Neurobiology of Aging 65 (2018) 77–85

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Quantitative cerebrovascular pathology in a community-based cohort of older adults

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ARTICLE INFO

Article history:
Received 28 July 2017
Received in revised form 8 January 2018
Accepted 9 January 2018
Available online 31 January 2018

Keywords:
Aging
Cerebral blood flow
Cerebrovascular disease
ASL
White matter disease
BOLD contrast
CVR

ABSTRACT

Cerebrovascular disease, especially small vessel pathology, is the leading comorbidity in degenerative disorders. We applied arterial spin labeling and cerebrovascular reserve (CVR) imaging to quantify small vessel disease and study its effect on cognitive symptoms in nondemented older adults from a community-based cohort. We evaluated baseline cerebral blood flow (CBF) using arterial spin labeling and percent signal change as a marker of CVR using blood-oxygen level-dependent imaging following a breath-hold stimulus. Measurements were performed in and near white matter hyperintensities, which are currently the standard to assess severity of vascular pathology. We show that similar to other studies (1) CBF and CVR are markedly reduced in the hyperintensities as well as in the tissue surrounding them, indicating susceptibility to infarction; (2) low CBF and CVR are significantly correlated with poor cognitive performance; and (3) in addition, compared to a 58.4% reduction in CBF, larger exhaustion (79.3%) of CVR was observed in the hyperintensities with a faster, nonlinear rate of decline. We conclude that CVR may be a more sensitive biomarker of small vessel disease than CBF.

1. Introduction

Small vessel cerebrovascular disease is a common occurrence in aging and related disorders such as Alzheimer's disease (AD) (Al-Bachari et al., 2014; Pantoni, 2010; Wardlaw et al., 2013). It is a major contributor to mixed dementia pathology and has similar risk factors as those for cognitive decline (White et al., 1996). Typical cerebrovascular pathology associated with dementia consists of cortical and subcortical infarcts, microbleeds, increased perivascular spaces, reduced perfusion, and tissue atrophy (Bots et al., 1997; Esiri et al., 1999). Histopathological studies show that individuals with AD show increased basal membrane thickening, collagenous deposits, and damaged pericytes in the microvasculature compared to age-matched older adults (Farkas and Luiten, 2001). The resulting vascular insufficiency causes neuronal damage and, subsequently, cognitive decline, which progresses slowly. Therefore, sensitive methods are needed to monitor the advancing vascular pathology to subsequently arrest disease progression.

Recent advances in neuroimaging have provided tremendous insights into small vessel disease, especially by distinguishing normal-appearing brain matter from pathological tissue. One important imaging measure is the volume of white matter hyperintensities (WMHs), that is, regions of brain tissue, which appear bright on a T2-weighted magnetic resonance imaging (MRI) scan, in deep white matter tissue (Au et al., 2006; Prins and Scheltens, 2015; de Groot et al., 2000). WMHs are thought to occur because of chronic hypoperfusion as a result of the small vessel disease. A higher volume of WMHs is associated with poorer cognitive outcome in older adults (Bahrani et al., 2017; Brickman et al., 2009; van Dalen et al., 2016; Prins and Scheltens, 2015). It is also associated with poor executive function, especially processing speed for executive tasks (Au et al., 2006; Smith et al., 2011). Although antihypertensive treatments manage to slow their development (Dufouil et al., 2005; Liao et al., 1996), these hyperintensities likely represent tissue that is damaged and is currently unresponsive to vascular therapies.

Cerebral blood flow (CBF) imaging is another imaging marker that can detect ischemic tissue (Detre et al., 1994; Wong et al., 1999). Similarly, cerebrovascular reserve (CVR) mapping using

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https://doi.org/10.1016/j.neurobiolaging.2018.01.006

Table 1
Demographic information (n = 28) and summary statistics

Description	Mean	Standard deviation
Age (years)	76.4	7.1
Gender	13 M/15 F	
APOE-ε4 carriers	5	
Mean arterial pressure (mm Hg)	91	11
Heart rate (bpm)	65	9
MMSE	28	1
Trails A	30	11
Trails B	80	31
Logical memory	15	3
White matter hyperintensities (% of total ICV)[a]	0.21	0.21

Key: APOE, apolipoprotein E; ICV, intracranial volume; MMSE, Mini–Mental State Examination.
[a] White matter hyperintensities burden range: 0.01–0.8, includes both periventricular and deep white matter hyperintensities.

hypercapnia induced by acetazolamide, breath-hold, or manipulating inhaled gas can identify tissue with low or exhausted vascular reserve (Bright and Murphy, 2013; Gückel et al., 1996; Kastrup et al., 1998). Reduced CBF reflects presence of primary vasculopathy such as atherosclerosis of large vessels, microvascular injury (basal membrane thickening, pericytic degeneration, and collagen deposits, mentioned earlier), or a reduced metabolic demand due to neuronal dysfunction/loss (Farkas and Luiten, 2001). A reduced CVR may indicate either microvascular injury or an exhausted reserve. We believe that a combinatorial approach may provide better understanding of the underlying vascular physiology. One study shows that CBF is reduced in the tissue surrounding the WMHs and does indeed indicate tissue at risk of infarction as seen on a longitudinal scan 2 years later (Promjunyakul et al., 2015). In general, WMHs have been extensively studied using CBF.

However, CVR measurements in WMHs and direct comparisons of sensitivity of CBF and CVR to detect progression of small vessel disease are limited with variable results. Sam et al. (2016) measured white matter (WM) integrity, T2, and CBF in WMHs and normal-appearing WM and found that reductions in CVR preceded hyperintensity development in normal WM. Another contrast-based study showed reduced baseline CBF and blood volume as well as reduced changes in CBF and blood volume in WMHs during an acetazolamide challenge, compared to normal-appearing WM (Marstrand et al., 2002). The cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy study measured similar baseline CBF and CVR (with acetazolamide) and reduced CVR (not CBF) in WMHs (Liem et al., 2009). Reduced CBF and CVR in the WMHs, compared to normal-appearing WM, have been reported in a wide variety of diseases such as type 2 diabetes (Novak et al., 2006), small vessel disease (Molina et al., 1999), and AD (Makedonov et al., 2013). In this study, we compare CBF and CVR to assess which biomarker is more sensitive to small vessel disease pathology and cognitive function in a community-based cohort of older adults.

Specifically, we explore CBF and CVR measurements as markers of ischemic tissue in and around the WMHs. We believe that these markers have the potential to detect normal-appearing tissue that is susceptible to ischemic events and which has a high risk of developing into hyperintensities. We hypothesize that, similar to CBF, CVR will also be reduced in the regions of the WMHs. It will also be lower in the tissue surrounding the hyperintensities. We used arterial spin labeling (ASL) to measure CBF and breath-hold blood-oxygen level-dependent (BOLD) imaging to measure CVR in a community-based cohort of older adults (Bright and Murphy, 2013; Detre et al., 1994). We performed comparisons of CBF and CVR in gray matter (GM), normal-appearing WM, and the hyperintensity regions. Correlation with overall cognitive and executive function was also assessed. The advantage of this study is that we applied a noninvasive approach to measure CBF and CVR. Furthermore, we used a simple breath-hold paradigm, which does not require any specialized equipment.

2. Material and methods

Thirty older adults (76.4 ± 7.1 years, 13 M/15 F) were recruited from the community-based Adult Changes in Thought cohort (ACT; Montine et al., 2012). ACT is a population-based study of dementia risk designed to prospectively examine the incidence of AD and dementia, as well as risk factors of these diseases, in a cohort representative of the Group Health Cooperative in Seattle. Nondemented subjects, who are cognitively normal or mildly cognitively impaired with no effect on daily living, are included in this cohort. All participants provided written informed consent to participate in the present study, which was conducted according to the Declaration of Helsinki and subsequent revisions. The study was approved by the Institutional Review Board at University of Washington, Seattle. Demographic data are shown in Table 1. All subjects underwent the National Alzheimer Coordinating Center Uniform Data Set cognitive battery including Trails A, Trails B, Mini–Mental State Examination (MMSE), and logical memory (Beekly et al., 2007; Folstein et al., 1975; Mack et al., 1992; Tombaugh, 2004; Wechsler, 1945, 2014). Cognitive diagnosis was adjudicated during a clinical case consensus diagnosis conference consisting of neurologists, psychiatrists, neuropsychologists, and other study clinicians. These subjects underwent both a pseudo-continuous ASL (pCASL) scan to measure CBF and a breath-hold BOLD MRI for measuring CVR on a Philips 3T Achieva scanner with a 32-channel SENSitivity Encoding (SENSE) coil reception. Of these, 2 subjects had low MMSE scores (20 and 22) and hence were excluded from this study.

2.1. Imaging

Each session included a structural T1-weighted image using a 3D-turbo field echo acquisition with TR/TE = 9.2/3.5 ms, resolution = $1 \times 1 \times 1$ mm^3 for image registration and segmentation purposes. FLuid Attenuated Inversion Recovery (FLAIR) images were acquired to detect WMHs with the following parameters: repetition time (TR)/inversion time (TI)/ echo time (TE) = 5000/1800/293 ms, resolution = $1 \times 1 \times 1$ mm^3. Pseudo-continuous ASL imaging parameters were TR/TE = 5000/35 ms, 30 pairs of control and label images, resolution = $3.5 \times 3.5 \times 5$ mm^3, background suppression (BS1 = 1710 ms and BS2 = 2860 ms), label plane 80 mm below the center of the imaging volume, labeling duration, τ = 1650 ms, post–labeling delay, ω = 2000 ms, total acquisition time = 5 minutes. For the 6-minute breath-hold BOLD MRI implementation, subjects were trained outside the scanner to perform 6 paced breaths followed by a breath-hold for 10–15 seconds (as feasible for the subject) and then by free breathing. The breath-hold was initiated at the end of an exhale (Bright and Murphy, 2013). Blocks of paced breathing, breath-hold, and free breathing were repeated for a total of 6 times. Other imaging parameters were resolution = $3.5 \times 3.5 \times 3.5$ mm^3, TR/TE = 2500/35 ms, dynamics = 122, and SENSE factor = 2. The same stimulus paradigm was repeated inside the scanner. The breathing pattern of the subject was recorded using respiratory bellows and used as the time course for analyses. The time course was also used to determine if subjects followed the breathing instructions inside the scanner.

2.2. Analyses

In order to quantify CBF, the pCASL perfusion weighted images were motion corrected and registered to the first dynamic image