

Aortic stiffness and cerebral microbleeds: The Framingham Heart Study

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Keywords

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Cerebral small vessel disease (CSVD) is the most common subtype of cerebrovascular disease contributing to stroke and dementia.^{1,2} Cerebral microbleeds (CMB) represent hemorrhage-prone CSVD, generally attributed to hypertensive angiopathy, cerebral amyloid angiopathy, or both. CMB result from progressive structural and functional alterations of the blood vessel wall, evolving over a period of years to decades before clinical stroke and dementia are diagnosed, thus providing an opportunity for early intervention and prevention when identified. Further, CMB may increase bleeding complications from anticoagulant, thrombolytic, and antiplatelet therapy, and increase risk of complications of anti-amyloid treatment in clinical trials for Alzheimer's dementia. Arterial stiffness may provide a mechanistic link between systemic vascular disease and CSVD by transmission of abnormal flow pulsations from the central arteries into the small cerebral arteries,³ or interfering with toxic product clearance from the brain via perivascular spaces.⁴ In patients with stroke, arterial stiffness has been associated with CMB.⁵ We aimed to study the relation of carotid-femoral pulse wave velocity (CFPWV), as a measure of aortic stiffness, and CMB prevalence in community dwelling individuals. We further studied modification of this relation by genetic factors, vascular risk factors, and treatments to further generate hypotheses for potential treatment targets and preventive strategies.

We included Framingham Heart Study (FHS) participants with available brain magnetic resonance imaging (MRI), arterial stiffness (tonometry) data, and covariate data. Exclusions included lack of these data, or neurological conditions affecting outcome assessment, including prevalent stroke or dementia.

All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board at the Boston University Medical Center.

CFPWV was assessed using arterial tonometry as previously described (Mitchell et al.,⁸ *Circulation* 2010; 121: 505–511). CMB were defined using standard criteria from published guidelines,⁶ with good intra and inter-rater reliability of ratings (kappa 0.78).⁷ CMB were assessed by location in the brain in four groups thought to reflect the underlying type of small vessel disease: any CMB (any form of hemorrhage-prone CSVD),

lobar only CMB (cerebral amyloid angiopathy), deep only CMB (hypertensive angiopathy), and mixed location CMB (interplay of both).

Covariates including demographic and clinical data were recorded at the exam cycle closest to the brain MRI. Descriptive statistics were obtained for sample characteristics, using mean (SD) or median (Q1, Q3), depending on the symmetry of the distribution to describe continuous variables and frequency counts (%) for categorical variables. CFPWV was modeled as a continuous variable as previously described.⁸ We used multivariable logistic regression analyses to calculate the odds ratio (OR) and 95% CIs for CMB per SD increase in CFPWV. Additional methodological details are provided in the online supplementary data.

We observed CMB in 224 of the 3798 participants included (5.9%). The median CFPWV was higher in persons with CMB. In multivariable analyses (Table 1), higher CFPWV was associated with CMB in all brain locations, but the associations were attenuated after adjusting for vascular risk factors and treatments, remaining modest only for CMB

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Table 1. Association of aortic stiffness (inverse CFPWV) with cerebral microbleeds.

	Any CMB	Lobar only	Deep only	Deep and mixed
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
<i>n</i>	224	182	42	68
Crude	1.86 (1.62, 2.14)	1.53 (1.29, 1.79)	2.41 (1.77, 3.29)	2.71 (2.1, 3.5)
Model 1	1.16 (0.94, 1.44)	0.98 (0.76, 1.26)	1.67 (1.04, 2.69)	1.64 (1.12, 2.42)
Model 2	1.18 (0.93, 1.52)	1.05 (0.79, 1.40)	1.51 (0.91, 2.52)	1.51 (1.00, 2.29)
Effect modification (based on model 2)				
Effect modifier	Any CMB	Lobar only	Any CMB	Lobar only
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex	Female		Male	
<i>n</i>	92	63	101	70
	0.96 (0.68, 1.36)	0.83 (0.55, 1.26)	1.45 (1.01, 2.07)	1.34 (0.87, 1.99)
<i>APOE</i> ϵ 4 allele	Yes		No	
<i>n</i>	43	32	141	95
	1.64 (0.97, 2.77)	1.61 (0.90, 2.88)	1.02 (0.77, 1.36)	0.84 (0.59, 1.19)

Negative inverse CFPWV, ms/m. Values represent change in OR per 1 SD increase in negative inverse CFPWV.

Model 1 adjusted for age, sex, and interval between MRI and exam.

Model 2 additionally adjusted for mean arterial pressure, hypertension (includes hypertension treatment), diabetes, smoking, total cholesterol, prevalent cardiovascular disease.

CFPWV, carotid-femoral pulse wave velocity; CMB, cerebral microbleeds; MRI, magnetic resonance imaging; OR, odds ratio.

in deep and mixed regions (OR 1.51, 95% CI 1.00–2.29). We observed that the association between CFPWV with any CMB presence was significant only in men ($p = 0.04$ for interaction; OR 1.45 (95% CI 1.01–2.07); Table 1). In participants with at least one *APOE* ϵ 4 allele, higher CFPWV showed a stronger relation to any and strictly lobar CMB ($p < 0.01$ for interaction) with OR 1.64 (95% CI 0.97–2.77) and OR 1.61 (95% CI 0.9–2.88) versus OR 1.02 (95% CI 0.77–1.36) and OR 0.84 (0.59–1.19) in participants with and without *APOE* ϵ 4 alleles, respectively, but the association did not reach statistical significance within the *APOE* ϵ 4-positive subgroup (Table 1).

Our study included a large sample of community dwelling adults representing the entire life span (age range 22–92 years old), showing that higher aortic stiffness was associated with the presence of deep and mixed CMB, and the relation is modified by sex and possibly by *APOE* genotype. Our results, which should be interpreted with caution as we did not account for multiple comparisons and some of the CMB outcome subgroups had a small number of events, serve to generate hypotheses for mechanisms underlying hemorrhage-prone CSVD. We concur with prior knowledge on the role of aortic stiffness in cerebral small vessel disease,⁹ and expand previous reports by including a larger sample with younger mean age than previous studies.

The observed associations of CFPWV with CMB after adjustment for hypertension history and other vascular risk factors suggest that arterial stiffness may play a role in the

pathophysiology of mixed CMB independent of hypertension. Aortic stiffness may relate to CSVD represented by CMB because of increased transmission of excessive pressure and flow pulsatility over prolonged periods, particularly for deep CMB given that deep cerebral arterioles are less effective at damping pulsatile forces. However, other mechanisms may be involved: aortic stiffness is associated with inflammation¹⁰ and endothelial dysfunction,¹¹ which are also processes involved in the pathophysiology of CMB.¹²

Strengths of our study include the large population-based prospective cohort study design, thoroughly characterized confounders, and reliable blinded assessments of exposures and outcomes. Limitations include small subgroups of CMB outcomes, limited generalizability of our findings to racial and ethnic minorities, and the fact that the exposure and outcomes are surrogate markers.

We submit that the relation between aortic stiffness and cerebral microbleeds is complex and affected by demographic and possibly genetic factors. Given that CMB detection may modify bleeding complications from commonly used treatments, further studies could be considered to explore the interplay of increased arterial stiffness with CMB and clinical outcomes (stroke and dementia) as potentially modifiable treatment and prevention targets.

Declaration of conflicting interests

Dr Mitchell is owner of Cardiovascular Engineering Inc. (a company that develops and manufactures devices to measure vascular

stiffness) and serves as a consultant to Novartis, Merck, and Servier. Dr Romero received speaker honoraria from Ferrer Group. The other authors report no potential conflicts of interest.

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Supplementary material

The supplementary material is available online with the article.

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