SUPPLEMENTAL MATERIAL

Title: Oxygen metabolic stress and white matter injury in patients with cerebral small vessel disease
Cover Title: Regional ischemia in cerebral small vessel disease

Authors: Peter Kang, MD, MSCI [1*], Chunwei Ying, BS [3]*, Yasheng Chen, DSc[1], Andria L. Ford, MD, MSCI [1,2†], Hongyu An, DSc, [1,2,3†], Jin-Moo Lee, MD, PhD, [1,2,3†]

[1] Department of Neurology, Washington University School of Medicine
[2] Mallinckrodt Institute of Radiology, Washington University School of Medicine
[3] Department of Biomedical Engineering, Washington University
* First co-authors
† Senior co-authors

Supplemental Tables

Supplementary Table I. Participant characteristics for the cohort used to generate the watershed region of interest.

	Variables	**Watershed ROI Cohort (n=32) ***
Demographics	Age (years, median, IQR)	37 (29.3 – 49.8)
	Female (n, %)	18 (56.3%)
	African-American (n, %)	16 (50%)†
Vascular Risk Factors	Ischemic Stroke (n, %)	0
	Transient Ischemic Attack (n, %)	0
	Hypertension	0
	Diabetes Mellitus	0
	Hyperlipidemia	0
Imaging Characteristics	WMH Volume (cm^3, median, IQR)	0 (0 – 0.33)
	WMH Volume to Whole Brain Ratio (ratio, median, IQR)	0 (0 – 0.0003)
	Lacunar Infarcts, n (%)	0 (0%)
	Lobar Microbleeds, n (%)	0 (0%)
	Deep Microbleeds, n (%)	0 (0%)
	Cortical Superficial Siderosis, n (%)	0 (0%)

WMH indicates white matter hyperintensities

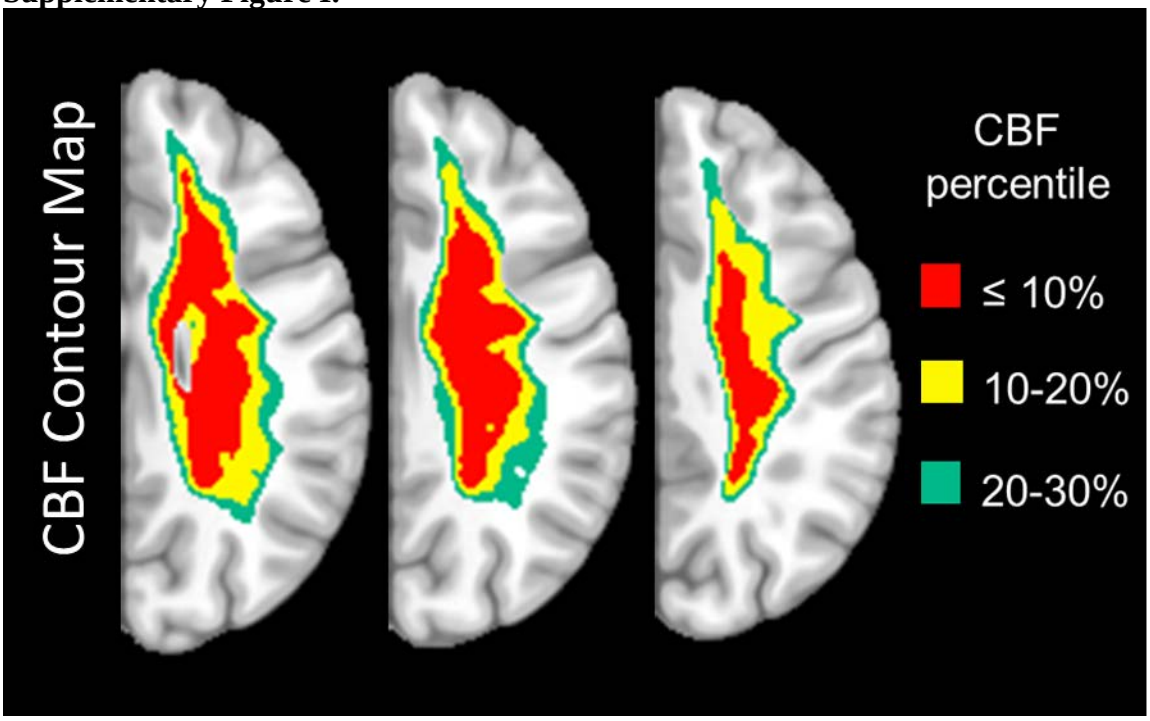
* There is overlap of 8 participants between the study and watershed ROI cohorts

† One participant identified as multiracial (African-American and white)

Supplementary Table II. Collinearity diagnostics for variables entered into the multivariate regression models in Table 2.

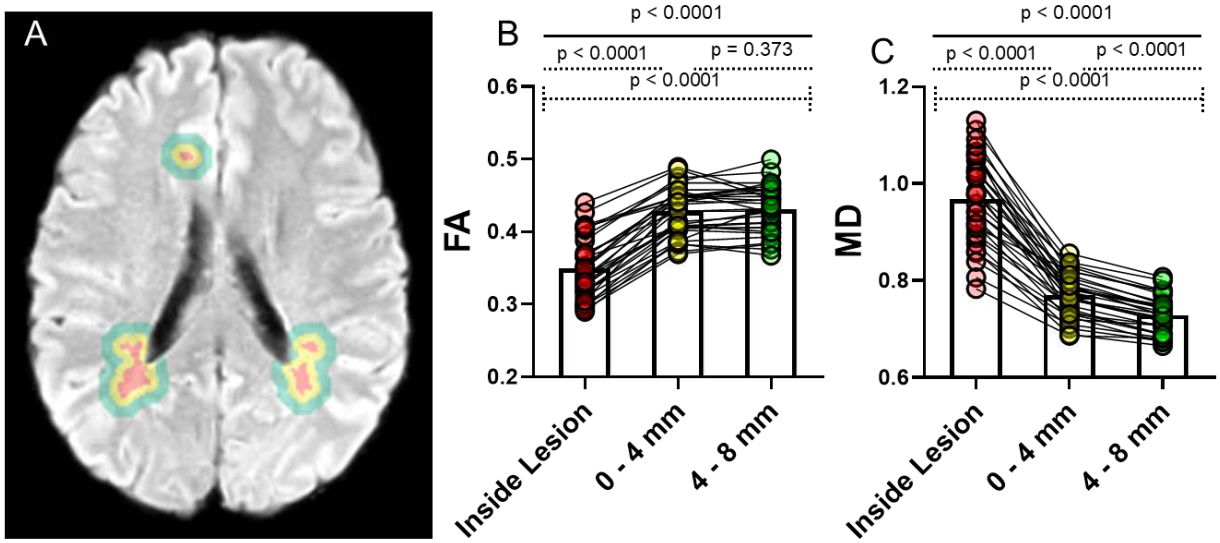
Outcome Variable	Predictor Variable	Variance Inflation Factor
Normalized WMH Volume	White matter OEF Ratio	2.525
	Watershed OEF Ratio	1.364
	Age	1.401
	Hypertension	1.364
	Diabetes Mellitus	1.525
	Hyperlipidemia	1.223
DTI FA	White matter OEF Ratio	1.987
	Watershed OEF Ratio	1.307
	Hypertension	1.592
	Diabetes Mellitus	1.307
	Race	1.342
	Sex	1.133
DTI MD	Watershed CBF	1.004
	White matter OEF Ratio	2.483
	Watershed OEF Ratio	1.334
	Age	1.419
	Hypertension	1.334
	Diabetes Mellitus	1.460
	Sex	1.122

Supplemental Figures and Figure Legends:
Supplementary Figure I.



Defining the physiologic watershed region in a healthy young cohort. Region of interest masks of the lowest 10th percentile (red), 10th-20th percentile (yellow), and 20th-30th percentile (green) cerebral blood flow (CBF) in a healthy cohort ≤ 55 years of age **(supplementary Table 1)** were generated to define the physiologic watershed. CBF is lowest in the deep white matter and increases as the region moves outward.

Supplementary Figure II.



Fractional anisotropy (FA) and mean diffusivity (MD) in regions surrounding white matter hyperintensities (WMH). WMH (red) and concentric contours, measuring 0-4 mm (yellow), and 4-8mm (green), surrounding each lesion were generated by dilating the WMH mask in three dimensions for each ROI, excluding cerebrospinal fluid and gray matter. Only participants with > 1cc of WMH volume were included in this analysis. **(A)**. Comparison of FA (B) and MD (C) values across the contours within each individual are shown (spaghetti plots). FA was lowest inside the lesions and significantly higher in the 0-4mm contours and the 4-8mm contours, but there was no significant difference in FA values between the 0-4mm and 0-8mm contours **(B)**. MD was highest inside the lesions and decreased with each progressive contour **(C)**.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	**(*a*)** Indicate the study's design with a commonly used term in the title or the abstract (page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 1)
Introduction		
Background/rationale	**2**	Explain the scientific background and rationale for the investigation being reported (pages 4-5)
Objectives	**3**	State specific objectives, including any prespecified hypotheses (page 5)
Methods		
Study design	4	Present key elements of study design early in the paper (page 5)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (page 5)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants (pages 5-6)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (pages 6-9)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (pages 6-9)
Bias	9	Describe any efforts to address potential sources of bias (page 9)
Study size	10	Explain how the study size was arrived at (this was an exploratory study)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (pages 9-10)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (pages 9-10)
		(*b*) Describe any methods used to examine subgroups and interactions (N/A)
		(*c*) Explain how missing data were addressed (N/A)
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (N/A)
		(*e*) Describe any sensitivity analyses (N/A)
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (this was an exploratory study)
		(b) Give reasons for non-participation at each stage (this was an exploratory study)
		(c) Consider use of a flow diagram (this was an exploratory study)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (pages 26-27)
		(b) Indicate number of participants with missing data for each variable of interest (page 26)
Outcome data	15*	Report numbers of outcome events or summary measures (pages 6-8)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (pages 10-12)

		(*b*) Report category boundaries when continuous variables were categorized (N/A)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (pages 10-12)
Discussion		
Key results	18	Summarise key results with reference to study objectives (page 13)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (page 17)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (pages 17-18)
Generalisability	21	Discuss the generalisability (external validity) of the study results (pages 17-18)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (page 18)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.