Original Article

Family History of Hypertension and Arterial Elasticity Characteristics in Healthy Young People

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Family history of hypertension is a primary predictor of high blood pressure (BP). This study attempted to determine whether there is a gradual increase in BP and an early change in arterial elasticity characteristics between young healthy individuals with or without a family history of hypertension and whether or not this increase is apparent in males as well as in females. A total of 270 normotensive healthy individuals (112 men and 158 women, aged 16 to 30 years) with or without a family history of hypertension, participated in conventional BP measurement and completed questionnaires covering basic information and a detailed family history of cardiovascular disease. Large arterial (capacitive) compliance (C_1) and small arterial (oscillatory or reflective) compliance (C_2) were derived from HDI/PulseWave CR-2000 (Hypertension Diagnostics, Minneapolis, USA). Based on family history information about parents and grandparents, three groups were formed: subjects with at least one hypertensive parent (group A), subjects with only hypertensive grandparents (group B), and subjects with normotensive parents and grandparents (group C). Men in group A had lower C_1 and C_2 along with higher systolic BP (SBP), diastolic BP (DBP), and heart rate than men in group C. Those in group B had intermediate C_1, C_2 and BP levels. C_1 had a linear relationship with SBP, DBP, and heart rate. In the logistic regression model of family history of hypertension, C_2 was lower in young normotensive males with parental hypertension (B=−0.315, exp B=0.73, p=0.03), independently of SBP, DBP, and heart rate. Among females, subjects with parental hypertension had higher systolic, mean arterial pressure, and pulse pressure (p<0.05), and there were no significant differences in C_1 and C_2 between those with and those without parental hypertension. In conclusion, compared with normotensive offspring of normotensive parents, normotensive offspring of hypertensive parents had increased BP and impaired arterial properties, namely large and small arterial compliance as measured noninvasively by HDI. These differences were exhibited conspicuously in men but not in women. Alteration in arterial function in young non-hypertensive subjects may be a risk factor for hypertension and may contribute to the progression to hypertension later in life. (*Hypertens Res* 2008; 31: 833–839)

***Key Words*: arterial elasticity, family history of hypertension, large and small arterial compliance**

Introduction

Impaired arterial compliance is an independent predictor of cardiovascular (CV) disease risk and mortality (*1*–*3*). Risk factors for CV disease mediate their effects by adversely altering the structure, endothelial function, and dynamic properties of the vasculature (*4*). The generalized structural and functional changes in the arterial circulation contribute to alterations in regional blood flow, progression of atherogenesis, and microvascular abnormalities. Some studies have shown that alterations in the pulsatile behavior of the vasculature may be a sensitive marker of arterial injury related to CV risk factors (*3*, *5*, *6*). But changes in pulsatile function are

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inhomogeneous within localized arterial segments of elastic and muscular arteries. In contrast to the marked heterogeneity of the physical characteristics of localized arterial segments, consistent and predictable changes occur in the arterial pulse contour regardless of the site of measurement. These changes reflect alterations in total arterial compliance and can be quantified with the pulse contour analysis technique, which assesses not only the physiological behavior of the large conduit arteries that serve a capacitance function but also that of the smaller arteries, which represent the predominant site of reflected waves or oscillations in the arterial bed (*5*). So we choose diastolic pressure pulse contour, which can be readily obtained noninvasively, to assess large arterial (capacitive) compliance (C_1) and small arterial (oscillatory or reflective) compliance (C_2). Hypertension, independent of other factors such as age and smoking, is a major risk factor for CV disease. A lot of studies have shown that people with hypertension have lower C_1 and C_2, especially C_2. It may be that vascular changes leading to hypertension begin early in life as a silent asymptomatic disease process and are associated with CV risk factors. The goal of this study is to compare the arterial elasticity characteristic indexes (C_1 and C_2) as well as blood pressure (BP) among offspring with different family histories of hypertension.

Methods

Subjects

Subjects were young healthy volunteers (aged 16 to 30 years), the majority (55.4%) of whom were students of the Medical Center of Peking University. The remainder were offspring of outpatients at the People's Hospital.

The subjects provided information on demographics and health and filled out questionnaires. No subjects had evidence of hypercholesterolemia, diabetes, or hypertension, smoked cigarettes, or had any history of CV disease or use of drugs or medications that might affect CV functions. All participants had consistently normal BP. They were seated for at least 15 min, followed by three casual BP readings taken with a mercury column sphygmomanometer according to standard assessments. Height and weight were measured twice, to 1 cm and 0.5 kg, respectively. Hypertension was defined as a conventional systolic BP (SBP) of ≥140 mmHg, diastolic BP (DBP) of ≥90 mmHg, or the current use of antihypertensive medications. Subjects with severe obesity (body mass index [BMI]>30 kg/m^2) or a prior diagnosis of hypertension were excluded. Also excluded were women who were or had been pregnant or lactating within the previous 12 months.

Offspring with or without a family history of hypercholesterolemia were defined as subjects whose parent(s) had not been diagnosed or had been diagnosed, respectively, with hypercholesterolemia. Offspring with or without a family history of diabetes were defined as subjects whose parent(s) had been or had not been diagnosed, respectively, with diabetes.

Table 1. General Information of Male and Female

	Male	Female
Age (years)	23.27±3.28	23.84±2.93
Height* (m)	1.72±0.06	1.62±0.05
Body weight* (kg)	58.71±10.25	56.21±8.83
BMI* (kg/m^2)	22.30±2.39	19.88±1.96
Systolic BP* (mmHg)	116.09±9.31	105.98±7.95
Diastolic BP* (mmHg)	63.74±7.40	60.95±6.20
MAP* (mmHg)	83.05±7.65	76.17±6.27
PP* (mmHg)	52.35±6.50	45.29±6.57
Pulse (bpm)	68.33±9.66	68.51±9.26
C_1 (×10 mL/mmHg)	17.97±3.80	18.28±4.63
C_2* (×100 mL/mmHg)	9.23±2.26	8.11±2.29

Values represent mean±SD. Values are derived from the Student's *t*-test with sex as factors. *$p<0.05$. BMI, body mass index; BP, blood pressure; MAP, mean arterial pressure; PP, pulse pressure. C_1, large arterial (capacitive) compliance; C_2, small arterial (oscillatory or reflective) compliance.

Subjects whose parents had no definite history of cholesterolemia or were diagnosed as having impaired glucose tolerance or impaired fasting glycemia were excluded. Hypertensive offspring were defined as subjects with at least one parent or grandparent who had been diagnosed with hypertension before the age of 60 years, with hypertension being present at least 1 year. Twenty-four subjects were rejected because of an ambiguous family history. The final sample consisted of 270 subjects, with 112 men and 158 women. They were divided into three groups according to the family history of hypertension: 1) subjects with at least one hypertensive parent (group A); 2) only hypertensive grandparents (group B); and 3) normotensive parents and grandparents (group C). The three groups had an even distribution in age and education.

Arterial Compliance Measurements

All arterial measurements were performed in the clinic, with compliance ascertained by an interview on the morning of the examination. Alcohol and caffeine were prohibited within 12 h of the study. After the subjects had rested for 15 min, radial arterial pulse waveforms were recorded by an acoustic transducer using the HDI/Pulse Wave CR-2000 Research Cardiovascular Profiling System (Hypertension Diagnostics, Minneapolis, USA). A wrist stabilizer was used to gently immobilize the right wrist and stabilize the radial artery during measurements. The stabilizer enhanced the reproducibility of the procedure. For each subject in the supine position, pressure waveforms were recorded for 30 s, digitized at 200 samples per second, and stored in a computer. A modified Windkessel model of the circulation was used to match the diastolic pressure decay of the waveforms and to quantify changes in arterial waveform morphology in terms of large arterial (capacitive) compliance, representative of the aorta

Table 2. Subjects Characteristics Based on Family History of Hypertension (FH) in Male

	Group A (n=39)	Group B (n=26)	Group C (n=47)
Systolic BP (mmHg)	120.12±9.72	114.50±7.34	113.62±8.96*
Diastolic BP (mmHg)	66.41±7.83	63.09±7.87	61.88±6.18*
Heart rate (bpm)	71.08±11.22	69.04±10.30	65.65±7.05*
C_1 (×10 mL/mmHg)	16.72±3.62	18.31±4.02	18.83±3.62*
C_2 (×100 mL/mmHg)	8.48±1.98	8.91±2.40	10.03±2.19**

Values represent mean±SD. Values are derived from ANOVA with FH as factors. *p<0.05, **p<0.01. BP, blood pressure; C_1, large arterial (capacitive) compliance; C_2, small arterial (oscillatory or reflective) compliance.

Table 3. Subjects Characteristics Based on Family History of Hypertension (FH) in Female

	Group A (n=58)	Group B (n=45)	Group C (n=55)
BMI (kg/m^2)	20.42±2.16	19.38±1.78	19.71±1.76*
Systolic BP (mmHg)	108.68±8.42	105.20±8.35	103.78±6.29**
MAP (mmHg)	78.24±5.80	75.46±6.63	74.56±5.92**
PP (mmHg)	46.92±7.28	45.12±6.27	43.70±5.66*
C_1 (×10 mL/mmHg)	17.17±4.82	18.47±4.44	19.29±4.39*
C_2 (×100 mL/mmHg)	8.42±2.46	8.25±2.18	7.69±2.18

Values represent mean±SD. Values are derived from ANOVA with FH as factors. *p<0.05, **p<0.01. BMI, body mass index; BP, blood pressure; MAP, mean arterial pressure; PP, pulse pressure. C_1, large arterial (capacitive) compliance; C_2, small arterial (oscillatory or reflective) compliance.

and major branches, and small arterial (oscillatory) compliance, representative of the distal part of the circulation including the arteriolar bed. This model for determining arterial compliance measures was described previously (*7*). In addition, BP levels were obtained from the HDI instrument.

Standardized techniques and protocols were used by trained field observers. All measurements were performed in duplicate, and average values were reported.

Statistical Methods

For database management and statistical analysis, SPSS software version 13.0 (SPSS, Chicago, USA) was used. Continuous measurements are presented as means±SD. Student's t-test was used to calculate the difference between the groups concerning continuous variables, and the χ^2 test was used for categorical variables. To determine the relationship between subject characteristics and family history of hypertension, we performed a two-way analysis of variance (ANOVA). Analyses by means of analysis of covariance (ANCOVA) were used to compare C_1 in the family history groups, with SBP, DBP, and heart rate as independent covariates. The relation between family history of hypertension (with or without parental hypertension) and C_2 was analyzed by logistic regression analysis. Statistical significance was considered at p<0.05.

Results

Table 1 lists the general data for male and female participants. Most of the indices were significantly different between genders, with men having larger values for height, body weight, BMI, SBP, DBP, mean arterial pressure (MAP), and pulse pressure (PP); and smaller values for C_2 than women (p<0.05). Thus, data were analyzed separately by sex.

Tables 2 and 3 show the BP and pulse waveform indices of the groups based on family history of hypertension for men and women, respectively. In males, as shown in Table 2, the casual SBP of group A was significantly higher than that of groups B and C. For DBP, MAP, PP, C_1, and C_2, the differences were significant only between the two extreme groups (A and C). C_1 had a linear relationship with SBP, DBP, and heart rate. The difference in C_1 among the groups was eliminated after adjustment for those three variables. In the logistic regression model of family history of hypertension, C_2 remained significantly lower in the offspring of hypertensive compared with those of normotensive parents (B=−0.315, exp B=0.73, p=0.03), after adjustment for the same three variables. We also investigated the history of coronary artery disease, diabetes mellitus, dyslipidemia, obesity, and cerebrovascular disease, but only a history of coronary artery disease or diabetes mellitus showed significant differences among the groups. Multiple factor variance analysis showed that a history of hypertension, instead of coronary artery disease or diabetes mellitus, had a significant influence

($p=0.031$, $r^2=0.088$) on C_2 in the male group.

The family history interaction showed that a positive family history was associated with lower C_1 and C_2 in males but not in females (see Tables 2 and 3). In females, as the table shows, the offspring in group A were higher than those in group C for BMI, SBP, MAP, and PP, but only the data of SBP, MAP, and PP showed significant differences. With regard to C_1, it turned out to be lower in the offspring in group A than in offspring in group C, but with no significant difference ($p=0.05$), as shown by Student's *t*-test. C_1 was intermediate in group B. Otherwise, there were no differences in C_2 among the three groups.

Age, height, and body weight were matched among the groups for both males and females.

Discussion

The ability to identify alterations in structure and function of the vasculature due to adverse anthropometric, hemodynamic, and metabolic factors is crucial to CV risk assessment at a preclinical stage. The earliest change in the structure and function of the vasculature involves a diminution in the amplitude and duration of the pressure waveform that interrupts the monoexponential decay of diastole. This change reflects a change in the stiffness or compliance characteristics of the arterial blood vessels (*8*). So changes in the pressure pulse waveform have been well described before significant augmentation of BP becomes apparent. Studies in asymptomatic young adults (*9*, *10*), also using diastolic pulse contour analysis, demonstrate that advancing age and increasing BP, adiposity, insulin, and triglyceride levels adversely impact the pulsatile arterial function measured in terms of large and small arterial compliance.

The method of combining the sexes masks the fact that parental hypertension may influence males and females differently. Decreases in the compliance of both large and small arteries in men *vs*. women were found in many studies (*11–13*), although paradoxically, given the protective effects of endogenous estrogen on the CV system in premenopausal women (*14*). These differences between the sexes in measurements of arterial pulsatile function have been attributed to the smaller body height and related size of the arterial tree in women; height is suggested to influence arterial wave reflections (*6*, *15*). Contradictory findings make it difficult to conclude whether parental BP is related primarily to BP in male or female offspring, and whether or not parental BP affects arterial compliance. So we analyzed the data separately between the sexes.

In our findings, compared to men with normotensive parents, men with hypertensive parents had lower C_1 and C_2. For women, however, C_1 and C_2 seemed to be not associated with family history, similar to findings London *et al*. (*15*) reported. But in our study population, the women in this age group also had lower BP than the men. So there may be two reasons for the insignificance of the difference ($p=0.05$). One is that the population was too small and that the difference in BP between the sexes was not significant enough to show a difference in C_1. The other is that C_1 is affected by some other factors that differ by sex. The most plausible factor is the role of steroid sex hormones in vascular protection and arterial function. Several studies have shown that vascular smooth muscle cells contain functional estrogen receptors (*16*, *17*) and that estrogens have short-term vascular effects, potentiating endothelium-dependent vasodilation in conductive and resistive arteries of premenopausal women (*18–20*) and decreasing arterial pulsatility and increasing arterial compliance (*21*, *22*). Only after menopause does BP elevation in women become as prevalent as it is in men of comparable age (*23*).

Shirakawa *et al*. (*24*) suggested that a family history of hypertension had an additive impact on the age-associated increase in the risk of hypertension. Tozawa *et al*. (*25*) showed that the greater the number of family members with hypertension was, the greater the prevalence of hypertension and BP in the probands, independent of conventional risk factors for hypertension. Our results also suggested that men in group A had higher SBP, DBP, and heart rate than men in group C. We also showed C_1 and C_2 were lower in group A. C_1 had a linear relationship with SBP, DBP, and heart rate. After adjustment for these three variables, the difference in C_1 among the groups was eliminated. But other than C_1, the lower C_2 in young normotensive men with parental hypertension was independent of the same three variables. That means the impact of hypertensive family history on C_2 was independent of those variables. So in females, BP differed significantly between groups A and C, and BP in C_1 was lower in A than in C. There were no differences in C_2 among the three groups, which also validates that the impact of hypertensive family history on C_2 is independent of BP and differs by sex. So the effects of hypertensive family history on C_2 differ from those on C_1. This was not reported in previous studies. Although a history of coronary artery disease or of diabetes mellitus differed significantly among the groups, neither disease was a significant covariate in the multiple factor variance analysis.

Some studies have dealt with large artery properties. Meaney *et al*. (*26*) studied 100 nonobese offspring of hypertensive or normotensive parents by means of an ultrasound technique, and reported that carotid stiffness was significantly higher in the offspring of the hypertensive parents, without adjustment for BP, which was already higher in this group. A prospective study provided evidence that increased aortic stiffness precedes hypertension (*27*). The Bogalusa Heart Study (*28*) also showed that childhood BP predicted arterial stiffness assessed at a mean of 26.5 years later by brachial-ankle pulse wave velocity. McVeigh *et al*. (*11*) showed that the rise in BP with aging, even within the normal range, was associated with a reduction in large arterial compliance estimates. Grey *et al*. (*29*) reported that C_1 might serve as a marker for vascular aging, which accounts for the influence of

age on morbid events. In our study, large arterial compliance, representative of the aorta and major branches, had a linear relationship with SBP, DBP, and heart rate. After adjustment for these variables, the differences in large arterial compliance were eliminated. This is consistent with earlier reports. These variables are the physiologic changes in the aorta; C_1, which had a linear relationship with each of them, might serve as a guide to vascular rather than chronological age.

To our knowledge, no study has dealt with large and small arterial compliance in young subjects at risk for hypertension. Grey *et al*. (*29*) reported that reduced small artery elasticity, as a measure of endothelial dysfunction, is significantly associated with CV events independent of age. Another study showed that small arterial compliance may correlate closely with BP (*30*). Our study has shown that C_2 was significantly lower in offspring of hypertensive parents, independent of SBP, DBP, and heart rate; thus, C_2 may prove to be an early and sensitive marker for the presence of disease.

The adverse associations of age and hemodynamic factors with arterial changes are associated with endothelial dysfunction, a characteristic feature of aging, hypertension, and atherosclerosis (*12*, *31*). Furthermore, sustained elevation in BP is known to produce mechanical stress and to stimulate arterial smooth muscle cell hyperplasia and hypertrophy as well as collagen synthesis, resulting in impaired arterial compliance (*32*), which may further increase BP and start a vicious cycle. However, the cross-sectional nature of the observational study cannot address causality in this relationship. A previous longitudinal study demonstrated that childhood BP is an independent predictor of arterial stiffness (*28*). Although impaired arterial compliance is considered an antecedent factor for hypertension (*33*), the early phase of high BP in youth is influenced by increases in sympathetic nervous system activity and peripheral vascular resistance resulting in arterial stiffness (*34*). The manifestation of later-phase hypertension is influenced more by increases in central vessel stiffness than by sympathetic activity (*35*, *36*). With respect to small arteries, reduced compliance may be a manifestation of endothelial dysfunction, which in turn is likely to increase BP.

Because our study was cross-sectional, the question of cause and consequence cannot be answered from our data. However, it adds to the longitudinal studies (*20*, *21*) because it suggests that increased BP and increased arterial compliance run in parallel in hypertensive families. This might be caused by genetic factors, shared environmental influences, or interaction thereof (*37*). Not only does the occurrence of two hypertensive parents increase the genetic component of elevated BP in offspring, but a shared environment (health habits inducive to hypertension) could further increase a child's tendency to become hypertensive. So we did not distinguish between offspring having only one hypertensive parent and those with two parents.

Among the positive aspects of this study is its sizeable sample of young healthy men and women. Nevertheless, it is important to note that our results may not be generalizable to all populations. The subjects were primarily college-educated men and women, the majority of whom worked in professional and skilled jobs at a large university. We may have excluded people most likely to have two hypertensive parents, thereby decreasing the strength of our findings relating BP and arterial compliance in offspring to parental hypertension.

Another limitation to note is that, although the measurements presented in this study are highly correlated with CV risk factors, especially BP variables, the ability to precisely interpret vascular stiffness, in terms of large and small arterial compliance, is somewhat limited. The measurements of arterial stiffness in this study are derived from a pulse wave contour of the radial artery, quite distant from the heart and central aorta, where modulation of diastolic pulse contours can occur. These various measurements are, however, reproducible and practical for epidemiologic studies. As such, they can provide some insight into the correlates or determinants of vascular changes related to aging and disease processes, thereby making them worthwhile.

The study of healthy offspring can provide a unique opportunity to investigate the precursors of hypertension in drug-free individuals before a diagnosis of hypertension has been made, and may be helpful in the evaluation of early vascular damage. Furthermore, the ability to identify individuals at greatest risk of hypertension enables high-risk younger populations to pay attention to diet and lifestyle early in life, resulting in a potential decrease in the incidence of hypertension. Because hypertension is predictive of future coronary heart disease, stroke, and renal disease, lowering BP in possibly hypertensive individuals could decrease morbidity and mortality rates.

It is concluded that, in a population of young subjects with no overt CV disease or symptoms at baseline, compared with normotensive offspring of normotensive parents, normotensive offspring of hypertensive parents have increased BP and impaired arterial properties, namely large and small arterial compliance as measured noninvasively by HDI. However, these differences were conspicuous only in men. It may be that alteration in arterial function is present already in young non-hypertensive subjects at risk for hypertension and may contribute to the progression to hypertension later in life. Our results show that measuring arterial compliance helps to identify patients at high risk for hypertension and re-emphasizes the importance of preserving arterial function in the primary prevention of hypertension. Nonetheless, an attempt to identify whether or not C_2 provides more sensitivity and specificity than the classic risk factors would require a larger population and a more rigorous assessment of risk factors.

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