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# Impaired dynamic cerebrovascular response to hypercapnia predicts development of white matter hyperintensities

Kevin Sam[a,b], John Conklin[b], Kenneth R. Holmes[c], Olivia Sobczyk[c], Julien Poublanc[b], Adrian P. Crawley[b], Daniel M. Mandell[b], Lakshmikumar Venkatraghavan[d], James Duffin[a,d], Joseph A. Fisher[a,c,d], Sandra E. Black[e,1], David J. Mikulis[b,*,1]

[a] Department of Physiology, The University of Toronto, Toronto, ON, Canada
[b] Division of Neuroradiology, Joint Department of Medical Imaging, University Health Network, Toronto, ON, Canada
[c] Institute of Medical Sciences, The University of Toronto, Toronto, ON, Canada
[d] Department of Anaesthesia, University Health Network, Toronto, ON, Canada
[e] L.C. Campbell Cognitive Neurology Research Unit, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

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ABSTRACT

*Purpose:* To evaluate the relationship between both dynamic and steady-state measures of cerebrovascular reactivity (CVR) and the progression of age-related white matter disease.
*Methods:* Blood oxygen level-dependent (BOLD) MRI CVR scans were acquired from forty-five subjects (age range: 50–90 years, 25 males) with moderate to severe white matter disease, at baseline and one-year follow-up. To calculate the dynamic ($\tau$) and steady-state (ssCVR) components of the BOLD signal response, the $P_{ET}CO_2$ signal waveform was convolved with an exponential decay function. The $\tau$ corresponding to the best fit between the convolved $P_{ET}CO_2$ and BOLD signal defined the speed of response, and the slope of the regression between the convolved $P_{ET}CO_2$ and BOLD signal defined ssCVR. ssCVR and $\tau$ were compared between normal-appearing white matter (NAWM) that remains stable over time and NAWM that progresses to white matter hyperintensities (WMHs).
*Results:* In comparison to contralateral NAWM, NAWM that progressed to WMH had significantly lower ssCVR values by mean (SD) 46.5 (7.6)%, and higher $\tau$ values by 31.9 (9.6)% (both $P < 0.01$).
*Conclusions:* Vascular impairment in regions of NAWM that progresses to WMH consists not only of decreased magnitude of ssCVR, but also a pathological decrease in the speed of vascular response. These findings support the association between cerebrovascular dysregulation and the development of WMH.


## 1. Introduction

In elderly individuals, magnetic resonance imaging (MRI) of cerebral white matter frequently shows patchy or confluent hyperintensity on T2-weighted images, termed "white matter hyperintensities" (WMHs) if they are of presumed vascular origin (Wardlaw et al., 2013). WMHs occur predominantly in the periventricular white matter, particularly around the horns of the lateral ventricles and in the centrum semiovale. Population-based studies show the prevalence of WMHs on MRI in elderly people to be 62–95% (Liao et al., 1997; Launer et al., 2006). Given this high prevalence in normally functioning elderly individuals, WMHs were initially considered benign. However, subsequent research showed that WMHs are associated with disability (Whitman et al., 2001; Blahak et al., 2009), cognitive decline (Verdelho et al., 2010), and progression to dementia (Schmidt et al., 2002; Gunning-Dixon and Raz, 2000). Nevertheless, the detailed pathophysiology of WMH progression remains poorly understood, and is the subject of this investigation.

The mechanisms leading to WMHs are complex. Age-related stenosis and hypoperfusion of medullary arterioles may cause low grade ischemic injury to deep white matter. In addition, impaired vascular autoregulation may contribute to the progression of WMHs in areas that are not well capillarized, predisposing white matter to hypoperfusion injury. Uh et al. (2010) found a reduction in both cerebrovascular reactivity (CVR) and cerebral blood flow (CBF) in regions of WMH compared to normal-appearing white matter (NAWM). They also noted that areas of WMH were characterized by significant blood-brain barrier leakage and abnormal diffusion MRI metrics.

* Corresponding author at: Toronto Western Hospital, Joint Department of Medical Imaging, McLaughlin Pavilion, 3rd Floor Room 431, 399 Bathurst St., Toronto, ON M5T 2S8, Canada.
*E-mail address:* mikulis@uhnres.utoronto.ca (D.J. Mikulis).
[1] Please note that Drs. Sandra E. Black and David J. Mikulis wish to be listed as co-senior authors.

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CVR is defined as the change in blood flow in response to a vasoactive stimulus. We have established a quantitative approach to measuring CVR using blood oxygen level-dependent (BOLD) MRI as a surrogate for blood flow and controlling the end-tidal partial pressures of carbon dioxide ($P_{ET}CO_2$) and oxygen ($P_{ET}O_2$) to provide a standardized vasoactive stimulus (Spano et al., 2013). By applying a square wave change in $P_{ET}CO_2$ during BOLD imaging, we are able to parse CVR into two different metrics: 1) steady-state component of CVR (ssCVR), which occurs after the vasodilatory response to the $CO_2$ stimulus is complete. Mathematically, it is the asymptote of the exponential rise in the BOLD signal in response to a rapid (step change) in arterial $PCO_2$ and 2) Tau ($\tau$), which represents the rate constant of this exponential and is a metric indicating how rapidly a vascular bed can respond to a step change in $PCO_2$. It is of physiological interest as it is an indicator of vascular compliance (Poublanc et al., 2015).

We measured these metrics in areas of WMH as well as in NAWM that progress to WMH on follow-up imaging, with particular attention to the speed of the vascular response. Supporting this approach is a recent study that found that the cerebral deep white matter has prolonged $\tau$ and reduced ssCVR compared to grey matter (Poublanc et al., 2015). We hypothesized that reduced ssCVR and prolonged $\tau$ would occur in WMHs as well as NAWM that progressed to WMH with time, when compared to NAWM that did not progress to WMH.

## 2. Methods

### 2.1. Subject recruitment and assessment

This prospective bi-centric study examined elderly subjects with moderate to severe WMH at two time points set one year apart (baseline and follow-up). This study conformed to the standards set by the latest revision of the Declaration of Helsinki and was approved by the Research Ethics Board of the University Health Network and Research Ethics Board of Sunnybrook Health Sciences Centre. Written informed consent was obtained from all participants. Subjects were recruited from outpatient neurology clinics at Toronto Western Hospital (TWH) and Sunnybrook Health Sciences Centre (SHSC). Magnetic resonance angiography (MRA) or computed tomography angiography (CTA) and T2-weighted fluid-attenuated inversion recovery (FLAIR) images of all patients were screened by experienced neuroradiologists (D.J.M. & D.M.M.). Subjects were enrolled based on the following inclusion criteria: (1) no recent white matter infarct (patients were excluded if they had a previous DWI positive white matter infarct within the 3 months preceding study enrolment); (2) no prior cortical infarct >2 cm or cavitary white matter lesion >2 cm; (3) over the age of 50; (4) MRI white matter disease burden ≥ Fazekas Grade 2; (5) no hemodynamically significant (i.e., >50%) ICA or vertebrobasilar stenosis on CTA or MRA; (6) no evidence of dissection; (7) no history of pulmonary or cardio-embolic disease.

Subjects with motion artifacts on BOLD images were excluded. Forty-five subjects (age range, 50 to 91 years; 25 males and 20 females) with moderate to severe WMHs met the inclusion criteria and were considered in the subsequent analysis (see Table 1 for subject characteristics).

**Table 1**
Baseline characteristics of subjects. Abbreviations: MoCA = Montreal Cognitive Assessment; WMH = white matter hyperintensities.

| Parameter | Value (total $n = 45$) |
|---|---|
| **Demographics** | |
| Age, in years, mean (SD) | 74 (9.4) |
| Men, n (%) | 25 (56) |
| Baseline WMH volume, ccs (SD) | 32 (25) |
| MoCA, mean (SD), 6 missing values | 25 (4) |
| **Vascular risk factors, n (%)** | |
| Ischemic stroke | 12 (27) |
| Transient ischemic attack | 6 (13) |
| Coronary artery disease | 7 (16) |
| Hypertension | 23 (51) |
| Hypercholesterolemia | 19 (42) |
| Diabetes mellitus | 3 (7) |
| Current smoking | 3 (7) |
| Obstructive sleep apnea | 5 (11) |

### 2.2. Image acquisition

Subjects underwent MRI scans on either a 3-Tesla GE system (Signa HDx platform, GE Healthcare, Milwaukee, Wis) or a 3-Tesla Philips Achieva system (Philips Medical Systems, Best, Netherlands) using an eight-channel phased array head coil. Subjects were asked to refrain from heavy exercise and drinking alcohol or caffeine on the day of each scan. The image acquisition parameters were as follows, with values provided for SHSC/TWH: T1-weighted 3D spoiled gradient echo sequence [slice thickness = 1.2 mm (SHSC)/1.5 mm (TWH); no interslice gap; matrix size = 256 × 256; field of view = 22 × 22 cm; nominal voxel size = 0.85 × 0.85 × 1.2/0.85 × 0.85 × 1.5 mm; flip angle = 8 / 20°; TE = 2.3/3 ms; TR = 7.8/9.5 ms] and BOLD fMRI using a T2*-weighted echoplanar imaging gradient echo sequence [slice thickness = 3.0/5.0 mm; field of view = 24 × 24 cm; matrix size = 64 × 64; nominal voxel size = 3.75 × 3.75 × 3/3.75 × 3.75 × 5 mm; flip angle = 85/90°; TE = 30 ms; TR = 2000 ms].

### 2.3. CVR measurement

CVR is defined as the change in blood flow in response to a vasoactive stimulus. BOLD MRI was used as a surrogate of blood flow (Poublanc et al., 2015; Sobczyk et al., 2015; Sam et al., 2015), and an abrupt step increase in the end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) was used as the vasoactive stimulus (Han et al., 2011). CVR was calculated as % change in BOLD/Δ $P_{ET}CO_2$, and a color scale ranging from blue to red was used to identify the magnitude of CVR. Negative CVR values were represented in shades of blue, and positive CVR values were represented as shades of yellow, orange, and red.

### 2.4. Vasodilatory stimulus (gas manipulation, end-tidal $pCO_2$ and $pO_2$ manipulation)

Control of end-tidal partial pressures of carbon dioxide and oxygen ($P_{ET}O_2$) was achieved using an automated gas blender that adjusts the gas composition and flow to a sequential gas delivery breathing circuit (RespirAct™, Thornhill Research Inc., Toronto, Canada) as previously described (Slessarev et al., 2007; Fierstra et al., 2013). The $P_{ET}CO_2$ sequence used during BOLD measurements was 40 mmHg for 60 s (normocapnia), followed by an abrupt hypercapnic step change to $P_{ET}CO_2$ of 50 mmHg for 90 s, a return to baseline for 90 s, a second hypercapnic step change for 120 s, and a return to baseline (Poublanc et al., 2015). Normoxia ($P_{ET}O_2$ ~110 mmHg) was maintained throughout.

### 2.5. Generating steady-state CVR and $\tau$ maps

$P_{ET}CO_2$ was first synchronized with the whole brain average BOLD signal using MATLAB software (Mathworks, Natick, Massachusetts, USA) to compensate for delays in breath sampling and blood flow transit time from the pulmonary to the cerebral circulation. BOLD responses were parsed into steady-state (ssCVR) and dynamic ($\tau$) components using a convolved $P_{ET}CO_2$ stimulus instead of the measured $P_{ET}CO_2$, as previously described (Poublanc et al., 2015). Briefly, the BOLD response was modeled as the $P_{ET}CO_2$ convolved with an exponential decay function [$\exp(-t/\tau)$] representing the hemodynamic response, where $t$ is time and $\tau$ is the time constant of the vascular response. $\tau$ was allowed to vary from 2 to 100 s in 2 s increments, giving rise to 50 convolved signals. The $\tau$ of the convolved $P_{ET}CO_2$ with the highest Pearson correlation