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ORIGINAL ARTICLE

Aortic stiffness is associated with the central retinal arteriolar equivalent and retinal vascular fractal dimension in a population along the southeastern coast of China

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The objective of this study was to evaluate the association of the central retinal arteriolar equivalent (CRAE) and the retinal vascular fractal dimension, two quantitative parameters that reflect microcirculation, with aortic stiffness. In this cross-sectional study, we identified the cardiovascular risk factors in 2169 subjects using a health questionnaire, physical examinations and laboratory examinations. We evaluated the aortic stiffness using noninvasive brachial-ankle pulse wave velocity (baPWV) and assessed the microcirculatory alterations with CRAE and retinal vascular fractal dimension, which were measured using fundus photography and semiautomatic quantitative software, respectively. The increase in baPWV (Q1–Q4) correlated with an increased likelihood of the central retinal artery narrowing and a reduction in the retinal vascular fractal dimension. Further adjustment of the cardiovascular risk factors diminished the association between baPWV and CRAE, but increased the association between baPWV and retinal vascular fractal dimension. Elevated baPWV correlates with reduced CRAE and retinal vascular fractal dimension. Such a finding supports macrocirculation- and microcirculation-associated hypotheses.
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Keywords: aortic stiffness; central retinal arteriolar; fractal dimension

INTRODUCTION

Recent advances in software development have enabled the quantitative analysis of the retinal blood vessels for cardiovascular disease research. The central retinal arteriolar equivalent (CRAE) has been shown to be associated with many cardiovascular risk factors.[1–6] Furthermore, it was found that a narrow central retinal artery correlated with coronary heart disease and hypertension and was independently predictive of cardiovascular diseases and peripheral arterial embolism that develop within 6 years. The human circulatory system operates on an optimal structural design, enabling adequate blood flow with minimal energy consumption. Therefore, a suboptimal microcirculation is considered harmful to the vascular integrity.[7] The retinal vascular fractal dimension is a mathematical indicator measuring the complexity of the retinal blood vessels. It has been shown that the retinal vascular fractal dimension is associated with mortality in hypertension,[8,9] diabetic retinopathy,[10,11] chronic kidney disease,[12] stroke[13–15] and coronary heart diseases.[16]

Early signs of atherosclerosis are associated with the loss of elasticity in large- and medium-sized arteries.[17,18] This increased arterial stiffness correlates with a series of cardiovascular risk factors, in addition to its association with age.[19–21] Indeed, increased aortic stiffness has proven to be an independent risk factor in cardiovascular illness and all-cause mortality.[22–26] Noninvasive brachial-ankle pulse wave velocity (baPWV) has been widely used to clinically determine aortic stiffness. Owing to the relatively easier measurement of the carotid-femoral pulse wave velocity, baPWV has been used in screening for vascular damage and cardiovascular risk assessment.

The correlation between arterial stiffness and microvascular diseases has been described.[27–30] However, the association of microvascular complexity and microcirculatory damage as a measure of retinal vascular fractal dimension in aortic stiffness has yet to be elucidated. Therefore, to evaluate the correlation between aortic stiffness and microvascular lesions, we designed this cross-sectional study to investigate the association of CRAE and retinal vascular fractal dimension with aortic stiffness in a Chinese population.

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METHODS

Subjects

Cluster sampling was performed from July 2011 through November 2011. The clusters were the individual administrative villages, and we sought to obtain 7 sampling units in 14 villages for two specified townships. The villages of Tailu, Beijiao and Xiubang in the Tailu township of Lienchiang county and the villages of Kungtung, Kunghsi, Yantai and Wenwo in the Haidao township of Xiapu county in Fujian Province were randomly selected for this cross-sectional investigation. Invitations to participate in the survey were sent to 4616 subjects who were sampled from the 8947 inhabitants, aged 30 years and above and registered in local areas based on the age stratification. A total of 3343 subjects participated in the survey. We excluded 1174 subjects from the analysis because of incomplete data (421 subjects), affliction with infectious disease (C-reactive protein level $>10\,mg\,l^{-1}$; 49 subjects) or atrial fibrillation (14 subjects), low ankle brachial index (<0.6; 15 subjects) and unqualified or unclear fundus photographs that affected the analysis (675 subjects). In the final analysis, only 2169 subjects were involved. This study was approved by the ethics committee of the Fujian Provincial Hospital, China. Informed consent was obtained from all participants following a detailed description of the potential benefits and risks associated with the study.

Data collection

The age, smoking habits, alcohol consumption, medical history (including hypertension, diabetes, coronary heart disease, stroke, liver and renal dysfunction, malignant tumors and peripheral vascular diseases) and family history were investigated using a questionnaire.

The blood pressure was measured with a standard vertical mercury sphygmomanometer. Before the measurement, the subjects were placed in a sitting position and allowed to rest quietly for more than 10 min. Then, the systolic and diastolic blood pressure of the right upper arm was measured. Blood pressure was measured three times, 5 min apart, and the mean blood pressure was estimated in triplicate.

Blood samples were collected from the subjects in the morning after 8 h of fasting to determine the plasma levels of triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting glucose, glycosylated hemoglobin (HbA_{1c}), hypersensitive C-reactive protein (hs-CRP) and serum uric acid (SUA).

Measurement of baPWV

The baPWV was measured by two competent and well-trained professionals, after the subjects rested quietly for 10 min. The arterial pulse waveform was recorded for 5 min using a fully automatic arteriosclerosis detector (Colin VP-1000 device; Colin Medical Technology Company, Komaki, Japan), displaying the baPWV automatically. The right baPWV was selected for data analyses.

Fundus photography and quantitative analysis of the retinal vascular parameters

High-resolution fundus photography using a digital non-mydriatic camera was performed on both eyes (Topcon NW-8, TOPCON CORPORATION, Tokyo, Japan and Nikon D90, Tokyo, Japan) with a capturing range of 45° using the optic disk as the center (Figures 1 and 2). A double-blind analysis of the photographs was performed by two professionally trained ophthalmologists, and high-quality fundus photographs were used for analysis. We used a semiautomated computer-based program (Singapore I Vessel Assessment version 3.0 software, jointly developed by Singapore National University and Singapore Eye Research Institute, Singapore) for the quantitative analysis. The CRAE was measured using the modified Knudtson–Parr–Hubbard formula[31] in the range of 0.5–1 DD from the disc margin, and the retinal vascular fractal dimension was measured in the range of 0.5–2 DD from the disc margin.

Definitions

Hypertension was defined as the systolic blood pressure of $\geqslant 140$ mm Hg and/or the diastolic blood pressure of $\geqslant 90$ mm Hg in the absence of antihypertensive drug therapy. The subjects with a history of hypertension and who were currently using antihypertensive drugs were also defined as hypertensive.[32]

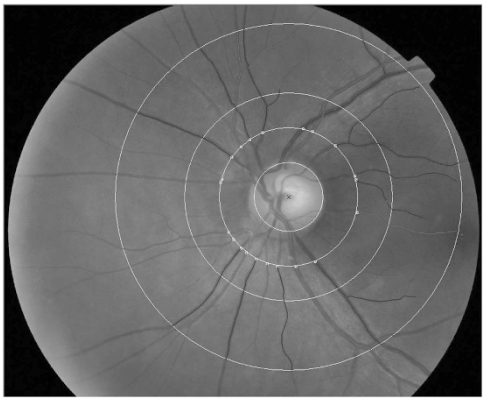

Figure 1 Retinal fundus photograph quantitatively assessed using the Singapore I Vessel Assessment version 3.0 software. Arterioles are in red, and venules are in blue. The measured area of the retinal vascular quantitative parameters were standardized and defined as the region from 0.5 to 2.0 disc diameters away from the disc margin. The full colour version of this figure is available at *Hypertension Research* online.

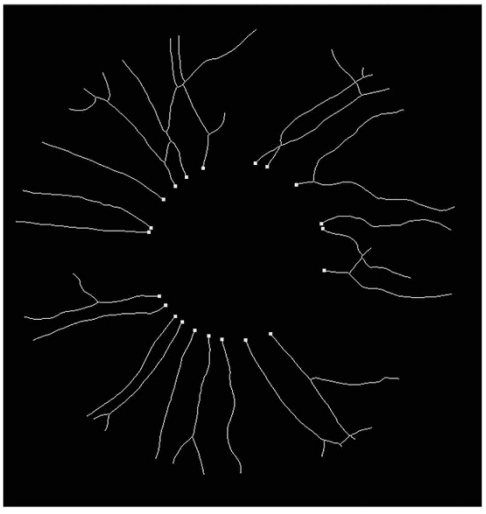

Figure 2 Retinal fundus photograph quantitatively assessed using the Singapore I Vessel Assessment version 3.0 software. The retinal vascular fractal dimension was calculated from the skeletonized line tracing using the box-counting method. The full colour version of this figure is available at *Hypertension Research* online.

Diabetes was defined as an HbA_{1c} of $\geqslant 6.5\%$. Additionally, patients with a history of diabetes, or who were currently using antidiabetic drugs were considered diabetic.[33]

The cutoff value for the normal and increased baPWV was $1400\,cm\,s^{-1}$.[34] The lowest quartile of CRAE was defined as the central retinal artery narrowing.[35] Similarly, the lowest quartile of the retinal vascular fractal dimension was defined as retinal vascular fractal dimension decreasing. The mean arterial blood pressure, the pulse pressure and the body mass index (BMI) were calculated using the following formulae: mean arterial blood pressure (mm Hg) = 1/3 systolic blood pressure+2/3 diastolic blood pressure; pulse pressure (mm Hg) = systolic blood pressure − diastolic blood pressure; BMI ($kg\,m^{-2}$) = body weight per height^2. The mean arterial blood pressure and the pulse pressure were grouped according to the quartile (Q1–Q4); BMI was grouped into normality or malnutrition ($<25\,kg\,m^{-2}$), overweight or obesity ($\geqslant 25\,kg\,m^{-2}$); HbA1c levels were assigned to the normal HbA1c group ($<6.5\%$)

and abnormal HbA1c group (⩾6.5%); and the LDL-C levels were assigned into the normal LDL group ($<3.3\,mmol\,l^{-1}$) and abnormal LDL-C group ($\geqslant 3.3\,mmol\,l^{-1}$). According to the Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) of the National Cholesterol Education Program, the serum lipid levels were grouped as the normal serum lipid group (LDL-C $<3.3\,mmol\,l^{-1}$, HDL-C $\geqslant 1.0\,mmol\,l^{-1}$, serum cholesterol level $<5.2\,mmol\,l^{-1}$ and triglyceride $<1.7\,mmol\,l^{-1}$) and the abnormal serum lipid group.

Statistical analysis

All statistical analyses were performed using the statistical software SPSS (Statistical Package for the Social Sciences) version 17.0.1 (SPSS Inc., Chicago, IL, USA), with a *P*-value <0.05 indicative of statistical significance.

After the baPWV stratification, the subjects' baseline characteristics were compared. The retinal vascular fractal dimension was normally distributed. Other variables were obtained from a large number of random and independent observations such that the arithmetic average of the observed values was approximately normally distributed. The skewness of the CRP was 93.23, which was much >1.96 times its standard error; hence, the CRP was considered right-skewed distributed. The skewed distributed variables were taken as approximately normal distributions after a logarithmic transformation was performed. The normally distributed or the approximately normally distributed data were expressed as the mean ± s.d., and the data with skewed distribution were described as the median (upper and lower quartiles). The count data were expressed as proportions.

The associations of the gender- and the age-adjusted baPWV, CRAE and the retinal vascular fractal dimension with the stratified cardiovascular risk factors were evaluated using analysis of covariance, and the stratified cardiovascular risk factors were used as continuous variables for the trend test. The changes in the retinal vascular parameters (CRAE and the retinal vascular fractal dimension) associated with the increase in baPWV (Q1–Q4) were assessed using analysis of covariance, with the stratified baPWVs used as continuous variables for the trend test. All data in the model were age- and gender-adjusted. The probability of changes in the retinal vascular parameters of the lower quartile group with the increase in baPWV (Q1–Q4) was investigated using a multivariate logistic regression, and two models were therefore designed. In the first model, the variables including gender, age, smoking habits and alcohol consumption were controlled. Conversely, in the second model, the variables including gender, age, smoking habits, alcohol consumption, diabetes, systolic blood pressure, BMI, abnormal lipid level, hs-CRP level and high SUA level were controlled.

RESULTS

The baseline characteristics of the 2169 subjects enrolled in this study and their grouping according to the baPWV are described in Table 1. The subjects enrolled in this study included 812 males and 1357 females, with a mean age 51.92 ± 11.91 years, a mean baPWV of $1417.72 \pm 338.07\,cm\,s^{-1}$, a mean CRAE of 134.10 ± 11.13 μm and a mean retinal vascular fractal dimension of 1.37 ± 0.05. The subjects were assigned to the normal group and the arteriosclerosis group according to their baPWV levels. The mean age, systolic blood pressure, diastolic blood pressure, arterial blood pressure, pulse pressure, BMI, triglyceride, total cholesterol, LDL-C, plasma fibrinogen, HbA1c, hs-CRP and SUA in the arteriosclerosis group were higher than those in the normal group, whereas the mean HDL-C level in the arteriosclerosis group was lower than that in the normal group. In addition, the percentage of male subjects, smoking habits, alcohol consumption and the prevalence of diabetes in the arteriosclerosis group were greater than those in the normal group. The mean CRAE (132.68 ± 11.73 μm) and the mean retinal vascular fractal dimension (1.35 ± 0.05) in the arteriosclerosis group were lower than those in the normal group (135.06 ± 10.61 μm and 1.89 ± 0.05).

Table 1 Characteristics of study population (baPWV status)

Characteristics	*All*	*Normal (baPWV $<1400\,cm\,s^{-1}$)*	*Increased baPWV (baPWV $\geqslant 1400\,cm\,s^{-1}$)*
Subjects (*n*)	2169	1296	873
Age (years)	51.92 ± 11.91	46.54 ± 9.52	59.91 ± 10.54
SBP (mm Hg)	126.94 ± 21.94	116.16 ± 14.68	142.94 ± 21.15
DBP (mm Hg)	78.55 ± 11.85	74.50 ± 10.05	84.58 ± 11.77
MABP (mm Hg)	94.67 ± 14.10	88.36 ± 10.82	104.04 ± 13.17
Pulse pressure (mm Hg)	48.39 ± 15.88	41.66 ± 10.13	58.37 ± 17.54
HR (per min)	71.22 ± 9.28	70.78 ± 8.71	71.87 ± 10.03
BMI ($kg\,m^{-2}$)	23.83 ± 3.42	23.32 ± 3.38	24.58 ± 3.33
Triglyceride ($mmol\,l^{-1}$)	0.86 ± 0.50	0.92 ± 0.64	0.76 ± 0.01
Total cholesterol ($mmol\,l^{-1}$)	5.03 ± 1.05	4.88 ± 1.02	5.24 ± 1.06
HDL-C ($mmol\,l^{-1}$)	1.23 ± 0.33	1.23 ± 0.32	1.22 ± 0.34
LDL-C ($mmol/l^{-1}$)	2.79 ± 0.88	2.65 ± 0.82	2.99 ± 0.94
FPG (mmol l)	5.31 ± 1.50	5.17 ± 1.10	5.53 ± 1.93
HbA1c (%)	5.72 ± 0.68	5.59 ± 0.49	5.90 ± 0.87
hs-CRP ($mg\,l^{-1}$)	0.52 (0.31, 1.34)	0.38 (0.25, 1.00)	0.79 (0.48, 1.93)
SUA ($\mu mol\,l^{-1}$)	315.04 ± 84.82	306.98 ± 83.84	327.00 ± 84.91
baPWV ($cm\,s^{-1}$)	1417.72 ± 338.07	1202.81 ± 120.12	1736.76 ± 303.60
CRAE (μm)	134.10 ± 11.13	135.06 ± 10.61	132.68 ± 11.73
Retinal vascular fractal dimension	1.37 ± 0.05	1.89 ± 0.05	1.35 ± 0.05
Gender (%male)	812 (37.4)	419 (32.3)	393 (45.0)
Cigarette smoking (%)	415 (19.1)	213 (16.4)	202 (23.1)
Alcohol drinking (%)	341 (15.7)	164 (12.7)	176 (20.2)
Diabetes (%)	272 (12.5)	99 (7.6)	173 (19.8)

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, systolic blood pressure; CI, confidence interval; CRAE, central retinal arteriolar equivalent; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hypersensitive; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; hs-CRP, hypersensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MABP, mean arterial blood pressure; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride.
Homogeneous continuous variables were reported as mean ± s.d.; heterogeneous continuous variables were described as medians or percentiles (25th to 75th). Categorical variables were reported as percentage (95% CI).

Table 2 Cardiovascular risk stratification: baPWV/CRAE/retinal vascular fractal dimension

		baPWV	*CRAE*	*Retinal vascular fractal dimension*
	N	*Mean (s.e.) (cm s^{-1})*	*Mean (s.e.) (μm)*	*Mean (s.e.)*
Age (years)				
Quintiles				
Youngest, 30–39	356	1203.770 (14.856)	134.484 (0.628)	1.388 (0.003)
Second, 40–49	647	1280.656 (10.878)	134.241 (0.460)	1.380 (0.002)
Third, 50–59	575	1430.568 (11.251)	133.718 (0.476)	1.366 (0.002)
Fourth, 60–69	418	1653.547 (12.901)	132.877 (0.546)	1.342 (0.002)
Oldest, 70–90	173	1877.765 (19.926)	133.900 (0.843)	1.319 (0.004)
Diabetes				
Absent	1897	1408.554 (6.225)	133.863 (0.263)	1.366 (0.001)
Present	272	1530.131 (16.801)	133.712 (0.709)	1.359 (0.003)
Hypertension				
Absent	1350	1319.822 (7.040)	134.961 (0.327)	1.373 (0.001)
Present	819	1592.652 (8.958)	132.054 (0.416)	1.354 (0.002)
SBP (mm Hg)				
Quartiles				
First, 80–110	539	1254.669 (12.153)	137.151 (0.575)	1.382 (0.002)
Second,111–124	545	1333.984 (10.272)	134.515 (0.486)	1.369 (0.002)
Third,125–138	539	1434.264 (10.091)	132.600 (0.477)	1.362 (0.002)
Fourth,139-224	546	1654.833 (10.661)	131.457 (0.504)	1.352 (0.002)
DBP (mm Hg)				
Quartiles				
First,50–70	539	1301.558 (11.900)	136.513 (0.522)	1.374 (0.002)
Second,71–78	545	1366.965 (11.426)	134.738 (0.501)	1.372 (0.002)
Third,79–86	539	1442.583 (10.924)	132.579 (0.479)	1.361 (0.002)
Fourth,87–140	546	1567.704 (10.821)	131.718 (0.475)	1.356 (0.002)
MABP (mm Hg)				
Quartiles				
First, 61–84	539	1268.725 (11.963)	137.121 (0.552)	1.377 (0.002)
Second, 85–93	545	1340.238 (10.585)	134.301 (0.488)	1.373 (0.002)
Third, 94–103	539	1440.816 (10.363)	133.272 (0.478)	1.362 (0.002)
Fourth,104–153	546	1626.445 (10.557)	130.948 (0.487)	1.352 (0.002)
Pulse pressure (mm Hg)				
Quartiles				
First, 8–38	539	1316.672 (12.184)	135.672 (0.545)	1.372 (0.002)
Second, 38–45	545	1355.064 (11.074)	133.846 (0.496)	1.370 (0.002)
Third, 46–56	539	1418.191 (10.876)	133.689 (0.487)	1.364 (0.002)
Fourth, 56–134	546	1603.590 (11.507)	132.329 (0.515)	1.356 (0.002)
BMI (kg m^{-2})				
Normal or malnutrition, <25	1473	1402.623 (6.945)	134.626 (0.289)	1.368 (0.001)
Overweight or obesity, $\geqslant 25$	696	1449.659 (10.157)	132.992 (0.423)	1.360 (0.002)
LDL-C (mmol l^{-1})				
Normal, <3.3	1692	1412.109 (6.715)	134.058 (0.280)	1.366 (0.001)
Abnormal, $\geqslant 3.3$	477	1464.543 (12.399)	133.152 (0.518)	1.363 (0.002)

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CRAE, central retinal arteriolar equivalent; DBP, diastolic blood pressure; LDL-C, low density lipoprotein cholesterol; MABP, mean arterial blood pressure; SBP, systolic blood pressure; TC, total cholesterol.
Data are means and s.e., adjusted gender and age if applicable. All tests for trends are significant ($P<0.05$).

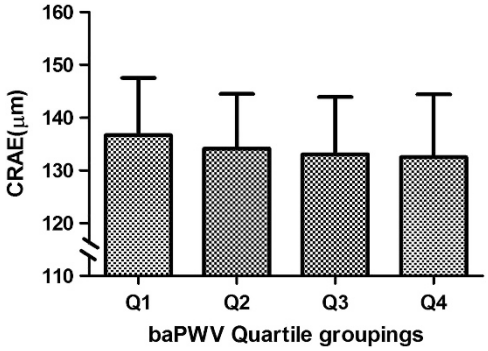

Figure 3 The CRAE distribution in the baPWV quartile groupings.

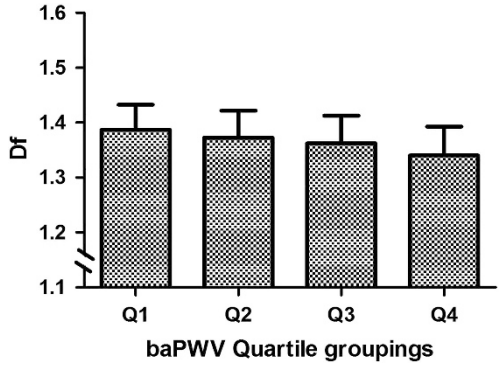

Figure 4 Retinal vascular fractal dimension distribution in the baPWV quartile groupings.

Adjusting for the gender and age, the baPWV gradually increased with the increase in age, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, pulse pressure, BMI, total cholesterol and LDL-C, whereas the CRAE and retinal vascular fractal dimension were gradually reduced. The baPWVs in the diabetic and hypertensive subjects were higher than those in the non-diabetic or non-hypertensive subjects, whereas the CRAEs and retinal vascular fractal dimensions in the diabetic and hypertensive subjects were lower than those in the non-diabetic or non-hypertensive subjects ($P<0.05$) (Table 2).

The CRAE and retinal vascular fractal dimension decreased with the increase in the quartile of baPWV (Q1–Q4) ($P<0.05$) (Figures 3 and 4), and analysis of covariance was statistically significant after the gender and age were adjusted ($P<0.001$) (Table 3). Defining baPWV as a dependent variable, CRAE and retinal vascular fractal dimension as independent variables, and adjusting for the gender, age, smoking habits and alcohol consumption, logistic regression analysis revealed that the likelihood of the central retinal artery narrowing (odds ratio = 3.093; 95% confidence interval: 2.010–4.760; $P<0.001$) and the retinal vascular fractal dimension decreasing (odds ratio = 3.746; 95% confidence interval: 2.312–6.070; $P<0.001$) increased with the elevated baPWV (Q1–Q4). Further adjustment of the cardiovascular risk factors diminished the association between baPWV and CRAE, but increased the association between baPWV and the retinal vascular fractal dimension (Table 4).

Table 3 Association of baPWV with CRAE and retinal vascular fractal dimension

	N	*CRAE (μm)* Mean (s.e.)	*Retinal vascular fractal dimension* Mean (s.e.)
baPWV (cm s^{-1})			
Q1, 770–1169	539	136.730 (0.527)	1.375 (0.002)
Q2,1170–1346	546	134.290 (0.481)	1.367 (0.002)
Q3,1347–1599	539	133.121 (0.479)	1.365 (0.002)
Q4,1600–3746	545	132.283 (0.539)	1.355 (0.002)
P-value[a]		<0.001	<0.001

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CRAE, central retinal arteriolar equivalent.
Data are means and s.e., adjusted gender and age.
[a]Test for trends.

DISCUSSION

Our findings showed that the CRAE and the retinal vascular fractal dimension were reduced with an increase in baPWV, independent of gender, age, smoking habits, alcohol consumption, diabetes, hypertension, BMI, abnormal serum lipid level, hs-CRP level and the SUA level. The association of the large- and medium-sized arterial stiffness with the retinal arteriolar diameter and the retinal vascular complexity provides an important perspective from which to evaluate the correlation between the aorta and the arteriole or the microvasculature. The correlation between the arterial stiffness and the retinal microvascular changes has been recently proved in clinical trials.[27–30] However, the mechanisms underlying the correlation remain unclear. Changes in the structure and the blood flow velocity of the arteriole or the microvascular structures carrying nutrients may affect the aortic function.[36–39] Atherosclerosis of the large- and medium-sized arteries increases the blood flow to the arteriole with high pulsatility index, resulting in vascular damage.[40] In addition, the interaction promotes the progression of atherosclerosis. Conversely, the pathology leading to changes in aortic walls and arterioles, including endothelial dysfunction, modified collagen ratio and atherosclerosis, may develop in parallel with the atherosclerosis of the large- and medium-sized arteries.

baPWV and CRAE

Although the study methods used were different, the correlation between the aortic stiffness and the retinal arteriolar narrowing has been widely investigated. It has been reported that the general retinal arteriolar narrowing correlates with clinical stroke,[41] impaired cardiac systolic function[42] and subclinical leukodystrophy.[43] A study involving black and white subjects showed that increased carotid artery stiffness was associated with decreased arteriole-to-venule ratio in middle-aged people.[28] In addition, a multiethnic study of atherosclerosis involving 3425 participants from multiple ethnic backgrounds revealed that the increased arterial stiffness was associated with retinal arteriolar narrowing, although such a link was not apparent in Chinese women.[29]

The present study involved the inhabitants from the southeastern coast of China. We found a negative correlation between baPWV and CRAE after the cardiovascular risk factors including systolic blood pressure, diabetes, BMI and abnormal serum lipid level were adjusted, indicating that the baPWV increases with the reduction in CRAE. It suggested that hypertension affects arterial stiffness through altered arterial compliance, elasticity, distensibility and arterial wall

Table 4 Multiple logistic regression of CRAE/retinal vascular fractal dimension by baPWV

	OR (95% CIs) CRAE/retinal vascular fractal dimension lowest quartile				
baPWV	*Q1*	*Q2*	*Q3*	*Q4*	*P-value*[a]
CRAE					
Model 1[b]	1.000 (Ref.)	2.001 (1.394, 2.872)	2.889 (1.967, 4.243)	3.093 (2.010, 4.760)	<0.001
Model 2[c]	1.000 (Ref.)	1.759 (1.224, 2.528)	2.083 (1.408, 3.081)	1.635 (1.031, 2.595)	<0.001
Retinal vascular fractal dimension					
Model 1[b]	1.000 (Ref.)	1.905 (1.277, 2.842)	2.028 (1.335, 3.080)	3.746 (2.312, 6.070)	<0.001
Model 2[c]	1.000 (Ref.)	1.808 (1.215, 2.690)	2.021 (1.321, 3.093)	3.815 (2.297, 6.334)	<0.001

baPWV, brachial ankle pulse wave velocity; BMI, body mass index; CI, confidence interval; CRAE, central retinal arteriolar equivalent; hs-CRP, hypersensitive C-reactive protein; OR, odds ratio; Q1–Q4, quartiles of baPWV; SUA, serum uric acid.
[a]Test for trends.
[b]Model 1: adjusted by gender, age, cigarette smoking and alcohol consumption.
[c]Model 2: adjusted by diabetes, systolic blood pressure, BMI, dyslipidemia, hs-CRP and SUA.

composition. The vascular stiffness enables more rapid reflux of the peripheral blood, leading to increased central systolic and pulse pressure.[43] Multiple lines of evidence support the correlation between CRAE and hypertension, pointing to a further link between baPWV and CRAE.[2,4–6,44–47] The key factor linking baPWV and CRAE may be the increased pulsatility index of the blood flow entering the small blood vessels, which is caused by the huge differences in arterial blood pressure,[29] or the injury to the arteriole supplying nutrients, as well as structural and functional alterations of the aortic wall.[36–38]

Other studies evaluating the increased ambulatory arterial stiffness index imply a greater presence of subclinical organ damage in primary hypertensive patients. This finding was somewhat consistent with our results that blood pressure may have a part in the relationship between baPWV and CRAE.[48]

baPWV and retinal vascular fractal dimension

The retinal vascular fractal dimension is a measure of the retinal vascular complexity and is more stable than CRAE. Our results also showed that the correlation between baPWV and the retinal vascular fractal dimension may be stronger than that between baPWV and CRAE. It has been shown that the retinal vascular fractal dimension measurement was not affected by the resolution of the fundus photograph and was hardly affected by the vascular pulsation. In addition, it was not affected by the number of regional blood vessels even if the measurement was based on the vascular bifurcation, the bifurcation angle and the length of the blood vessel between the bifurcations.[9] It was suggested that the retinal vascular fractal dimension should be used to reflect the occurrence, severity and target organ injury in hypertensive patients and the patient response to antihypertensive drugs.[49–51] Similar to CRAE, the retinal vascular fractal dimension is a predictor of cardiovascular disease.[52] Based on the evidence available so far, it is considered that an increased baPWV and a reduced retinal vascular fractal dimension are independently observed in hypertensive subjects,[9] and a stronger correlation between baPWV and the retinal vascular fractal dimension was observed in hypertensive subjects than in non-hypertensive subjects. Hypertension reportedly promotes vascular remodeling and sparse distribution of microblood vessels, and the arteriolar narrowing in hypertension causes an increased resistance to distal blood flow and compensatory sparse distribution of the microvascular network that is characterized by reduced retinal vascular fractal dimension.[49]

To our knowledge, this is the first study to evaluate the association between the quantitative parameters of the retinal blood vessels and aortic stiffness in Chinese inhabitants. The present study involved a series of cardiovascular risk factors including SUA, and used non-invasive baPWV to describe aortic stiffness, which facilitated the enrollment of additional study subjects. However, the current study has the following limitations: (1) this study is not a prospective study and cannot identify the causal relationship between the retinal vascular parameters and aortic stiffness; (2) a few subjects were not enrolled in the study because of noncompliance, leading to possible selection bias; and (3) we did not use the combination of carotid-femoral pulse wave velocity, carotid artery intima-media thickness and plain MRI scanning of the aorta to reflect the systemic atherosclerotic changes.

Conclusion

This is the first study to evaluate the association between the quantitative parameters of the retinal blood vessels and aortic stiffness in Chinese inhabitants. The study indicates that the CRAE and the retinal vascular fractal dimension were reduced with an increase in baPWV. The association of the large- and medium-sized arterial stiffness with the retinal arteriolar diameter and the retinal vascular complexity provides an important perspective to evaluate the correlation between the aorta and the arterioles or microvasculature. Similar to CRAE, the retinal vascular fractal dimension is a predictor of cardiovascular diseases. The current study revealed that the correlation between baPWV and the retinal vascular fractal dimension was significantly stronger in hypertensive subjects than in non-hypertensive subjects

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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