ARTICLE

Comparison of pulse wave velocity and pulse pressure amplification in association with target organ damage in community-dwelling elderly: The Northern Shanghai Study

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Abstract

This study aimed to investigate the discrepancy between pulse wave velocity (PWV) and pulse pressure amplification (PPA) in association with hypertensive target organ damage (TOD) in the elderly. From June 2014 to August 2015, 1599 participants aged >65 years old from communities located in northern Shanghai were recruited. Carotid-femoral pulse wave velocity (cfPWV), peripheral blood pressure (BP), central BP and other TOD indicators, including the ratio of the early ventricular filling velocity (E) to the peak velocity of the tissue Doppler velocity of septal mitral annulus (E/Ea), left ventricular mass index (LVMI), carotid intima-medium thickness (CIMT), estimated glomerular filtration rate (eGFR), and urinary albumin–creatinine ratio (ACR), were determined for each participant. PPA was defined as the peripheral-to-central pulse pressure ratio. In multivariable linear regression analysis, cfPWV was significantly associated with CIMT ($\beta = 12.83 \pm 4.28$ μm per SD; $P = 0.003$) and eGFR ($\beta = -1.85 \pm 0.69$ ml/min/1.73 m^2 per SD; $P = 0.007$), whereas PPA was significantly associated with E/Ea ($\beta = -0.25 \pm 0.10$ per SD; $P = 0.01$) and LVMI ($\beta = -3.00 \pm 0.78$ g/m^2 per SD; $P < 0.001$). Similarly, in multivariable logistic regression analysis, cfPWV was significantly associated with arterial plaque (odds ratio [OR], 1.21 [95% confidence interval [CI], 1.05–1.39]; $P = 0.007$), peripheral artery disease (OR, 1.22 [95% CI, 1.06–1.42]; $P = 0.007$), chronic kidney diseases (OR, 1.24 [95% CI, 1.01–1.54]; $P = 0.04$) and microalbuminuria (OR, 1.21 [95% CI, 1.07–1.37]; $P = 0.002$), while PPA was tightly associated with left ventricular hypertrophy (OR, 0.85 [95% CI, 0.72–0.99]; $P = 0.04$) and diastolic dysfunction (OR, 0.78 [95% CI, 0.64–0.96]; $P = 0.02$). In conclusion, cfPWV is a vessel-related and renal-related biomarker, while PPA is a cardiac-related biomarker in community-based elderly.

Introduction

Carotid-femoral pulse wave velocity (cfPWV) is known to represent critical subclinical target organ damage (TOD), has significant prognostic value and is tightly associated

with other TOD, such as carotid intima-medium thickness (CIMT), carotid artery plaque, left ventricular mass index (LVMI), estimated glomerular filtration rate (eGFR) and urinary albumin–creatinine ratio (ACR). Furthermore, as the gold standard measurement of arterial stiffness [1], the value of cfPWV in predicting cardiovascular (CV) events and mortality in various populations has been validated [2–4] and was recommended by the European Society of Hypertension and the European Society of Cardiology (ESC) as a clinical biomarker for CV risk stratification in patients with hypertension [5]. However, recent studies have shown that, in elderly populations, pulse pressure amplification (PPA) rather than cfPWV, acted as an important biomarker with prognostic significance for CV events and mortality [6, 7]. Nonetheless, the differences between these biomarkers and their relationships with other TOD remain unclear. We therefore analyzed cfPWV and PPA in a community-based elderly population located in

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northern Shanghai, and compared their relationships with other TOD. Our goal was to clarify the differences between cfPWV and PPA in association with other TOD in the elderly.

Methods

Participants

The Northern Shanghai study (NSS) is an ongoing community-based prospective study designed to build a comprehensive CV risk scoring system. The protocol of the NSS was published previously [8]. From June 2014 to August 2015, 1721 long-term elderly residents (age ≥65 years old) in northern Shanghai were invited; 1599 (92.9%) of those invited were enrolled and initially examined. A framework of CV risk assessment, including all of the CV risk factors and TOD, was developed with financial support from the Shanghai municipal government (Grant ID. 2013ZYJB0902). Subjects with serious heart disease (NYHA class IV) or end stage renal disease (chronic kidney disease >4) or history of stroke within 3 months were excluded. All participants were instructed to refrain from eating, smoking, caffeine use, alcohol consumption and vasoactive medication on the morning of the examination. A variety of measurements planned in the study protocol were performed on each participant, including biochemical tests, four-limb blood pressure (BP) measurement, carotid and cardiac ultrasonography and cfPWV measurement. Each subject's medical and family histories were obtained using a standardized structured questionnaire. This study was conducted with the approval of the Shanghai Tenth People's Hospital Institutional Review Board, and informed consent was obtained from all participants.

Anthropometric measurements, standard questionnaires and biochemistry measurements

Medical and family histories of all participants were obtained using a standardized structured questionnaire that included age, gender, information about smoking, drinking and exercise habits, diagnosis and treatment history of hypertension, diabetes mellitus and family history of CV diseases (CVD). Height, weight, and waist and hip circumference were measured by one trained investigator. The body mass index (BMI) was calculated as body weight in kg divided by the square of body height in meters; body surface area (BSA) was calculated using the formula: BSA $(m^2) = 0.0061 \times body\ height\ (m) + 0.0128 \times body\ weight\ (kg) - 0.1529$ [9]. The waist/hip circumference ratio was also calculated.

After obtaining informed consent, a sample of venous blood was drawn and a sample of urine was also collected. The serum fasting glucose, creatinine (Cr), triglyceride and total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were measured with standard methods on the venous blood sample, while urinary albumin and creatinine were measured from the urine sample. The eGFR was calculated with the abbreviated MDRD formula: eGFR (ml/min per 1.73 m^2) = $175 \times Cr(mg/dl)^{-1.234} \times age(years\ old)^{-0.179} \times 0.79$ (if female) [10]. The urinary ACR was calculated using the formula: ACR (mg/g) = urinary albumin / urinary creatinine. eGFR < 60 ml/min per 1.73 m^2 was defined as chronic kidney disease and ACR >30 mg/g was defined as microalbuminuria.

Brachial, central BP and PPA

After resting in a supine position for 5 min, brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by a validated oscillometry-based device (Omron Health Care, Kyoto, Japan) at 2-min intervals; the averaged value was calculated for further analysis. The SphygmoCor system (AtCor Medical, Sydney, Australia) was used to measure central BP. First, the radial waveform was recorded by one trained and experienced physician using a tonometry-based probe. Next, the central waveform was automatically estimated by the built-in software using a validated generalized transfer function. Finally, the central waveform was calibrated by the calculated brachial mean and diastolic BP to obtain the central SBP and DBP. PPA was defined as the peripheral-to-central pulse pressure ratio and was calculated using the formula: PPA = (brachial SBP − brachial DBP)/(central SBP − central DBP).

Carotid-femoral pulse wave velocity (cfPWV)

cfPWV was measured by two trained observers blinded to other results using applanation tonometry (SphygmoCor, AtCor Medical, Australia), according to the European Expert Consensus on Arterial Stiffness [11]. The body surface distances from the suprasternal notch to the right carotid artery and the right femoral artery were measured with a non-elastic tape; their difference was calculated as the traveling distance of the pulse wave. Pulse wave recordings were performed consecutively at the right common carotid and right common femoral arteries. An ECG recording was simultaneously performed to provide a reference for R-timing. cfPWV was calculated from measurements of pulse transit time and the traveling distance [PWV = distance (m)/transit time (s)] [12] by the integrated software, which could automatically process each set of pulse wave and ECG data. The quality and reproducibility of the tonometry measurements were automatically tested;

Table 1 Characteristics of participants by gender

	Overall ($n = 1599$)	Men ($n = 711$)	Women ($n = 888$)	P
Cardiovascular risk factors				
Age, years	71.4 ± 6.1	71.3 ± 6.1	71.4 ± 6.1	0.95
Smoker, n (%)	366 (22.9)	351 (49.4)	15 (1.7)	**<0.001**
Family history of premature CVD, n (%)	324 (20.3)	124 (17.4)	200 (22.6)	**0.01**
Waist/Hip circumference	0.88 ± 0.06	0.90 ± 0.06	0.87 ± 0.06	**<0.001**
Body mass index, kg/m^2	23.9 ± 3.5	23.9 ± 3.3	23.9 ± 3.6	0.92
Fasting plasma glucose, mmol/L	5.69 ± 1.70	5.72 ± 1.67	5.67 ± 1.73	0.55
Total cholesterol, mmol/L	5.22 ± 1.01	4.92 ± 0.99	5.46 ± 0.96	**<0.001**
Triglycerides, mmol/L	1.61 ± 0.93	1.54 ± 0.85	1.66 ± 1.00	**0.007**
High-density lipoprotein cholesterol, mmol/L	1.38 ± 0.36	1.28 ± 0.33	1.46 ± 0.36	**<0.001**
Low-density lipoprotein cholesterol, mmol/L	3.20 ± 0.85	3.04 ± 0.85	3.33 ± 0.83	**<0.001**
Systolic blood pressure, mmHg	134.3 ± 17.7	134.3 ± 16.8	134.3 ± 18.4	0.95
Diastolic blood pressure, mmHg	78.9 ± 9.1	80.0 ± 9.2	78.1 ± 9.0	**0.002**
Asymptomatic target organ damage				
Pulse pressure amplification	1.02 ± 0.26	1.07 ± 0.26	0.99 ± 0.26	**<0.001**
Left ventricular mass index, g/m^2	92.2 ± 29.3	92.4 ± 29.4	92.1 ± 29.3	0.82
Left ventricular hypertrophy, n (%)	290(18.1)	83(11.7)	207(23.3)	**<0.001**
E/Ea	9.75 ± 3.64	9.3 ± 3.5	10.1 ± 3.7	**<0.001**
Left ventricular diastolic dysfunction, n (%)	160(10.0)	63(8.9)	97(10.9)	0.24
Carotid intima-medium thickness, μm	612.1 ± 148.2	633.0 ± 159.5	595.5 ± 136.4	**<0.001**
Plaque in left carotid artery, n (%)	899 (56.5)	417 (59.1)	482 (54.4)	0.06
Plaque in right carotid artery, n (%)	817 (51.3)	384 (54.3)	433 (48.9)	**0.03**
Carotid-femoral pulse wave velocity, m/s	9.42 ± 2.30	9.35 ± 2.41	9.47 ± 2.21	0.32
Left ankle-brachial index	1.04 ± 0.13	1.04 ± 0.13	1.03 ± 0.13	0.60
Right ankle-brachial index	1.05 ± 0.13	1.05 ± 0.14	1.05 ± 0.12	0.40
Estimated GFR, ml/min/1.73 m^2	92.5 ± 24.5	88.6 ± 26.4	95.5 ± 22.4	**<0.001**
Urinary albumine–creatinine ratio, mg/g	54.9 ± 181.6	51.1 ± 108.3	58.0 ± 224.4	0.43

Data are means ± standard deviation or numbers with percentages in parenthesis

CVD cardiovascular disease, *E/Ea* the ratio of the early ventricular filling velocity (E) to the peak velocity of tissue Doppler velocity of septal mitral annulus, *GFR* glomerular filtration rate

Estimated GFR was calculated with modified MDRD formula for Chinese

an operator index greater than 80% indicated a reliable measurement.

Ankle-brachial index (ABI)

Four-limb BPs were automatically and simultaneously measured by the VP-1000 (Omron, Japan). Measurements performed by the same staff member, who was trained and blinded to other data. Bilateral ABI, the ratio of ankle SBP and brachial SBP, could be read from the device and the lower value was used for further analyses. An ABI < 0.9 was defined as peripheral artery disease.

Echocardiograph and ultrasonography

Cardiac and carotid ultrasonography was performed by an experienced cardiologist who was unaware of other results, using the MyLab 30 Gold CV machine (ESAOTE SpA, Genoa, Italy), with a 3.5 MHz probe and a 7.5 MHz probe for echocardiograph and carotid ultrasound scans, respectively.

After longitudinally and transversely scanning the common, internal and external carotid arteries for the presence of arterial plaque, a plaque-free arterial segment on the left common carotid artery was chosen to measure CIMT, which was taken as the distance between the lumen–intima interface and the media–adventitia interface. The measurement of CIMT was repeated three times, and the average

Table 2 Determinants of carotid-femoral pulse wave velocity and pulse pressure amplification

	cfPWV		PPA	
	$\beta \pm SE$	P	$\beta \pm SE$	P
Cardiovascular risk factors				
Age, years	0.12 ± 0.01	**<0.001**	-0.004 ± 0.001	**<0.001**
Gender	-0.36 ± 0.13	**0.008**	0.09 ± 0.02	**<0.001**
Waist/hip circumference	2.50 ± 0.98	**0.006**	0.06 ± 0.12	0.58
Body mass index, kg/m^2	-0.002 ± 0.02	0.92	-0.004 ± 0.002	0.08
Plasma glucose, mmol/L	0.20 ± 0.03	**<0.001**	0.002 ± 0.004	0.51
Smoking	0.16 ± 0.15	0.29	-0.02 ± 0.02	0.25
Family history of CVD	0.10 ± 0.13	0.45	-0.01 ± 0.02	0.64
Systolic BP, mmHg	0.04 ± 0.00	**<0.001**	0.006 ± 0.00	**<0.001**
LDL cholesterol, mmol/L	0.09 ± 0.06	0.15	-0.01 ± 0.01	0.21
HDL cholesterol, mmol/L	-0.26 ± 0.16	0.10	-0.01 ± 0.02	0.75

Determinants of carotid-femoral pulse wave velocity and pulse pressure amplification was analyzed by the multivariable linear regression analysis

β the regression coefficient of variables, *cfPWV* carotid-femoral pulse wave velocity, *PPA* pulse pressure amplification, *CVD* cardiovascular diseases, *BP* blood pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

value was utilized for further analyses. Increased CIMT was defined as CIMT > 0.9 mm.

M-mode echocardiography was used to obtain linear measurements of the left ventricular (LV) cavity [LV end-diastolic diameter and LV end-systolic diameter (LVESD)], interventricular septum thickness (IVST) and posterior wall thickness (PWT). The LV mass (LVM) was estimated using the American Society of Echocardiography (ASE)-recommended formula [13]: $LVM(g) = 0.8 \times 10.4 \times [(IVST + PWT + LVDD)^3 - LVDD^3] + 0.6$, and indexed to BSA as LV mass index (LVMI). Left ventricular hypertrophy (LVH) was defined as LVMI > 125 g/m^2 in men and 110 g/m^2 in women.

The left atrial transverse and vertical diameter was measured in the four-chamber view. The parasternal view of 2-dimensional echocardiography was used to obtain the internal diameter of left atrium in end-systole. The left atrial volume (LAV) was estimated by the ellipse model formula [14] and was indexed to BSA as the left atrial volume index (LAVI).

The peak E (early diastolic) and A (late diastolic) velocities were measured by continuous wave Doppler in the four-chamber view. The primary early diastolic velocities (Ea) were measured by tissue Doppler signals in the lateral septum. The ratio of E/Ea in the lateral septum was calculated to evaluate the LV function. Left ventricle diastolic dysfunction (LVDD) was defined as E/Ea ≥ 15 m/s or 15 m/s > E/Ea > 8 m/s but with other evidence of abnormal left ventricle function: (1) LAVI > 40 ml/m^2; (2) LVMI > 149 g/m^2 (male) or LVMI > 122 g/m^2 (female) [15, 16]. All echocardiography procedures followed the recommendations of the ASE.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) for normally distributed variables and as numbers (percentages) for qualitative data. Multivariable linear regression analysis was applied to analyze the influential factors of cfPWV and PPA. Associations of TOD with cfPWV and/or PPA were analyzed by the multivariable linear regression and the logistic regression. All analyses were performed using SAS (statistical analysis system, version 9.2, World Headquarters SAS Institute Inc, America). P values ≤0.05 were considered to be statistically significant.

Results

Clinical characteristics

The study included 1599 participants, 711 (44.5%) of whom were male and with a mean age of 71.4 ± 6.1 years old. The characteristics of participants are presented in Table 1. Compared to women, men had a higher proportion of smokers and a lower proportion of family history of premature CVD. The waist/hip circumference ratio was higher in males while the total cholesterol, triglyceride, HDL cholesterol and LDL cholesterol levels were higher in females. In terms of asymptomatic TOD, males had higher PPA, CIMT and lower eGFR, LVH and E/Ea values than females.

Multivariable linear regression analysis was used to assess the influential factors of cfPWV and PPA (Table 2). Both cfPWV and PPA were significantly and independently

Table 3 Association of target organ damage with carotid-femoral pulse wave velocity and/or pulse pressure amplification

| | Risk factors + cfPWV[a] | | Risk factors + PPA[a] | | Risk factors + cfPWV + PPA[b] | | | |
| | cfPWV | | PPA | | cfPWV | | PPA | |
	$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P
Cardiac TOD								
E/Ea	−0.14 ± 0.11	0.19	−0.25 ± 0.10	**0.01**	−0.17 ± 0.11	0.11	−0.27 ± 0.10	**0.008**
LVMI, g/m^2	−0.09 ± 0.82	0.91	−3.00 ± 0.78	**<0.001**	−0.47 ± 0.83	0.57	−3.02 ± 0.78	**<0.001**
Vascular TOD								
CIMT, μm	12.83 ± 4.28	**0.003**	−7.24 ± 4.06	0.07	11.44 ± 4.30	**0.008**	−5.68 ± 4.08	0.16
Renal TOD								
eGFR, ml/min/1.73 m^2	−1.85 ± 0.69	**0.007**	−0.84 ± 0.65	0.20	−1.98 ± 0.69	**0.004**	−1.03 ± 0.66	0.12
ACR, mg/g	8.84 ± 5.59	0.11	−5.56 ± 5.16	0.28	7.50 ± 5.61	0.18	−4.75 ± 5.21	0.36

Association of target organ damage with carotid-femoral pulse wave velocity and/or pulse pressure amplification was analyzed by the multivariable linear regression analysis. The model was adjusted by age, gender, waist/hip circumference, body mass index, fasting plasma glucose, smoking, family history of cardiovascular diseases, systolic blood pressure, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol

cfPWV carotid-femoral pulse wave velocity, *PPA* pulse pressure amplification, *β* the regression coefficient of variables, *TOD* target organ damage, *E/Ea* the ratio of the early ventricular filling velocity (E) to the peak velocity of tissue Doppler velocity of septal mitral annulus, *LVMI* left ventricular mass index, *CIMT* carotid intima-medium thickness, *eGFR* estimated glomerular filtration rate, *ACR* urinary albumine–creatinine ratio

[a] Two independent variable were separately added to each regression model

[b] Two independent variable were added to one regression model together

associated with age, male gender and SBP ($p < 0.01$), whereas cfPWV was significantly associated with waist/hip ratio ($p < 0.01$) and plasma glucose ($p < 0.01$).

## Association of TOD with cfPWV and/or PPA by multivariable linear regression analysis

Table 3 displays the association of TOD with cfPWV and/or PPA analyzed by the multivariable linear regression analysis. When cfPWV and PPA were separately entered into the regression model together with other conventional CV risk factors, cfPWV was significantly associated with CIMT ($\beta = 12.83 \pm 4.28$ μm per SD; $P = 0.003$) and eGFR ($\beta = -1.85 \pm 0.69$ ml/min/1.73 m^2 per SD; $P = 0.007$), whereas PPA was significantly associated with E/Ea ($\beta = -0.25 \pm 0.10$ per SD; $P = 0.01$) and LVMI ($\beta = -3.00 \pm 0.78$ g/m^2 per SD; $P < 0.001$). When cfPWV and PPA were both entered into the model with similar adjustments, cfPWV was significantly associated with CIMT ($\beta = 11.44 \pm 4.30$ μm per SD; $P = 0.008$) and eGFR ($\beta = -1.98 \pm 0.69$ ml/min/1.73 m^2 per SD; $P = 0.004$), while PPA was significantly associated with E/Ea ($\beta = -0.27 \pm 0.10$ per SD; $P = 0.008$) and LVMI ($\beta = -3.02 \pm 0.78$ g/m^2 per SD; $P < 0.001$).

Figure 1 displays the regression coefficients of the multivariable linear regression analysis with the same adjustment strategy when cfPWV and PPA were entered into the model separately. Only PPA had a significant regression coefficient with LVMI ($\beta = -3.00 \pm 0.78$ g/m^2 per SD; $P < 0.001$) and E/Ea ($\beta = -0.25 \pm 0.10$ per SD; $P = 0.01$),

whereas only cfPWV had significant regression coefficients with CIMT ($\beta = 12.83 \pm 4.28$ μm per SD; $P = 0.003$) and eGFR ($\beta = -1.85 \pm 0.69$ ml/min/1.73 m^2 per SD; $P = 0.007$).

Association of TOD with cfPWV and/or PPA by multivariable logistic regression analysis

Table 4 displays the association of TOD with cfPWV and/or PPA analyzed by the multivariable logistic regression analysis. When cfPWV and PPA were separately entered into the regression model together with other conventional CV risk factors, cfPWV was significantly associated with arterial plaque (odds ratio [OR], 1.21 [95% confidence interval [CI], 1.05–1.39] per SD; $P = 0.007$), peripheral artery disease (OR, 1.22 [95% CI, 1.06–1.42] per SD; $P = 0.007$), chronic kidney diseases (OR, 1.24 [95% CI, 1.01–1.54] per SD; $P = 0.04$) and microalbuminuria (OR, 1.21 [95% CI, 1.07–1.37] per SD; $P = 0.002$), whereas PPA was significantly associated with LVH (OR, 0.85 [95% CI, 0.72–0.99] per SD; $P = 0.04$) and LVDD (OR, 0.78 [95% CI, 0.64–0.96] per SD; $P = 0.02$). When cfPWV and PPA were both entered into the model with similar adjustment, cfPWV was significantly associated with arterial plaque (OR, 1.20 [95% CI, 1.04–1.37] per SD; $P = 0.01$), peripheral artery disease (OR, 1.21 [95% CI, 1.05–1.40] per SD; $P = 0.01$), chronic kidney diseases (OR, 1.28 [95% CI, 1.03–1.58] per SD; $P = 0.02$) and microalbuminuria (OR, 1.20 [95% CI, 1.06–1.36] per SD; $P = 0.005$), while PPA was significantly associated with LVH (OR, 0.85 [95% CI,
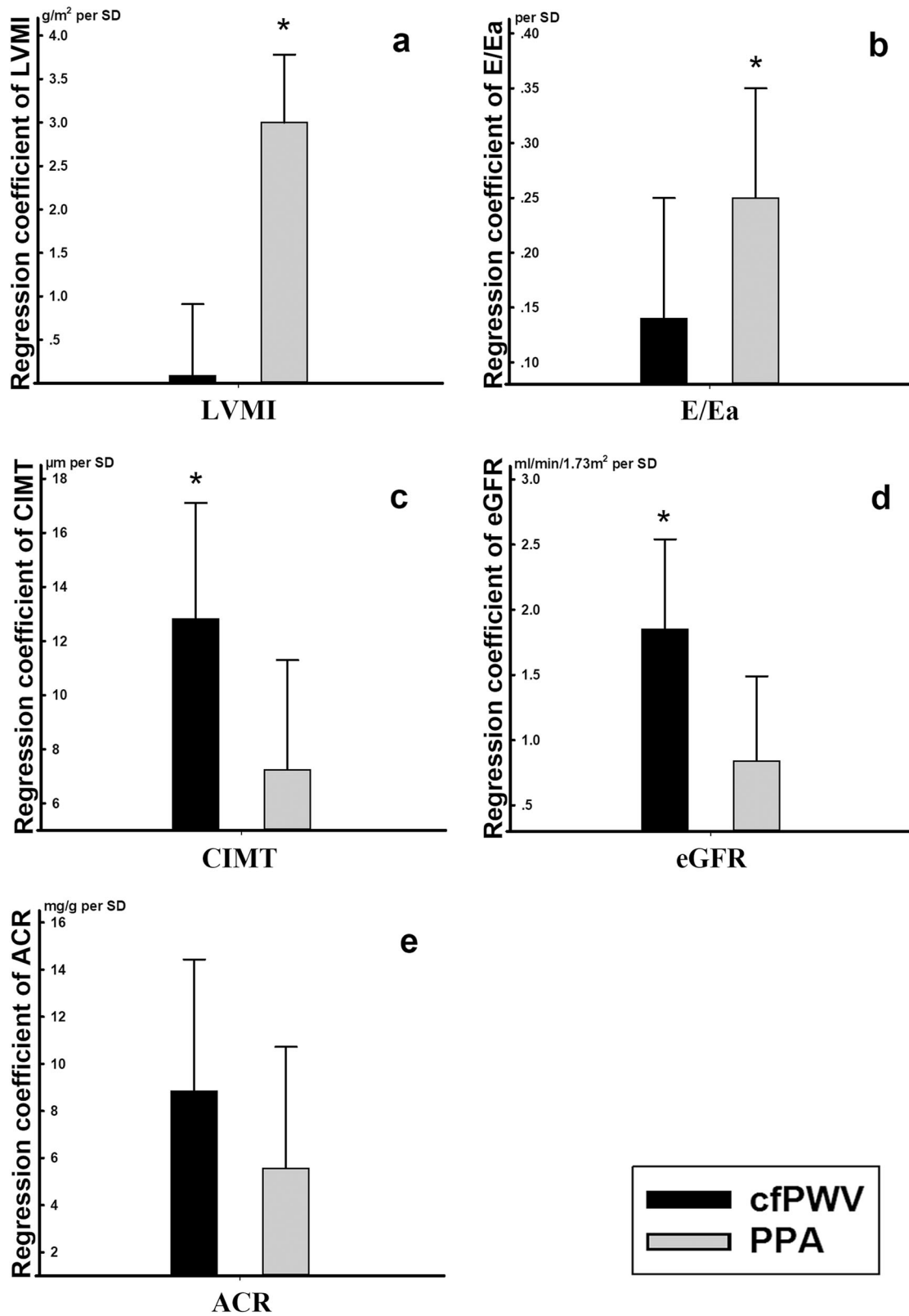
Fig. 1 Regression coefficients of target organ damage with the carotid-femoral pulse wave velocity and/or pulse pressure amplification (**a** LVMI, **b** E/Ea, **c** CIMT, **d** eGFR, **e** ACR) The regression coefficient of variables and standard deviation (SD) are presented. Asterisk represents variables that were significantly associated ($p < 0.05$). cfPWV carotid-femoral pulse wave velocity, PPA pulse pressure amplification, TOD target organ damage, E/Ea the ratio of the early ventricular filling velocity (E) to the peak velocity of tissue Doppler velocity of septal mitral annulus, LVMI left ventricular mass index, CIMT carotid intima-medium thickness, eGFR estimated glomerular filtration rate, ACR urinary albumin–creatinine ratio

0.73–1.00] per SD; $P = 0.05$) and LVDD (OR, 0.79 [95% CI, 0.64–0.97] per SD; $P = 0.02$).

Figure 2 displays the OR and 95% CI in the multivariable logistic regression analysis with the same adjustment strategy when cfPWV and PPA were entered into the model separately. Only PPA had significant OR with LVH (OR, 0.85 [95% CI, 0.72–0.99] per SD; $P = 0.04$) and LVDD (OR, 0.78 [95% CI, 0.64–0.96] per SD; $P = 0.02$), whereas only cfPWV had significant OR with arterial plaque (OR, 1.21 [95% CI, 1.05–1.39] per SD; $P = 0.007$), peripheral artery disease (OR, 1.22 [95% CI, 1.06–1.42] per

SD; $P = 0.007$), chronic kidney diseases (OR, 1.24 [95% CI, 1.01–1.54] per SD; $P = 0.04$) and microalbuminuria (OR, 1.21 [95% CI, 1.07–1.37] per SD; $P = 0.002$).

Discussion

In this study, we assessed cfPWV and PPA in a community-based elderly population located in northern Shanghai and compared their relationships with other TOD. Our results showed that: (1) cfPWV, as an indicator of arterial stiffness,
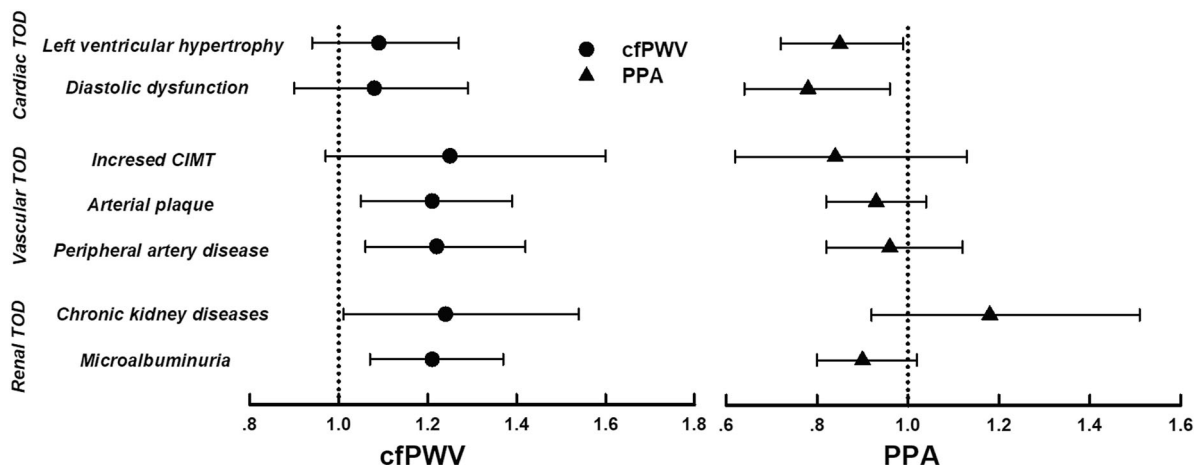
Table 4 Association of target organ damage with carotid-femoral pulse wave velocity and/or pulse pressure amplification

| | Risk factors + cfPWV [a] | | | Risk factors + PPA[a] | | | Risk factors + cfPWV + PPA[b] | | | | | |
| | cfPWV | | | PPA | | | cfPWV | | | PPA | | |
	OR	CI	P	OR	CI	P	OR	CI	P	OR	CI	P
Cardiac TOD												
Left ventricular hypertrophy	1.09	0.94, 1.27	0.24	0.85	**0.72, 0.99**	**0.04**	1.07	0.92,1.24	0.41	0.85	**0.73, 1.00**	**0.05**
Diastolic dysfunction	1.08	0.90, 1.29	0.41	0.78	**0.64, 0.96**	**0.02**	1.06	0.88,1.27	0.54	0.79	**0.64, 0.97**	**0.02**
Vascular TOD												
Increased CIMT	1.25	0.97, 1.60	0.09	0.84	0.62, 1.13	0.25	1.19	0.92,1.55	0.19	0.86	0.64,1.16	0.33
Arterial plaque	1.21	**1.05, 1.39**	**0.007**	0.93	0.82, 1.04	0.20	1.20	**1.04, 1.37**	**0.01**	0.94	0.83,1.06	0.31
Peripheral artery disease	1.22	**1.06, 1.42**	**0.007**	0.96	0.82, 1.12	0.58	1.21	**1.05, 1.40**	**0.01**	0.98	0.84,1.15	0.84
Renal TOD												
Chronic kidney diseases	1.24	**1.01,1.54**	**0.04**	1.18	0.92,1.51	0.20	1.28	**1.03, 1.58**	**0.02**	1.23	0.96,1.58	0.10
Microalbuminuria	1.21	**1.07,1.37**	**0.002**	0.90	0.80,1.02	0.09	1.20	**1.06, 1.36**	**0.005**	0.92	0.81,1.04	0.18

Association of target organ damage with carotid-femoral pulse wave velocity and/or pulse pressure amplification was analyzed by the multivariable logistic regression analysis. The model was adjusted by age, gender, waist/hip circumference, body mass index, fasting plasma glucose, smoking, family history of cardiovascular diseases, systolic blood pressure, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol

cfPWV carotid-femoral pulse wave velocity, *PPA* pulse pressure amplification, *TOD* target organ damage, *CIMT* carotid intima-medium thickness

[a] Two independent variable were separately added to each regression model

[b] Two independent variable were added to one regression model together

Fig. 2 Odds ratio (OR) and 95% Confidence Interval (CI) of target organ damage with the carotid-femoral pulse wave velocity and/or pulse pressure amplification. cfPWV carotid-femoral pulse wave velocity, PPA pulse pressure amplification, TOD target organ damage, CIMT carotid intima-medium thickness

was not only significantly associated with vascular TOD, such as increased CIMT, arterial plaque and peripheral artery disease, but also significantly associated with renal TOD, such as chronic kidney diseases and micro-albuminuria; (2) PPA, as an indicator of cardiac pressure load, was significantly associated with cardiac TOD, such as LVH and LVDD. Similar to our results, PPA, rather than cfPWV, was shown to be significantly associated with higher prevalence of heart disease [17], LVMI and treatment-induced LVMI change [18] in previous studies.

In our study, PPA or cfPWV were added to each regression model separately and then were added to one regression model together. Because cfPWV and PPA are both parameters of arterial stiffness, they are tightly correlated. To avoid the problem of multicollinearity, we presented the results using multivariable linear and logistic regression analyses including cfPWV and PPA separately. Nevertheless, in our hypothesis, cfPWV and PPA were different indexes and might have different impacts on artery stiffness. To compare the relationship between other TOD with cfPWV and PPA, we performed the analysis with cfPWV and PPA together to determine which one to keep in the model. Both analyses had similar findings, which supports the different roles of cfPWV and PPA as we previously hypothesized.

In the multivariable linear analyses, cfPWV was significantly associated with eGFR but not ACR. Although both eGFR and ACR are biomarkers of renal function, there are some differences between the parameters. After leaking through the glomerulus, albumin is excreted into the urine and then reabsorbed by the tubules. Hence, presence of albuminuria suggests damage in both the glomerulus and the tubules [19]. In contrast, worsening of eGFR only suggests damage in the glomerulus [20]. As a vascular biomarker, cfPWV reflects the vessel elasticity of the aorta and is significantly associated with arterial changes, including glomerulus damage, but not associated with damage in the tubules. Moreover, for patients with elevated serum creatinine (low eGFR), the ACR may be overestimated and cannot truly reflect the severity of albuminuria because of the reduction in the amount of creatinine excreted in the urine. Although ACR was not significantly associated with cfPWV when it was presented as a continuous variable in the quantitative analysis, micro-albuminuria (defined by ACR > 30 mg/g), as the pathophysiological definition of ACR, was significantly associated with cfPWV. It seems that the association of ACR with cfPWV only exists at the pathophysiological level, but not at the physiological level.

Numerous clinical investigations have provided solid evidence that cfPWV was an independent predictor of CV and all-cause mortality in different populations, including patients with end-stage renal disease [21–23], hypertension [24], diabetes or glucose intolerance [25] and the general population [3, 26]. cfPWV also predicted the occurrence of stroke-related death in the overall population (RR 1.39 [95% CI, 1.08 to 1.72]; $P = 0.02$) [27]. In the Framingham study [2], higher aortic PWV was independently associated with a 48% increase in CVD risk ($P = 0.002$) and the integrated discrimination improvement was 0.7% ($P < 0.05$) after cfPWV was added to a standard risk factor model. However, in the elderly, the predictive significance of cfPWV for all-cause mortality became controversial. In a meta-analysis that included 17,635 participants [28], the association of CV events and cfPWV was found to decrease with age (1.89, 1.77, 1.36, and 1.23 for age ≤ 50, 51–60, 61–70, and >70 years, respectively; all $P < 0.001$). In the PARTAGE (predictive values of BP and arterial stiffness in institutionalized very aged population) study, which enrolled a total of 1126 subjects (mean age, 88 ± 5 years) living in French and Italian nursing homes, cfPWV failed to predict all-cause and CV mortality after adjustment for conventional CV risk factors, while PPA was significantly associated with all-cause and CV mortality [6]. Several other studies have also demonstrated the significant association between PPA and CV complications [7, 29, 30].

Theoretically, aortic stiffness normally begins to increase in middle age because of aging-associated physiological changes, but some diseases or CV risk factors can accelerate the progress of aortic stiffening through different pathological modalities [31–33]. In theory, aortic stiffening accelerates the return of the backward pressure waveform [34], resulting in various adverse hemodynamic consequences, such as isolated systolic hypertension, increased left ventricular afterload and impaired coronary perfusion. The latter may further promote ventricular stiffening and hypertrophy [35], leading to LVDD and heart failure [36]. For a given BP, lower PPA indicates higher central pulse pressure, which means higher left ventricular afterload. This may explain why PPA is significantly associated with cardiac TOD. On the other hand, previous investigations [37–39] indicated that the association between age and cfPWV was appropriately expressed by a quadratic nonlinear model instead of a linear model. The increase in PWV with age was rapid in elderly subjects, which may help to explain why cfPWV is significantly associated with both CV and all-cause mortality in middle age or younger populations but failed to predict all-cause and CV mortality in the elderly.

Because cfPWV is a vascular marker and has more pronounced prognostic value in the middle-aged population, routine PWV assessment beginning in middle-age is recommended. However, in the elderly population, especially those with high CV risk, considering the prognostic value of PPA in this cohort, we recommend those patients

undergo a PPA measurement and that the results be taken into account in patients' treatment strategy.

This is the first large-scale study assessing both cfPWV and PPA and their association with TOD in a community-based elderly population. The major limitation of the study is its cross-sectional design, which hampers the causality assessment. Nevertheless, the NSS is an on-going prospective study, and with follow-up, we will be able to present more prognostic data in the near future. More specifically, the prognostic data will be helpful for understanding the role of cfPWV and PPA and their relationships with modifications of other TOD.

Conclusions

In summary, in the community-based elderly population, cfPWV is a vessel-related and renal-related biomarker, whereas PPA is a cardiac-related biomarker.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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