, visceral fat area.

SBP or PP Mediated the Association Between VFA and baPWV in the Mediation Analysis

To better understand the relationships among VFA, baPWV and BP, mediation analysis was performed to examine the direct and indirect (BP-mediated) effects of VFA on baPWV. As shown in Figure 2, VFA demonstrated a significant total effect on baPWV (total effect = 5.90; 95% CI 2.23–9.57) in the whole cohort. The indirect effect (through SBP or PP) of VFA on baPWV was prominent (indirect effect through SBP = 2.08; percent mediation through SBP = 35.3%; indirect effect through PP = 2.07; percent mediation through PP = 35.1%). After adjusted for age ≥75 years old, gender, smoking, T2DM, CCB and statins, the mediation effect of SBP and PP on the VFA-baPWV association were 53.3% (indirect effect



	Model 1	Model 2
Total effect	5.90(2.23-9.57)	4.28(0.09-8.46)
Direct effect (Path A)	3.82(0.25-7.39)	1.99(-2.13-6.11)
Indirect effect (Path BC)	2.08(0.59-3.91)	2.28(0.62-4.73)
Percent mediation (%)	35.3	53.3

	Model 3	Model 4
Total effect	5.90(2.23-9.57)	4.28(0.09-8.46)
Direct effect (Path A)	3.82(0.15-7.50)	2.21(-1.97-6.38)
Indirect effect (Path BC)	2.07(0.60-3.80)	2.07(0.51-4.38)
Percent mediation (%)	35.1	48.4

Figure 2 Mediation effect of blood pressure in the association between visceral fat area and brachial-ankle pulse wave velocity. (**A**) Mediation Analysis Model of SBP on the association between VFA and baPWV. (**B**) Mediation Analysis Model of PP on the association between VFA and baPWV. Model 1 and 3: Unadjust. Model 2 and 4: Adjust for age ≥75 years old, gender, smoking, type 2 diabetes mellitus, calcium channel blocker and statins.
Abbreviations: VFA visceral fat area; baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; PP, pulse pressure.

was 2.28, 95% CI 0.62–4.73) and 48.4% (indirect effect was 2.07, 95% CI 0.51–4.38), respectively. We failed to discover DBP mediated the association between VFA and baPWV in the mediation analysis (indirect effect was 0.50, 95% CI −0.41–2.14) (Supplemental Figure 1).

Discussion

Our findings suggest that in the patients of HFpEF, VFA was associated with baPWV, and this association might be partly mediated via SBP or PP. The results intensified the value of developing effective complex interventions that target SBP and PP as means to delay or improve arterial stiffness in abdominal-obese HFpEF patients.

The purpose of the present study was to better understand the risk factors of arterial stiffness in patients with HFpEF. As one of the risk factors of HFpEF,[23] visceral fat leads to the increase in adipocyte size, production of biologically active molecules (eg, proinflammatory cytokines and adipokines), promotion of oxidative stress and the increasing tone of sympathetic nervous system and level of BP,[24] which may contribute to the decrement of arterial compliance. Previous studies had demonstrated obesity parameters, including VFA, BMI, WC, HC, WC/HC, AC, body fat mass and fat percentage, were correlated with arterial stiffness.[25,26] However, abdominal obesity had been shown to be the most prevalent form of Chinese HFpEF patients compared with systemic obesity,[11–13] and visceral fat area may correlate better with arterial stiffness in Chinese and American population in all measures of obesity,[25,26] which was consistent with our results. These findings may account for the emergence of VFA as a better facilitator for baPWV within HFpEF. However, the previous studies had focused exclusively on the primary effect of visceral fat on baPWV and ignored possible complex mechanisms and processes, such as BP between them.

In this study, we found SBP and PP were associated with both visceral fat and arterial stiffness, which was consistent with previous studies.[27,28] Both the Dallas Heart Study and another study enrolled 1189 Singaporean women who identified a positive association between BP and visceral fat.[27,29] Elevated BP had been confirmed as an essential risk factor for arterial stiffness.[28,30] However, those studies only provided a hypothesis that BP could bridge the gap between visceral fat and arterial stiffness, and the extent to which BP mediates this effect remains unclear. Gender, ageing, T2DM and smoking had been documented to contribute to the increase in arterial stiffness through several pathological pathways.[31–33] Meanwhile, pharmacological interventions have been of great value in reducing the stiffness of artery, such as antihypertensives, statins, antidiabetics and anti-inflammatory drugs.[31] By lowering central blood pressure, CCB might be beneficial in reducing PWV.[34] Through increasing the bioavailability of nitric oxide, CCB could improve the function of endothelia.[35] Probably due to the profibrotic action of the renin–angiotensin system, ACEI and ARB drugs

were superior to other antihypertensive agents in reducing arterial stiffness.[34] Studies had also proved that statins may have additional benefits in lowering PWV through their anti-inflammatory and antioxidant effects on arterial wall.[34] Whether these factors would impact the effect of BP on baPWV is unclear.

To the best knowledge of us, this is the first study to demonstrate that the VFA-baPWV association might be partly mediated through SBP or PP. Although this conclusion was based on the statistic of this cross-sectional study, it may remind us that targeting SBP and PP might be a mean to delay or ameliorate arterial stiffness in abdominal-obese HFpEF patients.

However, we failed to reveal DBP to be a mediator of the relationship between VFA and baPWV. Liu discovered the association of increased-childhood BMI and its cumulative burden with adult aortic-femoral pulse wave velocity (afPWV) was predominantly mediated through the long-term-increasing trend of both SBP and DBP.[10] However, in the HFpEF cohort, participants were aged, suffered from arterial stiffness, with more metabolic disorders and a tendency of isolated systolic hypertension.[36,37] All these factors contributed to the result that only SBP mediated the association of VFA and baPWV. A prospective design will be needed to reveal the nature relationships among VFA, BP and baPWV in the future.

The partly mediated efforts of SBP and PP imply a number of underlying mechanisms mediated VFA-baPWV association, which may have several explanations. Firstly, when fat is deposited around visceral organs, adipokines such as leptin and pro-inflammatory factors are secreting simultaneously, ultimately leading to chronic inflammation and activation of oxidative stress and sympathetic nerves.[24] Persistent inflammation is a character of HFpEF.[38] Secondly, chronic inflammation, activated oxidative stress and sympathetic nerve will increase blood pressure level and decrease arterial elasticity.[24,39] Reduced arterial elasticity and increased arterial stiffness require more force to accommodate blood flow and then lead to the increase of SBP and PP.[40,41] Thirdly, elevated blood pressure also promotes the remodeling and fibrosis of vascular, which eventually leads to the development of arterial stiffness.[40,42] Overall, excessive visceral fat deposition not only accelerates the process of arterial stiffness by directly promoting chronic inflammation and activating neuroendocrine but also increases the level of BP in various ways.

We found that VFA, SBP and PP were risk factors for arterial stiffness, and SBP or PP might mediate the VFA-baPWV association. Therefore, our study provided evidence that clinicians might prevent arterial stiffness and decrease the level of SBP and PP by losing weight or changing lifestyles, especially in HFpEF patients, which may help to impede the development of diastolic dysfunction of LV. When necessary, in HFpEF patients with abdominal obesity, strategies to control SBP and PP and reduce abdominal adiposity may help to prevent the development of arterial stiffness.

Strengths and Limitations

This is the first study using mediated analysis to reveal the mediator effects of SBP and PP on the association of VFA with baPWV, and the availability of targeted measures of VFA, BP and baPWV enhanced the reproducibility of our findings. However, there are some limitations. First, as a cross-sectional study, we could not confirm the causal relationship. A prospective design will be needed to reveal the nature relationships among VFA, BP and baPWV in the future. Second, the small sample study was comprised of HFpEF patients from Chongqing, China, which may limit the generalizability of the results (for example, the relationship between other obesity parameters and baPWV). Third, baPWV rather than carotid-femoral PWV (the gold assessed standard of arterial stiffness) or cardio-ankle vascular index (considered to be less dependent on BP than baPWV) was used to evaluate the degree of arterial stiffness. However, study had revealed baPWV as a simple and noninvasive manner can be used to access the degree of arterial stiffness.[43] Fourth, aortic arch PWV was recommended to be a method to measure the arterial stiffness of local vessel recently by Doppler-derived, single-beat technique or cardiovascular magnetic resonance (CMR), which has been found to be particularly helpful in HFpEF.[44] However, study has reported that baPWV had a superior correlation with central aortic PWV measured by CMR than carotid-femoral PWV,[45] which suggested that baPWV might provide qualitatively similar data in comparison of aortic PWV. Lastly, peripheral artery disease was not excluded in the study, which may affect the baPWV values.

Conclusion

In this study, we have provided evidence that the association of visceral fat with baPWV in HFpEF group may be partly accounted for SBP or PP. This finding suggested that SBP or PP might be an important potential target for preventing arterial stiffness in obese-HFpEF patients.

Data Sharing Statement

With reasonable request, all individual deidentified participant data of the study will be available from Dongying Zhang forever (email: zhangdongying@cqmu.edu.cn), including laboratory and imaging data. Other documents about this study will not be available because of the privacy of participants.

Ethics Approval

All procedures were followed the instructions of local ethic committee (approval NO. 2020-606).

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Author Contributions

All authors made a significant contribution to the study, whether that is in the conception, acquisition of data, analysis, or in all these areas; took part in drafting, revising or reviewing the article; reviewed and agreed all versions of this article; approved published this article on this journal; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Røe ÅT, Sjaastad I, Louch WE. Heart failure with preserved ejection fraction. *Tidsskrift for den Norske laegeforening*. 2017;137(18). doi:10.4045/tidsskr.16.1068
2. Shah SJ. Precision medicine for heart failure with preserved ejection fraction: an overview. *J Cardiovasc Transl Res*. 2017;10(3):233–244. doi:10.1007/s12265-017-9756-y
3. Lau ES, Panah LG, Zern EK, et al. Arterial stiffness and vascular load in HFpEF: differences among women and men. *J Card Fail*. 2022;28(2):202–211. doi:10.1016/j.cardfail.2021.10.019
4. Chi C, Liu Y, Xu Y, Xu D. Association between arterial stiffness and heart failure with preserved ejection fraction. *Front Cardiovasc Med*. 2021;8:707162. doi:10.3389/fcvm.2021.707162
5. Strasser B, Arvandi M, Pasha EP, Haley AP, Stanforth P, Tanaka H. Abdominal obesity is associated with arterial stiffness in middle-aged adults. *Nutr Metab Cardiovasc Dis*. 2015;25(5):495–502. doi:10.1016/j.numecd.2015.01.002
6. Choi HS, Cho YH, Lee SY, et al. Association between new anthropometric parameters and arterial stiffness based on brachial-ankle pulse wave velocity. *Diabetes Metabol Syndr Obes*. 2019;12:1727–1733. doi:10.2147/DMSO.S211542
7. Kim HL, Ahn DW, Kim SH, et al. Association between body fat parameters and arterial stiffness. *Sci Rep*. 2021;11(1):20536. doi:10.1038/s41598-021-00175-z
8. Najjar SS, Scuteri A, Shetty V, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol*. 2008;51(14):1377–1383. doi:10.1016/j.jacc.2007.10.065
9. AlGhatrif M, Strait JB, Morrell CH, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. *Hypertension*. 2013;62(5):934–941. doi:10.1161/HYPERTENSIONAHA.113.01445
10. Liu Y, Yan Y, Yang X, et al. Long-term burden of higher body mass index and adult arterial stiffness are linked predominantly through elevated blood pressure. *Hypertension*. 2019;73(1):229–234. doi:10.1161/HYPERTENSIONAHA.118.12106
11. Chandramouli C, Tay WT, Bamadhaj NS, et al. Association of obesity with heart failure outcomes in 11 Asian regions: a cohort study. *PLoS Med*. 2019;16(9):e1002916. doi:10.1371/journal.pmed.1002916

12. Tromp J, Teng TH, Tay WT, et al. Heart failure with preserved ejection fraction in Asia. *Eur J Heart Fail*. 2019;21(1):23–36. doi:10.1002/ejhf.1227
13. Chen J, Li M, Hao B, et al. Waist to height ratio is associated with an increased risk of mortality in Chinese patients with heart failure with preserved ejection fraction. *BMC Cardiovasc Disord*. 2021;21(1):263. doi:10.1186/s12872-021-02080-9
14. Haykowsky MJ, Nicklas BJ, Brubaker PH, et al. Regional adipose distribution and its relationship to exercise intolerance in older obese patients who have heart failure with preserved ejection fraction. *JACC Heart Fail*. 2018;6(8):640–649. doi:10.1016/j.jchf.2018.06.002
15. Fang H, Berg E, Cheng X, Shen W. How to best assess abdominal obesity. *Curr Opin Clin Nutr Metab Care*. 2018;21(5):360–365. doi:10.1097/MCO.0000000000000485
16. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40(40):3297–3317. doi:10.1093/eurheartj/ehz641
17. Liu Z, Hu W, Zhang H, et al. EAT thickness as a predominant feature for evaluating arterial stiffness in patients with heart failure with preserved ejection fraction. *Diabetes Metab Syndr Obes*. 2022;15:1217–1226. doi:10.2147/DMSO.S356001
18. Gao M, Wei YX, Lyu J, et al. 中国成年人代谢异常相关的体质指数和腰围切点研究 [The cut-off points of body mass index and waist circumference for predicting metabolic risk factors in Chinese adults]. *Zhonghua liu xing bing xue za zhi*. 2019;40(12):1533–1540. Chinese. doi:10.3760/cma.j.issn.0254-6450.2019.12.006
19. Endocrinology Branch of Chinese Medical Association DBoCSoTCM, Obesity and Diabetes Surgeons Committee of Surgeons Branch of Chinese Medical Association. Multidisciplinary diagnosis and Treatment consensus for Obesity based on clinic (2021). *Chin J Endocrinol Metabol*. 2021;37(11):959–972.
20. Chua KY, Lin X, Wang Y, Chong YS, Lim WS, Koh WP. Visceral fat area is the measure of obesity best associated with mobility disability in community dwelling oldest-old Chinese adults. *BMC Geriatr*. 2021;21(1):282. doi:10.1186/s12877-021-02226-6
21. Hu W, Zhang H, Liu Z, et al. Relationship between adipose tissue distribution and arterial stiffness in HFpEF. *Nutrition*. 2022;102:111726. doi:10.1016/j.nut.2022.111726
22. Hayes AF, Scharkow M. The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: does method really matter? *Psychol Sci*. 2013;24(10):1918–1927. doi:10.1177/0956797613480187
23. Campbell DJ, Gong FF, Jelinek MV, et al. Threshold body mass index and sex-specific waist circumference for increased risk of heart failure with preserved ejection fraction. *Eur J Prev Cardiol*. 2019;26(15):1594–1602. doi:10.1177/2047487319851298
24. Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Localization of fat depots and cardiovascular risk. *Lipids Health Dis*. 2018;17(1):218. doi:10.1186/s12944-018-0856-8
25. Li G, Yao T, Wu XW, et al. Novel and traditional anthropometric indices for identifying arterial stiffness in overweight and obese adults. *Clin Nutr*. 2020;39(3):893–900. doi:10.1016/j.clnu.2019.03.029
26. Sutton-Tyrrell K, Newman A, Simonsick EM, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. *Hypertension*. 2001;38(3):429–433. doi:10.1161/01.HYP.38.3.429
27. Thu WPP, Sundström-Poromaa I, Logan S, Kramer MS, Yong EL. Blood pressure and adiposity in midlife Singaporean women. *Hypertens Res*. 2021;44(5):561–570. doi:10.1038/s41440-020-00600-2
28. Paini A, Aggiusti C, Bertacchini F, et al. Relationship between arterial stiffness and unattended or attended blood pressure values. *J Hypertens*. 2020;38(2):243–248. doi:10.1097/HJH.0000000000002232
29. Yano Y, Vongpatanasin W, Ayers C, et al. Regional fat distribution and blood pressure level and variability: the Dallas Heart Study. *Hypertension*. 2016;68(3):576–583. doi:10.1161/HYPERTENSIONAHA.116.07876
30. Park JS, Shin JH, Park JB, et al. Relationship between arterial stiffness and variability of home blood pressure monitoring. *Medicine*. 2020;99(30):e21227. doi:10.1097/MD.0000000000021227
31. Boutouyrie P, Chowienczyk P, Humphrey JD, Mitchell GF. Arterial stiffness and cardiovascular risk in hypertension. *Circ Res*. 2021;128(7):864–886. doi:10.1161/CIRCRESAHA.121.318061
32. Lamacchia O, Sorrentino MR. Diabetes mellitus, arterial stiffness and cardiovascular disease: clinical implications and the influence of SGLT2i. *Curr Vasc Pharmacol*. 2021;19(2):233–240. doi:10.2174/18756212MTA1aMzIwy
33. Park JS. Smoking cessation as a target of arterial destiffening. *Korean Circ J*. 2020;50(4):370–371. doi:10.4070/kcj.2020.0045
34. Janić M, Lunder M, Sabovič M. Arterial stiffness and cardiovascular therapy. *Biomed Res Int*. 2014;2014:621437. doi:10.1155/2014/621437
35. Silva IVG, de Figueiredo RC, Rios DRA. Effect of different classes of antihypertensive drugs on endothelial function and inflammation. *Int J Mol Sci*. 2019;20(14):3458. doi:10.3390/ijms20143458
36. Jin X, Nauta JF, Hung CL, et al. Left atrial structure and function in heart failure with reduced (HFrEF) versus preserved ejection fraction (HFpEF): systematic review and meta-analysis. *Heart Fail Rev*. 2022;27(5):1933–1955. doi:10.1007/s10741-021-10204-8
37. Tsai TY, Cheng HM, Chuang SY, et al. Isolated systolic hypertension in Asia. *J Clin Hypertens*. 2021;23(3):467–474. doi:10.1111/jch.14111
38. Pugliese NR, Pellicori P, Filidei F, et al. Inflammatory pathways in heart failure with preserved left ventricular ejection fraction: implications for future interventions. *Cardiovasc Res*. 2022;20:58.
39. Seravalle G, Grassi G. Obesity and hypertension. *Pharmacol Res*. 2017;122:1–7. doi:10.1016/j.phrs.2017.05.013
40. Harvey A, Montezano AC, Lopes RA, Rios F, Touyz RM. Vascular fibrosis in aging and hypertension: molecular mechanisms and clinical implications. *Can J Cardiol*. 2016;32(5):659–668. doi:10.1016/j.cjca.2016.02.070
41. Strandberg TE, Pitkala K. What is the most important component of blood pressure: systolic, diastolic or pulse pressure? *Curr Opin Nephrol Hypertens*. 2003;12(3):293–297. doi:10.1097/00041552-200305000-00011
42. Balligand JL, Feron O, Dessy C. eNOS activation by physical forces: from short-term regulation of contraction to chronic remodeling of cardiovascular tissues. *Physiol Rev*. 2009;89(2):481–534. doi:10.1152/physrev.00042.2007
43. Cheng YB, Li Y, Sheng CS, Huang QF, Wang JG. Quantification of the interrelationship between brachial-ankle and carotid-femoral pulse wave velocity in a workplace population. *Pulse*. 2016;3(3–4):253–262. doi:10.1159/000444645
44. Pugliese NR, Balletti A, Armenia S, et al. Ventricular-arterial coupling derived from proximal aortic stiffness and aerobic capacity across the heart failure spectrum. *JACC Cardiovasc Imaging*. 2022;15(9):1545–1559. doi:10.1016/j.jcmg.2022.03.024
45. Kim EK, Chang SA, Jang SY, et al. Brachial-ankle pulse wave velocity as a screen for arterial stiffness: a comparison with cardiac magnetic resonance. *Yonsei Med J*. 2015;56(3):617–624. doi:10.3349/ymj.2015.56.3.617