

# Inter-Relations of Orthostatic Blood Pressure Change, Aortic Stiffness, and Brain Structure and Function in Young Adults

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**Background**—Relations of orthostatic change in blood pressure with brain structure and function have not been studied thoroughly, particularly in younger, healthier individuals. Elucidation of factors that contribute to early changes in brain integrity may lead to development of interventions that delay or prevent cognitive impairment.

**Methods and Results**—In a sample of the Framingham Heart Study Third Generation (N=2119; 53% women; mean age±SD, 47±8 years), we assessed orthostatic change in mean arterial pressure (MAP), aortic stiffness (carotid-femoral pulse wave velocity), neuropsychological function, and markers of subclinical brain injury on magnetic resonance imaging. Multivariable regression analyses were used to assess relations between orthostatic change in MAP and brain structural and neuropsychological outcomes. Greater orthostatic increase in MAP on standing was related to better Trails B-A performance among participants aged <49 years ( $\beta\pm SE$ , 0.062±0.029;  $P=0.031$ ) and among participants with carotid-femoral pulse wave velocity <6.9 m/s ( $\beta\pm SE$ , 0.063±0.026;  $P=0.016$ ). This relation was not significant among participants who were older or had stiffer aortas. Conversely, greater orthostatic increase in MAP was related to larger total brain volume among older participants ( $\beta\pm SE$ , 0.065±0.029;  $P=0.023$ ) and among participants with carotid-femoral pulse wave velocity ≥6.9 m/s ( $\beta\pm SE$ , 0.078±0.031;  $P=0.011$ ).

**Conclusions**—Blunted orthostatic increase in MAP was associated with smaller brain volume among participants who were older or had stiffer aortas and with poorer executive function among persons who were younger or who had more-elastic aortas. Our findings suggest that the brain is sensitive to orthostatic change in MAP, with results dependent on age and aortic stiffness. (*J Am Heart Assoc.* 2017;6:e006206. DOI: 10.1161/JAHA.117.006206.)

**Key Words:** aging • aortic stiffness • cognitive impairment • magnetic resonance imaging • orthostatic hypotension

Aging and alterations in the baroreflex predispose individuals to impaired regulation of blood pressure (BP) upon standing, which is associated with higher risk for syncope<sup>1</sup> and stroke.<sup>2</sup> Aging is also associated with a pronounced elevation in aortic stiffness. Several community-based studies have shown associations between elevated aortic stiffness and flow pulsatility with lower brain structural integrity and function.<sup>3–8</sup> Aortic stiffness, as assessed by carotid-femoral pulse wave velocity (CFPWV), is associated with orthostatic hypotension in older, community-based

samples.<sup>9,10</sup> Furthermore, we have recently shown that greater aortic stiffness is associated with a blunted increase in mean arterial pressure (MAP) upon standing in younger individuals,<sup>11</sup> which may be an early important indicator of, or contributor to, cognitive impairment.

Aortic stiffness is associated with microvascular lesions and impaired cognitive function. Higher aortic stiffness leads to impedance matching, which increases the amount of potentially damaging pulsatility that penetrates into the cerebral microcirculation.<sup>12,13</sup> As a high flow and low impedance organ,

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## Clinical Perspective

### What Is New?

- Relations of orthostatic change in mean arterial pressure (MAP), aortic stiffness, and brain structure and function have not been thoroughly examined in a large, community-based cohort of young to middle-aged adults.
- Greater orthostatic increase in MAP was related to better executive function among younger participants and among participants with less-stiff aortas.
- Greater orthostatic increase in MAP was related to larger total brain volume among older participants and among participants with stiffer aortas.
- Among older participants and participants with stiffer aortas, coupling between orthostatic change in MAP and total brain volume was enhanced.

### What Are the Clinical Implications?

- The brain is sensitive to blunted orthostatic change in MAP, which depends on age and aortic stiffness.
- Older individuals and individuals with stiffer aortas may be more dependent on orthostatic increase in MAP to maintain cerebral perfusion and prevent subclinical ischemic damage and cognitive decline.
- Elucidation of mechanisms whereby novel vascular factors, such as increased aortic stiffness, contribute to subclinical changes in brain structure and function may inform development of interventions or therapies that prevent or delay the onset of cognitive decline.

the brain is particularly susceptible to pulsatile damage. Higher stiffness is also associated with blunted microvascular reactivity.<sup>14</sup> Therefore, the combination of blunted orthostatic increase in MAP and blunted microvascular reactivity may potentially lead to tissue hypoperfusion, ischemia, and brain injury. The relations of orthostatic change in BP with brain integrity and markers of subclinical injury have not been studied thoroughly, particularly among a younger, healthier cohort. Identifying factors that contribute to early alterations to brain integrity may lead to preventive measures that can be implemented before the manifestation of symptomatic cognitive impairment. Given that the role of aortic stiffness on the putative associations between orthostatic change in BP and brain structure and cognition remains unknown, we examined inter-relations of orthostatic BP change, aortic stiffness, and brain structure and function among a sample of younger adults of the community-based Framingham Heart Study.

## Methods

The study sample was drawn from the Framingham Third Generation Cohort, which has been described previously.<sup>15</sup>

Central hemodynamics, brain volume, and brain infarcts on magnetic resonance imaging (MRI) and neuropsychological function were assessed in the Third Generation cohort at the second examination cycle (2008–2011; N=3411). Participants were excluded for the following reasons: incomplete tonometry or hemodynamic assessment (n=193); history of stroke, dementia, or other significant neurological illness (n=11); age <30 years (n=115) because of low cardiovascular risk; missing neuropsychological assessment (n=973); and missing brain MRI data (n=190). Written informed consent was obtained from all study participants, and the research protocol was approved by the Institutional Review Board at Boston University School of Medicine (Boston, MA).

## Noninvasive Hemodynamics Acquisition and Analyses

Aortic stiffness was assessed as previously described.<sup>16</sup> Following 5 minutes of rest, auscultatory BP was measured in the right arm using a standard upper arm cuff in the supine position. Using a custom tonometer, noninvasive arterial tonometry with simultaneous ECG was obtained from brachial, radial, femoral, and carotid arteries. Tonometric data were digitized and transferred to the core laboratory (Cardiovascular Engineering, Inc., Norwood, MA) for blinded analyses. Using the electrocardiographic R-wave, tonometry waveforms were signal-averaged and synchronized.<sup>17</sup> MAP was calculated as the signal-averaged integral of the brachial pressure waveform, calibrated with the systolic and diastolic cuff pressures. CFPVW was calculated from tonometry waveforms and body surface measurements adjusted for parallel transmission in the brachiocephalic artery and aortic arch; the suprasternal notch was used as a fiducial point.<sup>12</sup>

To assess orthostatic change in BP, a second BP measurement was taken in the standing position after the hemodynamic acquisition, beginning 2 minutes after standing from a supine position.<sup>11</sup> Orthostatic change in BP was defined as the difference in MAP while standing versus MAP while supine. A negative value for change in orthostatic MAP indicates a drop in MAP upon standing. MAP was selected a priori as the BP measure (and explanatory variable) for this investigation because systolic and diastolic pressures generally diverge upon standing whereas MAP should consistently increase. Also, we previously have shown that orthostatic changes in MAP (compared with systolic, diastolic, and pulse pressures) has the strongest relation to measures of aortic stiffness.<sup>11</sup>

## Neuropsychological Testing and Assessment of Depressive Symptoms

A neuropsychological battery was administered to the participants that examined numerous broad cognitive domains as

defined by the Cattell-Horn-Carroll model.<sup>18</sup> Our battery included Logical Memory Delayed and Visual Reproductions Delayed from the Wechsler Memory Scales, Similarities from the Wechsler Adult Intelligence Scales, and Trail Making B-A. The mathematical sign for Trail Making B-A was reversed such that higher scores indicated faster processing speed and superior executive functions. Higher scores on Logical Memory Delayed and Visual Reproductions Delayed indicate better verbal and visual memory, respectively. Higher scores on the task of Similarities indicate superior verbal comprehension and reasoning. All tests are widely used and well validated.<sup>19</sup> Neuropsychological testing was performed by trained research assistants and neuropsychologists. The Center for Epidemiologic Studies Depression Scale was used to assess depressive symptoms; participants with a score  $\geq 16$  were classified as having depressive symptoms.

### Brain MRI

Total brain volume, white matter hyperintensity volume, lateral ventricular volume, and lacunes of presumed vascular origin (deep lacunes) were evaluated as previously described.<sup>20</sup> Images were assessed using 3-dimensional T<sub>1</sub>-weighted coronal spoiled gradient-recalled acquisition and fluid-attenuated inversion recovery sequences. Brain volumes were expressed relative to total cranial volume on fluid-attenuated inversion recovery to correct for differences in head size. Segmentation and quantification of brain volumes have been described previously.<sup>21–23</sup> To assess lateral ventricular volumes, central cerebrospinal fluid spaces were analyzed (excluding the temporal horn). The STRIVE (STandards for Reporting Vascular changes on nEuroimaging) criteria were used to determine the presence of lacunes.<sup>24</sup> Scans were reviewed by technicians blinded to identifying and clinical information.

### Statistical Analyses

CFPWV was inverted to limit heteroscedasticity; the inverted value was multiplied by  $-1000$  to convert units to ms/m and rectify directionality of the association with aortic stiffness. White matter hyperintensity volumes and Trail Making B-A scores were log-transformed to normalize the distribution. Orthostatic change in MAP and all continuous outcome measures were transformed to a standard normal distribution.

Multivariable linear regression analysis was used to assess relations between orthostatic change in MAP and each neuropsychological outcome. Minimal models for neuropsychological outcomes were adjusted for age, sex, education, and time between hemodynamic measurement and assessment of the outcome measures. Expanded models additionally

adjusted for heart rate, corresponding supine MAP, the fourth quartile of waist to hip ratio, fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, hypertension treatment, diabetes mellitus, current smoking, presence of depressive symptoms, prevalent cardiovascular disease, and prevalent atrial fibrillation. Linear or logistic regression analysis was used to assess relations between orthostatic change in MAP and each MRI structural outcome, adjusting for all the above-mentioned covariates except education. Using the minimally adjusted models, we tested interactions of sex, age (defined as  $\geq 49$  versus  $< 49$  years), and level of aortic stiffness as assessed by CFPWV (defined as  $\geq 6.9$  versus  $< 6.9$  m/s) with orthostatic change in MAP by incorporating corresponding interaction terms in the analysis. Age and CFPWV were dichotomized using the median values.

All analyses were performed with SAS software (version 9.4 for Windows; SAS Institute Inc., Cary, NC). Two-tailed  $P < 0.05$  was considered statistically significant for the analysis, except for the tests of interaction, where  $P < 0.10$  was considered significant.

### Results

The analysis sample included 2119 participants (1121 [53%] women). The sample characteristics are presented in Table 1. The sample was comprised of young to middle-aged adults who were relatively healthy. Standing was associated with a substantial increase in MAP. Neuropsychological and brain MRI outcome measures are presented in Table 2.

In the whole sample, we did not find significant relations between orthostatic change in MAP and any neuropsychological outcomes (Table 3). However, we found evidence of effect modification by age ( $P = 0.098$ ) and level of aortic stiffness ( $P = 0.077$ ) of the relations of orthostatic change in MAP with Trails B-A performance (executive function). We observed no significant interactions by sex. Among younger participants, greater orthostatic change in MAP was related to higher (indicating faster) Trails B-A performance (age  $< 49$ ;  $\beta \pm SE$ ,  $0.062 \pm 0.029$ ;  $P = 0.031$ ); this relation was not significant among older participants (age  $\geq 49$ ;  $\beta \pm SE = -0.030 \pm 0.033$ ;  $P = 0.364$ ). Similarly, among participants with CFPWV  $< 6.9$  m/s, greater orthostatic change in MAP was related to higher Trails B-A performance ( $\beta \pm SE = 0.063 \pm 0.026$ ;  $P = 0.016$ ); this relation was not significant among participants with CFPWV  $\geq 6.9$  m/s ( $\beta \pm SE = -0.040 \pm 0.035$ ;  $P = 0.258$ ). We did not find significant effect modification by age, sex, or CFPWV ( $P = 0.146$ – $0.952$ ) on the relation between orthostatic change in MAP and other neuropsychological outcomes (Logical Memory Delayed, Visual Reproductions Delayed, and Similarities).

In the whole sample, there were no significant relations between orthostatic change in MAP and any brain MRI measure (Table 4). Secondary analyses for interactions for

**Table 1.** Sample Characteristics (N=2119)

Variable	Value*
Age, y	46.9±8.0
Women, n (%)	1121 (52.9)
Waist/hip ratio	0.92±0.08
Total cholesterol, mg/dL	187±34
High-density lipoprotein cholesterol, mg/dL	60±18
Triglycerides, mg/dL	111.2±78.0
Fasting glucose, mg/dL	96±17
Hypertension treatment, n (%)	380 (18.0)
Prevalent cardiovascular disease, n (%)	42 (2.0)
Diabetes mellitus, n (%)	96 (4.5)
Prevalent atrial fibrillation, n (%)	26 (1.2)
Smoker, n (%)	192 (9.07)
Depressive symptoms, n (%)	198 (9.4)
Time between clinical and MRI/neuropsychological exams, y	1.7±0.9
Education, n (%)	
No high school diploma	13 (0.6)
High school diploma	287 (13.6)
Some college	651 (30.8)
College degree	1163 (55.0)
Hemodynamic variables	
Heart rate, beats/min	64.3±9.9
Carotid-femoral PWV, m/s median (25th, 75th percentile)	6.9 (6.2, 7.8)
Supine mean arterial pressure, mm Hg	87.1±10.9
Change in mean arterial pressure upon standing, mm Hg	6.5±7.7

MRI indicates magnetic resonance imaging; PWV, pulse wave velocity.

\*Values are mean±SD, except as noted.

the association of orthostatic change in MAP with brain MRI outcomes revealed significant effect modification by age ( $P=0.037$ ) and level of aortic stiffness ( $P=0.022$ ) of the relations of orthostatic change in MAP with total brain volume (Figure). We observed no significant interactions by sex. Among older participants, greater orthostatic change in MAP was related to higher total brain volume (age  $\geq 49$ ;  $\beta \pm SE = 0.065 \pm 0.029$ ;  $P=0.023$ ); this relation was not significant among younger participants (age  $< 49$ ;  $\beta \pm SE = -0.0003 \pm 0.034$ ;  $P=0.992$ ). Similarly, among participants with CFPWV  $\geq 6.9$  m/s, greater orthostatic change in MAP was related to higher total brain volume ( $\beta \pm SE = 0.078 \pm 0.031$ ;  $P=0.011$ ); this relation was not significant among participants with CFPWV  $< 6.9$  m/s ( $\beta \pm SE = -0.0108 \pm 0.032$ ;  $P=0.740$ ). We did not find significant effect modification by age, sex, or CFPWV ( $P=0.125$ –

**Table 2.** Neuropsychological and Brain MRI Outcome Measures

Measures	Value*
Neuropsychological outcomes (N=2119)	
Trails B-A, time to completion in min, median (25th, 75th percentile)	0.53 (0.38, 0.73)
Logical memory delayed, number recalled correct	11.55±3.75
Visual reproductions delayed, number recalled correct	8.84±2.61
Similarities, number correct, median (25th, 75th percentile)	18.0 (15.0, 19.0)
Brain MRI outcomes <sup>†</sup> (N=1929)	
Total brain volume, %	88.5±2.7
WMH volume, %, median (25th, 75th percentile)	0.0003 (0.0002, 0.0007)
Lateral ventricular volume, %	1.2±0.8
Positive for deep lacunes, n (%)	61 (3.2)

MRI indicates magnetic resonance imaging; WMH indicates white matter hyperintensities.

\*All values are mean±SD, except as noted.

<sup>†</sup>Brain MRI volumes are percent of intracranial volume.

0.969) of the relation between orthostatic change in MAP and other brain MRI measures (white matter hyperintensity volume, lateral ventricular volume, or deep lacunes).

## Discussion

### Principal Findings

We investigated the relations between orthostatic change in MAP and brain structural and neuropsychological outcomes in a sample of the Framingham Heart Study Third Generation. In the whole sample of broad age ranges, we did not observe significant relations between orthostatic change in MAP and brain structure or function. However, a greater orthostatic increase in MAP was related to better executive function among participants younger than 49 years of age and among participants with CFPWV  $< 6.9$  m/s. This relation was not observed among older participants or among participants with stiffer aortas. Furthermore, greater orthostatic change in MAP was related to higher total brain volume among participants aged  $\geq 49$  years and among participants with CFPWV  $\geq 6.9$  m/s. Our results indicate that the brain's sensitivity to orthostatic change in MAP is dependent on age and extent of aortic stiffness.

### Orthostatic Change in MAP and Structural and Neuropsychological Outcomes

Multiple studies have investigated the relation between orthostatic hypotension and cognition among the elderly



**Table 3.** Relations of Orthostatic Change in MAP With Neuropsychological Outcomes

Neuropsychological Outcomes	Minimal Model*		Expanded Model†	
	$\beta \pm SE$	<i>P</i> Value	$\beta \pm SE$	<i>P</i> Value
Trail Making B-A	0.013±0.022	0.559	0.006±0.024	0.806
Logical memory delayed	−0.018±0.021	0.399	−0.028±0.023	0.220
Visual reproductions delayed	0.019±0.021	0.369	0.004±0.023	0.876
Similarities	−0.020±0.021	0.338	−0.038±0.024	0.109

\*Minimal models adjusted for age, sex, time between clinical and neuropsychological exams, and education. MAP indicates mean arterial pressure.

†Expanded models additionally adjusted for heart rate, corresponding supine MAP, the fourth quartile of waist to hip ratio, fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, hypertension treatment, diabetes mellitus, smoking, presence of depressive symptoms, prevalent cardiovascular disease, and prevalent atrial fibrillation.

and in the setting of vascular and neurodegenerative dementias. However, debate about relations between brain structure and function and orthostatic hypotension remains controversial. Many studies have not shown a significant relation between hypotension and cognition.<sup>25–28</sup> Conversely, a few studies have shown significant relations between orthostatic hypotension and cognitive or subclinical brain injury. Mehraian et al observed a significant relation between orthostatic hypotension and poorer cognition as assessed by the cognitive efficiency profile among elderly participants.<sup>29</sup> In addition, silent cerebral infarcts were more common among elderly hypertensive individuals with orthostatic hypotension as compared with those with a normal orthostatic response.<sup>30</sup> In the present study, we did not observe significant relations between orthostatic change in BP (as a continuous variable as compared with categorical orthostatic hypertension as in the aforementioned studies) and cognitive function or brain MRI outcomes. We did, however, observe a trend toward relations between orthostatic change in MAP and performance on the test of Similarities (comprehension and reasoning;  $P=0.109$ ). The association between hypertension and Alzheimer's disease is complex and not fully elucidated; however, high BP at midlife is associated with higher risk of cognitive impairment in late life.<sup>5,31,32</sup> Although the foregoing analyses

adjusted for presence of hypertension treatment, hypertension can often be inadequately treated; therefore, residual confounding by degree of BP elevation may persist. In contrast, our sample was comprised of younger individuals with only an 18% prevalence of hypertension. Our observation that orthostatic change in MAP was not related to cognitive function or brain MRI structural measures within the whole sample may be a manifestation of the relatively constrained range of abnormalities in MAP response in our relatively young cohort. In addition, it is possible that orthostatic change in MAP may not be an adequate surrogate for parallel changes in cerebral blood flow. Thus, mechanisms controlling autoregulation of the brain may provide adequate cerebral blood flow despite a relatively substantial, but transitory, change in MAP at the level of the brain. However, in the present study, we did not measure cerebral blood flow, so the extent of putative cerebral hypoperfusion caused by blunted orthostatic MAP increase remains speculative.

Among older individuals, aortic stiffness is associated with overt orthostatic hypotension.<sup>9,10</sup> Considering the aforementioned studies among older participants, our study among relatively younger and healthier participants suggests that there are important differential effects of orthostatic change in MAP. We observed significant effect modification by age

**Table 4.** Relations of Orthostatic Change in MAP on Structural Brain MRI Outcomes

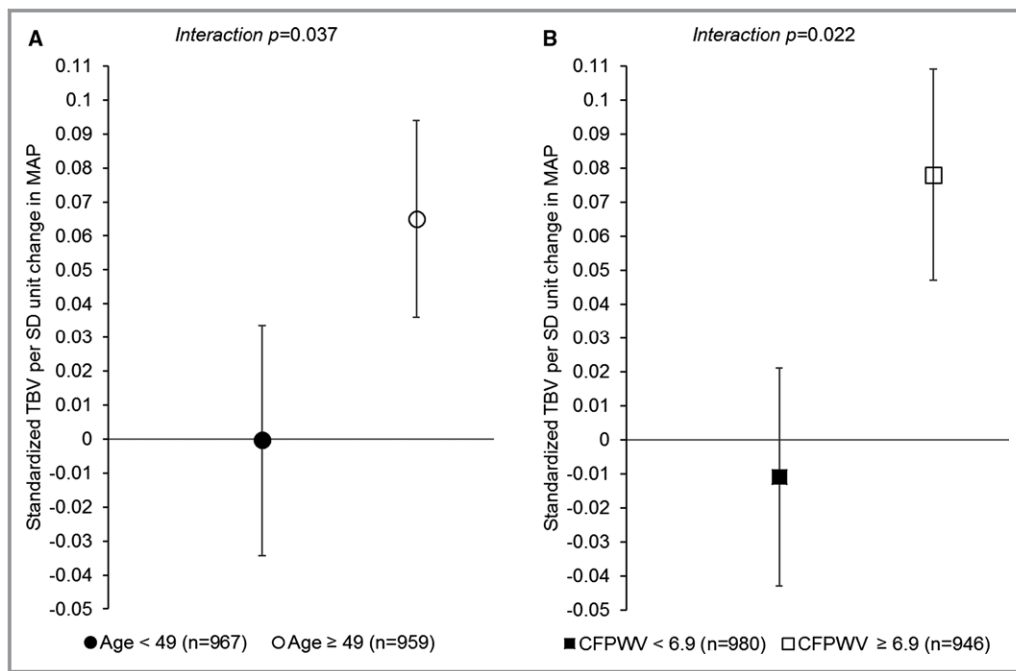
Brain MRI Outcomes	Minimal Model*		Expanded Model†	
	$\beta \pm SE$	<i>P</i> Value	$\beta \pm SE$	<i>P</i> Value
Total brain volume	0.037±0.022	0.094	0.043±0.025	0.081
WMH volume	−0.005±0.020	0.810	0.003±0.022	0.897
Lateral ventricular volume	−0.006±0.022	0.780	−0.016±0.024	0.515
Deep lacunes present‡	1.22 (0.94, 1.58)	0.139	1.32 (0.99, 1.76)	0.056

MAP indicates mean arterial pressure; MRI, magnetic resonance imaging; WMH indicates white matter hyperintensities.

\*Minimal models adjusted for age, sex, and time between clinical and MRI exams.

†Expanded models additionally adjusted for heart rate, corresponding supine MAP, the fourth quartile of waist to hip ratio, fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, hypertension treatment, diabetes mellitus, smoking, presence of depressive symptoms, prevalent cardiovascular disease, and prevalent atrial fibrillation.

‡Odds ratios with 95% confidence intervals were reported for deep lacunes present.



**Figure.** Analysis of effect measure modification for the association of orthostatic change in MAP with total brain volume. Summaries of the regression coefficients ( $\pm$ SE) for relations between brain volume and orthostatic change in MAP by median age (A) and by median CFPWW (B) are presented. CFPWW indicates carotid-femoral pulse wave velocity; MAP, mean arterial pressure; TBV, total brain volume.

and extent of aortic stiffness on the relation between orthostatic change in MAP and brain MRI structure and neuropsychological exam performance. Consistent with the previous studies, the deleterious effects on MRI measures by orthostatic change in BP are enhanced with advancing age and elevated aortic stiffness. Whereas earlier studies of the effect of aortic stiffness or orthostatic changes in BP on brain integrity and function have included elderly participants, the present study stratifies participants at a stage of life when aortic stiffness begins to rise dramatically and subclinical markers of brain damage and cognitive impairment begin to accumulate. Furthermore, we could observe these modest differential effects at a CFPWW threshold of 6.9 m/s, which is relatively low. Thus, our study indicates that middle-aged individuals with blunted orthostatic change in MAP and concurrent stiff aortas may begin to experience brain atrophy as indicated by smaller total cranial volumes. Contrary to previous studies in elderly participants,<sup>29,30</sup> we did not observe a significant relation between blunted MAP increase and poorer cognitive function among older participants, whereas we did observe a significant relation among younger participants. First, we would like to underscore that our sample was relatively young as compared with previous reports. In addition, unlike the aforementioned studies, we assessed the relation of orthostatic change in MAP alone as a continuous variable whereas many previous studies defined orthostatic hypotension as a dichotomous variable, where a

substantial decrease of either systolic BP ( $-20$  mm Hg) or diastolic BP ( $-10$  mm Hg) was considered prevalent orthostatic hypotension. The latter approach pools the contributions of reductions in pulse pressure and MAP into a single phenotype, making it impossible to determine whether orthostatic change in MAP alone was related to cognitive outcomes in older individuals. Our data suggest that even a modest blunting of orthostatic MAP at a younger age ( $<49$  years) may be an early marker of incipient cognitive impairment. However, further studies assessing the age-related consequences of orthostatic MAP changes are warranted.

### Aortic Stiffness May Enhance Effects of Orthostatic Change in MAP on Cognition

Blunted orthostatic change in MAP may lead to cerebral hypoperfusion potentially contributing to subclinical brain damage and cognitive impairment. Multiple studies have shown that regions of the brain that are highly susceptible to a change in blood flow, such as the frontal lobe, have exhibited hypoperfusion during episodes of orthostatic hypotension,<sup>33–36</sup> which could lead to impaired executive functions. In addition, Robertson et al recently showed that regional cerebral hypoperfusion was related to orthostatic hypotension and may be involved in progression in Lewy body dementias.<sup>37</sup>

To sustain cerebrovascular perfusion upon standing, MAP must increase to counter gravity; however, individuals who have a blunted orthostatic increase in MAP may experience insufficient brain perfusion if they also have impaired cerebrovascular reactivity. Microvascular reactivity is impaired in the presence of higher aortic stiffness.<sup>14</sup> In addition, we showed that aortic stiffness and microvascular remodeling contribute to the progression of structural and functional damage to the brain among the elderly.<sup>3,8</sup> Diminished change in orthostatic blood pressure is more prevalent among older individuals as a result of age-associated remodeling of arteries and decline in autonomic nervous system and baroreceptor sensitivity.<sup>29</sup> However, we recently showed among middle-aged individuals that the relation between elevated aortic stiffness and blunted orthostatic change in MAP suggests that the function of strain-sensitive baroreceptors may be attenuated in individuals with stiffer arteries earlier in life.<sup>11</sup> The present study further indicates that individuals with stiff arteries and blunted orthostatic response may have enhanced risk for hypoperfusion attributed to the combined effects of insufficient increase in MAP and an impaired cerebral microvascular response. We speculate that the combination of hypoperfusion attributed to blunted orthostatic change in MAP and microvascular dysfunction may underlie the loss of the beneficial effect of higher orthostatic change in MAP on executive function (as indicated by Trails B-A) among older participants and participants with elevated stiffness. However, additional studies are warranted to assess the role of cerebrovascular dysfunction and orthostatic change in MAP on cognitive function.

## Limitations

The limitations of our study should be considered. We used a cross-sectional design; this type of observational study design limits our ability to establish temporal relations among orthostatic change in MAP, neuropsychological and brain MRI outcomes, and aortic stiffness. We did not account for multiple testing; thus, the reader should consider that our investigation is more susceptible to type 1 error. Because the neuropsychological assessment and orthostatic change in MAP were assessed at close time points, we were unable to determine a causative role of orthostatic change in MAP on decline in executive function and induction of brain injury, particularly among individuals who are older and/or have stiffer aortas. Given that the brain plays a major role in BP regulation, aortic stiffness could cause microvascular brain damage that interferes with the orthostatic BP response. Thus, autonomic dysfunction caused by subclinical neurodegenerative disease may explain the observation that blunted orthostatic MAP increase is associated with smaller brain volumes and impaired executive function. Additional work

using longitudinal designs observing the relation between orthostatic change in MAP and cognitive and brain structural outcomes is warranted. However, the current study includes a large, well-characterized sample with detailed and validated neuropsychological assessment. We studied a younger to middle-aged sample with a median age of 49 years. A major strength of the present study is that the median age of our sample is positioned precisely at the turning point where hemodynamic variables assume a markedly different age trajectory.<sup>38</sup> Therefore, we were able to assess and demonstrate important differences in relations of brain measures with orthostatic MAP response, aortic stiffness, and age on either side of this transitional age. However, additional studies in older participants are required to establish whether these associations apply in older individuals where deficits in cognition are more prevalent. In addition, because our cohort is comprised of white participants of European descent, our findings may not be generalizable to other ethnic groups.

## Conclusion

In this community-based sample of younger to middle-aged participants, a greater orthostatic increase in MAP was related to better executive function among younger participants and among participants with less-stiff aortas. In addition, among older participants and participants with stiffer aortas, coupling between orthostatic change in MAP and total brain volume was enhanced, suggesting that older individuals and those with a stiffened aorta have enhanced dependency on the orthostatic increase in MAP that normally accompanies change from supine to upright posture. Thus, these findings indicate that the brain is sensitive to orthostatic change in MAP, which is dependent on age and extent of aortic stiffness. Because aging is associated with a sharp increase in aortic stiffness, older individuals disproportionately have stiff aortas. Thus, the brains of older individuals in this sample may be sensitive to orthostatic change in MAP, which may be dependent primarily on age. Whether change in orthostatic BP is predictive of future brain injury or cognitive function in the setting of older age or elevated aortic stiffness remains to be seen. Yet, our study further accentuates the importance of understanding how novel, and potentially modifiable, factors contribute to subclinical changes in brain structure and function earlier in life when interventions that are directed toward important vascular targets may prevent or delay the onset of cognitive decline.

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