Neurovascular decoupling is associated with severity of cerebral amyloid angiopathy

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ABSTRACT

Objectives: We used functional MRI (fMRI), transcranial Doppler ultrasound, and visual evoked potentials (VEPs) to determine the nature of blood flow responses to functional brain activity and carbon dioxide (CO₂) inhalation in patients with cerebral amyloid angiopathy (CAA), and their association with markers of CAA severity.

Methods: In a cross-sectional prospective cohort study, fMRI, transcranial Doppler ultrasound CO₂ reactivity, and VEP data were compared between 18 patients with probable CAA (by Boston criteria) and 18 healthy controls, matched by sex and age. Functional MRI consisted of a visual task (viewing an alternating checkerboard pattern) and a motor task (tapping the fingers of the dominant hand).

Results: Patients with CAA had lower amplitude of the fMRI response in visual cortex compared with controls ($p = 0.01$), but not in motor cortex ($p = 0.22$). In patients with CAA, lower visual cortex fMRI amplitude correlated with higher white matter lesion volume ($r = -0.66$, $p = 0.003$) and more microbleeds ($r = -0.78$, $p < 0.001$). VEP P100 amplitudes, however, did not differ between CAA and controls ($p = 0.45$). There were trends toward reduced CO₂ reactivity in the middle cerebral artery ($p = 0.10$) and posterior cerebral artery ($p = 0.08$).

Conclusions: Impaired blood flow responses in CAA are more evident using a task to activate the occipital lobe than the frontal lobe, consistent with the gradient of increasing vascular amyloid severity from frontal to occipital lobe seen in pathologic studies. Reduced fMRI responses in CAA are caused, at least partly, by impaired vascular reactivity, and are strongly correlated with other neuroimaging markers of CAA severity. *Neurology*® 2013;81:1659-1665

GLOSSARY

BOLD = blood oxygen level-dependent; **CAA** = cerebral amyloid angiopathy; **CO₂** = carbon dioxide; **DEF** = dynamic end-tidal forcing; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **fMRI** = functional MRI; **ICH** = intracerebral hemorrhage; **PETCO₂** = partial pressure of end-tidal carbon dioxide; **VEP** = visual evoked potential; **WMH** = white matter hyperintensity.

Cerebral amyloid angiopathy (CAA) is best recognized clinically as a cause of frequent recurrent intracerebral hemorrhages (ICHs) and microbleeds, reflecting loss of vascular integrity due to β -amyloid deposition.¹ However, accumulating evidence suggests that impaired vascular reactivity is another feature of CAA. In a mouse model of severe CAA, there was decreased vasodilation in response to whisker barrel stimulation and to carbon dioxide (CO₂) inhalation, a vasodilatory stimulus.² In a small study of patients with probable CAA, posterior cerebral artery flow velocity responses were lower than controls when viewing a visual stimulus, but middle cerebral artery flow velocity responses to CO₂ inhalation were relatively preserved.³ It was not clear whether the differential responses observed in the visual and CO₂ experiments were due to the different arteries tested, the different types of vasodilatory stimulus used, or were because the lower response in the visual experiment was due to lower brain metabolic activity rather than impaired vasodilation.³ Finally, a recent study showed reduced functional MRI (fMRI)

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activation in CAA with a smaller amplitude and longer time to peak of the blood oxygen level-dependent (BOLD) signal in response to a visual stimulation task.⁴

We hypothesized that patients with CAA would exhibit impaired vasodilation in posterior brain arteries leading to reduced CO₂ reactivity and lower blood flow responses to occipital lobe metabolic activity with preserved visual evoked potentials (VEPs). These hypotheses were tested in a prospective cross-sectional study of patients with CAA and matched controls.

METHODS Population. Patients with CAA and controls were recruited as part of a prospective, funded, longitudinal study. Patients with CAA ($n = 18$) presented with a possible CAA-related clinical syndrome (lobar ICH in 9 patients, CAA-associated inflammation in 4, and transient neurologic symptoms in 5) and had MRI evidence of multiple lobar ICHs, microbleeds, or superficial siderosis without other evident cause, consistent with the diagnosis of probable CAA by the pathologically validated Boston criteria.^{1,5} Patients were recruited from an inpatient stroke service or an outpatient cognitive assessment clinic. Exclusion criteria included ICH affecting the occipital pole, low visual acuity ($>20/50$), visual field defect on neurologic examination, moderate to severe dementia (defined as a Clinical Dementia Rating score >1.0), or nonfluency in English (because they might have difficulty with task instructions). To exclude acute effects of ICH, patients were studied more than 90 days after symptomatic stroke. Patients with CAA-associated inflammation were included only if they were in remission, as documented by resolution of cerebral edema on MRI fluid-attenuated inversion recovery imaging. Dementia was diagnosed according to *DSM-IV* criteria, and mild cognitive impairment was diagnosed according to previous consensus criteria.⁶ Controls were recruited from the community by advertising in a newsletter, were verified by neurologist interview to not have a history of stroke or dementia, and were matched 1:1 to a CAA case by age (± 5 years) and sex.

Measurements. Structural MRI was performed on a 3.0T MR scanner (Signa VHi; GE Healthcare, Waukesha, WI), and included fluid-attenuated inversion recovery and T2*-weighted gradient-recalled echo. Sequence parameters are provided in table e-1 on the *Neurology*[®] Web site at www.neurology.org. White matter lesion volume was assessed by a single rater using Quantomo, a custom-designed software application (Cybertrials, Inc., Calgary, Canada). In brief, this software uses a 3-dimensional, threshold-based, region growing segmentation method incorporated from the open-source Insight Segmentation and Registration Toolkit (National Library of Medicine, Bethesda, MD). Before volume measurement, the magnetic resonance data were preprocessed using a 3-dimensional bilateral noise filter⁷ and a parametric bias field correction filter.⁸ Automated lesion boundaries were generated from user-placed seeds. Manual editing tools allowed correction of mislabeling, if required. To account for differences in subject head size, white matter hyperintensity (WMH) volumes were normalized to the average head size for the study population using a scaling factor. The scaling factor was derived for each subject by dividing the mean midsagittal cross-sectional area (for all subjects) by the individual subject's midsagittal cross-sectional intracranial area, a validated surrogate of total

intracranial volume.⁹ Cerebral microbleeds were identified by a single rater on the gradient-recalled echo images. Raters were blinded to clinical information and other study measurements (fMRI, CO₂ reactivity, and VEP results).

The fMRI was performed during 2 separate tasks using a block design: a) passive viewing of a contrast-reversing checkerboard stimulus using Presentation software (version 14.0; Neurobehavioral Systems, Albany, CA), activating primary visual cortex in the occipital lobe; and b) finger tapping, activating primary and supplementary motor cortex in the posterior frontal lobe. In the visual task, the subjects viewed an 8-Hz contrast-reversing checkerboard stimulus for 40 seconds followed by a blank screen for 40 seconds; there were 4 blocks. In the motor task, the subjects were visually cued to tap the first and second finger of their dominant hand (right hand, 32 subjects; left hand, 2 subjects) at 1.5 Hz for 40 seconds, followed by rest for 40 seconds; again, there were 4 blocks. Because of stroke-related hemiparesis, one subject with CAA performed the finger tapping with their nondominant right hand. Two subjects with CAA did not complete the finger-tapping task because of difficulty following the instructions.

Functional MRI data were analyzed using FSL (FMRIB Software Library version 4.1.6, Oxford, UK). After skull removal,¹⁰ the data were corrected for slice timing and motion,¹¹ smoothed and filtered using a high-pass temporal filter. Resulting z statistic images were thresholded using clusters determined by $z > 2.3$ and significance threshold of $p < 0.05$. The 50 most active voxels (2.8 cm³) in the primary visual cortex (for the visual task) or the primary motor cortex (for the motor task) were selected as a region of interest, and the amplitude of the BOLD response deflection from baseline (expressed as a percentage change in the signal) was compared between the CAA group and control group. Brain images and maps were aligned to the standardized space of the Montreal Neurological Institute brain to permit comparisons between groups in a common coordinate system. The sizes of the regions of activation in the groups were determined within specified regions encompassing primary visual cortex (for the visual task) and primary motor and sensory cortex (for the motor task) (see appendix e-1 for details). One patient with a hemorrhage affecting the primary motor cortex was excluded from analysis of the motor task.

Transcranial Doppler ultrasound measurement of cerebral blood flow responses to euoxic hypercapnia began with a routine diagnostic assessment to exclude significant intracranial stenoses (Spencer Technologies, Seattle, WA). Bilateral probes insonating the posterior cerebral artery and contralateral middle cerebral artery were fixed in place using a headset (Spencer Marc 600; Spencer Technologies). The left posterior cerebral artery second segment (P2) and right middle cerebral artery first segments were insonated. Five CAA and 4 control subjects did not have adequate bony windows and therefore could not undergo the assessment. Beat-to-beat blood pressure was monitored continuously via finger photoplethysmography (Finapres; Finapres Medical Systems BV, Amsterdam, the Netherlands). The hypercapnic test was administered using the technique of dynamic end-tidal forcing (DEF) using dedicated software (BreatheM 2.40; University Laboratory of Physiology, Oxford, UK).¹² Briefly, the subject breathed through a mouthpiece connected to the DEF system with their nose occluded. The DEF system uses a negative feedback loop to maintain partial pressure of end-tidal CO₂ (PETCO₂) and O₂ at desired levels independent of both the rate and depth of breathing. The hypercapnic test started with 10 minutes of air breathing to determine resting PETCO₂ and O₂ values. Subsequently, the hypercapnic test started with 2 minutes of euoxic isocapnic baseline where PETCO₂ was elevated to 1.5 mm Hg

Table 1 Characteristics of patients with CAA and controls

Characteristic	CAA (n = 18)	Control (n = 18)
Age, y	72.0 ± 7.0	69.8 ± 7.0
Sex, female	6	6
Hypertension	13 ^a	3 ^a
Taking antihypertensive	14 ^a	3 ^a
Diabetes	3	0
Coronary heart disease	2	1
Hypercholesterolemia	10	6
Current smoker	1	1
WMH volume, mL	27.2 (7.8, 50.6) ^a	4.3 (3.1, 8.4) ^a
No. of microbleeds	45 (5, 132) ^a	0 (0, 0) ^a

Abbreviations: CAA = cerebral amyloid angiopathy; WMH = white matter hyperintensity. Values are mean ± SD, number of participants, or median (25th percentile, 75th percentile). ^a $p \leq 0.05$ for difference between patients with CAA and controls.

above resting values. Next, PETCO₂ was increased to 6.5 mm Hg above resting values for 2 minutes while end-tidal partial pressure of O₂ was maintained euoxic. The test concluded with 2 minutes of euoxic isocapnic recovery. Data from the last 15 seconds of baseline and hypercapnia were averaged and used to calculate CO₂ reactivity as the percent change in blood flow velocity per mm Hg increase in exhaled CO₂: percent change in mean blood flow velocity/(hypercapnia PETCO₂ – baseline PETCO₂).

Occipital lobe VEPs were recorded using the Queen's Square standard electrode placement, consistent with American Clinical Neurophysiology Society guidelines.¹³ Subjects were seated 1.5 m from a monitor that presented a 2-Hz contrast-reversing black and white checkerboard pattern. One hundred responses were averaged and repeated at least once to ensure reproducibility. The amplitude of the P100 potential (microvolts) was calculated by determining the difference between the N75 and P100 peaks. VEP P100 amplitudes are known to correlate well with fMRI and ultrasound measures of brain metabolic activity.^{14,15}

Statistical analysis. The primary prespecified study hypothesis was that the amplitude of the BOLD response in the primary visual cortex would be lower in patients with CAA compared with controls. The study sample size was derived from preliminary work identifying blood flow velocity differences between CAA and controls on transcranial Doppler ultrasound.³ BOLD fMRI amplitudes, CO₂ reactivity index, and VEP P100 amplitudes were approximately normally distributed and were compared between groups by paired *t* tests according to the matched pair (case and control).¹⁶ Because the prevalence of hypertension differed between the groups, linear regression was used to determine whether the association between CAA and BOLD fMRI amplitude was independent of age, sex, or hypertension. Among patients with CAA, the associations between BOLD fMRI amplitude and each of WMH volume and number of microbleeds (log-transformed to normal distributions) were determined using the Pearson correlation coefficient, and displayed graphically as scatterplots with WMH volume and microbleed count graphed on a logarithmic scale because of right-skewed distributions. Analyses were done using SAS version 9.2 (SAS Institute, Cary, NC).

Standard protocol approvals, registrations, and patient consents. The study was performed with written consent from all participants and was approved by our institutional review board.

RESULTS Characteristics of the 18 patients with CAA and 18 age- and sex-matched controls are provided in table 1. Patients with CAA were 72 ± 7.0 years of age. Compared with controls, patients with CAA were more likely to be treated with anti-hypertensive medications.

The region of fMRI activation was smaller in patients with CAA than in controls for both visual (28.3 cm³ vs 41.5 cm³) and motor tasks (21.1 cm³ vs 61.3 cm³) (figure 1). The group average time courses of the BOLD fMRI response of the 50 most active voxels in the visual cortex are shown in figure 2. A reduced fMRI amplitude was observed in patients

Figure 1 Functional MRI responses in patients with CAA and controls

Group blood oxygen level-dependent functional MRI responses for the motor (left) and visual (right) tasks. Reduced functional MRI activation is observed for patients with CAA. Red-to-yellow color scale indicates the significance of activity, expressed as a z score ranging from 3.1 (red) to 6.0 (yellow). CAA = cerebral amyloid angiopathy.

Figure 2 Functional MRI BOLD responses in patients with CAA and controls

Group average time curves of BOLD fMRI signal in patients with CAA and controls, expressed as the percent change from baseline, in the 50 most active voxels in the primary visual cortex during the visual stimulation task. Percentage increase in BOLD fMRI signal is reduced in patients with CAA compared with controls. Error bars indicate the SEM. BOLD = blood oxygen level-dependent; CAA = cerebral amyloid angiopathy; fMRI = functional MRI.

with CAA. This was confirmed by *t* test; the amplitude of the BOLD fMRI response was 28% less in patients with CAA compared with controls ($3.57\% \pm 0.94\%$ vs $2.57\% \pm 1.05\%$, $p = 0.01$) (figure 3). By contrast, the BOLD fMRI amplitude response of the 50 most active voxels in the primary motor cortex was only 15% smaller in patients with CAA compared with controls ($2.24\% \pm 0.96\%$ vs $1.90\% \pm 0.73\%$, $p = 0.22$) (figure 3). Visual and motor BOLD amplitude responses were moderately correlated ($r = 0.42$, $p = 0.01$). The amplitude of the VEP P100 was the same in CAA compared with controls ($5.5 \pm 2.4 \mu\text{V}$ vs $4.8 \pm 2.8 \mu\text{V}$, $p = 0.45$).

The CO_2 reactivity index showed a trend toward lower vascular reactivity in the posterior cerebral artery, which supplies the occipital lobe ($1.76\% \pm 1.50\%$ per mm Hg in CAA compared with $3.30\% \pm 2.31\%$ per mm Hg in controls, $p = 0.08$), and in the middle cerebral artery ($2.40\% \pm 1.64\%$ per mm Hg in CAA compared with $3.56\% \pm 1.77\%$ per mm Hg in controls, $p = 0.10$).

The difference in the BOLD fMRI amplitude in the visual cortex between patients with CAA and controls remained significant in separate sensitivity analyses excluding 5 patients with CAA who had occipital hemorrhage, 3 patients with mild dementia, or 4 patients with CAA with inflammation, and in a multivariable analysis adjusting for antihypertensive medication use (table e-2). Patients with CAA with inflammation

Figure 3 BOLD response amplitude is lower in patients with CAA than in controls

BOLD fMRI amplitude responses are lower in patients with CAA than in controls in the visual task (A) ($p = 0.01$) but not the motor task (B) ($p = 0.22$). The horizontal bar indicates the mean response of the group. Significance testing is by paired *t* test. BOLD = blood oxygen level-dependent; CAA = cerebral amyloid angiopathy; fMRI = functional MRI.

had similar reduced visual BOLD fMRI responses as other patients with CAA (table e-3).

Within the patients with CAA, lower BOLD fMRI amplitude in the visual cortex correlated with a higher number of microbleeds ($r = -0.72$, $p = 0.001$) and higher volume of WMH ($r = -0.68$, $p = 0.002$) (figure 4). Correlations with BOLD fMRI amplitude in the primary motor cortex during the motor task were not as strong (for microbleeds: $r = -0.38$, $p = 0.18$; for white matter lesion volume: $r = -0.36$, $p = 0.18$). In this group of patients with CAA, WMH and microbleeds were not associated with age or hypertension in univariate analyses ($p > 0.30$ for all comparisons).

DISCUSSION Our data confirm 2 previous pilot studies suggesting decreased brain task-related blood flow reactivity in CAA,^{3,4} and provide new evidence to suggest that the physiologic basis of the reduced

Figure 4 Lower fMRI responses are correlated with higher WMH volume and microbleed count

In patients with CAA, lower BOLD fMRI activity in visual cortex is correlated with (A) higher WMH volume (normalized to average subject head size, see the Methods section for details) ($p = 0.002$) and (B) higher microbleed count ($p = 0.001$). The “ r ” indicates the Pearson correlation coefficient. Neither age nor hypertension was related to either WMH or microbleed count ($p > 0.05$ for all comparisons). BOLD = blood oxygen level-dependent; CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; fMRI = functional MRI; ICH = intracerebral hemorrhage; WMH = white matter hyperintensity.

signal is impaired vasodilation, not decreased metabolic activity. Additionally, our data are the first to suggest there is a gradient of increasingly impaired vasodilation from anterior (frontal) to posterior (occipital) brain regions that matches the known distribution of vascular amyloid deposition in CAA as identified pathologically¹⁷ and on PET amyloid imaging.^{18,19} Impaired vasodilation is highly correlated with higher WMH volume and higher microbleed counts, suggesting that it is an important feature of the disease and marker of CAA severity.

The combination of lower BOLD fMRI amplitude responses with normal VEP amplitudes implies

that there is decoupling of vascular and neuronal responses in CAA. Blood flow responses, as measured by BOLD fMRI amplitude, were reduced despite no detectable difference in cortical electrical potential generation, as measured by VEP. Therefore, the reduced BOLD response measured on fMRI reflects, at least in part, reduced delivery of blood flow due to impaired vasodilation rather than reduced blood flow due to lower metabolic rate of activity of the occipital lobe. To further ensure that we studied patients without significant occipital lobe neuronal dysfunction, we excluded patients with hemorrhages in the occipital pole, visual field defects, or poor visual acuity, and observed patients during the experiment to ensure that they attended well to the task. Two previous studies have found decreased occipital visual task-related blood flow responses in CAA and suggested they were caused by decreased vascular reactivity^{3,4}; however, the present study is the first to directly show neurovascular decoupling in patients with CAA.

The presence of impaired vasodilation in CAA is further supported by the strong trends toward reduced CO₂ reactivity measured in the posterior cerebral artery and middle cerebral artery. Because 5 subjects could not complete transcranial Doppler testing because of poor cranial windows, a recognized limitation of this technique,²⁰ our study was somewhat underpowered to detect a difference in CO₂ reactivity between CAA and controls at the conventional statistical threshold of $p < 0.05$. Additional larger studies will be needed to confirm the deficit in CO₂ reactivity suggested by the present study.

The principal limitation of the present study is the small sample size; nonetheless, we were able to confirm differences in BOLD fMRI signal change in CAA compared with controls and associations between BOLD fMRI signal change and microbleed count and WMH. However, larger studies will be needed to determine whether measures of vascular reactivity in CAA are associated with clinical manifestations of CAA such as recurrent lobar hemorrhage or cognitive impairment. PET amyloid imaging was not done in the present study; future studies should investigate whether regions of impaired vascular reactivity correlate with regions of increased amyloid deposition. We analyzed the amplitude of the BOLD fMRI response as our prespecified outcome; however, there is evidence that time to peak response is prolonged in CAA,⁴ and additional studies are needed to fully characterize the nature of abnormal blood flow responses in CAA, including which features best differentiate CAA from controls and which are most sensitive to change over time.

Future longitudinal studies are needed to identify when impaired vascular reactivity appears in CAA, how it changes over time, and whether changes in vascular reactivity predict brain injury and hemorrhage.

The marked impairment in vascular reactivity in CAA as well as the strong correlations with other markers of CAA-related brain injury suggests that impaired vascular reactivity is a core feature of the pathophysiology of CAA. The associations between the degree of impaired reactivity and the number of microbleeds and WMH volume, which were stronger than the correlation between microbleeds and WMH, suggest that impaired reactivity may be an early feature in CAA that precedes the development of either microbleeds or WMH. Studying presymptomatic and symptomatic CAA mutation carriers could facilitate an improved understanding of the temporal course of changes in CAA biomarkers; this approach was recently used to identify the temporal course of biomarker changes in hereditary Alzheimer disease.²¹

If impaired vascular reactivity is indeed an early characteristic of CAA and a mechanism of brain injury, then it could be used as either a surrogate marker or treatment target for clinical trials in CAA. Vascular reactivity could be an ideal surrogate marker for early-phase trials because this impairment in function might be reversible over short time periods, in contrast to WMH and hemorrhage, which are irreversible and would require significant follow-up time to record progression or incident events. Decreased blood flow delivery due to impaired vasodilation could contribute to microinfarction²² and ischemic white matter demyelination²³ in CAA and could be a marker of vessel-wall changes that eventually lead to decreased vascular integrity resulting in microbleeds and ICH.

AUTHOR CONTRIBUTIONS

Stefano Peca: participated in study design, collected and analyzed fMRI data, drafted sections of the manuscript, critically reviewed and revised the manuscript. Cheryl R. McCreary: participated in study design, collected structural MRI data, drafted sections of the manuscript, critically reviewed and revised the manuscript. Emily Donaldson, Gopukumar Kumarpillai, and Nandavar Shobha: performed subject assessments, critically reviewed and revised the manuscript. Karla Sanchez: analyzed MRI data for white matter lesions, critically reviewed and revised the manuscript. Anna Charlton: coordinated the study, critically reviewed and revised the manuscript. Craig D. Steinback, Andrew Beaudin, and Daniela Flück: acquired and analyzed transcranial Doppler ultrasound data, critically reviewed and revised the manuscript. Neelan Pillay: supervised acquisition and analysis of visual evoked potential data, critically reviewed and revised the manuscript. Gordon H. Fick: reviewed statistical output and advised on choice of statistical tests, critically reviewed and revised the manuscript. Marc J. Poulin: supervised acquisition and analysis of transcranial Doppler ultrasound data, critically reviewed and revised the manuscript. Richard Frayne: designed MRI acquisition protocols, critically reviewed and revised the manuscript. Bradley G. Goodyear: designed fMRI protocols, supervised acquisition and analysis of fMRI data, critically reviewed and revised the manuscript. Eric E. Smith: conceived of the study, secured study funding, participated in study design, drafted sections of the manuscript, critically reviewed and revised the manuscript.

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