Aging Reduces Cerebral Blood Flow Regulation Following an Acute Hypertensive Stimulus

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Abstract:
Aging increases arterial stiffness which has a negative impact on cerebral blood flow (CBF) regulation (decreases CBF and increases CBF pulsatility). The association between arterial stiffness and CBF pulsatility may, in part, explain the relationship between elevated blood pressure (BP) fluctuations and end-organ disease with aging. To understand the mechanisms by which large BP alterations influence cerebral blood flow regulation in both young and old, we examined the effects of age on central and cerebral blood flow regulation following an acute hypertensive stimulus (resistance-exercise (RE)). Measurements were obtained pre and immediate, 5-, and 30-min post-RE in young (n=35) and older (n=26) adults. Measurements included cerebral blood velocity (CBv), CBv pulsatility, central pulse wave velocity (PWV), beta-stiffness index (β) and carotid blood flow pulsatility. Central hemodynamics and BP were continuously recorded. Mean CBv increased immediately post-RE only in the young and decreased below baseline at 5-min post-RE in both groups (interaction, p<0.05). Older adults had a greater increase in CBv pulsatility immediately post-RE compared to the young (interaction, p<0.05). Mean BP was higher and carotid pulsatility was lower in the older group and increased immediately post-RE in both groups (p<0.05). PWV increased immediately post-RE (p<0.05). There were no changes in β. In conclusion, with aging, greater central arterial stiffness leads to a greater transmission of pulsatile blood velocity from the systemic circulation to the cerebral circulation following an acute hypertensive stress.

New and Noteworthy:
Reductions in cerebral blood flow and increases in flow pulsatility with aging is associated to cerebrovascular disease; however, little is known about how an acute hypertensive stimulus effects cerebral blood flow regulation in an aged population. Following the hypertensive stimulus, older adults elicit an attenuated increase in cerebral blood velocity and greater transmission of pulsatile velocity to the brain compared to young adults, demonstrating reduced cerebral blood flow regulation to elevated blood pressure responses with aging.

Key Words: arterial blood pressure, age, arterial stiffness, cerebral blood flow, cerebral pulsatility
Introduction

Cerebral vascular disease (CVD) is the 5th leading cause of death in the United States (23). Emerging evidence over the past few decades links age-related vascular health to brain structure and function (16), with the greater risk of CVD in older adults being partially attributable to increased stiffness of the large elastic arteries (30, 31, 50, 54). Increased central artery stiffness is associated with increased mortality and morbidity with advancing age (7, 29, 30, 42). Elevated arterial stiffness stems from reductions in elasticity of large central arteries, which attenuates their ability to dampen fluctuations in blood pressure and flow, thus contributing to increased systolic blood pressure and pulse pressure with age (24). The brain is highly vulnerable to the damaging effects of pulsatile flow and pressure during aging, and pulsatility is associated with increased risk of stroke (26) and cognitive dysfunction in older individuals (31, 46).

Pulsatile blood pressure and flow can be transmitted into the cerebral circulation (31), increasing the risk of end-organ damage (43), which may affect cerebral blood flow regulation. Maintaining adequate cerebral perfusion is of vital importance due to the high metabolic requirements of the brain, and dysfunction in cerebral blood flow regulation renders the brain susceptible to periods of both hypo- and hyperperfusion. It has been suggested that, cerebral blood flow regulation declines with aging (5, 49, 50, 53, 55, 58). If cerebral blood flow regulation is impaired with aging, an abrupt and transient increase in blood pressure may expose the brain to damaging pulsatile shear forces. Therefore, aging adults may be more susceptible to cerebrovascular damage and increased risk of cerebrovascular events during this potentially vulnerable time period, due to impaired cerebral blood flow regulation.
Resistance exercise (RE) places a large hemodynamic stress on the arterial system, with large increases in both systolic and diastolic blood pressure (2, 22, 28). High intensity RE has been shown to increase arterial stiffness (32), with recent evidence suggesting that RE may contribute to reductions in cerebral blood velocity (CBv) at rest (21). Cerebral blood flow regulation may also be temporarily disturbed in the early recovery period following acute RE (22, 39). Therefore, the use of RE as an acute hypertensive stimulus may provide a unique physiological stress to the cardiovascular system for the exploration of the relationship between arterial stiffness, carotid blood flow pulsatility, and cerebral blood flow regulation with aging.

The purpose of this study was to examine central and local artery stiffness, systemic hemodynamics and cerebral blood flow regulation in young and older adults following an acute hypertensive stimulus. We hypothesized older adults would exhibit increased arterial stiffness and reduced cerebral blood flow regulation compared to younger adults, both at rest and following acute RE (hypertensive stimulus).

Methods

Participants

Thirty-five young (18-35 years; male = 18) and twenty-six older adults (50-70 years, male = 12) completed this cross-sectional study. All participants were non-smokers and free from diagnosed cardiovascular, respiratory, metabolic or inflammatory diseases. Additional exclusion criteria included: diagnosed orthopedic injury, pregnancy, hormone replacement therapy, bleeding disorders, use of beta blockers and/or more than two anti-hypertensive medication ( table 1.), use of anticoagulant medications, or regular use of medications primarily used to reduce inflammation (e.g. aspirin, steroids, multivitamin, etc.). All subjects arrived at the laboratory for testing 4 hours post-prandial, having abstained from alcohol and caffeine consumption and
exercise for the previous 24 hours. Premenopausal women were tested within days 1-7 of menses or if taking oral contraceptives, during the “blank pill” week. The study was approved by the Institutional Review Board of the University of Illinois at Chicago. Subjects were recruited from the Chicago area and provided written informed consent prior to participation.

Study Design

Participants completed two study visits, a familiarization/medical screening session and one experimental session. During the familiarization/medical screening session, each participant completed a health history and physical activity questionnaire and were then familiarized with the maximal knee extension/flexion exercise protocol and all measures. On the day of the experimental session, height and weight were obtained prior to participants being seated on the force dynamometer. After 15 min of quiet rest in a semi-recumbent position, all baseline measures were recorded for a 5 min period. Participants then completed three sets of 10 repetitions of maximal isokinetic concentric/concentric knee extension/flexion contractions. All measures were repeated immediately (0-5 min), 5-10, and 30-35 min post-RE.

Acute Hypertensive Stimulus - Resistance Exercise

Unilateral isokinetic knee flexor and extensor peak and average torque were measured using a Biodex System 3 force dynamometer (Shirley, NY). Participants were seated semi-recumbently, at a 70° angle on the dynamometer according to the manufacturer’s recommendation. The dynamometer axis of rotation was aligned with the lateral epicondyle of the femur. A pad was positioned against the calf of the participant for force exertion. A tibial pad was then placed between the fibular malleolus and the femoral epicondyle. The thighs, pelvis, and torso were stabilized by straps. An anatomical reference position of 90° knee flexion was established, and isokinetic torque measured at a fixed angular speed of 60°/second. Resistance was applied in
direct proportion to a participant’s maximal effort. A warmup/familiarization set of 30 repetitions of isokinetic concentric/concentric unilateral knee flexion/extension with minimal load (180°/second) was performed. The experimental condition consisted of 3 sets of 10 repetitions at maximal exertion, with 30 seconds of rest between each set.

*Experimental Measurements:*

*B

*Body Composition*

Lean body mass was determined via a whole body dual energy x-ray absorptiometry scan (GE, IDXA, Madison, WI) during the familiarization/medical screening session. Lean body mass was used to normalize peak strength measures obtained from exercise, for both extension and flexion. Waist circumference was measured at the level of the umbilicus for all subjects.

*Carotid Intima Media Thickness (cIMT)*

cIMT was assessed, only during baseline, with high-fidelity ultrasound (Hitachi Aloka Alpha 7, Japan) using a high frequency (5-13 MHz) linear array probe. The cIMT of the common carotid artery was measured using the edge of the media-adventitia border to the leading edge of the intima (41). Average cIMT measurements were made over a 5-mm segment of the artery at end diastole, approximately 1-2 cm. proximal to the carotid bifurcation using edge detection software over the entire segment.

*Hemodynamics*

Beat-to-beat heart rate (HR) was obtained from a standard limb lead electrocardiogram (MP150; BioPac Systems Inc., Goleta, CA). Brachial arterial blood pressure (bSBP, bDBP,bPP, bMAP) was measured using non-invasive finger photoplethysmography (Finometer Pro, FMS, Netherlands). Cardiac output (Q) and stroke volume (SV), calculated via Modelflow, were
adjusted to aortic diameter (left ventricular outflow track) measured via ultrasound (Hitachi Aloka Alpha 7, Japan) and indexed to body surface area (BSA) via the Du Bois method (11).

**Transcranial Doppler**

Cerebral blood velocity (CBv) of the right middle cerebral artery was measured using a 2-MHz transcranial Doppler ultrasound probe (TOCM Neurovision, MultiGON Industries, INC. Elmsford, NY) fitted with a headpiece cushioned to hold the probe at the temporal window. The velocity waveform, recorded at 1 KHz (MP150; BioPac Systems Inc., Goleta, CA) was stored offline for analysis of beat-to-beat systolic, diastolic and mean blood velocities, as well as resistance and pulsatility indices (WinCPRS, Absolute Aliens Oy, Turku, Finland). The resistance and pulsatility indices are indicators of cerebral blood flow regulation in time domain (57). Transmission of pulsatile blood velocity from the extracranial circulation to the intracranial circulation was investigated by the inverse of Gosling’s dampening factor; the ratio of blood velocity pulsatility from the proximal to the distal arterial segments (17). Transmission of pulsatile blood velocity was calculated from the ratio of MCA velocity pulsatility (distal) to carotid pulsatility (proximal) indices (17, 59).

**End-Tidal CO₂**

End-tidal CO₂ was measured using a mask covering the nose and mouth for gas collection (CO2100C BioPac Systems Inc., Goleta, CA). The CO₂ module was calibrated prior to each test with a gas of known CO₂ concentration (5%).

**Carotid Artery Blood Flow**

Common carotid artery blood flow (CABF) was measured approximately 1-2 cm proximal to the carotid bifurcation with a high-fidelity ultrasound using a high frequency (5-13 MHz) linear array probe (Hitachi Aloka Alpha 7, Japan). Carotid artery diameter and blood velocity were
measured simultaneously, via Doppler ultrasound, with the probe on the skin over the carotid artery at a 30° insonation angle and the velocity gate within the center of the arterial lumen with the largest possible sample volume. CABF measurement were performed during the last minute of seated baseline and during the first minute of each of the recovery time points following RE. Carotid artery diameter during end-diastole was measured manually as the distance between the surface of the near arterial wall to the surface of the far wall. An average of three cardiac cycles of carotid artery diameters and velocities were averaged and used to calculate CABF and carotid pulsatility index via automated software (Hitachi Aloka Alpha 7, Japan).

**Central Pulse Wave Velocity**

PWV was calculated from 6-10 brachial pressure wave forms measured in the right arm using an automated microprocessor-controlled ambulatory blood pressure monitor (Mobil-O-Graph 24 PWA, I.E.M, Stolberg, Germany). The pulse wave analysis algorithms (ARCSolver method) have been validated against invasive (18) and non-invasive (13) reference methods and is highly reproducible to within 0.05 m/s ($r = 0.81$) (18). PWV was obtained during the last minute of seated baseline and during the first minute of each of the recovery time points following RE.

**Carotid Arterial Stiffness and Blood Pressure**

Common carotid artery β-stiffness index was measured using high-fidelity ultrasound (Hitachi Aloka Alpha 7, Japan) and calculated as follows: $\|(\ln P_1/P_0)/((D_1-D_0)/D_0)\|$; where $P_1$ and $P_0$ are the highest (systolic) and lowest (diastolic) carotid pressures and $D_1$ and $D_0$ are the maximum (systolic) and minimum (diastolic) diameters (33). Additionally, a carotid artery pressure waveform was obtained (average of 10 sec epoch) using applanation tonometry (SphygmoCor, AtCor Medical, Australia). To assess carotid blood pressure ($cSBP$, $cDBP$, $cPP$), the waveform was calibrated to $bMAP$ and $bDBP$. Previous work demonstrates high reproducibility of this
technique within 4 mmHg for central pressure (r = 0.89) (20). β-stiffness index and carotid blood pressure were assessed during minutes 0-2 of seated baseline and during minutes 1-3 of each of the recovery time points following RE.

**BP and CBv Oscillations in the Low Frequency (LF) Region**

A five-minute data recording was used for transfer function analysis (TFA) at baseline and immediately, 5, and 30-min post-RE to identify dynamic cerebral autoregulation in the frequency domain. The beat-to-beat data of MAP and mean CBv were linearly interpolated and resampled according to guidelines established by the International Cerebral Autoregulation Research Network (8). Temporal sequence analyses and spectral analyses (Fast Fourier Transformation Algorithm) were conducted on the BP and mean CBv time series in order to identify peaks of oscillations in the low frequency (LF) region (0.04 and 0.15 Hz). LF power is attributed to sympathetic activity (38). After determination of coherence between signals (i.e. MAP, CBv), indicated by a slope greater than 0.4 (10), the TFA magnitude (gain) and phase angle (°) were determined. These parameters reflect the relative amplitude and time relationship between the changes in arterial pressure and cerebral blood flow velocity over a specified frequency range (10, 22).

**Data and Statistical Analyses**

A power analysis was conducted on preliminary mean CBv response data collected in our laboratory. The data involved pre- and post-RE responses (Effects size f = 0.174), from a young cohort (n=20, 18-35 yrs) to determine the appropriate sample size. Using a power of 0.80, it was determined that a sample size of 48 subjects (n=24 per group) was required to detect the interaction effects (age-by-exercise) with an alpha set at p<0.05 using a repeated measures statistical test. All continuous recorded data (HR, arterial pressure, Q, SV, end-tidal CO₂, and
CBv) was analyzed during the last minute of seated baseline and during the first minute of each of the recovery time points following RE. Descriptive data are reported as mean ± SD. Normality was assessed using the Shapiro-Wilk test and non-normal data was log transformed (Mean CBv and Diastolic CBv). Group differences in baseline characteristics, maximal leg strength, and peak blood pressure were determined using independent Student $t$-tests. A 2x4 repeated measures analysis of variance (ANOVA) (age [young v old] x exercise effect [baseline, immediate, 5-min, 30-min]) was performed to evaluate the hemodynamic response to acute RE. Post-hoc analyses were conducted using the Bonferroni adjustment for multiple comparisons. A bi-variate correlation (continuous variables, r) or a point-biserial correlations (categorical variables, rpb) were used when appropriate to evaluate the relationships between aging, carotid stiffness parameters, and cerebral hemodynamics. SPSS version 24.0 (IBM Corporation, Armonk, NY) was used for analysis and an a priori significance level was set at $p<0.05$.

**Results**

**Descriptive Characteristics, Maximal Leg Strength and Peak Brachial Blood Pressure**

Older adults were heavier, and had a greater BMI, BSA, waist circumference, cIMT, and aortic diameter compared with young individuals (Table 1, $p<0.05$). No group differences were observed for resting heart rate or height ($p>0.05$). Absolute maximal leg strength did not differ between groups (Table 2, $p>0.05$), however, when peak strength measures were normalized to lean body mass, young adults had higher peak knee extension and flexion ($p<0.05$). Peak brachial BPs obtained during the RE were higher in older adults ($p>0.05$).

**Peripheral and Central Hemodynamics**

Heart rate, SV, bSBP, bDBP, bPP, bMAP, cSBP and cPP increased immediately post-RE in both groups (Table 3 and Figure 1, $p<0.05$). All returned to baseline values at 30-min post-RE, expect
Heart rate, which remained elevated in both groups (p<0.001). SV and Q increased immediately post-RE in both groups (p<0.0001). In older adults, Q returned to baseline at 5-min post-RE and further decreased below baseline at 30-min post-RE (p<0.002). In younger adults, Q remained elevated at all recovery time points post-RE (p<0.02). Q and SV was indexed to BSA and reanalyzed (Table 3); the overall findings remained the same between groups.

Aortic and Carotid Artery Stiffness

PWV was higher in the older group and increased immediately following RE in both groups (Table 3, p<0.0001). PWV remained elevated above baseline at 5-min post-RE only in the young adults (p=0.006). β-stiffness index was greater in older adults (age effect, p<0.0001) but did not change in response to RE in either group (Table 3, p=0.19). Please note, all arterial stiffness data was analyzed with 58 subjects, due to poor signal quality of the arterial pressure and distensibility wave forms in two young adults and one older adult subject during the experiments.

Carotid Artery Blood Flow

CABF was not different between groups and did not change post-RE (Table 3, p>0.11). Carotid pulsatility index (Pi) was higher in the young group at all time points (p<0.0001). Following RE, carotid Pi increased and remained elevated at 5-min post-RE before returning to baseline at 30-min post RE in both groups (Figure 2, p<0.02).

Cerebral Blood Flow Regulation

Mean and diastolic CBv increased immediately post-RE in the young group while decreasing below baseline at 5-min post-RE in both groups (Figure 1 & 2, interaction, p<0.04). Systolic CBv increased immediately post-RE in both groups but was higher in young adults (p<0.03). Mean CBv pulsatility and resistance indices increased immediately post-RE in both groups.
In young adults, mean CBv pulsatility index remained elevated at 5-min post-RE (p<0.0001) and returned to baseline at 30-min post-RE. Transmission of pulsatile blood velocity from the extracranial circulation to the intracranial circulation was higher at rest in the older adults (p<0.0001) and increased immediately post-RE only in the older adults (Figure 3, p = 0.008). Please note, all CBv data was analyzed with 60 subjects, due to the inability to obtain and/or maintain high quality CBv signals in one older adult subject during the experiments.

**End-tidal CO₂**

End-tidal CO₂ increased immediately post-RE (p<0.0001) in both groups, and returned to baseline at 5-min post-RE only in the older adults (p<0.002) (Figure 1.).

**Point-biserial correlations.** As expected, both PWV and β-stiffness index were correlated with age, additionally, transmission of pulsatile blood velocity to the cerebral circulation had a strong relationship with age immediately post-RE (rₜₙ =0.666, p<0.001, Table 4). MCAv Pi, CABF Pi, and MCAv are correlated with age (p<0.01 for all), Table 3.

**Cerebral Autoregulation in the Frequency Domain**

LF power of MAP increased immediately post-RE and remained elevated above baseline at 5- and 30-min post-RE in both groups (Table 5, p<0.0001). Young adults had higher mean CBv LF power (p=0.02). Mean CBv LF power increased at the 30-min post-RE in both groups (p<0.05). The LF phase angle for both groups increased at 5-min post-RE (p<0.05) and returned back to baseline at 30-min post-RE (Table 5). Gain was not different between groups and did not change following RE (p>0.05).

**Discussion**

In this study, cerebral and systemic arterial hemodynamics following high intensity RE...
were investigated in young and older adults. Immediately following the acute RE, an increase in aortic arterial stiffness and systemic BP occurred, accompanied by an increase in carotid and cerebral blood velocity pulsatility. However, despite older adults obtaining higher BP responses during RE bouts, mean cerebral blood velocity only increased post-RE in the young adults. Additionally, our findings suggest a potential mismatch between extracranial blood velocity/pulsatility and intracranial blood velocity/pulsatility following acute RE with aging, which appears to resolve by 30-min post-RE. This was demonstrated within the older adults by greater transmission of pulsatile blood velocity to the cerebral circulation immediately following the stimulus, demonstrating reduced cerebral blood flow regulation to acute elevations in blood pressure with aging.

Arterial Stiffness Effects on Cerebral Blood Flow Regulation

Recent evidence suggest arterial stiffness, pressure/flow pulsatility, and cerebral perfusion are interrelated (31, 51, 52). In our study, we found an increase in central arterial stiffness and CBv pulsatility immediately following RE, which remained elevated in young adults at 5-min post-RE. However, older adults had a greater increase in both central arterial stiffness and CBv pulsatility responses immediately following RE. These findings suggest that increased central atrial stiffness does affect CBv pulsatility following an acute hypertensive stimulus.

To our knowledge, there is currently only one study that has investigated the effects of an acute increase in arterial stiffness stemming from RE on CBv pulsatility (27). Lefferts et al. (27) demonstrated that increased carotid arterial stiffness does not affect CBv or pulsatility following an acute bout of upper body RE in young healthy subjects. One possible explanation for the different results may be the timing at which recovery measurements were performed. Lefferts et
al. (27) obtained the first measurement 10-min post-RE, whereas our current study obtained measures immediately and at 5- and 30-min post-RE. Therefore, we potentially captured an important time period following the exercise stimulus and further demonstrated the importance of timing of hemodynamic and vascular measurements following an acute hypertensive stimulus.

Systemic Hemodynamic Effects on Cerebral Blood Flow Regulation

In young adults the changes in mean CBv with high intensity RE were consistent with the current literature, showing an increase of ~15%-30% in mean CBv upon completion of RE (12, 22). The increase in mean CBv was not observed in the older adults in our study. This was unexpected considering the older adults achieved a higher MAP following the RE than the young adults. It is important to note that cerebral pulsatility was higher in the older adults immediately following RE compared to the young adults. These data therefore appear to demonstrate a potential disruption in cerebral blood flow regulation (indexed via mean CBv and pulsatility index) among older adults, which may impact brain tissue health, via acute periods of cerebral hypoperfusion. Arterial blood pressure is one of the primary factors contributing to alterations in CBv when pressure falls outside the regulatory range (25, 34). Therefore, based on older adults reaching a peak MAP of 170 mmHg during the stimulus, it was expected that this greater increase in perfusion pressure would result in a larger increase in mean CBv following RE. However, mean CBv following RE did not increase in the older adults despite a larger hypertensive response. These findings are contrary to recent evidence suggesting that there is less hysteresis with aging (3). It is important to also consider our data from a different view point, to one of possible resiliency that occurs with aging. Interestingly, hysteresis in the cerebral pressure-flow relationship may protect against cerebral hyper-perfusion, with ageing, during periods of acute hypertension that has been related to elevated cerebral sympathetic nervous
system activity with aging (4). Additionally, these findings may be an indication of intact cerebral autoregulation, which functions as a high pass filter, permitting quick changes in MAP to determine subsequent changes in mean CBv (9, 60). We found no differences between groups in our dynamic cerebral autoregulation data, as measured via TFA in the frequency domain. This may be due to the fact that TFA is based on analysis of two linearly related variables, which may not be the case between BP and CBv and most other dynamic cerebral autoregulation (56). Therefore, other methods for assessment of cerebral autoregulation must be explored that take into account the nonlinear relationship between BP and CBv (19). For example, TFA performed on different frequencies of forced oscillations that can be induced by oscillatory LBNP or repeated squat-to-stands (48).

In addition to arterial BP effects on CBv, Q is another factor that directly impacts cerebral blood flow and velocity. There is a linear relationship between Q and mean CBv both at rest and during exercise in humans (35) and the relationship becomes increasingly dependent on Q with aging (6). However, in this study both mean CBv and Q were elevated above baseline immediately following RE only in the young adults. Older adults had increased Q without the concomitant increase in mean CBv immediately post-RE. One possible explanation as to why Bronzwaer et al. (6) demonstrated greater dependence of mean CBv on Q with aging, may be due to the different exercise stimulus, the handgrip test, used to assess the relationship. Our participants were asked to perform a leg RE stimulus (larger muscle mass recruitment) that resulted in a larger increase in Q which may affect the mean CBv response differently with aging. There is a further mismatch between the systemic and cerebral circulation at 5-min post-RE, with mean CBv dropping below baseline levels in both age groups. A similar response is seen during maximal aerobic exercise, where Q peaks at a similar time as CBv, but remains
elevated above baseline during the remainder of recovery, while CBv decreases (15). This suggests that the decrease in CBv is not due to reduced cardiac function at 5-min post-RE, but rather due to other factors that contribute to CBv regulation during recovery from maximal RE, such as CO₂ (40).

The cerebral circulation is intrinsically regulated by the CO₂ tension in the arterial system, with hypercapnia increasing and hypocapnia decreasing CBF (47). Therefore, it is important to consider the regulatory effect that arterial CO₂ tension has on CBv, which may explain CBv responses during recovery. End-tidal CO₂ increased immediately following RE and decreased during the remainder of the recovery period similar to CBv. Cerebral reactivity to CO₂ is greater in response to hypercapnia compared to hypocapnia (36, 40). In humans there is a large increase in nitric oxide in the brain during hypercapnia, which is a major contributor to vasodilation of the cerebral vessels directly impacting CBF (37). Therefore, the increase in mean CBv immediately following the RE and subsequent reduction in mean CBv at 5-min post-RE in our young adults may be attributed to the initial hypercapnic response, followed by the hypocapnic response observed at 5 and 30-min post-RE, potentially demonstrating the contribution of the chemoreflex to the control of the cerebral vasculature following an acute hypertensive stimulus. However, this rationale does not explain the reduction in mean CBv in the older adults while in a eucapnic state at 5- and 30-min post-RE. Therefore, the reduction in CBv in the older adults during recovery may be due to other extrinsic or intrinsic mediating factors not measured in this study.

Pulsatile Transmission of Blood Velocity from the Extracranial to Intracranial Circulations

The elastic, central vasculature dampens fluctuations in blood flow and pressure to the vital organs. Aging causes a reduction in the viscoelastic properties of the large central arteries
and results in a stiffening of the arterial wall. Therefore, with increased in central arterial stiffness the resulting pulsatile blood flow and pressure can be transmitted to the cerebral circulation (31), increasing the risk of end-organ damage and cerebrovascular events (26, 43).

This relationship was observed in this study as older adults exhibited increased arterial stiffness and impaired cerebral blood flow regulation (indexed via mean CBv and pulsatility index) compared to younger adults, both at rest and following RE, which resulted in a greater transmission of pulsatile blood velocity to the brain. This greater transmission of pulsatile blood velocity to the cerebral circulation and reduced cerebral blood velocity responsiveness exposes the brain to potentially damaging pulsatile shearing forces in the older adults. Therefore, aging adults may be more susceptible during this potentially vulnerable period of time following an acute hypertensive stimulus.

Methodological Considerations

It is important to note; this is the first study to assess cerebrovascular responses to an acute hypertensive stimulus in an older group of adults. However, the lack of an older cerebrovascular-impaired group for clinical comparison purpose is a limitation of this study. A portion of our older adults were taking thyroid medication, anti-hypertensive medications and statins which may have effects on CBF responses, however, the current literature remains inconclusive with regards to the effects of these medications on CBF regulation (14, 44). Additionally, following a sensitivity analysis, reanalysis of data with the removal of all medicated subjects, the overall findings remained the same. Furthermore, we did not measure cholesterol values in this study, and cannot perform a cardiovascular risk score, which may provide additional information on the health status of our older adults. Cardiorespiratory fitness with ageing is an important factor that may also have an influence on cerebral blood flow regulation (1). Unfortunately, we did not
include any measurements of aerobic capacity within our study and therefore cannot assess the possible influence that reduced cardiorespiratory fitness might have on cerebral blood flow regulation with aging. Additionally, inferences from TCD analyses are limited because it is assumed that changes in CBv indicate changes in cerebral blood flow. This can only be true if the cross-sectional area of the insonated vessel remains constant. When comparing our data to other literature, it should also be considered that all measurements were performed in the seated position, whereas most other studies perform measurements in the supine position. Recent evidence suggests that body position may have effects on vascular function and should be taken into consideration when comparing arterial stiffness measurements between studies measuring in different positions (45).

Summary

Differential responses to acute RE occurred in cerebral and carotid hemodynamics between the young and older adults. Immediately upon completion of the high intensity RE, increases in systemic BP and central arterial stiffness were observed, as well as increases in carotid and cerebral blood velocity pulsatility in both groups. However, with aging, greater central arterial stiffness leads to a greater transmission of pulsatile blood velocity from the systemic circulation to the cerebral circulation for 5-min following RE. In addition, despite obtaining higher BP during RE in the older group, mean CBv did not increase immediately post-RE, whereas the young group had significant increases in mean CBv immediately post-RE. These differential age responses suggest reduced cerebral blood flow regulation to RE with aging.

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Figure Captions

Figure 1. Resting and recovery mean cerebral blood velocity, mean brachial arterial pressure, and end-tidal CO$_2$ responses following an acute hypertensive stimulus. (n=60, older=25). Mean ± SD. * denotes difference from baseline, p<0.032. † denotes age differences, p<0.044.

Figure 2. Resting and recovery cerebral blood velocity and dynamics responses following an acute hypertensive stimulus. (n=60, older=25). Mean ± SD. * denotes difference from baseline, p<0.031. † denotes age differences, p<0.039.

Figure 3. Resting and recovery transmission of pulsatile blood velocity responses following an acute hypertensive stimulus. * denotes difference from baseline, p=0.008. † denotes age differences, p<0.0001.


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Figure 1. Resting and recovery mean cerebral blood velocity, mean brachial arterial pressure, and end-tidal CO₂ responses following an acute hypertensive stimulus. (n=60, older=25). Mean ± SD. * denotes difference from baseline, p<0.032. † denotes age differences, p<0.044.
Figure 2. Resting and recovery cerebral blood velocity and dynamics responses following an acute hypertensive stimulus. (n=60, older=25). Mean ± SD. * denotes difference from baseline, p<0.031. † denotes age differences, p<0.039.
Figure 3. Resting and recovery transmission of pulsatile blood velocity responses following an acute hypertensive stimulus. * denotes difference from baseline, p=0.008. † denotes age differences, p<0.0001.
Table 1. Descriptive characteristics in young and older participants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (M/F)</td>
<td>35 (18/17)</td>
<td>26 (12/14)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>26 ± 5</td>
<td>60 ± 6 †</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.8 ± 9.1</td>
<td>167.4 ± 9.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.9 ± 10.6</td>
<td>81.7 ± 8.2 †</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 ± 3.2</td>
<td>30.1 ± 5.5 †</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.77 ± 0.17</td>
<td>1.93 ± 0.24 †</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>81.7 ± 8.2</td>
<td>102.9 ± 12.8 †</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>66 ± 9</td>
<td>63 ± 8</td>
</tr>
<tr>
<td>cIMT (mm)</td>
<td>0.42 ± 0.05</td>
<td>0.62 ± 0.09 †</td>
</tr>
<tr>
<td>Aortic Diameter (mm)</td>
<td>21.2 ± 1.9</td>
<td>22.4 ± 2.6 †</td>
</tr>
<tr>
<td>Medications (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Statins</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Anti- Hypertensive</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Mean ± SD. † Age Difference, p<0.05. Body mass index (BMI), Body surface area (BSA), carotid intima-media thickness (cIMT).
Table 2. Peak brachial blood pressure and maximal leg strength responses in young and older participants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>bMAP (mmHg)</td>
<td>132 ± 14</td>
<td>170 ± 23</td>
</tr>
<tr>
<td>bSBP (mmHg)</td>
<td>170 ± 19</td>
<td>209 ± 33</td>
</tr>
<tr>
<td>bDBP (mmHg)</td>
<td>105 ± 13</td>
<td>116 ± 20</td>
</tr>
<tr>
<td>bPP (mmHg)</td>
<td>65 ± 12</td>
<td>93 ± 19</td>
</tr>
<tr>
<td>Knee Extension (Nm)</td>
<td>129.7 ± 37.1</td>
<td>112.1 ± 36.8</td>
</tr>
<tr>
<td>Knee Flexion (Nm)</td>
<td>68.5 ± 18.8</td>
<td>62.1 ± 25.2</td>
</tr>
<tr>
<td>Knee Extension/LM (Nm/kg)</td>
<td>2.9 ± 0.4</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>Knee Flexion/LM (Nm/kg)</td>
<td>1.1 ± 0.2</td>
<td>0.9 ± 0.3</td>
</tr>
</tbody>
</table>

Mean ± SD. † Age Difference, p<0.05. Brachial mean BP (bMAP), brachial systolic BP (bSBP), brachial diastolic BP (bDBP), brachial pulse pressure (bPP), lean mass (LM).
Table 3. Resting and recovery hemodynamic and arterial stiffness responses following an acute hypertensive stimulus.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age</th>
<th>Baseline</th>
<th>Immediate</th>
<th>5-minute</th>
<th>30-minute</th>
<th>Time</th>
<th>Age</th>
<th>Time*Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (bpm)</td>
<td>Young</td>
<td>66 ± 9</td>
<td>88 ± 14a</td>
<td>75 ± 11a</td>
<td>73 ± 9a</td>
<td>&lt;0.0001</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>63 ± 8</td>
<td>78 ± 11a</td>
<td>68 ± 9a</td>
<td>67 ± 9a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV (ml)</td>
<td>Young</td>
<td>76 ± 16</td>
<td>91 ± 20a</td>
<td>81 ± 18</td>
<td>72 ± 15</td>
<td>&lt;0.0001</td>
<td>0.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>80 ± 21</td>
<td>89 ± 26a</td>
<td>75 ± 19a</td>
<td>70 ± 19a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVi (ml/m²)</td>
<td>Young</td>
<td>43 ± 9</td>
<td>51 ± 10a</td>
<td>45 ± 9</td>
<td>41 ± 9</td>
<td>&lt;0.0001</td>
<td>0.11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>42 ± 13</td>
<td>46 ± 14a</td>
<td>39 ± 10</td>
<td>37 ± 10a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q (L/min)</td>
<td>Young</td>
<td>5.0 ± 0.9</td>
<td>7.9 ± 1.4a</td>
<td>6.0 ± 1.3a</td>
<td>5.3 ± 1.0a</td>
<td>&lt;0.0001</td>
<td>0.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>5.2 ± 1.3</td>
<td>6.9 ± 1.9a</td>
<td>5.2 ± 1.2</td>
<td>4.8 ± 1.2a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qi (L/min/m²)</td>
<td>Young</td>
<td>2.9 ± 0.6</td>
<td>4.5 ± 0.8a</td>
<td>3.4 ± 0.7a</td>
<td>3.0 ± 0.6a</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>2.7 ± 0.8</td>
<td>3.6 ± 1.1a</td>
<td>2.7 ± 0.7</td>
<td>2.5 ± 0.6a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bSBP (mmHg)</td>
<td>Young</td>
<td>124 ± 9</td>
<td>139 ± 15a</td>
<td>125 ± 11</td>
<td>125 ± 9</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>143 ± 17</td>
<td>166 ± 22a</td>
<td>141 ± 18</td>
<td>144 ± 18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bDBP (mmHg)</td>
<td>Young</td>
<td>72 ± 7</td>
<td>76 ± 9</td>
<td>72 ± 7</td>
<td>76 ± 6</td>
<td>&lt;0.0001</td>
<td>0.47</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>73 ± 6</td>
<td>77 ± 6</td>
<td>74 ± 6</td>
<td>76 ± 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bPP (mmHg)</td>
<td>Young</td>
<td>51 ± 6</td>
<td>63 ± 10a</td>
<td>53 ± 7</td>
<td>49 ± 5</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>70 ± 16</td>
<td>89 ± 19a</td>
<td>67 ± 15</td>
<td>68 ± 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>Young</td>
<td>5.1 ± 0.4</td>
<td>5.6 ± 0.6a</td>
<td>5.3 ± 0.4a</td>
<td>5.2 ± 0.3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>8.6 ± 1.0</td>
<td>9.3 ± 1.1a</td>
<td>8.6 ± 1.0</td>
<td>8.7 ± 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid β-stiffness index</td>
<td>Young</td>
<td>5.7 ± 1.2</td>
<td>5.7 ± 1.2</td>
<td>5.8 ± 1.3</td>
<td>6.1 ± 1.2</td>
<td>0.19</td>
<td>&lt;0.0001</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>11.9 ± 2.7</td>
<td>11.3 ± 3.2</td>
<td>11.8 ± 2.6</td>
<td>11.8 ± 2.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABF (ml/min)</td>
<td>Young</td>
<td>520 ± 111</td>
<td>534 ± 101</td>
<td>509 ± 105</td>
<td>513 ± 105</td>
<td>0.11</td>
<td>0.45</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>542 ± 120</td>
<td>549 ± 116</td>
<td>523 ± 112</td>
<td>544 ± 126</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD, a different from baseline, p<0.05. Cardiac output (Q), stroke volume (SV), Indexed to BSA (i), brachial systolic BP (bSBP), brachial diastolic BP (bDBP), brachial pulse pressure (bPP), pulse wave velocity (PWV, n = 58 (Older = 25)), beta (β), and carotid artery blood flow (CABF, n = 58 (Older = 25)).
Table 4. Age correlated with increased arterial stiffness parameters, elevated transmission of pulsatile blood velocity to cerebrovasculature, and reduced cerebral blood flow regulation immediately post resistance exercise.

<table>
<thead>
<tr>
<th>Variables</th>
<th>$r_{pb}$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV (m/s)</td>
<td>0.919</td>
<td>0.001</td>
</tr>
<tr>
<td>β-stiffness index</td>
<td>0.776</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulsatile Transmission</td>
<td>0.666</td>
<td>0.001</td>
</tr>
<tr>
<td>MCAv Pi</td>
<td>0.334</td>
<td>0.009</td>
</tr>
<tr>
<td>CABF Pi</td>
<td>-0.453</td>
<td>0.001</td>
</tr>
<tr>
<td>MCAv</td>
<td>-0.319</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Pulse wave velocity (PWV); β (Beta), Middle cerebral artery velocity (MCAv), Carotid artery blood flow (CABF), Pulsatility index (Pi).
Table 5. Resting and recovery cerebral autoregulation responses following an acute hypertensive stimulus.

<table>
<thead>
<tr>
<th>Age</th>
<th>Baseline</th>
<th>Immediate</th>
<th>5-minute</th>
<th>30-minute</th>
<th>Time</th>
<th>Age</th>
<th>Time*Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP LF Power (mmHg²)</td>
<td>Young</td>
<td>5.72 ± 3.89</td>
<td>5.78 ± 4.18</td>
<td>7.58 ± 4.86ₐ</td>
<td>8.73 ± 5.17ₐ</td>
<td>&lt;0.0001</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>4.43 ± 2.92</td>
<td>5.49 ± 6.42</td>
<td>6.74 ± 5.57ₐ</td>
<td>7.67 ± 5.77ₐ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CBv LF Power (cm/s²)</td>
<td>Young</td>
<td>4.53 ± 2.80</td>
<td>4.93 ± 3.41</td>
<td>5.77 ± 3.96</td>
<td>5.93 ± 4.08ₐ</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>2.97 ± 2.80</td>
<td>3.36 ± 2.81</td>
<td>3.51 ± 2.61</td>
<td>3.86 ± 3.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF Coherence (Index)</td>
<td>Young</td>
<td>0.71 ± 0.11</td>
<td>0.64 ± 0.12</td>
<td>0.67 ± 0.13</td>
<td>0.72 ± 0.12</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>0.64 ± 0.15</td>
<td>0.62 ± 0.12</td>
<td>0.65 ± 0.11</td>
<td>0.65 ± 0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF Phase(°)</td>
<td>Young</td>
<td>47 ± 15</td>
<td>46 ± 19</td>
<td>56 ± 15</td>
<td>46 ± 14</td>
<td>0.02</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>46 ± 18</td>
<td>47 ± 15</td>
<td>51 ± 15</td>
<td>47 ± 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF Gain (cm/s * mmHg⁻¹)</td>
<td>Young</td>
<td>0.84 ± 0.26</td>
<td>0.84 ± 0.36</td>
<td>0.80 ± 0.25</td>
<td>0.76 ± 0.22</td>
<td>0.32</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>0.72 ± 0.24</td>
<td>0.69 ± 0.21</td>
<td>0.71 ± 0.22</td>
<td>0.68 ± 0.26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD (n/older = 57/23). ₐ different from baseline p<0.05. Mean arterial pressure (MAP), low frequency (LF), and cerebral blood velocity (CBv).