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Authors

Sible, Isabel J
Jang, Jung Yun
Dutt, Shubir
[et al.](#)

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Older Adults With Higher Blood Pressure Variability Exhibit Cerebrovascular Reactivity Deficits

Isabel J. Sible,^{1,*} Jung Yun Jang,^{2,*} Shubir Dutt,^{1,3} Belinda Yew,^{1,4} John Paul M. Alitin,² Yanrong Li,² Anna E. Blanken,^{5,6} Jean K. Ho,² Anisa J. Marshall,¹ Arunima Kapoor, MSc⁷ Fatemah Shenasa,⁷ Aimée Gaubert,² Amy Nguyen,² Virginia E. Sturm,^{6,8,9} Mara Mather,³ Kathleen E. Rodgers,¹⁰ Xingfeng Shao,¹¹ Danny J. Wang,¹¹ and Daniel A. Nation^{2,7,9}

BACKGROUND

Elevated blood pressure (BP) variability is predictive of increased risk for stroke, cerebrovascular disease, and other vascular brain injuries, independent of traditionally studied average BP levels. However, no studies to date have evaluated whether BP variability is related to diminished cerebrovascular reactivity, which may represent an early marker of cerebrovascular dysfunction presaging vascular brain injury.

METHODS

The present study investigated BP variability and cerebrovascular reactivity in a sample of 41 community-dwelling older adults (mean age 69.6 [SD 8.7] years) without a history of dementia or stroke. Short-term BP variability was determined from BP measurements collected continuously during a 5-minute resting period followed by cerebrovascular reactivity during 5-minute hypocapnia and hypercapnia challenge induced by visually guided breathing conditions. Cerebrovascular reactivity was quantified as percent change in cerebral perfusion by pseudo-continuous arterial spin labeling (pCASL)-MRI per unit change in end-tidal CO₂.

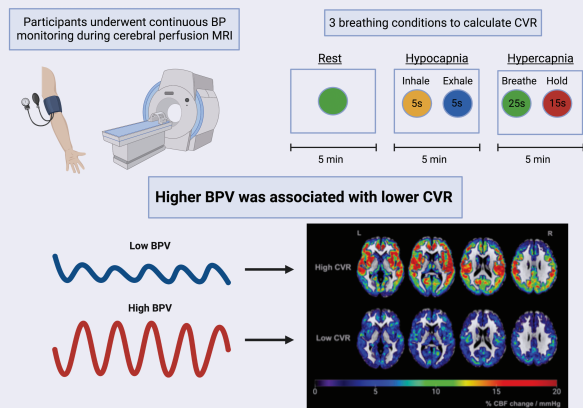
RESULTS

Elevated systolic BP variability was related to lower whole brain cerebrovascular reactivity during hypocapnia ($\beta = -0.43$ [95% CI $-0.73, -0.12$]; $P = 0.008$; adjusted $R^2 = .11$) and hypercapnia ($\beta = -0.42$ [95% CI $-0.77, -0.06$]; $P = 0.02$; adjusted $R^2 = 0.19$).

CONCLUSIONS

Findings add to prior work linking BP variability and cerebrovascular disease burden and suggest BP variability may also be related to prodromal markers of cerebrovascular dysfunction and disease, with potential therapeutic implications.

GRAPHICAL ABSTRACT



Keywords: aging; blood pressure; blood pressure variability; cerebrovascular reactivity; hypertension.

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Correspondence: Daniel A. Nation (dnation@uci.edu).

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¹Department of Psychology, University of Southern California, Los Angeles, CA 90089, USA; ²Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA 92697, USA; ³Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA; ⁴Department of Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA; ⁵San Francisco Veterans Affairs Health Care System, San Francisco, CA, 94121, USA; ⁶Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, San Francisco, CA, 94158, USA; ⁷Department of Psychological Science, University of California Irvine, Irvine, CA 92697, USA; ⁸Department of Neurology, University of California, San Francisco, San Francisco, CA, 94158, USA; ⁹Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, 94158, USA; ¹⁰Center for Innovation in Brain Science, Department of Pharmacology, The University of Arizona, Tucson, AZ, 85721, USA; ¹¹Laboratory of Functional MRI Technology, Mark and Mary Stevens Neuroimaging and Informatics Institute, University of Southern California, Los Angeles, CA, 90033, USA.

*Authors contributed equally.

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Hypertension is strongly linked with increased risk for stroke, cerebrovascular disease, and dementia.^{1,2} The established link was further supported by findings from the SPRINT trial suggesting intensive blood pressure (BP) lowering was associated with fewer cardiovascular event outcomes (e.g., stroke),³ slower progression of white matter hyperintensities,⁴ and decreased risk for incident mild cognitive impairment.⁵ These results have fueled interest in other aspects of BP control that could potentially further reduce cardiovascular, cerebrovascular, and dementia risk.⁶ BP variability (BPV), or the change in BP over a period of seconds to minutes (known as “short-term” BPV) or months to years (known as “long-term” BPV or “visit-to-visit” BPV), is now an emerging risk factor for stroke, cerebrovascular disease, and dementia, independent of average BP levels.^{7–9} Specifically, a growing number of studies have found that elevated BPV is related to cognitive decline,⁸ progressions of dementia,^{10,11} and greater cerebrovascular lesion burden on MRI (e.g., white matter hyperintensities, cerebral infarcts, and cerebral microbleeds)⁹ and postmortem evaluation (e.g., atherosclerosis in the Circle of Willis and arteriolosclerosis).^{12,13} However, less is known about the relationships between BPV and putative markers of cerebrovascular dysfunction or prodromal disease that may be important for cognitive functioning. One such marker is cerebrovascular reactivity (CVR), which represents the ability of the brain’s vessels to dilate and constrict in response to vasoactive stimuli.¹⁴ Diminished CVR is predictive of stroke and transient ischemic attack,^{15,16} and lower CVR is associated with cognitive impairment in older adults.¹⁷ Additionally, CVR and cognitive functioning were improved in patients with carotid artery atherosclerosis after carotid endarterectomy.¹⁸ Furthermore, 1 recent study found that, compared to healthy younger adults, cognitively unimpaired older adults had attenuated CVR in response to both hypocapnia and hypercapnia breathing conditions.¹⁹ Together these findings support the hypothesis that CVR may be an early marker of vascular dysfunction that predates vascular brain injury relevant to dementia risk.

Hypertension can diminish CVR, possibly through increased tortuosity, arterial remodeling, or shifts in the cerebral autoregulatory curve.^{20,21} However, less is known about how other aspects of BP, such as BPV, may be related to CVR. The present study investigated the relationship between BPV collected continuously over a 5-minute resting period and CVR during hypocapnia and hypercapnia breathing conditions during pseudo-continuous arterial spin labeling (pCASL)-MRI in a sample of community-dwelling older adults.

METHODS

Participants

Study participants were recruited from ongoing studies of aging at the University of California Irvine (UCI) and the University of Southern California (USC), and from the local Orange County and Los Angeles communities via flyers, word-of-mouth, and community outreach events. Inclusion criteria required participants to be aged 55–90 years and

living independently in the community. Exclusionary criteria included: History of dementia, stroke, traumatic brain injury, learning disability, or other major systemic, psychiatric, or neurological disorder known to affect the central nervous system. All research participants underwent neuropsychological testing and obtained a Mattis Dementia Rating Scale-2 (DRS-2)²² total score > 126, an established cutoff to rule out major neurocognitive impairment.²² The study was approved by the Institutional Review Boards at UCI and USC and all participants provided their written informed consent.

BPV data was not collected on all participants enrolled in the combined ongoing studies at USC and UCI ($n = 126$) and some participant data were not included due to procedural errors or noise. Therefore, the present study included 41 older adult participants (aged 55–88 years) who underwent continuous BP monitoring over a 5-minute resting period and breath control tasks during pCASL-MRI to induce hypocapnia and hypercapnia and determine CVR.

Measures

MRI protocols. Participants underwent brain MRI on the same make and model device (3T Siemens MAGNETOM Prisma) at either UCI ($n = 23$) or USC ($n = 18$). Three types of scans were collected from all participants: (i) structural MRI; (ii) cerebral perfusion pCASL-MRI; and (iii) T2-fluid attenuated inversion recovery (FLAIR) MRI. First, a structural brain MRI was collected to obtain T1-weighted magnetization prepared rapid gradient-echo (MP-RAGE) sequence for high resolution anatomical images (TR = 2,300 ms; TE = 2.98 ms; TI = 900 ms; slice thickness = 1.20 mm; flip angle = 9°; field of view = 256 mm). Next, whole brain cerebral blood flow (CBF) was determined from cerebral perfusion imaging using a pCASL method with background suppressed gradient and spin echo (GRASE) readout, as previously described.^{19,23} The following sequence parameters were used for pCASL-MRI: TR = 5,000 ms; TE = 36.3 ms (USC)/ 37.46 ms (UCI); FOV = 240 mm; resolution = $2.5 \times 2.5 \times 3.4$ mm³; slice thickness = 3.42 mm; number of slices = 24; labeling duration = 1517 ms; post-labeling delay = 2000 ms; number of measurements = 1 M0 image + 1 dummy image + 15 pairs of tag-control images (32 total acquisitions); total scan time = 5:25. As previously described,¹⁹ pCASL preprocessing included the following: Motion correction, co-registration to structural T1-weighted image, spatial smoothing with a 6 mm full-width at half-maximum Gaussian kernel, tag-control subtraction. Finally, participants also underwent T2-FLAIR MRI sequence (TR = 10,000 ms; TE = 91 ms; TI = 2,500 ms; slice thickness = 5.0 mm; flip angle = 150°; field of view = 220 mm) to determine white matter lesion burden as previously described.²³ Severity of white matter lesions was estimated by one rater blinded to other study measures as Fazekas scores²⁴ (0–3).

Breathing protocols. Participants underwent three separate, sequential 5-minute breathing paradigms during brain pCASL-MRI, as described elsewhere^{19,23}: (i) resting condition

(breathe normally); (ii) paced breathing/hypocapnia (0.1 Hz breathing); (iii) breath hold/hypercapnia (15-second breath holds). To increase protocol compliance, participants were instructed on each breathing paradigm first during training exercises outside of the scanner and then guided with visual stimuli during each scan, as previously described.^{19,23} For (i) resting condition, participants were instructed verbally before the scan to breathe normally and were presented during the scan with either a static green circle (USC) or a blank slide (UCI); For (ii) paced breathing/hypocapnia, participants were shown a circle that was alternately filled with yellow for 5 seconds (“inhale”) and blue for 5 seconds (“exhale”); and For (iii) breath hold/hypercapnia, participants were shown a circle that alternately filled with green for 25 seconds (“breathe normally”) and red for 15 seconds (“hold breath”) and were instructed to exhale before and after each breath hold.

Capnography assessment. End-tidal CO₂ (etCO₂) was measured during each pCASL-MRI via a Phillips Medical Systems MRI-compatible carbon dioxide device and nasal cannula, as described elsewhere.¹⁹ Briefly, etCO₂ was determined at every expiration for the hypocapnia condition, and the maximum etCO₂ per breath hold was used for the hypercapnia condition. Participants who failed to adhere to each condition (e.g., breathing through the mouth as evidenced by no discernable positive peaks in etCO₂ waveform) were excluded from analyses.

CVR assessment. CVR was estimated as the percent change in CBF per unit change in etCO₂, based on established methods.^{14,19,25} The following was used to calculate whole-brain CVR maps for each participant for each breathing paradigm:

$$\text{CVR} = \frac{100 \times (CBF_{\text{maximum}} - CBF_{\text{minimum}}) / CBF_{\text{minimum}}}{\text{etCO}_{2\text{maximum}} - \text{etCO}_{2\text{minimum}}}$$

BP assessment. BP was collected continuously using a Biopac MRI-compatible BP monitoring device during the 5-minute resting pCASL-MRI scan, as previously described.²³ Briefly, data were processed offline using a custom pipeline scripted in AcqKnowledge.^{23,26} Intraindividual BPV was calculated as variation independent of mean (VIM), an increasingly used index of BPV that is uncorrelated with average BP levels.^{10,23,27–31} We conducted a bivariate correlation between BPV and average BP to confirm that BPV was not significantly correlated with average BP levels (systolic: $r = -0.04$, $P = 0.80$; diastolic: $r = 0.003$, $P = 0.99$). VIM was calculated as: $\text{VIM} = \text{standard deviation (SD)} / \text{mean}^x$, where the power x was derived from nonlinear curve fitting of BP SD against average BP using the nls package in R Project, as previously described.^{12,23,27,29,30} The present investigation focused on systolic BPV based on prior work suggesting systolic, and not diastolic, short-term BPV is related to simultaneous CBF in older adults.²³

Other measurements. Blood samples from venipuncture were used to determine APOE e4 carrier status (≥ 1 e4 allele), as previously prescribed.³² Body mass index (BMI [kg/m²]) was calculated from study screening body measurements. Participants self-reported antihypertensive medication use at study screening and participants were categorized as those taking antihypertensive medication (all classes) vs. those who were not.

Data availability statement. Study data and code are available upon request.

STATISTICAL ANALYSIS

BPV and CVR data were screened for outliers (± 3 SD from the mean), resulting in the removal of one participant’s whole brain CVR during hypocapnia. Multiple linear regression was used to examine the relationship between BPV and whole brain CVR during the hypocapnia and hypercapnia breathing conditions separately. All models were controlled for age and sex. Sensitivity analyses included the following covariates (separate models tested to preserve statistical power): (i) antihypertensive medication use; (ii) severity of white matter hyperintensities (e.g., Fazekas score, 0–3); (iii) BMI; (iv) average BP; and (v) MRI site (UCI and USC) (see [Supplementary Table S1](#)). All analyses were 2-sided with significance set at $P < 0.05$. All analyses were carried out in the R Project.

RESULTS

Clinical and demographic information are summarized in [Table 1](#).

During hypocapnia, elevated systolic BPV was related to significantly lower whole brain CVR ($\beta = -0.43$ [95% CI $-0.73, -0.12$]; $P = 0.008$; adjusted $R^2 = 0.11$) ([Figure 1A](#)). Higher systolic BPV was also associated with significantly lower whole brain CVR during hypercapnia ($\beta = -0.42$ [95% CI $-0.77, -0.06$]; $P = 0.02$; adjusted $R^2 = 0.19$) ([Figure 1B](#)).

Sensitivity analyses

All hypocapnia findings remained significant when controlling for (i) antihypertensive medication use; (ii) severity of white matter hyperintensities (e.g., Fazekas score, 0–3); (iii) BMI; (iv) average BP; and (v) MRI site (UCI and USC) (see [Supplementary Table S1](#)). All sensitivity analyses for hypercapnia findings remained significant, except for antihypertensive medication use ($P = 0.06$) (see [Supplementary Table S1](#)).

DISCUSSION

Findings indicate elevated short-term BPV is associated with lower CVR during hypocapnia and hypercapnia breathing conditions in a sample of community-dwelling, cognitively unimpaired older adults, independent of average BP levels. A number of studies link higher BPV with greater cerebrovascular disease burden on MRI and postmortem

Table 1. Demographic and clinical information.

	Total sample (N = 41)
Age (years)	69.6 (8.7)
Sex (male/female)	14/27
Education (years)	16.2 (2.7)
APOE-ε4 carriers (n, %)	19 (46.3%)
DRS-2 total (scaled score)*	11.7 (2.4)
Body mass index (kg/m ²)	25.5 (4.8)
Fazekas score (n, %)	
0	3 (7.3%)
1	24 (58.5%)
2	11 (26.8%)
3	3 (7.3%)
Antihypertensive use (n, %)	13 (31.7%)
Systolic BP(mmHg)	
Average	132.7 (21.0)
VIM	3.4 (2.0)
Diastolic BP(mmHg)	
Average	76.2 (12.4)
VIM	5.2 (2.9)

Means and SDs has shown unless otherwise indicated.

*DRS-2 total scaled scores are age- and education-adjusted.

Abbreviations: APOE e4 = apolipoprotein e4; DRS-2 = Dementia Rating Scale – second edition; BP = blood pressure; VIM = variability independent of mean

evaluation.^{9,12,13} The present findings add to this work by suggesting BPV may also be associated with prodromal cerebrovascular dysfunction that could presage cerebrovascular disease and related cognitive impairment.

BP is naturally highly dynamic, and fluctuations occur spontaneously and in response to internal (e.g., emotional) and external (e.g., physical exertion) stimuli.⁷ However, these BP changes must be regulated to ensure adequate pressure and flow of blood to the body's organs. Over time, autoregulatory forces such as baroreflex function may wane, leaving BP levels less regulated and more variable.³³ The brain is especially vulnerable to disruptions in CBF given its high metabolic demand.³⁴ A number of studies suggest the smaller vascular compartments (i.e., arterioles and capillaries) are often where most age-related cerebral arterial changes occur.³⁵ Consistently, elevated BPV over the short-term and long-term has been linked with arterial remodeling and stiffening^{36,37} as well as microvascular damage.^{9,12,13} Furthermore, it has been hypothesized that arterial stiffening may amplify BP fluctuations, and that their combined effect may be even more detrimental to arterial health.⁹ It is unclear whether elevated BPV is a cause or effect—or even an index—of arterial stiffening^{7,38} and longitudinal and/or interventional studies may help clarify this relationship. However, BPV is increasingly being considered an important independent marker of vascular change that may predate vascular brain injury and dementia risk.

Diminished CVR is predictive of stroke and white matter hyperintensities and may reflect prodromal cerebrovascular dysfunction.^{15,16} Just as age-related arterial stiffening may exacerbate BPV, stiffer arteries may impact CVR by limiting the cerebral vessels' ability to mount a response to vasoactive stimuli.³⁹

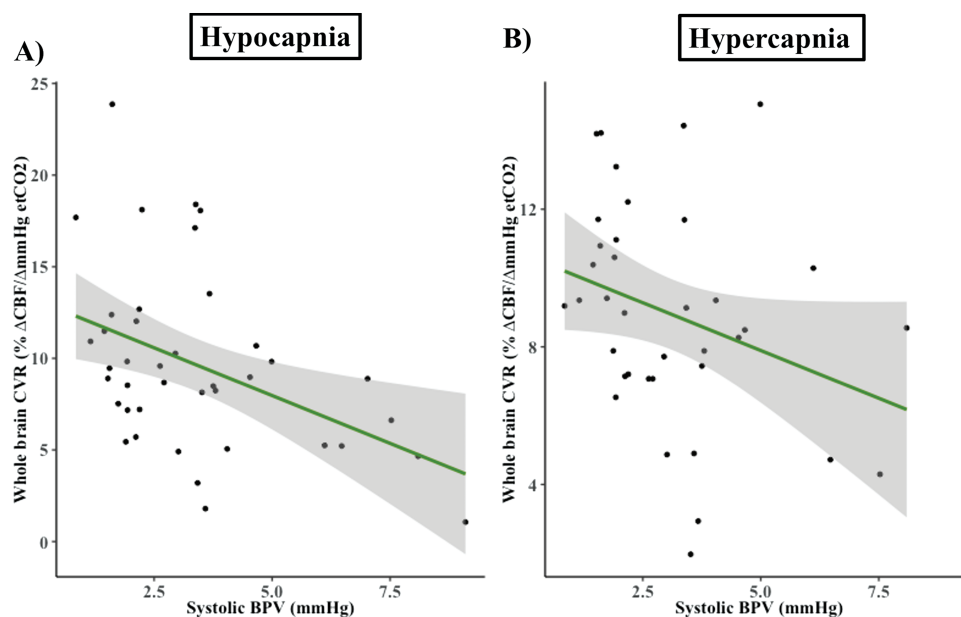


Figure 1. Elevated short-term systolic BPV is associated with CVR during hypocapnia and hypercapnia. Scatterplots display the relationship between short-term systolic BPV and whole brain CVR during (A) hypocapnia and (B) hypercapnia. Lines are shaded with 95% CI. Abbreviations: BPV = blood pressure variability.

Specifically, arterial stiffening may dampen dilation and constriction of the vessel walls and lead to a less robust CVR response. Hypertension may additionally attenuate CVR by shifting the cerebral autoregulatory curve, which could in turn establish more opportunities for hypoperfusion, microvascular damage, and cerebrovascular disease.^{20,21} Our findings add to this literature by suggesting that BPV, independent of average BP levels, may be a risk indicator for emerging cerebrovascular dysfunction and disease. Importantly, results are in line with prior work linking BPV to frank cerebrovascular disease burden detectable on MRI⁹ and autopsy,^{12,13} and may elucidate relationships with even earlier markers of cerebrovascular dysfunction.

Recent BPV research has highlighted that aspects of antihypertensive treatment other than lowering average BP levels may be important for brain health outcomes. For example, some studies suggest that certain antihypertensive classes, or a combination of classes, may reduce BPV and the risk of stroke.⁴⁰ Due to the relatively small sample size, it was not possible to assess differential antihypertensive class effects on BPV and CVR. However, this remains an important area for future research.

To the best of our knowledge, no studies to date have examined the relationship between BPV and CVR. While most studies on CVR have focused on either hypocapnia or hypercapnia,¹⁴ the present investigation included both breathing conditions. This allowed us to appreciate relationships with periods of vasoconstriction and vasodilation. The study is limited by the small sample size with relatively minimal cerebrovascular risk (e.g., 66% had Fazekas scores ≤ 1). Future work with larger samples and varying degrees of vascular disease may help to further elucidate cerebrovascular risk associated with BPV and CVR.

Elevated BPV is associated with lower CVR in community-dwelling older adults without history of dementia or stroke. Findings add to prior work linking high BPV to cerebrovascular disease burden on MRI and at postmortem evaluation and suggest BPV may be an understudied vascular risk indicator associated with prodromal cerebrovascular disease.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

None.

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