This is a post print -version af an article published in Hypertension on July 3, 2017, available online https://doi.org/10.1161/HYPERTENSIONAHA.117.09444

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Influence of Child and Adult Elevated Blood Pressure on Adult Arterial Stiffness:

The Cardiovascular Risk in Young Finns Study

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Short title: Blood Pressure Changes and Arterial Stiffness

Total Word Count: 5525

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Abstract

Elevated blood pressure in childhood has been associated with increased adult arterial stiffness, the independent predictor of cardiovascular and all-cause mortality. The favorable blood pressure change from childhood to adulthood and the risk of high adult arterial stiffness has not been reported. We examined the effect of child and adult blood pressure on pulse wave velocity assessed in adulthood among 1540 white adults followed-up 27 years since baseline (1980, aged 6–18 years). Childhood elevated blood pressure was defined according to the tables from the National High Blood Pressure Education Program. In adulthood, blood pressure was classified as elevated if systolic blood pressure ≥120 mmHg, diastolic blood pressure ≥80 mmHg or self-reported use of antihypertensive medications. Pulse wave velocity was measured in 2007 by whole-body impedance cardiography, and high pulse wave velocity was defined as values at or above the age-, sex-, and heart-rate specific 80th percentile. Individuals with persistently elevated blood pressure and individuals with normal child, but elevated adult blood pressure had increased risk of high adult pulse wave velocity (relative risk [95% confidence interval]) 3.18[2.22-4.55] and 2.64[1.79-3.88], respectively) in comparison with individuals with normal (both child and adult) blood pressure. In contrast, individuals with elevated blood pressure in childhood but not in adulthood did not have significantly increased risk of high pulse wave velocity (1.26[0.80-1.99]). The results were consistent when different definitions for child and adult elevated blood pressure were applied. These findings highlight the importance of blood pressure control in the primary prevention of cardiovascular diseases.

Key Words: epidemiology, blood pressure, hypertension, arteriosclerosis, elasticity

Arterial stiffness is a surrogate marker for cardiovascular diseases (CVD) and, assessed as pulse wave velocity (PWV), is generally accepted as an independent predictor of cardiovascular events and all-cause mortality.[1,2] The stiffness of elastic arteries increases with advancing age because pulsatile mechanical stress, generated by left ventricle, causes fatigue and fracture of elastin lamellae in arterial wall.[3] High systolic blood pressure (BP) increases the load on the heart and the stresses on arteries, hence accelerating cardiovascular degeneration and atherosclerosis.[4]

We and others have shown that childhood systolic BP is an independent predictor of PWV in adulthood[5-7] and that BP, especially elevated BP, is tracking from childhood to adulthood[8,9]. Previous report from 4 longitudinal childhood cohort studies showed that the effect of elevated BP in childhood on carotid atherosclerosis is markedly reduced if these individuals become normotensive adults.[10] We have also reported that favorable change in risk profile from childhood to adulthood was inversely associated with the arterial stiffness.[11] However, to the best of our knowledge, no information has been published concerning the effect of BP changes from childhood to adulthood on adult PWV.

Therefore, the aim of the present study was to analyze the combined effects of child and adult elevated BP on adult PWV using 1540 participants (aged 33 to 45 years) of the prospective Cardiovascular Risk in Young Finns Study followed up for 27 years since 1980.

Methods

Subjects

The Cardiovascular Risk in Young Finns Study is an ongoing multicenter (5 university cities in Finland with medical schools) follow-up study of atherosclerosis precursors of Finnish children and adolescents.[12] In 1980, 4320 participants (aged 3, 6, 9, 12, 15, and 18 years) were randomly chosen from the Finnish national population register to obtain a sample that would represent Finnish children and adolescents reasonably well. A total of 3596 of those invited participated in the first cross-sectional study. Although data were available for participants aged 3 years in 1980 (n = 577), they were not included in the analyses because BP measures were collected using an ultrasound device. 1357 participants missed follow up in adulthood and 76 participants have died; 2 of these deaths were due to atherosclerotic disease. In 2007, 1586 subjects (aged 33-45 years) had PWV measurements taken. The subjects with incomplete childhood data (n = 10), subjects with type 1 (n = 11) or type 2 (n = 13) diabetes, and female patients who were pregnant (n = 12) were excluded. Therefore, 1540 individuals who had complete BP and PWV data were included. All the participants and/or their parents gave written informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki and received local ethics committee approval.

Clinical Measurements

In childhood and adulthood, height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BP was measured with a standard mercury sphygmomanometer in 1980 and a random zero sphygmomanometer (Hawksley & Sons Ltd, Lansing, United Kingdom) in 2001 and in 2007. All measurements were taken on the right arm after the participant had been seated for 5 minutes. Cuff size was chosen according to arm circumference. Systolic BP was recorded for Korotkoff's first phase. Diastolic BP was recorded at both Korotkoff's fourth and fifth phases. Korotkoff's fifth phase results have been used in the analyses because in 1980 in all age groups, diastolic BP was better achieved with Korotkoff's fifth phase (no missing values in this study population) than Korotkoff's fourth phase (absent in 2.5% of subjects). This was consistent with results reported previously by Uhari et al.[13] Readings to the nearest integer of millimeters of mercury were performed 3 times on each participant. The mean of these 3 measurements was used in the analyses.

Classification of BP Levels

Elevated BP in childhood was defined according to BP tables issued by the National High Blood Pressure Education Program (NHBPEP)[14] and in adulthood according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood pressure[15]. BP status in youth was classified as normal if systolic and diastolic BP (fifth phase) were <90th percentile for age, sex, and height by using the NHBPEP tables, and elevated if systolic or diastolic BP were ≥90th percentile. BP status in adulthood was classified as normal if systolic BP <120 mm Hg and diastolic BP <80 mm Hg, and elevated if systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg. In addition, adult BP status was considered elevated among those self-reporting the use of antihypertensive medications. Four groups based on childhood and adult BP levels were defined for comparison of outcomes: (1) control group, participants who had a normal BP in childhood and normal BP as an adult; (2) resolution group, participants who had elevated BP in childhood but not as an adult; (3) incident group, participants with a normal BP in childhood who had elevated BP as an adult; and (4) persistent group, participants who had elevated BP in childhood and as an adult.

Definition and Classification of High PWV in Adulthood

We used a commercially available circulation monitoring device (CircMon™, JR Medical Ltd.) to determine arterial PWV. CircMon™ includes a whole-body impedance cardiography channel, a distal impedance plethysmogram channel, and an ECG channel, and it records the continuous heart-synchronous changes in the body's electrical impedance. When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases. The CircMon™ software measures the time difference between the onset of the decrease in the whole-body impedance signal and, subsequently, in the distal plethysmogram signal from a popliteal artery at knee joint level. The measurement is triggered by the R wave of the ECG. The PWV can be determined from the distance and the time difference between the 2 recording sites. The repeatability index and the reproducibility index of the PWV (impedance cardiography) were good (99% and 87%, respectively)[16], and the correlation between PWV (impedance cardiography) and gold standard PWV(applanation tonometry) was very good (r=0.82)[17]. A detailed description of the method[6,18], the validation study[17], and reference values[19] have been reported previously. While no consensus clinical definition of high PWV currently exist for young adults, we defined high PWV in adulthood as values at or above the age-, sex-, and heart-rate specific 80th percentile.

Statistical Methods

The comparisons between groups were performed using age- and sex-adjusted linear regression analysis for continuous variables and χ^2 tests for categorical variables. Relative risks and 95% confidence intervals were calculated by using Poisson regression to examine the associations between BP groups and adult high PWV. All analyses were adjusted for age, sex, and adult BMI. In addition, a linear trend over BP groups was tested with a regression analysis. Sex×BP and age×BP interaction effects on high PWV were tested and there were no significant interaction.

Several sensitivity analyses were performed to examine the influence of different child and adult BP definitions[20,21], and adiposity status on the magnitude of the associations. To examine the influence of BMI on change in BP status between childhood and adulthood, we present mean change in BMI (adult minus child) of age- and sex-specific z scores for each BP group (control, resolution, incident, and persistent). Logistic regression analysis was used to examine the differences between the control group and the remaining BP groups.

All analyses were performed with SPSS® Statistics (release 24.0.0.0, IBM Corp.). Statistical significance was inferred at a 2-tailed P value <0.05.

Results

The baseline (1980) characteristics of study participants (n = 1540) and nonparticipants (n = 1479) are shown in Table 1. There were more males among nonparticipants (P < 0.001), they were younger (P = 0.003), and had slightly higher systolic BP (P=0.005) and diastolic BP (P=0.046). There was no difference in height, BP status, BMI, or BMI status.

The characteristics of the study subjects in 1980 and in 2007 by PWV status in adulthood are shown in Table 2. There was no difference in sex, age, height, BMI, or systolic BP between low- and high-PWV groups in the baseline. Those having high adult PWV had slightly higher diastolic BP values (P = 0.005) and higher prevalence of elevated BP in childhood (P = 0.007). In 2007 the BP and BMI differences were more evident, and the absolute differences in the prevalence of elevated BP (49.4% vs 74.8%, P <0.001) and in PWV (7.8 m/s vs 10.1 m/s, P <0.001) were remarkable.

The risk of high PWV among participants whose elevated BP resolved by adulthood was not significantly different from those in the control group (Table 3). Risks were higher among participants who had elevated BP in adulthood (incident and persistent groups) in comparison with the control group. Individuals in the resolution group had lower risk of increased PWV (RR, 0.39; 95% confidence interval, 0.26–0.58) in comparison with those with persistently elevated BP.

In linear regression analyses, a significant trend in adult PWV over BP groups was observed (P<0.001). PWV was almost the same in control and resolution group, 7.65 m/s and 7.66 m/s (P=0.28), respectively. In incident group, PWV was slightly lower than in persistent group, 8.76 m/s and 8.85 m/s, respectively, but the difference was not statistically significant (P=0.33).

Sensitivity Analyses

To test the robustness of our findings, we performed analyses using other standardized cut-points corresponding to the 70th, 75th, 85th, and 90th percentiles of PWV with essentially similar results (Table S1). Analyses that used alternate BP status definitions were consistent with the observation that the risk of high PWV in the resolution group was not significantly different from the risk in the control group. Results remained essentially the same when International Child Blood Pressure References Establishment Consortium tables were used to define elevated BP in childhood (Table S2), when recently recommended pharmacological treatment cut-point 140/90 mmHg was used in adulthood (Table S3), or when more stringent BP cutoffs were used (Table S4).

Adult adiposity status did not change the risks (Table 4), although BMI z score in the resolution group significantly decreased, and in the incident group significantly increased between childhood and adulthood in comparison with the control group (Table S5). Relative risks remained also essentially similar when analysis was adjusted for change in BMI (adult minus child) z score (Table S6).

The analyses were also repeated after exclusion of those individuals using antihypertensive medication (n=117, 7.6% of the whole cohort) with essentially similar findings.

Discussion

This study showed that risk of high adult PWV was not significantly increased among participants with favorable BP change (elevated in childhood but normal in adulthood) compared to those with persistently normal BP. Individuals having elevated BP in adulthood had increased risk of high PWV irrespectively of their BP status in childhood. These findings were consistent in both sexes and independent of adiposity status. We found also that subjects having high PWV in adulthood had higher prevalence of elevated BP in childhood.

In previous reports, BP was strongly associated with PWV, and there was evidence supporting the hypothesis that arterial stiffness represents a cause rather than consequence of hypertension.[22,23] However, elevated BP is already directly associated with PWV in childhood[24], and pediatric BP predicts PWV in adulthood[5]. Additionally, elevated BP in childhood and adolescence has been linked with cardiovascular morbidity and premature death.[25,26] In the present analyses resolution of elevated BP from childhood to adulthood was related to decreased risk of high PWV in adulthood suggesting that the effects of elevated child BP could be reversed if normal BP levels are achieved in adulthood. This was consistent with previous reports concerning favorable adiposity and BP status changes from childhood to adulthood and improved risk profile.[10,27] This also supported the previous finding of the temporal relationship between elevated BP and vascular stiffness.[28]

These associations between elevated BP and risk of high arterial stiffness correlate perfectly with the mechanical stress hypothesis and from the point of view of the large elastic arteries; elevated BP can be looked upon as an accelerated form of aging and especially beyond age 30 years.[3] Elevated BP, caused initially by increased peripheral resistance or cardiac output, causes a direct increase in the diameter and stiffness of elastic arteries because elastic arteries are stiffer at higher rather than lower pressures. Treatment of hypertension leads to a decrease in stiffness, since the reduction of BP unloads the stiff components of the arterial wall, leading to a passive decrease in stiffness. However, because of the greater arterial medial degeneration in hypertensive subjects, the arteries may remain stiffer.[29] All these findings underline the combined deleterious effect of arterial stiffness and elevated BP in the pathogenesis of CVD and that risk modifications should be started in childhood. Atherosclerotic process has its roots in childhood, and fetal and early-life health may have strong influence on it, increasing the risk of hypertension, stroke, and heart disease in the later midlife.[30]

Adiposity status in adulthood has been reported to be associated with arterial stiffness.[31] Change in adiposity status from childhood to adulthood has been reported to have impact on BP status in adulthood[27], but favorable BP changes from childhood to adulthood was related to reduced risk of carotid atherosclerosis independently of adiposity status[10]. Because of that we adjusted all analyses for adult BMI levels. We also performed sensitivity analyses separately for normal weight and overweight/obese participants, and adjusted for BMI change instead of adult BMI, with essentially similar results. BMI changes were most favorable in the resolution group supporting weight management. It is also important to keep in mind that other favorable lifestyle changes (e.g. increased physical activity, nutrition) could be confounders in these BMI change analyses.

From a clinical point of view, elevated BP and increased arterial stiffness are slightly challenging combination. Elevated BP, and especially hypertension, is a major modifiable risk factor for atherosclerotic process, and it could be monitored quite easily by brachial BP measures and managed by medications.[15,20] Increased arterial stiffness assessed by PWV, on the other hand, is a marker of arteriosclerotic process, which could be pathologic or inevitable with aging.[32,33] PWV measures are not yet in clinical use, and there are no effective therapeutic interventions against stiffening process, although regular exercise and vasodilating drugs may slow it down.[3,33] Additionally, increased stiffness has been associated especially with the decline in cognitive and renal function, both of which are microcirculatory complications.[34,35] Atherosclerosis and arteriosclerosis do coexist with complications in the same subject, challenging the prevention of CVD. In order to improve CVD prevention in clinical work, the understanding of these two simultaneous processes is essential.

The strength of this study is the large randomly selected cohort of young adults followed for 27 years since childhood. However, our study has some limitations that need to be considered in the interpretation of our findings. First, the CircMon™-based PWV measurement method is not yet widely used in epidemiologic settings, apparently limiting comparability of our findings with observations from other cohorts. However, PWV values measured by CircMon™ are highly comparable to those measured by the gold standard method, tonometric carotid-femoral measurement.[17] Also reference values for PWV measured with CircMon™ method are comparable to those observed in other studies in which varying methods of measurement have been used, indicating the generalizability of our findings.[19,32] Second, bias due to nonparticipation in the follow-up study needs to be considered. In this study, 42.8% of the original cohort was included in the analyses. Third, the high prevalence of elevated BP in childhood could partially be explained by white coat effect which should be taken account in the interpretation. However, high prevalence of elevated BP in childhood defined by the NHBPEP tables has also been reported in other white cohorts.[10] Additionally, as shown in Table 1, participants had slightly better characteristics than nonparticipants in 1980, possibly leading to an underestimation of associations. Finally, the ethnic homogeneity of our study cohort limits the generalizability of our results to white European subjects.

Perspectives

Our study demonstrated that individuals with high adult BP had increased risk of high adult PWV, independently of BP status (normal or elevated) in childhood, in comparison with persistently normotensive individuals. However, the risk was reduced if elevated BP during childhood resolved by adulthood. These findings strengthen the importance of achieving normotension in the primary prevention of CVD. Further studies, including repeated PWV measures, are needed to evaluate the changes in BP determinants, e.g. adiposity status, physical activity, diet, and socioeconomic status, and the impact of the change in BP status on PWV progression.

Sources of Funding

The Young Finns Study has been financially supported by the Academy of Finland: grants 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research ; Finnish Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; and Diabetes Research Foundation of Finnish Diabetes Association.

Disclosures

None.

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Novelty and Significance

What Is New?

- We analyzed the combined effects of child and adult elevated blood pressure on the risk of increased adult arterial stiffness assessed as pulse wave velocity.

What Is Relevant?

- The effect of elevated blood pressure in childhood on the risk of high pulse wave velocity was markedly reduced if these individuals had normal blood pressure in adulthood.
- Elevated blood pressure in adulthood was associated with increased risk of high pulse wave velocity independently of blood pressure status in childhood.

Summary

We observed that the change from elevated blood pressure status in childhood to normal blood pressure status in adulthood was associated with an attenuated risk of high pulse wave velocity.

Table 1. Baseline Characteristics of Study Participants and Nonparticipants (Subjects Lost or Excluded) in 1980

Variable	Participants	Nonparticipants	P Value
n (males/females)	1540 (687/853)	1479 (782/697)	<0.001
Age, y	12.1 (4.1)	11.6 (4.1)	0.003
Height, cm	150.0 (20.1)	148.0 (20.4)	0.25
Systolic BP, mmHg	114 (11)	114 (12)	0.005
Diastolic BP, mmHg	68 (10)	69 (10)	0.046
BP status, n (%)			
Normal	816 (53.0)	752 (50.8)	
Elevated	724 (47.0)	727 (49.2)	0.13
BMI, kg/m^2	18.3 (3.1)	18.2 (3.2)	0.21
BMI status, n (%)			
Normal	1393 (90.5)	1311 (88.6)	
Overweight	125 (8.1)	142 (9.6)	
Obese	22 (1.4)	26 (1.8)	0.26

Values are mean (SD) for continuous variables or n (%) for dichotomous variables unless stated otherwise. BP was classified as elevated if systolic or diastolic BP were ≥90th percentile with the use of the NHBPEP tables for age, sex, and height. Overweight and obesity were defined by using international cut points. Comparison between participants and nonparticipants were performed using age- and sex-adjusted linear regression analysis for continuous variables and χ^2 tests for categorical variables.

BMI indicates body mass index; BP, blood pressure; and NHBPEP, National High Blood Pressure Education Program.

Table 2. Baseline (1980) and Follow-up (2007) Characteristics of Study Subjects by Pulse Wave Velocity Status in Adulthood

Variable		Low PWV	High PWV	P Value
n (males/females)		1234 (552/682)	306 (135/171)	0.89
1980				
	Age, y	12.1 (4.1)	12.0 (4.2)	0.76
	Height, cm	150.2 (20.2)	149.3 (19.8)	0.31
	BMI, kg/m^2	18.4 (3.2)	18.2 (3.0)	0.27
	Systolic BP, mmHg	114 (11)	114 (12)	0.12
	Diastolic BP, mmHg	68 (10)	70 (10)	0.005
	BP status, n (%)*			
	Normal	675 (54.7)	141 (46.1)	
	Elevated	559 (45.3)	165 (53.9)	0.007
2007				
	Age, y	39.1 (4.1)	39.0 (4.2)	0.76
	Height, cm	171.9 (9.1)	171.4 (9.1)	0.30
	BMI, kg/m^2	25.9 (4.5)	26.9 (5.3)	0.001
	Systolic BP, mmHg	119 (14)	128 (15)	<0.001
	Diastolic BP, mmHg	75 (11)	81 (11)	<0.001
	BP status, n (%)†			
	Normal	624 (50.6)	77 (25.2)	
	Elevated	610 (49.4)	229 (74.8)	<0.001
	PWV, m/s	7.8 (1.1)	10.1 (1.4)	<0.001

Low PWV was defined as values below the age-, sex-, and heart-rate-specific 80th percentile. High PWV was defined as values at or above the age-, sex-, and heart-rate-specific 80th percentile. Values are mean (SD) for continuous variables or n (%) for dichotomous variables unless stated otherwise. Comparisons between groups were performed using age- and sex-adjusted linear regression analysis for continuous variables and χ^2 tests for categorical variables. BMI indicates body mass index; BP, blood pressure; PWV, pulse wave velocity; NHBPEP, National High Blood Pressure Education Program.

* Child BP was classified as elevated if systolic or diastolic BP were ≥90th percentile by using the NHBPEP tables for age, sex, and height.

† Adult BP was classified as elevated if systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg or self-reporting the use of antihypertensive medications.

Table 3. Relative Risks and 95% Confidence Intervals of High Pulse Wave Velocity (≥80th Percentile) According to Blood Pressure Group in Childhood and Adulthood

Child-Adult BP Group*	n/N	RR	95%CI	p
Control	45/442	1.00	ref	ref
Resolution	32/259	1.26	(0.80-1.99)	0.33
Incident	96/374	2.64	(1.79-3.88)	<0.001
Persistent	133/465	3.18	(2.22-4.55)	<0.001

All analyses adjusted for age, sex, and adult BMI. BMI indicates body mass index; BP, blood pressure; CI, confidence interval; n, number of subjects having high PWV; N, number of subjects in group; NHBPEP, National High Blood Pressure Education Program; PWV, pulse wave velocity; and RR, relative risk.

*Child BP was classified as elevated if systolic or diastolic BP were ≥90th percentile by using the NHBPEP tables for age, sex, and height. Adult BP was classified as elevated if systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg. In addition, adult BP status was considered elevated among those self-reporting the use of antihypertensive medications. BP groups were as follows: control group, normal BP in childhood and normal BP as adults; resolution group, elevated BP in childhood but not as adults; incident group, normal BP in childhood, but elevated BP as adults; and persistent group, elevated BP in childhood and as adults.

Table 4. Relative Risks and 95% Confidence Intervals of High Pulse Wave Velocity (≥80th Percentile) According to Blood Pressure Group in Childhood and Adulthood and adult Body Mass Index status. Compared to Table 3 this analysis was performed stratified by adult adiposity status.

Child-Adult BP Group*	Normal weight				Overweight/obese†			
	n/N	RR	95%CI	p	n/N	RR	95%CI	p
Control	28/255	1.00	ref	ref	17/187	1.00	ref	ref
Resolution	20/152	1.19	(0.67-2.11)	0.57	12/107	1.26	(0.60-2.65)	0.54
Incident	30/138	2.25	(1.32-3.86)	0.003	66/236	3.24	(1.86-5.65)	<0.001
Persistent	50/169	2.91	(1.82-4.65)	<0.001	83/296	3.40	(1.99-5.82)	<0.001

All analyses adjusted for age and sex. BP indicates blood pressure; CI, confidence interval; n, number of subjects having high PWV; N, number of subjects in group; PWV, pulse wave velocity; and RR, relative risk.

*Child BP was classified as elevated if systolic or diastolic BP were ≥90th percentile by using the National High Blood Pressure Education Program tables for age, sex, and height. Adult BP was classified as elevated if systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg. In addition, adult BP status was considered elevated among those self-reporting the use of antihypertensive medications. BP groups were as follows: control group, normal BP in childhood and normal BP as adults; resolution group, elevated BP in childhood but not as adults; incident group, normal BP in childhood, but elevated BP as adults; and persistent group, elevated BP in childhood and as adults.

†A cut-point of 25 kg/m2 was used to define overweight and 30 kg/m2 for obesity