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Sex modification of the association of the radial augmentation index and incident hypertension in a Chinese community-based population

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ABSTRACT

BACKGROUND Arterial stiffness, as assessed by aortic ultrasound and pulse wave velocity, is associated with incident hypertension. However, there is still no consensus on whether the augmentation index (AI) affects new onset of hypertension. This study investigated the relationship of radial AI (rAI) and incident hypertension in a Chinese community-based population without hypertension at baseline.

METHOD A total of 1,615 Chinese non-hypertensive participants from an atherosclerosis cohort in Beijing, China were included in our analysis. Baseline rAI normalized to heart rate of 75 beats/min (rAIp75) was obtained using HEM-9000AI. New-onset hypertension was defined as blood pressure ≥ 140/90 mmHg or self-reported hypertension or taking anti-hypertensive medications at the follow up survey. Multivariate regression models were used to evaluate the impact of rAIp75 on the risk of new-onset hypertension.

RESULTS After a mean 2.35-year follow-up, 213 (13.19%) participants developed incident hypertension. No significant relation between rAIp75 and incident hypertension was observed in the whole population after adjustment for possible confounders (adjusted odds ratio (OR) and 95% confidence interval (CI): 1.09 [0.95−1.27]; P = 0.2260). However, rAIp75 was significantly associated with incident hypertension in women, but not in men (adjusted OR and 95% CI: 1.29 [1.06−1.56], P = 0.0113 for women; 0.91 [0.72−1.15], P = 0.4244 for men; P for interaction = 0.0133).

CONCLUSIONS Sex modified the effect of the rAI on incident hypertension in a Chinese, community-based, non-hypertensive population. Screening of the rAI could be considered in women with a high risk of hypertension for the purpose of primary intervention.

Hypertension is the leading global preventable risk factor for cardiovascular disease (CVD) and premature death.[1] With an aging population and increasing numbers of people living unhealthy lifestyle, China is experiencing an increasing prevalence of hypertension.[2] Therefore, investigating early predictors of the onset of hypertension is crucial for taking precautions against this medical and societal problem.

Arterial stiffness, which is evaluated by carotid-femoral pulse wave velocity (the current gold standard) and ultrasound measurements of the aorta or carotid artery, is an independent predictor of incident hypertension.[3–6] Similarly, the augmentation index (AI), which reflects the interaction between the incident pressure wave and reflected pressure wave, can identify the function of the systemic arterial tree, including the reflectance properties derived from the distal part of the arterial tree.[7,8] Because the AI reflects the development and progression of hypertension, the AI might play a role in screening and precaution of new-onset hypertension.

Previous studies on whether the AI can predict the onset of hypertension have not reached a con-

sistent conclusion.[3,9–11] Therefore, we conducted a study based on a Chinese community population to further examine the relationship between the AI and incident hypertension. Because of the differences in manifestation and morbidity of CVD between sexes,[12,13] increasing attention has been paid to sex differences in blood pressure (BP) and arterial function. Accordingly, we further investigated whether the relationship between the AI and hypertension is affected by sex.

METHODS

Study Population

Participants were those who participated in an atherosclerosis cohort survey, which was performed in Gucheng and Pingguoyuan communities of Shijingshan District in Beijing, China. A total of 9540 residents aged older than 40 years were recruited during December 2011 to April 2012. In 2014, 5962 participants with baseline genetic testing were invited for a follow-up visit, and 3823 of them visited from May 2014 to July 2014. There were no significant differences in baseline characteristics between respondents and non-respondents. We finally included 1615 participants in the present study after excluding those who were without baseline rAI normalized to a heart rate of 75 beats per minute (rAIp75) data and had already been diagnosed with hypertension at baseline. This study was approved by the ethics committee of Peking University First Hospital, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each participant.

Data Collection

Information regarding sociodemographic status, medical history, and lifestyle factors was examined using a standardized questionnaire that was specific for the health check-up. Anthropometric measurements were taken according to a standard operating procedure. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Current smoking was defined as smoking one cigarette per day for at least half a year. Current drinking was defined as drinking once per week for at least half a year.

After overnight fasting, a venous blood sample was obtained from each participant. Fasting blood glucose, 2 h glucose concentration in the standard 75 g oral glucose tolerance test, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglyceride concentrations were measured using a Roche C8000 Automatic Analyzer. Serum creatinine (μmol/L) levels were measured using an enzymatic method and then the estimated glomerular filtration rate (eGFR) was estimated using the equation derived from the Chronic Kidney Disease Epidemiology Collaboration.

A seated peripheral (brachial) BP measurement was obtained from each participant after a 5-min rest using an Omron HEM-7117 electronic sphygmomanometer (Omron Health Care, Kyoto, Japan) with the standard method of calibration and appropriately sized cuffs. Triplicate measurements on the right arm were taken with ≥ 1 minute between successive readings. Pulse at rest was obtained simultaneously when measuring BP. Each patient's peripheral systolic BP (SBP) and diastolic BP (DBP) used in the analysis were calculated as the mean of 3 consecutive measurements.

The rAI and rAIp75 were obtained from the radial arterial waveform as measured by an arterial applanation tomometry probe, which was equipped with an array of 40 micropiezo-resistive transducers (HEM-9000AI; Omron Healthcare, Kyoto, Japan). The first and second peaks of peripheral systolic pressure (SP1 and SP2) and brachial DBP were automatically determined using the fourth derivatives for each radial arterial waveform, and averaged. The rAI was calculated as follows: (SP2–brachial DBP)/(SP1–brachial DBP) × 100 (%).

New-onset hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg or self-reported history of hypertension or receiving antihypertensive medications at the follow-up survey. Diabetes mellitus at baseline was defined as any self-reported history of diabetes mellitus, fasting blood glucose levels ≥ 7.0 mmol/L, oral glucose tolerance test ≥ 11.1 mmol/L, or receiving hypoglycemic drugs. Dyslipidemia at baseline was defined as any self-reported history of hyperlipidemia, triglyceride levels ≥ 1.70 mmol/L (150 mg/dL), total cholesterol levels ≥ 5.18 mmol/L (200 mg/dL), low-density lipoprotein cholesterol levels > 3.37mmol/L (130 mg/dL),

high-density lipoprotein cholesterol levels < 1.04 mmol/L (40 mg/dL), or receiving lipid-lowering medications. Cardiovascular disease (CVD) at baseline was defined as any self-reported history of coronary heart disease, stroke, or transient ischemic attack.

Statistical Analysis

Data are expressed as mean ± SD for normally distributed variables. The differences in values between baseline characteristics were assessed using the Student's *t* test or ANOVA for continuous variables and the Pearson's χ^2 test for categorical variables. To further characterize the shape of the association between baseline rAIp75 and incident hypertension in the general population and in different sexes, smooth curve fittings (penalized spline method) were conducted.

Multivariate logistic regression analysis, which was adjusted for age, sex, BMI, estimated glomerular filtration rate (eGFR), SBP, DBP, current smoking status, current drinking status, diabetes mellitus, dyslipidemia, CVD, hypoglycemic medications, and lipid-lowering medications, was performed to investigate the effects of baseline rAIp75 on the risk of incident hypertension. We also performed subgroup and interactive analyses to examine the modification effect of sex on the relationship between baseline rAIp75 and new-onset hypertension. Odds ratios (ORs) of incident hypertension were reported according to a 10% increase and tertiles of rAIp75 levels. In addition, if necessary, a receiver-operating characteristic curve analysis was performed to identify the best cut-off point of the rAIp75 for predicting the incident hypertension.

A *P* value of < 0.05 (2-sided) was considered statistically significant for all tests. All analyses were performed using Empower(R) (www.empowerstats.com, X&Y solutions, Inc., Boston MA) and R (http://www.R-project.org).

RESULTS

Table 1 shows the baseline characteristics of all participants in general and categorized by tertiles of rAIp75 and sex. A total of 1 615 participants were included in the analysis. The mean age at baseline was 54.19 ± 7.47 years old. Mean (SD) baseline SBP and heart rate were 123.01 ± 9.85 mmHg and 77.90 ± 10.56 beats/min, respectively. The prevalence of diabetes mellitus, dyslipidemia, and CVD was 14.92%, 65.76%, and 5.54%, respectively. Mean baseline rAIp75 was 80.75% ± 11.81%. Participants with a higher rAIp75 were more likely to be women, they were older, and they had lower rates of current smoking and current drinking ($P < 0.05$ for all). Among the participants, 1 099 (68.05%) were women. Female participants tended to be younger, and had a lower BMI, SBP and DBP, but higher rAIp75, than male participants ($P < 0.05$ for all). Female participants were more likely to have better kidney function and lower rates of current smoking, current drinking, and diabetes mellitus ($P < 0.05$ for all). Heart rate and the prevalence of dyslipidemia and CVD were not significantly different between female and male participants.

After a mean follow-up time of 2.35 years, 213 (13.19%) participants developed incident hypertension. No significant association between rAIp75 and incident hypertension was observed in the whole population after adjusting for possible confounders, including sex (adjusted OR and 95% CI: 1.09 [0.95–1.27], $P = 0.226\,0$). The risk of new-onset hypertension was also graded related to baseline rAIp75 as tertiles in the multivariate regression model. Compared to participants with the lowest rAIp75, higher risks of incident hypertension were not observed among those with higher rAIp75 (adjusted OR and 95% CI for T2 *vs.* T1: 0.89 [0.59, 1.33]; T3 *vs.* T1: 1.13 [0.75, 1.70]; *p* for trend: 0.5224) (Table 2).

Figure 1 shows a linear association between rAIp75 and incident hypertension in women, but a non-linear association was observed in the whole population or in men. Subgroup and interactive analyses between sex and rAIp75 are shown in Table 3. The effects of baseline rAIp75 on incident hypertension were modified by sex (*P* for interaction: 0.013 3). Every 10% increase in rAIp75 increased the risk of new-onset hypertension by 29% (adjusted OR and 95% CI: 1.29 [1.06–1.56], $P = 0.011\,3$) in female participants, while baseline rAIp75 could not predict the possibility of incident hypertension in male participants (adjusted OR and 95% CI: 0.91 [0.72–1.15], $P = 0.424\,4$). When ORs of incident hypertension were reported as tertiles of rAIp75, the results were quite similar (*P for* interaction: 0.037 5; OR and 95%CI for T2 *vs.* T1: 1.01 [0.60,1.72], T3 *vs.* T1: 1.74 [1.05, 2.87]

Table 1 Baseline characteristics of all eligible participants.

Variables	Entire Sample Total	Entire Sample by tertiles of rAIp75, %				Entire sample by Sex		
		T1 (< 73.00)	T2 (73.00–88.00)	T3 (> 88.00)	*P* value	Male	Female	*P* value
N	1615	505	560	550	–	516	1099	–
Age, yrs	54.19 ± 7.47	53.43 ± 7.46	54.46 ± 7.38	54.60 ± 7.55	0.023	55.79 ± 7.88	53.44 ± 7.16	< 0.001
Female	1099 (68.05%)	226 (44.75%)	404 (72.14%)	469 (85.27%)	< 0.001	–	–	–
BMI, kg/m^2	25.23 ± 3.25	25.43 ± 3.27	25.17 ± 3.22	25.12 ± 3.25	0.265	25.54 ± 3.01	25.09 ± 3.34	0.009
eGFR, mL/min per 1.73 m^2	97.50 ± 11.15	97.13 ± 11.39	97.86 ± 10.46	97.47 ± 11.61	0.566	94.38 ± 11.57	98.96 ± 10.64	< 0.001
rAIp75	80.75 ± 11.81	67.62 ± 6.75	80.59 ± 2.78	92.96 ± 7.24	< 0.001	74.39 ± 11.72	83.73 ± 10.62	< 0.001
SBP, mmHg	123.01 ± 9.85	123.43 ± 9.42	123.31 ± 9.78	122.31 ± 10.29	0.12	125.12 ± 8.96	122.02 ± 10.10	< 0.001
DBP, mmHg	71.44 ± 7.64	71.64 ± 7.42	71.49 ± 7.42	71.21 ± 8.06	0.636	73.49 ± 7.71	70.48 ± 7.42	< 0.001
Heart Rate, beats/min	77.90 ± 10.56	77.42 ± 10.45	78.36 ± 10.84	77.87 ± 10.35	0.353	77.18 ± 11.12	78.24 ± 10.27	0.06
Current Smoking	321 (19.88%)	154 (30.50%)	97 (17.32%)	70 (12.73%)	< 0.001	289 (56.01%)	32 (2.91%)	< 0.001
Current Drinking	370 (22.91%)	172 (34.06%)	111 (19.82%)	87 (15.82%)	< 0.001	285 (55.23%)	85 (7.73%)	< 0.001
Disease								
Diabetes Mellitus	241 (14.92%)	80 (15.84%)	82 (14.64%)	79 (14.36%)	0.777	118 (22.87%)	123 (11.19%)	< 0.001
Dyslipidemia	1062 (65.76%)	327 (64.75%)	354 (63.21%)	381 (69.27%)	0.088	325 (62.98%)	737 (67.06%)	0.107
CVD, n(%)	88 (5.54%)	29 (5.74%)	31 (5.54%)	28 (5.09%)	0.892	35 (6.78%)	53 (4.82%)	0.106
Medication								
Hypoglycemic Medications	96 (5.95%)	30 (5.95%)	36 (6.44%)	30 (5.45%)	0.786	52 (10.12%)	44 (4.00%)	< 0.001
Lipid-lowering Medications	84 (5.24%)	20 (3.97%)	35 (6.32%)	29 (5.31%)	0.229	30 (5.85%)	54 (4.95%)	0.451

Data presented as mean ± SD for continuous variables and percentage for dichotomous variables. BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; rAIp75: radial augmentation index normalized to heart rate of 75 beats/min; SBP: systolic blood pressure.

for women; T2 *vs.* T: 1.25[0.68, 2.23], T3 *vs.* T1: 0.85 [0.45, 1.63] for men). Receiver operated characteristic curve analysis showed that the cut-off value of rAIp75 for predicting the incident hypertension in women was 85.50% (area under the curve: 0.578 4, sensitivity: 0.530 8, specificity: 0.587 2).

DISCUSSION

The present study had the following findings during the follow-up of 2.35 years in a Chinese community-based population without hypertension at baseline: although arterial stiffness, as assessed by the rAIp75, was not associated with the new onset of hypertension in the general population, sex acted as a modifier of this relationship. We found that rAIp75 was significantly associated with incident hypertension in women, but not in men.

Although the exact cause of hypertension is still unknown, significant advances have been made in understanding of its pathogenesis, such as the role of the renin–angiotensin–aldosterone system, the sympathetic nervous system, and the kidney.[14] Additionally, vascular factors, especially arterial stiffness, have recently emerged as important factors in development of hypertension. Recent research has shown that arterial stiffness can antedate and contribute to the pathogenesis of hypertension.[15] Evidence that arterial stiffness predates hypertension includes the finding in basic studies that disrupting elastin in the aortic wall precedes development of increased BP.[16,17] Additionally, cohort studies showed that baseline BP was not an independent predictor of longitudinal changes in markers of arterial stiffness.[3,18,19] Furthermore, premature return of reflected waves in late systole, which leads to augmentation of a late systolic pressure peak, may explain the causal relationship between arterial stiffness and hypertension.[9,20]

Previous studies have shown that indicators of

Table 2 Multivariate regression for the effect of the baseline rAIp75 on the development of incident hypertension.

Variables	Crude Mode (n = 1615)		Adjusted Model 1 (n = 1615)		Adjusted Model 2 (n = 1600)	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
rAIp75 continuous, per 10% increase						
	1.06 (0.94–1.20)	0.329	1.12 (0.97–1.29)	0.133	1.09 (0.95–1.27)	0.226
rAIp75 categories						
T1 (< 73.00%)	1	–	1	–	1	–
T2 (73.00%–88.00%)	0.90(0.63,1.30)	0.582	0.88 (0.59,1.31)	0.531	0.89 (0.59,1.33)	0.618
T3 (>88.00%)	1.08 (0.76,1.54)	0.667	1.18 (0.79,1.35)	0.426	1.13 (0.75,1.70)	0.569
P for trend	–	0.645	–	0.387	–	0.522

Adjust Model 1 for age, sex, SBP, DBP; adjust Model 2 adjust for: age, sex, BMI, eGFR, SBP, DBP, current smoking status, current drinking status, diabetes mellitus, dyslipidemia, CVD, hypoglycemic medications and lipid-lowering medications. BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; rAIp75: radial augmentation index normalized to heart rate of 75bpm; SBP: systolic blood pressure.

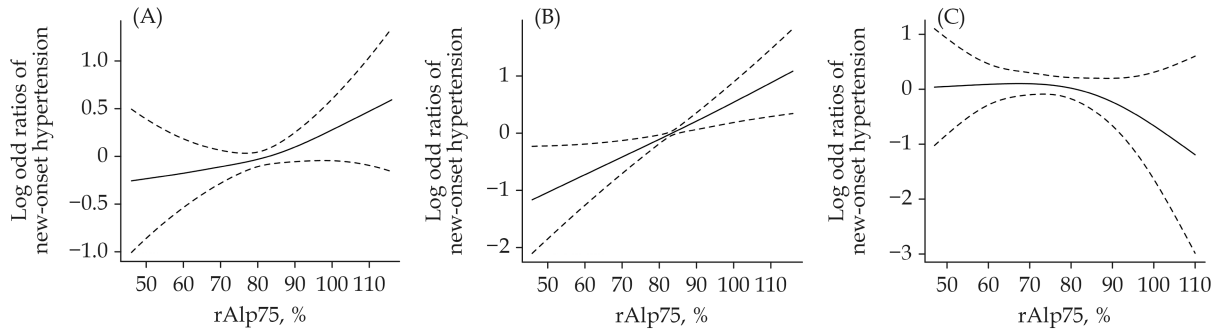

Figure 1 Smooth curve of rAIp75 and incident hypertension in the general population (A), female group (B), and male group (C). rAIp75: radial augmentation index normalized to heart rate of 75 beats/min.

Table 3 Interactive effect between sex and the rAIp75 on the development of incident hypertension.

Variables	Male (n = 510)		Female (n = 1090)		P value for interaction
	OR (95%CI)	P value	OR (95%CI)	P value	
rAIp75 continuous, per 10% increase					
	0.91 (0.72–1.15)	0.424	1.29 (1.06–1.56)	0.011	0.013
rAIp75 categories					
T1 (< 73.0%)	1	–	1	–	
T2 (73.0%–88.0%)	1.25 (0.68–2.23)	0.475	1.01 (0.60–1.72)	0.963	0.038
T3 (> 88.0%)	0.85 (0.45–1.63)	0.629	1.74 (1.05–2.87)	0.032	

Variables in the model: age, sex, BMI, eGFR SBP, DBP, current Smoking status, current drinking status, diabetes mellitus, dyslipidemia, CVD, hypoglycemic medications and lipid-lowering medications. BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; rAIp75: radial augmentation index normalized to heart rate of 75 beats/min; SBP: systolic blood pressure.

arterial stiffness, including ultrasound-assessed aortic elasticity[5,6] and applanation tonometry of PWV[3,4,21] (known as a marker of large arteries), are predictors of development of hypertension. However, whether the AI (representing the functional status of central and peripheral arteries) can predict new hypertension has not been fully studied. Studies from Japanese male cohorts showed that the ability of the AI to predict incident hypertension varied with follow-up times.[9–11] The long-term study (9 years) confirmed the predictive relationship between the AI and new-onset hypertension in men,[11] while short-/medium-term studies (3/5 years) negated this relationship.[9–11] From this perspective, it seems reasonable that our shorter follow-up time (2.35 years) study showed no significant association

between AI and incident hypertension in men. Another study from Framingham Offspring cohort suggested that AI was a predictor of incident hypertension in the general population of women and men, which was different from our study.[3] However, we noted that there was also a difference in follow-up time between these two studies, with the former being followed for up to 7 years.

Recently, Ji, *et al*.[22] reported that women compared with men exhibited a steeper increase in BP that began as early as in the third decade and continued through the life course. Furthermore, pulse pressure, a marker of arterial stiffness, increased more predominantly in women than in men since the same time and throughout the life course. This suggested that the more pronounced progression of arterial stiffness in women may play an important role in the earlier BP rise in women than in men. The mechanisms of the sex difference in the rate of arterial stiffness growth were not fully delineated. But there was evidence that genetic inheritance and environmental exposure, such as sex hormones and lifestyles, contribute a faster growth speed of arterial stiffness in women.[23,24]

Besides, the difference in aortic diameter between sex could be a factor influencing the effect of arterial stiffness on BP. A previous study showed that the rate of stiffening paralleled increased BP in women, but became dissociated in men over time. The study further demonstrated that a greater rate of aortic dilatation in men than in women slowed the increase in BP, which acted as a protective factor for hypertension.[25] However, information on aortic diameter was not obtained in our study, and thus was not included in our multiple regression analyses. Further research is required to identify the role of this factor.

Notably, measurement of the AI in the Framingham Heart study[3] was derived from carotid tonometry, while in our study, it was derived from radial tonometry. This difference in the measurement methods may have contributed to the different results between the studies. Central aortic AI conveys the most information about cardiovascular status, but direct measurement requires invasively inserting a catheter into the heart. Therefore, central aortic AI is estimated by non-invasive methods in most cases.[26–28] AI obtained from carotid tonometry is considered well approximated to the central aortic AI, but technical challenge for operators and poor tolerance of subjects limit it application in large populations.[29] Another approach for determining central AI is by calculating the aortic pressure waveform from radial arterial waveform using a transfer function, but the accuracy of this approach for the determination of central aortic AI has been disputed due to inter-subject variability of the transfer function.[30,31] Radial AI, directly assessed from radial tonometry without the use of a transfer function, was reported to be strongly correlated with central AI, whether measured by carotid pulse wave or synthesized aortic pulse wave derived from radial pulse wave by the use of a transfer function.[30,32–35] In addition, the rAI has been reported to provide prognostic information that it is associated with target organ damage and cardiovascular risk.[36–39] So rAI might be a promising surrogate of central AI.

The present study has some limitations as follows. First, the follow-up time of the present study was relatively short. Therefore, whether sex modification on the predictive effect of the rAI on hypertension will change with an extension of follow-up time needs to be further investigated. Second, the rAI but not the central AI was chosen to be an indicator to evaluate arterial stiffness in our study. Further studies are required to determine the similarities and differences between these two measurements in the effect on the risk of incident hypertension. Third, because we studied a Chinese community-based population, this has limited ability for generalizing our results to other race-ethnic populations.

In conclusion, our study shows that, in a Chinese community-based population, arterial stiffness as evaluated by the rAI is associated with incident hypertension of women in the short term. Therefore, the level of rAI will help identify women at risk of rapidly developing hypertension and benefit them through early prevention.

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