Autoregulation of White Matter Cerebral Blood Flow to Arterial Pressure Changes in Normal Subjects

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Abstract

Endothelial dysfunction causing impaired cerebrovascular vasodilatory capacity in response to reduced blood pressure has been proposed as a mechanism of white matter (WM) disease development. This study investigated autoregulation of CBF to blood pressure reduction in WM and gray matter (GM) in normal subjects recruited as controls for a study of cerebrovascular function in human immunodeficiency virus positive subjects. They underwent baseline CBF and oxygen extraction fraction measurement by MRI before and after mean arterial pressure (MAP) reduction. Autoregulatory Index (AI) was computed as CBF AI = %CBF change/% MAP change. Thirty of 44 subjects achieved target MAP reduction. MAP was reduced -13.65 ± 2.35 (range 10 to 20) %. WM AI of -0.61 ± 1.23 was significantly more negative than GM AI of 0.02 ± 0.44 (paired t test, p= 0.016). WM CBF fell (paired Wilcoxon, p= 0.03) whereas GM CBF did not change (paired Wilcoxon, p=0.92). WM AI was different from 0 (p=0.011, one-sample t-test vs 0), whereas GM AI was not (p=0.913, one-sample t-test vs 0). These data demonstrate that maintenance of CBF to 10-20% reductions in MAP is less effective in WM than in GM. This may put WM at higher risk for ischemic damage.

NEWS AND NOTEWORTHY

To our knowledge, this is the first study of white matter autoregulation of CBF to sustained reductions of arterial pressure in human subjects.

INTRODUCTION

Through compensatory vasodilation and vasoconstriction, the physiological mechanism of cerebral autoregulation normally maintains cerebral blood flow (CBF) within a narrow range in the face of 20-30% fluctuations cerebral perfusion pressure (CPP). Major increases and decreases in CBF occur with increases and decreases in CPP outside these bounds [1,2]. Responses of CBF to changes in CPP can be assessed directly by quantitative measurements of CBF or indirectly by measurements of arterial blood flow velocity or by reciprocal changes in venous blood oxygenation [2-7]. Changes in CPP can be monitored from spontaneously occurring fluctuations or induced by altering systemic mean arterial pressure (MAP) through pharmacological or other interventions.2,5,6 Cerebral small vessel disease (CSVD) is a group of neuropathological processes caused by dysfunctions of small blood vessels in the brain. Disease of these vessels is responsible for primary intracerebral hemorrhages and discrete small cerebral infarcts (lacunar infarcts) in the deep gray nuclei and white matter. In addition, CSVD causes more diffuse widespread white matter (WM) lesions referred to as leukoaraiosis or white matter hyperintensities (WMH), which are characterized by demyelination, axonal loss and gliosis without frank infarction [8,9].

Endothelial dysfunction has been proposed to play a key role in development of CSVD [9-11]. Endothelial dysfunction can cause arterioles to vasodilate poorly in response to reductions in blood pressure potentially causing ischemic damage. Support for this idea comes from studies showing impaired CBF vasodilatory responses to hypercapnea in WM in patients with WMH [12-15]. However, these studies do not provide specific data on WM autoregulation of CBF since cerebrovascular responses to carbon dioxide can be dissociated from autoregulatory responses to changes in MAP [16-18]. Specific data on WM autoregulation to changes in CPP are sparse [19-21].

To directly measure autoregulation of CBF in WM in response to reduction in MAP, we have adapted to magnetic resonance imaging (MRI) a procedure originally developed for positron emission tomography and now report results from 30 normal subjects [6,20,22].
MATERIALS AND METHODS

Participants

Subjects were recruited as age and sex matched normal controls who had tested negative for the virus for a study of cerebrovascular function in adults living with the human immunodeficiency virus. Exclusion criteria were: known history of migraine, stroke or TIA, radiological evidence of cerebral infarcts on MRI, low MAP (< 80 mm Hg) at baseline, concurrent treatment with specific antihypertensive alpha-1 receptor blockers (doxazosin, terazosin, prazosin) or hydralazine, pregnancy, standard MRI contraindications (e.g., claustrophobia, history or documentation of implanted ferromagnetic material or medical devices such as cardiac pacemaker), known advanced aortic stenosis, known allergy to nicardipine, resting heart rate < 60 or > 130 beats/minute, significant atrioventricular conduction abnormalities (2nd or 3rd degree AV block) on baseline EKG, history of internal carotid artery stenosis/occlusion, and baseline MR brain revealing abnormal areas ≥ 1.5 cm on FLAIR scout image. For this analysis, two subjects with hypertension were excluded as well.

Magnetic Resonance Imaging

All MR measurements were acquired on a 3T whole-body MR scanner (Trio, Siemens Healthcare, Erlangen, Germany). MR perfusion images were acquired with pseudo-continuous arterial spin labeling (pCASL) [23,24]. Label and control images were acquired alternately with a single shot gradient echo acquisition. The total labeling and control pulse durations were 2 seconds. A post labeling delay time of 1000 ms between the labeling or control pulses and the image acquisition was utilized. The labeling plane was placed 80 mm inferior to the imaging center. FOV was 220 mm² and matrix size was 64×64. Sixteen slices with a slice thickness of 5 mm without interslice gaps were acquired. TR/TE= 4000/11 msec. Forty pairs of label and control images were acquired. The total data acquisition time was 5 minutes and 20 seconds. The labeling and control images were averaged separately and a low pass Gaussian filter with a full-width-half maximum (HWHM) of 11.4 mm (about 3.3 pixels) was utilized to improve signal to noise ratio (SNR). Quantitative CBF maps were calculated similar to a published method [25].

An asymmetric spin echo (ASE) single shot echo planar imaging (EPI) sequence was utilized to measure oxygen extraction fraction (OEF). OEF = [(SaO2-SvO2)/SaO2] where SaO2 is the arterial oxygen saturation and SvO2 in the venous oxygen saturation. An ASE EPI sequence is a variation of a single shot SE EPI sequence allowing variable time intervals between the π/2 and π pulses. The TE is the echo time, where τ is the time interval between the τ pulse and TE/2. By varying τ while keeping TE constant, susceptibility-induced magnetic field changes can be evaluated. The relaxation rate R2' is proportional to the product of the concentration of deoxyhemoglobin and the venous cerebral blood volume (vCBV). OEF can be measured if both R2' and vCBV can be acquired. Details of this method can be found in previous publications [26-28].

Each session included a high resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) imaging with voxel size of 1×1×1 mm³ for anatomical reference for subsequent image registration and normalization.

MAP Reduction

MAP reduction was carried out in the scanner suite. A nurse, physician and MRI technician were at the bedside during the entire period of study lasting approximately 2 hours. Blood pressure was measured with an automatic external cuff every 5 minutes. Each participant was also connected to a MRI compatible electrocardiogram (ECG) machine and pulse oximeter. An initial MRI scan (FLAIR scout image) was obtained to ascertain MRI eligibility. Baseline CBF and OEF MRI scans were performed. MAP was then lowered with IV nicardipine infusion starting at 2.5 mg/hr and then adjusted every 10 min +/- 1.25 mg/hr to a maximum of 15 mg/hr to achieve a target MAP that was lower by ≥ 10% but no more than 15% of the baseline value. After the MAP was stable for 10 minutes, MRI was then repeated to measure CBF and OEF. IV nicardipine was discontinued and participants were monitored (ECG, BP and heart rate) for an additional 30 minutes. Once the monitoring parameters returned to baseline, each participant was discharged.

Image Analysis

The International Consortium for Brain Mapping (ICBM, McConnell Brain Imaging Centre, Montreal, Canada) template was utilized as an atlas to define regions of interest (ROIs). A nonlinear symmetric diffeomorphic registration algorithm was utilized for aligning atlas T1 to each participant patient’s T1 images (ANTS, PICSL, Philadelphia, PA, USA) [29,30]. A six-parameter rigid image registration was performed to align pCASL, ASE, and T1 images from the same participants across all scans using FMRIB Software Library (FSL) version 3.2 (Oxford, UK). T1 images of each participant subject were segmented into WM, gray matter (GM), and cerebrospinal fluid using the Markov Random Field-based tissue segmentation approach provided in FSL 3.2 [31]. Regions of interest (ROIs) were manually defined to cover all acquired slices in both hemispheres. For each subject, the GM and WM masks generated from T1 segmentation were utilized to obtain CBF and OEF from the WM, and GM Possible subject movement was corrected by Analysis of Functional Neuroimage software. Each region was manually delineated on high-resolution T1 images.

Measurement of Autoregulation

Autoregulation was measured by the Autoregulatory Index (AI) for WM and GM. AI= - (%Change in CBF)/(%Change in MAP) [32,33]. We used the minus sign so that a reduction in CBF with the reduction in MAP will result in a negative number.

Statistical Analysis

Data sets were inspected for outliers. All data sets were tested with the Shapiro-Wilk test for normality and Levene’s test for homogeneity of variances. Data sets that did not exhibit a normal/Gaussian distribution and homogeneous variances were analyzed with non-parametric equivalent tests. The primary analysis was the comparison of AI in WM to AI in GM by paired t-test with the threshold for statistical significance set at p = 0.05. Additional explanatory analyses were performed. The p-values
for these analyses are presented without correction for multiple comparisons and should be interpreted with this limitation. Statistical calculations were performed using R 4.0.2. (www.r-project.org, downloaded 8/19/20). Unless otherwise stated, values are reported as mean ± standard deviation.

This study was approved by the University of North Carolina Chapel Hill Institutional Review Board. All participants provided written informed consent before participating.

RESULTS

Forty-four normal subjects without hypertension were enrolled. Fourteen failed to achieve minimum target MAP reduction at the maximum dose of nicardipine. Thirty completed the blood pressure reduction protocol. There were 29 men and one woman. Mean age was 29 years with range from 20-50. They were free of hypertension, diabetes mellitus and heart disease.

MAP was reduced -13.65 ± 2.35 (range 10 to 20)%; WM AI of -0.61 ± 1.23 was significantly more negative than GM AI of 0.02 ± 0.44 (paired t test, p= 0.016) (Figure 1). WM CBF fell between baseline and reduced MAP (paired Wilcoxon, p= 0.03) whereas GM CBF did not change (paired Wilcoxon, p=0.92). WM AI was different from 0 (p=0.011, one-sample t-test vs 0), whereas GM AI was not (p=0.913, one-sample t-test vs 0).

There was substantial inter-subject variability in both WM AI and GM AI. The coefficients of variation for the individual pairs of WM and GM CBF at baseline and during MAP reduction were 11.5 ± 7.3% and 7.6 ± 6.0% respectively. To determine if these variable changes in CBF were accompanied by the expected physiological reciprocal changes in OEF, we assessed the degree of correlation between the individual per cent changes in CBF and per cent changes in OEF for WM and GM (Figures 2,3) (https://figshare.com/s/c6760a1f6c3337b70c90f DOI 10.6084/m9.figshare.13246733). Correlation was poor for both WM (Spearman rho=0.25, p=0.17) and GM (Spearman rho=0.06, p=0.75).

DISCUSSION

In this study of 30 normal subjects, we have demonstrated that mean WM AI is negative and significantly lower than mean GM AI for the same decrement in MAP. Accompanying the mean negative WM AI, there was a decrease in WM CBF and WM AI was less than zero. There was no change in GM CBF and GM AI was not different from zero, indicating effective maintenance of GM CBF. These data demonstrate that maintenance of CBF in WM by compensatory vasodilation was less effective than in GM during these MAP decreases. Comparable findings of worse vasodilatory cerebrovascular reactivity in WM than GM in response to hypercapnia have been reported [10,34,35] Worse autoregulation in WM could make WM more susceptible than GM to ischemic damage during episodes of reduced CPP due to systemic arterial hypotension.

Previous human studies of responses of WM CBF to changes in blood pressure are so different in subjects and/or methodology from the present study that comparisons are difficult. Matsushita et al measured the response of whole brain CBF to induced arterial hypotension in 51 hypertensive patients with previous strokes. Impaired whole brain autoregulation was significantly more prevalent in patients with more severe periventricular WM lesions but no specific data are provided on WM CBF [19]. Zazulia et al., reported no change in regional CBF in areas of WMH in eight patients with Alzheimer’s disease after 9-16% reduction in MAP [20]. Neither study provided data from normal control subjects. Horsfield and colleagues measured the cerebral circulatory response during the first minute after a sudden transient drop in MAP of 19% ± 11% induced by thigh cuff deflation using blood-oxygen dependent magnetic resonance imaging signal as a surrogate for CBF. They reported a greater initial signal drop in gray matter (1.81% ± 0.67%) than in white matter (1.18% ± 0.59%; p=0.001, d= 1.75) with white matter exhibiting a significantly faster recovery. In both, signal returned to baseline within 20 seconds and both data after one minute are provided [21]. Our CBF measurements were made after 10
minutes of steady-state MAP reduction.

We chose a target reduction in MAP of 10-15% of the baseline to remain within the normal autoregulatory range. Studies in anesthetized experimental animals during induced hypotension show an autoregulatory plateau in WM similar to that of GM with the lower limit at approximately 60 mmHg, less than 50% of baseline MAP. Neither of these studies compared the changes in WM CBF to GM CBF within the plateau range [36,37]. We measured CBF at only two levels of MAP. Since GM CBF remained constant, this was within the autoregulatory range for GM. However, we cannot reliably distinguish whether the reduced WM CBF was due to a lower WM AI within the autoregulatory plateau or a higher lower limit of WM autoregulation such that the second measurement was performed below this lower limit. In either case, these finding still demonstrate that there is less effective maintenance of CBF in WM during these modest changes in MAP.

IV nicardipine infusion was chosen as the pharmacological agent to lower MAP as it is easily titrated to desired BP target with no correlation between patient’s weight and dose response [38]. Minimal dose adjustments are required to achieve and maintain therapeutic effect within a narrow range [39]. No detrimental antihypertensive effects have been reported in patients ≥65 years [38]. Additionally, nicardipine has no significant effect on intracranial pressure, does not decrease heart rate, has no detrimental effects on the cardiac conduction system, and is not associated with coronary steal [38]. Adverse events reported are generally not serious, and most are expected consequences of vasodilation. In this study, we encountered no adverse events. We have had considerable experience using this drug to study
autoregulation with positron emission tomography in patients with ischemic stroke, intracerebral hemorrhage and Alzheimer’s disease without serious adverse events.

As noted by others, we found substantial variability in the measurements of AI in both GM and WM [7,32]. Measurement variability can be due to measurement imprecision and biological variability. Under the conditions of stable cerebral metabolic rate of oxygen that have been demonstrated during induced hypotension in normal human subjects, biological variations in CBF will be accompanied by reciprocal changes in OEF [3,5,40-43]. We found no such relationship. Furthermore, the coefficients of variation for the paired CBF measurements were within the ranges reported for intra-subject test-retest variability [44]. This leads us to conclude that measurement imprecision is an important contributor to the variability in measured AI.

One of the limitations of our study is that it included 29 men and only one woman. This was a consequence of sex matching to the experimental group of people living with human immunodeficiency virus. We do not know if these findings are sex specific to males. A second limitation is the absence of pCO2 monitoring. Arterial pCO2 affects the rapidity of the CBF response to induced hypotension but CBF returns to normal within 10 seconds with pCO2 22-47 mm Hg [4]. Given the time course of these experiments, this effect would not be manifest. Schmidt et al determined that the lower limit of whole brain autoregulation to induced hypotension was not significantly different whether or not corrected for pCO2 [5].

In summary, we have demonstrated adaptation to MRI of method for studying autoregulation of CBF to arterial pressure changes in WM in normal subjects. Given the data on the safe application of the original method with positron emission tomography in ischemic stroke, intracerebral hemorrhage and Alzheimer’s disease, this method is practically applicable for study of cerebral small vessel disease and other conditions affecting WM [6,20,22]. Furthermore, in normal subjects, these data demonstrate that maintenance of CBF in WM to 10-20% reductions in systemic arterial pressure is less effective that data demonstrate that maintenance of CBF in WM to 10-20% healthy brain assessed by magnetic resonance imaging. PLoS One. 2009; 285: 191-194.

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REFERENCES


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