Abstract- SLOW RECOVERY OF CEREBRAL PERFUSION DURING HYPOTENSION IN ELDERLY HUMANS

Purpose: The study sought to test the hypothesis that the function of maintaining cerebral perfusion is diminished in elderly adults due to compromised cerebral autoregulation (CA) and cardiovascular systemic mechanisms with aging.

Methods: Thirteen healthy elderly (67.5±1.1 yr) and 13 young (25.8±1.0 yr) adults signed a consent form and passed a physical exam to be enrolled in the study, which was approved by the IRB at UNTHSC. Heart rate (HR), mean arterial pressure (MAP), and cerebral blood flow velocity of the middle cerebral artery (V_{MCA}) were continuously measured during systemic hypotension induced by a rapid cuff deflation after 3-min supra-systolic occlusion with bilateral thigh cuffs. This hypotension elicited a transient decrease in V_{MCA} i.e. ΔV_{MCA} and a reflexive increase in HR i.e. ΔHR. Duration and rate of the recovery response from the nadir of MAP and V_{MCA} were compared between the groups.

Results: Rapid cuff deflation after 3-min supra-systolic occlusion to the legs significantly decreased MAP (ΔMAP) in both the elderly (-14.1±1.1 mmHg) and young (-16.5±1.2 mmHg) groups which were not significantly different. This hypotension elicited similar significant hypoperfusion to the brain as indicated by ΔV_{MCA} in the elderly (-7.9±0.9 cm/s) and young (-9.5±1.0 cm/s) groups. However, the time elapsed from deflation to the nadir of MAP and V_{MCA} (T_0) and recovery time (T_r) of these variables from the nadir to return to baseline were significantly prolonged in the elderly subjects. The rates of relative changes in HR (%ΔHR/s, elderly vs young groups: 1.42±0.20 vs 4.02±0.42 %/s), MAP (%ΔMAP/sec, elderly vs young groups: 0.93±0.11 vs 1.93±0.20 %/s) and V_{MCA} (%ΔV_{MCA}/sec, elderly vs young groups: 1.72±0.02 vs 2.97±0.40 %/s) during recovery were diminished in elderly vs. young adults. Overall T_R-ΔV_{MCA} was significantly explained by the rates of %ΔHR, %ΔMAP, and %ΔV_{MCA}. However, the T_R-ΔV_{MCA}/vasomotor-factor slope (-3.0±0.9) was steeper (P=0.046) than the T_R-ΔV_{MCA}/cardiac-factor slope (-1.1±0.4). The T_R-ΔV_{MCA}/CA-factor slope (-2.3±0.5) was greater (P=0.055) than the T_R-ΔV_{MCA}/cardiac-factor slope; but it did not differ from the T_R-ΔV_{MCA}/vasomotor-factor slope.

Discussion: Maintenance of MAP was regulated by vasomotion and HR factors; whereas regulation of V_{MCA} seemed to be affected by intrinsic and systemic mechanisms. Both T_0 and T_R were remarkably shorter for V_{MCA} than MAP, suggesting the presence of cerebral autoregulation, which evoked an early rebound of V_{MCA} from its nadir before MAP reached the nadir and explained a quick recovery of V_{MCA} before MAP completed its restoration. Nonetheless, both T_0 and T_R were significantly longer in the elderly subjects. In addition to the response rate of V_{MCA}, relative change rates of both MAP and HR were significantly diminished with aging, which explained a prolonged recovery of cerebral perfusion during hypotension.

SIGNATURE PAGE

SLOW RECOVERY OF CEREBRAL PERFUSION DURING

HYPOTENSION IN ELDERLY HUMANS

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TITLE PAGE

SLOW RECOVERY OF CEREBRAL PERFUSION DURING HYPOTENSION IN ELDERLY HUMANS

INTERNSHIP PRACTICUM
REPORT

Presented to the Graduate Council of the Graduate School of Biomedical Sciences University of North Texas Health Science Center at Fort Worth in Partial Fulfilment of the Requirements

For the Degree
of

Master of
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By

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Table of Abbreviations

ABP	Arterial blood pressure
BP	Blood pressure
CA	Cerebral autoregulation
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CCRI	Cerebral blood flow/cardiac output ratio index
CO	Cardiac output
CPP	Cerebral perfusion pressure
CVC	Cerebral vascular conductance
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FVR	Forearm vascular resistance
HR	Heart rate
HUT	Head-up tilt method
ICA	Internal carotid artery
LBNP	Low body negative pressure
MAP	Mean arterial pressure
MCA	Middle cerebral artery
NO	Nitric oxide
SBP	Systolic blood pressure
ScO2	Cerebral tissue oxygen saturation
T_0	Time to nadir
T_R	Recovery time
TCD	Transcranial doppler
VA	Vertebral artery
V_{MCA}	Cerebral blood flow velocity of middle cerebral artery

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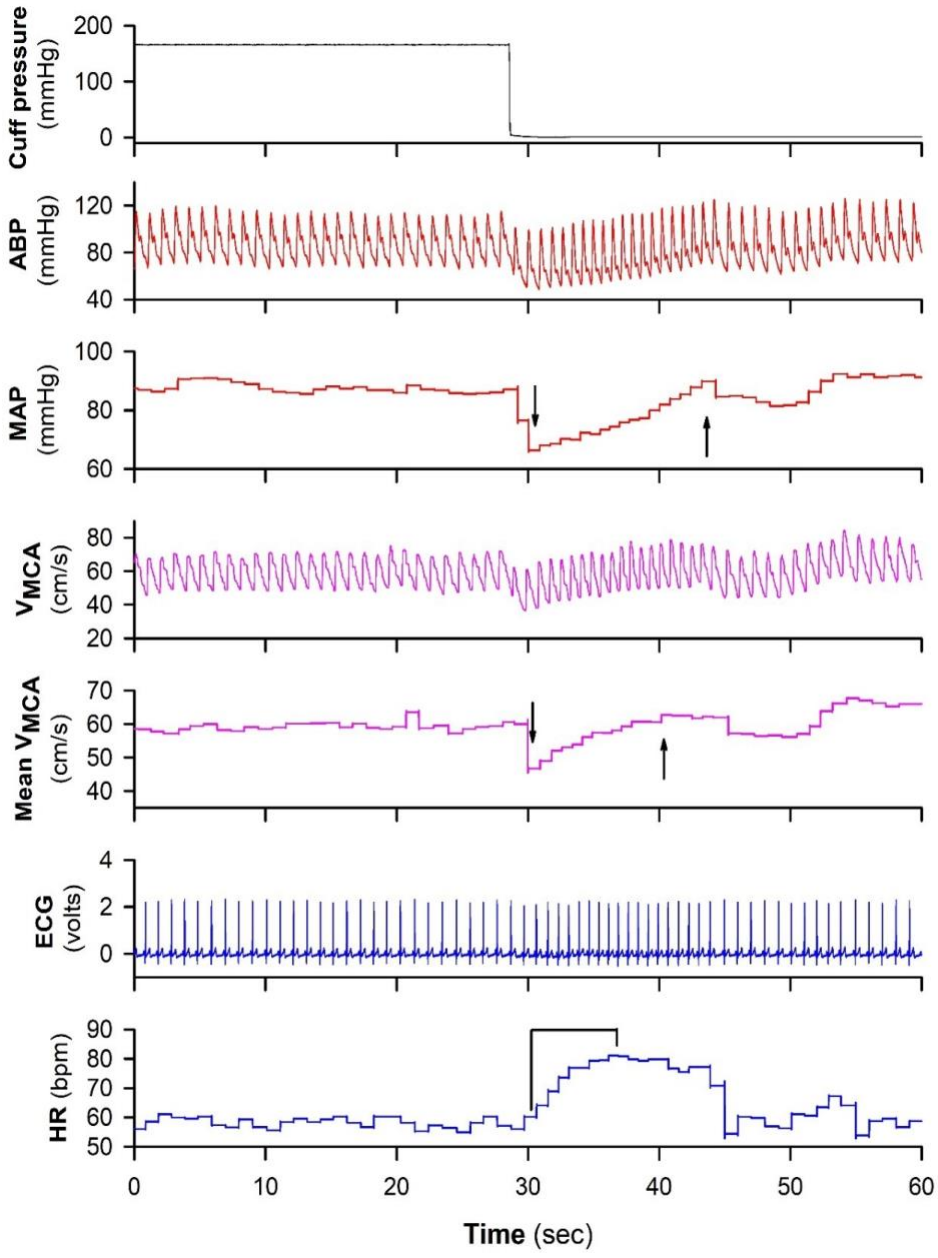


Figure 1: The hemodynamic response to transient systemic hypotension induced by deflating bilateral thigh cuffs after 3 min of suprasystolic inflation in one representative subject. From top to bottom: trace of bilateral thigh cuff pressure before and after deflation; arterial blood pressure (ABP); mean arterial pressure (MAP); middle cerebral arterial blood flow velocity (V_{MCA}); mean V_{MCA}; electrocardiogram (ECG) and heart rate (HR). Down and up arrows indicate time to reach the nadir of the response following the cuff deflation (T_0) and time to completely recover from the nadir to baseline (T_R), respectively. Following cuff deflation, MAP and mean V_{MCA}, were decreased and associated with reflex tachycardia.

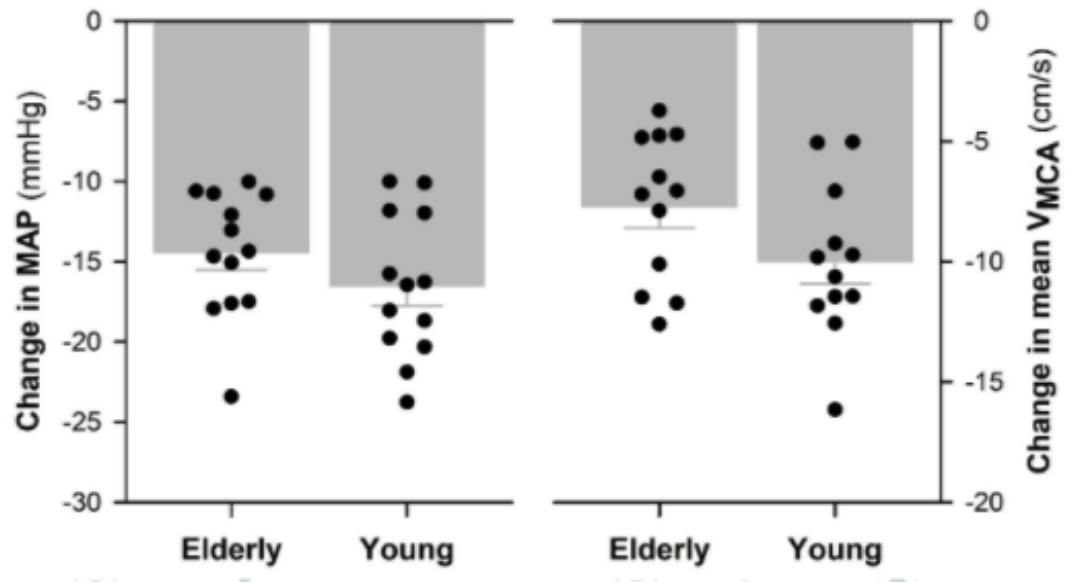


Figure 2: Systemic Hypotension and cerebral hypoperfusion following bilateral cuff deflation after supra-systolic cuff inflation. There is no difference in decreases of mean arterial pressure (MAP) or flow velocity of the middle cerebral artery (V_{MCA}) between the elderly and young groups.

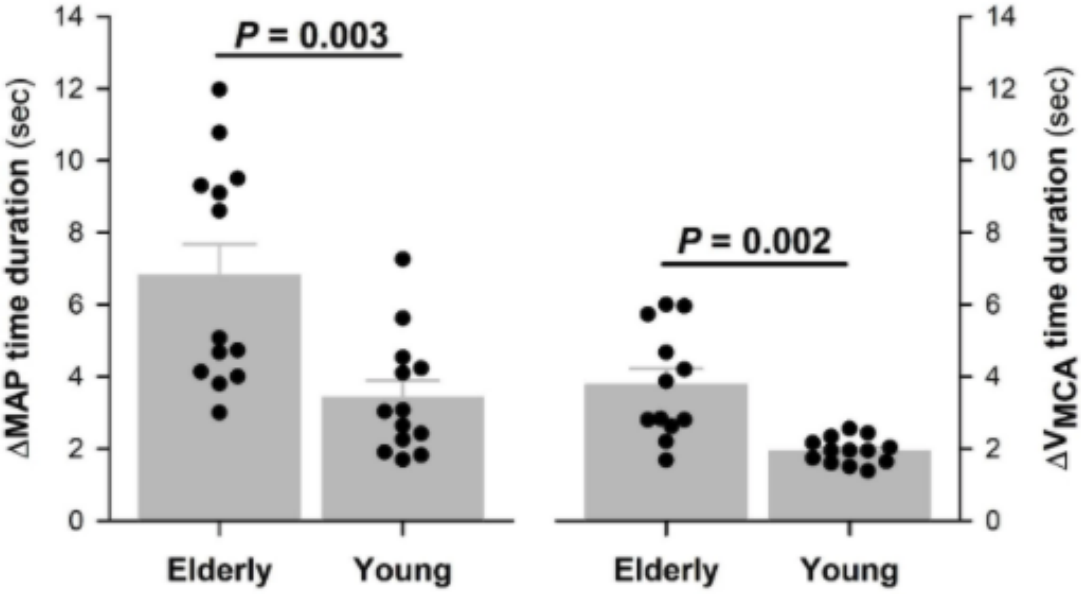


Figure 3: Time duration to reach nadir of MAP and V_{mca} following bilateral cuff deflation after supra-systolic inflation.

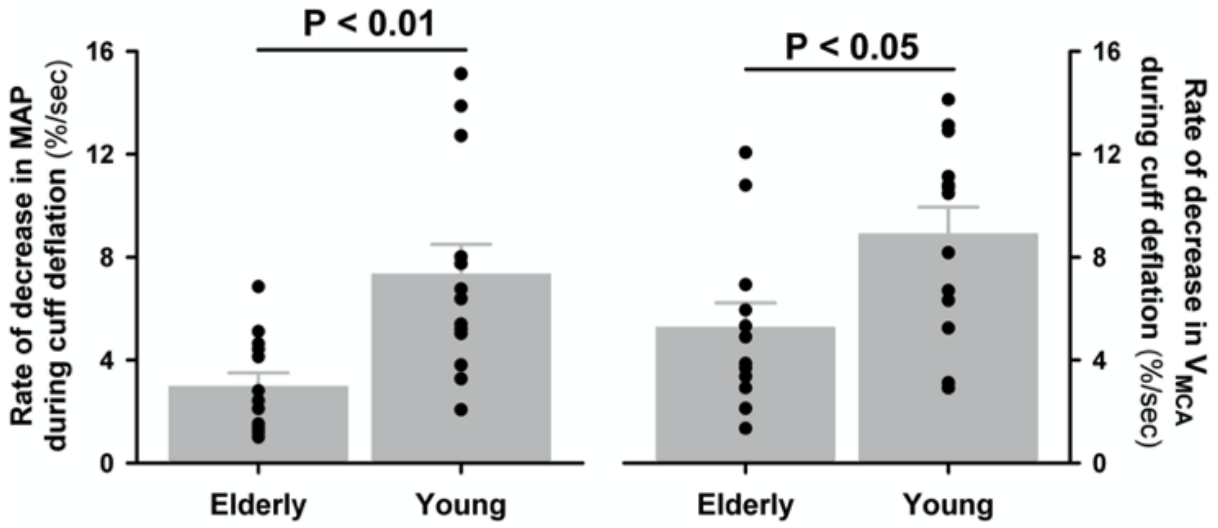
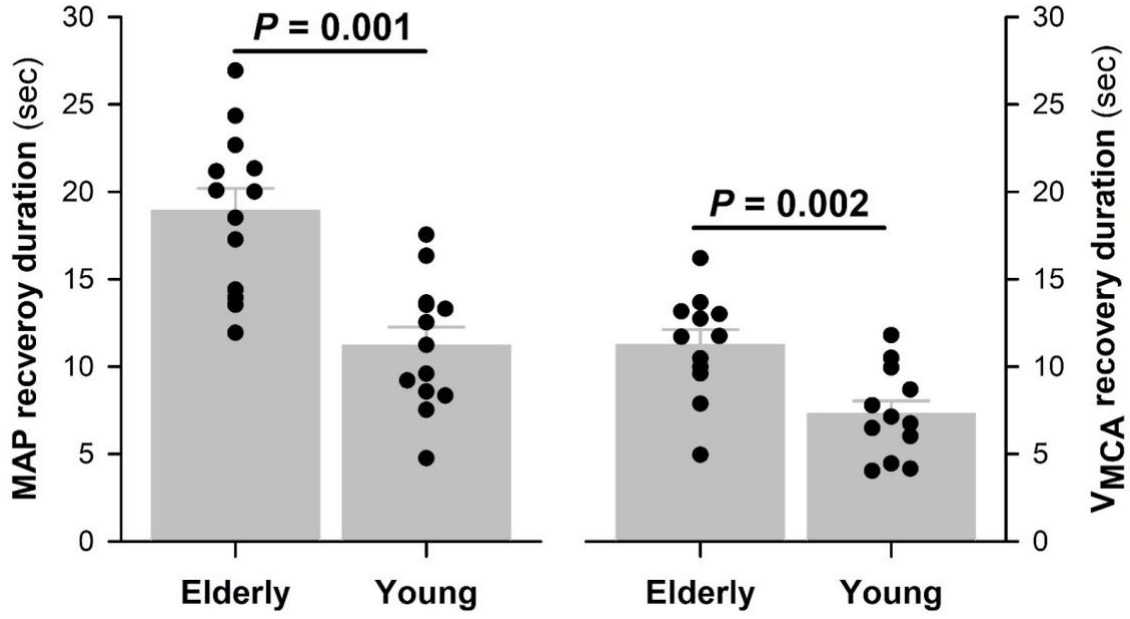


Figure 4: The rate of relative changes in MAP and V_{mca} following bilateral cuff deflation after supra-systolic inflation.



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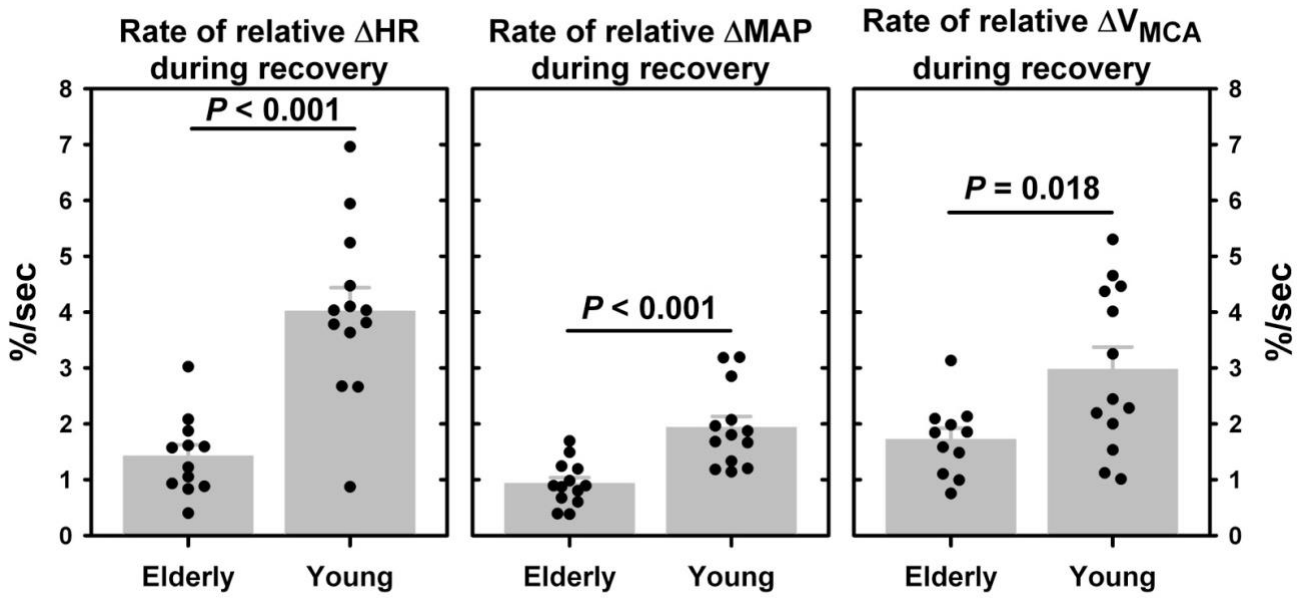

Figure 6: Hemodynamic responses during recovery.

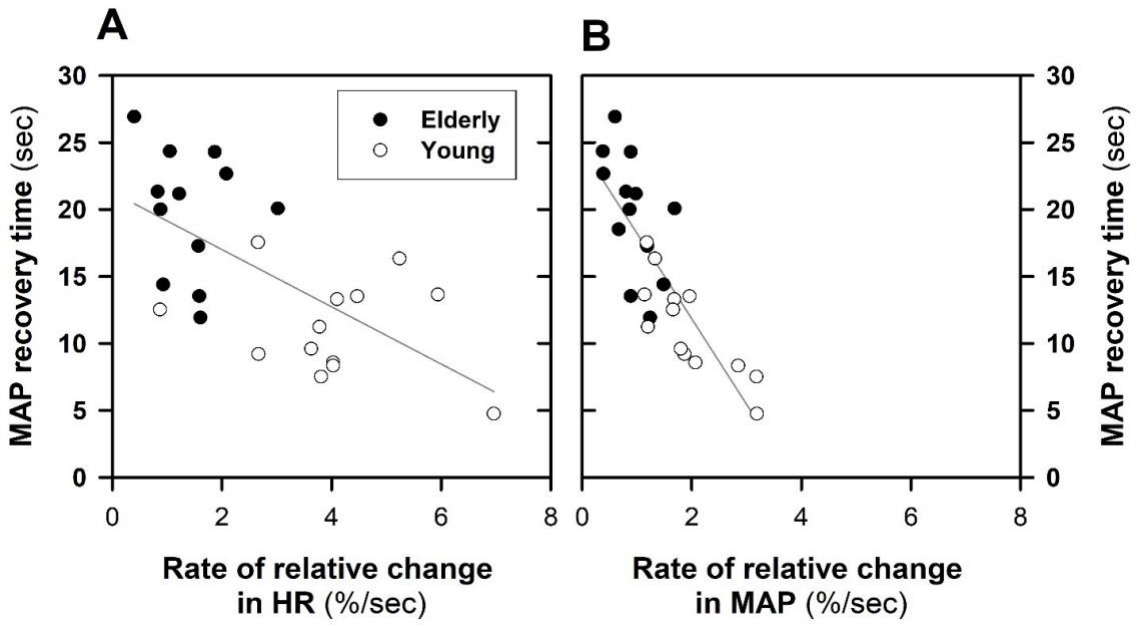

Figure 7: Contributions to Recovery from Systemic Hypotension.
Panel A: y (MAP-T_R) = β_0 + β_1(%ΔHR rate) = 21.3(β_0) – 2.14(β_1).
Panel B: y (MAP-T_R) = β_0 + β_1(%ΔMAP rate) = 24.6(β_0) – 6.39(β_1).
The slope (β_1) is significantly (P < 0.001) greater in MAP-TR/%ΔMAP rate (panel B) than MAP-T_R/%ΔHR rate (panel A).

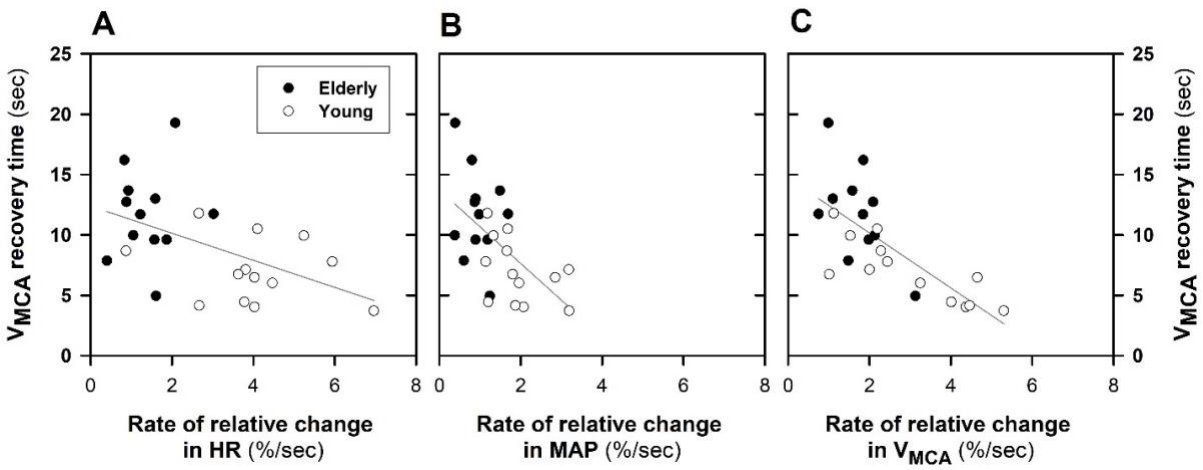

Figure 8: Contributions to Recovery from Cerebral Hypoperfusion.
Panel A: y (ΔV_{MCA}-T_R) = β_0 + β_1 (%ΔHR rate) = 12.4(β_0) - 1.12(β_1).
Panel B: y (ΔV_{MCA} -T_R) = β_0 + β_1 (%ΔMAP rate) = 13.7(β_0) – 3.03(β_1).
Panel C: y (ΔV_{MCA} -T_R) = β_0 + β_1 (%ΔV_{MCA} rate) = 14.7(β_0) – 2.28(β_1).
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	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	V_{MCA} (cm/s)	ScO_2 (%)	CVC (unit)
Elderly	59 ±3	125 ±4	68 ±2	87 ±3	45.8 ±1.3	62.7 ±1.6	0.53 ±0.02
Young	68 ±3*	116 ±3	63 ±2	80 ±2*	58.3 ±1.0*	69.0 ±1.6*	0.73 ±0.03*

Table 1. Baseline variables

HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, ScO_2: cerebral tissue oxygen saturation, CVC: cerebral vascular conductance. *denotes a significant difference between two groups. Variables represent group mean ± standard error of the mean (n = 13 in each group).

Chapter 1: Background and Literature

The US population is rapidly aging. The number of Americans aged 65 and older will increase from 54 million in 2020 to 80 million by 2040 while those over 85 will double in 2040 (The US Population Is Aging, 2020). Aging is a public health issue and studying age-related diseases and determining the molecular processes that worsen with age is vital in improving healthcare needs and delivery to the elderly population. Some protective factors against aging include higher levels of education, a healthy diet, low to moderate alcohol intake, and regular exercise.

Aging and the brain

It is well established that the human brain shrinks with increasing age and also undergoes various molecular, structural and functional changes (Peters et al. 2006). The microvascular endothelium is in direct contact with blood flow and is involved in the regulation of cerebral blood flow (CBF) through the production of vasoactive substances such as nitric oxide (NO) and endothelins. Aging is associated with endothelial dysfunction causing a reduction in NO availability in the cerebral circulation (Mayhan, Faraci et al. 1990). Age-related endothelial dysfunction likely contributes to the chronic cerebral hypoperfusion observed in aging and consequent cerebral dysfunction (Sabayan, Westendorp et al. 2014). Age-related decline in microvascular NO production, therefore, is likely to exert multifaceted detrimental effects on cerebrovascular, neuronal, astrocytic and microglial functions. Moreover, there is growing evidence implicating endothelial dysfunction in the pathogenesis of Alzheimer's disease (Toth, Tarantini et. al. 2017).

Aging is a strong risk factor for cerebrovascular disease (Zhu, Tseng et al. 2011). Chronic intermittent cerebral hypoperfusion and reduced CBF is associated with white matter lesions and cognitive decline (O'Sullivan, Duggan et al. 2003) post-stroke dementia (Firbank, He et al. 2011), and late-life depression. A higher prevalence of orthostatic hypotension has been reported in patients with Alzheimer's disease vs. cognitively normal adults and is associated with worse performance on cognitive tests (Mehrabian, Duron et al. 2010).

Aging and brain blood flow

Numerous studies demonstrated that total CBF decreases significantly in elderly group vs. younger adults (Kashimada, Machida et al. 1994; Tarumi, Zhang et al. 2018). Duscheck et. al (2007) identified a deficient regulation of cerebral blood flow in persons with low blood pressure leading to poorer cognitive performance, particularly involving attention and memory. They found that blood flow through middle cerebral arteries was bilaterally reduced in hypotensive individuals.

The decrease in blood flow affects both sedentary men and women (Ainslie, Cotter et al. 2008), but women tend to have higher levels of CBF than men (Lu, Xu et al. 2011). Because aging is associated with generalized cerebral atrophy, the observed decreases in CBF reflect an overall decrease in cerebral perfusion, without any disturbance of regional perfusion or oxygen consumption (Ainslie, Cotter et al. 2008). This age-related reduction of CBF may reflect decreased cerebral metabolic rate (Marchal, Rioux et al. 1992) in the form of impaired neuronal and glial mitochondrial metabolism. The brain is the body's most metabolically active organ and is completely dependent on CBF to maintain adequate metabolism. Across the adult lifespan, age decreases cerebral oxygen and glucose consumption by ~5% per decade, and these reductions of metabolic rate are coupled to the concurrent decrease in CBF (Leenders, Perani et al. 1990, Petit-Taboue, Landeau et al. 1998).

Using transcranial doppler ultrasonography, Bakker et. al demonstrated that cerebral blood flow velocity (CBFV) also declines significantly with increased age up to 90 years (Bakker, Leeuw et al. 2004). Giannattasio et al. showed impairment of baroreceptor modulation of the sympathetic drive to the peripheral circulation in elderly subjects, particularly the speed of reflex adjustments to normal and abnormal stimuli which could account for the reduced ability of elderly people to maintain blood pressure and blood volume (Giannattasio, Ferrari et al. 1994).

Aging effects on arterial blood pressure

Vascular compliance represents the ability of a vessel to distend and increase volume with increasing pressure. Aging has effects on both arterial compliance and pulse pressure, which is directly correlated with an increase in the amplitude of CBF pulsatility (Tarumi, Khan et al. 2014). Zieman et al. (2005) using echo-tracking techniques showed that aging is associated with increased contents of collagen relative to elastin in the vascular wall, and increased collagen cross-linkages due to advanced glycation end products (Zhu, Tseng et al. 2011). These changes in the extracellular matrix stiffen the proximal aorta and carotid artery. Disproportionate stiffening of the proximal aorta as compared with the carotid arteries reduces wave reflection and thereby facilitates transmission of excessive pulsatile energy into the cerebral microcirculation, leading to microvascular damage, disrupting cerebral blood flow, increasing white matter intensities (Tarumi et. al 2014) and impairing function in the brain. (Mitchell, Buchem et al. 2011). This phenomenon disrupts the neuronal environmental in the brain. Central arterial stiffening may also lead to blood pressure (BP) dysregulation and cognitive decline. The stiffening of barosensory arteries, such as the aorta and carotid artery, can blunt the sensitivity of baroreceptor function (Monahan, Dinenno et al. 2001), which in turn may contribute to the dysregulation of arterial BP, CPP, and ultimately, CBF.

Xing et al. (2017) reported that the fluctuations of CBF during postural changes are also increased in older adults vs. their counterparts. Cerebral blood flow/cardiac output ratio index (CCRI) decreased by 1.3% per decade in humans. Age, body mass index, carotid-femoral pulse wave velocity, and arterial pressure all correlated inversely with CBF. The study showed that a

smaller fraction of cardiac output (CO) is directed to the brain as one ages. This may be due to the fact that since there is a decrease in brain metabolic rate with aging, there may be less demand for CBF. Alternatively, age-related increases in arterial stiffness may result in decreases in CBF and thus CCRI despite increases in arterial perfusion pressure.

However, some studies demonstrate the opposite effect of aging on arterial pressure and cerebral perfusion pressure. Aging is normally associated with a gradual increase in mean arterial pressure (Franklin, Gustin et al. 1997). Heightened sympathetic neural activity and impaired peripheral vasodilatory function caused by endothelial dysfunction) are likely to increase total peripheral resistance and therefore mean arterial pressure in older adults (Hart, Joyner et al. 2012). Direct intracranial pressure monitoring using an intra-parenchymal probe demonstrated a negative correlation between age and intracranial pressure in patients with head injury (Czosnyka, Balestreri et al. 2005). If this observation can be extrapolated to healthy aging adults, age may increase cerebral perfusion pressure (CPP) due to the effects of both increased mean arterial pressure and decreased intracranial pressure. In the face of elevated CPP, the cerebrovascular bed may undergo compensatory remodelling by increasing resistance in order to protect the delicate brain tissues from over perfusion.

Aging and cerebral autoregulation

Cerebral autoregulation (CA), the complex process that maintains cerebral perfusion despite changes in arterial pressure, is a protective mechanism preventing brain ischemia when blood pressure falls and guarding against capillary damage when blood pressure is elevated. Furthermore, the brain has a very high metabolic demand for oxygen while the neurons do not have sufficient energy reserves leading to a constant need for stable perfusion in the brain (Toth, Tarantini et al. 2017).

Cerebral autoregulation can be evaluated by measuring blood flow changes in response to steady-state changes (static) or during the response to a rapid change in blood pressure (dynamic). Tiecks et al. showed that in normal humans, dynamic CA yields similar results as static testing of intact and pharmacologically impaired CA. However, dynamic studies are easier to perform, do not require invasive maneuvers, like pharmacological interventions, and involve shorter acquisition times, facilitating longitudinal studies (Fantini, Sassaroli et. al 2006).

Aging is associated with decreased low-frequency variability of blood pressure, CBF and heart rate, and impaired cardiovagal baroreflex and dynamic CA (Tarumi, Zhang et al. 2018). Dysregulated CA in the elderly limits CBF compensation with chronic hypotension, leading to cerebral under perfusion (Kennelly, Collins et al. 2012). Studies in rats show similar results (Fujishima, Sadoshima et al. 1984). There is strong evidence that aging diminishes the compensatory dilatation of brain stem arterioles during hypotension and modifies the autoregulatory plateau of CBF, which seems to increase the risk of brain stem ischemia during hypotensive conditions (Toyoda, Fujii et. al 1997). Furthermore, increased BP and CBF variability during repeated postural changes indicate diminished cardiovascular regulatory

capability in older adults and increased hemodynamic stress on the cerebral circulation (Xing, Tarumi et al. 2017). These observations suggest that postural changes causing temporary hypotension may cause transient cerebral hypoperfusion and increase the risk of falls and syncope in older adults.

Systemic factors affecting brain blood flow

Besides cerebral autoregulation, cardiovascular systemic factors substantially impact regulation of CBF and recovery from hypotension. Impaired cardiovascular regulation may lead to impaired regulation of CBF (Tarumi and Zhang, 2018). Among the elderly, lower cardiac indices relate to lower cerebral blood flow in the temporal lobes. (Jefferson, Liu et al. 2017).

Cardiovascular function can be inhibited pharmacologically to study its effects on the cerebral system in humans. Hypotension was induced through adrenergic blockade and combined adrenergic-cholinergic blockade using injection of metoprolol tartate and glycopyrrolate. Dynamic CA was decreased in adrenergic-cholinergic blockade, underscoring the importance of cardiac factors in dynamic CA regulation (Ogoh, Tzeng et al. 2010).

The $\propto_1$ alpha-1 adrenergic blocker Prazosin causes vasodilation and a decrease in blood pressure. In thigh cuff release experiments, prazosin attenuated arterial baroreflex mediated peripheral vasoconstriction as evidenced by a slower recovery of mean arterial pressure after cuff release. Prazosin also attenuated the rate of CA development. (Ogoh, Brothers et al. 2008). The effects of prazosin demonstrate the importance of vasomotor factors in CA. However, the relative contribution of vasomotion and cardiac factors to maintaining cerebral perfusion remains unclear.

Methods to study regulation of cerebral blood flow

It is well known that both chronic hypotension and hypertension can lead to reductions in CBF. In human subjects, blood pressure can be lowered non-invasively by applying **lower body negative pressure (LBNP)**. In this method, progressively more intense negative pressures are applied to the subject's lower body within a sealed chamber to inflict hypotension (Shi, Wray et al. 2000; Lewis, Smith et al. 2015) which consequently decreases V_{MCA} (Durocher, Carter et al. 2015). Lewis et al. (2015) showed that LBNP reduces the diameter of the internal carotid (ICA) and vertebral arteries (VA) which contributes to the decline in cerebral perfusion. Shi et al. (2000) demonstrated that LBNP causes orthostatic hypotension in elderly because of a diminished HR response compared to younger subjects.

Head-up-tilt method (HUT) can also be used as an orthostatic stress to study cerebral hemodynamics. Subjects in a supine position on a manually operated tilt table are raised from horizontal to 70-degree tilt, a maneuver that lowers cerebral perfusion by pooling of blood in lower parts of the body. HUT causes a significant reduction of CBF by a homogenous

reduction in the four cerebral vessels including right and left ICA and VA (Van Campen, Verheugt et al. 2018). However, the reduction in cerebral blood flow velocity is prolonged in HUT compared to LBNP due to gravitational effects (Bronzwaer, Verbree et al. 2017).

Sorond et al. (2009) applied **sit-to-stand methods** to alter blood pressure. In this procedure, subjects rest in a seated position for a few minutes followed by immediately standing upright for 1 minute. This maneuver causes hypotension and cerebral hypoperfusion. Although this protocol causes minimal discomfort and causes a decrease in sympathetic tone, it may cause hypocapnia leading to variation in cerebral autoregulation (Sorond, et al. 2009).

Chapter 2: Research Project

SPECIFIC AIMS

Cerebral autoregulation, the maintenance of cerebral blood flow in the face of changes in blood pressure, results from several mechanisms including myogenic, neurogenic, endothelial and metabolic responses. Cerebrovascular endothelium releases vasodilators e.g. nitric oxide (NO) and vasoconstrictors including thromboxane A2 and endothelin-1 (Silverman & Peterson, 2020). Previous studies have established the role of NO in cerebral autoregulation. Studies in cats demonstrated that NO participates in both the regulation of basal tone of cerebral microvessels and CBF autoregulation (Kobari, Fukuuchi et al. 1994). Systemic administration of the NO precursor L-arginine increased CBF velocity in humans (Silverman & Peterson, 2020). However, aging is associated with impaired cerebrovascular endothelial function through the production of ROS in brain vasculature which leads to disrupted autoregulation and slow recovery during hypotension. This cerebrovascular impairment increases the risks of falls resulting in injuries (Toth, Tarantini et. al. 2017).

Previous research has demonstrated that CA is preserved in young subjects during systemic arterial hypotension following deflation of thigh cuffs, which is essential to prevent orthostatic syncope (Guo, Tierney et. al. 2006). However, control of blood pressure and cerebral blood flow velocity may be impaired in the elderly (Claassen, 2018). Orthostatic syncope is more prevalent in older adults and increases the risk of falls.

We hypothesize that recovery of cerebral perfusion is slower in elderly than in younger adults due to aging-related impaired cardiovascular function. This hypothesis will be addressed by completing the following specific aims:

Specific Aim 1: To compare the effects of hypotension on cerebral blood flow in elderly vs. young humans

Specific Aim 2: To define the contributions of cardiac, vasomotor and intrinsic mechanisms in recovery of cerebral autoregulation during systemic hypotension.

SIGNIFICANCE AND INNOVATION

Changes in systemic blood pressure outside the effective autoregulatory range of 60-150 mm Hg (Guo et al. 2006) or when CA mechanisms are impaired have a marked impact on cerebral blood flow. A decrease in MAP tends to decrease CBF, while regulatory mechanisms cause vasodilation to maintain CBF in the face of systemic hypotension. These cerebrovascular responses to MAP changes depend upon intact CA; in pathological conditions where CA is impaired, CBF changes in parallel with MAP (Fantini, Sassaroli et. al 2006)

The various methods discussed above have been applied to study the effects of MAP variability on cerebral blood flow. The thigh cuff release protocol on awake humans was first introduced by Aaslid et. al in 1989 to assess dynamic CA (Aaslid et al. 1989) when it was concluded that this non-invasive technique is more clinically relevant than procedures on animals. Since then, this method has been used by numerous researchers studying effects of induced hypotension (Tiecks, Lam et al. 1995; Mahony, Panerai et. al 2000; Guo, Tierney et al. 2006; Panerai, Saeed et al. 2015).

In this method, bilateral thigh cuffs are inflated to 20mm Hg above peak systolic pressure, occluding the dorsalis pedis artery (Mahony, Panerai et. al 2000; Ogoh, Tzeng et al. 2010) and then rapidly deflated to initiate reperfusion. Arterial hypotension induced by the sudden release of inflated thigh cuffs results produced abrupt drops in mean arterial pressure and cerebral blood flow velocity, followed by a rapid return of cerebral blood flow to baseline in healthy subjects (Panerai, Saeed et al. 2015). Preliminary data using thigh cuffs indicated a marked decrease in MAP and V_{MCA} which completely recovered to baseline values within 10-12 s (Guo, Tierney et al. 2006). Several studies demonstrated that, across subjects, mean V_{MCA} returned to baseline faster than MAP due to intrinsic mechanisms (Tzeng, Lucas et al. 2010; Kolodjaschna, Berisha et al. 2005; Aaslid et al. 1989; Mahony, Panerai et al. 2000; Tiecks, Lam et al. 1995). Conversely, when dynamic CA is impaired, the return of CBFV to baseline is much slower, often following the mean BP signal closely (Tiecks, Lam et al. 1995)

Because LBNP could induce presyncope, we determined that it is not safe to apply LBNP to elderly subjects. The thigh cuff protocol was considered to be safer for our elderly research subjects. In addition, the thigh cuff maneuver is less dependent on a precise knowledge of the BP time course than other BP lowering methods. The indeed, rapid return of CBFV to baseline, while BP remains low, allows quantification of its rate of return, which is directly related to the efficiency of dynamic CA (Aaslid, Lindegaard et al. 1989) making this method most useful for our addressing our study questions.

The work described above supports the application of thigh cuff inflation-deflation as a safe and effective means to study the effects of acute hypotension in young and elderly subjects. As of yet, the mechanisms responsible for the effects of aging on cerebral perfusion remain obscure. Our current study is significant because it is the first to address the effect of aging on cerebral blood flow using the thigh cuff maneuver, and addresses the critical **knowledge gap**

regarding the physiological mechanisms leading to potentially detrimental changes in cerebral perfusion in elderly persons with systemic hypotension.

METHODS

Study participants:

Thirteen healthy elderly (67.5±1.1 yr, 3 women) and 13 young (25.8±1.0 yr, 3 women) adults signed a consent form and passed a physical exam to be enrolled into the study. The research protocol was approved by the IRB at the University of North Texas Health Science Center at Fort Worth. All subjects were asymptomatic for disease before their enrolment. Although neither weight (elderly: 77.1 ± 2.6 kg; young adults: 70.1 ± 3.7 kg; P = 0.13) nor height (elderly: 1.72 ± 0.02 m; young adults: 1.75 ± 0.02 m; P = 0.51) differed between young and elderly subjects, body mass index was significantly greater (P = 0.033) in the elderly (26.1 ± 1.1 kg/m^2) than the young adults (22.9 ± 0.9 kg/m^2).

Measurements:

Each subject's beat-to-beat heart rate (HR) was determined from a standard electrocardiographic lead (BIOPAC Model ECG100C, Santa Barbara, CA). Systolic and diastolic arterial pressures (SBP and DBP) were obtained using radial arterial tonometry (Colin Model 7000 Tonometer, San Antonio, TX) placed on the non-dominant arm. Mean arterial pressure (MAP) was computed as the sum of 1/3 SBP and 2/3 DBP. We (Wray, Formes et al. 2001) and others (Kemmotsu, Ueda et al. 1991, Zorn, Wilson et al. 1997) previously validated this non-invasive arterial pressure measurement against intra-arterial blood pressure measurements. Blood flow velocity of the middle cerebral artery (V_{MCA}) was monitored by transcranial Doppler (TCD) sonography using a 2 MHz probe (EZ-Dop DWL Elektronische System, Germany) placed over subject's left temporal window. The position and angle of the TCD probe was fixed to the head using a custom-made ring held by a Velcro band throughout the test. The gain and depth of the TCD signals were set at ≤30% and ≤50mm, respectively. Regional cerebral oxygen saturation (RcO_2) was determined by near infrared (NIR) spectroscopy by using a sensor placed on right side of the forehead (Somanetics Model 4100 INVOS Cerebral Oximeter, Troy, MI) with analog output sampled at 1 s intervals. All measurements were continuously captured on a BIOPAC SYSTEM 150 (Santa Barbara, CA) data acquisition system and digitized on-line at 400 Hz.

Study protocol:

Before each experiment, the subjects completed an orientation session in the lab during which they were familiarized with the testing procedures and methods of measurement. All experiments were performed in the morning with an ambient room temperature of 23 – 24°C. After instrumentation, placement of uninflated blood pressure cuffs (wide x length: 4.5" x 30", Aspen Labs, Englewood, CO) on each thigh, and the subject resting in the supine position ≥10 min, the subject's baseline cardiovascular variables were recorded for 3 min. Cuff pressures were continuously monitored by pressure transducers (Validyne Engineering Model DP45, Northridge, CA).

After the completion of collecting cardiovascular variables at rest, the thigh cuffs were rapidly inflated (Hankinson Model AG101 Cuff Inflator Air Source and Model E-20 Rapid Cuff Inflator, Bellevue, WA) to a pre-set supra-systolic pressure (≥30 mmHg above SBP). After 3-min occlusion, the subjects were requested to hold the breath at the end of normal expiration. Then, both cuffs were rapidly deflated by disconnecting the extension tube (internal diameter ~8 mm).

Data analysis and statistics:

Figure 1 presents a typical example of the cardiovascular responses and recoveries following cuff occlusion-deflation. Cardiovascular variables during a ≥1 min period before cuff inflation were averaged to represent the initial baseline (B_0). Data from a 15s segment shortly before cuff deflation was designated as the baseline for cardiovascular response (B_1). After deflation, the time elapsed from the deflated cuff pressure reaching 0 mmHg to MAP and V_{MCA} reaching their respective nadirs, MAP_{min} and V_{MCAmin}, was defined as the response time (T_0) for each variable. A difference between MAP_{min} (or V_{MCAmin}) and B_1-MAP (or B_1-V_{MCA}) was calculated as the decrease in MAP, i.e., index of systemic hypotension (or in V_{MCA}, index of cerebral hypoperfusion). The time duration from MAP_{min} and V_{MCAmin} to the point of full recovery (B_R), which were similar as their B_1 values, was identified as the recovery time (T_R). Percent increase in MAP (%ΔMAP) or V_{MCA} (%ΔV_{MCA}) during recovery from the deflation-induced hypotension was calculated from {[B_R-MAP - MAP_{min}] x 100}/B_R-MAP (or {[B_R-V_{MCA} - V_{MCAmin}] x 100}/ B_R-V_{MCA}). The rate of recovery or increase in MAP (or V_{MCA}) was estimated from %ΔMAP/T_R (or %ΔV_{MCA}/T_R). In addition, the tachycardic response (ΔHR), i.e. the HR difference between the peak-HR at the end of response and B_1-HR, was determined during the recovery from the cuff occlusion-deflation induced systemic hypotension. The rate of increase in HR during the recovery period was calculated as the percent increase in HR (%ΔHR) divided by the duration of HR response (in sec), where %ΔHR = [ΔHR x 100]/peak-HR.

Two-factor analysis of variance (ANOVA) was performed to assess the differences in the baseline variables between B_0 and B_1 (cuff factor) and between the two age groups (age factor). A post-hoc Duncan multiple comparison analysis for repeated measure was applied when the

main effect was determined to be significant. Student's t-test was performed to determine the difference in cardiovascular responses during cuff occlusion-deflation maneuver between two age groups. Pearson correlation was performed to examine the association between different cardiovascular variables and the slopes of the associations were compared. The slopes of the associations were compared using the z-statistics (PATERNOSTER, BRAME et al. 1998). Results are presented as group mean ± standard error of the mean (SE). Values of $P \leq 0.05$ were taken to indicate statistical significance. Statistical analysis system (SAS) software was used for data analyses.

RESULTS

Hemodynamic responses to suprasystolic thigh occlusion

Table 1 summarizes the cardiovascular variables at baseline (B_0) before the cuff inflation protocol. Resting blood pressure was higher, whereas HR, V_{MCA} and ScO_2 were lower in the elderly than the young subjects. Inflation of the thigh cuffs with supra-systolic pressure did not significantly affect HR, MAP or V_{MCA} (the cuff factor P = 0.138 for HR, P = 0.493 for MAP, P = 701 for V_{MCA}), although the age factor remains significant for HR (P = 0.041), MAP (P = 0.003), and V_{MCA} (P = 0.001) based on two-factor ANOVA. With cuffs inflated, HR, MAP and V_{MCA} in the elderly and young adults, respectively, were 59 ± 3 and 68 ± 2 beats/min, 89.3 ± 2.2 and 81.5 ± 2.3 mmHg and 47.1 ±1.3 and 57.8 ± 1.1 cm/sec.

Response to cuff occlusion-deflation

Rapid cuff deflation after 3-min supra-systolic thigh occlusion significantly ($P < 0.05$) decreased MAP (ΔMAP) in both the elderly (-14.1 ± 1.1 mmHg) and young adults (-16.5 ± 1.2 mmHg) (Figure 2). The magnitudes of ΔMAP were not significantly different between the two groups (P = 0.16), although the percentage decrease in MAP tended to be greater (P = 0.051) in the elderly (-16.0 ± 1.5%) than the young (-20.2 ± 1.4%) groups. The time duration to reach the nadir (T_0) of systemic hypotension was twice as long (P = 0.003) in the elderly (6.8 ± 0.9 s) than in the young adults (3.4 ± 0.5 sec), see Figure 3. Furthermore, the rate of percent decrease in MAP was significantly slower (P = 0.003) in the elderly (-3.0 ± 0.5 %/s) than the young (-7.3 ± 1.2 %/s) groups (Figure 4).

Associated with the systemic hypotension, there were transient decreases in V_{MCA} (ΔV_{MCA}) in both the elderly (-7.9 ± 0.9 cm/s) and young (-9.5 ± 1.0 cm/s) subjects. Although the magnitudes of ΔV_{MCA} were similar (P = 0.23) in the two groups, the T_0 for V_{MCA} to reach its nadir of was significantly shorter (P = 0.002) in the young (1.9 ±0.1 s) than elderly (3.8 ± 0.4 s) subjects. Furthermore, the percent decrease in V_{MCA} was no different (P = 0.935) in the elderly (-16.7 ± 2.0%) and young (-16.5 ± 1.7%) subjects. However, the rate of the percentage

decrease in V_{MCA} was significantly slower (P = 0.018) in the elderly (-5.3 ± 0.9 %/s) than the young adults (-8.9 ± 1.0 %/s).

In both groups, the T_0 was much shorter for ΔV_{MCA} than ΔMAP following the cuff deflation, suggesting an early recovery in cerebral perfusion mediated by cerebral autoregulation (CA) or intrinsic cerebrovascular mechanisms. The T_0 ratio of $\Delta V_{MCA}/\Delta MAP$ was 0.58 ± 0.05 and 0.66 ± 0.07 in the elderly and young groups, respectively. There was no significant difference in this time ratio between the groups (P = 0.32).

Recovery from cuff deflation

The time duration for MAP recovery (T_R) was significantly longer (P < 0.01) in the elderly (19.7 ±1.3 s) than young adults (11.2 ±1.0 s) (Figure 5). Similarly, the T_R for V_{MCA} was longer (P < 0.01) for the elderly (11.7 ±1.1 s) than young adults (7.0 ±0.7 s) groups. The T_R for MAP and the T_R for V_{MCA} were positively correlated (r = 0.64, P < 0.01). During the recovery from the systemic hypotension, HR increased in both the elderly (+8.9 ± 1.3 bpm) and young (+22.1 ± 1.7 bpm) subjects, but the increase was smaller (P < 0.01) in the elderly than young subjects (Figure 6). The rate of relative change in HR during recovery was significantly (P < 0.01) slower in the elderly (1.42 ± 0.20 %/s) than young adults (4.02 ±0.42 %/s).

Furthermore, the rates of relative increases in MAP (P < 0.001) and V_{MCA} (P = 0.015), respectively, during recovery were significantly smaller in the elderly (0.93 ± 0.11 %/s and 1.72 ± 020 %/s, respectively) than young adults (1.93 ± 0.20 %/s and 2.97 ± 0.40 %/s, respectively). Statistically significant linear correlations emerged (Figure 6) between %ΔHR and %ΔMAP (r = 0.63, P < 0.001), between %ΔHR and $\%\Delta V_{MCA}$ (r = 0.47, P = 0.021), and between %ΔMAP and $\%\Delta V_{MCA}$ (r = 0.57, P = 0.004).

Factors contributing to the recovery

Figure 7 illustrates that MAP- T_R (s) was significantly explained by the rates of %ΔHR (cardiac factor) and %ΔMAP (vasomotor factor) during recovery. However, the MAP- T_R: rate of %ΔMAP slope (-6.39 ± 0.89, R^2 = 0.67, P < 0.001) was significantly greater (P < 0.001) than the MAP- T_R: rate of %ΔHR slope (-2.14 ± 0.55, R^2 = 0.39, P < 0.001), indicating that the vasomotor factor was more important than the cardiac factor in effecting recovery from systemic hypotension.

Figure 8 demonstrates that the recovery time from the cerebral hypoperfusion was significantly affected by both systemic (cardiac and vasomotor) factors and CA and/or cerebrovascular intrinsic mechanisms. Again, the V_{MCA}- T_R: rate of %ΔMAP slope (-3.03 ± 0.87, R^2 = 0.35, P = 0.002) was significantly greater (P = 0.046) that the V_{MCA}- T_R: rate of %ΔHR slope (-1.12 ±

0.40, R^2= 0.25, P = 0.011), indicating that the vasomotor factor was more important than the cardiac factor in accelerating the recovery from cerebral hypoperfusion. Furthermore, the V_{MCA}- T_R: rate of $\%\Delta V_{MCA}$ slope (-2.28 ± 0.45, R^2 = 0.54, P < 0.001) tended to be greater (P = 0.055) than the V_{MCA}- T_R: rate of %ΔHR slope. However, there was no appreciable difference (P = 0.44) in the slopes of the cerebral hypoperfusion recovery time between the vasomotor factor and the CA factor.

DISCUSSION

The results of this study demonstrate that the recovery from cerebrovascular hypoperfusion during systemic hypotension was significantly prolonged in the elderly subjects because of the impaired mechanisms of cerebral autoregulation and systemic (cardiac and vasomotor) regulatory functions. Although there is no significant difference between vasomotor factors and cerebral autoregulation in contribution to the recovery from cerebrovascular hypoperfusion, vasomotor factors are more important than cardiac factors in maintaining both cerebral perfusion and MAP during hypotensive challenge.

Aging and cerebral autoregulation

During the thigh-cuff occlusion-deflation protocol, the cerebrovascular intrinsic mechanism and/or CA were active, because either V_{MCA}- T_0 or V_{MCA}- T_R were shorter than MAP- T_0 or MAP- T_R in the elderly and young subjects. These shorter V_{MCA}- T_0 and V_{MCA}- T_R, indicative of active CA, explained why V_{MCA} recovery preceded MAP recovery. These data suggested that the time courses of the recovery from the V_{MCA} nadir (T_0) or to full V_{MCA} recovery (T_R), regardless of the age effect, were partially independent of MAP- T_0 or MAP- T_R, although the thigh-cuff occlusion-deflation induced systemic hypotension produced cerebrovascular hypoperfusion. However, both V_{MCA}- T_0 and V_{MCA}- T_R were prolonged appreciably in the elderly vs. the young adults, indicating an age-related impairment of CA.

Previously, a population-based study reported that V_{MCA} responses to changes in arterial PCO_2 declined with increasing age (Bakker, Leeuw et al. 2004), suggesting that cerebrovascular reserve is diminished with aging. Cerebral blood flow assessed from transcranial Doppler measurements of V_{MCA} also declined with age (Ainslie, Cotter et al. 2008). Recently, Klein et al. (Klein, Bailey et al. 2020) reported that ΔV_{MCA} was significantly greater in elderly vs. young adults during transient increases in arterial pressure associated with stand-to-sit postural changes. They suggested that impaired endothelial function and increased vascular stiffness with aging likely contributed to the altered transient cerebral pressure-flow responses in elderly subjects (Klein, Bailey et al. 2020). The present study demonstrated that the rate of decrease in V_{MCA} immediately after the thigh-cuff deflation-induced hypotension, i.e., the T_0 phase, as well as the rate of increase in V_{MCA} during recovery from cerebrovascular hypoperfusion, i.e., the T_R phase, were shorter in the elderly than young adults. These data suggested that the age-related

impairment of CA or intrinsic cerebrovascular mechanisms could likely explain the prolonged V_{MCA}- T_R in the elderly subjects.

Aging and cardiac regulation

We previously demonstrated that reflexive tachycardia responses decline with aging, which may explain the transient hypotension at the onset of orthostatic challenge imposed by lower-body negative pressure (LBNP) in elderly subjects (Shi, Wray et al. 2000). After cardiac-vagal blockade using atropine or glycopyrrolate, the young subjects had systemic hypotension similar to that of the elderly subjects at the onset of LBNP (Shi, Wray et al. 2000). The importance of cardiac regulation is further confirmed by the observation that CA during thigh-cuff occlusion-deflation protocols is compromised by cardiac autonomic blockade of the HR response in healthy young subjects (Ogoh, Tzeng et al. 2010).

In addition to CA, adequate cerebrovascular perfusion also depends on a cardiac factor, cardiac output (CO) that is determined by cardiac contractility and HR, and on vasomotor factors, primarily MAP which, along with intracranial pressure, determines cerebral perfusion pressure. It is well recognized that cardiac index (CO÷body surface area) and left ventricular ejection fraction, decline with age (Kuikka and Länsimies 1982). Low cardiac index is associated with low cerebral perfusion to the temporal lobes (Jefferson, Liu et al. 2017) and low brain volume (Jefferson, Himali et al. 2010) in elderly adults. The present study indicated that reflexive tachycardic responses were predictive of both MAP recovery duration, i.e., MAP- T_R (Figure 7) and V_{MCA} recovery duration, i.e., V_{MCA}- T_R (Figure 8) from systemic hypotension. However, the rate of relative increase in HR during hypotension was diminished in the elderly as compared with the young subjects, which was associated with prolonged MAP- T_R and V_{MCA}- T_R in the elderly.

Aging and vasomotor regulation

Although both MAP- T_R and V_{MCA}- T_R were attributable to cardiac and vasomotor factors in the present study, the slopes of MAP- T_R /rate of %ΔMAP and V_{MCA}- T_R /rate of %ΔMAP were steeper than the slopes of MAP- T_R /rate of %ΔHR and V_{MCA}- T_R /rate of %ΔHR. These data suggested that vasomotor factors contributed more to cerebrovascular perfusion recovery from systemic hypotension than did cardiac factors, although both were significantly predictive of MAP- T_R and V_{MCA}- T_R.

Arterial pressure increases with age (Franklin, Gustin et al. 1997). Greater aortic stiffness is associated with reduced cerebral blood flow and increased cerebral vascular resistance (Jefferson, Cambronero et al. 2018). Previously, it was reported that maintenance of arterial pressure and responses of forearm vascular resistance (FVR) during sustained LBNP were similar in healthy elderly and young subjects (Taylor, Hand et al. 1992, Shi, Gallagher et al. 1996). Furthermore, changes in MAP during perturbations of the carotid arterial baroreceptor were not significantly different between the young and elderly (Shi, Gallagher et al. 1996).

Although sympathetic nerve activity assessed by peroneal microneurography was augmented, the increased FVR during LBNP was attenuated in the elderly vs. the younger subjects (Davy, Seals et al. 1998), suggesting an aging-related dissociation of sympathetic neuro transmission from vasomotor responses. Nonetheless, overall systemic vascular resistance appeared to be augmented in the elderly vs. younger adults during LBNP because of the attenuated decrease in CO of the elderly group with a similarly maintained arterial pressure (Taylor, Hand et al. 1992; Guo, Schaller et al. 2005).

In the present study, the ΔMAP magnitude induced by the cuff occlusion-deflation was similar in the elderly and young adults. However, both MAP- T_0 and MAP- T_R were prolonged in the elderly vs. their younger counterparts. A prolonged MAP- T_0 with the same ΔMAP magnitude in elderly was likely indicative of age-related endothelial dysfunction. As a result, elderly subjects were unable to adjust to physiological changes as quickly as younger adults. On the other hand, the prolonged MAP- T_R in the elderly subjects was explained by the diminished compensatory vasomotor response, probably mediated by a less effective reflex sympathetic neuro transmission to the smooth muscle of the vasculature associated with aging (Davy, Seals et al. 1998). Furthermore, the age-related impairment of cardiac reflex responses likely contributed to prolongation of MAP- T_R in the elderly subjects.

Study limitations and technique considerations

The thigh-cuff technique may elicit marked sympathetic neural activation associated with supra-systolic cuff inflation, muscular pain throughout the duration of cuff occlusion, and hyperventilation following cuff-release (Sorond, Serrador et al. 2009; Tzeng, Lucas et al. 2010). However, neither MAP nor HR differed with or without cuff occlusion, indicating that the cuff occlusion-stimulated sympathetic activity and/or pain sensation were likely minimal. Although we used TCD methods to study V_{MCA}, it should be noted that flow velocity may not always be equivalent to flow if the diameter of the MCA changes. However, MCA diameter remains fairly constant (Serrador, Picot et al. 2000) without significant change in end-tidal PCO_2 during the cuff deflation protocol (Guo, Tierney et al. 2006). Furthermore, direct visualization of the MCA during brain surgery suggests that, in the presence of stimuli known to affect cerebral blood flow, the diameter of the MCA changes only minimally. Because MCA diameter is nearly constant, beat-to-beat changes in mean MCA flow velocity may represent predominantly beat-to-beat changes in cerebral blood flow (Zhang, Zuckerman et al. 1998).

It is well recognized that V_{MCA} increases with physical fitness (Ainslie, Cotter et al. 2008). Indeed, aerobic exercise training improves regional CBF in sedentary older men (Kleinloog, Mensink et al. 2019). During low-to-moderate intensity dynamic exercise, enhanced neuronal activity is accompanied by cerebral perfusion increases of ~10–30% (Braz, Fisher. et al. 2016). V_{MCA} differed between the elderly and young subjects, which may affect the V_{MCA} responsiveness. The physical fitness related differences in cerebral autoregulation merit investigation. This study can also be repeated using different hypotension-inducing protocols

such as the sit-to-stand method and head-up tilt. Comparing aging effects using different techniques may reduce variation and improve accuracy of our results.

SUMMARY AND CONCLUSIONS

Both systemic factors and cerebral autoregulation contribute to the recovery from cerebral hypoperfusion induced by systemic hypotension. However, maintenance of cerebral perfusion and normotension during the cuff occlusion-deflation induced systemic hypotension is due more to vasomotor than cardiac factors. Aging is associated with diminished systemic responses and cerebral autoregulation, which explains the slower recovery from cerebral hypoperfusion in elderly adults.

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