Impaired visual evoked flow velocity response in cerebral amyloid angiopathy

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ABSTRACT

Objective: Animal models of cerebral amyloid angiopathy (CAA) exhibit abnormal vascular reactivity. We determined whether vascular reactivity, measured by transcranial Doppler ultrasound (TCD), is reduced in humans with CAA.

Methods: Cases were recruited from an established prospective study of CAA. Healthy controls were recruited from a study of normal aging. Evoked mean flow velocity increase in the posterior cerebral artery (PCA) was measured while subjects viewed a flashing alternating checkerboard stimulus. In a separate but partially overlapping cohort we measured the mean flow velocity increase in the middle cerebral artery (MCA) while subjects inhaled carbon dioxide.

Results: The visual evoked mean flow velocity increase was 8.0 ± 6.1% in CAA (n = 11) compared to 17.4 ± 5.7% in controls (n = 9, $p = 0.002$). The PCA pulsatility index, a marker of distal vascular resistance, was higher in CAA (CAA 1.35 ± 0.35, control 1.04 ± 0.14, $p = 0.03$). Among CAA subjects, lower visual evoked mean flow velocity increase was associated with a higher number of hemorrhages seen on MRI ($r = -0.87$, $p = 0.0005$) and higher MRI white matter hyperintensity volume ($r = -0.67$, $p = 0.02$). The MCA response to carbon dioxide did not differ between CAA and control in 20 subjects (9 CAA, 11 control, $p = 0.54$).

Conclusions: Cerebral amyloid angiopathy (CAA) was associated with decreased vascular reactivity in response to visual stimulation, possibly reflecting the occipital predilection of the disease. The association of posterior cerebral artery (PCA) evoked flow velocity response with elevated PCA pulsatility index and MRI markers of small vessel disease suggests that abnormal PCA evoked flow velocity in CAA is caused by pathology of the distal resistance vessels.
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GLOSSARY

AD = Alzheimer disease; **CAA** = cerebral amyloid angiopathy; **FLAIR** = fluid-attenuated inversion recovery; **GRE** = gradient recalled echo; **ICA** = intracranial area; **ICC** = intraclass correlation coefficient; **MCA** = middle cerebral artery; **nWMH** = normalized white matter hyperintensity; **PCA** = posterior cerebral artery; **TCD** = transcranial Doppler ultrasound; **VMRI** = vasomotor reactivity index.

Sporadic cerebral amyloid angiopathy (CAA) is characterized by deposition of beta-amyloid in the media of small arteries.[1] Animal and in vitro studies show that beta-amyloid is toxic to vascular smooth muscle,[2] and histopathologic studies show loss of smooth muscle cells in CAA.[1] Mice that overexpress mutant amyloid precursor protein have reduced response to many vasodilatory stimuli.[3-6] Exposure of the mouse neocortex to exogenous abeta(1-40), the main constituent of vascular amyloid, reduces resting cerebral blood flow and the response to vasodilators.[7]

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In humans, it is unknown whether CAA affects vascular reactivity or cerebral blood flow, a possibility suggested by associations between CAA and ischemic brain lesions such as infarction,[8] microinfaction,[9] and white matter lesions.[10] We hypothesized that persons with probable CAA have decreased vascular responses to vasodilatory stimuli, and that the degree of response correlates with MRI markers of CAA. Because CAA preferentially affects posterior brain regions,[11-14] we performed an experiment to test whether the visual evoked flow velocity in the posterior cerebral artery (PCA), measured by transcranial Doppler (TCD) ultrasound, was reduced in CAA compared to controls.

METHODS

Study population. CAA subjects were recruited from a prospective longitudinal study of consecutive subjects with lobar ICH.[15,16] All had probable CAA according to the Boston Criteria.[17] Subjects were excluded if they had dementia, non-CAA cerebrovascular diseases (ischemic stroke or intracranial/extracranial atherosclerotic disease causing >50% arterial stenosis), current smoking, or diabetes. Hypertensive subjects had no antihypertensive medication changes within 90 days. For studies of visual evoked flow velocity, subjects were additionally excluded for seizure, visual acuity less than 20/50 (corrected) on Snellen card, or hemianopia. For studies of carbon dioxide (CO_2) reactivity, subjects with seizure or visual abnormalities were included but those with coronary heart disease, cardiac arrhythmia, significant pulmonary disease, or panic anxiety were excluded.

The 14 participating CAA subjects presented with hemorrhagic stroke (n = 8), seizure (n = 3), memory symptoms (n = 2), or gait impairment (n = 1). To avoid confounding by the acute ICH, subjects with hemorrhagic stroke were studied a mean of 2.5 years after hemorrhage (range 124 days–7.2 years). Index hemorrhagic strokes were present in the left frontal lobe (n = 2), right frontal lobe (n = 1), left parietal lobe (n = 1), right parietal lobe (n = 2), left temporal lobe (n = 1), or left occipital lobe (n = 1); median ICH volume was 9.0 cm^3 (interquartile range 6.4–24.0 cm^3) in the seven subjects with available CT data. None had surgical hematoma evacuation or raised intracranial pressure. The sole subject with a 6.4 cm^3 occipital hemorrhage had no visual symptoms at the time of testing. Both subjects presenting with memory symptoms made 3 errors (of 37 possible) on the Information-Memory-Concentration subscale of the Blessed Dementia Test,[18] indicating very mild impairment, and did not have dementia.

In addition, we studied a single subject with hereditary CAA caused by the Iowa-type amyloid precursor protein mutation.[19] This 42-year-old man presented with mild cognitive impairment but no impairment in activities of daily living. He had controlled hypertension but no stroke, coronary heart disease, hypercholesterolemia, or smoking. MRI showed no microbleeds on the gradient recalled echo (GRE) sequence and a low volume (0.84 cm^3) of normalized white matter hyperintensity (nWMH) on fluid-attenuated inversion recovery (FLAIR) sequence (see MRI measurements for explanation of methods). Results for this subject are reported separately from the main cohort.

Control subjects met all inclusion and exclusion criteria and did not have a history of ICH, CAA, or other neurologic disease. They were recruited from the Harvard Cooperative Program on Aging, a community-based registry of healthy aged subjects, recruited through advertising, who have indicated a willingness to participate in research studies.[20]

Study subjects provided informed consent and the study procedures were approved by the local Institutional Review Board.

TCD measurements. First, routine TCD was performed using a DWL Multi-Dop X8 (DWL corporation, Germany). No subjects had abnormal waveforms that suggested cervical or intracranial stenosis. Probes were fixed in place using a headset (Spencer Marc 600, Spencer Technologies, Seattle, WA). Blood pressure was noninvasively measured every 10–15 heartbeats (Vasotrac device by Medwave, St Paul, MN). Subjects taking antihypertensives continued their usual dose, except that dosing was not allowed within 2 hours of TCD.

Time synchronized data were acquired using Powerlab (AD Instruments, Colorado Springs, CO) and processed using Chart software (AD Instruments). TCD waveform envelopes were passed through a 10-Hz low-pass filter to reduce high frequency artifact. Pulsatility index was defined as peak-systolic velocity minus end-diastolic velocity, divided by mean flow velocity.[21]

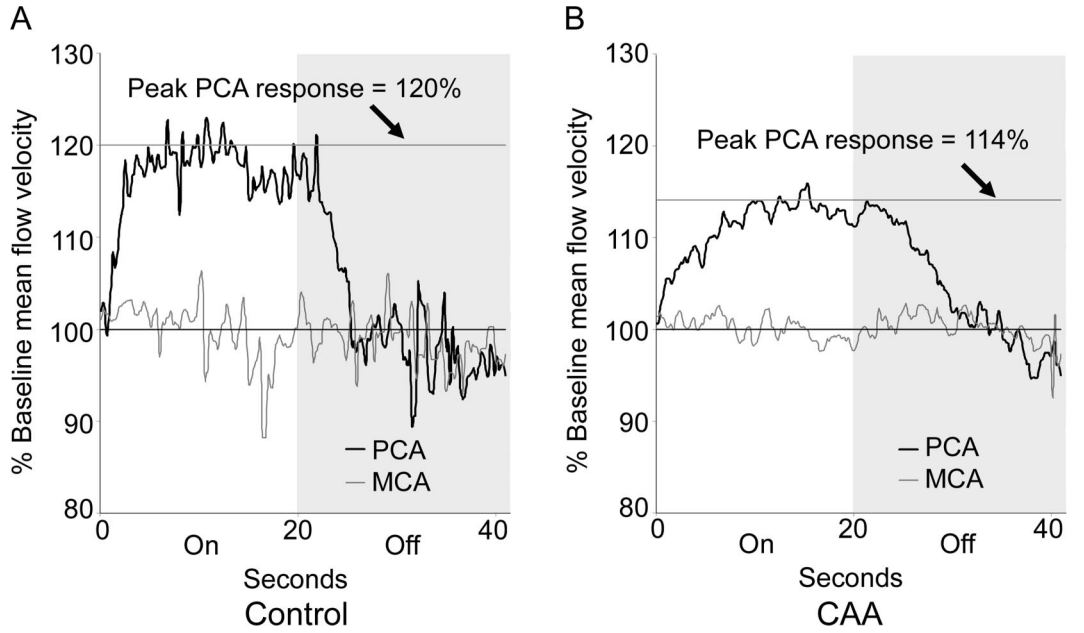
The P2 segments of the PCA, with flow direction away from the probe, were insonated at 65 mm depth and the side with optimal signal was selected. The contralateral MCA was insonated at 50 mm depth as a negative control. The visual stimulation paradigm consisted of ten 40-second epochs of a 10-Hz alternating checkerboard stimulus for 20 seconds ("on" period), followed by a blank screen for 20 seconds ("off" period). A study neurologist verified that the subject was awake and attending to the stimulus.

The subject's visual evoked flow velocity response was determined by averaging the epochs, normalized to the epoch-specific baseline value, and graphing the result using a 45-point triangular (Bartlett) window for smoothing. The subject peak evoked PCA mean flow velocity (peak PCA response) was calculated as the maximum PCA mean velocity expressed as percent of baseline (figure 1).

In eligible subjects we also measured the MCA blood flow velocity response to CO_2 inhalation because it is the best-studied measure of vascular reactivity.[22] Subjects breathed room air through a mouthpiece attached to a capnometer (Traverse Medical Monitors Capnometer Model 2200, Saline, MI) while MCA mean flow velocity was monitored at 50 mm depth bilaterally. After 90 seconds of baseline recording the intake gas was changed to 5% carbogene (5% CO_2, 95% O_2) for 90 seconds. A second trial was performed after ≥5 minutes rest. The 20 cardiac cycles preceding initiation and termination of the carbogene gas were selected and averaged in order to determine the baseline MCA mean velocity, peak MCA mean velocity, and change in end-tidal CO_2 concentration. The vasomotor reactivity index (VMRI) was calculated as the percent change in MCA velocity, compared to baseline, divided by the increase in end-tidal CO_2 in mm Hg, as in other studies.[22,23] The bilateral MCA responses in both trials were averaged because there were no significant differences by side or trial. Some subjects who participated in the visual experiment did not participate in the CO_2 reactivity experiment, and vice versa, because of differing exclusion criteria or technical limitations related to attenuation of the ultrasound beam by the skull. Those who participated in both experiments did so on the same day, separated by ≥30 minutes.

MRI and CT measurements. MRI was performed in CAA but not healthy controls. MRI data were acquired on 1.5 Tesla Signa scanners (GE Medical Systems, Milwaukee, WI).[24-26] Quanti-

Figure 1 Examples of evoked flow velocity changes in the PCA and MCA of a 77-year-old control subject (A) and a 73-year-old subject with CAA (B)



A 10-Hz flashing checkerboard stimulus was viewed during the "on" period. The curves represent an average of ten 40-second epochs. The peak increase from baseline in the PCA (PCA peak response), determined after smoothing using a triangular window, was 20% in the control subject and 14% in the CAA subject. PCA = posterior cerebral artery; MCA = middle cerebral artery; CAA = cerebral amyloid angiopathy.

tative WMH volume was determined by computer-assisted segmentation, using the MRI FLAIR sequence, as previously published.[25] To correct for head size we used the sagittal midline cross-sectional intracranial area (ICA) as a surrogate measure of the intracranial volume[24] and normalized WMH volume to head size (nWMH) by dividing the subject's WMH volume by the ratio of the subject's ICA to the mean ICA of the study population.[25] The number of hemorrhages, including microbleeds, were counted on the MRI GRE sequence.[26] To determine the correlation between TCD measurements and MRI lesions within and without the perfusion territory of the insonated PCA branch, a region of interest was manually drawn, using MRIcro software, according to anatomic landmarks derived from published atlas images.[27] ICH volumes were calculated by manually tracing a region of interest encompassing the ICH.[28] MRI and CT measurements were performed blinded to the TCD results. We have previously shown high interrater reliability, by intraclass correlation coefficient (ICC), for measurements of nWMH (ICC = 0.98),[25] mid-sagittal ICA (ICC = 0.97),[24] MRI hemorrhages (ICC = 0.97),[26] and ICH volume (ICC = 0.99).[28]

Statistical analysis. Comparisons of proportions were by Fisher exact test. PCA peak response and VMRI were normally distributed and were compared across groups by *t* test. Pearson correlations were used to compare age, TCD MFVs, peak PCA response, and VMRI. Because nWMH and MRI hemorrhages have a right-skewed distribution, comparisons with those variables were by Wilcoxon rank sum test or Spearman correlation, as appropriate. Analyses were performed using SAS version 9.1.3 (Cary, NC).

RESULTS Subjects were recruited between September 2003 and November 2006. There were 27 subjects for the visual evoked flow velocity experiment; 20 had adequate bone windows for insonation (11 CAA, 9 control). CAA cases and healthy controls did not differ in age, sex, or the prevalence of vascular risk factors (table). There were no significant group differences in the proportions taking antihypertensives, HMG-CoA reductase inhibitors, or serotonin reuptake inhibitors (data not shown). PCA mean flow velocity at baseline was similar in CAA and control; however, CAA subjects had a higher PCA pulsatility index (table).

The peak PCA response to visual stimulation in CAA was <50% of controls ($p = 0.002$, figure 2) and occurred later in the epoch (CAA 20 ± 5 seconds, control 13 ± 6 seconds, $p = 0.02$). Peak PCA response occurred after the 20 second "on" period in four CAA subjects. When subjects with peak PCA response after 20 seconds were excluded, the amplitude of the peak PCA response remained lower in CAA (CAA 9.3 ± 6.7%, control 18.1 ± 5.2%, $p = 0.02$). Markedly diminished PCA peak response (4.8%, i.e., 2.2 standard deviations below the control mean, figure 2) was observed in the 42-year-old subject with hereditary CAA.[19]

By contrast, the peak MCA response during visual stimulation, measured as a negative control, was substantially lower than the PCA response and did not differ between CAA and controls (CAA 3.3 ± 2.4%, control 4.9 ± 2.7%, $p = 0.19$). Mean arterial blood pressure during the "on" period was no different than the "off" period (mean difference 0.2 ± 1.2

Table Study population characteristics

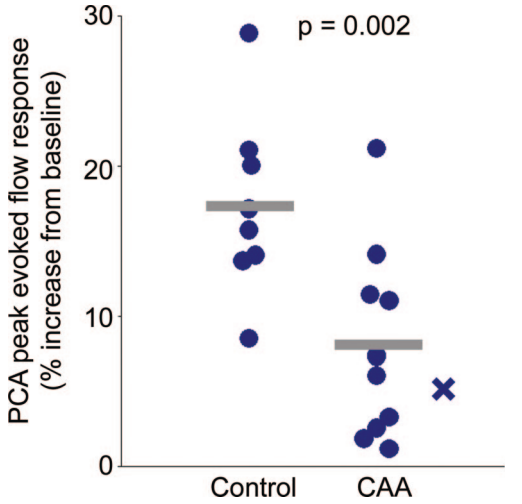
Characteristic	CAA, n = 11	Control, n = 9	p
Age, y	73.5 ± 7.4	70.9 ± 7.9	0.46
Female	4	2	0.64
Hypertension	5	3	0.67
CHD	0	0	0.99
Hypercholesterolemia	4	2	0.64
Past smoker*	4	6	0.37
Baseline systolic BP (mm Hg)	135 ± 18	146 ± 16	0.16
Baseline diastolic BP (mm Hg)	73 ± 12	81 ± 10	0.17
PCA MFV (cm/sec)	34.8 ± 11.1	30.4 ± 8.6	0.35
PCA pulsatility index	1.35 ± 0.35	1.04 ± 0.14	0.02

All patients with hypertension were taking antihypertensive medication. See text for definition of pulsatility index.
*Current smokers were excluded from the study.
CAA = cerebral amyloid angiopathy; CHD = coronary heart disease; BP = blood pressure; PCA = posterior cerebral artery; MFV = mean flow velocity.

mm Hg, $p = 0.62$) in 15 subjects where blood pressure was monitored.

Peak PCA response was higher in those with lower baseline PCA pulsatility index (figure 3), but did not differ by age, sex, hypertension, hypercholesterolemia, past history of smoking, or baseline blood pressure ($p > 0.20$). The difference in peak PCA response persisted after exclusion of the 5 CAA subjects where PCA insonation was performed ipsilateral to hemorrhagic stroke ($p = 0.005$), the 8 CAA subjects with any hemorrhagic stroke ($p = 0.003$), the sole CAA subject with occipital hemorrhagic stroke ($p = 0.004$), or the 2 CAA subjects with memory symptoms ($p = 0.008$). Peak PCA response was not correlated with ICH volume in the 7 subjects with hemorrhagic stroke and available CT data ($r = -0.07$, $p = 0.88$).

Figure 2 **Peak PCA evoked flow velocity response to the visual stimulation task is reduced in CAA (8.0 ± 6.1%) compared to similar-aged controls (17.4 ± 5.7%)**

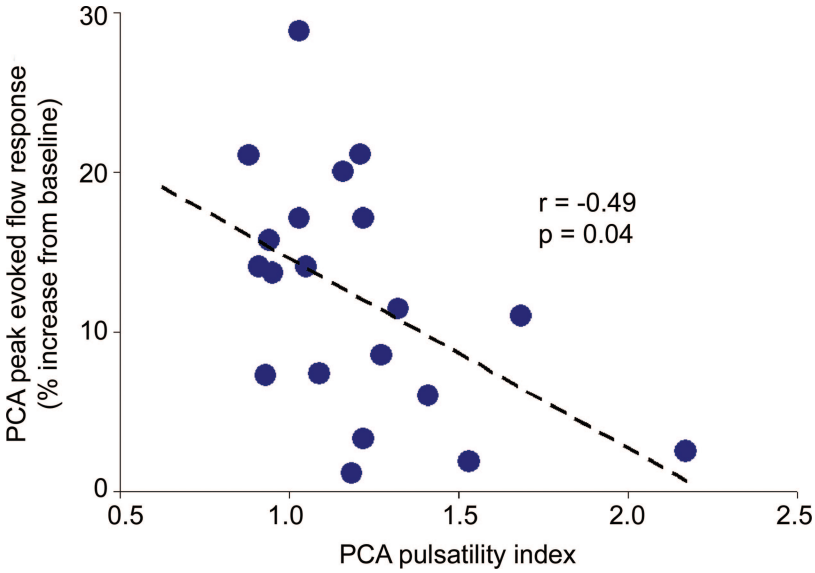


Bars indicate group means. Filled circles represent sporadic cerebral amyloid angiopathy (CAA) or control posterior cerebral artery (PCA) response. The X shows the PCA peak response from a single 42-year-old stroke-free man with hereditary CAA; this subject's data are not included in the calculation of the sporadic CAA group mean or significance testing.

MRI in CAA subjects (n = 11) showed median nWMH volume was 9.4 cm^3 (interquartile range 6.2–36.4 cm^3) and median number of hemorrhages on MRI GRE sequence was 8 (interquartile range 2–33). Occipital hemorrhages ipsilateral to the insonated PCA were seen in five subjects (four had microbleeds, range 1–14, and one had a small 6.4 cm^3 ICH). A strong trend toward decreased peak PCA response remained after excluding these five subjects with ipsilateral microbleeds or hemorrhages (CAA 11.2 ± 6.5%, control 17.5 ± 5.7%, $p = 0.07$). Among all CAA subjects, peak PCA response was lower in those with higher nWMH volume ($p = 0.02$) and more MRI hemorrhages ($p = 0.0005$) (figure 4). The findings were similar when the analysis was restricted to MRI lesions outside the territory of the insonated PCA (for nWMH $r = -0.56$, $p = 0.07$; for MRI hemorrhages $r = -0.87$, $p = 0.0005$).

CO_2 reactivity was determined in an overlapping cohort of sporadic CAA subjects and healthy controls, recruited according to the same methods. There were 25 subjects who participated in the CO_2 reactivity experiment; 20 had adequate bone windows for insonation (9 CAA, 11 control). Age and sex were similar (CAA 4/9 female, age 72.8 ± 7.5 years; control 5/11 female, age 70.6 ± 7.0 years). There were no differences in prevalence of hypertension, coronary artery disease, hypercholesterolemia, or past history of smoking ($p > 0.20$). There was no difference in MCA mean flow velocity (CAA 43.0 ± 13.4 cm/second, control 44.7 ± 7.6 cm/second, $p = 0.73$) or MCA pulsatility index (CAA 1.18 ± 0.20, control 1.12 ± 0.20, $p = 0.53$). CO_2 reactivity, calculated as VMRI, was similar in CAA and control (CAA 4.98 ± 1.96% per mm Hg, control 5.45 ± 1.34% per mm Hg, $p = 0.54$). VMRI did not differ by age, sex, hypertension, hypercholesterolemia, or past history of smoking ($p > 0.20$). The number of hemorrhages and nWMH volume were not correlated with VMRI ($p > 0.20$). Because of differing exclusion criteria or technical limitations in insonating the MCA or PCA, only 13 subjects (6 CAA, 7 control) were eligible for and completed both the visual and CO_2 experiments. In these 13 subjects VMRI was not correlated with PCA peak response to visual stimulation ($r = -0.26$, $p = 0.39$).

Figure 3 Posterior cerebral artery (PCA) pulsatility index is higher in those with lower PCA evoked flow velocity response to the visual stimulation task

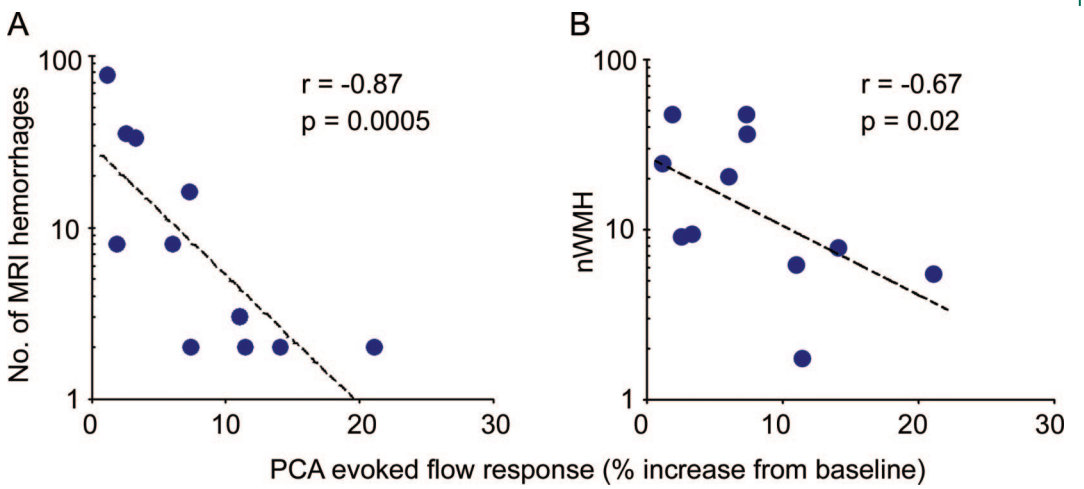


DISCUSSION In this study, TCD ultrasound was used to measure the maximum PCA mean flow velocity increase in response to a complex visual stimulus. TCD measurements of increased flow velocity in response to functional tasks have been shown to correlate with fMRI measures of activation.[29] The peak PCA response in healthy controls was similar to the 14–20% increase observed in similar studies,[30] while in CAA subjects it was reduced and delayed. The peak PCA response occurred after the 20-second "on" period in 4 CAA subjects; it is possible that the amplitude of the peak PCA response in these subjects may have been larger had the experimental design included a longer "on" period. Taken together our data suggest both a decreased rate of response as well as decreased maximum response. The observed responses were not accounted for by changes in recorded physiologic parameters, including systemic blood pressure, and were not related to the size of acute ICH in those with hemorrhagic stroke. CAA cases and healthy controls were similar with respect to other factors known to influence vascular reactivity, including age, sex, history of hypertension, and use of antihypertensive medications.

It is likely that the reduced visual evoked mean flow velocity in CAA was caused by dysfunction related to chronic vascular amyloid deposition. This is supported by the observations that decreased peak PCA response correlated with increased pulsatility index, indicative of increased distal vascular resistance,[21] and an increased burden of MRI lesions frequently associated with small vessel disease (figure 4). Many CAA subjects had hemorrhagic stroke while controls were stroke-free, raising the possibility of confounding by chronic effects of stroke. However, symptomatic hemorrhages in the CAA group were small and none were associated with raised intracranial pressure or surgical intervention. Subjects were studied more than 120 days after stroke onset to allow time for resolution of acute disturbances in blood flow, if present.[31] Notably, a significant reduction in visual-evoked PCA peak response could be seen even in the small group of CAA subjects without history of hemorrhagic stroke, and in the single younger subject with hereditary CAA but no stroke.

Decreased occipital neuronal activity, without vascular dysfunction, is an unlikely explanation for

Figure 4 PCA evoked flow velocity response to the visual stimulation task is lower in those with more MRI hemorrhages (A) and higher nWMH volume (B)



Because of right-skewed distributions, the number of MRI hemorrhages and nWMH volume are plotted on a logarithmic scale and statistical testing is by Spearman correlation coefficient. PCA = posterior cerebral artery; nWMH = MRI white matter hyperintensity volume normalized to average subject head size.

the study results. Subjects were observed and noted to attend to the visual task. Visual function was intact in the study subjects as evidenced by normal visual acuity and the absence of visual field defects. The exclusion of subjects with ipsilateral hemorrhagic stroke did not change the results. A strong trend toward decreased peak PCA response was present even after excluding subjects with ipsilateral occipital microbleeds. Therefore the decreased peak PCA response is likely a result of global CAA severity rather than occipital lobe tissue damage from hemorrhage. Alzheimer disease (AD) pathology is associated with CAA[1] but probably did not influence the study results. AD is not associated with reduced functional hyperemia in primary visual cortex[32] and TCD studies have not found a difference in PCA visual evoked flow velocity between AD and controls.[33,34] Nonetheless, in the absence of simultaneous measurements of neuronal electrical activity or metabolism we cannot completely exclude the possibility that decreased neuronal metabolism was primarily responsible for the observed decreased flow velocity.

There was more MRI nWMH, and more MRI hemorrhages, in those with lower peak PCA evoked flow velocity. These relationships were similar when restricted to MRI lesions outside the perfusion territory of the insonated artery, suggesting that peak PCA response is a marker of global MRI lesion burden. The reduced PCA peak response in the single younger subject with hereditary CAA and low burden of MRI lesions suggests that vascular dysfunction, at least in hereditary CAA, may precede hemorrhage or severe white matter changes. MRI WMH have previously been associated with TCD measurements of vascular CO_2 reactivity,[21,35] while the relationship between WMH and impaired functional hyperemia has been less studied.

We measured only a relatively small decrease in MCA CO_2 reactivity in CAA. A single large study previously found a relationship between TCD-measured CO_2 reactivity and declining serum abeta(1-40) over time, which the authors proposed may reflect accumulating vascular amyloid deposition.[36] Our study does not have enough power to distinguish small or moderate differences in CO_2 reactivity between CAA and controls. Nonetheless, our study data show that PCA visual evoked flow velocity correlates better with CAA than MCA CO_2 reactivity. The relatively preserved MCA response to CO_2, in contrast to the reduced PCA response to the visual stimulation task, may be the result of either preferential involvement of the posterior brain regions by CAA,[11-14] or CAA-related differential impairment of vasodilation in response to neuronal activity[37] compared to CO_2.[38] Our study data, while not conclusive, are consistent with the posterior predominance of CAA because the pulsatility index, a marker of small vessel disease, was increased in the PCA but not the MCA in CAA compared to controls.

The major limitation of the current study is the small sample size. Future studies with more subjects will address the relationship between reduced visual evoked flow velocity and clinical consequences of CAA, such as incident hemorrhage.

Our finding that CAA is associated with decreased functional hyperemia has potentially important implications. The decreased vascular response to physiologic stimuli suggests a possible mechanism by which CAA could be associated with decreased blood flow and brain ischemia. It is possible that impaired functional hyperemia is the mechanism by which CAA, in the absence of hemorrhagic stroke, has been associated with cognitive dysfunction even when controlling for AD pathology.[14,39,40] Whether therapeutic interventions can improve vascular function in CAA, and whether such interventions would result in less CAA-related clinical disability, remains to be demonstrated.

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