Original Research *Highlight article*

Mechanisms maintaining cerebral perfusion during systemic hypotension are impaired in elderly adults

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Impact statement

Postural orthostasis, and the resultant cerebral under-perfusion and unsteadiness worsen with aging, increasing the risk of falling in elderly adults. Intrinsic cerebral pressure-flow autoregulation and reflex autonomic regulation of systemic vascular resistance and cardiac output contribute to the recovery of cerebral blood flow from postural hypotension, but with aging these mechanisms may be slower to respond. We evaluated in young and elderly adults the contributions of cerebral vasodilation, systemic vasoconstriction, and heart rate to the recovery of cerebral perfusion following a sharp drop in systemic arterial pressure produced by abrupt bilateral thigh-cuff deflation. Cerebral perfusion recovered more gradually in the elderly subjects due to slower cerebral vasodilation and systemic vasoconstriction. Thus, systemic and cerebral vasomotion are the predominant mechanisms restoring cerebral perfusion during acute systemic hypotension, and both are impaired in the elderly.

Abstract

Postural hypotension abruptly lowers cerebral perfusion, producing unsteadiness which worsens with aging. This study addressed the hypothesis that maintenance of cerebral perfusion weakens in the elderly due to less effective cerebrovascular autoregulation and systemic cardiovascular responses to hypotension. In healthy elderly ($n=13$, 68 ± 1 years) and young ($n=13$, 26 ± 1 years) adults, systemic hypotension was induced by rapid deflation of bilateral thigh cuffs after 3-min suprasystolic occlusion, while heart rate (HR), mean arterial pressure (MAP), and blood flow velocity of the middle cerebral artery (V_{MCA}) were recorded. V_{MCA}/MAP indexed cerebrovascular conductance (CVC). Durations and rates of recovery of MAP and V_{MCA} from their respective postdeflation nadirs were compared between the groups. Thigh-cuff deflation elicited similar hypotension and cerebral hypoperfusion in the elderly and young adults. However, the time elapsed ($T\Delta$) from cuff deflation to the nadirs of MAP and V_{MCA}, and the time for full recovery (T_R) from nadirs to baselines were significantly prolonged in the elderly subjects. The response rates of HR (ΔHR, i.e. cardiac factor), MAP (ΔMAP, i.e. vasomotor factor), and CVC following cuff deflation were significantly slower in the elderly. Collectively, the response rates of the cardiac, vasomotor, and CVC factors largely explained T_{RVMCA}. However, the T_{RVMCA}/ΔMAP slope (-3.0 ± 0.9) was steeper ($P=0.046$) than the T_{RVMCA}/ΔHR slope (-1.1 ± 0.4). The T_{RVMCA}/ΔCVC slope (-2.4 ± 0.6) was greater ($P=0.072$) than the T_{RVMCA}/ΔHR slope, but did not differ from the T_{RVMCA}/ΔMAP slope ($P=0.52$). Both cerebrovascular autoregulatory and systemic mechanisms contributed to cerebral perfusion recovery during systemic hypotension, and the vasomotor factor was predominant over the cardiac factor. Recovery from cerebral hypoperfusion was slower in the elderly adults because of the age-diminished rates of the CVC response and cardiovascular reflex regulation. Systemic vasoconstriction predominated over increased HR for restoring cerebral perfusion after abrupt onset of systemic hypotension.

Keywords: Cerebral autoregulation, cerebral blood flow velocity, cerebrovascular conductance, heart rate, hypotension, thigh-cuff inflation–deflation

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Introduction

Normal aging exacerbates transient systemic hypotension at the onset of orthostatic challenges, for example lower body negative pressure (LBNP)[1] or when rising from sitting to standing.[2] This age-related orthostasis may explain increasing prevalence of lightheadedness and unsteadiness in elderly adults upon standing.[3–6] Orthostatic intolerance in the elderly is associated with marked cerebral hypoperfusion as indicated by decreased blood flow velocity of the middle cerebral artery (V_{MCA}) during postural changes[2] or by diminution of cerebral tissue oxygenation during LBNP.[7–9]

Adequate cerebral perfusion during transient systemic hypotension is maintained by an intrinsic mechanism, cerebral pressure-flow autoregulation,[10,11] and by the cardiac[12] and vasomotor[13] systemic responses effected by the autonomic nervous system. Systemic hypotension can be elicited by rapid imposition of LBNP in elderly, but not in young subjects.[1] However, LBNP does produce transient systemic hypotension in young adults when cardiac responses to hypotension are blocked with atropine or glycopyrrolate, resembling the hypotensive response to LBNP in elderly adults.[1] Also in young adults, cardiac autonomic blockade[12] or vasomotor blockade with α_1-adrenergic antagonist prazosin[13] slowed V_{MCA} recovery from cerebral hypoperfusion induced by transient systemic hypotension. These findings underscore the pivotal contributions of cardiovascular reflex regulation to maintaining cerebral perfusion. Although it is well recognized that aging impairs cardiovascular function[9] and reduces cerebral blood flow (CBF),[14] data are scant regarding the relative contributions of cardiac and vasomotor factors to impairment of cerebral perfusion during systemic hypotension in elderly adults. To address this question, this study compared the age-related differences in the contributions of cardiovascular versus cerebral autoregulatory mechanisms to the recovery of cerebral hypoperfusion following transient systemic hypotension.

Abruptly rising from a seated position to standing causes a transient systemic hypotension, but also decreases the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$),[2] indicating hypocapnia which favors reactive cerebral vasoconstriction that limits cerebrovascular autoregulation.[15] Bolus intravenous injection of vasodilator agents, such as sodium nitroprusside[16] and nitroglycerin,[17] lowers mean arterial pressure (MAP) and, thus, cerebral perfusion pressure (CPP). However, these vasoactive agents stimulate cerebral vasodilation which maintains or increases CBF during the drug-induced systemic hypotension, suggesting systemic hypotension failed to elicit cerebral hypoperfusion. After bilateral application of suprasystolic pressure via thigh cuffs to limit blood flow to the lower limbs, rapid cuff deflation nonpharmacologically induces significant, albeit transient, reductions in systemic arterial pressure and CBF, indicated by decreased V_{MCA}, permitting assessment of dynamic cerebral autoregulation.[15,18,19] In relaxed, healthy human subjects, thigh-cuff inflation does not alter MAP, heart rate (HR), or $P_{ET}CO_2$[11] although it might elicit transient somatic sensations during the suprasystolic cuff occlusion.

This study compared the changes in V_{MCA}, cerebrovascular conductance (CVC), HR, and MAP in response to rapid release of 3-min bilateral suprasystolic compression of the thighs. We assessed the duration and rate of the recovery from cerebral hypoperfusion during the transient systemic hypotension initiated by thigh-cuff deflation. CBF is the product of CVC and CPP, the latter a function of MAP. We hypothesized that both cerebral autoregulation effected by the intrinsic CVC response, and CPP, maintained by systemic vasomotor and cardiac responses stabilizing MAP, were essential for recovery of CBF from cerebral hypoperfusion imposed by abrupt systemic hypotension. The results demonstrate that diminished cerebral autoregulation and cardiovascular responses impede recovery of CBF during abrupt hypotension in elderly adults. Furthermore, systemic vasomotion makes a greater contribution to the recovery of CBF than does the cardiac response.

Materials and methods

Study participants

Thirteen healthy elderly (67.5 ± 1.1 years, 3 women) and 13 young adults (25.8 ± 1.0 years, 3 women) subjects signed a consent form and passed a physical examination before enrolling into the study. The study protocol and methods, which were conducted in accordance with local and Federal guidelines and regulations and the Declaration of Helsinki, were approved by the North Texas Regional Institutional Review Board (IRB) at the University of North Texas Health Science Center (#2016-139). All subjects provided a written informed consent before being enrolled in the study. In addition, all participants were asymptomatic for disease. There were no significant differences in weight (elderly: 77.1 ± 2.6 kg; young: 70.1 ± 3.7 kg; $P = 0.13$) or height (elderly: 1.72 ± 0.02 m; young: 1.75 ± 0.02 m; $P = 0.51$) between the groups, although body mass index was higher ($P = 0.033$) in the elderly (26.1 ± 1.1 kg/m^2) than the young (22.9 ± 0.9 kg/m^2) adults. The number of subjects required to attain $1 - \beta = 0.80$ at $\alpha = 0.05$ was estimated from the results of a previous study of age-related differences of cerebrovascular responses to hypoxia.[20]

Measurements

During the experiment, the subject's beat-to-beat HR was determined from a standard electrocardiographic lead (BIOPAC Model ECG100C, Santa Barbara, CA). Systolic and diastolic arterial pressures (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) were measured by radial arterial tonometry (Colin Model 7000 Tonometer, San Antonio, TX) on the nondominant arm. MAP was computed as SBP/3 + DBP•2/3. This noninvasively measured arterial pressure has been validated by its high correlation with the radial arterial pressure measured using intraradial arterial catheter in our laboratory.[21] CBF V_{MCA} was monitored by transcranial Doppler (TCD) sonography using a 2-MHz probe (EZ-Dop DWL Elektronische System, Germany) placed on the left side of the head within the subject's temporal window. Throughout the protocol, the position and angle of the TCD probe were fixed using a custom-made ring held by a Velcro band around the head. The gain and depth of the TCD signals were set at $\leqslant$30% and $\leqslant$50 mm, respectively. Mean V_{MCA} was calculated as systolic $V_{MCA}/3$ + diastolic V_{MCA} • 2/3. CVC was estimated as mean V_{MCA}/MAP. Breath-by-breath breathing frequency (f_{br}) and $P_{ET}CO_2$ were measured by mass spectrometry (Perkin-Elmer, 1100 Medical Gas Analyzer, St Louis, Missouri) via a capillary tube placed in the subject's left nostril. Measured variables were continuously recorded by a computer interfaced with a data acquisition system (BIOPAC SYSTEM MP150, Santa Barbara, CA) and digitized online at 400 Hz.

Study procedure

Before the experiment, all subjects were oriented to the testing procedures, methods of measurement, and thigh-cuff inflation and deflation to be used during testing. The study protocol was conducted as described previously.[11] All experiments were performed between 08:00 and 12:00 at an ambient temperature of 23–24°C. Blood pressure cuffs (11 cm width • 76 cm length; Aspen Labs, Englewood, CO) were placed around the upper thighs. After instrumentation, the subject rested in the supine position for ⩾10 min, and then, baseline cardiovascular variables were recorded for approximately 3 min. Pressure inside the cuffs was monitored continuously by pressure transducers (Validyne Engineering Model DP45, Northridge, CA). After baseline variables were measured, the thigh cuffs were inflated to a preset suprasystolic pressure (⩾30 mmHg above the subject's SBP) and maintained for 3 min with a Hankinson Model AG101 Cuff Inflator Air Source and Model E-20 Rapid Cuff Inflator (Bellevue, WA). The subject was asked to maintain normal breathing with the cuff inflated. After 3-min thigh occlusion, the extension tube was disconnected to rapidly deflate the cuff, producing transient systemic hypotension as a result of vasodilation in the legs.[11] Data were recorded for another ⩾1 min after cuff deflation.

Data analysis

A 60-s span of continuous data obtained before thigh-cuff inflation was averaged to represent the initial baseline (B_0) values. Another approximately 15-s span of data was averaged during cuff occlusion prior to deflation as the predeflation (B_1) values. The times from the deflated cuff pressure reaching 0 mmHg to the respective nadirs of MAP (MAP_{min}) and V_{MCA} (V_{MCAmin}) were defined as the respective response times, that is $T\Delta_{MAP}$ and $T\Delta_{VMCA}$. The differences between the predeflation (B_1) MAP and V_{MCA} values and the respective nadirs equaled ΔMAP, an index of systemic hypotension, and ΔV_{MCA}, an index of cerebral hypoperfusion. Recovery times (T_R) were the times for MAP and V_{MCA} recoveries from MAP_{min} and V_{MCAmin} to their respective B_1 values, designated B_{RMAP} and B_{RVMCA} to represent the postocclusion recovery values. Percent increase in MAP (%ΔMAP) during recovery from MAP_{min} equaled

$$100\% \bullet \left[\left(B_{RMAP} - MAP_{min} \right) / B_{RMAP} \right]$$

and the rate of MAP recovery equaled $\%\Delta MAP/T_{RMAP}$. The percent increase in V_{MCA} following its nadir V_{MCAmin} was computed in a similar manner:

$$\%\Delta V_{MCA} = 100\% \bullet \left[\left(B_{RVMCA} - V_{MCAmin} \right) / B_{RVMCA} \right]$$

The CVC response (ΔCVC) and tachycardiac response (ΔHR), that is the differences in CVC and HR between their respective peak values, CVC_{peak} and HR_{peak} versus their values at the start of their responses, that is CVC_{1st} or HR_{1st}, were determined during the recovery from the cuff occlusion–deflation induced systemic hypotension. The rates of relative increase in CVC (i.e. $\%\Delta CVC/T_{CVC}$) or HR (i.e. $\%\Delta HR/T_{HR}$) during the recovery period were calculated from the percent increases in CVC (%ΔCVC) and HR (%ΔHR) divided by the time durations (s) of the CVC and HR responses, T_{CVC} and T_{HR}, where

$$\%\Delta CVC/T_{CVC} = 100\% \bullet \left[\left(CVC_{peak} - CVC_{1st} \right) / CVC_{peak} \right] / T_{CVC}$$

and

$$\%\Delta HR/T_{HR} = 100\% \bullet [(HR_{peak} - HR_{1st}) / HR_{peak}] / T_{HR}$$

Because the slope values $\%\Delta CVC/T_{CVC}$ and $\%\Delta HR/T_{HR}$ have the same units (%/s), their contributions to recovery of cerebral perfusion can be compared directly.

Statistics

Student's *t*-test was performed to determine differences in baseline values between the two age groups. Two-factor analysis of variance (ANOVA) was performed to compare the B_0 and B_1 values within each group (i.e. cuff factor) and to compare values between the two age groups (i.e. age factor). Duncan's multiple comparison analysis for repeated measures was employed *post hoc* when ANOVA detected a statistically significant main effect. The Pearson correlations were calculated to assess associations between different cardiovascular variables. The slopes of the associations were compared using *z*-statistics for two-tailed hypotheses.[22] Results are presented as group mean ± standard error of the mean (SEM). The *P* values ⩽0.05 were taken to indicate statistical significance. Statistical analyses were conducted with statistical analysis system software (SAS version 9.4).

Results

Baseline values

Table 1 summarizes the baseline (B_0) values for cardiovascular variables before cuff inflation. Resting MAP was higher, and HR and V_{MCA} were lower in the elderly versus the young adults. $P_{ET}CO_2$ and F_{br} did not differ statistically between the two groups.

Inflation of the thigh cuffs to suprasystolic pressure to occlude perfusion of the lower legs did not affect MAP, V_{MCA}, CVC, and HR (Table 2). There were no significant differences between the resting baseline (B_0), cuff occlusion (B_1), and postocclusion recovery (B_R) values (cuff factor *P* values: 0.49 for MAP, 0.70 for V_{MCA}, 0.76 for CVC, and 0.14 for HR), indicating that neither thigh-cuff inflation to suprasystolic pressures nor the postocclusion hypotension-recovery maneuver altered appreciably the steady-state values of monitored variables in either the elderly or young adult subjects. In contrast, two-factor ANOVA revealed a statistically significant age factor, with *P* values equaling 0.003 for MAP, 0.001 for V_{MCA}, 0.001 for CVC, and 0.041 for HR. Furthermore, the respective B_1 values in the elderly versus young adults for F_{br} (14.8 ± 0.4 versus 15.6 ± 0.4 br/min) and $P_{ET}CO_2$ (42.3 ± 0.4 versus 41.8 ± 0.3 mmHg) were not affected significantly by the cuff factor ($P = 0.63$ for F_{br}; $P = 0.19$ for $P_{ET}CO_2$).

Table 1. Baseline cardiorespiratory variables in elderly and young adults.

	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	V_{MCA} (cm/s)	CVC (unit)	F_{br} (br/min)	$P_{ET}CO_2$ (mmHg)
Elderly	59 ± 3	125 ± 4	68 ± 2	87 ± 3	45.8 ± 1.3	0.53 ± 0.02	14.0 ± 0.6	43.1 ± 0.6
Young	68 ± 3*	116 ± 3	63 ± 2	80 ± 2*	58.3 ± 1.0*	0.73 ± 0.02*	15.9 ± 0.7	42.2 ± 0.3

HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; V_{MCA}: mean flow velocity of the middle cerebral artery; CVC: cerebral vascular conductance; F_{br}: breathing frequency; $P_{ET}CO_2$: partial pressure of end-tidal CO_2.
Values are group means ± SEM; $n = 13$ except $n = 12$ for F_{br} and $P_{ET}CO_2$ in elderly group.
*$P < 0.05$ versus the elderly group.

Table 2. Cardiovascular data before cuff inflation (B_0), during cuff occlusion (B_1), and at full recovery following cuff deflation (B_R).

Group	MAP (mmHg)			V_{MCA} (cm/s)			CVC (unit)			HR (beats/min)		
	B_0	B_1	B_R	B_0	B_1	B_R	B_0	B_1	Δ	B_0	B_1	Δ
Elderly	87 ± 3	89 ± 2	91 ± 3	45.8 ± 1.3	47.1 ± 1.3	48.5 ± 1.6	0.53 ± 0.02	0.52 ± 0.03	+0.10 ± 0.01	59 ± 3	58 ± 3	+9 ± 1
Young	80 ± 2	82 ± 2	81 ± 2	58.3 ± 1.0	57.8 ± 1.1	59.0 ± 1.6	0.73 ± 0.02	0.72 ± 0.03	+0.11 ± 0.01	68 ± 3	61 ± 2	+22 ± 2

MAP: mean arterial pressure; V_{MCA}: blood flow velocity of the middle cerebral artery; CVC: cerebral vascular conductance; HR: heart rate. B_0: resting baseline data before cuff inflation; B_1: baseline data with suprasystolic occlusion before the cuff deflation; B_R: the recovery data following the cuff deflation after 3-min suprasystolic occlusion; Δ: the difference between the peak and the first pulse of the CVC and HR responses following cuff deflation (see Figure 1(F) and (G)).
Two-factor ANOVA detected no statistically significant within-group differences between B_0, B_1, and B_R values of any variable, although the age factor was statistically significant for all four variables.

Responses to cuff deflation

Figure 1 presents hemodynamic responses to abrupt deflation of the thigh cuffs following 3-min occlusion in an elderly subject. Cuff pressure fell from 170 to ~0 mmHg within ~0.1 s (Figure 1(A)), producing transient declines in phasic arterial blood pressure (Figure 1(B)), MAP (Figure 1(C)), and phasic (Figure 1(D)) and mean (Figure 1(E)) V_{MCA}, and transient increases in CVC (Figure 1(F)) and HR (Figure 1(G)), without altering appreciably ventilation monitored by $P_{ET}CO_2$ (Figure 1(H)). In this experiment, MAP reached its postocclusion nadir, 56 mmHg (MAP_{min}) 4.1 s after cuff pressure reached 0 mmHg, and recovered to its baseline, 85 mmHg (B_{RMAP}) 15.1 s after cuff deflation (Figure 1(C)); thus, MAP response time ($T\Delta_{MAP}$) was 4.1 s and recovery time (T_{RMAP}) equaled 11.0 s. The rate of MAP recovery, that is $100\% \bullet ((B_{RMAP} - MAP_{min})/B_{RMAP})/T_{RMAP}$, which equaled 3.1%/s in this experiment, indexed the systemic vasomotor factor. The V_{MCA} response time ($T\Delta_{VMCA}$) from cuff deflation to V_{MCA} nadir (V_{MCAmin}) was 2.6 s, and V_{MCA} recovered to its baseline (B_{RVMCA}) within 11.7 s of cuff deflation (Figure 1(E)), yielding a V_{MCA} recovery time (T_{RVMCA}) of 9.1 s (Figure 1(E)). The first detectable increases in CVC (CVC_{1st}) and HR (HR_{1st}) occurred 2.6 and 4.3 s after cuff deflation, and the respective peak recoveries, that is CVC_{peak} and HR_{peak} occurred 9.3 and 13.4 s after deflation, yielding response durations (brackets) for CVC ($T\Delta_{CVC}$) and HR ($T\Delta_{HR}$) of 6.7 and 9.1 s, respectively. The relative response rates of CVC and HR, that is $100\% \bullet ((CVC_{peak} - CVC_{1st})/CVC_{peak})/T_{CVC}$ and $100\% \bullet ((HR_{peak} - HR_{1st})/HR_{peak})/T_{HR}$, which indexed the cerebral regional and cardiac factors, respectively, equaled 3.3 and 0.7%/s in this experiment.

As expected, abrupt cuff deflation after 3-min bilateral suprasystolic vascular occlusion of the legs caused MAP to fall appreciably ($P < 0.001$) in both the elderly (−14.1 ± 1.1 mmHg) and young (−16.5 ± 1.2 mmHg) adults. The magnitudes of unit systemic hypotension in the two age groups were not statistically different ($P = 0.159$), although the percentage decrease in MAP tended to be greater ($P = 0.051$) in the young adults (−20.2 ± 1.4%) than their elderly counterparts (−16.0 ± 1.5%). The time from cuff release to MAP_{min}, that is $T\Delta_{MAP}$, was twice as long ($P = 0.003$) in the elderly (6.8 ± 0.9 s) than in young adults (3.4 ± 0.5 s). Furthermore, the rate of percent decrease in MAP was significantly slower ($P = 0.003$) in the elderly (−3.0 ± 0.5%/s) versus young (−7.3 ± 1.2%/s) adults, indicating age-associated attenuation in flow-mediated vasodilation in the legs.

Transient decreases in V_{MCA} in both the elderly (−7.9 ± 0.9 cm/s; −16.7 ± 2.0%) and the young adults (−9.5 ± 1.0 cm/s; −16.5 ± 1.7%) were associated with the systemic hypotension. The unit ($P = 0.233$) and percent ($P = 0.935$) changes in V_{MCA} elicited by systemic hypotension were statistically similar in the two groups. However, the time from cuff release to the nadir of cerebral perfusion (V_{MCAmin}), that is $T\Delta_{VMCA}$, was significantly shorter ($P = 0.002$) in the young adults (1.9 ± 0.1 s) than their elderly counterparts (3.8 ± 0.4 s), a difference which paralleled the age-related difference in systemic hypotension onset.

In both age groups, $T\Delta_{VMCA}$ following cuff deflation was significantly shorter ($P < 0.007$) than $T\Delta_{MAP}$, suggesting earlier recovery of cerebral perfusion mediated by an intrinsic cerebral mechanism, for example cerebrovascular autoregulation, that preceded the recovery in CPP.

Recovery from cuff deflation

The durations of MAP recovery (T_{RMAP}) and V_{MCA} recovery (T_{RVMCA}) were longer ($P < 0.001$ and $P < 0.01$, respectively) in the elderly (T_{RMAP}: 19.7 ± 1.3 s; T_{RVMCA}: 11.7 ± 1.1 s) than young adults (T_{RMAP}: 11.2 ± 1.0 s; T_{RVMCA}: 7.0 ± 0.7 s). Although T_{RMAP} and T_{RVMCA} were positively correlated ($r = 0.64$, $P < 0.002$), T_{RVMCA} was shorter ($P < 0.005$) than T_{RMAP}

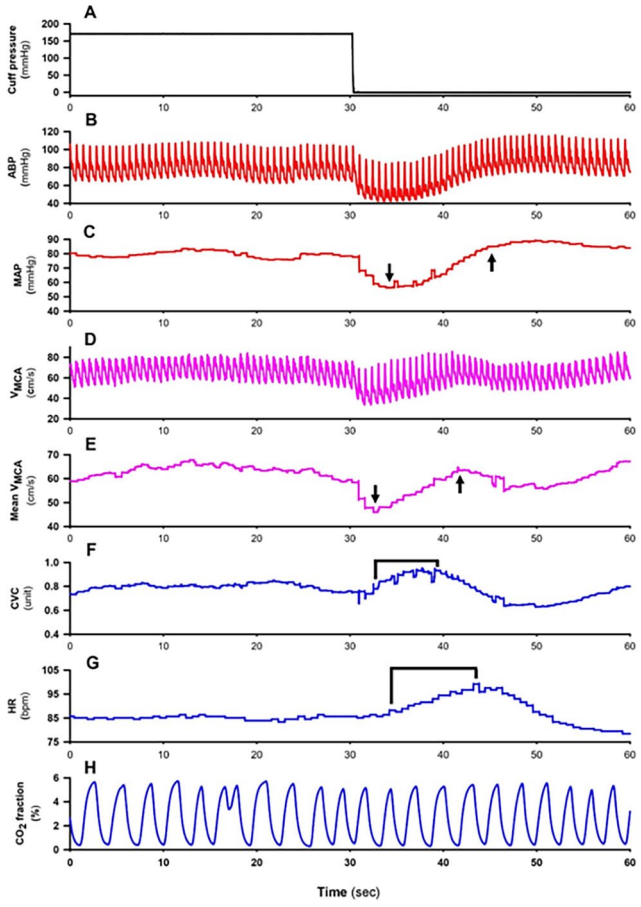

Figure 1. Response to rapid cuff deflation after 3-min bilateral suprasystolic thigh occlusion.
Data from a representative experiment in an elderly subject: (a) Cuff pressure showing deflation at 30 s; (b) phasic arterial blood pressure; (c) mean arterial pressure computed from ABP; (d) phasic middle cerebral artery blood flow velocity (V_{MCA}); (e) mean V_{MCA} derived from the phasic V_{MCA}; (f) estimated cerebrovascular conductance; (g) heart rate derived from the standard limb lead II of electrocardiogram; and (h) breath-by-breath fractional expired CO_2. Elapsed times from cuff pressure reaching 0 mmHg to the nadirs (↓ in panels C and D) of systemic hypotension (i.e. MAP_{min}) and cerebral hypoperfusion (i.e. V_{MCAmin}) are the respective MAP and V_{MCA} response times, $T\Delta_{MAP}$ and $T\Delta_{VMCA}$. ↑ indicates the points of full recovery of MAP and V_{MCA} to the respective baseline values B_{RMAP} and B_{RVMCA}. The elapsed times (brackets) between the initial increases in CVC (F) and HR (G), that is CVC_{1st} and HR_{1st}, and the peak increases in CVC and HR, that is CVC_{peak} and HR_{peak}, respectively, represent the response durations for CVC ($T\Delta_{CVC}$) and HR ($T\Delta_{HR}$).

in both age groups, indicating CBF recovery was at least partially independent of the slower MAP recovery.

During recovery from the systemic hypotension, CVC and HR increased significantly in both the elderly ($+0.10 \pm 0.01$ unit and $+8.9 \pm 1.3$ bpm) and the young ($+0.11 \pm 0.01$ unit and $+22.1 \pm 1.7$ bpm) adults (Table 2). The CVC increase did not differ between the two age groups ($P = 0.68$) but the tachycardic response was greater in the young than the elderly ($P < 0.001$). However, the rate of the CVC increase during recovery from hypotension was significantly ($P = 0.021$) slower in the elderly ($1.89 \pm 0.25\%/s$) than young ($2.90 \pm 0.31\%/s$) adults. Furthermore, the rate of the relative increase in HR during recovery was significantly ($P < 0.001$) slower in the elderly ($1.42 \pm 0.20\%/s$) than the young ($4.02 \pm 0.42\%/s$) adults. The rates of percentage increases in MAP and V_{MCA} during recovery were significantly slower ($P < 0.001$ and $P = 0.015$, respectively) in the elderly (0.93 ± 0.11 and $1.72 \pm 0.20\%/s$) than young adults (1.93 ± 0.20 and $2.97 \pm 0.40\%/s$). The response rates of these variables were directly correlated (%ΔHR versus %ΔMAP: $r = 0.63$, $P < 0.001$; %ΔHR versus $\%\Delta V_{MCA}$: $r = 0.47$, $P = 0.021$; %ΔMAP versus $\%\Delta V_{MCA}$: $r = 0.57$, $P = 0.004$; %ΔMAP versus %ΔCVC: $r = 0.44$, $P = 0.029$; and $\%\Delta V_{MCA}$ versus %ΔCVC: $r = 0.68$, $P = 0.001$).

Factors contributing to recovery of CBF

T_{RMAP} was significantly explained by the recovery rates of both the cardiac (%ΔHR/s) (Figure 2A) and the vasomotor (%ΔMAP/s) (Figure 2B) factors following their respective postdeflation nadirs. However, the slope of T_{RMAP}/R_{MAP} (-6.39 ± 0.89, $r = 0.82$, $P < 0.001$) was significantly greater ($P < 0.001$) than that of T_{RMAP}/R_{HR} (-2.14 ± 0.55, $r = 0.62$, $P < 0.001$), indicating that the vasomotor factor made the greater contribution to MAP recovery from systemic hypotension.

Figure 3 demonstrates that the recovery time from cerebral hypoperfusion (i.e. T_{RVMCA}) was significantly affected by both systemic (cardiac and vasomotor) factors and the cerebral intrinsic mechanism, that is CVC factor. Again, the slope of T_{RVMCA}/R_{MAP} (-3.03 ± 0.87; $P = 0.002$) was significantly greater ($P = 0.046$) than that of T_{RVMCA}/R_{HR} (-1.12 ± 0.40; $P = 0.011$), indicating that the vasomotor factor (Figure 3B) made a greater contribution than the cardiac factor (Figure 3A) to the rate of the recovery from cerebral hypoperfusion. Furthermore, the slope of T_{RVMCA}/R_{CVC} (-2.37 ± 0.57; $P < 0.001$) tended to be greater ($P = 0.072$) than that of T_{RVMCA}/R_{HR}. However, the slopes of T_{RVMCA} versus R_{MAP} (Figure 3B) and R_{CVC} (Figure 3C) did not differ significantly ($P = 0.52$).

Discussion

This study demonstrated that cerebral perfusion is slower to recover from acute systemic hypotension following bilateral thigh-cuff occlusion-release in elderly versus young adults because of a diminished CVC response mediated by cerebral regional mechanisms or cerebrovascular autoregulation and systemic (cardiac and vasomotor) regulatory functions. Although systemic vasomotor and CVC mechanisms contributed to similar extents to recovery of cerebral perfusion from abrupt systemic hypotension, the contributions of systemic vasomotor mechanisms predominated over the contributions of the cardiac responses.

Aging and cerebral autoregulation

During the thigh-cuff occlusion–deflation protocol, cerebral intrinsic mechanisms and/or cerebrovascular pressure-flow autoregulation were active, because the TΔ and T_R values for V_{MCA}, that is $T\Delta_{VMCA}$ and T_{RVMCA}, were significantly shorter than the analogous MAP variables $T\Delta_{MAP}$ and T_{RMAP} in both elderly and young adults. The shorter $T\Delta_{VMCA}$ and T_{RVMCA}, representing more rapid V_{MCA} recovery from nadir to baseline, indicated effective cerebrovascular autoregulation in

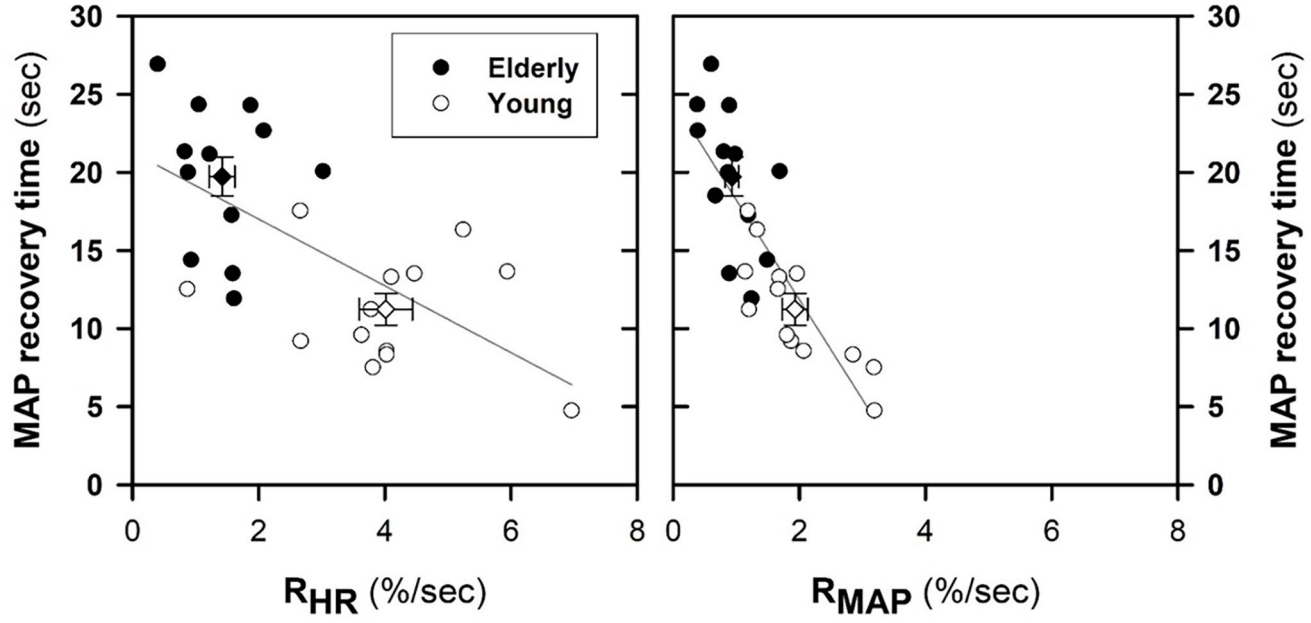

Figure 2. Factors determining mean arterial pressure recovery rate.
Recovery time of mean arterial pressure (T_{RMAP}) following cuff deflation is significantly explained by the relative response rates of (panel A) heart rate (R_{HR}, i.e. cardiac factor) where T_{RMAP} equaled -2.14 ± 0.55 ($R^2 = 0.39$; $P < 0.001$) and (panel B) mean arterial pressure (R_{MAP}, i.e. vasomotor factor) where T_{RMAP} equaled -6.39 ± 0.89 ($R^2 = 0.67$; $P < 0.001$). The T_{RMAP}/R_{MAP} slope (panel B) is markedly steeper than the T_{RMAP}/R_{HR} slope (panel A). Closed and open circles denote individual data points from elderly and young subjects, respectively. Diamonds (closed: elderly subjects; open: young subjects) represent mean ± SEM.

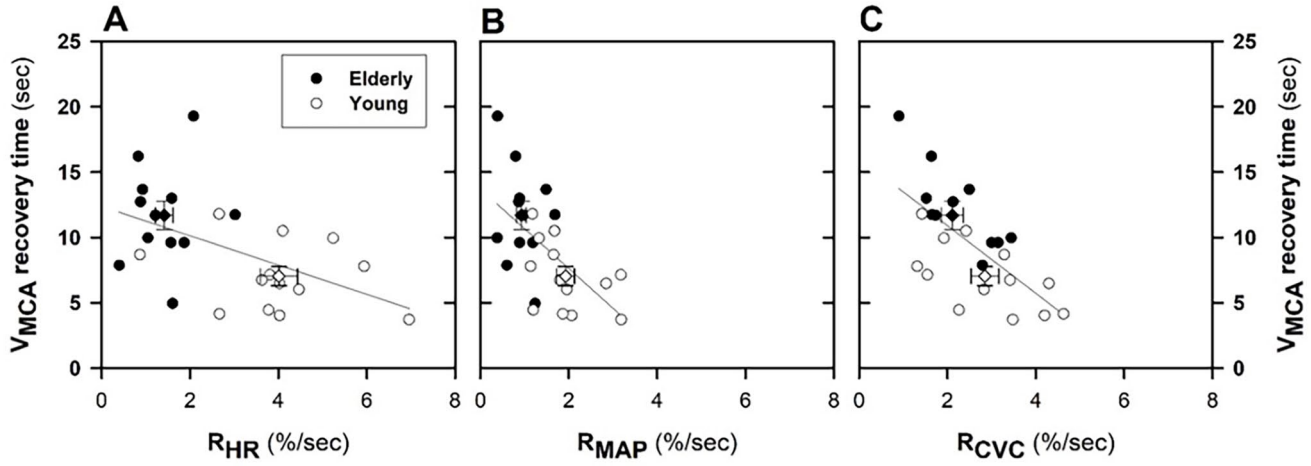

Figure 3. Factors determining velocity of the middle cerebral artery recovery rate.
Recovery time of middle cerebral artery flow velocity (T_{RVMCA}) is significantly explained by the rates of relative changes in (panel A) heart rate (R_{HR}, i.e. cardiac factor), where T_{RVMCA} equaled -1.12 ± 0.40 ($R^2 = 0.25$; $P = 0.011$), (panel B) mean arterial pressure (R_{MAP}, i.e. vasomotor factor), where T_{RVMCA} equaled -3.03 ± 0.87 ($R^2 = 0.35$; $P = 0.002$), and (panel C) estimated cerebrovascular conductance (R_{CVC}, i.e. CVC factor), where T_{RVMCA} equaled -2.37 ± 0.57 ($R^2 = 0.43$; $P < 0.001$). The T_{RVMCA}/R_{MAP} and T_{RVMCA}/R_{CVC} slopes are not significantly different, but both are steeper than the T_{RVMCA}/R_{HR} slope. Closed and open circles denote individual data points from elderly and young subjects, respectively. Diamonds (closed: elderly subjects; open: young subjects) represent mean ± SEM.

advance of the MAP response. These data suggested that the duration (T_{RVMCA}) from V_{MCA} nadir to full recovery was at least partially independent of MAP recovery, regardless of the subject's age, despite the fact that the cerebral hypoperfusion resulted from the systemic hypotension that ensued upon cuff release. However, both $T\Delta_{VMCA}$ and T_{RVMCA} were significantly longer in the elderly than young adults, indicating age-related slowing of cerebrovascular responses to both the cuff deflation–induced systemic hypotension and subsequent recovery from the resultant cerebral hypoperfusion. The slower CVC responses suggested impairment of cerebral autoregulation with advanced age.

A population-based study demonstrated aging-associated attenuation of V_{MCA} responses to changes in arterial CO_2,[23] suggesting that aging diminished cerebrovascular reserve. Moreover, CBF assessed from TCD V_{MCA} measurements also decreased with age.[24,25] Klein *et al.*[26] reported that increases in V_{MCA} during transient increases in arterial pressure associated with postural change from standing-to-sitting were augmented in elderly versus young adult subjects.

The authors suggested that impaired endothelial function and increased vascular stiffness with aging were the most likely contributors to the altered transient cerebral pressure-flow responses in elderly subjects.[26] This study demonstrated both a slower decline in V_{MCA} immediately after the thigh-cuff occlusion–deflation induced systemic hypotension, that is the TΔ phase, and attenuated rate of increase in CVC during recovery from cerebrovascular hypoperfusion, that is the T_R phase, in the elderly versus young adults. These results suggested that attenuation with aging of cerebral autoregulation or cerebral intrinsic mechanisms could likely explain the prolonged T_{RVMCA} in the elderly subjects.

Aging and cardiac regulation

The previously reported transient hypotension at the onset of LBNP-imposed orthostatic challenge in elderly subjects was at least partially ascribable to attenuation of the reflexive tachycardic response to LBNP.[1] After cardiac vagal blockade using atropine or glycopyrrolate, young adults exhibited systemic hypotension at LBNP onset similar to the response in the elderly.[1] Further confirming the importance of cardiac regulation for maintaining cerebral perfusion is the observation in healthy young adults that cerebral autoregulation is compromised by autonomic blockade interrupting HR responses to thigh-cuff occlusion–deflation.[12]

In addition to cerebral autoregulation, adequate cerebrovascular perfusion also depends on the cardiac factor, namely cardiac output, that is stroke volume times HR, and on vasomotor factors, primarily MAP which, along with intracranial pressure, determines CPP. Cardiac index (cardiac output/body surface area) declines with age in association with decreased left ventricular ejection fraction.[27] Low cardiac index correlates with low perfusion of the cerebral temporal lobes[28] and decreased brain volume[29] in the elderly. This study showed the reflexive tachycardiac response to acute systemic hypotension to be predictive of both MAP recovery duration, that is T_{RMAP} (Figure 2), and V_{MCA} recovery duration, that is T_{RVMCA} (Figure 3). However, R_{HR}, the rate of relative HR increase during hypotension challenge, slowed appreciably in the elderly versus young subjects. This aging-associated attenuation of reflexive tachycardia was one of the underlying mechanisms of T_{RMAP} and T_{RVMCA} prolongation in the elderly adults.

Aging and vasomotor regulation

Although the cardiac factor partially explained both T_{RMAP} and T_{RVMCA}, the slope of T_RV_{MCA} versus the vasomotor factor %ΔMAP/s was significantly greater than the slope of T_RV_{MCA} versus the cardiac factor R_{HR} (Figure 3). This result suggested that systemic vasoconstriction contributed more powerfully than increased cardiac output to the recovery of cerebrovascular hypoperfusion following abrupt, transient systemic hypotension.

Systemic arterial pressure increases with age.[30–32] Increased aortic stiffness is associated with increased cerebrovascular resistance and lower CBF.[33] Maintenance of arterial pressure and responses of forearm vascular resistance during sustained LBNP were found to be similar in healthy elderly and young subjects.[34–36] Furthermore, MAP responses to perturbations of the carotid arterial baroreceptor were comparable in young and elderly adults.[34] Although sympathetic nerve activity evaluated by peroneal microneurography was augmented, forearm vasoconstriction during LBNP was attenuated in elderly versus young adults,[37] suggesting aging-associated dissociation of sympathetic nerve activity to vasomotor responses. Nonetheless, overall systemic or peripheral vascular resistance appeared to be augmented in the elderly subjects during LBNP based on an attenuated decrease in cardiac output with arterial pressure maintenance similar to young adults.[9,35,36]

In this study, cuff deflation produced ΔMAP of similar magnitudes in the elderly and young adults. However, both $T\Delta_{MAP}$ and T_{RMAP} were prolonged in the elderly subjects. Prolonged $T\Delta_{MAP}$ in the elderly despite unaltered ΔMAP likely indicated age-related endothelial dysfunction. As a result, the elderly subjects did not adjust to physiological challenges as quickly as their younger counterparts during hyperemia-mediated vasodilation following cuff deflation. On the contrary, prolonged T_{RMAP} in the elderly subjects was explained by the diminished compensatory vasomotor response, probably due to less effective reflex sympathetic neurotransmission to the vascular smooth muscle.[37] Furthermore, age-related impairment of the cardiac reflex response contributed appreciably to T_{RMAP} prolongation in the elderly (Figure 2). Because MAP is the product of cardiac output and peripheral vascular resistance, the weaker influence of the cardiac factor suggests peripheral vascular resistance to be the more powerful factor maintaining MAP during hypotensive challenge.

Study limitations and technique considerations

Cardiac output is the product of HR and stroke volume. Multiple factors determine stroke volume, including left ventricular contractility, compliance, preload and afterload, and filling time. Most of these factors decrease with aging. However, stroke volume was not measured in this study, so the cardiac factor was only partially evaluated. Nonetheless, because the cardiac vagal response is faster than cardiac sympathetic response, yet vagal innervation of the left ventricle is sparse, the reflex HR response seems to be the more important factor maintaining cardiac output and, thus, MAP during the initial response to acute systemic hypotension.

Although V_{MCA} measurement by TCD sonography is one of the most common and facile methods to study moment-to-moment changes in CBF, it is acknowledged that V_{MCA} might not always represent MCA flow. The two variables are strictly proportional only if MCA diameter is unchanged. Importantly, when $P_{ET}CO_2$ is stable as was the case during the present cuff inflation–deflation protocol, MCA diameter remains fairly constant.[38] The contributions of CPP, that is MAP, and of CVC to CBF recovery from abrupt cerebral hypoperfusion were comparable, suggesting that both the systemic driving force MAP and regionally regulated CVC are important in maintaining CBF. However, because this study was conducted in healthy human subjects in a closed-loop system, the time courses of contributions by the CVC, cardiac and vasomotor responses remain unknown.

In addition, because MAP equals cardiac output times total peripheral resistance, the relative contributions of the cardiac and vasomotor factors to MAP maintenance during hypotensive challenge must be isolated. Future studies also should define the physiological mechanisms mediating MAP and CBF.

Suprasystolic cuff inflation imposes ischemia on the leg musculature which may elicit discomfort causing sympathoexcitation. This effect was likely not significant in this study because there were no differences in MAP and HR between the baseline values before cuff inflation (B_0) versus values during cuff inflation (B_1) in both age groups. Primary aging is commonly associated with secondary aging, that is physical inactivity, which in return may accelerate the normal aging process. V_{MCA} is increased with physical fitness,[24] and cerebral perfusion seems to be better maintained in physically active elderly subjects than their age-matched sedentary counterparts during LBNP.[7,8] Physical exercise training has been found to improve orthostatic tolerance during LBNP in elderly subjects[8] and to alleviate age-related endothelial dysfunction.[39,40] Studies investigating physical fitness or exercise training-related differences in the contributions of cerebral autoregulation and systemic factors to maintaining cerebral perfusion in elderly individuals are warranted.

Conclusions

Both systemic factors and cerebral intrinsic mechanisms contribute to the recovery of cerebral perfusion from systemic hypotension in healthy elderly and young adults. The contributions of peripheral vasoconstriction, that is the vasomotor factor, are more substantial than HR, that is the cardiac factor, for maintaining cerebral perfusion and restoring arterial pressure following abrupt systemic hypotension. Aging-associated attenuation of systemic responses and cerebral autoregulation slow the recovery of cerebral perfusion during systemic hypotension in elderly individuals.

AUTHORS' CONTRIBUTIONS

KA, XC, and XS conceived and planned experiments and performed experiments. KA, XC, ZZ, RM, and XS analyzed the data. KA, XC, SR, SD, ZZ, RM, and XS interpreted the results of experiments, approved final version of article, and edited the article. KA, XC, RM, and XS prepared figures and drafted article.

DECLARATION OF CONFLICTING INTERESTS

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ETHICAL APPROVAL

The study protocol and methods were conducted in accordance with local guidelines, Federal regulations, and the Declaration of Helsinki. Both the protocol synopsis and informed consent were approved by the North Texas Regional IRB at the University of North Texas Health Science Center. All subjects provided a written informed consent before being enrolled in the study.

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