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Central Arterial Stiffness and Retinal Vessel Calibers: The Atherosclerosis Risk in Communities Study - Neurocognitive Study (ARIC-NCS)

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Abstract

Background: The retinal microvasculature provides a window to the cerebral vasculature and enables examination of changes in retinal caliber that may mimic those occurring in cerebrovascular disease. The association of central arterial stiffness and retinal vessel caliber in a population sample is not fully understood.

Methods: In 1,706 older adults (mean age 76.3, 58.1% female) from the population-based Atherosclerosis Risk in Communities Study, we examined the cross-sectional association of central arterial stiffness (carotid-femoral pulse wave velocity (cfPWV)) with retinal vessel calibers (central retinal arteriolar equivalent (CRAE) and central retinal vein equivalent (CRVE)). We estimated the association of cfPWV with CRAE narrowing (<25th percentile) and CRVE widening (>75th percentile) after adjustment for age, sex, race-field center, body mass index, smoking, and type 2 diabetes. We tested for effect modification by sex, hypertension, and type 2 diabetes.

Results: Carotid-femoral PWV (m/s) was not associated with the odds of CRAE narrowing (odds ratio (OR): 0.99; 95% CI: 0.95, 1.03). The association of cfPWV with CRVE widening was stronger in those without hypertension (OR: 1.10; 95% CI: 1.01, 1.20) versus those with

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hypertension (OR: 1.01 95% CI: 0.96, 1.05) and slightly stronger in those with type 2 diabetes (OR: 1.07; 95% CI: 1.00, 1.14) versus without type 2 diabetes (OR: 1.01; 95% CI: 0.96, 1.06).

Conclusions: In older adults, cfPWV was associated with wider retinal venular caliber, particularly in individuals without hypertension. Central arterial stiffening may be associated with cerebral microvascular changes, as exhibited in its retinal vasculature component.

Keywords

arterial stiffness; retinal photography; small vessel disease; aging; cerebral vasculature; the ARIC study

Introduction

Due to the structural and functional similarities of the retinal and cerebral vessels, non-invasive measures of retinal vessels are of interest in the study of cerebral microvascular disease [1]. Retinal macro- and microvascular abnormalities are associated with risk of stroke [2, 3], large and small cerebral ischemic lesions on magnetic resonance imaging [4–6], and microvascular abnormalities are particularly associated with reduced cognitive function [7–10]. Thus, specific attention has focused on alterations in retinal arteriolar and retinal venule widths, or calibers, representing a window into similar alterations in the cerebral vasculature [11, 12].

Associations between central artery stiffness and various manifestations of cerebral small vessel disease have been reported, including lacunar strokes [13, 14], microbleeds [15], white matter hyperintensities [14, 16, 17], and white matter integrity [18]. Prior studies have shown that carotid arterial stiffness [19] and aortic distensibility [20] are also associated with retinal vessel calibers independent of blood pressure or hypertension in population-based studies. However, most reports evaluated the ratio of the arteriolar and venular calibers or the wall-to-lumen ratio of the retinal arteries [21, 22], rather than both calibers separately. It is now known that retinal arteriolar and venular calibers have differential associations with vascular risk factors. Narrower arteriolar caliber is strongly associated with hypertension [23], whereas wider venular caliber is associated with hyperglycemia and diabetes, higher body mass index [23, 24], and markers of inflammation [23, 25, 26]. Prior studies did not use central arterial stiffness measured by carotid-femoral pulse wave velocity (cfPWV), which is the gold standard measure of central aortic stiffness. Finally, most studies of the association between central arterial stiffness and retinal characteristics have focused on specific cohorts, such as individuals with type 2 diabetes [27, 28] or persons with stroke or other clinically-defined populations [29, 30].

A more detailed characterization of associations between central artery stiffness measured by carotid-femoral pulse wave velocity and retinal vessel diameters in a population-based study can offer insights into similar pathogenesis of cerebral vessels. Thus, the aim of this study was to quantify the cross-sectional association of central arterial stiffness with retinal vascular calibers (central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE)). We hypothesized that central arterial stiffness would be associated with

narrower retinal arteriolar caliber (CRAE narrowing) and wider retinal venular caliber (CRVE widening).

Methods

Study participants

The Atherosclerosis Risk in Communities (ARIC) Study is a population-based, longitudinal study of 15,792 participants aged 45–64 years at the time of their enrollment in 1987–1989 from the following four US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Details of the baseline visit have been described [31]. This investigation included 2,044 participants who attended the visit 5 examination between 2011 and 2013 and had graded retinal fundus photography scans and measures of arterial stiffness. Participants provided written informed consent, and the ARIC study was approved by the Institutional Review Boards at all field centers and other study agencies.

We excluded participants with retinal abnormalities in both eyes (age-related macular degeneration, vein occlusions, retinopathy, macular edema, and other pathologies; n=70), body mass index (BMI) ≥40 kg/m^2 (n=57) or missing BMI (n=4), major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2; (n=74), Minnesota code 8–1-2 with evidence of low quality PWV waveforms (n=9), self-reported history of aortic or peripheral revascularization or aortic graft (n=40), echocardiographic evidence of aortic stenosis or moderate or greater aortic regurgitation (n=11), or missing covariates of interest (mean arterial pressure (MAP), n=5; cigarette smoking history, n=13; hypertension status, n=15, and diabetes status, n=13), cfPWV greater than three standard deviations away from the mean (n=15), participants who self-identified as Asian or Native American from any site (n=2), and black participants from Minnesota or Maryland sites (n=10) were also excluded due to small numbers. The final analytic set included 1,706 participants after the exclusions.

Study staff asked participants to bring all prescription and nonprescription medications taken within the prior two weeks, to not consume food or drinks, and to refrain from tobacco and vigorous physical activity after midnight prior to the clinic visit or for 8 hours prior to the visit. Participants underwent a blood draw, B-mode scan of the abdominal aorta, standard 12-lead electrocardiogram, anthropometry, assessment of functional abilities, and interviewer-administered questionnaires to obtain medical history and lifestyle information. Body weight was measured to the nearest 0.1 kilogram and height was recorded to the nearest centimeter. Three seated blood pressure measurements were obtained after a five-minute rest using an oscillometric automated sphygmomanometer (Omron HEM-907 XL, Omron Co. Ltd., Kyoto, Japan) and the average of the last two measurements was used.

Hypertension was defined as systolic blood pressure (SBP) ≥140 mm/Hg, diastolic blood pressure (DBP) ≥90 mm/Hg, or anti-hypertensive medication use. Diabetes was defined as fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, anti-diabetic medication use, or self-reported physician diagnosis of diabetes. Prevalent coronary heart disease (CHD) and stroke were defined by baseline status, ARIC cohort surveillance data, and adjudication through 2013, where the event occurred prior to the participant’s visit 5 examination.

Standard resting 12-lead ECGs were digitally acquired using a GE MAC 1200 electrocardiograph (GE, Milwaukee, WI) at 10 mm/mV calibration and a speed of 25 mm/s. ECGs were centrally processed using GE 12-SL Marquette Version 2001 (GE, Milwaukee, Wisconsin) at the Epidemiological Cardiology Research Center at the Wake Forest School of Medicine.

Retinal Characteristics

Digital, non-mydriatic retinal fundus photographs were taken and evaluated by the Ocular Epidemiology Reading Center at the University of Wisconsin-Madison. CRAE and CRVE were calculated using a semiautomatic method used previously by ARIC [32, 33]. Data from a randomly selected eye were included (block randomization); if missing data, the other eye was selected (n=745).

Pulse wave velocity

Details of the PWV methodology used in ARIC have been reported [34]. Briefly, technicians measured PWV using the automated waveform analyzer VP-1000 Plus (Omron Co., Ltd., Kyoto, Japan) [35] after participants were supine for 5 to 10 minutes. Carotid and femoral arterial pressure waveforms were acquired by applanation tonometry sensors on the left common carotid artery and left common femoral artery. Bilateral brachial and posterior-tibial arterial pressure waveforms were detected by plethysmographic and an oscillometric pressure sensor wrapped on both arms and ankles. Higher values of cfPWV indicate arterial stiffness.

PWV was calculated as distance divided by transit time. Distance for carotid femoral PWV (cfPWV) was measured with a segmometer (Rosscraft, Surray, Canada) and calculated as the carotid to femoral distance minus the distance between the suprasternal notch to carotid. Technicians obtained two measurements and the results were averaged. Outliers, defined as values three standard deviations above or below the mean, were excluded for the analyses. Repeat visits were conducted for a subset of participants at each field center approximately 4 to 8 weeks later (n = 79; mean age 75.7 years; 46 females). The intra-class correlation coefficients and 95% confidence intervals (95% CIs) for single measurements were 0.70 (0.59, 0.81) for cfPWV [36] and approximately 0.82 for averaged cfPWV measurements, according to the Spearman-Brown formula.

Statistical analysis

Participant characteristics overall and by CRAE narrowing and CRVE widening were estimated as means and standard deviations or frequencies and percent, where appropriate. We used analysis of covariance to estimate adjusted means and the 95% confidence intervals (CI) of PWV by quartiles of CRAE and CRVE adjusted for age and sex.

Multivariable logistic regression analysis was used to separately evaluate the association of cfPWV with CRAE narrowing (<25^{th} percentile) or CRVE widening (>75^{th} percentile). The lower 25^{th} percentile cut point was 132.6 μm for CRAE and the upper 75^{th} percentile cut point was 219.7 μm for CRVE. We modeled cfPWV as a continuous variable and as a standard deviation change (per 3.00 m/s). Analyses were adjusted for age, sex, race-field

center, body mass index, smoking (current, former, and never as the referent category), and type 2 diabetes. In a second model, we additionally adjusted for hypertension and/or MAP. As *a priori* hypotheses, we tested for interactions by sex, hypertension, and type 2 diabetes. P-values were two-sided with statistical significance of $P<0.05$ (SAS, version 9.2, SAS Institute, Inc., Cary, NC). We conducted a sensitivity analysis excluding participants with coronary heart disease and adjusting for inflammation (high-sensitivity C-reactive protein (hs-CRP), which is associated with cerebral venular widening.

Results

Participant characteristics

Among the 1.706 study participants, 58.1% were female and 21% were black (Table 1). The mean age was 76.3 years and the mean BMI was 27.6 kg/m^2. Compared to those without CRAE narrowing, those with CRAE narrowing had, on average, a higher MAP, SBP, and DBP, and a lower prevalence of current smokers and type 2 diabetes. A different pattern was seen with CRVE widening. Compared to those without CRVE widening, those with CRVE widening had a higher prevalence of type 2 diabetes. They also had lower MAP, SBP, and DBP, higher fasting glucose, and a higher prevalence of current smokers, hypertension, and black participants.

Association between age- and sex-adjusted mean cfPWV by retinal vessel calibers quartiles

The age- and sex-adjusted mean cfPWV did not significantly differ across CRAE and CRVE quartiles (Figure 1). Although not statistically significant, the mean cfPWV was higher in the second CRAE quartile (12.05 m/s) compared to the other CRAE quartiles (range: 11.57 to 11.59 m/s), and the mean cfPWV was higher in the fourth quartile of CRVE (12.07 m/s) compared to the other CRVE quartiles (range: 11.44 to 11.65 m/s, in Q1 and Q3, respectively). Among those with hypertension, the association of the mean cfPWV with CRAE quartiles was similar to the overall results, whereas among those without hypertension, the mean cfPWV was similar across CRAE quartiles (Figure 2). For CRVE, the pattern of mean cfPWV values by CRVE quartiles was similar in both those with and without hypertension, although the increase in mean cfPWV from the first to fourth CRVE quartile was more prominent in those without hypertension.

Association of cfPWV with CRAE narrowing and CRVE widening

In multivariable logistic regression, cfPWV (per m/s) was not associated with the odds of CRAE narrowing (odds ratio (OR) 0.99; 95% confidence interval (CI): 0.95, 1.03) after adjusting for age, sex, smoking status, BMI, type 2 diabetes, and race-center (Table 2). Results were similar after adjusting for hypertension and MAP. Each m/s increase in cfPWV was associated with a 1.03 higher odds of CRVE widening (95% CI: 0.99, 1.07) after adjusting for age, sex, smoking status, BMI, type 2 diabetes, and race-center. Associations were stronger after additional adjustment for hypertension and MAP (OR per m/s: 1.05; 95% CI: 1.00, 1.09).

We detected evidence of effect modification by hypertension (interaction p=0.04) and modest effect modification by type 2 diabetes (interaction p=0.12) in the association between cfPWV and CRVE. We did not find evidence of effect modification for cfPWV and CRAE. In those without hypertension, cfPWV was associated with a higher odds of CRVE widening (OR: 1.10; 95% CI: 1.01, 1.20) with adjustment for age, sex, smoking status, BMI, type 2 diabetes, and race-center (Table 3). The magnitude of the association was stronger after additional adjustment for MAP. In those with hypertension, the association between cfPWV and CRVE widening was weaker for cfPWV (OR 1.01; 95% CI: 0.96, 1.05) and was stronger after adjustment for MAP, but not statistically significant. In those with type 2 diabetes, cfPWV was associated with a 1.07 times higher odds of CRVE widening (95% CI: 1.00, 1.14) and was statistically significant after additional adjustment for hypertension and MAP (Supplemental Table 1). In contrast, in those without type 2 diabetes, the association of cfPWV and CRVE was weaker (OR per m/s: 1.01; 95% CI: 0.96, 1.06) and did not change when additionally adjusting for hypertension and MAP.

In a sensitivity analysis, the results did not change after adjusting for high-sensitivity C-reactive protein. After excluding participants with prevalent coronary heart disease (n=240), the association of cfPWV and CRAE narrowing was the same, but the association of cfPWV and CRVE widening was stronger. Results were also the same in a complete case analysis (i.e. only including those with both CRAE and CRVE measures, N=1,610). Lastly, the results were consistent when analyzing CRAE and CRVE as continuous variables.

Discussion

In this study of older adults, higher cfPWV was associated with CRVE in those without hypertension, but was not significantly associated with CRAE narrowing. Additionally, the association between cfPWV and CRVE widening varied by hypertension and diabetes status, which was not the case for CRAE narrowing. When additionally adjusting for hypertension and/or MAP, the results did not change for CRAE, but were stronger for CRVE. Different associations between the cfPWV and the type of vessels suggest that retinal arteriolar and venular caliber abnormalities are influenced by different vascular risk factors, possibly reflecting a different underlying pathogenesis.

Few studies of arterial stiffness and retinal vessel calibers included the standard PWV measurement for arterial stiffness, and their results are not consistent. In a study of hypertensive individuals (n=181; mean age 54 years), cfPWV was negatively associated with CRAE and positively associated with CRVE [37]. However, in another study of hypertensive individuals (n=88; mean age 54 years), cfPWV was negatively associated with both CRAE and CRVE, but the association was not robust to additional covariate adjustment [38]. In 223 normotensive and newly diagnosed hypertensive adults, cfPWV was associated with narrower CRAE, but not with CRVE [29]. Similar results were shown in ischemic stroke patients where cfPWV was associated with narrower CRAE, although CRVE was not included in the analysis [30]. These studies included participants with hypertension or stroke, and in fairly small numbers, in contrast to this population-based study of much older adults. Additionally, few studies included both CRAE and CRVE measurements, which were included in this study.

Beyond cfPWV, other markers of arterial stiffness and vascular disease are associated with retinal diameters. In a prior ARIC report, pulsatile carotid arterial diameter change was associated with the arteriole-to-venule ratio, though these calibers were not included individually in the analysis [19]. This association was independent of hypertension status. However, in this study, we observed effect modification by hypertensive status. In the Multi-Ethnic Study of Atherosclerosis, reduced aortic distensibility was associated with retinal arteriolar narrowing, but not with venular caliber [20]. Another MESA study showed that reduced brachial large-artery compliance, a peripheral measure of arterial stiffness, was associated with smaller retinal arteriolar caliber, whereas small-artery compliance was associated with larger venular caliber [39]. Both MESA study results were independent of blood pressure and hypertension medications and the population was younger than this study. Indicators of atherosclerosis, higher ankle-arm index and carotid plaque score, were associated with wider CRVE in the Rotterdam study, and estimates were stronger when accounting for blood pressure [24]. Similarly, our study showed arterial stiffness was associated with larger venular caliber and the associations were stronger after accounting for hypertension status and MAP. Our study and others suggest the association of arterial stiffness with CRAE and CRVE represent different pathophysiologic mechanisms, and hypertension status and blood pressure affects these associations.

Historically, studies typically evaluated the association of blood pressure with arteriole-to-venule ratio because it was thought that venular vessel calibers are unaffected by blood pressure. Now, the focus has shifted to both retinal arteriolar and venular calibers as important and distinct markers of disease [24, 40]. CRVE widening predicts hypertension [41, 42], stroke [43–45], and dementia [46]. Further, blood pressure level is consistently associated with CRAE narrowing [23], whereas hyperglycemia, obesity [23, 24], and inflammation [23, 25] are associated with CRVE widening. We observed these distinct profiles of covariates for the arteriolar and venular vessels, and our results also suggest a stronger association of cfPWV with venular diameters versus arteriolar diameters in older age.

Arterial stiffness is increased in persons with diabetes and the association is stronger in those with microvascular complications [47]. In studies of participants with type 2 diabetes, cfPWV [28] and heart-femoral PWV [27] were associated with retinopathy. However, these studies did not include retinal vessel calibers. In the present study, there was a modest effect modification where the association of arterial stiffness and retinal venular widening was stronger among those with diabetes compared to those without diabetes. In diabetes, the arterial stiffening and microvasculature complications may be exacerbated by hypertrophic remodeling seen in diabetes [48, 49] and elevated advanced glycosylation end-products (AGEs) [50, 51], which cross-link with collagen and elastin resulting in decreased vascular elasticity. Altogether, this suggests that shared mechanisms could magnify the association between arterial stiffness and retinal venular widening in those with type 2 diabetes.

Given the established association of blood pressure with CRAE, we expected to observe an association of CRAE with arterial stiffness. The lack of association between cfPWV and CRAE may reflect the older age of our examinees. In a meta-analysis of individual data, CRAE narrowing was associated with incident hypertension in participants <60 years old,

but not in participants ≥70 years old [41]. This was not observed with CRVE widening. Similarly, in the Rotterdam study, the association of arteriolar diameters and blood pressure was stronger in younger participants and not significant after 80 years old, whereas the association of venular diameters and blood pressure was weaker and there was no association when stratified by age [24]. Although we did not observe an association between cfPWV and CRAE, we observed differences in the association between cfPWV and CRVE by hypertension status where the effect was stronger among those without hypertension. The lack of association in hypertension may be due to the older age of the participants, consistent with the prior studies of blood pressure.

Arteries stiffen with age and exposure to risk factors. Elevated arterial stiffness is accompanied by high pulse pressure that is transmitted to the microvasculature leading to hypoperfusion and vascular remodeling [52], with detrimental effects on end-organs, particularly the brain. Arterial stiffness has emerged as a risk factor for adverse morphologic and functional changes in the brain, but the expense and burden of magnetic resonance imaging, alternate non-invasive methods to study this association are needed, such as the quantification of retinal vessels characteristics. The retinal microvasculature serves as an index of cerebral small vessel pathologies, supported by evidence that retinal microvascular abnormalities are associated with lower cognitive function [7, 8] and cerebral ischemic lesions on magnetic resonance imaging [4–6]. The relation of retinal venular widening with cerebral small vessel disease is not clear, and indeed difficult to explain since wide venules should not impair blood flow. However, studies have shown venular widening is associated with lower cerebral oxygen supply [53], stroke [3], progression of cerebral small vessel disease [54], and vascular dementia [46], suggesting that venular widening could relate to cerebral hypoperfusion and ischemia in the brain through associated processes such as inflammation, and they could also be related to vascular risk factors such as arterial stiffness. Thus, the relationship between central arterial stiffness and retinal vascular calibers may indicate other mechanisms underlying the observed associations between cfPWV and cerebral ischemic abnormalities on magnetic resonance imaging.

There are limitations of the current study to consider. The cross-sectional design precludes the assessment of temporality and causality in the observed associations. Some PWV and retinal measurements were not collected due to technical limitations, low quality retinal images, participant factors, and scheduling conflicts. We excluded retinal measures with certain pathologies that would prevent obtaining a good measure of the arterioles/veins. Additionally, we did not include ungraded retinal measures (e.g. issue with focus, washed out, or disk head not visible) or measures with less than six arteries or venues graded to address potential concerns with the focus of the retinal image using fundus photography. Another limitation to consider is the potential for survival bias due to attrition over the course of >25 years of follow-up. The surviving cohort members likely are healthier and more vigorous than those who did not take part in the examination, which would tend to attenuate the observed associations. The internal validity of the associations estimated in this study is supported by our multivariable statistical adjustment for participant characteristics that influenced attrition, and we deem our results from this population-based cohort to be generalizable to other populations of older adults of comparable demographic characteristics.

Conclusions

Understanding the association of central arterial stiffness and retinal characteristics enables testable hypotheses regarding the pathogenesis of cerebral abnormalities of vascular origin. In a population-based study with a gold-standard measure of central arterial stiffness, we found central arterial stiffness to be associated with CRVE widening in those without hypertension, suggesting that macrovascular arterial stiffness may play a role in or be an indicator of microvascular retinal changes that mimic cerebral vascular disease. The different associations of cfPWV and CRAE and CRVE suggest that diverse pathogenic processes are involved in macrovascular and microvascular changes that should be investigated further; both CRAE and CRVE deserve attention as disease-related phenotypes. Central arterial stiffening may be associated with cerebral microvascular changes, as exhibited in its retinal vasculature component.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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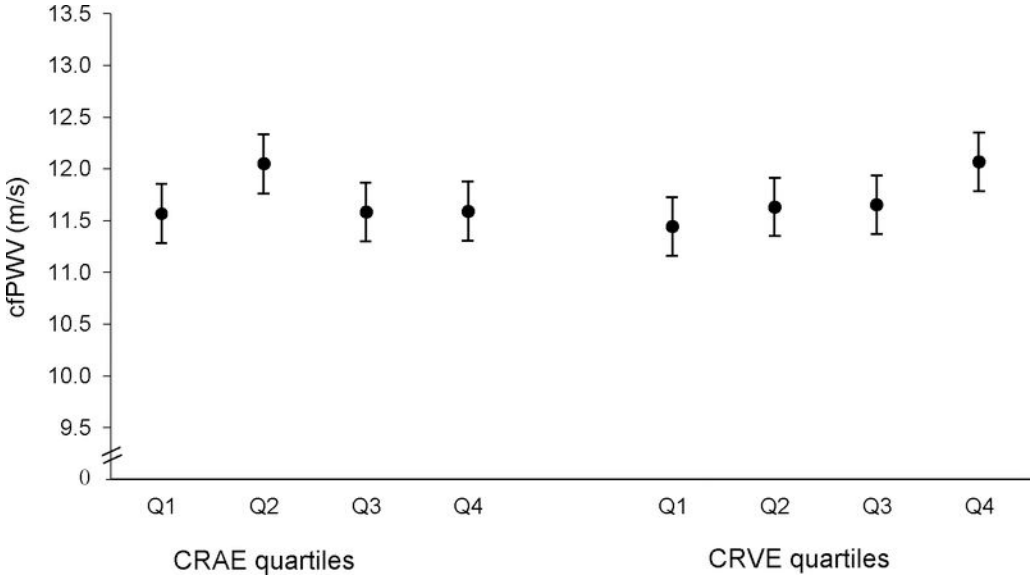

Figure 1.

Age- and sex-adjusted mean carotid-femoral pulse wave velocity (cfPWV, m/s) by quartiles of central retinal arteriolar equivalent (CRAE) and central retinal vein equivalent (CRVE) with 95% confidence limits. The age- and sex-adjusted mean cfPWV did not significantly differ across CRAE and CRVE quartiles. Although not statistically significant, the mean cfPWV was higher in the second CRAE quartile compared to the other CRAE quartiles, and the mean cfPWV was higher in the fourth quartile of CRVE compared to the other CRVE quartiles.

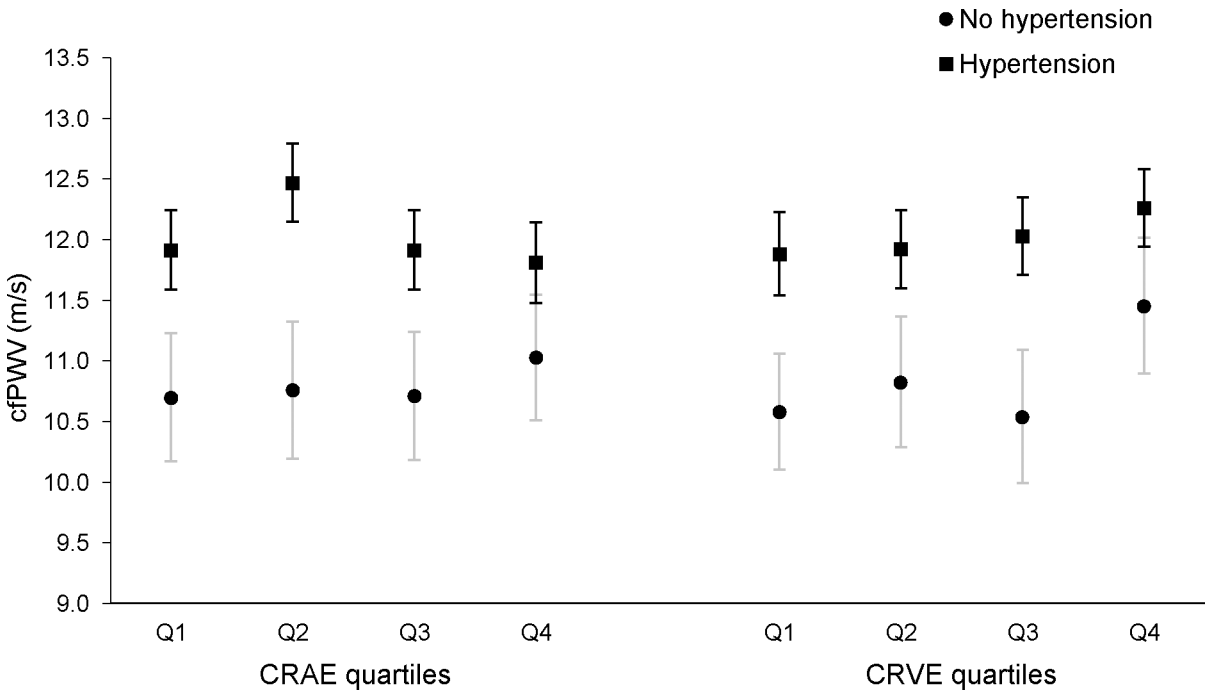

Figure 2.

Age- and sex-adjusted mean carotid-femoral pulse wave velocity (cfPWV, m/s) by quartiles of central retinal arteriolar equivalent (CRAE) and central retinal vein equivalent (CRVE) with 95% confidence limits in those with hypertension (square, black lines) and without hypertension (circles, light gray lines). In those with hypertension, the association of the mean cfPWV with CRAE quartiles was similar to the overall results, whereas in those without hypertension, the mean cfPWV was similar across CRAE quartiles (Figure 2). For CRVE, the pattern of mean cfPWV values by CRVE quartiles was similar in both those with and without hypertension, although the increase in mean cfPWV from the first to fourth CRVE quartile was more prominent in those without hypertension.

Table 1.

Participant characteristics overall and by CRAE narrowing and CRVE widening in the Atherosclerosis Risk in Communities study (n=1,706)

	All		CRAE narrowing (<25th percentile)				CRVE widening (>75th percentile)			
	n=1,706		No (n=1,245)		Yes (n=414)		No (n=1,243)		Yes (n=414)	
Characteristic	**n**	**% or mean (SD)**	**n**	**% or mean (SD)**	**n**	**% or mean (SD)**	**n**	**% or mean (SD)**	**n**	**% or mean (SD)**
Age (years)	1706	76.3 (5.2)	1245	76.1 (5.2)	414	77.1 (5.2)	1243	76.6 (5.2)	414	75.6 (5.1)
Female	991	58.1	750	60.2	217	52.4	718	57.8	246	59.4
Black	359	21.0	265	21.3	76	18.4	190	15.3	162	39.1
Body Mass Index (kg/m^2)	1706	27.6 (4.4)	1245	27.8 (4.5)	414	27.1 (4.3)	1243	27.5 (4.4)	414	28.1 (4.5)
Mean arterial pressure (mmHg)	1706	87.5 (11.2)	1245	87.0 (11.1)	414	88.9 (11.2)	1243	87.8 (11.3)	414	86.9 (10.8)
Systolic blood pressure (mmHg)	1706	130.6 (17.4)	1245	130.1 (17.6)	414	132.1 (16.9)	1243	131.2 (17.4)	414	128.7 (17.1)
Diastolic blood pressure (mmHg)	1706	66.0 (10.1)	1245	65.5 (10.1)	414	67.2 (10.3)	1243	66.1 (10.2)	414	65.9 (9.6)
LDL cholesterol (mg/dL)	1696	105.3 (34.9)	1239	105.3 (34.7)	411	104.8 (33.8)	1237	105.5 (34.5)	410	106.1 (35.8)
HbA1c (%)	1699	5.9 (0.8)	1240	5.9 (0.8)	412	5.8 (0.7)	1238	5.9 (0.7)	412	6.0 (0.9)
Fasting glucose (mg/dL)	1701	111.8 (27.1)	1242	112.3 (27.2)	412	109.9 (26.6)	1240	111.3 (27.0)	412	113.9 (28.1)
High Sensitive C-Reactive Protein (mg/L)	1703	3.5 (6.0)	1243	3.5 (6.1)	413	3.3 (5.9)	1241	3.4 (5.7)	413	3.8 (6.8)
cfPWV (m/s)	1706	11.7 (3.0)	1245	11.7 (3.0)	414	11.6 (3.0)	1243	11.6 (2.9)	414	12.0 (3.1)
CRAE (μm)	1657	205.0 (23.4)	1205	210.0 (21.8)	405	189.3 (20.8)	1243	194.9 (16.2)	414	235.1 (14.1)
CRVE (μm)	1659	142.5 (15.5)	1245	149.1 (11.2)	414	122.8 (8.2)	1212	139.3 (14.7)	398	151.8 (14.1)
Cigarette smoking										
Current	82	4.8	68	5.5	11	2.7	47	3.8	33	8.0
Former	805	47.2	575	46.2	203	49.0	581	46.7	199	48.1
Never	819	48.0	602	48.4	200	48.3	615	49.5	182	44.0
Education										
< High school	216	12.7	169	13.6	35	8.5	131	10.5	78	18.9
High school	584	34.3	437	35.2	129	31.2	439	35.3	133	32.2
> High school	904	53.1	637	51.2	250	60.4	672	54.1	202	48.9
Diabetes	523	30.7	399	32.0	102	24.6	363	29.2	150	36.2
Hypertension	1240	72.7	908	72.9	298	72.0	890	71.6	312	75.4
Prevalent coronary heart disease	229	13.7	169	13.9	54	13.2	173	14.2	47	11.5
Prevalent stroke	52	3.0	33	2.7	16	3.9	39	3.1	12	2.9

cfPWV: carotid-femoral pulse wave velocity; CRAE: central retinal arteriolar equivalent; CRVE: central retinal vein equivalent; SD: standard deviation

Table 2.

Association (prevalence odds ratio) of carotid-femoral pulse wave velocity (cfPWV) and covariates with central retinal arteriolar equivalent (CRAE) narrowing (<25th percentile) in the Atherosclerosis Risk in Communities study (n=1,659)

	Model 1	Model 1 + HTN and MAP
	OR (95% CI)	**OR (95% CI)**
cfPWV, m/s	0.99 (0.95, 1.03)	0.97 (0.93, 1.01)
Age, years	**1.04 (1.01, 1.06)**	**1.04 (1.02, 1.07)**
Female	**0.69 (0.55, 0.88)**	**0.69 (0.55, 0.87)**
Former smoker (vs. never smoker)	1.00 (0.79, 1.26)	1.02 (0.81, 1.29)
Current smoker (vs. never smoker)	**0.45 (0.23, 0.87)**	**0.47 (0.24, 0.92)**
Body mass index, kg/m^2	0.98 (0.95, 1.00)	0.97 (0.95, 1.00)
Diabetes	**0.73 (0.56, 0.96)**	0.77 (0.59, 1.01)
Hypertension		0.93 (0.71, 1.23)
Mean arterial pressure, mmHg		**1.02 (1.01, 1.03)**

Also adjusted for race-center; bold indicates p<0.05; HTN: hypertension; MAP: mean arterial pressure; OR: odds ratio

Table 3.

Association (prevalence odds ratio) of carotid-femoral pulse wave velocity (cfPWV) and covariates with central retinal vein equivalent (CRVE) widening (>75th percentile) by hypertension status (p-value for interaction = 0.04) in the Atherosclerosis Risk in Communities study (n=1,657)

	No Hypertension, n=455		**Yes Hypertension, n=1,202**	
	Model 1	**Model 1 + MAP**	**Model 1**	**Model 1 + MAP**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
cfPWV, m/s	**1.10 (1.01, 1.20)**	**1.15 (1.05, 1.26)**	1.01 (0.96, 1.05)	1.02 (0.97, 1.07)
Age, years	**0.93 (0.89, 0.98)**	**0.91 (0.87, 0.96)**	0.98 (0.96, 1.01)	0.98 (0.95, 1.01)
Female	0.67 (0.41, 1.09)	0.66 (0.40, 1.09)	1.30 (0.98, 1.73)	1.31 (0.99, 1.76)
Former smoker (vs. never smoker)	1.23 (0.74, 2.02)	1.30 (0.78, 2.15)	1.33 (1.00, 1.77)	1.29 (0.97, 1.72)
Current smoker (vs. never smoker)	2.46 (0.95, 6.40)	2.13 (0.79, 5.74)	**2.83 (1.55, 5.17)**	**2.75 (1.50, 5.05)**
Body mass index, kg/m^2	1.03 (0.97, 1.09)	1.04 (0.98, 1.10)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)
Diabetes	0.65 (0.35, 1.21)	0.55 (0.29, 1.06)	1.29 (0.97, 1.72)	1.22 (0.91, 1.63)
Mean arterial pressure, mmHg		**0.95 (0.92, 0.98)**		**0.98 (0.97, 1.00)**

Additionally adjusted for race-center; bold indicates p<0.05; cfPWV: carotid-femoral pulse wave velocity; CI: confidence interval; OR: odds ratio; MAP: mean arterial pressure