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RESEARCH ARTICLE

APOE4 carriers display loss of anticipatory cerebrovascular regulation across the Alzheimer's disease continuum

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Abstract

BACKGROUND: Maintenance of cerebral blood flow during orthostasis is impaired with aging and associated with cognitive decline, but the effect of the apolipoprotein ε4 allele (*APOE4*) is unknown.

METHODS: Older adults (n = 108) (*APOE4* carriers, n = 47; non-carriers, n = 61) diagnosed as having normal cognition (NC), mild cognitive impairment (MCI), or Alzheimer's disease (AD) underwent transcranial Doppler ultrasound assessment of middle cerebral artery blood velocity (MCAv) and beat-to-beat mean arterial blood pressure (MAP) during a sit-to-stand transition. Anticipatory and orthostasis-induced MCAv and MAP responses were compared between genotypes and diagnostic classifications.

RESULTS: Cognitively normal *APOE4* carriers showed greater anticipatory MCAv increase, greater MCAv decrease with orthostasis, and shorter latency of peripheral MAP responses to orthostasis compared to non-carriers. MCAv and MAP responses were delayed and attenuated across the *APOE4* disease continuum, with no differences between genotypes in MCI and AD.

DISCUSSION: Unique cerebral and peripheral vascular compensation observed in *APOE4* carriers may be neuroprotective for AD development.

KEYWORDS
Alzheimer's disease, apolipoprotein E ε4, dynamic cerebral autoregulation, mild cognitive impairment, transcranial Doppler ultrasound

Highlights

- APOE4 carriers with NC show greater anticipatory increases in MCAv prior to orthostasis and decreases during orthostasis.
- APOE4 carriers with NC show faster peripheral MAP responses during orthostasis.
- APOE4 carriers with MCI and AD display loss of anticipatory MCAv responses.
- APOE4 carriers with MCI and AD display slower peripheral MAP responses.

- Unique cerebral and peripheral vascular compensation observed in *APOE4* carriers may be neuroprotective for AD development.

1 | BACKGROUND

Possession of the *Apolipoprotein* ε4-allele (*APOE4*) is an established central player in the pathogenesis of Alzheimer's disease (AD).[1–4] Increasing evidence points to impairments in cerebrovascular function and a greater decline in cerebral blood flow (CBF) in *APOE4* carriers that may contribute to cognitive impairment and dementia.[5–9] Older adults with normal cognition (NC) who carry *APOE4* demonstrate a greater decline in CBF with aging compared to non-carriers[10] and an earlier blood–brain barrier breakdown that predicts subsequent cognitive decline.[9] Older adult *APOE4* carriers with NC, lower cerebrovascular function, and greater amyloid beta deposition have lower cognitive executive function, an interaction that is not present in non-carriers.[11,12] Interestingly, differences in cerebrovascular function have even been detected in young adult *APOE4* carriers, who show reduced cerebrovascular reactivity to carbon dioxide compared to non-carriers.[13] Together, these results implicate differences in cerebrovascular function between *APOE* genotypes that may influence their vulnerability to the development of AD.

Regulation of CBF velocity under states of hemodynamic challenge, such as those induced during orthostasis, can be measured using transcranial Doppler (TCD) ultrasound.[14–16] CBF responses during orthostasis offer functional insights into the cerebrovascular system not gleaned from resting states alone, particularly in older adult populations[17] and diseased brain states.[18] In response to hypotension induced during transition from seated to standing positions, the cerebral microvasculature typically dilates quickly to increase blood flow to the brain.[19] Impaired ability to regulate the cerebral pressure/flow relationship results in repeated, exaggerated drops in cerebral perfusion that could damage neuronal tissue over time.[20,21] Abnormalities in CBF responses to orthostasis have been observed in older adults[17] and a range of diseased brain states (e.g., stroke,[22,23] concussion,[24,25] and diabetes[26]); however, their relationships to cognitive impairment and dementia have been inconsistent, with some studies finding no differences in orthostasis-induced CBF decreases in MCI and AD and others show subtle differences.[27–30] One study found that transgenic *APOE4*-expressing mice have reduced CBF and an inability to increase CBF to meet the demands of active brain areas; this resulted in local hypoxia causing white matter damage and cognitive dysfunction.[8] These findings suggest that *APOE4* may impair vasodilatory mechanisms involved in cerebrovascular regulation, which are necessary for effective responses during orthostasis, potentially leading to downstream damage to the brain parenchyma.

In addition to differences in cerebrovascular health and function, emerging evidence suggests that *APOE4* carriers may display earlier signs of neurovascular compensation during cognitive and motor tasks compared to their non-carrier (*APOE3 or APOE2*) peers.[8,31] For example, older adults with NC who carry *APOE4* show greater cognitive–motor dual-task interference during gait,[31] and animal models of *APOE4* show an impaired ability to match CBF with increases in task-related brain activity compared to *APOE3*.[8] Greater prefrontal cortical activity, implicated in cognitive dual-task interference,[32] can be engaged in an anticipatory manner prior to movement initiation.[33] The prefrontal cortex has also been strongly implicated in the regulation of cardiovascular function.[34,35] However, whether or how differences in cortically mediated whole-body behaviors may interact or influence differences in cerebrovascular function observed between *APOE4* carriers and non-carriers is unclear.

Considering differences in neurovascular brain function between *APOE4* carriers and non-carriers are detected even at a young age, yet only half of heterozygous *APOE4* carriers develop AD,[36] there must be contributing neuroprotective factors that influence AD development. Further, cerebral blood velocity and blood pressure regulation have been implicated in dysfunctional vascular regulation across a number of age-related and neuropathologic disease states.[22–26] Here, we hypothesized that older adult *APOE4* carriers would show a dysfunctional cerebrovascular response to orthostasis compared to their non-carrier peers but that *APOE4* carriers with NC would also display vascular compensation. We further hypothesized that older adults with MCI and AD would be characterized by greater cerebrovascular dysfunction and the absence of vascular compensation in *APOE4* carriers. We tested the effect of *APOE4* genotype on anticipatory and orthostatic changes in cerebral blood velocity and beat-to-beat peripheral mean arterial blood pressure (MAP) in a group of older adults classified as having NC, MCI, or early-stage AD.

2 | METHODS

2.1 | Participants

This project leveraged the University of Kansas Alzheimer's Disease Research Center (KU ADRC). The recruitment and enrollment process for the ongoing KU ADRC Clinical Cohort (P30 AG072973) focuses on maintaining a cohort of approximately 500 participants annually, consisting of NC and cognitively impaired individuals who are characterized as having either MCI or AD. Inclusion criteria target individuals 60 years of age and older for NC and any age for MCI/AD with a study partner, while exclusion criteria were (1) significant neurological conditions or (2) large vessel strokes. New participants undergo comprehensive baseline (BL) evaluations, including clinical, cognitive, imaging, and biomarker assessments, with annual follow-ups to track

TABLE 1 Participant characteristics.

Diagnosis	*APOE* status	Mean	SD	*P*
NC				
Age (years)	Non-carrier, $n = 43$	74.6	5.7	0.058
	ε4 carrier, $n = 22$	72.0	6.5	
Systolic BP (mmHg)	Non-carrier	128	14	0.678
	ε4 carrier	126	21	
Diastolic BP (mmHg)	Non-carrier	74	8	0.410
	ε4 carrier	72	11	
Race	Non-carrier	42 (W); 1 (B); 0 (≥2)		>0.754
	ε4 carrier	20 (W); 2 (B); 0 (≥2)		
Education (years)	Non-carrier	17	3	0.965
	ε4 carrier	17	3	
Sex (F/M)	Non-carrier	28/15		0.030
	ε4 carrier	11/11		
MMSE	Non-carrier	28.0	1.1	0.659
	ε4 carrier	28.4	1.8	
MoCA	Non-carrier	26.5	2.1	0.693
	ε4 carrier	26.4	2.9	
MCI				
Age (years)	Non-carrier, $n = 10$	74.6	7.4	0.741
	ε4 carrier, $n = 15$	73.7	4.0	
Sex (F/M)	Non-carrier	4/6		0.155
	ε4 carrier	2/8		
Systolic BP (mmHg)	Non-carrier	128	19	0.853
	ε4 carrier	126	16	
Diastolic BP (mmHg)	Non-carrier	74	11	0.566
	ε4 carrier	76	6	
Race	Non-carrier	8 (W); 1 (B); 1 (≥2)		>0.211
	ε4 carrier	13 (W); 2 (B); 0 (≥2		
Education (years)	Non-carrier	19	4	0.07
	ε4 carrier	17	3	
MMSE	Non-carrier	27.2	1.9	0.236
	ε4 carrier	25.8	3.0	
MoCA	Non-carrier	23.3	2.9	0.846
	ε4 carrier	23.0	3.7	
AD				
Age (years)	Non-carrier, $n = 8$	71.1	7.9	0.426
	ε4 carrier, $n = 10$	74.1	6.5	
Sex (F/M)	Non-carrier	2/5		0.065
	ε4 carrier	4/5		
Systolic BP (mmHg)	Non-carrier	127	14	0.613
	ε4 carrier	130	13	
Diastolic BP (mmHg)	Non-carrier	74	7	0.906
	ε4 carrier	74	6	
Race	Non-carrier	8 (W); 0 (B); 0 (≥2)		>0.180
	ε4 carrier	8 (W); 2 (B); 0 (≥2)		

(Continues)

TABLE 1 (Continued)

Diagnosis	*APOE* status	Mean	SD	*P*
Education (years)	Non-carrier	17	4	0.439
	ε4 carrier	16	3	
MMSE	Non-carrier	23.0	6.9	0.505
	ε4 carrier	21.0	4.7	
MoCA	Non-carrier	16.3	6.3	0.700
	ε4 carrier	17.5	5.5	

Abbreviations: AD, Alzheimer's disease; B, Black; ≥2, more than 2 races; BP, blood pressure at baseline prior to sit-to-stand assessment; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NC, normal cognition; SD, standard deviation; W, White.

cognitive and physical health. Participants who enrolled in the KU ADRC Clinical Cohort between September 6, 2019 and April 23, 2024 were included in the present analysis if they (1) were willing to complete an additional study visit involving neurovascular assessment, (2) had complete APOE genotyping available during this timeframe, and (3) had the presence of a TCD ultrasound signal. A total of 124 genotyped participants completed neurovascular assessment TCD screening, and 16 participants did not possess a visible TCD signal and were excluded from subsequent assessment and analyses. The remaining participants ($n = 108$) (with NC [$n = 65$], mild cognitive impairment [MCI, $n = 25$], or early AD [$n = 18$]) were included in the present sit-to-stand assessment and analyses (Table 1). The experimental protocol was approved by the KU Institutional Review Board (IRB No.: STUDY 00147888 and 0011132), and all participants provided written informed consent.

2.2 | Clinical neuropsychological test battery

All participants completed a standard in-person clinical and cognitive evaluation on a separate day, during which the Clinical Dementia Rating (CDR) scale and the United States Alzheimer's Disease Research Center network neuropsychological test battery was performed by a trained clinician and psychometrist, respectively.[37,38] Clinical and cognitive data were reviewed, and each participant was classified as having NC, MCI, or AD at a consensus diagnostic conference.[39] Participants also completed a Mini-Mental State Examination (MMSE)[40] and Montreal Cognitive Assessment (MoCA)[41] (Table 1).

2.3 | Sit-to-stand protocol and data acquisition

The KU ADRC conducts a BL neurovascular visit upon enrollment in the cohort in interested participants. We used TCD ultrasound to assess middle cerebral artery blood velocity (MCAv) during a sit-to-stand positional transfer. A 2-MHz TCD probe (RobotoC2MD, Multigon Industries) was used to record right MCAv over the temporal window. The left MCA was used if the right MCA signal was absent. Continuous beat-to-beat MAP was recorded through a cuff around the left middle finger (Finapres Medical Systems, Amsterdam, the Netherlands). A five-lead electrocardiogram (Cardiocard; Nasiff Associates, Central Square, New York) continuously recorded heart rhythm and was used to synchronize MCAv and MAP across the cardiac cycle.[42,43] A capnograph (BCI Capnocheck Sleep 9004, Smiths Medical, Dublin, OH, USA) recorded continuous expired end tidal carbon dioxide ($P_{ET}CO_2$) through a nasal canula, and participants were instructed to breathe through their nose throughout the 3-min duration of the sit-to-stand recording. All data were recorded at 500 Hz. Data were continuously recorded during a single sit-to-stand transition. During the first minute of the recording, the participant remained seated quietly. At the 60-s mark of the recording, the experimenter verbally cued the participant to stand and remain standing for 2 min. Time-synchronized raw data were acquired through an analog-to-digital unit (NI-USB-6212, National Instruments, Austin, TX, USA) and customized MATLAB software (The MathWorks Inc., Natick, MA, USA).

2.4 | Quantification of anticipatory and autonomic responses

Recordings of MCAv and MAP were visually inspected and discarded when R–R intervals were >5 Hz or changes in peak MCAv or MAP exceeded 10 cm/s or 10 mmHg in a single cardiac cycle, respectively. Trials with <85% of samples were discarded from analysis. Mean MCAv and MAP were calculated from the area under the curve (AUC) for each cardiac cycle.[44] The onset of the sit-to-stand event was identified at 60 s into the recording, and the onset beat = 0 was identified as the beat immediately following $t = 60$ s. Two mean BL metrics were computed within the 30 beats immediately preceding the onset of the sit-to-stand transition, in which BL1 = −31 to −16 beats and BL2 = −15 to −1 beats, and sit-to-stand cue onset = beat 0. Automated identification of the post-stand MCAv and MAP nadir (lowest point after standing) and latency in seconds from the onset time = 0 to nadir were identified within the first 20 beats immediately following the onset of sit-to-stand (Figure 1) and were visually confirmed for accuracy. We calculated the percentage change in anticipatory ([BL2−BL1]/[BL1*100%]) and orthostatic post-stand responses ([nadir-BL2]/[BL2*100%]).

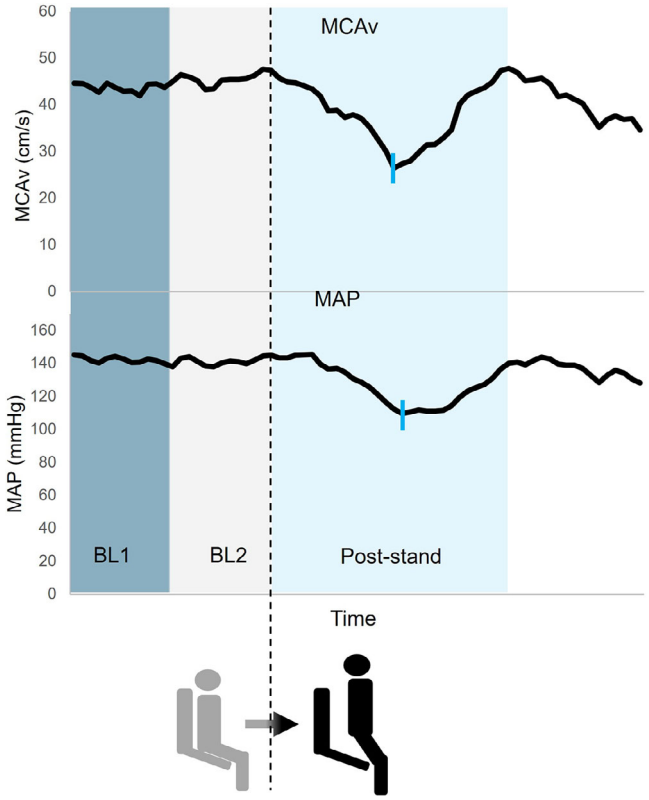

FIGURE 1 Sit-to-stand experimental paradigm and exemplar MCAv and MAP responses. BLs 1 and 2 were computed as 31–16 cardiac beats and 15–1 cardiac beat immediately prior to the sit-to-stand cue (broken line). The lowest values for each MCAv and MAP were identified within the first 20 cardiac beats after the sit-to-stand (blue hash mark). BL, baseline; MCAv, middle cerebral artery blood velocity.

TABLE 2 Participant distribution of APOE isoforms.

APOE isoform	No. participants
ε3/ε3	58
ε2/ε3	4
ε3/ε4	36
ε4/ε4	10
ε2/ε4	0

Abbreviation: APOE, apolipoprotein E.

2.5 | *APOE* genotyping

Taqman single-nucleotide polymorphism (SNP) allelic discrimination assays (Thermo Fisher Scientific) were used to determine *APOE4*, *APOE3*, and *APOE2* alleles to the two *APOE*-defining SNPs, rs429358 (C_3084793_20) and rs7412 (C_904973_10), using whole blood samples stored at −80°C.[45,46] Individuals were classified as an *APOE4* carrier in the presence of one or two *APOE4* alleles (e.g., ε3/ε4, ε4/ε4). Individuals with homozygous E3 (i.e., ε3/ε3) or ε2/ε3 were classified as non-carriers. The specific APOE isoforms of the participant cohort can be found in Table 2.

2.6 | Statistical analyses

We tested for normality and heterogeneity of variance of all data used for analyses using Kolmogorov–Smirnov and Levene tests, respectively. Age and sex were included as covariates to control for sex differences and trending age differences between *APOE4* carrier and non-carrier groups (Table 1). First, we compared absolute MCAv and MAP metrics across time during the sit-to-stand transition between *APOE4* carriers and non-carriers for each NC, MCI, and AD diagnostic group. We used separate two-way mixed ANOVAs with factors of genotype (*APOE4* carrier, non-carrier) and time (BL1, BL2, post-stand) for each diagnostic group. We compared MCAv and MAP anticipatory (BL1–BL2) and orthostatic response (BL2 to post-stand) changes within subjects and between subjects at each time point. Post hoc analyses were performed for significant interaction effects using independent *t*-tests (between subjects at each timepoint) and paired *t*-tests (within subjects between each time point). A post hoc power analysis across all participants showed that this dataset was 80.3% (MAP) and 52.4% (MCAv) powered to detect a significant time-by-genotype interaction effect with an a priori level of significance set to 0.05.

We then used two-way independent ANOVAs to compare change in MCAv and MAP during the sit-to-stand transition relative to baseline (BL1) in *APOE4* carriers and non-carriers diagnostically classified as NCs, MCI, and AD. Two-way independent ANOVAs were used to compare the magnitude of MCAv and MAP anticipatory responses, orthostatic responses, and orthostatic response latencies between *APOE4* carriers and non-carriers within each diagnosis classification NC, MCI, and AD and between each diagnosis classification within each genotype. For MCAv change, a post hoc power analysis showed that this dataset was powered to detect a significant genotype-by-diagnosis interaction at 76.1% (anticipatory response), 69.5% (orthostatic response), and 71.6% (orthostatic response latency) with a significance set to 0.05. For MAP change, post hoc power analyses showed that this dataset was powered to detect a significant genotype-by-diagnosis interaction at 73.9% (anticipatory response), 66.5% (orthostatic response), and 97.0% (orthostatic response latency). All analyses were performed using SPSS version 29 with an a priori level of significance set to 0.05.

3 | RESULTS

For two participants (NC, *APOE4*, $n = 1$; AD, *APOE4*, $n = 1$), MAP data were unavailable due to technical issues with the device and were discarded from this part of the analysis. Two different participants (NC, *APOE4*, $n = 1$; AD, *APOE4*, $n = 1$) had <85% samples available free of artifact on TCD signals and were discarded from this part of the analysis.

Within each diagnostic group (NC, MCI, AD), there were no significant differences between *APOE4* carriers and non-carriers in age ($p > 0.58$), MMSE ($p > 0.236$), or MOCA score ($p > 0.693$), BL blood pressure (systolic, $p > 0.613$; diastolic, $p > 0.410$), or group-level hypertension (Table 1). There were no significant differences in years

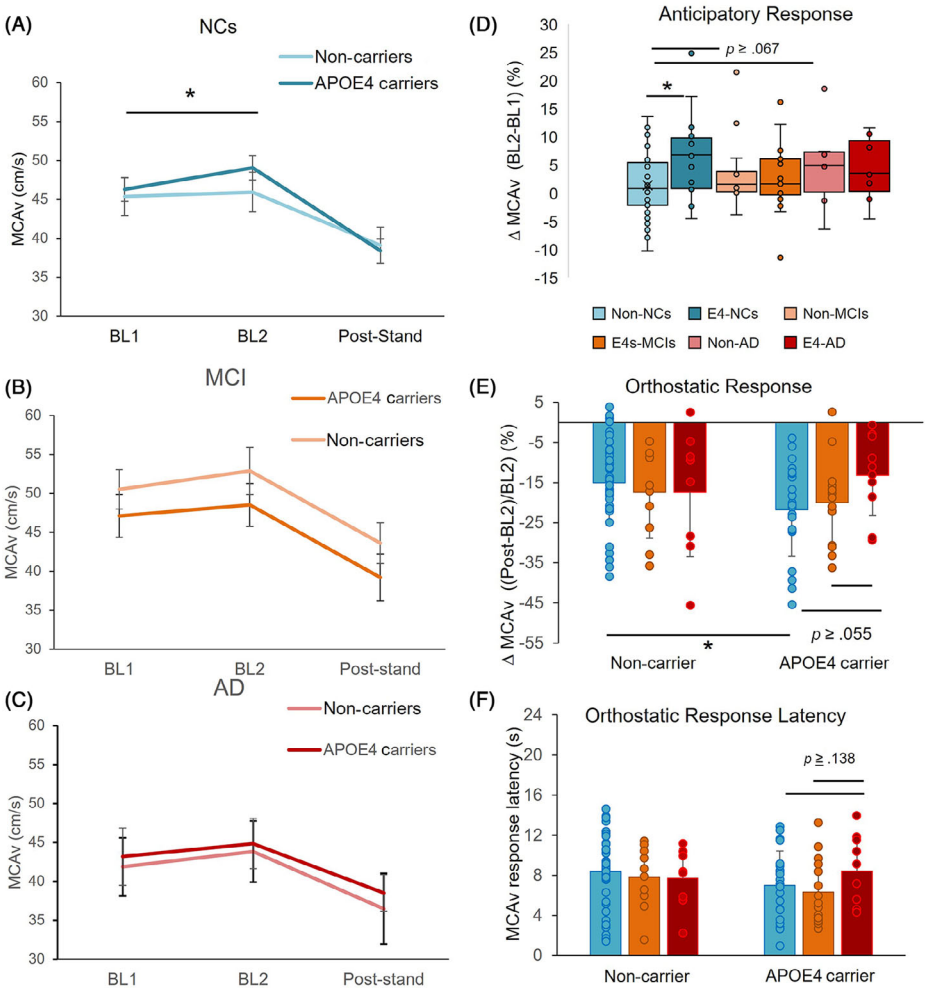

FIGURE 2 Cerebrovascular responses to orthostasis in *APOE4* carriers and non-carriers with normal cognition (NC), MCI, and AD. *APOE4* carriers with NC showed an anticipatory increase in MCAv between BL1 and BL2 just before standing (A), while non-carriers showed no anticipatory change. The magnitude of anticipatory increase in MCAv relative to BL1 was greater in NC *APOE4* carriers compared to non-carriers. NC non-carriers tended to show lesser anticipatory increase compared to MCI and AD non-carriers, but this difference did not reach statistical significance (D). MCAv did not show a significant change over time during sit-to-stand in older adults diagnosed with MCI (B) and/or AD (C), regardless of genotype. *APOE4* carriers showed greater post-stand decreases in MCAv compared to non-carriers (E). There were no significant differences in MCAv response latency between genotypes ($p \geq 0.138$). $^{**}p < 0.05$ for within-subject post hoc tests for significant interaction effects. $^{**}p < 0.05$ for between-subject post hoc tests for significant interaction effects. *APOE4*, apolipoprotein ε4 allele; AD, Alzheimer's disease; BL, baseline; MCAv, middle cerebral artery blood velocity; MCI, mild cognitive impairment; NC, normal cognition.

of education or in the proportion of participants who identified with each category of race observed between *APOE4* carriers and non-carriers within each diagnostic subgroup (Table 1). Notably, 93.5% of participants in this study identified as White, consistent with the lack of racial diversity that is prevalent across studies involving AD.[47] In the NC group, there was a greater proportion of females in the non-carrier compared to the *APOE4* carrier genotype ($p = 0.030$), with no sex differences in the MCI or AD diagnostic group ($p > 0.065$). For $P_{ET}CO_2$ we observed no interaction effects ($p \geq 0.116$), differences between *APOE4* genotypes for NCs, MCI, or AD diagnoses ($p \geq 0.172$), or changes across time ($p \geq 0.073$) (Figure S1). Consistent with the expected cardiovascular responses to orthostasis,[48] we observed that heart rate increased between BL2 and post-stand, regardless of diagnosis (NCs,8.5 ± 10.7 bpm; MCI, 13.1 ± 16.3 bpm; AD, 7.7 ± 6.7 bpm) ($p < 0.001$); however, there were no interaction effects ($p \geq 0.304$) or differences between *APOE4* carriers and non-carriers ($p \geq 0.183$) in heart rate response or heart rate at any timepoint (Figure S1).

3.1 | Effect of *APOE* genotype on cerebrovascular responses to orthostasis across disease progression

Cognitively normal *APOE4* carriers showed a greater anticipatory increase and greater orthostasis-induced decrease in MCAv compared to non-carriers (Figure 2A,D). AD progression (MCI and AD) was characterized by a loss of anticipatory increase in MCAv and blunted MCAv responses to orthostasis compared to NC, while no effect of diagnosis was present in non-carriers (Figure 2B,C,E,F).

3.1.1 | Within-subject effect of APOE4

Cognitively normal older adults showed a time-by-genotype interaction ($F_{2,59}$ = 3.35, p = 0.038); *APOE4* carriers showed a significant within-group anticipatory increase in MCAv between BL1 and BL2 (p = 0.004) that did not occur in non-carriers (p = 0.125) (Figure 2A). Both groups showed a significant decrease in MCAv between BL2 and post-stand (p < 0.001) (Figure 2A). There were no between-group differences in absolute MCAv at any time point (p > 0.285). In contrast, there was no time-by-genotype interaction for anticipatory MCAv increase in older adults diagnosed with MCI (F_{242} = 0.116, p = 0.891) or AD (F_{226} = 0.334, p = 0.719). For each MCI and AD diagnostic groups, there were no main effects of time (MCI: p = 0.070; AD: p = 0.367) or genotype (MCI: p = 0.229; AD: p = 0.474) (Figure 2B,C).

3.1.2 | Between-subject effect of diagnosis

In *APOE4* carriers, AD progression (MCI and AD) was characterized by a loss of anticipatory increase in MCAv, while no effect of diagnosis was present in non-carriers. Anticipatory change in MCAv showed a diagnosis-by-genotype interaction effect ($F_{5,10}$ = 3.05, p = 0.026), with no main effects of diagnosis or genotype (p > 0.521). NC *APOE4* carriers showed greater anticipatory increases in MCAv compared to NC non-carriers (p = 0.004), but no statistical difference compared to *APOE4* carriers at the MCI and early AD stages of disease ($p \geq$ 0.490) (Figure 2D). While non-carriers with MCI and AD tended to show greater anticipatory MCAv increase on average compared to non-carrier NCs, this difference did not meet our adopted level of significance ($p \geq$ 0.067).

For orthostasis-induced MCAv response, no diagnosis-by-time interaction ($F_{5,106}$ = 1.68, p = 0.192) or main effects (genotype, $F_{5,106}$ = 0.42, p = 0.521; diagnosis, $F_{5,106}$ = 0.59, p = 0.559) were observed for the magnitude of MCAv change ($F_{5,106}$ = 1.68, p = 0.192) (Figure 2E) or latency of response (p > 0.192) (Figure 2F) (p > 0.192). NC *APOE4* carriers showed greater reduction in MCAv compared to non-carriers (p = 0.023) (Figure 2E). No group differences were observed at the MCI and early AD compared to non-carriers (p > 0.480). However, orthostasis-induced decreases in MCAv tended to decrease in *APOE4* carriers with MCI and AD compared to *APOE4* carriers with NC ($p \geq$ 0.055) (Figure 2E). *APOE4* carriers with early-stage AD tended to show slower MCAv response latencies compared to those with MCI or NC, but this difference did not meet our adopted level of significance ($p \geq$ 0.138) (Figure 2F).

3.2 | Effect of APOE4 on peripheral vascular responses to orthostasis across disease progression

For peripheral MAP, *APOE4* carriers with NC showed no difference in anticipatory change (Figure 3A, D) or orthostasis-induced decrease in MAP (Figure 3E) but did demonstrate shorter latencies of orthostasis-induced MAP responses (Figure 3F). Disease progression did not affect the magnitude of anticipatory or orthostatic changes in peripheral MAP in either *APOE4* carriers or non-carriers with MCI (Figure 3B) or AD (Figure 3C).

3.2.1 | Within-subject effect of APOE4

Cognitively normal older adults showed no significant time-by-genotype interaction ($F_{2,59}$ = 2.30, p = 0.109). While non-carriers with NC displayed a higher blood pressure at BL1 on average than *APOE4* carriers (non-carriers: 94 ± 23 mmHg, *APOE4* carrier: 87 ± 30 mmHg), there was no main effect of genotype among high within-group variability ($F_{2,60}$ = 0.36, p = 0.550). There was a main effect of time ($F_{2,60}$ = 221.69, p < 0.001), in which MAP was higher at BL2 compared to BL1 regardless of genotype (p = 0.031) and was lower at the post-stand time point regardless of genotype (p < 0.001) (Figure 3A). Likewise, there were no significant time-by-genotype interaction effects ($p \geq$ 0.153) in older adults with MCI or AD (Figure 3B,C). There were no significant anticipatory increases in MAP for either MCI (p = 0.207) or AD (p = 0.205), but both groups showed significant orthostasis-induced decreases in MAP between BL2 and post-stand (p < 0.001) regardless of genotype (Figure 3B,C).

3.2.2 | Between-subject effect of diagnosis

There were no diagnosis-by-genotype interaction effects for either anticipatory (Figure 3D) or orthostasis-induced change in MAP (Figure 3E) (p > 0.707). There was a main effect of genotype for orthostasis-induced MAP change (p = 0.049), in which *APOE4* carriers showed less reduction in MAP during orthostasis compared to non-carriers (Figure 3E). There were no main effects of diagnosis for either anticipatory or orthostasis-induced changes in MAP (p > 0.416).

There was a significant disease-by-genotype interaction for orthostatic MAP response latency (F_{5104} = 3.537, p = 0.033), in which a shorter latency of orthostasis-induced MAP response was observed in NC *APOE4* carriers compared to non-carriers (*APOE4* = 9.2 ± 2.7 s; non-carriers = 11.4 ± 2.6 s, p = 0.003) (Figure 3F). This difference between genotypes was also present at the MCI disease stage (p = 0.007). No difference in orthostatic MAP response latency was observed between genotypes in early AD (p = 0.743) (Figure 3F).

4 | DISCUSSION

This study provides novel insights into the effects of the *APOE* genotype on mechanistic regulation of cerebral and peripheral vascular responses to orthostasis over the early stages of AD progression. The sit-to-stand paradigm provided a hemodynamic challenge to the cerebrovascular system[14–16,49] that exposed differences in cerebrovascular regulation between *APOE4* carriers and non-carriers. Here, *APOE4* carriers with NC showed greater drops in MCAv during orthostasis as well as higher anticipatory increases in MCAv and faster peripheral

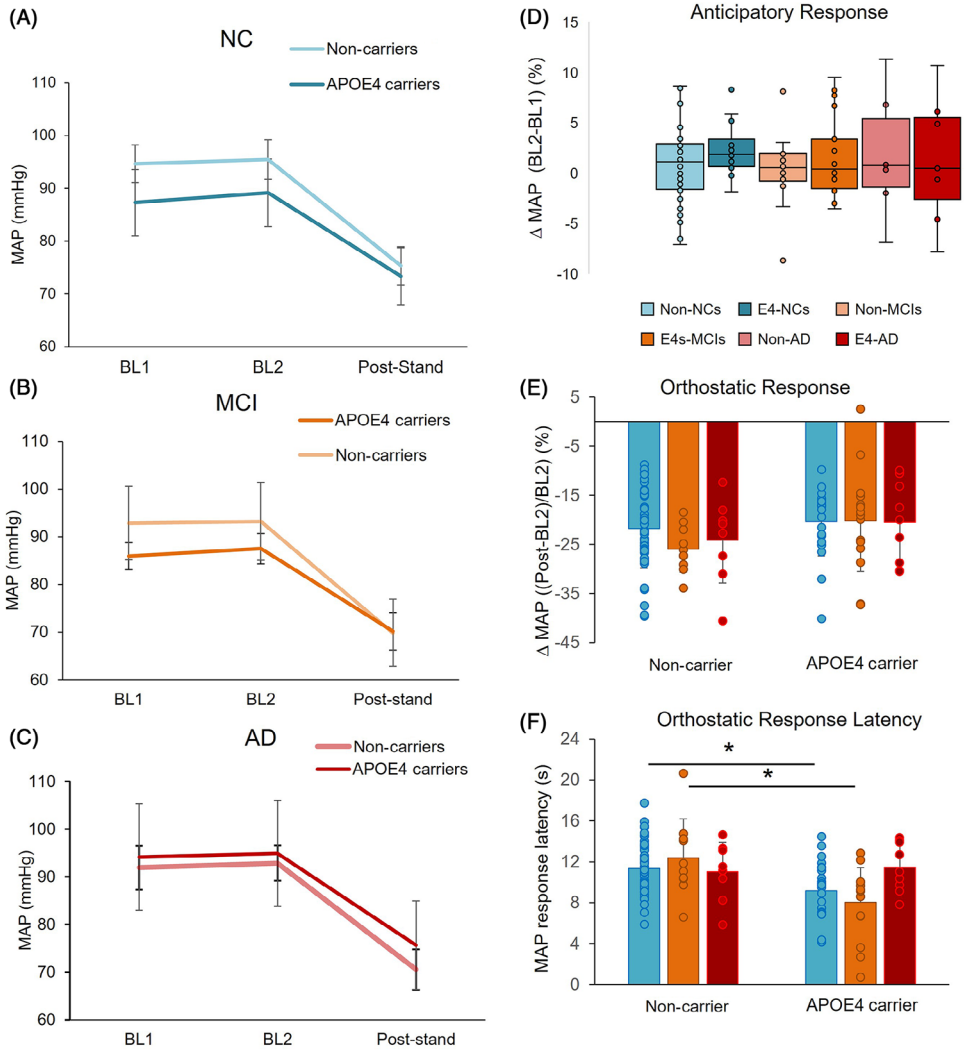

FIGURE 3 Mean arterial blood pressure (MAP) responses to orthostasis in *APOE4* carriers and non-carriers with normal cognition (NC), MCI, and AD. There were no differences in anticipatory increase in MAP between BL1 and BL2 between *APOE4* carriers and non-carriers in NC (A), MCI (B), or AD (C) groups. No differences were observed in anticipatory change in MAP between diagnostic groups as a function of APOE4 genotype (D). Regardless of diagnosis, APOE4 carriers showed less reduction in orthostatic MAP change compared to non-carriers (E). Cognitively normal APOE4 carriers and APOE4 carriers with MCI showed significantly shorter MAP response latencies compared to non-carriers, while there were no differences in AD between genotypes (F). $^*p < 0.05$ for between-subject post hoc tests for significant interaction effects. AD, Alzheimer's disease; APOE4, apolipoprotein ε4 allele; MCI, mild cognitive impairment.

MAP responses compared to their non-carrier peers. These functional cerebrovascular differences may reflect genotype-specific vascular adaptations to counteract an impaired cerebral pressure/flow relationship during orthostasis. Consistent with previous research in AD, we found that baseline resting cerebral blood velocity tended to show a (non-significant) decrease over disease progression.[29,50,51] However, the magnitude of orthostasis-induced drops in MCAv and MAP remained consistent[28] and even showed a trend toward attenuation (lesser drop) of MCAv in MCI and AD diagnoses compared to NCs who carried *APOE4* (Figure 2E), potentially reflecting heightened sympathetic drive observed across AD progression.[52–54] Together, our findings extend the knowledge of AD-related impairments and progression in cerebrovascular regulation to understand differential physiologic responses in individuals who carry the *APOE4* allele within hemodynamic behavioral contexts, which may play a role in their increased vulnerability to AD.[55] Importantly, our findings identify vascular compensatory strategies in *APOE4* carriers that may serve as a target for treatment efforts during a window of therapeutic opportunity.

The present results provide novel evidence that *APOE4* carriers utilize vascular compensation strategies that may counteract genotype-specific impairments in cerebrovascular regulation. Greater anticipatory increases in MCAv (Figure 2A,D) in *APOE4* carriers may potentially serve as compensatory neurovascular adaptations to chronically impaired cerebrovascular regulation, that is, greater drop in MCAv during orthostasis compared to non-carriers (Figure 2E). This anticipatory increase in MCAv is consistent with greater recruitment of prefrontal cortical regions during mobility in individuals with NC, older adult *APOE4* carriers,[31] and heightened excitability of the prefrontal cortex

in patients with AD.[56,57] Notably, the prefrontal cortex can strongly influence the regulation of cardiovascular function.[34,35] Differences in anticipatory MCAv increase were not present in MCI and AD between genotypes (Figure 2B,C,D), implicating that these compensatory adaptations may be lost as *APOE4* carriers progress into clinical syndrome. Greater increases in anticipatory MCAv may reflect greater cerebrovascular contractility, resulting in exaggerated changes in vasoconstriction and dilation in response to changes in blood pressure in the present study, greater cerebral vasomotor activity may be engaged in anticipation of hemodynamic blood flow reduction, resulting in more effective cerebrovascular regulation during orthostasis (Figure 2A). However, higher cerebral vasomotor activity could also lead to chronically reduced CBF, especially if blood pressure becomes elevated.[58]

Greater anticipatory vascular compensation for dysfunctional hemodynamic regulation may also be consistent with recent research implicating *APOE4* as a driver of AD processes through a gain of abnormal neuronal function, rather than a loss of normal function.[59] However, without longitudinal assessments, it remains possible that older adults in the NC group reflect a "healthy survivor" bias, in which greater anticipatory MCAv and faster orthostatic MAP responses contribute to increased neurocognitive resilience.[44] Future studies measuring cortical activity and that employ targeted modulation of key brain regions will help elucidate underlying neural mechanisms that may explain these differences in cerebral and peripheral anticipatory vascular responses in *APOE4* carriers.

Our findings provide evidence that impaired vascular responses to hemodynamic challenge in *APOE4* carriers are cerebral specific. We observed the clinical presence of orthostatic hypotension, that is, reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg (MAP of 13 mmHg within 3 min of standing),[48] in the majority of participants (79%) across all subgroups (Figure 3). However, there were no differences in the magnitude of orthostatic peripheral MAP changes between genotypes or across all stages of disease diagnosis (Figure 3D). Faster peripheral vascular responses to orthostasis in *APOE4* carriers with NC, indicated by shorter MAP response latencies (Figure 3F), may also be consistent with vascular compensation for greater orthostatic drops in MCAv in this subgroup.

Similar to anticipatory cerebrovascular responses, we found that faster MAP responses during orthostasis were present only in *APOE4* carriers with NC and MCI while showing longer delays compared to other diagnostic groups in *APOE4* carriers with AD (Figure 3F). These results could be explained by a potentially adaptive role of heightened sensitivity of the arterial baroreflex[60] in *APOE4* carriers without AD. Autonomic dysfunction of blood pressure regulation has been associated with AD pathology of the insular cortex, which may negatively affect baroreflex mechanisms of blood pressure control.[61] The present results support distinct phenotypes of cerebrovascular dysfunction in *APOE4* carriers and non-carriers that are influenced by the presence of AD and have implications for precision-based prevention and treatment approaches.

There were two unexpected observations involving non-carriers in this study: (1) anticipatory MCAv tended to increase in the MCI stage of disease (Figure 2B), though the genotype-by-time interaction did not reach statistical significance to warrant post hoc testing, and (2) baseline (BL1) MCAv in non-carriers with MCI (50.5 cm/s) tended to be higher than in those with NC (45.3 cm/s) and AD (41.9 cm/s) (Figure 2A-C). While these patterns did not reach statistical significance in exploratory analyses ($p \geq 0.065$), they may identify directions for future investigation involving dissociable effects of *APOE4* in the MCI stage of AD processes. While a decrease in CBF is a consistent finding in AD,[29,50,51] a paradoxical increase in cerebral perfusion has also been reported in the early stages of neurodegenerative diseases such as Parkinson's disease.[62] This initial period of increased cerebral perfusion is posited to be a compensatory response to the emergence of orthostatic hypotension in these patient populations.[62] Consistent with this hypothesis, non-carriers with MCI and AD in the present study tended to show greater orthostatic drops in MCAv (Figure 2E) and MAP (Figure 3E) compared to non-carriers with NC, which could have influenced their tendency toward higher levels of cerebral blood velocity observed at BL. These observations further support distinct phenotypes of cerebrovascular dysfunction in *APOE4* carriers and non-carriers; here, *APOE4* carriers display an absence of effective vascular compensation while non-carriers display an engagement in vascular compensation during early stages of cognitive dysfunction (MCI). Future studies are needed to determine the effectiveness of targeted treatments for brain vascular health in resisting cognitive decline in each *APOE* phenotype of cerebrovascular dysfunction.

4.1 | Limitations

The relatively small sample size involved in the secondary analyses of the present study may have been underpowered to detect genotype-by-diagnosis interactions, as suggested by our post hoc power analyses (e.g., 69.5% powered to detect interactions for MCAv orthostatic response change; Figure 2E). As such, patterns identified in the present analyses, such as a smaller MCAv orthostatic response in APOE4 carriers with AD compared to NC APOE4 carriers, would benefit from further exploration in larger studies as a primary and targeted outcome. Despite controlling for sex in the present statistical analyses, the differences in sex between genotypes in the NC subgroup should be carefully considered in the interpretation of the results, as the biological variable of sex can interact with aging and brain vascular function to influence cognitive function.[12] Although we did not observe statistical differences in BL blood pressure between participant groups (Table 1), participants in this study presented with high between-individual variability in BL blood pressure, which could influence results.

While previous studies using magnetic resonance (MR)-based imaging showed no changes in cerebral vessel diameter in response to change in $P_{ET}CO_2$,[63] it is possible that changes in MCA vessel diameter could have influenced the present results and were not captured in our TCD measures of MCAv. Further, MR-based quantification of white matter hyperintensities associated with atherosclerosis have been associated with CBF decline in pathologic conditions and could affect CBF regulation during orthostasis.[64,65] People with MCI and

AD may be increasingly prescribed antihypertensive medications,[28,66] which may have an effect on cerebral and peripheral responses to orthostasis and could not be controlled for in the present study. During the sit-to-stand, other factors, including neurovascular coupling, sympathetic activity, and cardiac output, can affect cerebral and peripheral responses to orthostasis and were not captured in the present study. A low proportion (<7%) of participants in the present study identified as non-White (Table 1), which significantly limits the generalizability of results and warrants larger studies that exemplify representative recruitment of individuals with diverse demographic and non-demographic characteristics.[47]

4.2 | Conclusions

For the first time, our findings show that hemodynamic challenge exposes *APOE* genotype-specific deficits in cerebrovascular responses to orthostasis in older adults who carry the ε4-allele. Our findings also reveal greater anticipatory increases in cerebral blood velocity and faster arterial pressure responses to orthostasis, consistent with vascular compensatory mechanisms, in NC *APOE4* carriers that may be lost as AD progresses. Further, differences in cerebral and peripheral vascular function in older adults with NC, MCI, and AD implicate that *APOE4* carriers and non-carriers present distinct phenotypes of brain vascular function during hemodynamic challenge that may be clinically relevant to cognitive function. These findings may be used to identify specific features of cerebrovascular dysfunction that could be targeted through precision-based approaches in individuals at high genetic risk of AD.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose. Author disclosures are available in Supporting Information.

CONSENT STATEMENT

All human subjects in this study provided written informed consent.

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