

Association of arterial stiffness in non-hypertensive offspring with parental hypertension: the Hanzhong adolescent hypertension cohort study

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Abstract. – **OBJECTIVE:** Arterial stiffness may be an early marker for vascular changes associated with hypertension in young adults. Individuals with a family history of hypertension are at high risk of developing hypertension. We investigated whether arterial stiffness measured, such as mean arterial pressure (MAP) and brachial to ankle pulse wave velocity (baPWV), were increased in normotensive offspring with a parental history of hypertension.

PATIENTS AND METHODS: We compared MAP and baPWV in a sample of 1953 non-hypertensive participants (974 men, mean age 42±3 years) recruited in the previous Hanzhong adolescent hypertension cohort study. Standardized questionnaires, physical examinations and laboratory tests were used to obtain information, with a particular focus on family hypertension history, anthropometric, hemodynamic, and biochemical factors.

RESULTS: A total of 1039, 759, 155 participants had 0, 1, and 2 parents with hypertension, respectively. Parental hypertension was associated with elevated offspring MAP (in multivariable-adjusted models, B=1.5 mm Hg, 95% CI 0.8-2.2 for 1 parent with hypertension; B=3.0 mm Hg, 95% CI 1.8-4.3, for 2 parents with hypertension; $p<0.001$ for each). A significant positive correlation was also observed between MAP and baPWV ($r=0.543$, $p<0.001$). BaPWV displayed a similar correlation with parental hypertension in age-adjusted, sex-adjusted and body mass index (BMI)-adjusted models (B=23.1 cm/s, 95% CI 8.0-38.1, for 1 parent with hypertension, $p<0.01$; B=53.0 cm/s, 95% CI 25.8-80.2, $p<0.001$ for 2 parents with hypertension), but associations were attenuated in multivariate models after adjustment for MAP. In multivariable-adjusted models, logistic regression analysis showed that the risk of belonging to the upper quartile of MAP was significantly in-

creased for offspring whose parents had hypertension (OR=1.5, 95% CI 1.2-1.9, for 1 parent with hypertension; OR=2.3, 95% CI 1.6-3.4, for 2 parents with hypertension; $p<0.001$ for each). Similarly, the odds ratios of belonging to the upper quartile of baPWV increased (OR=1.3, 95% CI 1.1-1.6, for 1 parent with hypertension, $p<0.05$; OR=2.1, 95% CI 1.5-3.0, for 2 parents with hypertension, $p<0.001$, in age-sex-BMI-adjusted models), and were then brought down in the fully adjusted models including MAP, but the increase remained significant for 2 parents with hypertension (OR=1.6, 95% CI 1.0-2.3, $p<0.05$).

CONCLUSIONS: These findings provide evidence that arterial stiffness is higher in young to middle-aged normotensive subjects with a family history of hypertension, suggesting that increased arterial stiffness may occur in the early stages during the pathogenesis of hypertension.

Key Words:

Arterial stiffness, Ankle-brachial pulse wave velocity, Normotensive, Family history.

Abbreviations

BaPWV, brachial-ankle pulse wave velocity; MAP, mean arterial pressure; BMI, body mass index.

Introduction

The association between arterial stiffness and hypertension is well established¹⁻⁴. However, it remains controversial whether arterial stiffness represents a cause or consequence of hypertension. There is a widely held belief that increased arterial stiffness in hypertensive individuals is

largely a manifestation of long-standing hypertension-related damage that stiffens the arteries^{5,6}. In our previous study⁷, we also found that above-average systolic blood pressure (SBP) in children and adolescents may increase the risk of developing long-term arterial stiffness. However, observations from the Framingham Heart Study raised the possibility that elevated blood pressure and new-onset hypertension are antedated by increased arterial stiffness¹. Similar relationships between vascular stiffness and later life high blood pressure have also been observed in a Japanese study, the Atherosclerosis Risk In Communities study (ARIC), and the Baltimore Longitudinal Study of Aging (BLSA)²⁻⁴. These conflicting results indicate the need for further study to clarify the temporal relationship between vascular stiffness and hypertension.

Parental hypertension is a risk factor for young adults, given that hypertension is a heritable condition and hypertension in parents has a strong independent association with elevated BP levels and incident hypertension over the course of a person's lifetime^{8,9}. In the Framingham Heart Study, arterial stiffness measured *via* carotid-femoral pulse wave velocity (cfPWV) and MAP seemed to be heritable and have genetic determinants¹⁰. An Italian twin study¹¹ also demonstrated substantial genetic and unshared environmental influences on carotid intima-media thickness and arterial stiffness. These findings suggest that arterial stiffness could well be a heritable phenotype. Therefore, offspring of parents with hypertension would have greater arterial stiffness than those of parents without hypertension even before the development of clinical hypertension, presumably because arterial stiffness is involved in the early stages of hypertension development. Up to now there are only a limited number of small-scale studies¹²⁻¹⁶ reporting changes in arterial stiffness in subjects with parental hypertension and a firm conclusion has yet to be reached. Meanwhile, arterial stiffness may be measured through a variety of techniques. Brachial-ankle pulse wave velocity (baPWV) provides a simple and non-invasive approach and exhibits similar validity, reproducibility, and clinical significance achieved with cfPWV^{17,18}, but was not used in the studies mentioned above. The purpose of the current study was to compare levels of arterial stiffness obtained from baPWV and mean arterial pressure (MAP) between non-hypertensive, young-to middle-aged offspring in different classifications of parental hypertension from the Hanzhong adolescent hypertension cohort.

Patients and Methods

Study Population

The Hanzhong adolescent hypertension cohort study was designed and initiated in 1987, and the details have been previously described⁷. At baseline, 4623 school children and adolescents aged 5-18 years were enrolled from 26 rural areas of three towns (Qili, Laojun and Shayan) in Hanzhong city, Shaanxi, China. For the present investigation, we included participants (35-48 years old, $n=2770$) who had undergone the latest follow-up examinations in March, 2017, of whom 2490 had baPWV records. Participants with prevalent hypertension ($n=505$), prevalent cardiovascular disease (CVD, $n=3$), or missing values of other variables ($n=29$) were excluded. A total of 1953 (974 men, 979 women) individuals were eligible for the primary analyses in this study. Items in the regular follow-up included standardized questionnaires, a physical examination, and assessment of cardiovascular risk factors. The Academic Committee of the First Affiliated Hospital of Xi'an Jiaotong University approved the study protocol and all participants provided written informed consent before participating.

General Examinations and Laboratory Tests

General participant data were collected through a pre-tested and clearly structured interview questionnaire. Covariates included demographic characteristics (sex, age and occupation), medical history, and family medical history (especially detailed information on parental history of hypertension). Lifestyle factors (smoking status, alcohol drinking status, physical inactivity, and diet) were also recorded. A diagnosis of diabetes mellitus was made if the fasting blood glucose (FBG) level was ≥ 7.0 mmol/L or the participant was taking antidiabetic drugs or insulin. For the diagnosis of dyslipidemia, at least one of the following National Cholesterol Education Program Adult Treatment Panel III (ATPIII) Criteria must be met: total cholesterol (TC) ≥ 5.7 mmol/L; triglycerides (TG) ≥ 1.7 mmol/L; low-density lipoprotein cholesterol (LDL-C) ≥ 3.6 mmol/L; females with high-density lipoprotein cholesterol (HDL-C) < 1.29 mmol/L or males with HDL-C < 1.03 mmol/L or a history of cholesterol-lowering medication use¹⁹. Smoking status was classified as current, former or non-smokers according to WHO guidelines, with a current smoker defined as someone who smoked daily or occasion-

ally in the past 30 days²⁰. Current drinkers were defined as those who had consumed alcoholic drinks at least 12 times in the previous year²¹. Weight (wearing light clothes), standing height, waist circumference (WC, at the level of the umbilicus), and hip circumference (the largest circumference between the umbilicus and the thigh) were measured to the nearest 0.1 kg or 0.1 cm. BMI was calculated as kilograms per square meter (kg/m^2). The waist-to-hip ratio (WHR) was calculated by dividing the WC by the hip circumference.

After an overnight fast, a venous blood sample was collected from each participant for measurement of serum biochemical parameters, including creatinine, alanine aminotransferase, FBG, TG, TC, HDL-C and LDL-C, uric acid, creatinine and alanine aminotransferase *via* standardized automated methods.

Blood Pressure Measurement and Definition of Hypertension

BP was obtained on the right arm of the participant in the sitting position using an automated measurement device (HEM-907 XL, Omron Healthcare, Lake Forest, IL, USA) according to current guidelines²². Trained and certified staff members were instructed to set the monitor to automatically wait for 5 minutes before obtaining 3 measurements at 1-minute intervals. The average of the 3 BP measurements was used for analysis. Hypertension was defined as a diagnosis by a clinician, use of antihypertensive medications, or $\text{SBP} \geq 140$ mmHg and/or diastolic BP (DBP) ≥ 90 mmHg. MAP was calculated as $(\text{SBP} + 2 * \text{DBP}) / 3$. Pulse pressure was calculated as $(\text{SBP} - \text{DBP})$.

BaPWV Measurement

BaPWV values were acquired using a non-invasive automatic oscillometric device (BP-203RPE, Colin, Komaki, Japan) as previously described⁷. The procedure was conducted on participants with no consumption of tobacco, coffee, tea, or alcohol for at least three hours and no exercise for at least 30 minutes prior to measurement, in a room at 22°C to 25°C. Electrocardiographic (ECG) electrodes were placed on both wrists, and a microphone for phonocardiogram (PCG) was attached to the left side of the chest. Occlusion cuffs connected to the plethysmographic and oscillometric sensors were tied around both the upper arms and ankles while the subject lay in the supine position. ECG and PCG were used to provide timing markers for the device. Time difference ΔT (s) was defined as the time interval between the wave front of the brachial waveform and that of

the ankle waveform. The path length from the supra-sternal notch to the brachium (Lb) or the ankle at the same side (La) was automatically calculated using the following equations: $Lb = 0.2195 \times \text{height} - 2.0734$, $La = 0.8129 \times \text{height} + 12.328$, and $\text{BaPWV (cm/s)} = (La - Lb) / \Delta T$. The average values on both sides were used for data analysis. The BP was measured *via* the oscillometric sensor and the heart rate was also simultaneously recorded during the measurement of baPWV.

Statistical Analysis

Participants were assigned into 3 groups based on their classifications of parental hypertension: 0 parents, 1 parent, and 2 parents. Basic offspring characteristics of the three groups were compared using Analysis of Variance (ANOVA) or χ^2 -test, depending on the type of data. ANOVA and analysis of covariance (ANCOVA, adjusted for age, sex, and BMI) were used for detecting differences in arterial stiffness between the 3 groups. The relationship between MAP and baPWV was investigated *via* simple correlation analysis. The correlations between parental hypertension and offspring arterial stiffness were analyzed by multiple linear regression. We used the offspring arterial stiffness measures as dependent variables and included parental hypertension as an independent categorical variable (0, 1 or 2, as noted above). Based on the classification of parental hypertension, odds ratios were derived through multiple logistic regression for those in the upper sex-specific quartiles of the different arterial stiffness measures. All models were performed in 2 steps. Initially, we adjusted for age, sex, and BMI. Subsequently, we adjusted for diabetes mellitus, dyslipidemia, smoking status, drinking status, heart rate, WHR, FBG, TC, TG, HDL-C, LDL-C, serum uric acid, serum creatinine (all covariates may influence vascular stiffness). In addition, models of baPWV were adjusted for MAP values. All statistical analysis was performed with SPSS 18.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was inferred at a 2-tailed p -value < 0.05 .

Results

General Characteristics of Subjects

A total of 1039, 759, and 155 participants had 0, 1, and 2 parents with hypertension, respectively.

Demographic, anthropometric and laboratory characteristics of the study population in each group are presented in Table I. Our sample was

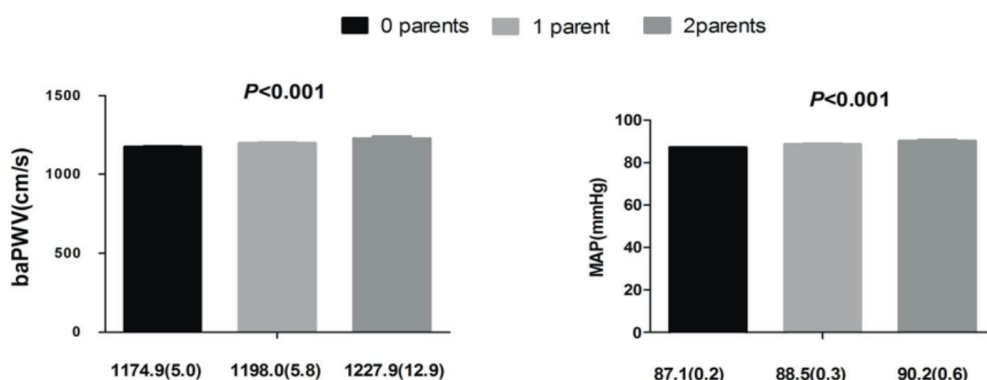


Figure 1. Age-sex-BMI-adjusted mean levels of arterial stiffness measures. *p*-values indicate trends <0.001 for all measures (based on analysis of covariance). Values are expressed as mean \pm SD. baPWV, brachial to ankle pulse wave velocity; MAP, mean arterial pressure.

composed of young- to middle-aged individuals, with a mean age of 43 years and a male-to-female ratio of 0.99. The overall exposure to risk factors for hypertension and CVD was low. The three groups were similar with regard to sex ratio, height, medical history, lifestyle, occupation, BMI, WHR, lipid profile and other biochemical parameters. However, there were small but significant differences in SBP, DBP, MBP, and baPWV between the three groups.

Age-Sex-BMI-Adjusted Mean Levels of Arterial Stiffness

As frequently reported, men had much higher MAP and baPWV than women (1244.5 \pm 167.3 cm/s vs. 1131.9 \pm 161.6 cm/s; 90.6 \pm 7.3 mmHg vs. 85.3 \pm 8.7 mmHg, respectively). Mean levels of arterial stiffness measures based on parental hypertension classifications were presented in the Figure 1 after adjustment for age, sex and BMI. Increased MAP and baPWV in the offspring were observed with an additional hypertensive parent (Figure 1).

Relationship Between MAP and baPWV

Simple correlation analysis showed a positive correlation between MAP and baPWV ($r=0.543$, $p<0.001$, Figure 2).

Associations Between Parental Hypertension and Offspring Arterial Stiffness Measures

In the multiple linear regression model with MAP as the dependent variable, offspring with a positive family history of arterial hypertension had higher MAP compared to offspring with normotensive parents, independently from age, sex, and

BMI (*p*-values indicate trends <0.001 , as shown in Table II). After adjustment for multiple risk factors (diabetes mellitus, dyslipidaemia, smoking, drinking, heart rate, WHR, FBG, TC, TG, HDL-C, LDL-C, serum uric acid, and serum creatinine), the observed associations between parental hypertension status and MAP remained highly statistically significant (in multivariable-adjusted models, $B=1.5$ mm Hg, 95% CI 0.8-2.2, for 1 parent with hypertension; $B=3.0$ mm Hg, 95% CI 1.8-4.3, for 2 parents with hypertension; $p<0.001$ for each). BaPWV displayed a similar pattern with parental hypertension in age-, sex- and BMI-adjusted models ($B=23.1$ cm/s, 95% CI 8.0-38.1, for 1 parent with hypertension, $p<0.01$; $B=53.0$ cm/s, 95% CI 25.8-80.2, for 2 parents with hypertension, $p<0.001$). Associations of baPWV with risk factors were

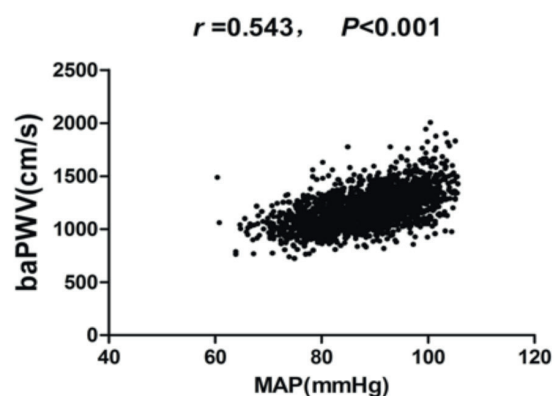


Figure 2. Relationship between MAP and baPWV. baPWV, brachial to ankle pulse wave velocity; MAP, mean arterial pressure.

attenuated in multivariate models with further adjustment for MAP (B=9.2 cm/s, 95% CI -3.9-22.4, for 1 parent with hypertension; B=21.8 cm/s, 95% CI -2.1-45.6, for 2 parents with hypertension; $p>0.05$ for each) (Table II).

Furthermore, logistic regression analysis showed that the odds ratio of belonging to the sex-specific upper quartile of MAP was significantly increased for offspring with 1 hypertensive parent after multivariable adjustment (OR=1.5, 95% CI 1.2-1.9, $p<0.001$). It was even higher for offspring with 2 hypertensive parents (OR=2.3, 95% CI 1.6-3.4, $p<0.001$). Similarly, offspring with 1 hypertensive parent showed an increased odds ratio of belonging to the sex-specific upper quartile of baPWV (OR=1.3, 95% CI 1.1-1.6, $p<0.05$) and those with

2 hypertensive parents a further increased odds ratio (OR=2.1, 95% CI 1.5-3.0, $p<0.001$) in models with adjustment for age, sex, and BMI. However, additional adjustment for MAP had a negative impact on baPWV-associated changes in odds ratios, but the increase remained significant for offspring with 2 hypertensive parents (OR=1.6, 95% CI 1.0-2.3, $p<0.05$) (Table II).

Discussion

Main Findings

The key finding of the present study was that SBP, DBP, MAP, and baPWV were significantly higher in offspring of hypertensive parents com-

Table I. Baseline characteristics of normotensive participants based on family history of arterial hypertension.

Variable	0 parents	1 parent	2 parents	p-value
No. of subjects	1039	759	155	
Male/Female, N (ratio)	541/498 (1.09)	365/394 (0.93)	68/87 (0.78)	0.071
Age	43±3	42±3	43±3	0.254
Occupation				0.680
Farmer, N (%)	514 (49.5%)	382 (50.3%)	79 (51.0%)	
Worker, N (%)	206 (19.8%)	147 (19.4%)	29 (18.2%)	
Businessman, N (%)	105 (10.1%)	79 (10.4%)	16 (10.1%)	
Manager, N (%)	108 (10.4%)	76 (10.0%)	17 (10.7%)	
Other occupations, N (%)	106 (10.2%)	75 (9.9%)	14 (8.8%)	
Diabetes mellitus, N (%)	25 (2.4%)	20 (2.6%)	2 (1.3%)	0.609
Dyslipidemias, N (%)	76 (7.3%)	62 (8.2%)	9 (5.8%)	0.556
Current smoking, N (%)	378 (36.4%)	241 (31.8%)	49 (31.6%)	0.096
Drinking, N (%)	281 (27.0%)	189 (24.9%)	37 (23.9%)	0.489
Physical inactivity, N (%)	170 (16.4%)	129 (17.0%)	28 (18.1%)	0.845
Diet				
Reduce salt intake, N (%)	132 (12.7%)	80 (10.5%)	20 (12.9%)	0.344
Weight control, N (%)	110 (10.6%)	68 (9.0%)	18 (11.6%)	0.417
Potassium rich food, N (%)	89 (8.6%)	54 (7.1%)	13 (8.4%)	0.524
Height (cm)	162.5±7.9	161.9±7.8	161.7±7.3	0.138
Weight (kg)	62.5±10.0	62.2±10.0	61.1±10.1	0.281
BMI (kg/m ²)	23.6±3.0	23.7±3.0	23.3±2.8	0.215
Waist/Hip ratio	0.91±0.07	0.91±0.07	0.90±0.07	0.563
Heart rate (bpm)	74±10	73±10	73±10	0.815
SBP (mmHg)	116.8±10.4	118.2±10.5	119.7±10.5	<0.001
DBP (mmHg)	72.4±8.0	73.7±8.1	74.8±9.1	<0.001
Pulse pressure (mmHg)	44.3±6.7	44.5±6.7	44.9±6.8	0.619
MAP (mmHg)	87.2±8.3	88.6±8.4	89.8±9.0	<0.001
TC (mmol/l)	4.5±0.8	4.5±0.8	4.6±0.8	0.671
HDL-C (mmol/l)	1.2±0.3	1.2±0.3	1.2±0.3	0.262
LDL-C (mmol/l)	2.5±0.7	2.5±0.6	2.5±0.6	0.292
TG (mmol/l)	1.6±1.4	1.5±0.9	1.5±1.4	0.258
FBG (mmol/l)	4.7±1.2	4.7±1.1	4.7±0.9	0.969
Serum uric acid (μmol/l)	276.8±75.6	273.9±71.5	273.1±78.7	0.650
Serum creatinine (μmol/l)	75.8±14.0	75.1±13.8	75.0±12.9	0.487
BaPWV (cm/s)	1177.2±169.8	1195.6±176.4	1224.2±181.5	0.002

Values are expressed as mean±SD or percentages. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; FBG, fasting blood glucose; BaPWV, brachial to ankle pulse wave velocity.

Table II. Associations between parental hypertension and offspring arterial stiffness measures.

Model/ Variable	1 parent		2 parents		p-values for trends
	Adjusted for age, sex, and BMI	Multivariable adjustment	Adjusted for age, sex, and BMI	Multivariable adjustment	
Linear regression, estimates (95% CI)					
MAP	1.5 (0.7-2.2)*	1.5 (0.8-2.2)*	3.1 (1.8-4.4)*	3.0 (1.8-4.3)*	<0.001
BaPWV	23.1 (8.0-38.1) †	9.2 (-3.9-22.4)	53.0 (25.8-80.2)*	21.8 (-2.1-45.6)	<0.001
Logistic regression, odds ratio (95% CI) of belonging to the upper quartile					
MAP	1.50 (1.20-1.88)*	1.51 (1.20-1.89)*	2.30 (1.59-3.34)*	2.31 (1.58-3.37)*	<0.001
BaPWV	1.31 (1.05-1.64)‡	1.15 (0.90-1.47)	2.11 (1.47-3.04)*	1.57 (1.04-2.34)‡	<0.001

Estimates were made with having 0 hypertensive parents as the reference. Odds ratios refer to those of belonging to the upper quartile of the respective variable. Multivariable analyses were adjusted for age, sex, diabetes mellitus, dyslipidemias, smoking status, drinking status, heart rate, BMI, waist/hip ratio, FBG, TC, TG, HDL-C, LDL-C, serum uric acid, serum creatinine. Besides, model of baPWV was additionally adjusted for MAP. P values for trends obtained from age, sex and BMI-adjusted models. Upper quartile reference values were >91.7 and >96.3 mmHg for MAP among women and men, and >1238.5 and >1340.6 cm/s for women and men for baPWV. MAP, mean arterial pressure; baPWV, brachial to ankle pulse wave velocity; BMI, body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. * $p < 0.001$. † $p < 0.01$. ‡ $p < 0.05$

pared with offspring of non-hypertensive parents. Analysis with full adjustment for multiple potential confounding variables upheld the associations for MAP. By contrast, the relationship between parental hypertension and offspring baPWV was attenuated when MAP was included in multiple variable adjustments. We were also able to show that the odds ratio of belonging to the upper quartile of MAP was 1.5 for individuals with a single hypertensive parent and 2.3 for those with both parents having hypertension. With baPWV, the odds ratios of belonging to the upper quartile were 1.3 and 2.2, respectively, for the above two groups. Additionally, we found a significant positive correlation between MAP and baPWV.

Cross-Sectional Studies on the Interaction Between Arterial Stiffness and Hypertension

To the best of our knowledge, this study was the first to explore the relationship between parental hypertension and offspring baPWV as a measure of arterial stiffness in a large population-based cohort. These results were in line with results from the Framingham Heart Study, in which arterial stiffness indices (including MAP, cfPWV, forward pressure wave amplitude and augmentation index) were assessed in 1564 non-hypertensive Framingham Heart Study third-generation partic-

ipants with positive or negative parental history of arterial hypertension. It observed greater arterial stiffness in offspring of parents with hypertension¹². However, the odds ratios of belonging to the upper quartiles of arterial stiffness indices were different from ours, probably as a result of different sets of inclusion criteria used, since the Framingham Heart Study enrolled offspring with prevalent hypertension. Similar results were found in 143 offspring recruited from 150 nuclear Greek families aged 14 to 30 years and 233 Polish and Czech offspring aged 17-40 years. In those studies, the central augmentation index and PWV (cfPWV and crPWV) were significantly higher in offspring with a positive parental history of arterial hypertension^{13,14}. Tebi et al¹⁵ involving 110 normotensive Egyptian individuals between 20 and 30 years reported similar findings, with the aortic and carotid stiffness parameters and the stiffness index of the digital volume pulse exhibiting higher values in normotensive offspring of hypertensive parents. Compared with these family-based studies, our study was more representative of the general population, particularly the Chinese population. Notably, the lack of association of arterial stiffness with a family history of hypertension has also been reported. Rajzer et al¹⁶ measured cfPWV in 70 young normotensive students with negative findings. This might be partially due to the relatively young age

(22.3±2.1 years), at which early damage in blood vessels would be difficult to detect.

Understanding how arterial stiffness and BP evolve over time has proved challenging. The Cardiovascular Risk in Young Finns Study, with a follow-up period spanning 27-year, has concluded that age and childhood SBP are independently associated with PWV in adulthood⁵. Also, according to the Bogalusa Heart Study, BP levels in childhood can predict arterial stiffness 26.5 years later⁶. However, the Framingham Heart Study has shown that higher BP at an initial examination is not associated with progressive aortic stiffening, suggesting that aortic stiffness is a cause rather than a consequence of hypertension in middle aged and older individuals¹. As a cross-sectional study, our data alone only demonstrate that increased BP and increased arterial stiffness run parallel to each other in hypertensive families and therefore cannot be effectively used to address the cause-and-effect issue. Nevertheless, our findings may still serve to substantiate the trends revealed by longitudinal studies¹⁻⁴. The observed association may signify early interaction between genetic and environmental factors, eventually leading to the development of hypertension, but the underlying mechanisms need to be clarified.

Strong Relationship Between MAP and Parental Hypertension

Based on our results, MAP in offspring seems to have a stronger association with parental hypertension, compared with baPWV. Several mechanisms have been proposed to explain this phenomenon. First, MAP is an important parameter for blood pressure elevation in young to middle aged adults, with both SBP and DBP accounted for. Second, hypertension is the result of several contributing factors, each exerting its influence on MAP values, but high arterial stiffness is only one of them. Another clue may be gleaned from a notable finding by the Anglo-Cardiff Collaborative Trial (ACCT) that pulse wave velocity increases rather late in life (>50 years)²³. Furthermore, PWV has a large number of clinical correlates that may potentially mediate the association with parental hypertension, such as abnormal glucose metabolism, increased body mass index, and abnormal lipids, as described in the Framingham offspring cohort²⁴.

The relationship between PWV and MAP is indeed complex. Our study found a significant positive correlation between MAP and baPWV ($r=0.543$, $p<0.001$). An increase in MAP results

in an increase in vessel diameter and creates a less optimal pressure-diameter relationship for the blood vessel, where the energy is transferred from elastic lamellae to stiffer collagens and smooth muscle cells. Fortier et al²⁵ showed a positive correlation of MAP with cfPWV and carotid-radial PWV. The aortic-brachial PWV ratio is independent of blood pressure and possesses a major advantage over the conventional aortic PWV. Yet another study in 89 patients undergoing peritoneal dialysis with strict volume control identified several determinants of arterial stiffness progression, of which, MAP played the most important role and was independent of age, history of cardiovascular disease, blood glucose, left atrium diameter and left ventricular mass index²⁶. Future investigations are needed to explore how aging, MAP, BP, and PWV interact with each other.

Genetic Evidence Linking Hypertension with Arterial Stiffness

Our findings showed that parental hypertension carries an increased risk for high arterial stiffness and elevated BP in offspring are consistent with a genetic component in hypertension and arterial stiffness, as shown in others' studies. Recently, several genome-wide association studies (GWAS) have identified a number of genetic loci with potential involvement in blood pressure regulation and hypertension development. The list includes more than 25 rare mutations and 53 single nucleotide polymorphisms (SNPs), in addition to common genetic variants²⁷⁻³². Increasing evidence^{10,11,33-36} also supports a genetic contribution to arterial stiffness. In a family-based study in Brazil, Alvim et al³⁴ estimated that the heritability of carotid-femoral PWV was about 0.27 in the general population. In another family-based study, Mitchell et al¹⁰ investigated 1480 participants representing 817 pedigrees in the Framingham Study offspring cohort and showed that heritability estimates were moderate for cfPWV (0.40). One meta-analysis of data from GWAS, including 20,634 participants generated interesting insight. Common genetic variation in a locus in the BCL11B gene desert once thought to harbor 1 or more gene enhancers was actually associated with high cfPWV and elevated cardiovascular disease risk³⁵. The association of the ATP2B1 gene with a heightened risk of developing hypertension, BP traits and increased cfPWV was validated in the Chinese population³⁶. Taken together, these studies underscore the importance of genetic factors in the pathogenesis of arterial stiffness.

Strengths and Limitations

The Hanzhong adolescent hypertension cohort study allowed us to evaluate data from a large randomly selected sample of individuals. Participants were all recruited from a rural area who lived in a homogenous environment and had similar lifestyles and dietary habits, which helped eliminate environmental confounders. However, several limitations with the present study must be acknowledged. First of all, in developing countries like China, large proportions of hypertension patients in many communities are undiagnosed and therefore the accuracy of self-reported family history could be problematic. For family history, we used a simple inquiry in our study. Previous studies have shown that, compared with a detailed questionnaire, this method is able to correctly identify the majority of individuals with no significant family history, but still misses a significant proportion of individuals with positive family history. Consequently, the discriminatory accuracy of a simple enquiry needs to be taken into account when interpreting the findings³⁷. Other limitations included the cross-sectional nature of the study, which makes understanding precise relationships between variables difficult, and the lack of high-quality data supporting the validity of family history in risk prediction. Moreover, our study sample comprised relatively healthy young-aged to middle-aged community-dwelling individuals of the Chinese population and could limit the generalizability of our observations to other age groups and ethnicities.

Conclusions

We found that parental hypertension was associated with increased values of arterial stiffness indices, including MAP and baPWV, among non-hypertensive, young-aged to middle-aged adults. The cross-sectional findings suggest that alterations in arterial function may be already present in non-hypertensive offspring who are at risk for hypertension. There may be a need for targeted interventions in order to prevent the development of hypertension in these individuals.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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