



The association between orthostatic blood pressure changes and subclinical target organ damage in subjects over 60 years old

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Abstract

Background Although recent studies have indicated that both orthostatic hypotension and orthostatic hypertension independently predict cardiovascular events, the underlying mechanisms are still controversial. The aim of the study was to investigate the relationships between orthostatic changes and organ damage in subjects over 60 years old. **Methods** This is a prospective observational cohort study. One thousand nine hundred and ninety-seven subjects over 60 years old were enrolled. Participants were grouped according to whether they had a drop ≥ 20 mmHg in systolic or ≥ 10 mmHg in diastolic BP (orthostatic hypotension), an increase in mean orthostatic systolic blood pressure ≥ 20 mmHg (orthostatic hypertension), or normal changes within 3 min of orthostatism. Multiple regression modeling was used to investigate the relationship between orthostatic hypotension, orthostatic hypertension and subclinical organ damage with adjustment for confounders. **Results** Orthostatic hypotension and orthostatic hypertension were found in 461 (23.1%) and 189 (9.5%) participants, respectively. Measurement of carotid intima-media thickness (IMT), brachial-ankle pulse wave velocity (baPWV), clearance of creatinine, and microalbuminuria were associated with orthostatic hypotension; measurement of IMT and baPWV were associated with orthostatic hypertension in a crude model. After adjustment, IMT [odds ratio (OR), 95% confidence interval (CI) per one-SD increment: 1.385, 1.052–1.823; $P = 0.02$], baPWV (OR = 1.627, 95% CI: 1.041–2.544; $P = 0.033$) and microalbuminuria (OR = 1.401, 95% CI: 1.002–1.958; $P = 0.049$) were still associated with orthostatic hypotension, while orthostatic hypertension was only associated with IMT (OR = 1.730, 95% CI: 1.143–2.618; $P = 0.009$). **Conclusions** Orthostatic hypotension seems to be independently correlated with increased carotid atherosclerosis, arterial stiffness and renal damage in subjects over 60 years old. Orthostatic hypertension correlates with carotid atherosclerosis only.

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1 Introduction

Orthostatic blood pressure dysregulation is common among elderly people due to the aging process itself as well

as to dysautonomia. Orthostatic hypotension (OH), the most common orthostatic blood pressure dysregulation, predominates in approximately 20%–30% of individuals over 65 years of age^[1,2] and is associated with an increased cardiovascular disease (CVD) unrelated mortality.^[3–6] On the contrary, orthostatic hypertension (OHT) has been less thoroughly analyzed.^[7] The reported prevalence varies because different criteria have been adopted to define it.^[8] Recent researches reveal orthostatic hypertension as an emerging hemodynamic cardiovascular risk factor, particularly in older people.^[7,9] This condition seems to correlate with a greater risk of clinical and subclinical CVD events and higher mortality in the elder population.^[8–10] However, the underlying mechanisms are still the subject of debate,

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particularly on the association between directions of orthostatic blood pressure response and organ damages such as arteriosclerosis progression. To the best of our knowledge, no published data are available on the association between orthostatic hypertension and subclinical target organ damage in Chinese over 60 years old.

Based on these premises, we hypothesized that not only orthostatic hypotension, but also orthostatic hypertension may be associated with subclinical target organ damage. The aim of the present study was thus to examine whether orthostatic changes in blood pressure (defined as orthostatic hypotension and hypertension) were associated with subclinical target organ damage based on the data of Kailuan study (registration number: chiCTR-TNC-1100-1489).

2 Methods

2.1 Data source and subjects

The data for this analysis came from the Kailuan study (trial registration number: ChiCTR-TNRC-11001489), a prospective cohort study from June 2006 to October 2007, based on the Kailuan community in the industrial and modern Tangshan City of China. Health records of 101,510 residents (81,110 males and 20,400 females, aging from 18 to 98 years) in 11 hospitals responsible for healthcare of the Kailuan community were established, as previous description.^[11] The recruited residents satisfied the following criteria: (1) age ≥ 18 years; (2) providing informed consent; and (3) updating their health status according to the follow-up protocol. All participants underwent questionnaire assessment, clinical examination, and laboratory assessments every two years. The study aligned with the guidelines of the Helsinki Declaration and was approved by the Ethics Committees of Kailuan General Hospital with written informed consent from all participants.

Retired participants of Kailuan study (age over 60 years) who underwent their health examinations at Kailuan General Hospital, Kailuan Linxi Hospital, or Kailuan Zhaogezhuang Hospital were abstracted by cluster sampling, with 25% of the population randomly selected as the study candidates. Participants who had taken antipsychotic, anti-Parkinson, antidepressant, α -receptor antagonist drugs within the previous two weeks or with incomplete data were excluded. The study subjects underwent physical examinations and, with their consent, rescheduled a new appointment for blood pressure measurement in different positions, ultrasound examination of cervical blood vessels, pulse wave velocity examination, and urinary microprotein detection.

2.2 Questionnaire assessment and anthropometric index

Face-to-face interviews of participants were performed by trained physicians and nurses. Self-reported information on demographics (age and sex) and lifestyle factors (smoking status, drinking habits, physical inactivity and obesity) were obtained. Body height and weight were measured at the examination center and the body mass index (BMI, kg/m^2) were calculated. Hypertension was defined as the presence of systolic blood pressure (BP) ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or current use of antihypertensive medication. Diabetes mellitus was defined as at least the presence of one of the following criteria: fasting plasma glucose ≥ 7.0 mmol/L, HbA1c $\geq 6.5\%$, or use of glucose-lowering drugs, history of 2 h post-load glucose ≥ 11.1 mmol/L. Smoking was defined as at least an average of one cigarette per day for the last year and alcohol use was defined as drinking alcohol more than 100 mL per day at least for one year. Physical exercise was defined as aerobic exercise longer than 30 min once and more than 3 times per week.

2.3 Definition of orthostatic hypertension and hypotension

A standardized protocol for measurements of an auscultatory blood pressure was executed by a trained physician using a mercury sphygmomanometer with appropriate cuff sizes. The mid-point of the right upper arm was ascertained by measuring the length from the tip of the shoulder to the tip of the elbow and dividing this length by 2. The tape was wrapped around the straightened arm at the midpoint identified and the cuff was checked to ensure that it was neither too tight nor too loose. The measurement was recorded to nearest 0.1 cm. Three readings each of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in sitting position were measured at a one-minute interval after participants had quiet rest in chair after 15 min. The average of three times measurements was used for data analysis. Clinostatic blood pressure was documented as the average of 3 readings with 30-s intervals in the right arm of participants at supine position after a 5-min rest. Orthostatic blood pressure and heart rate were then measured after 1 and 3 min of orthostatism. Orthostatic hypotension was defined as a drop of SBP ≥ 20 mmHg or a decrease of DBP ≥ 10 mmHg in one of the two measures, in accordance with the guidelines of the Consensus Committee of the American Autonomic Society and the American Academy of Neurology.^[12] Due to the paucity of formal consensus on definition of orthostatic hypertension, we adopted the most common-used one, an increase over 20 mmHg in SBP calculated as the mean of the orthostatic SBP measurements minus the clinostatic blood pressure before standing.^[8]

2.4 Laboratory data collection and calculation

Fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-sensitivity C-reactive protein (hs-CRP), and serum creatinine (Cr) were obtained at the initial study visit. All these biochemical data were measured using a 7600 Biochemistry Auto-Analyzer (Hitachi, Tokyo, Japan) at the central laboratory of Kailuan General Hospital by the same medical staffs. A 5-mL midstream urine specimen was obtained from the first-morning void urine for every subject. Participants were required to avoid exercise the day before sample collected. Urine albumin in fresh urine samples was determined in laboratory within 24 h after collection. Microalbuminuria (ALBU) was assessed by immunoturbidimetry (Uppergold U2, Shanghai Upper Bio-tech Pharmaceutical Co., Ltd, China) with spot urine sample. In this study, increased ALBU was defined as $ALBU \geq 30$ mg/L.^[13] Creatinine clearance (CCr) was estimated using the Cockcroft-Gault equation.^[14]

2.5 Brachial-ankle pulse wave velocity measurement

In this study, baPWV was measured independently by trained nurses using a noninvasive vascular screening device (OMRON, BP-203RPE III, Japan). Participants refrained from smoking or drinking beverages for 24 h before the examination and were examined twice in supine position after resting in air-conditioned room (22–25 °C) for at least 5 min. The arms and ankles were wrapped in cuffs, electrodes of the electrocardiogram were placed on both wrists, and a microphone to detect heart sounds was placed on the left edge of the sternum. The lower edge of the arm cuff was placed 2–3 cm above the transverse striation of the cubital fossa, while the lower edge of the ankle cuff was placed 1–2 cm above the superior aspect of the medial malleolus. The second reading of two measurements in all participants and the higher value of the left and right baPWV were used for data analysis.

2.6 Ultrasonographic examination

A B-mode ultrasound machine (Philips, HD-15) equipped with a 5–12 MHz linear scan type B-mode probe was used for IMT detection. All participants were kept in the supine position. The IMT was measured at the most clearly depicted position, from the far wall of the bilateral common carotid artery 1 cm proximal to the carotid bifurcation. Longitudinal section of the rear arterial wall and outside of any plaque detected were selected for measurements. In accordance with the method of Hedblad, *et al.*,^[15] the higher value for the left and the right common carotid artery IMT

was taken for analysis. A common carotid IMT ≥ 1.00 mm was defined as an increase in IMT.

2.7 Statistical methods

Data were analyzed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). To test for normal distribution, the Kolmogorov–Smirnov test was applied. Continuous and normal distributed variables were presented as mean values \pm SD, while categorical variables were presented as frequencies. Data showing abnormal distribution were expressed as median (interquartile range). Inter-group comparisons were performed by one-way ANOVA analysis. Categorical variables were described by frequency with percentages and compared using χ^2 -test. We used logistic regression to assess the association of OH/OHT with subclinical target organ damage, i.e., IMT, baPWV, CCr and ALBU. Multivariate model was first adjusted for age and sex and a final model additionally adjusted for sitting systolic blood pressure, sitting diastolic blood pressure, body mass index, fasting blood glucose, low-density lipoprotein cholesterol, high-sensitive C reactive protein, current smoker, drinking, exercise, previous history of hypertension and previous history of diabetes. Odds ratios (ORs) were calculated per one SD increment in the analyzed parameter unless specifically indicated. All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics

A total of 1997 participants with complete data were included in the statistical analysis. The mean age was 66.94 ± 5.77 years and 67.5% were males. In the sample as a whole, the prevalence of orthostatic hypotension and hypertension were 23.1% and 9.5%, respectively. As shown in Table 1, participants with normal orthostatic (ONT) changes in blood pressure (BP) were significantly younger than those with orthostatic hypotension or with orthostatic hypertension (both $P < 0.001$). No significant difference emerged for gender (P for overall comparisons = 0.552).

Compared with participants under normal orthostatic BP changes, participants with orthostatic hypotension had significantly elder age ($P < 0.001$), higher level of low density lipoprotein cholesterol ($P < 0.001$) and had more frequently been diagnosed with hypertension ($P = 0.035$) or diabetes ($P < 0.001$). Participants with orthostatic hypertension had elder age ($P = 0.012$), higher body mass index level ($P =$

Table 1. Participants' characteristics by changes in their orthostatic blood pressure.

Variables	Orthostatic hypotension (n = 461)	Normal changes (n = 1347)	Orthostatic hypertension (n = 189)	Orthostatic hypotension vs. normal changes, P value	Orthostatic hypertension vs. normal changes, P value	Overall comparison, P value
Age, yrs	67.95 ± 5.94	66.50 ± 5.59	67.62 ± 6.19	< 0.001	0.012	< 0.001
Male	320 (69.4%)	897 (66.6%)	131 (69.3%)	0.275	0.509	0.495
BMI, kg/m ²	25.52 ± 3.40	25.20 ± 3.35	25.90 ± 3.86	0.141	0.027	0.047
Heart rate, beats/min	72.48 ± 11.60	71.53 ± 10.31	74.63 ± 11.18	0.164	0.002	0.005
FBG, mmol/L	6.08 ± 1.85	5.80 ± 1.59	5.91 ± 1.59	0.007	0.476	0.025
LDL-C, mmol/L	2.99 ± 1.04	2.80 ± 0.79	2.87 ± 0.74	< 0.001	0.417	0.002
HDL-C, mmol/L	1.50 ± 0.42	1.53 ± 0.44	1.55 ± 0.47	0.216	0.660	0.373
TG, mmol/L	1.67 ± 1.20	1.53 ± 1.15	1.55 ± 0.99	0.042	0.828	0.126
Creatine, μmol/L	78.58 ± 17.40	77.08 ± 19.43	78.45 ± 16.36	0.196	0.423	0.365
Hs-CRP, mg/L	1.46 (0.74,2.71)	1.16 (0.68,2.30)	1.40 (0.80,2.65)	0.728	0.562	0.762
Current smoker	91 (25.9%)	293 (28.9%)	36 (26.7%)	0.302	0.685	0.536
Drinking	83 (23.6%)	262 (25.8%)	36 (26.7%)	0.434	0.835	0.679
Exercise	262 (74.4%)	769 (75.6%)	105 (78.4%)	0.667	0.521	0.666
Blood pressure measurement						
Sitting systolic BP, mmHg	139.36 ± 21.63	136.57 ± 20.60	141.03 ± 18.24	0.031	0.019	0.013
Sitting diastolic BP, mmHg	83.94 ± 10.66	83.16 ± 10.94	85.89 ± 11.46	0.252	0.007	0.020
Clinostatic systolic BP, mmHg	145.25 ± 21.46	135.8 ± 18.28	134.19 ± 20.94	< 0.001	0.282	< 0.001
Clinostatic diastolic BP, mmHg	82.63 ± 10.77	78.77 ± 10.30	79.98 ± 10.87	< 0.001	0.136	< 0.001
Clinostatic heart rate, beats/min	75.18 ± 12.82	73.16 ± 10.93	75.23 ± 13.75	0.001	0.023	0.001
1 min standing SBP, mmHg	128.14 ± 23.51	134.36 ± 19.29	150.60 ± 25.29	< 0.001	< 0.001	< 0.001
1 min standing DBP, mmHg	76.65 ± 11.80	81.43 ± 10.76	85.74 ± 11.81	< 0.001	< 0.001	< 0.001
1 min standing heart rate, beats/min	83.69 ± 13.98	80.58 ± 13.12	81.84 ± 13.32	< 0.001	0.228	< 0.001
3 min standing SBP, mmHg	134.22 ± 23.50	136.93 ± 18.60	155.40 ± 22.86	0.013	< 0.001	< 0.001
3 min standing DBP, mmHg	78.81 ± 12.03	82.53 ± 10.72	87.78 ± 12.23	< 0.001	< 0.001	< 0.001
3 min standing heart rate, beats/min	80.88 ± 13.69	79.12 ± 12.11	80.57 ± 12.35	0.010	0.138	0.02
Hypertension	233 (50.7%)	602 (44.9%)	106 (56.4%)	0.035	0.004	0.003
Diabetes	95 (20.6%)	168 (12.5%)	29 (15.3%)	< 0.001	0.295	< 0.001

Data are expressed as mean ± SD, median (interquartile range) or *n* (%), as appropriate. BMI: body mass index; BP: blood pressure; DBP: diastolic blood pressure; FBG: fasting blood sugar; HDL-C: high density lipoprotein cholesterol; hs-CRP: high sensitive C-reaction protein; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; TG: triglyceride.

0.047), higher levels of sitting SBP ($P = 0.019$), and had more frequently been diagnosed with hypertension ($P = 0.004$) than subjects with normal orthostatic changes in BP.

3.2 Association between orthostatic changes of blood pressure and target organ damage

Table 2 presented the comparisons of subclinical target organ damage in those with or without orthostatic changes of BP. The average levels of baPWV [1754.50 (1560.75, 1972.50) vs. 1640.50 (1473.00, 1786.00) cm/s, $P < 0.001$], IMT (1.04 ± 0.19 vs. 1.02 ± 0.19 mm, $P = 0.014$) and ALBU (34.62 ± 62.07 vs. 26.27 ± 51.96 mg/L, $P = 0.007$) were significantly higher in the OH group than in the ONT

group. The average levels of baPWV [1710.50 (1498.00, 1918.00) vs. 1640.50 (1473.00, 1786.00) cm/s, $P < 0.001$] and IMT (1.10 ± 0.24 vs. 1.02 ± 0.19 mm, $P < 0.001$) in the OHT group were higher significantly than in the ONT. None difference was observed on CCr among three groups ($P > 0.05$).

3.3 Multiple logistic regression analysis of factors influencing target organ damage indices in different models

Model 1 assumed ALBU, baPWV, IMT, CCr as dependent variables, OH and OHT as the independent variable respectively. Nonconditional logistical regression analysis

Table 2. Association between orthostatic BP states and subclinical target organ damage.

	Orthostatic hypotension (<i>n</i> = 461)	Normal changes (<i>n</i> = 1347)	Orthostatic hypertension (<i>n</i> = 189)	Orthostatic hypotension vs. normal changes, <i>P</i> value	Orthostatic hypertension vs. normal changes, <i>P</i> value	Overall comparison, <i>P</i> value
IMT, mm	1.04 ± 0.19	1.02 ± 0.19	1.10 ± 0.24	0.014	< 0.001	< 0.001
BaPWV, cm/s	1754.50 (1560.75, 1972.50)	1640.50 (1473.00, 1786.00)	1710.50 (1498.00, 1918.00)	< 0.001	< 0.001	< 0.001
cCr, mL/min per 1.73 m ²	78.54 ± 19.27	82.60 ± 41.15	80.23 ± 20.06	0.074	0.645	0.186
ALBU, mg/L	34.62 ± 62.07	26.27 ± 51.96	23.54 ± 28.28	0.007	0.552	0.015

Data are expressed as mean ± SD or median (interquartile range). ABI: ankle brachial index; ALBU: urinary microalbumin; BaPWV: Brachial-ankle pulse wave velocity; BP: blood pressure; cCr: clearance of creatine; IMT: intima-media thickness.

Table 3. Multiple logistic regression models for prediction of subclinical organ damage in different models.

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
IMT, mm						
OH	1.571 (1.290–1.911)	< 0.001	1.492 (1.196–1.863)	< 0.001	1.385 (1.052–1.823)	0.02
OHT	2.283 (1.653–3.153)	< 0.001	2.156 (1.536–3.028)	< 0.001	1.730 (1.143–2.618)	0.009
BaPWV, cm/s						
OH	7.583 (5.357–10.735)	< 0.001	1.870 (1.276–2.741)	0.001	1.627 (1.041–2.544)	0.033
OHT	5.500 (3.329–9.088)	< 0.001	1.329 (0.781–2.262)	0.295	1.468 (0.736–2.930)	0.276
CCr, mL/min per 1.73 m ²						
OH	1.260 (1.014–1.566)	0.037	1.177 (0.920–1.506)	0.194	1.304 (0.986–1.724)	0.063
OHT	1.129 (0.802–1.589)	0.487	1.040 (0.724–1.494)	0.831	1.111 (0.746–1.653)	0.605
ALBU, mg/L						
OH	1.628 (1.241–2.138)	< 0.001	1.610 (1.226–2.115)	0.001	1.401 (1.002–1.958)	0.049
OHT	1.070 (0.690–1.658)	0.762	1.047 (0.675–1.625)	1.047	0.732 (0.410–1.307)	0.292

Model 1, crude; Model 2, adjusted for age and sex; Model 3, adjusted for age, sex, sitting systolic blood pressure, sitting diastolic blood pressure, body mass index, fasting blood glucose, low-density lipoprotein cholesterol, high-sensitive C reactive protein, current smoker, drinking, exercise, previous history of hypertension and previous history of diabetes. ALBU: urinary microalbumin; baPWV: Brachial-ankle pulse wave velocity; Ccr: clearance of creatine; CI: confidence index; IMT: intima-media thickness; OH: orthostatic hypotension; OHT: orthostatic hypertension; OR: odd ratio.

was carried out to determine the effect of OH and OHT on ALBU, baPWV, IMT and CCr. The results indicated that OH was a risk factor for decreased CCr, increased baPWV, ALBU and IMT. OHT was a risk factor for baPWV and IMT increment (Table 3). Model 2 was based on Model 1, with corrections for age and sex. Model 3 was based on Model 2, with adjustment for potential risk factors such as age, sex, sitting SBP, sitting DBP, BMI, FBG, LDL-C, hs-CPR, current smoker, drinking, exercise, history of hypertension and history of diabetes. The findings indicated that OH was a risk factor for increased IMT (OR = 1.385, 95% CI: 1.052–1.823, *P* = 0.02), baPWV (OR = 1.627, 95% CI: 1.041–2.544, *P* = 0.033) and ALBU (OR = 1.401, 95% CI: 1.002–1.958, *P* = 0.049). OHT was a risk factor of increased IMT (OR = 1.730, 95% CI: 1.143–2.618, *P* = 0.009) and the correlation between OHT and baPWV was not statically significant after adjustment for associated factors (Table 3).

4 Discussion

In this large sample of community-based subjects aged over 60 years, nearly 33% of the population presented with abnormal BP responses to standing: 23.1% met the definition of OH and 9.5% met the definition of OHT. The average values of baPWV, IMT and ALBU were higher in the OH group than in the OHT group and the average levels of baPWV and IMT were higher in OHT group than in the OHT group. Multiple variate logistic regression analysis revealed that OH was an independent risk factor for target organ damage, as reflected by various indices, while OHT significantly associated with increased IMT. These data suggested that abnormal orthostatic BP changes were closely related to target organ damage and may serve as potential/subclinical markers for cardiovascular risk evaluation among community-dwelling individuals aging over 60 years.

Orthostatic hypotension is frequent in the elder population, with a prevalence of 15% to 25%,^[16] in accordance with our observation. Orthostatic hypotension results from failure of neural and circulatory mechanisms to compensate for the reduction in venous return during the upright posture, probably correlated with baroreceptors in the carotid artery, aorta, and cardiopulmonary region. Baroreceptors respond to the drop in blood pressure and induce cardiac changes as part of the sympathetic reflex to preserve a constant level of arterial pressure and maintain cerebral perfusion against the force of gravity.^[17] Age-associated reductions in baroreflex function have been demonstrated to be associated with the occurrence of OH.^[17] Arterial stiffening is suggested to be another potential mechanism for OH, as the arterial stretch over segments with the baroreceptors is a key determinant in baroreflex activation.^[18–20] The reduction in cardiac output is also a concern, especially in the elderly probably with stiff and noncompliant aged heart, which results in impaired diastolic filling and consequently decreased stroke volume.^[16]

Emerging evidences suggest that orthostatic BP changes are associated with poor cardiovascular outcomes including stroke^[5] and coronary heart disease.^[4,21] Some studies report that the presence of orthostatic hypotension increases the risk of non-cardiovascular mortality or all-cause mortality in elderly population.^[3,10,22,23] However, the underlying mechanisms are still unclear. Whether or not orthostatic blood pressure response is associated with arteriosclerosis and vascular remodeling remains a subject of debate. Previous studies report that patients with OH have increased arterial stiffness, brachial-ankle pulse wave velocity, or carotid to femoral pulse wave velocity compared with healthy individuals.^[24,25] Orthostatic hypotension-related IMT increment in older nondiabetic adults^[26] and in middle aged individuals^[4] are also demonstrated, indicating that results of the present study in elder community-based population are generalizable although methods for arterial stiffness measurement differ. Potential explanations for the association between atherosclerosis and OH include: first, atherosclerosis risk factors such as hypertension, age, and diabetes mellitus are also related to OH (the correlation between OH and atherosclerosis risk factors such as hypertension, age, and diabetes mellitus is also demonstrated in our study). Second, the sensitivity of the baroreceptors in the arterial wall deteriorates as artery stiffens with aging. The relationship between OH and renal damage remains further exploration for the paucity of data describing the relationship between postural BP responses and kidney damage. It has been reported that ALBU is useful as a marker of endothelial dysfunction atherosclerosis and is associated with end-organ damage and cardiovascular events.^[27,28] A study examining deter-

minants of OH in middle-aged male adults presents a cross-sectional association between postural SBP impairment and lower glomerular filtration rate.^[29] A longitudinal study of middle-aged community-dwelling adults demonstrates an increased risk of incident kidney dysfunction with OH.^[30] To the best of our knowledge, we report for the first time that OH is associated with the increment of ALBU. However, the relationship between OH and renal damage in elder population remains to be further studied.

There is a dearth of information relating to the prevalence of OHT among the elderly and its clinical implications.^[31] Aries, *et al.*^[32] find a favorable outcome in patients with acute stroke if a significant blood pressure rise occurs during early upright position. However, another study demonstrate that OHT is related to all-cause and cardiovascular mortality in a group of community-dwelling elderly patients.^[10] It is an underappreciated and understudied clinical phenomenon which needs focused basic science and clinical inquiry.

One cross-sectional study reveals an association between OHT and peripheral arterial disease in 800 subjects aged from 40 to 75 years.^[33] Another cross-sectional investigation on 241 elderly hypertensive patients observes an increased prevalence of advanced silent cerebrovascular disease in OHT.^[34] It is also found to be associated with higher cardiovascular morbidity and mortality independent of sitting BP levels and major comorbidities in an old frail population.^[35] To the best of our knowledge, this is the first study to indicate an association between OHT and subclinical target organ damage in a general population. In this study on subjects aged over 60 years, OHT occurred in 9.1% subjects, similar to findings from a previous study with a 6.4% prevalence of OHT.^[26] In addition, we demonstrate that IMT is significantly associated with OHT. The hypothetical mechanisms might include primary hyperactivation of vasoconstrictors during orthostasis. Increase of BP on standing can also involve similar vascular mechanisms as those found in essential hypertension, which may accelerate atherosclerosis in peripheral artery. Moreover, Nocturnal hypertension, often associated with orthostatic hypertension,^[36] has been shown to promote carotid and systemic atherosclerosis by increasing the tonic pressure load during sleep.^[37]

Above all, our study has added to the evidence that OH and OHT have relationship with the risk for target organ damage. These well-established predictors of mortality and cardiovascular morbidity (i.e., IMT, baPWV and ALBU) offer a plausible explanation for the increased risk of various fatal and nonfatal events observed in OH or OHT. Because of the cross-sectional design of our study, we could not establish a causal relationship between orthostatic BP

changes and subclinical target organ damage. However, postural BP change may increase arterial wall stress through both mechanical injuries and release of vasoactive substances such as nitric oxide,^[38] which may accelerate the progression of atherosclerosis. Moreover, OH and OHT often occurs in patients with autonomic failure. Previous studies observe in these patients that the tension of the postganglionic sympathetic nerve increases, the regulatory function of the pressure sensor decreases significantly, and the arterial structure could also change.^[39] Changes in arterial structure often present as an increase in the wall-to-lumen ratio. Arterial wall thickening probably attributes to increased arterial stiffness, which can lead to increased baPWV and IMT. As arterial stiffness increases, the regulatory function of the pressure sensors inside the artery wall might be affected, which in turn influences the orthostatic changes of BP.

This study has several limitations. First, it was a cross-sectional study, so it could not establish a causal relationship between orthostatic BP changes and target organ damage. Second, 47% coexisted with hypertension and 14% suffered from diabetes mellitus. The high concurrent proportion of hypertension and diabetes mellitus supposed to have influence on the prevalence of OH and OHT in subjects over 60 years old. Thirdly, some other factors influencing hemodynamic homeostasis such as sodium consumption was not applicable from our data resource. Furthermore, subjects were not asked to withhold prescription medication use prior to participation, which might have influenced the BP and HR responses to standing. In addition, our results apply only to subjects over 60 years old. Further investigation is required to determine whether our conclusions can be extended to other population. Nevertheless, this study is instructive with respect to orthostatic blood pressure management and the prevention of subclinical target organ damage in subjects over 60 years old.

In conclusion, our study demonstrates that both OH and OHT are significant risk factors for target organ damage, as determined by the indices including baPWV, IMT and ALBU, in community-based subjects over 60 years old. The association of OH with ALBU and kidney damage requires further study. Other than adding to our knowledge of the relationship between orthostatic blood pressure changes and target organ damage, the study underlines the importance of orthostatic BP changes on evaluating and possibly managing subclinical target organ damage. However, further studies are necessary to confirm the replicability of our results and to determine whether they can be extrapolated to a wider population.

Competing interests

The authors declare that they have no competing interests.

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References

- 1 Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007; 120: 841–847.
- 2 Veronese N, Bolzetta F, De Rui M, *et al.* Serum 25-hydroxyvitamin D and orthostatic hypotension in old people: the Pro.V.A. study. *Hypertension* 2014; 64: 481–486.
- 3 Xin W, Lin Z, Mi S. Orthostatic hypotension and mortality risk: a meta-analysis of cohort studies. *Heart* 2014; 100: 406–413.
- 4 Rose KM, Tyroler HA, Nardo CJ, *et al.* Orthostatic hypotension and the incidence of coronary heart disease: the atherosclerosis risk in communities study. *Am J Med* 2000; 13: 571–578.
- 5 Eigenbrodt ML, Rose KM, Couper DJ, *et al.* Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987-1996. *Stroke* 2000; 31: 2307–2313.
- 6 Jones CD, Loehr L, Franceschini N, *et al.* Orthostatic hypotension as a risk factor for incident heart failure: the atherosclerosis risk in communities Study. *Hypertension* 2012; 59: 913–918.
- 7 Robertson D. Orthostatic hypertension: the last hemodynamic frontier. *Hypertension* 2011; 57: 158–159.
- 8 Kario K. Orthostatic hypertension—a new haemodynamic cardiovascular risk factor. *Nat Rev Nephrol* 2013; 9: 726–738.
- 9 Eguchi K, Kario K, Hoshida S, *et al.* Greater change of orthostatic blood pressure is related to silent cerebral infarct and cardiac overload in hypertensive subjects. *Hypertens Res* 2004; 27: 235–241.
- 10 Veronese N, De Rui M, Bolzetta F, *et al.* Orthostatic changes in blood pressure and mortality in the elderly: The Pro.V.A Study. *Am J of Hypertens* 2015; 28: 1248–1256.
- 11 Wu S, Huang Z, Yang X, *et al.* Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern Chinese industrial city. *Circ Cardiovasc Qual Outcomes* 2012; 5: 487–493.
- 12 Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *J Neurol Sci* 1996; 144: 218–219.

- 13 Ogedegbe G, Spruill TM, Sarpong DF, *et al.* Correlates of isolated nocturnal hypertension and target organ damage in a population-based cohort of African Americans: the Jackson Heart Study. *Am J Hypertens* 2013; 26: 1011–1016.
- 14 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41.
- 15 Hedblad B, Wikstrand J, Janzon L, *et al.* Low-Dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: Main results from the β -Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation* 2001; 103: 1721–1726.
- 16 Arnold AC, Shibao C. Current concepts in orthostatic hypotension management. *Curr Hypertens Rep* 2013; 15: 304–312.
- 17 Cheng YC, Vyas A, Hymen E, Perlmutter LC. Gender differences in orthostatic hypotension. *Am J Med Sci* 2011; 342: 221–225.
- 18 Monahan KD. Effect of aging on baroreflex function in humans. *Am J Physiol Regul Integr Comp Physiol* 2007; 293: R3-R12.
- 19 Angell James JE. The effects of changes of extramural, 'intra-thoracic', pressure on aortic arch baroreceptors. *J Physiol* 1971; 214: 89–103.
- 20 Avolio AP, Deng FQ, Li WQ, *et al.* Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation* 1985; 71: 202–210.
- 21 Gemignani T, Matos-Souza JR, Franchini KG, Nadruz WJr. Leg blood pressure measured in orthostatic posture is associated with left ventricular mass in normotensive subjects. *Am J Hypertens* 2012; 25: 1083–1087.
- 22 Verwoert GC, Mattac-Raso FU, Hofman A, *et al.* Orthostatic hypotension and risk of cardiovascular disease in elderly people: The Rotterdam Study. *J Am Geriatr Soc* 2008; 56: 1816–1820.
- 23 Angelousi A, Girerd N, Benetos A, *et al.* Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. *J Hypertens* 2014; 32: 1562–1571.
- 24 Sung SH, Chen ZY, Tseng TW, *et al.* Wave Reflections, arterial stiffness, and orthostatic hypotension. *Am J Hypertens* 2014; 27: 1446–1455.
- 25 Takahashi M, Miyai N, Nagano S, *et al.* Orthostatic blood pressure changes and subclinical markers of atherosclerosis. *Am J Hypertens* 2015; 28: 1134–1140.
- 26 Fedorowski A, Ostling G, Persson M, *et al.* Orthostatic blood pressure response, carotid intima-media thickness, and plasma fibrinogen in older nondiabetic adults. *J Hypertens* 2012; 30: 522–529.
- 27 Pedrinelli R, Dell'Omo G, Penno G, Mariani M. Non-diabetic microalbuminuria, endothelial dysfunction and cardiovascular disease. *Vasc Med* 2001; 6: 257–264.
- 28 Pignoli P, Tremoli E, Poli A, *et al.* Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986; 74: 1399–1406.
- 29 Fedorowski A, Stavenow L, Hedblad B, *et al.* Consequences of orthostatic blood pressure variability in middle-aged men (The Malmo Preventive Project). *J Hypertens* 2010; 28: 551–559.
- 30 Franceschini N, Rose KM, Astor BC, *et al.* Orthostatic hypotension and incident chronic kidney disease: the Atherosclerosis Risk in Communities Study. *Hypertension* 2010; 56: 1054–1059.
- 31 Fessel J, Robertson D. Orthostatic hypertension: when pressor reflexes overcompensate. *Nat Clin Pract Nephrol* 2006; 2: 424–431.
- 32 Aries MJ, Bakker DC, Stewart RE, *et al.* Exaggerated postural blood pressure rise is related to a favorable outcome in patients with acute ischemic stroke. *Stroke* 2012; 43: 92–96.
- 33 Fan XH, Wang Y, Sun K, *et al.* Disorders of orthostatic blood pressure response are associated with cardiovascular disease and target organ damage in hypertensive patients. *Am J Hypertens* 2010; 23: 829–837.
- 34 Kario K, Eguchi K, Hoshida S, *et al.* U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. *J Am Coll Cardiol* 2002; 40: 133–141.
- 35 Agnoletti D, Valbusa F, Labat C, *et al.* Evidence for a prognostic role of orthostatic hypertension on survival in a very old institutionalized population. *Hypertension* 2016; 67: 191–196.
- 36 Okamoto LE, Gamboa A, Shibao C, *et al.* Nocturnal blood pressure dipping in the hypertension of autonomic failure. *Hypertension* 2009; 53: 363–369.
- 37 Shintani Y, Kikuya M, Hara A, *et al.* Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the Ohasama study. *J Hypertens* 2007; 25: 1704–1710.
- 38 Montalcini T, Gorgone G, Pujia A. Association between pulse pressure and subclinical carotid atherosclerosis in normotensive and hypertensive post-menopausal women. *Clin Exp Hypertens* 2009; 31: 64–70.
- 39 Garland EM, Gamboa A, Okamoto L, *et al.* The Renal Impairment of Pure Autonomic Failure. *Hypertension* 2009; 54: 1057–1061.