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Age-related progression of arterial stiffness and its elevated positive association with blood pressure in healthy people

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ABSTRACT

Objective: Arterial stiffness occurs as a consequence of age and arteriosclerosis, but the mechanics of the progression of arterial stiffness along with age is not fully explored. We aim to investigate the age-related progression of arterial stiffness through the examination of 4659 healthy subjects aged from 20 to 75. **Methods**: The cardio-ankle vascular index (CAVI) was used as a marker of arterial stiffness. Piecewise linear regression model was utilized to analyze the association between different stages of age and arterial stiffness. The mean CAVI values of age groups were calculated to fit the linear regression and curvilinear regression models. We also constructed multiple regression models to examine the interactions of blood pressure and age on CAVI. **Result**: The regression coefficients (β) of piecewise linear regression of each age group (<35, 35–44, 45–59, >59) were 0.07062, 0.03133, 0.03840 and 0.07272 for men, and 0.03342, 0.02025, 0.04826 and 0.10604 for women, respectively. The highest R square came from curvilinear regression for men ($R^2 = 0.9220$), and piecewise linear regression for women ($R^2 = 0.9454$). The interactions between each type of blood pressure and age were significant (all $P < 0.001$). **Conclusion**: There were various increased trends between different stages of age. Age-related progression of arterial stiffness could be better explained by a growth curve, rather than a straight line. In addition, blood pressure has an increasingly positive association with CAVI values as age increases.

1. Introduction

Arterial stiffness is the reduced capability of an artery to expand and contract in response to pressure changes [1]. The main cause for age-related stiffness is due to the loss of elasticity of the arterial walls from mechanical stress [2]. Numerous data have indicated a linear relationship between arterial stiffness and age [3–5]. Others have also found accelerated stiffening between 50 and 60 years of age [6]. The recent research by Su-Yeon Choi et al. [7] reported an age-stratified increase of arterial stiffness in healthy Koreans adults in 2013. These researches suggest that the issue of age-related progression of arterial stiffness have not been fully explored.

Cardio-ankle vascular index (CAVI) is a non-invasive method of measuring arterial stiffness that developed in 2004 [8,9]. However, while pulse wave velocity (PWV) is influenced by BP at the measuring time, CAVI is independent of BP, which makes it more stable and precise than other PWV methods [10]. Thus, CAVI has better reproducibility for clinical practice [8,11,12].

In this study, we aim to investigate the relationship between arterial stiffness with the progression of age in a large number of healthy Chinese subjects. We focused on two aspects of age-related progression of arterial stiffness: 1) the variation and trend of arterial stiffness among young adults, middle aged adults and the elderly, 2) the optimal fitting growth curve of arterial stiffness along with aging.

2. Subjects and methods

Data from a total of 16,340 subjects who finished the examination of arterial stiffness using CAVI were collected from the Medical Examination Center of the Chongqing Medical University. Subjects who had known or were treated for hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, renal dysfunction, abnormal white blood cell, heart disease, stroke or gout were excluded from

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this total population. We also excluded subjects who were not in previous cases but satisfied the flowing criteria: systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure ≥90 mmHg, fasting blood glucose (FPG) >7.0 mmol/L, total cholesterol (TC) ≥6.22 mmol/L, high-density lipoprotein cholesterol (HDL-C)≤ 1.04 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥4.14 mmol/L, triglyceride (TG) ≥2.26 mmol/L, urine creatinine (UCr) ≥130 mg/dL or uric acid (UA) ≥420umol/L. Furthermore, we excluded subjects with a low ankle-brachial index (ABI <0.9) because their case may lead to inaccurate CAVI values [8]. At last, 4659 of remaining subjects were regarded as healthy population with less risk factors for cardiovascular diseases and included in this study.

2.1. Medical examination

The medical examination was conducted by the Medical Examination Center of Chongqing Medical University, which had obtained ISO 15189 certification since 2006. The routine medical examination includes a physical examination, a fasting blood sample, and ultrasonography.

Height, body weight, and waist circumference (WC) were measured in the physical examination. Blood pressure was also measured in the left arm using a standard mercury sphygmomanometer after subjects sits quietly for at least 5 min. Fasting blood sampling was obtained from the antecubital vein in the morning, and the serum was separated and centrifuged after blood coagulation. Blood cells, hemoglobin, platelet, FPG, TG, TC, HDL-C, LDL-C, UCr, UA, and more were measured with standard laboratory procedures using automatic biochemical analyzer. Abdominal ultrasonography was performed by experienced technicians on HD7 ultrasound system.

2.2. Measurement of cardio-ankle vascular index

CAVI was measured by a Vasera VS-1000 vascular screening system with subjects resting in a supine position. Electrodes for electrocardiography were placed on both wrists, and a microphone was placed on the sternum for phonocardiography. Both ankles and brachium were secured with cuffs. The subjects then rested for 5–10 min before the examinations were performed. PWV, SBP, and DBP were automatically measured to calculate the values for right and left CAVI, as follows: $\mathrm{CAVI} = a[\{2\rho \times 1/(\mathrm{SBP} - \mathrm{DBP})\} \times \{\ln(\mathrm{SBP}/\mathrm{DBP}) \times \mathrm{PWV}^2\}] + b$, where a and b are constant and ρ is blood density. The left and right CAVI values were then used to calculate the average CAVI values, which were used to analyze.

The ankle-brachial index (ABI) was also calculated at the same time by dividing the value of the upper arm BP by the value of the lower arm BP. ABI reflects the possibility of peripheral artery occlusive disease (PAOD) in subjects [13], ABI value of less than 0.9 indicates the possibility of PAOD due to decreased blood flow [14].

2.3. Definition

The subjects in this study were ranged from 20 to 75 years old. According to World Health Organization, people age 18 to 44 are defined as young, 45–59 as middle age, and over 60 years old as elderly. However, the National Bureau of Statistics of China has a different system of dividing age, which defined the young as aged 15–34. We combined the two systems and came up with four distinct age groups. Subjects with ages <35, 35–44, 45–59, and >59 were organized into the Early Young-Adult group, the Late Young-Adult group, the Middle-Aged Adult group, and the Elderly group, respectively.

2.4. Statistical analysis

The piecewise linear regression model was used to analyze the increments of β regression coefficients ($\Delta\beta$) between different stages of age for CAVI in men and women. To investigate the growth curve of arterial stiffness, the mean CAVI value of each age was calculated; linear regression model and curvilinear regression model were used to fit the data of mean CAVI values by each age. To examine the interactions between age and SBP, DBP and PP on the dependent variable CAVI, multiple regression models were used on the three blood pressure indices and the relevant variables were centered around their means values to reduce errors caused by different scales. Data were analyzed using SAS 9.1.

3. Results

We included 28.5% of all examined subjects in this study who were less at-risk with cardiovascular disease and were regarded as the healthy population. The characteristics of the healthy population were summarized in Table 1. Their average age was 45.24 ± 10.76 for men (ranging from 20 to 75 years old) and 44.90 ± 9.79 for women (ranging from 21 to 74 years old). 17.57% of men and 15.50% of women were less than 35 years old, 30.89% of men and 32.57% of women were from 35 to 44 years old, and 41.82% and 45.46% were from 45 to 59 years old, and 9.73% of men and 6.47% of women were more than 59 years of age. The mean CAVI was 7.29 ± 0.84 for men and 6.96 ± 0.81 for women. All variables, except age and TC, show a significant difference between men and women (all $P < 0.05$). Supplemental Table 1 provided the CAVI means and percentile values according to quintiles of age by gender.

We performed piecewise linear regression analysis to assess the variation and trend of arterial stiffness among Early Young-Adult, Late Young-Adult, Middle-aged Adult and the Elderly. The piecewise linear function were specified by four slopes, one for each age group (<35, 35–44, 45–59, >59); and three breakpoints, with the

Table 1
General information of subjects.

Variables	Total (4659)	Men ($n = 2169$)	Women (2490)	P value
Age (year)	45.06 (10.25)	45.24 (10.76)	44.90 (9.79)	0.3459
<35 (%)	16.46 (767)	17.57 (381)	15.50 (386)	–
35–44 (%)	31.79 (1481)	30.89 (670)	32.57 (811)	–
45–59 (%)	43.76 (2039)	41.82 (907)	45.46 (1132)	–
>59 (%)	7.98 (372)	9.73 (211)	6.47 (161)	–
Height (cm)	162.03 (8.02)	168.05 (6.04)	156.78 (5,42)	<0.0001
Weight (kg)	59.42 (9.34)	65.27 (8.58)	54.33 (6.59)	<0.0001
BMI (kg/m^2)	22.56 (2.53)	23.08 (2.55)	22.10 (2.42)	<0.0001
WC (cm)	77.09 (7.91)	81.47 (7.13)	73.27 (6.45)	<0.0001
SBP (mmHg)	114.84 (11.85)	117.26 (11.07)	112.74 (12.10)	<0.0001
DBP (mmHg)	71.89 (8.51)	73.96 (8.13)	70.09 (8.43)	<0.0001
PP (mmHg)	42.95 (8.90)	43.31 (8.37)	42.64 (9.33)	0.0001
WBC (/L)	5.80 (1.22)	6.00 (1.21)	5.63 (1.20)	<0.0001
TC (mmol/L)	4.65 (0.67)	4.65 (0.65)	4.65 (0.68)	0.6852
TG (mmol/L)	1.07 (0.39)	1.16 (0.39)	1.00 (0.38)	<0.0001
HDL-C (mmol/L)	1.59 (0.35)	1.48 (0.30)	1.70 (0.35)	<0.0001
LDL-C (mmol/L)	2.65 (0.59)	2.75 (0.57)	2.57 (0.59)	<0.0001
FPG (mmol/L)	5.05 (0.41)	5.06 (0.43)	5.03 (0.40)	0.0040
UCr (mg/dL)	66.54 (14.38)	78.29 (10.37)	56.30 (8.27)	<0.0001
UA (umol/L)	303.30 (65.24)	343.79 (51.93)	268.02 (54.26)	<0.0001
CAVI (m/s)	7.11 (0.84)	7.29 (0.84)	6.96 (0.81)	<0.0001

Continuous variables are given as the mean (standard deviation) or median (quartile range); Categorical variables are given as a percentage (number). BMI: body mass index. WC: waist circumference. SBP: systolic blood pressure. DBP: diastolic blood pressure. PP: pulse blood pressure, was calculated as SBP - DBP. TC: total cholesterol. TG: triglyceride. FPG: fasting blood glucose. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. UCr: urine creatinine. UA: uric acid. CAVI: cardio-ankle vascular index.