Carotid Atherosclerosis is Associated with Middle Cerebral Artery Pulsatility Index

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ABSTRACT

BACKGROUND AND PURPOSE: **Pulsatility index (PI) in the middle cerebral artery (MCA) is considered a measure of peripheral vascular resistance. Several established cardiovascular risk factors are common for both MCA PI and carotid atherosclerosis. Accordingly, in the present study we hypothesized an association between ultrasound-derived indices of carotid atherosclerosis and MCA PI.**

METHODS: **All residents in Akershus County, born in 1950, were invited to a cardiovascular examination, The Akershus Cardiac Examination (ACE) 1950 Study (2012-2015). A thorough ultrasound examination was performed to assess indices of atherosclerosis in the carotid arteries, and PI in the MCAs. In all, 3154 (85.1%) had adequate transcranial and carotid data. Associations between indices of carotid atherosclerosis and MCA PI were assessed by regression analyses adjusted for established cardiovascular risk factors.**

RESULTS: **Mean age was 64 (standard deviation [SD]: .6) years, and 1,357 (43%) were women. Mean MCA PI was .97 (SD: .17). Participants in the upper quartile of MCA PI had higher pulse pressure, more frequently hypertension, diabetes mellitus, and a history of coronary artery disease. Both carotid plaque score (B .007 [95% CI: .003-.010]) and carotid intimamedia thickness (B .173 [95% CI: .120-.226]) were significantly associated with MCA PI in adjusted analysis. The model R^2 was .055.**

CONCLUSION: **In a population-based sample of middle-aged adults, ultrasound-derived indices of carotid atherosclerosis were independently associated with MCA PI. However, the overall explained variance of MCA PI was low, suggesting other factors than atherosclerosis and cardiovascular risk factors to play an important role for MCA PI.**

Keywords: Carotid atherosclerosis, middle cerebral artery, pulsatility index, transcranial Doppler, ultrasound.

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Introduction

Cerebrovascular disease is one of the leading causes of death and disability worldwide, and will continue to represent a challenge to healthcare services in the future.[1,2]

There are three main etiologies of ischemic stroke; cardioembolic source, large artery atherosclerosis, and cerebral small vessel disease (SVD).[3] Atherosclerosis in large arteries and SVD coexist; however, results from studies assessing their association are diverging.[4–6]

Ultrasound measures of large artery atherosclerosis and cerebral hemodynamics are widely used in risk estimation of cardiovascular disease and evaluation of stroke etiology.

The key neuroimaging modality for diagnosing SVD is the use of MRI.[7] MRI is a costly examination, which requires advanced technical equipment, and the availability is often limited. Pulsatility index (PI) in the middle cerebral artery (MCA) is proposed as inexpensive and broadly accessible ultrasound marker of SVD.[8,9]

PI of the MCA, created as a measure of peripheral vascular resistance, is calculated as the difference between the peak systolic and end diastolic flow velocities divided by the mean velocity.[10]

The association between ultrasound markers of carotid atherosclerosis and MCA PI in the general population is not

known. Still, as MCA PI and large artery atherosclerosis are associated with age, diabetes mellitus, and hypertension,[11–13] it is plausible that carotid atherosclerosis is associated with MCA PI. Accordingly, in a large cohort from the general population, we hypothesized that ultrasound-derived indices of carotid atherosclerosis are associated with MCA PI, also in analyses that are adjusted for established cardiovascular risk factors.

Methods

Study Population

The present study is based on the Akershus Cardiac Examination (ACE) 1950 Study, a prospective population-based age cohort study established to investigate the development and progression of cardiovascular and cerebrovascular disease. All men and women born in 1950 and residing in Akershus County ($n = 5827$) were invited. The baseline examinations were performed from 2012 to 2015 on two study sites. In total, 3,706 individuals were enrolled (participation rate: 63.6%). Participants completed an ultrasound examination of the carotid arteries and of the MCAs, standardized clinical examination, and a questionnaire assessing medical history and lifestyle. The study outline has been described previously.[14]

Ethics

Informed consent was obtained from all participants. The ACE 1950 Study was approved by The Regional Committees for Medical and Health Research Ethics in Norway (reference number 2011/1475), and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Clinical Examination and Demographic Data

Blood pressure was measured in a sitting position after 10 minutes of rest. Three readings were recorded, and mean blood pressure was defined as the mean of the second and third reading. Hypertension was defined as systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg, and/or use of antihypertensive medication. Body mass index (BMI) was calculated according to the standard formula (kg/m²). Obesity was defined according to the World Health Organization definition (BMI ≥30 kg/m²).[15] Diabetes mellitus was defined by the presence of one or more of the following criteria: self-reported diagnosis of diabetes mellitus, HbA1c ≥6.5%, fasting plasma glucose ≥7.0 mmol/L, or the use of antidiabetic drugs. Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/L and/or low-density lipoprotein ≥4.1 mmol/L, and/or use of lipid-lowering medication.[16] History of stroke or transient ischemic attack, and smoking habits were self-reported. Higher education was defined as >12 years of formal education. Coronary artery disease was defined as self-reported myocardial infarction or previous percutaneous coronary intervention or coronary artery bypass grafting surgery. The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate estimated glomerular filtration rate (eGFR).[17] Chronic kidney disease was defined as eGFR <60 mL/minute/1.73 m^2.

Transcranial Ultrasound

Transcranial ultrasound was performed with the ultrasound scanner Vivid E9 (GE Healthcare, Horten, Norway), equipped with a M5S sector probe. Images were digitally stored on custom software (Echopac, GE Vingmed).

We used a transtemporal acoustic window for pulse wave transcranial color-coded Doppler, and insonated MCA at a depth of approximately 55 mm. A poor temporal bone window was defined as inability to identify the midbrain structures and lack of Doppler signal. Systolic velocity was measured in both MCAs in the whole length of MCAs first segment (M1). Peak systolic velocity, end diastolic velocity, and PI were observed and recorded. The PI value was automatically calculated by the Doppler machine. If automatic recording of PI was not possible, only peak systolic and end diastolic velocities were registered. A mean PI was calculated by averaging the MCA PI from both sides. If the participant only had a good temporal window on one side, unilateral PI was considered mean PI.[18] Mean peak systolic velocity and end diastolic velocity were calculated the same way. The mean flow velocity, which may serve as a marker of cerebral blood flow, was defined as $1/3 \times$ (peak systolic velocity $+ 2 \times$ end diastolic velocity), and computed manually.[19] Figure 1 illustrates the recorded transcranial color coded Doppler image.

Carotid Ultrasound

Ultrasound of both carotid arteries was performed with a 9 L linear array transducer, and the methodology related to carotid artery ultrasound has previously been reported.[20] In short, carotid plaque was defined according to the latest version of the Mannheim Carotid Intimamedia Thickness (cIMT) and Plaque Consensus.[21] The carotid plaque score was calculated to express carotid plaque burden. The carotid artery was divided into four segments (common carotid artery, bifurcation, internal carotid and external carotid artery). Plaque thickness was measured, and the segments were divided into four categories: 0 points, no plaque; 1 point, <2.5 mm; 2 points, 2.5-3.5 mm; and 3 points, >3.5 mm, based on the thickest plaque of each segment. The scores of each segment were added, giving a plaque score ranging from 0 to 24.[22] Carotid artery stenosis severity was assessed in accordance with Consensus Panel gray scale and Doppler US criteria;[23] peak systolic velocity <125 cm/s was considered normal, 125 to 230 cm/seconds defined 50 to 69% stenosis, and >230 cm/seconds defined >70% stenosis. Plaque morphology was registered as presence of one or more echolucent plaques. cIMT was measured with the use of a semiautomatic tracking system (Vivid E9) in the far wall of the common carotid artery, and in a region free from plaque. The mean values of measurements from both sides were used for analyses.

We examined inter- and intrarater reliability twice during the study period. For this assessment, we randomly selected 25 examinations and analyzed measurements of plaque diameter and plaque morphology. Both tests with Cronbach $\kappa = .999$.

Statistical Analyses

Continuous variables are presented as means with SD, or median with interquartile range (IQR), depending on distribution. Categorical variables are presented as numbers and proportions (%). Between-group differences were assessed using independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for skewed continuous data, and $\chi 2$ test, or Fisher's exact test where appropriate, for categorical data. We assessed correlations by Spearman's rank correlation coefficient.

As MCA PI was approximately normally distributed, linear regression analysis was used to assess the association with

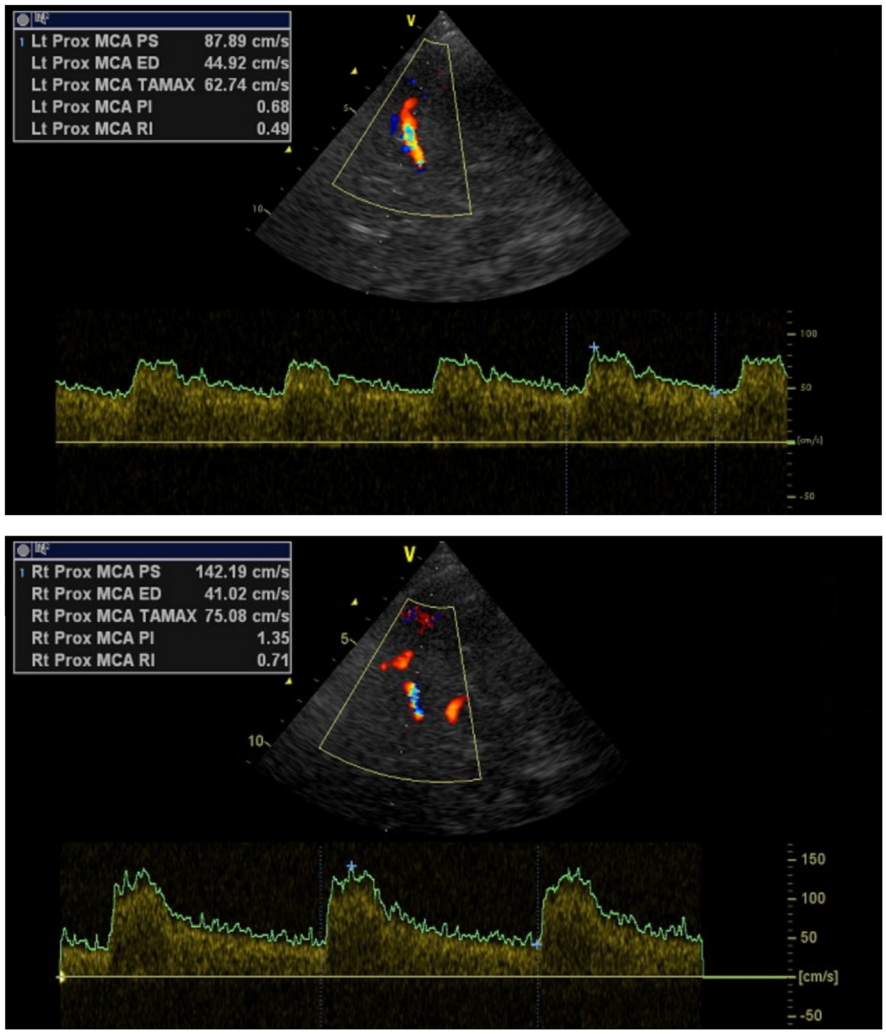

Fig 1. We used a transtemporal acoustic window for pulse wave transcranial color-coded Doppler, and insonated MCA at a depth of approximately 55 mm. Systolic velocity was measured in both MCAs in the whole length of MCAs first segment (M1). Peak systolic velocity, end diastolic velocity, and PI were registered. The upper image shows PI within the lower quartile, whereas the lower image shows PI within the upper quartile.

carotid plaque score, cIMT, and echolucent plaques as main explanatory variables. Results were presented with beta value (B) as regression coefficient, with 95% confidence intervals (CI), and corresponding *P*-values. The summarized and partial R^2 of the models were used to calculate the proportion of the explained variance associated with each explanatory variable. In model#1 univariate associations were presented. In model#2 the multivariable regression analyses, with all indices of carotid atherosclerosis in one model, were adjusted for; age, sex, BMI, hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease, history of stroke/TIA, and current daily smoking. Logistic regression models with odds ratios (OR) were constructed in the same manner as the linear regression models according to the upper quartile of MCA PI. Distribution of cardiovascular risk factors and cerebral hemodynamics according to MCA PI were assessed by comparing individuals in the upper quartile with the lower quartiles of MCA PI.

Statistical significance was assumed at a two-sided *P*-value of .05. Data were analyzed using SPSS version 25 (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

Of the 3,706 subjects who were enrolled in the ACE 1950 Study, 3,154 (85.1%) participants had adequate transcranial and carotid data. Mean age was 64 years and 43% were women. Median plaque score was 2, and mean cIMT .73 mm. In all, 491 (16%) had echolucent plaques, 60 (1.9%) had a carotid artery stenosis of 50-69%, 6 (.2%) had a stenosis of >70%, and 7 (.2%) had total occlusion. The MCA mean peak systolic velocity was 81 cm/seconds, mean end diastolic velocity was 32 cm/seconds, and mean flow velocity was 49 cm/seconds. Mean PI was .97. In all, 685 (22%) of the population was obese, 1,957 (62%) had hypertension, 1,648 (52%) had hypercholesterolemia, and 273 (9%) had diabetes mellitus.

Participants in the upper quartile of MCA PI had significantly higher pulse pressure, and the prevalence of hypertension, diabetes mellitus, and history of coronary artery disease was more frequent. Carotid plaque score and cIMT was higher, whereas MCA mean flow velocity and end diastolic velocity was lower in this group (Table 1).

Table 1. Baseline Characteristics According to MCA PI

Quartiles of MCA PI	Total	Q 1-3	Q4	P
Mean PI	.97 (.17)	.90 (.09)	1.17 (.17)	
n	3154	2346	808	
Cardiovascular risk factors				
Female sex	1357 (43.0%)	1009 (43.0%)	348 (43.1%)	.976
Age (years)	64 (.6)	64 (.6)	64 (.7)	.004
Higher education	1477 (47.0%)	1096 (46.9%)	381 (47.3%)	.847
BMI (kg/m²)	27.1 (4.3)	27.0 (4.3)	27.3 (4.2)	.106
Obesity	685 (21.7%)	505 (21.5%)	180 (22.3)	.655
SBP (mmHg)	138 (18)	136 (18)	143 (20)	<.001
DBP (mmHg)	77 (10)	78 (10)	76 (10)	<.001
PP (mmHg)	61 (14)	58 (13)	67 (15)	<.001
Hypertension	1957 (62.1%)	1368 (58.3%)	589 (72.9%)	<.001
Coronary artery disease	238 (7.5%)	163 (6.9%)	75 (9.3%)	.030
Stroke/TIA	119 (3.8%)	80 (3.4%)	39 (4.8%)	.068
Diabetes mellitus	273 (8.7%)	171 (7.3%)	102 (12.6%)	<.001
Hypercholesterolemi	1648 (52.4%)	1233 (52.6%)	415 (51.6%)	.577
Chronic kidney disease	118 (3.7%)	87 (3.7%)	31 (3.8%)	.868
Current daily smoking	458 (14.5%)	334 (14.2%)	124 (15.3%)	.440
Cardioprotective agents	1149 (36.4%)	774 (33.0%)	375 (46.4%)	<.001
Lipid-lowering agents	842 (26.7%)	607 (25.9%)	235 (29.1%)	.075
Carotid ultrasound				
Plaque score median (IQR)	2 (1-4)	2 (1-3)	3 (2-4)	<.001
Degree of carotid stenosis				
50-69	60 (1.9%)	35 (1.5%)	25 (3.1%)	.004
>70	6 (.2%)	4 (.2%)	2 (.2%)	.650
Occlusion	7 (.2%)	7 (.3%)	0 (.0%)	.120
cIMT	.73 (.11)	.72 (.11)	.76 (.12)	<.001
Echolucent plaques	491 (15.6)	362 (15.4%)	129 (16.0%)	.718
Transcranial ultrasound				
Peak systolic velocity cm/s	81 (19)	80.7 (17.8)	81.4 (20.4)	.380
End diastolic velocity cm/s	32 (8)	33.9 (8.0)	27.8 (7.4)	<.001
Mean flow velocity cm/s	49 (12)	50.0 (11.3)	46.2 (12.2)	<.001

MCA = middle cerebral artery; PI = pulsatility index; Q = quartile; *n* = numbers; BMI = body mass index; IQR = inter quartile range; cIMT = carotid intimamedia thickness; Obesity = BMI ≥30 kg/m²; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; TIA = transient ischemic attack; chronic kidney disease, defined as estimated glomerular filtration.
Rate <60 mL/minute/1.73 m². Categorical variables are presented as numbers (percentages). Continuous variables are presented as mean (SD) unless otherwise stated.

Table 2. Associations between Measures of Carotid Atherosclerosis and MCA PI

	Effect size	Model#1	Model#2
Carotid plaque burden	B (95% CI)OR (95% CI)¥	.010 (.007-.013)*1.14 (1.10-1.18)*	.007 (.003-.010)*1.11 (1.06-1.16)*
cIMT	B (95% CI)OR (95% CI)¥	.212 (.162-.263)*13.72 (6.89-27.35)*	.173 (.120-.226)*7.57 (3.58-16.00)*
Echolucent plaques	B (95% CI)OR (95% CI)¥	.003 (−.013-.019)1.04 (.84-1.30)	−.009 (−.025-.008).88 (.70-1.12)

MCA = middle cerebral artery; PI = pulsatility index; B = beta coefficient; (95%CI) = 95% confidence interval; OR = odds ratio.
¥ quartile 4 versus quartile 1-3 of MCA PI; cIMT, carotid intima-media thickness. Model #1, unadjusted; Model #2, adjusted for age, sex, body mass index, hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease, history of stroke/transient ischemic attack, and current daily smoking, and with all measures of carotid atherosclerosis in the same model.
* *P*-value < .001.

Indices of Carotid Atherosclerosis and MCA PI

MCA PI correlated significantly with the carotid plaque score ($r = .132$; $P < .001$) and cIMT ($r = .161$; $P < .001$), but not with echolucent plaques ($r = .003$; $P = .855$). In multivariable regression analyses, both carotid plaque score (B .007 [95% CI: .003-.010]; OR: 1.11 [95% CI: 1.06-1.16]), and cIMT (B .173 [95% CI: .120-.226]; OR: 7.57 [95% CI: 3.58-16.00]) remained significantly associated with MCA PI. There was no association with echolucent plaques (Table 2). Figure 2 illustrates the adjusted linear associations between MCA PI and both carotid plaque score and cIMT. In the linear regression analysis model R^2 was .055. Based on partial R^2, cIMT accounted for 23% of the explained variance of MCA PI, whereas carotid plaque score accounted for 9%.

Discussion

The principle finding of the present study of middle-aged subjects recruited from the general population, is that carotid atherosclerosis, quantified by carotid plaque score and cIMT, is associated with MCA PI, even after adjustment for other cardiovascular risk factors. However, the overall explained variance of MCA PI was low, suggesting other factors than atherosclerosis and traditional cardiovascular risk factors to play an important role for MCA PI.

Both carotid plaque and cIMT are used as markers of atherosclerosis, and are associated with increased risk of cardiovascular events.[24,25] cIMT reflects the thickness of both tunica intima and tunica media, the innermost two layers of the arterial wall. Particularly in its initial phase, the atherosclerotic

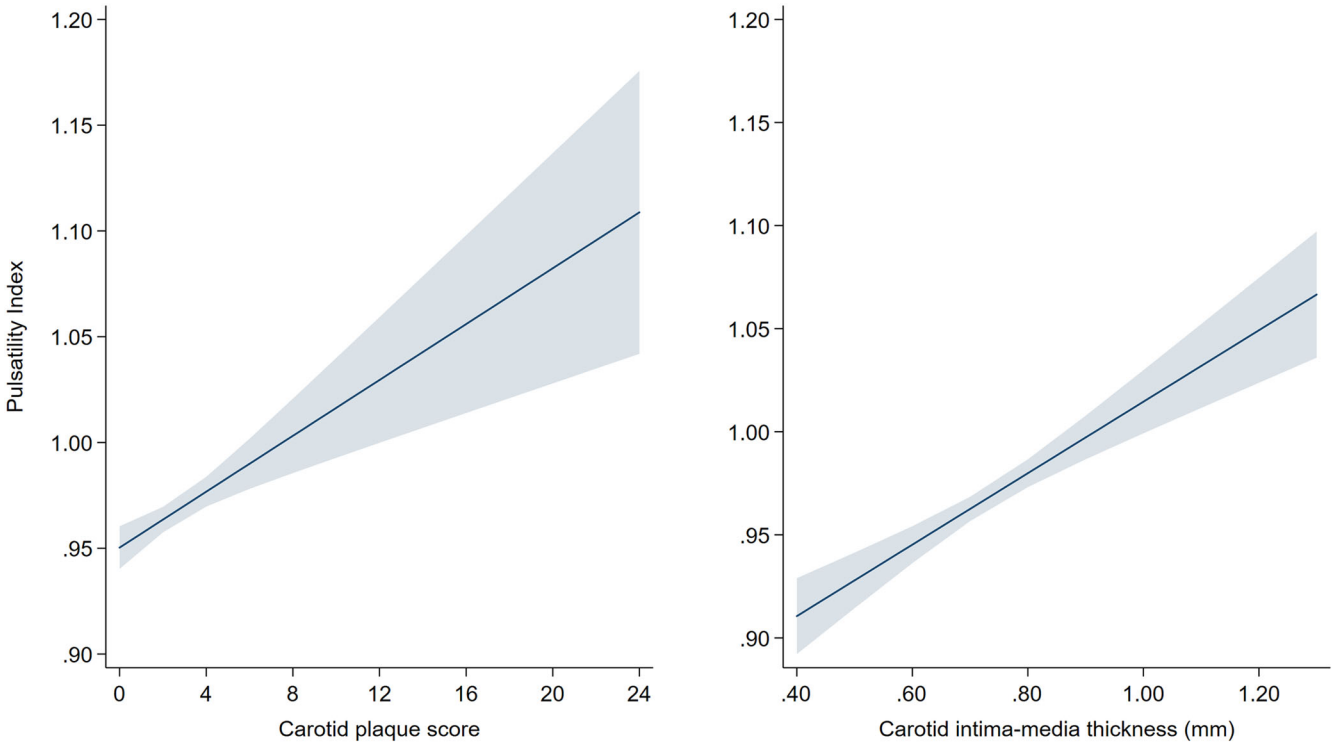

Fig 2. Linear association, with 95% confidence interval, between pulsatility index and carotid plaque score (left), and between pulsatility index and carotid intimamedia thickness (right). Adjustments were made for age, sex, body mass index, hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease, history of stroke/transient ischemic attack, current daily smoking, and with all indices of carotid atherosclerosis in the same model.

process is restricted to the intimal layer.[26] cIMT has hereby been thought to reflect the early stages of atherosclerosis, whereas plaques represent the more advanced stages. However, increased cIMT may also represent hypertensive medial hypertrophy.[27,28] Several recent studies have found measures of carotid plaque to be more strongly associated with cardiovascular risk and other cardiovascular risk factors than measurements of cIMT.[25,29,30] Methodolocial issues in measuring cIMT might contribute to this difference.[31]

In our study, we found that cIMT explained a greater proportion of the variance in MCA PI than carotid plaque score. Little is known about the association of cIMT and IMT at different sites in the arterial three. However, if thickening of cIMT represents a general thickening of the inner layers of the arteries, including the smaller vessels, this could increase peripheral vascular resistance in accordance to Poiseuille's law,[32] and hereby give an increase in MCA PI.

Stiffening of large elastic arteries is associated with carotid plaque, cIMT, and MCA PI, and might be a contributor to the associations in the present study.[33,34] Large artery stiffness has even been proposed as the pathophysiologic link between increased MCA PI and SVD.[35,36] This is based on the notion that stiffening of large elastic arteries causes an increased pulsatile flow that is transmitted to the microsirculation, causing damage to the tissue through impaired function of different regulatory systems, ultimately causing SVD.

Evaluation of plaque morphology remains crucial in the assessment of carotid atherosclerosis, as echolucent plaques are associated with increased risk of ischemic cerebrovascular events.[37,38] Echolucency corresponds to lipid-rich necrotic cores or intraplaque hemorrhages, more commonly found in symptomatic carotid stenosis.[39,40]

We found no association between echolucent plaques and MCA PI. The reason for this might be found in different underlying pathologic entities. Carotid plaque score, cIMT, and MCA PI may be closer linked to the systematic changes associated with stiffening of the large elastic arteries, whereas echolucent plaques are more closely linked to lipid status and inflammation.[41,42] The latter is supported by a study finding association between echogenic plaques and aortic stiffness, but not with echolucent plaques.[43]

Only a small proportion of the variance of MCA PI was explained by our multivariable linear regression model, suggesting other factors to play an important role for the measure of MCA PI. When considering MCA PI as a measure of SVD, this is in line with the most recent reports on SVD.[6,44]

In our study, we could confirm an association between MCA PI and both hypertension and diabetes mellitus. Further, we found that participants in the upper quartile of MCA PI more frequently had a history of coronary artery disease. MCA PI was associated with elevated systolic blood pressure, lower diastolic blood pressure, and increased pulse pressure. Since pulse pressure is associated with arterial stiffness,[45] this lends support to the link with stiffening of large elastic arteries.

Significantly more participants in the upper quartile of MCA PI had a carotid artery stenosis of 50-69%, whereas there was no significant difference in the fraction of participants with a stenosis of >70%, or with total occlusion. In all, these participants comprised a very small fraction of the study population. Lastly, MCA PI was associated with significantly lower end diastolic

and mean flow velocity. In line with this, other studies have found PI to be associated with a decrease in mean blood flow velocity.[11,46] Mean flow velocity measured with transcranial Doppler is considered an indirect measure of cerebral blood flow, but the reliability of this surrogate marker of cerebral blood flow is yet uncertain.[47]

The current study has a cross-sectional design in an unselected population-based cohort, where all residents in a geographical region, with equal access to healthcare services, were invited to participate. In age cohorts, the impact of age is diminished, whereas the generalizability to other populations is more limited. Of the eligible cohort, 63% participated, and nonresponse bias must be taken into account, as we have no information on individuals who actively refused or were unable to participate. However, the participation rate is similar to other contemporary population-based studies.[48]

A great strength of the study is the thorough ultrasound examination of both carotid arteries, and even more important, of both MCAs. Further, the feasibility of transcranial Doppler in this cohort is very high, with a large proportion having an acoustic window for measurement of cerebral hemodynamics. Imaging of SVD by MRI and assessment of large artery stiffness would have extended the implication of the present findings, as it would have enabled us to validate MCA PI as a marker of SVD, and explore the pathophysiologic link with arterial stiffness. Lastly, it is important to emphasize that the results of our study are mainly applicable to subjects without carotid stenosis or eventual tandem lesions. Cerebral autoregulatory mechanisms will in these situations often reduce peripheral cerebral resistance.[49]

In a population-based sample of middle-aged adults, ultrasound-derived indices of carotid atherosclerosis and MCA PI were associated, even after adjustment for established cardiovascular risk factors. However, the overall explained variance of MCA PI was low, suggesting other factors than atherosclerosis and cardiovascular risk factors to play an important role for MCA PI.

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