Hypertension

ORIGINAL ARTICLE

Intracranial Carotid Arteriosclerosis Mediates the Association Between Blood Pressure and Cerebral Small Vessel Disease

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BACKGROUND: Intracranial arteriosclerosis could explain the association between blood pressure (BP) and cerebral small vessel disease (CSVD). Therefore, we tested whether intracranial carotid artery calcification (ICAC) mediates the association between BP and CSVD and determined pathophysiological mechanisms based on ICAC subtypes.

METHODS: One thousand four hundred fifty-eight stroke-free participants from the Rotterdam Study (mean age, 68 years; 52% women) underwent nonenhanced computed tomography scans to quantify ICAC volume (mm^3) between 2003 and 2015. ICAC was categorized into intimal and internal elastic lamina calcifications. CSVD included white matter hyperintensities volume, the presence of lacunes, and cerebral microbleeds visualized on magnetic resonance imaging. Office BP included systolic BP, diastolic BP, pulse pressure, and mean arterial pressure. Mediation analysis included a 2-way decomposition to determine the direct association between BP and CSVD and the indirect or mediated effect (negative or positive mediations expressed in %) of log-ICAC volume on such association.

RESULTS: BP and log-ICAC were correlated and were also associated with CSVD. In all participants, total log-ICAC volume mediated the association of diastolic BP (−14.5%) and pulse pressure (16.5%) with log-white matter hyperintensities. Internal elastic lamina log-ICAC volume mediated −19.5% of the association between diastolic BP and log-white matter hyperintensities; intimal log-ICAC volume did not mediate associations. For lacunes, total and internal elastic lamina log-ICAC volume mediated the association of diastolic BP (−40% and −45.8%) and pulse pressure (26.9% and 18.2%). We did not observe mediations for cerebral microbleeds.

CONCLUSIONS: Intracranial arteriosclerosis mediates the association between BP and CSVD. Internal elastic lamina calcification, considered a proxy of arterial stiffness, is the leading mechanism explaining the link between BP and CSVD. **(*Hypertension*. 2023;80:618–628. DOI: 10.1161/HYPERTENSIONAHA.122.20434.)** • **Supplemental Material**

Key Words: blood pressure ■ cerebral small vessel disease ■ intracranial carotid calcification ■ mediation analysis ■ population science

The presence of cerebral small vessel disease (CSVD), characterized by microvascular damage of the small arteries in the brain parenchyma, has been associated with dementia and stroke.[1] White matter hyperintensities, lacunes, and cerebral microbleeds are the most common types of CSVD which are recognized as of presumed vascular origin.[1,2] Despite advances in our knowledge on the pathogenesis of these types of CSVD,[1,2] many aspects with regard to the underlying causes remain unknown. Two important contributing causes within the multifactorial cause of CSVD are hypertension and arteriosclerosis in the cerebral arteries.[1] Indeed, optimal blood pressure (BP) control reduces the progression of white matter hyperintensities[3,4] and intracranial carotid artery calcification (ICAC)—a marker of cerebral arteriosclerosis—has been

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NOVELTY AND RELEVANCE

What Is New?

Intracranial carotid artery calcification primary consist of intimal and internal elastic lamina calcification, therefore, from an etiological perspective, intracranial carotid artery calcification subtypes might elucidate how hypertension leads to cerebral small vessel disease.

What Is Relevant?

High systolic blood pressure (BP) and pulse pressure were positively related with intracranial carotid artery calcification volume, whereas larger internal elastic lamina volume was associated with lower diastolic (BP).

Internal elastic lamina volume mediated the association between diastolic BP (negative mediation) and pulse pressure (positive mediation) with cerebral small vessels disease including white matter hyperintensities and lacunes.

Clinical/Pathophysiological Implications?

Because internal elastic lamina calcification is a proxy of arterial stiffness, modification of the arterial system resulting in chronic hypoperfusion (due to lower diastolic BP) and high pulsatile transmission (due to high pulse pressure) to the cerebral microcirculation are potential physiopathological mechanisms explaining how BP links to subclinical cerebrovascular damage.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CSVD	cerebral small vessel disease
ICAC	intracranial carotid artery calcification
IEL	internal elastic lamina

associated with white matter hyperintensities, lacunes, and cerebral microbleeds.[5]

Although high BP and ICAC are independently related to CSVD of presumed vascular origin, they are also strongly correlated and therefore, might interplay in the process of leading to CSVD. Between the 2 risk factors, the study of ICAC offers a more clear understanding from the etiological perspective. Based on histology reports, ICAC consists of 2 types of arteriosclerotic lesions[6] that might underlay how high BP leads to CSVD. The unstable atherosclerotic plaques localized in the intimal layer of the intracranial carotid artery might rupture as a consequence of distress due to high BP, occlude cerebral arteries, and lead to CSVD.[7] For nonatherosclerotic elastic lamina (IEL) calcification,[8] the calcium composition contributes to arterial compliance loss and stiffening of the vascular wall, leading to augmented pulse pressure in the capillaries, predisposing microvascular damage.[9,10] In elderly people whose cerebral perfusion is potentially impaired due to arterial loss compliance in the micro and macrocirculation,[11,12] ICAC might potentially mediate the association between high BP and CSVD of presumed vascular origin. Therefore, we aimed in this study to test the hypothesis that ICAC mediates the association between BP and CSVD. We further investigated the atherosclerotic and nonatherosclerotic subtypes of ICAC to identify underlying mechanisms explaining how BP might lead to CSVD.

METHODS

Data Availability

Requests to access the data may be sent to the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

Study Cohort

This study is embedded in the Rotterdam Study, an ongoing prospective population-based study investigating age-related diseases. Participants aged ≥45 years are interviewed at home and examined at the research center at baseline and during follow-up visits every 3 to 4 years. The design of the Rotterdam Study is described elsewhere in detail.[13] Between 2003 and 2006, 2524 participants randomly selected underwent a noncontrast multidetector computed tomography scan of the intracranial carotid arteries. Due to imaging artifacts, 60 examinations were not gradable, leaving 2464 participants available for analyses. Since 2005, out of those 2464 participants, 1681 participants underwent a brain magnetic resonance imaging (MRI) scan[13]; 250 scans were excluded because of incomplete acquisition or technical problems with processing. Additionally, participants with dementia or symptomatic stroke (n=153) or MRI-defined cortical infarcts (n=69) were excluded. In total, 1458 participants with complete BP (taken at the time of imaging scans), CT, and MRI data were included in the present study. The Institutional Review Boards of the Ministry of Health, Welfare, and Sports of the Netherlands, approved the Rotterdam study, complying with the Helsinki declaration.[14] All participants provided written informed consent.

BP Measurement and Clinical Characteristics

At each research center visit, after at least 5 minutes rest in a seated position, 2 BP measurements were taken on the right upper arm. The mean of these 2 measurements was used for that visit. Pulse pressure was the difference between

the systolic and diastolic BP, and mean arterial pressure was defined as systolic BP plus 2-times the diastolic BP, divided by 3. We selected the BP measurements taken during the CT scan assessment. Based on the average of the 2 BP measurements, hypertension was a systolic or diastolic BP ≥140 mm Hg or diastolic ≥90 mm Hg or use of antihypertensive medication. Cardiovascular risk factors were collected by interview, physical examination, and blood sampling.[13] Obesity was defined body mass index ≥30 kg/mt.[2] Diabetes was fasting serum glucose of ≥7.0 mmol/L or use of antidiabetic therapy. Smoking was categorized into never or ever smoked. History of cardiovascular diseases included previous myocardial infarction and coronary revascularization.

Assessment of ICAC

A 16-slice or 64-slice multidetector computed tomography scanner (Somatom Sensation 16 or 64, Siemens, Forchheim, Germany) was used to perform noncontrast computed tomography scanning.[15] The presence and type of calcification were investigated in the left and right intracranial carotid arteries by visualizing the trajectories of the arteries from the horizontal part of the petrous segment until the confluence with the other arteries of the Circle of Willis. After manual delineation, calcification volumes (mm^3) were computed by multiplying the number of pixels within the delineated area above 130 Hounsfield units by the pixel-size and slice increment.[16] The total ICAC volume was calculated by summing up the calcification volumes of the intracranial carotid arteries.

ICAC subtypes were distinguished by a method that was previously validated against histology.[6] The method consists in a composite score (0–11 points maximum) that weights the circularity, thickness, and continuity of the calcification. The given scores are used to categorize predominantly (1) intimal (<7 points; eg, thick, small, and irregular) or (2) IEL (≥7 points; eg, thin, elongated, circular). Participants with bilateral IEL calcifications or IEL calcifications combined with absent contralateral calcification were classified as IEL subtype—similar approach was used for intimal ICAC. Participants with one type of ICAC in one artery and a contrasting contralateral subtype were categorized as mixed subtype. The subtypes were classified by 2 observers. A consensus evaluation was performed in case of a discrepancy between the observers. The interobserver reproducibility agreement was 93.9% (Cohen kappa value=0.88).[17]

Brain MRI Acquisitions and Assessment of CSVD

Brain MRI scanning was performed using a 1.5-tesla MRI scanner (GE Sigma Excite; GE Healthcare). The scan protocol and sequence details have been previously described.[13] Four high-resolution axial sequences were obtained, including a T1-weighted sequence, a proton density–weighted sequence, a fluid-attenuated inversion recovery sequence, and a T2*-weighted gradient-recalled echo sequence to assess CSVD. All scans were inspected visually and corrected if needed. Trained research physicians rated the presence, number and location of lacunes and cerebral microbleeds.[13] Lacunes were defined as subcortical lesions between ≥3 and <15 mm with signal intensity similar to cerebral spinal fluid on all sequences, and a hyperintense rim on the fluid-attenuated inversion recovery sequence when located supratentorially.[18] Cerebral microbleeds were focal areas <10 mm of very low signal intensity on T2*-weighted imaging.[13] Fluid-attenuated inversion recovery (voxel size 0.78×1.12×2.5 mm^3) scans were used for the automated segmentation of white matter hyperintensities volume based on a k-nearest neighbor classification algorithm.[19] Enlarged perivascular spaces were defined as ovoid or linear lesions visible as hypointense on T1-weighted and hyperintense on T2-weighted sequences and considered dilated if the size exceeded ≥1 mm. The size and shape of lesions, as well as the presence of hyperintense rims on fluid-attenuated inversion recovery sequences was used to differentiate perivascular spaces from lacunes.

Statistical Analysis

For statistical analysis, we used SAS software, version 9.4, maintenance level 5. Continuous data were presented as mean±SD for normally distributed, and median (Q1–Q3) for nonparametric variables. Categorical data were shown as frequencies (%). Covariables were selected based on their biological importance as cerebrovascular risk factors, and included age, sex, body mass index, smoking habits, diabetes, total-to-high density lipoprotein cholesterol ratio, history of cardiovascular diseases, and use of antihypertensive treatment. All analyses were additionally adjusted by the time-interval between the MRI and computed tomography scans. Due to a nonparametric right-skewed distribution, we log-transformed total ICAC and white matter hyperintensities volumes. To investigate whether the type of CT-scanner (16-slice or 64-slice multidetector computed tomography) influences the classification of intimal and IEL calcifications, we calculated the percentange of participants with intimal and IEL calcifications according to the CT-scanner types.

Our analyzes consisted of (1) addressing the correlation between BP (systolic BP, diastolic BP, pulse pressure, and mean arterial pressure) components and log-ICAC volume; (2) examining the association of BP and ICAC with CSVD by applying multivariable regression modeling; and (3) the mediation analyses. All analyzes were conducted in the whole sample, and we also combined participants into 2 groups (1) participants with absent ICAC plus participants with intimal calcification and (2) participants with absent ICAC plus participants with IEL calcification. We regressed log-ICAC volume on covariables and use the residuals of the regressed log-ICAC to plot the association between BP and log-ICAC volume. Based on the physiological concept that systolic BP and pulse pressure are the pulsatile BP components,[20] while diastolic BP and mean arterial pressure are the steady BP components,[20] we constructed heatmaps to visualize the contributions of (1) systolic and diastolic BP and (2) pulse pressure and mean arterial pressure to log-ICAC volume. Before conducting mediation analysis, we examined the association of BP components and log-ICAC volume with CSVD in multivariable analysis; for which we applied linear regression model for white matter hyperintensities, and logistic regression models for lacunes and cerebral microbleeds. To determine whether ICAC mediated the association of BP with CSVD, we performed mediation analysis where BP measurements were the independent covariables, log-ICAC volume was the

mediator, and CSVD was the dependent variable.[21] We used a 2-way decomposition, and estimated the indirect and direct effects, and percentage (%) mediated by log-ICAC which included positive and negative mediation effects. If log-ICAC negatively mediated the association between BP and CSVD, it denoted that a low BP (high BP if the mediation was positive) combined with a large ICAC volume would lead to CSVD. Our correlation and mediations analyzes were adjusted by confounders selected based on their biological relevance with the exposure and outcome variables. A 2-tailed α level of ≤0.05 will be deemed statistically significant.

RESULTS

Baseline Characteristics

The study population had a mean age of 68.0 years old, and 52% (n=758) of the participants were women (Table 1). We observed lacunes and deep cerebral microbleeds in respectively 9.1% and 10.4% of the participants. The median white matter hyperintensities was 4.00 mL. Table 1 contains the summarized data of the baseline characteristics. We did not observe differences in the classification of participants with intimal and IEL ICAC based on 16-slice versus 64-slice CT scanners (P=0.786; data not shown). The median time between the CT and MRI scans was 1.39 years; the interquartile range was 0.58 and 6.09 years.

Table 1. Population Characteristics

Characteristics	All participants (n=1458)
Demographics	
Age, y	68.0±5.7
Women, no. (%)	758 (52.0)
Clinical characteristics	
Smoking, no. (%)	1017 (69.8)
Body mass index, kg/mt2	27.5±3.8
Obesity, no. (%)	319 (21.9)
Diabetes, no. (%)	168 (11.5)
Total serum cholesterol, mg/dL	5.7±1.0
HDL serum cholesterol, mg/dL	1.4±0.4
Total-to-HDL cholesterol ratio, mg/dL	4.2±1.2
Hypertension, no. (%)	1029 (70.6)
Systolic BP, mm Hg	144.3±18.7
Diastolic BP, mm Hg	80.4±10.5
Pulse pressure, mm Hg	63.8±16.0
Mean arterial pressure, mm Hg	101.7±11.5
Antihypertensive treatment, no. (%)	517 (35.5)
History cardiovascular diseases, no. (%)	75 (5.14)
Markers of CSVD	
White matter hyperintensities, mL	4 (2-8)
Lacunes, no. (%)	132 (9.05)
Microbleeds, no. (%)	127 (10.4)
ICAC	
Volume, mm^3	30 (3-102)
Absent calcification	307 (21.1)
Subtypes	
Predominantly elastic lamina calcification	497 (34.5)
Predominantly intimal calcification	503 (34.1)

The central tendency and the spread of continuously distributed variables are represented by the arithmetic mean (±SD) or the median (interquartile range). Categorical values represent the frequency and % within each group. BP indicates blood pressure; CSVD, cerebral small vessel disease; ICAC, intracranial carotid artery calcification; and HDL, high-density lipoprotein.

BP and Intracranial Arteriosclerosis

In all participants (Figure S1), a higher systolic BP (adjusted mean difference=0.006 per +10 mm Hg increase; P=0.024) and pulse pressure (adjusted mean difference=0.014 per +5 mm Hg increase; P<0.001) were associated with larger log-ICAC volume, whereas lower diastolic BP was related to higher log-ICAC volume (adjusted mean difference=−0.015 per +5 mm Hg increase; P=0.001). These associations were only observed in the group that included participants without and with IEL calcification (Figure 1; P≤0.001) and no among the group including individuals with IEL ICAC (Figure 1; P≥0.060). None of the BP components were associated with log-ICAC volume in participants with mixed ICAC (data not shown).

Heatmaps combining systolic and diastolic BP (Figure 2A) showed along the horizontal axis that the predicted log-ICAC volume increased with a higher systolic BP level (P=0.002). However, along the vertical axis, a lower diastolic BP level (P<0.001) added to the association conferred by systolic BP. This represents that having a higher systolic BP level combined with lower diastolic BP resulted in the largest predicted log-ICAC volume. We observed the same pattern in the group that included participants with absent ICAC and participants with IEL calcification (Figure 2B), but not in participants with intimal ICAC (Figure 2C). Combined with a lower mean arterial pressure level (P<0.001), a higher pulse pressure (P≤0.003) increased the predicted log-ICAC volume in all participants (Figure 2D) and in the group of participants without ICAC plus those with IEL calcification (Figure 2E).

BP and Intracranial Arteriosclerosis in Relation to CSVD

Among all participants (Table 2), each +1 SD (~2.02 mm^3) increase in the log-ICAC volume was associated with one-unit larger log-white matter hyperintensities volume (adjusted mean difference=0.08; P<0.001). Higher levels of the BP measurements showed a positive relationship with larger log-white matter hyperintensities (adjusted mean differences ranged from 0.02 to 0.04; P≤0.033). The presence of lacunes was only associated

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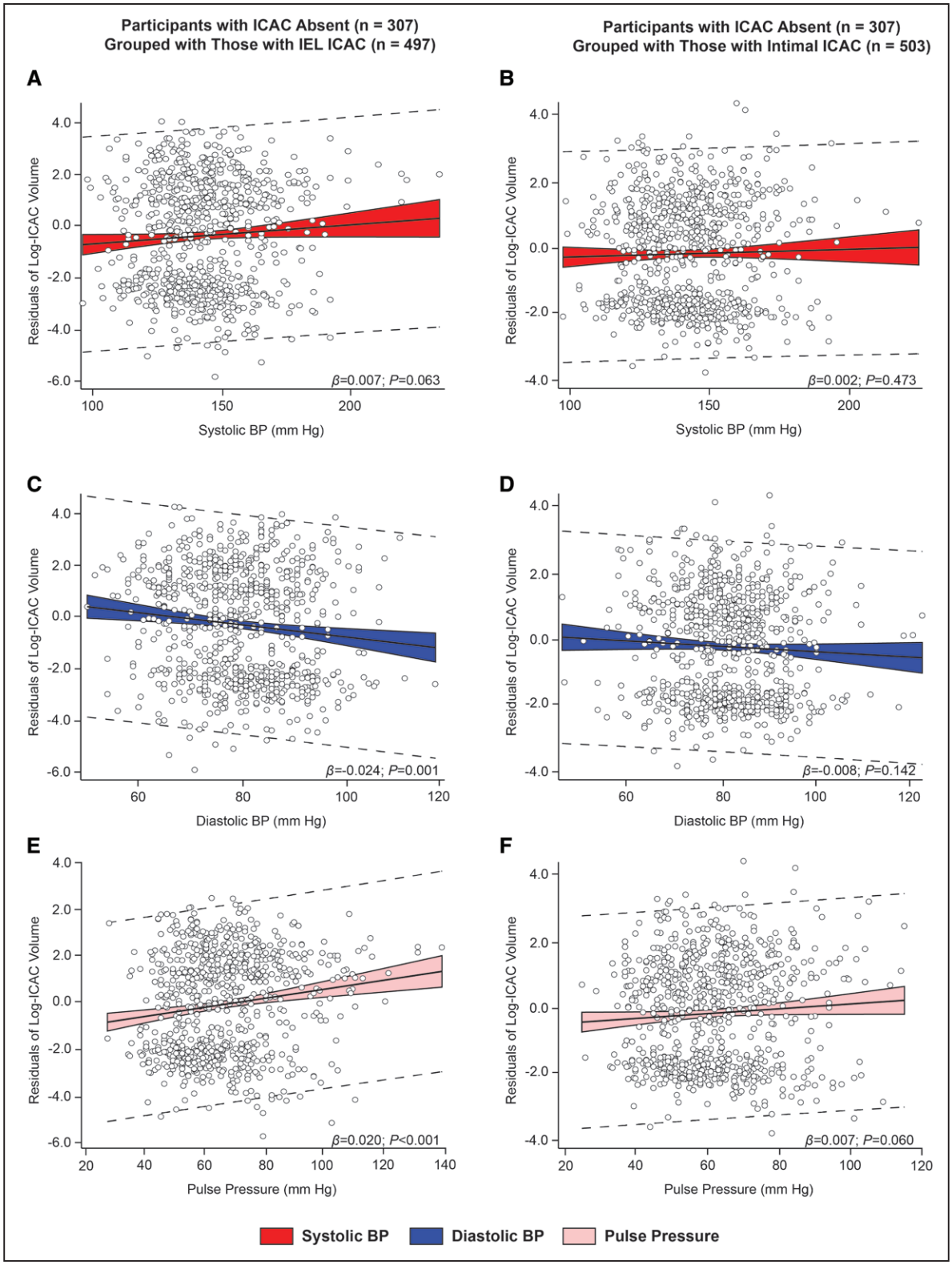

Figure 1. Association between blood pressure (BP) and intracranial carotid artery calcification (ICAC) volume according to morphological subtypes of ICAC.

Log-ICAC volume was regressed on age, sex, body mass index, smoking habits, diabetes mellitus, total-to-high density lipoprotein cholesterol ratio, history of cardiovascular diseases, time-interval between the MRI and computerized tomography scans, and use of antihypertensive treatment. **A**, **C**, and **E**, Association of systolic BP (**A**), diastolic BP (**C**) and pulse pressure (**E**) with residualized log-ICAC volume among participants without ICAC grouped with participants with IEL ICAC. **B**, **D**, and **F**, Show the same associations among participants without and with intimal ICAC. The residualized log-ICAC volume was then plotted against the BP components. P indicate the significant of the association. We did not observe significant associations between log-ICAC volume and mean arterial pressure in both groups of mophological subtypes of ICAC (P≥0.341, data not shown).

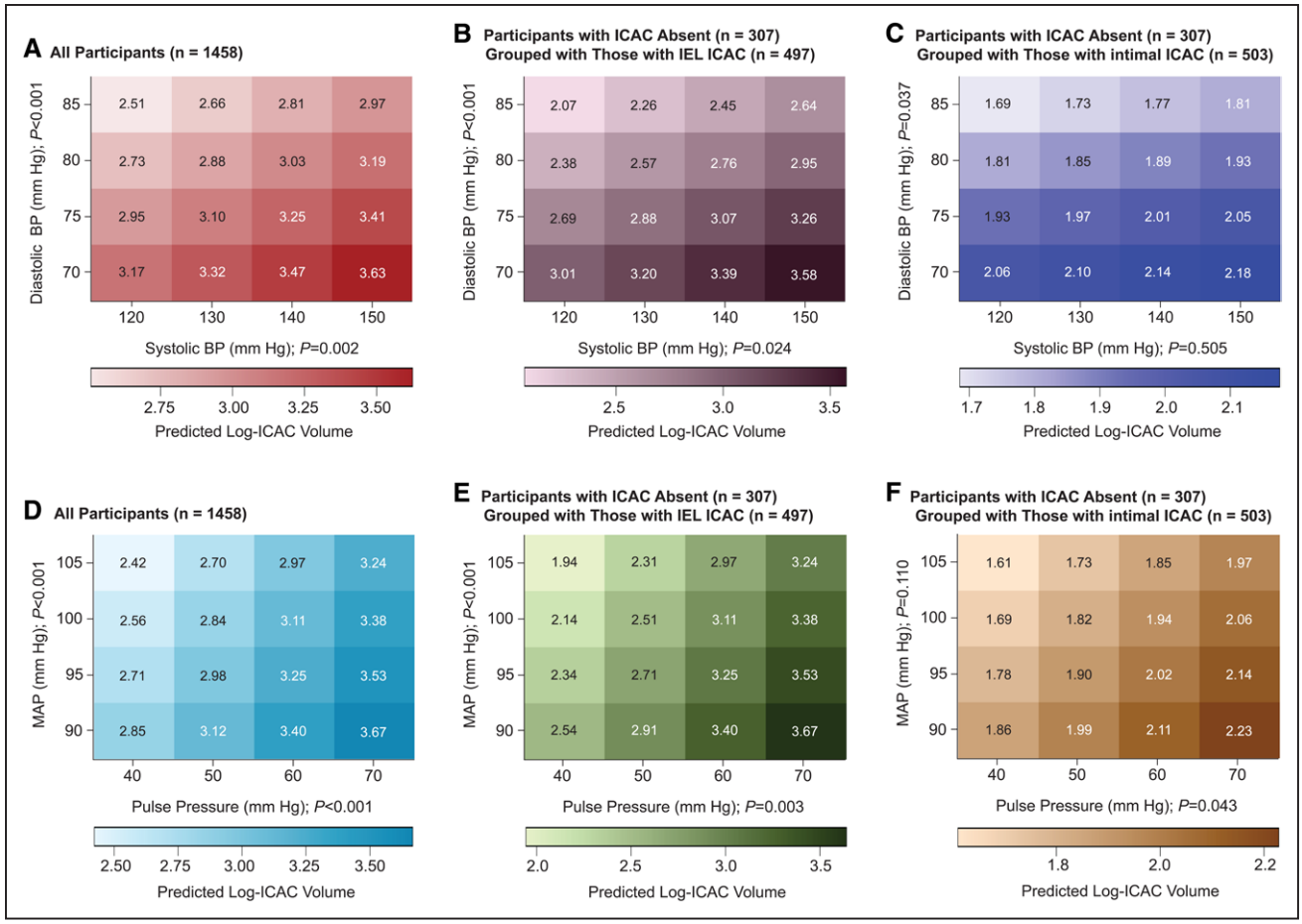

Figure 2. Contribution of blood pressure (BP) to intracranial carotid artery calcification (ICAC) in all participants and according to ICAC subtypes.

The numbers within the boxes indicate the predicted log-ICAC volume according to different BP categories. We used linear regression modelling to derived the predicted log-ICAC volume which was standardized to the average of the distributions in the whole study population for age, sex, body mass index, smoking habits, diabetes, total-to-high density lipoprotein cholesterol ratio, history of cardiovascular diseases, time-interval between the magnetic resonance imaging and computerized tomography scans, and use of antihypertensive treatment. **A**–**C**, Systolic BP in the horizontal axis plotted against diastolic BP in the vertical axis. **D**–**F**, The pulse pressure in the horizontal axis plotted against mean arterial pressure in the vertical axis. IEL indicates internal elastic lamina.

with higher log-ICAC volume (odds ratio, 1.41 per +1 SD increase [95% CI, 1.14–1.75]; *P*=0.001). For cerebral microbleeds (Table S1), a higher log-ICAC volume in all participants was associated with total cerebral microbleeds (odds ratio, 1.16 [95% CI, 1.02–1.33]; *P*=0.027). Neither BP components nor log-ICAC volume were associated with enlarged perivascular spaces (Table S2).

According to ICAC subtypes, BP components and log-ICAC volume were differently related to log-white matter hyperintensities and lacunes (Table 2) and deep cerebral microbleeds (Table S1). In the group that included participants without ICAC plus those with IEL calcification (Table 2), a higher log-ICAC volume, systolic BP, pulse pressure, and mean arterial pressure were positively associated with log-white matter hyperintensities (adjusted mean difference ranged from 0.03 and 0.22; *P* ≤0.014 to 0.001). Each +1 SD increment in log-ICAC volume or +10 mm Hg rise in the systolic BP was associated with 1.32 ([95% CI, 1.04–1.70]; *P*=0.020) and 1.14 ([95% CI, 1.01–1.30]; *P*=0.044) fold-increase in having lacunes; respectively. In the group that included participants with absent ICAC and participants with intimal ICAC, a higher systolic BP, diastolic BP, and mean arterial pressure were significantly associated with larger log-white matter hyperintensities volume (*P*≤0.040). Only a higher log-ICAC volume was significantly associated with lacunes (odds ratio, 1.06 [95% CI, 1.01–1.98]; *P*=0.029).

Mediation Analysis: BP → Intracranial Arteriosclerosis → CSVD

In mediation analysis, log-ICAC volume mediated the associations of diastolic BP (mediation effect, −14.5%) and pulse pressure (mediation effect, 16.5%) with log-white matter hyperintensities in all participants (Table 3). ICAC volume mediated the relationship of diastolic BP and log-white matter hyperintensities (mediation effect, −19.5%) only in the group that included participants

Table 2. Multivariable Association of CSVD With BP and Intracranial Carotid Arteriosclerosis

	Log-transformed white matter hyperintensities		Lacunes	
ICAC volume and BP	β coefficients (95% CI)*	*P* value	Odds ratios (95% CI)*	*P* value
All participants				
Log-ICAC volume, +1SD	0.08 (0.03 to 0.13)	<0.001	1.41 (1.14 to 1.75)	0.001
Systolic BP, +10 mm Hg	0.04 (0.01 to 0.06)	0.003	1.09 (0.99 to 1.21)	0.067
Diastolic BP, +5 mm Hg	0.02 (0.01 to 0.04)	0.033	1.04 (0.95 to 1.13)	0.431
Pulse pressure, +5 mm Hg	0.02 (0.01 to 0.03)	0.030	1.05 (0.99 to 1.11)	0.091
Mean arterial pressure, +5 mm Hg	0.03 (0.01 to 0.05)	0.004	1.06 (0.98 to 1.15)	0.146
Participants with ICAC absent+participants with IEL ICAC				
Log-ICAC volume, +1SD	0.06 (0.01 to 0.11)	0.024	1.32 (1.04 to 1.70)	0.020
Systolic BP, +10 mm Hg	0.05 (0.02 to 0.08)	0.004	1.14 (1.01 to 1.30)	0.044
Diastolic BP, +5 mm Hg	0.02 (−0.01 to 0.05)	0.127	1.05 (0.92 to 1.18)	0.484
Pulse pressure, +5 mm Hg	0.02 (0.01 to 0.04)	0.014	1.08 (1.00 to 1.17)	0.050
Mean arterial pressure, +5 mm Hg	0.03 (0.01 to 0.05)	0.014	1.09 (0.97 to 1.21)	0.130
Participants with ICAC absent+participants with intimal ICAC				
Log-ICAC volume, +1SD	0.04 (−0.03 to 0.11)	0.257	1.06 (1.01 to 1.98)	0.029
Systolic BP, +10 mm Hg	0.03 (0.01 to 0.07)	0.030	1.09 (0.94 to 1.27)	0.251
Diastolic BP, +5 mm Hg	0.03 (0.01 to 0.06)	0.040	1.04 (0.91 to 1.19)	0.586
Pulse pressure, +5 mm Hg	0.01 (-0.01, 0.03)	0.199	1.05 (0.96 to 1.16)	0.303
Mean arterial pressure, +5 mm Hg	0.03 (0.01 to 0.05)	0.018	1.06 (0.94 to 1.19)	0.354

BP indicates blood pressure; CSVD, cerebral small vessel disease; ICAC, intracranial carotid artery calcification; and IEL, internal elastic lamina.

*Estimates are given by each unit increment in the log-ICAC, or blood pressure measures and were accounted for age, sex, body mass index, smoking habits, diabetes, total-to-high-density lipoprotein cholesterol ratio, history of cardiovascular diseases, time-interval between the MRI and computerized tomography scans, and use of antihypertensive treatment.

with ICAC absent plus participants with IEL calcification. Although some indirect effects were non-significant, we observed that the proportions of mediation (%) by ICAC on the association between BP components and log-white matter hyperintensities were higher in participants with IEL (−19.5% to 9.53%) versus intimal ICAC (−3.38% to 4.44%) calcification.

ICAC volume mediated the association of diastolic BP and pulse pressure with lacunes in all participants (mediation effects, −40.0% to 26.9%; $P \geq 0.020$; Table 4) and when analysis included participants with ICAC absent plus participants with IEL calcification (mediation effects, −45.8% to 18.2%; $P \geq 0.052$). Similarly as we observed for white matter hyperintensities, although some indirect effects were not significant, the proportions of mediations were higher in participants with predominantly IEL calcification (−45.8% to 18.2%) than intimal (−18.2% to 15.0%) ICAC. We did not observe mediation effects for deep cerebral microbleeds (Table S3).

DISCUSSION

In this prospective population-based study, high systolic BP and pulse pressure, and low diastolic BP levels were associated with larger ICAC volume, especially in those with IEL calcification. We reported that increased systolic BP and pulse pressure combined with low levels of diastolic BP or mean arterial pressure resulted in the largest ICAC volume. In mediation analysis, ICAC volume mediated the association of diastolic BP and pulse pressure with white matter hyperintensities by −14.5% and 16.5% and lacunes by −40.0% and 26.9%; the mediation effects were driven by IEL calcification. No interactions were detected.

Intracranial Arteriosclerosis in Relation to BP

In agreement to previous publications,[22] high BP was associated with high ICAC volume. However, we have further elucidated such association as ICAC can result from high systolic and/or diastolic BP. Aging is characterized by increased systolic BP with a reduced diastolic BP due to arterial stiffness; elevating the pulse pressure.[12] Therefore, ICAC volume might differentially associate with the pulsatile and steady components of the BP, especially for the IEL subtype as it contributes to arterial compliance loss and stiffening of the vascular wall, augmenting pulse pressure.[8,23] This explains why high systolic BP and pulse pressure were positively related to log-ICAC volume while diastolic BP was negatively associated. Additionally, the heatmaps allowed us to visualize that large ICAC volume was correlated with high systolic BP or pulse pressure accompanied by low levels of the steady BP components. If large ICAC volume resulted

Table 3. Estimates of the Effect of BP on White Matter Hyperintensities due to Mediation and Interaction With ICAC

Mediation by log-ICAC volume	Log-transformed white matter hyperintensities				
	Direct effect		Indirect effect		
	Estimate (95% CI)*	*P* Value	Estimate (95% CI)*	*P* Value	% Mediated
All participants					
Systolic BP	0.037 (0.013 to 0.060)	0.003	0.002 (−0.001 to 0.004)	0.070	5.55%
Diastolic BP	0.027 (0.006 to 0.048)	0.013	−0.003 (−0.006 to −0.001)	0.015	−14.5%
Pulse pressure	0.015 (0.001 to 0.030)	0.046	0.003 (0.001 to 0.005)	0.011	16.5%
Mean arterial pressure	0.029 (0.010 to 0.048)	0.003	−0.001 (−0.002 to 0.001)	0.464	−2.22%
Participants with ICAC absent+participants with IEL ICAC					
Systolic BP	0.050 (0.018 to 0.083)	0.003	0.002 (−0.001 to 0.005)	0.192	3.85%
Diastolic BP	0.027 (−0.002 to 0.055)	0.068	−0.004 (−0.009 to 0.001)	0.046	−19.5%
Pulse pressure	0.025 (0.005 to 0.045)	0.014	0.003 (−0.001 to 0.006)	0.132	9.53%
Mean arterial pressure	0.034 (0.009 to 0.060)	0.009	−0.001 (−0.003 to 0.001)	0.365	−3.10%
Participants with ICAC absent+participants with intimal ICAC					
Systolic BP	0.038 (0.006 to 0.069)	0.019	0.001 (−0.001 to 0.002)	0.602	0.81%
Diastolic BP	0.030 (0.002 to 0.058)	0.033	−0.001 (−0.003 to0.001)	0.332	−3.38%
Pulse pressure	0.015 (−0.005 to 0.035)	0.149	0.001 (−0.001 to 0.002)	0.393	4.44%
Mean arterial pressure	0.031 (0.006 to 0.055)	0.014	0.001 (−0.001 to 0.002)	0.644	−0.77%

BP indicates blood pressure; ICAC, intracranial carotid artery calcification; and IEL, internal elastic lamina.

*Models were accounted for age, sex, body mass index, smoking habits, diabetes, total-to-high density lipoprotein cholesterol ratio, history of cardiovascular diseases, time-interval between the MRI and computerized tomography scans, and use of antihypertensive treatment. No significant interaction were detected, and the % of interactions ranged from −1.50% to 0.16%.

from high systolic and diastolic BP, then ICAC would have been explained by high mean arterial pressure with low or high pulse pressure. We hypothesize that IEL calcification either changes the hemodynamics of the vascular system by increasing the pulsatile BP components while decreasing the perfusion pressure to the brain, or the opposite. We cannot attest the direction of our hypothesis due to the cross-sectional design of our study and longitudinal studies are needed to clarify this.

Intracranial Arteriosclerosis Mediates the Association Between BP and CSVD

We reported that ICAC volume mediated the association between BP and CSVD. Such association was driven by IEL calcification—a proxy of arterial stiffness—rather than by intimal ICAC. We think that the volume of IEL calcification in subjects with intimal ICAC is not sufficient to cause changes in BP compared to the extend that IEL calcification accumulation does, which follows the uncorrelation in the occurrence of both ICAC simultaneously.[8] This also might also explain why we observed no associations between BP and ICAC in participants with intimal ICAC. On the other hand, we do not rule out the hypothesis that intimal ICAC might mediate the association between BP and CSVD. It is possible that abnormal circadian BP rhythms,[24] morning surge,[25] or high 24-hour BP variability[26] would destabilize the atherosclerotic plaque localized in the intracranial carotid artery, leading to cerebrovascular complications. This is based on numerous studies implicating the association of these ambulatory BP indexes with carotid plaque presence and vulnerability, and with major cerebrovascular outcomes.[24–26] Future studies utilizing ambulatory BP and ICAC would provide novel insights regarding the physiopathology of cerebrovascular outcomes in relation to BP dysregulations.

Potential Pathophysiology of the Mediation by Intracranial Arteriosclerosis

IEL calcification might mediate the association between BP level and CSVD through 2 mechanisms. First, a cerebral hypoperfusion state caused by calcification and lumen narrowing of the intracranial carotid artery. Severe ICAC correlates with carotid siphon stenosis,[27] which predisposes cerebral hypoperfusion.[28] To compensate the reduced perfusion pressure, one compensatory mechanism is the development of collaterals pathways to maintain blood flow, which has been found in IEL calcification.[29] However, if the hypoperfusion state remains, then the collaterals might exacerbate hemodynamic changes in the arterial system as microcirculation is the main determinant of vascular resistance.[20] In this context, the second mechanism plays its pivotal role—high pulse pressure due to arterial stiffness. In response to the

Table 4. Estimates of the Effect of BP on Lacunes due to Mediation and Interaction With ICAC

Mediation by log-ICAC volume	Lacunes				
	Direct effect		Indirect effect		
	Estimate (95% CI)*	*P* Value	Estimate (95% CI)*	*P* Value	% Mediated
All participants					
Systolic BP	0.089 (−0.019 to 0.198)	0.107	0.012 (−0.001 to 0.024)	0.063	11.5%
Diastolic BP	0.053 (−0.042 to 0.148)	0.274	−0.015 (−0.028 to −0.002)	0.020	−40.0%
Pulse pressure	0.041 (−0.023 to 0.105)	0.213	0.015 (0.004 to 0.026)	0.009	26.9%
Mean arterial pressure	0.065 (−0.019 to 0.150)	0.129	−0.003 (−0.011 to 0.005)	0.464	−4.81%
Participants with ICAC absent+participants with IEL ICAC					
Systolic BP	0.151 (−0.006 to 0.309)	0.060	0.013 (−0.004 to 0.031)	0.141	8.12%
Diastolic BP	0.064 (−0.069 to 0.196)	0.349	−0.020 (−0.040 to 0.001)	0.052	−45.8%
Pulse pressure	0.076 (−0.013 to 0.166)	0.093	0.017 (0.001 to 0.034)	0.054	18.2%
Mean arterial pressure	0.097 (−0.024 to 0.218)	0.115	−0.005 (−0.017 to 0.006)	0.361	−5.89%
Participants with ICAC absent+participants with intimal ICAC					
Systolic BP	0.096 (−0.069 to 0.261)	0.255	0.005 (−0.009 to 0.018)	0.484	4.73%
Diastolic BP	0.052 (−0.088 to 0.192)	0.464	−0.008 (−0.021 to 0.005)	0.223	−18.2%
Pulse pressure	0.046 (−0.054 to 0.146)	0.365	0.008 (−0.003 to 0.019)	0.137	15.0%
Mean arterial pressure	0.066 (−0.059 to 0.192)	0.302	−0.003 (−0.012 to 0.007)	0.613	−3.96%

BP indicates blood pressure; ICAC, intracranial carotid artery calcification; and IEL, internal elastic lamina.

*Models were accounted for age, sex, body mass index, smoking habits, diabetes, total-to-high density lipoprotein cholesterol ratio, history of cardiovascular diseases, time-interval between the MRI and computerized tomography scans, and use of antihypertensive treatment. No significant interactions were detected, and the % of interactions ranged from −23.6% to −0.72%.

cerebral hypoperfusion and new collaterals, the vascular resistance should physiologically raise both systolic and diastolic BP, elevating the mean arterial pressure to adequate the blood supply. However, the proxy of IEL calcification to arterial stiffness[9] is characterized by loss of the artery to distend, increasing blood flow velocity (high systolic BP) with reduced blood flow (decreased diastolic BP). This principle is observed in Figure 2B and 2E, and it is also explained by the negative mediation effect of IEL calcification on diastolic BP. This also increases pulsatile wave transmission from the aorta to the microcirculation, causing direct damage to the cerebral microvasculature.[30] It seems practicable to hypothesize that IEL calcification links BP and CSVD via indirect (hypoperfusion) and direct (high pulsatility waves) mechanisms.[31] Our interpretations supports previous descriptions[31] that systemic arterial stiffness potential lead to reduced cerebral blood flow,[32] impaired the ability of the brain to maintain blood flow,[33] and increased hydrodynamic impact of the pulse wave on the cerebral microcirculation.[34]

Intracranial Arteriosclerosis and BP Therapy to Prevent Cerebrovascular Outcomes

In clinical practice, the prevention of cerebrovascular pathologies through the control of BP is irrefutable,[3,4] but the clinical usage of ICAC is less clear despite being an independent risk factor for cognitive decline,[35] dementia,[35] and stroke.[7,16] Based on our findings, we hypothesize that the quantification of ICAC might guide future studies to clarify whether low diastolic BP is a causal risk factor for cerebrovascular pathologies or whether it underlies other confounding conditions such arterial stiffness and/or arteriosclerosis—which is the case for IEL calcification. We reported that IEL calcification mediated the association of diastolic BP (negatively) and pulse pressure (positively) with CSVD (% mediated, −45.8% to 18.2%), pointing at mechanisms linked to arterial stiffness and hypoperfusion. With this in mind, in elderly hypertensive patients with an advanced IEL calcification, adequate perfusion pressure to distal organs including the brain, eyes, and kidneys while lowering BP with antihypertensive treatment should be ensured. For instance, the SPRINT (Systolic BPIntervention Trial) showed that intensive BP treatment reduced cardiovascular risk[36] and white matter hyperintensities progression,[4] but it was also associated with hypotensive-related events,[36] lower hippocampal,[37] and total brain volumes[37] and did not reduce the risk for dementia[38] and stroke[36] outcomes. The SPRINT study findings regarding cerebrovascular outcomes remain unclear. Considering that approximately ~70% to 80% of elderly subjects have IEL ICAC,[22] future studies should phenotype structural and functional brain markers of cerebrovascular aging, including cerebral arteriosclerosis, and ensure to assess the potential protective role of different regimens of BP lowering in relation to cerebrovascular outcomes.

Methodological Considerations

Current computed tomography methods do not permit to differentiate how much of the ICAC is IEL or intimal. As we categorized ICAC subtypes into the most predominant type, there will be intimal ICAC misclassified in subjects with predominant IEL calcification, and vice versa. Nevertheless, the categorization method we used was previously demonstrated to show excellent correlation with histology findings.[6] Kockelkoren et al[6] reported that the majority of ICAC was either scored correctly according to their dominant type of calcification pattern (intimal versus IEL) as visualized on histology, or were scored as indistinguishable or absent. Furthermore, Vos et al[8] documented that IEL calcification was unrelated to the occurrence of intimal lesions. Additionally, the time difference between the calcification and CSVD assessments ranged from 0 to 11 years, with a median of 1.39 years. Hence, we adjusted all analyses for the time difference between these scans. It is however important to acknowledge that within our causal framework we assume that BP and ICAC precede CSVD, making this time difference potentially less of an issue. Nonetheless, longitudinal analyses including more detailed BP assessments should be done to validate our findings.

Perspectives

Intracranial arteriosclerosis, especially IEL ICAC, mediated the association between BP and CSVD. The mediation effect was stronger for diastolic BP and PP which were also correlated with IEL calcification. Because IEL calcification is a proxy of arterial stiffness, modification of the arterial system resulting in chronic hypoperfusion (due to lower diastolic BP) and high pulsatile transmission (due to high pulse pressure) to the cerebral microcirculation are potential physiopathological mechanisms explaining how BP leads to subclinical cerebrovascular damage.

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Disclosures

None.

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