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Assessing cerebrovascular autoregulation from critical closing pressure and resistance area product during upright posture in aging and hypertension

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Robertson AD, Edgell H, Hughson RL. Assessing cerebrovascular autoregulation from critical closing pressure and resistance area product during upright posture in aging and hypertension. Am J Physiol Heart Circ Physiol 307: H124–H133, 2014.—Static cerebral autoregulation (sCA) is believed to be resistant to aging and hypertensive pathology. However, methods to characterize autoregulation commonly rely on beat-by-beat mean hemodynamic measures and do not consider within-beat pulse wave characteristics that are impacted by arterial stiffening. We examined the role of critical closing pressure (CrCP) and resistance area product (RAP), two measures derived from the pulse wave, across supine lying, sitting, and standing postures in young adults, normotensive older adults, and older adults with controlled and uncontrolled hypertension (N = 80). Traditional measures of sCA, using both intracranial and extracranial methods, indicated similar efficiency across all groups, but within-beat measures suggested different mechanisms of regulation. At rest, RAP was increased in hypertension compared with young adults (P < 0.001), but CrCP was similar. In contrast, the drop in CrCP was the primary regulator of change in cerebrovascular resistance upon adopting an upright posture. Both CrCP and RAP demonstrated group-by-posture interaction effects (P < 0.05), with older hypertensive adults exhibiting a rise in RAP that was absent in other groups. The posture-related swings in CrCP and RAP were related to changes in both the pulsatile and mean components of arterial pressure, independent of age, cardiac output, and carbon dioxide. Group-by-posture differences in pulse pressure were mediated in part by an attenuated heart rate response in older hypertensive adults (P = 0.002). Examination of pulsatile measures in young, elderly, and hypertensive adults identified unique differences in how cerebral blood flow is regulated in upright posture.

middle cerebral artery; carotid arteries; Doppler ultrasound; pulse pressure

ORTHOSTATIC INTOLERANCE is a primary contributing factor to hospitalizations of older adults, with syncope being a prevalent trigger for admittance to emergency departments (46). Syncope and falls are often precipitated by symptoms of cerebral hypoperfusion, including dizziness and confusion (39). Even in young adults, cerebral blood flow (CBF) is lower when sitting or standing compared with lying supine (33, 41). Hence, a lower resting CBF, as observed in aging and hypertension (6), increases the risk for transient hypoperfusion in upright posture and emphasizes the need for effective cerebrovascular control. Cerebral autoregulation (CA) characterizes the efficiency in maintaining CBF despite changes in arterial blood pressure (ABP) (48) and is commonly assessed by the change in cerebrovascular resistance (CVR) for a given change in pressure (21, 26, 48). When considering CVR as the solitary regulator (i.e., CVR = ABP/CBF), CA has proven to be a robust physiological trait, resistant to aging (12, 14, 26, 34) and hypertensive pathology (12, 45, 53).

The definition of CA has been dichotomized as “dynamic,” involving rapid changes in pressure (25, 54), and “static,” involving steady-state changes over the course of minutes or longer (48). Both definitions of CA, however, are characterized by the relationship between mean flow and pressure, averaged across one or more cardiac cycles. Several observations point to a need to examine within-beat pulsatile characteristics. Importantly, posture-related shifts in pulse pressure (PP) have been shown to be a function of changes in systolic and diastolic pressures, independent of mean pressure (50). Despite similar posture-induced changes in mean pressure, PP is reduced in young adults and maintained in older adults during standing (29). Further, within-beat pulsatile characteristics are enhanced by arterial stiffening common to aging and hypertension (24, 51), yet their influence on CA has not been thoroughly examined. A comparison of CA in hypertension, through transfer function analysis (TFA) at the cardiac frequency (~1.0 Hz), found that hypertensive older adults retained autoregulatory function (45); however, the TFA approach still relies on dynamic fluctuations of mean pressure and velocity.

Critical closing pressure (CrCP) and resistance area product (RAP) are variables derived from the instantaneous relationship between ABP and CBF (or CBF velocity) (35). CrCP refers to the theoretical pressure at which CBF falls to zero and is believed to represent a marker of cerebrovascular wall tension (52). RAP characterizes vascular resistance according to the slope of the linear within-beat ABP-CBF relationship. Substituting CrCP and RAP for CVR in a model of cerebrovascular regulation might improve the model’s representation of a complex regulatory system by introducing consideration of the pulsatile relationship between pressure and flow. Preliminary work has shown CrCP and RAP are each responsive to hypertensive (10, 28) and hypotensive challenges (7, 55).

The aims of this study were to explore CrCP and RAP as regulators of static CA (sCA) during orthostatic stress in older adults with and without hypertension. With changes to the pulsatile component of blood pressure, we hypothesized that

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characterizing sCA by CrCP and RAP would reveal differences between young and older hypertensive adults. These hemodynamic variables may be more sensitive than mean beat-by-beat measures to detect differences in sCA due to the influence of pulsatile characteristics. As such, they may also be particularly useful in detecting autoregulatory differences between normotensive and hypertensive older adults associated with arterial stiffening. In addition, middle cerebral artery (MCA) hemodynamic measures were supplemented with examination of the extracranial internal carotid artery (ICA).

METHODS

Participants. A convenient sample of healthy young adults (n = 29; 16 women) and community-living older adults (n = 59; 34 women) was enrolled in this study. Participants were excluded based on the presence of stage II hypertension (ABP ≥ 160/100 mmHg), cognitive impairment, cerebrovascular or carotid artery disease, or self-reported co-morbidities, including a history of atrial fibrillation, myocardial infarction, heart failure, or other major chronic diseases. During an initial visit, seated blood pressure was assessed using auscultation, taken as the average of the second and third measurement in the morning while fasting and before medication. Older adults were grouped (Table 1) according to American Heart Association guidelines (9) as normotensive/prehypertensive (OLD: systolic pressure < 140 without use of ABP-lowering medication), controlled hypertensive (cHTN: systolic pressure < 140 with chronic use of ABP-lowering medication), or uncontrolled hypertensive (uHTN: systolic pressure ≥ 140). No participants had diastolic pressure ≥ 90 mmHg. Participants brought their medication to the lab for authentication. All participants provided written, informed consent to the procedures outlined in this study following approval from the Office of Research Ethics at the University of Waterloo.

Measurements. On a separate day, participants visited a climate-controlled laboratory for a vascular health assessment in the afternoon, at least 2 h following a light meal. Participants were instructed to take medications as per usual, but to avoid vigorous exercise, caffeine, nicotine, and alcohol on the day of the assessment. Heart rate was monitored using a three-lead ECG (lead II; Pilot 9200, Colin Medical Instruments, San Antonio, TX). Continuous ABP was monitored by finger-cuff photoplethysmography, calibrated to brachial artery systolic pressure using a return-to-flow technique, and reconstituted by infrared spectroscopy (Pilot 9200). Data were collected continuously at 1 kHz (PowerLab; AD Instruments, Colorado Springs, CO), and subsequent analysis was performed in Excel 2010 (Microsoft, Redmond, WA) and MatLab v7.9 (The MathWorks, Natick, MA).

Off-line analysis involved beat-by-beat averaging triggered to the ECG R-wave. All signals were low-pass filtered with a cutoff frequency of 15 Hz. Mean ABP was corrected to brain level (BBP_{MCA}), thereby accounting for the orthostatic pressure gradient between the brain and the heart in upright postures [correction factor = distance (in cm)/0.78 mmHg/cm blood]. Breath-by-breath values of end-tidal pressure of CO_{2} (PE_{TOT}) were obtained and time-matched for analysis.

Cerebral blood flow. Velocity through the right MCA was measured using a 2-MHz pulsed transcranial Doppler system (Neurovision Ultrasound Model 500V, Multigon Industries, Yonkers, NY; or Doppler Box, Compumedics DWL, Singen, DE) using standard search techniques (1) and recorded on the PowerLab system. Briefly, the transducer was positioned against the temporal window, with a slightly forward orientation and held in place with a fitted headband. The insonation depth between 50 and 60 mm is consistent with the proximal M1 segment (15). Traceability, velocity profile, signal strength, auditory pitch, and probe angle were used to confirm insonation of the MCA. Mean flow velocity (MFV) was taken as the time-averaged mean of the signal’s outer envelope.

Quantitative extracranial blood flow was measured in the right ICA. Duplex ultrasonography (HF38 6–13 MHz linear array transducer with Micromaxx System, Sonosite, Bothwell, WA; or L14–6s 8–12 MHz linear array transducer with M5 System, Mindray Bio-Medical Electronics, Shenzhen, CN) captured arterial diameter (gated to the R-spike on 3 consecutive cardiac cycles) and blood flow velocity (10–15 cardiac cycles). Mean blood flow (MBF) was computed as the product of the cross-sectional area and the intensity-weighted MFV. Effort was made to maintain the angle of insonation (~50° to 65°) constant across postures. As needed, the participants’ heads were tilted back and away from the sonographer to facilitate imaging. ICA flow (MBF_{ICA}) was measured at least 1 cm distal to the carotid bifurcation to minimize the turbulent influence of the carotid bulb. All imaging in the current study was completed by ADR. In 13 young participants, supine ICA measurements were repeated ~30 min apart. Repeatability analysis revealed arterial diameter to be more consistent than velocity [diameter: coefficient of variation (CV) 0.6–6.5%, intra-class correlation coefficient (ICC) 0.91; velocity: CV 2.3–20.1%, ICC 0.67]. The discrepancy between diameter and velocity is consistent with previous reports showing structural characteristics to have greater reproducibility (47). Blood flow was measured unilaterally on the right side, relying on the assumption of contralateral symmetry (44).

Cerebrovascular resistance. Resistance indexes that were calculated and interpreted as regulators of sCA included: J) beat-by-beat cerebrovascular resistance (CVR = BBP_{MCA}/MBF) and cerebrovascular resistance index (CVR_{J} = BBP_{MCA}/MFV); and 2) instantaneous resistance area product (RAP) and critical closing pressure (CrCP). The instantaneous variables, which characterize the within-beat relationship between blood pressure and blood flow velocity, were estimated by a two-point (mean-diastolic) method (37). Briefly, the mean and diastolic values of the blood pressure and blood flow velocity waves for each cardiac cycle were compared. RAP was calculated as (mean – diastolic pressure)/(mean – diastolic velocity), and CrCP was calculated as mean pressure – (mean velocity × RAP).

Table 1. Participant characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>YNG (n = 23)</th>
<th>OLD (n = 22)</th>
<th>cHTN (n = 23)</th>
<th>uHTN (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>25 ± 3</td>
<td>72 ± 6</td>
<td>73 ± 5</td>
<td>76 ± 6</td>
</tr>
<tr>
<td>Sex, % (n/total)</td>
<td>48 (11)</td>
<td>50 (11)</td>
<td>61 (14)</td>
<td>58 (7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 ± 4</td>
<td>27 ± 4</td>
<td>26 ± 4</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>Chronic medications</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>26 (6)</td>
<td>17 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR blocker</td>
<td>22 (5)</td>
<td>25 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>13 (3)</td>
<td>8 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca-channel blocker</td>
<td>4 (1)</td>
<td>17 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>35 (8)</td>
<td>33 (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Values are means ± SD or % (n). YNG, young adults; OLD, normotensive adults; cHTN, adults with controlled hypertension; uHTN, adults with uncontrolled hypertension; BMI, body mass index; ACE, angiotensin-converting enzyme, AR, angiotensin II receptor. |
sultantly, RAP reflects the inverse of the diastolic-mean slope of the pressure-velocity curve (where pressure lies on the y-axis), and CrCP reflects an extrapolation of the slope to the x-intercept, at which point velocity would theoretically be zero (Fig. 1). Although CrCP estimations are known to have large variability, the mean-diastolic method was recently shown to have good repeatability, as well as to result in fewer instances of negative values, compared with other strategies (37). To optimize confidence in our measures, an individual whose supine resting CrCP (30-beat average) had a mean-SD ratio < 5 was deemed to have excessive noise and was not included in the analysis.

**Static cerebral autoregulation.** Following at least 10 min of lying supine (SUP), participants moved to a seated position (SIT) for up to 5 min, and then to a standing position (STA). ICA measurements were taken during SUP and SIT only. Physiological measurements were averaged over 30 s in each posture, at least 90 s following the transition. Static cerebral autoregulation (sCA) was assessed by the relative change (% change) in hemodynamic characteristics in response to the relative change (% change) in BP<sub>MCA</sub> between postures. For MCA hemodynamic measurements, sCA was assessed by within-subject linear regression, modeling the %ΔMFV or %ΔCVR<sub>i</sub> in response to %ΔBP<sub>MCA</sub> over all three postures (e.g., %ΔMFV = A + β × %ΔBP<sub>MCA</sub>), where β represents the slope of the relationship between pressure and velocity (i.e., sCA efficiency) (N.B., such models will be abbreviated BP<sub>MCA</sub> → MFV, for example). For carotid hemodynamic measures, sCA was assessed by the slope of the line characterizing the %ΔMBF or %ΔCVR in response to %ΔBP<sub>MCA</sub> between SUP and SIT only. As sCA efficiency increases, slopes for flow-related variables will approach 0, and slopes for resistance-related variables will increase. To examine CrCP and RAP as autoregulatory variables, BP<sub>MCA</sub> → CrCP and BP<sub>MCA</sub> → RAP were also examined.

**Statistical analyses.** Continuous data were expressed as means ± SD. Categorical data were expressed as proportion (count). All statistical tests were performed using SAS v9.2. Group differences in cardiovascular and cerebrovascular hemodynamic measures between postures were examined using a mixed, linear, 2-way repeated measures ANOVA model (between-subject factors: group; within-subject factors: posture) with an autoregressive covariance structure using the Mixed procedure. Group differences in sCA were assessed by a one-way ANOVA model. All post hoc comparisons were performed with the Tukey-Kramer adjustment for multiple comparisons. Relationships between the supine-to-seated changes in mean and pulsatile pressure characteristics and the parallel changes in cerebral hemodynamic measures were assessed by pooled Pearson product correlations across the entire sample. Significant associations were followed by multiple linear regressions to assess independence of the relationships after adjusting for age, and changes in cardiac output and PET<sub>CO<sub>2</sub></sub>. A threshold for significance was set at α = 0.05.

**RESULTS**

Intracranial (MCA) and extracranial (ICA) cerebral hemodynamic characteristics were measured in 88 young, older, and hypertensive adults. Eight participants (6 YNG; 1 cHTN; 1 uHTN) were excluded from the analysis due to excessive noise in the estimation of supine CrCP. Further, inaccessible carotid windows prevented ICA hemodynamic measurements in nine older participants (5 OLD; 2 eHTN; 2 uHTN) and technological limitations of one imaging ultrasound system limited within-beat ICA hemodynamic measurement to 33 participants (6 YNG; 10 OLD; 12 eHTN; 5 uHTN).

In supine rest (Table 2), mean arterial pressure was elevated in older group compared with YNG, and in uHTN compared with OLD. Similarly, PP was greater in eHTN and uHTN compared with YNG, as well as uHTN compared with OLD. These differences were secondary to increases in systolic, but not diastolic, pressure in hypertensive adults. PET<sub>CO<sub>2</sub></sub> was lower in each older group compared with YNG, but no group differences were noted in resting heart rate or stroke volume and cardiac output after normalizing for body size. In the MCA, MFV was significantly lower in OLD and eHTN than YNG, and CVR<sub>i</sub> was elevated in all groups of older adults compared with YNG. Similar to CVR<sub>i</sub>, RAP was elevated in hypertensive adults compared with YNG, but CrCP was similar across all groups. In the extracranial circulation, MBF<sub>ICA</sub> differences between groups did not reach significance, but CVR was elevated in older adults compared with YNG, with a greater difference between uHTN and YNG than between OLD and YNG. Together, these resting hemodynamic characteristics suggest increasing arterial pressure in aging and hypertension is countered by an increased resistance profile, with only modest effects on markers of absolute blood flow.

With upright posture, the orthostatic gradient between the heart and the brain led to a reduction in BP<sub>MCA</sub> in all groups when sitting and standing (group-by-posture interaction: P = 0.005; Fig. 2A). The drop in BP<sub>MCA</sub> was greater in OLD than in YNG (Table 3). In response, CVR<sub>i</sub> was lower in upright postures compared with supine, and a group-by-posture interaction (P < 0.001) indicated that OLD and uHTN had a greater
indicated group differences: *vs. YNG, statistics are reported in RESULTS. Post hoc analysis of paired differences at each
6/10/12/5 for CrCPICA and RAPICA.

Table 2. Supine hemodynamic characteristics

<table>
<thead>
<tr>
<th>Central hemodynamics</th>
<th>YNG (n = 23)</th>
<th>OLD (n = 22)</th>
<th>cHTN (n = 23)</th>
<th>uHTN (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>117 ± 6</td>
<td>130 ± 13*</td>
<td>140 ± 11†</td>
<td>150 ± 20‡†‡</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>66 ± 6</td>
<td>70 ± 7</td>
<td>72 ± 9</td>
<td>72 ± 10</td>
<td>0.038§</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>84 ± 6</td>
<td>91 ± 7*</td>
<td>96 ± 8*</td>
<td>101 ± 14*†</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>51 ± 8</td>
<td>59 ± 13</td>
<td>68 ± 14*</td>
<td>78 ± 17*‡‡‡</td>
<td>0.001§</td>
</tr>
<tr>
<td>PetCO2, mmHg</td>
<td>43 ± 3</td>
<td>37 ± 4*</td>
<td>36 ± 4*</td>
<td>37 ± 4*†</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>59 ± 9</td>
<td>62 ± 10</td>
<td>64 ± 7</td>
<td>65 ± 7</td>
<td>0.084</td>
</tr>
<tr>
<td>SVi, (ml·beat⁻¹)m⁻²</td>
<td>52 ± 13</td>
<td>49 ± 10</td>
<td>51 ± 13</td>
<td>46 ± 10</td>
<td>0.478</td>
</tr>
<tr>
<td>COi, (l·min⁻¹)</td>
<td>3.1 ± 0.9</td>
<td>3.0 ± 0.8</td>
<td>3.2 ± 0.8</td>
<td>2.9 ± 0.5</td>
<td>0.687</td>
</tr>
<tr>
<td>TPRi, mmHg·(l·min⁻¹)⁻¹m⁻²</td>
<td>13 ± 4</td>
<td>8 ± 3*</td>
<td>10 ± 3</td>
<td>12 ± 5</td>
<td>0.003§</td>
</tr>
</tbody>
</table>

Intracranial hemodynamics

| MFV, cm/s              | 70 ± 12     | 56 ± 16*    | 56 ± 12*      | 58 ± 17       | 0.002§  |
| CVRi, mmHg·(cm·s⁻¹)⁻¹ | 1.2 ± 0.3   | 1.7 ± 0.5*  | 1.8 ± 0.3*    | 1.9 ± 0.7*    | <0.001§ |
| CrCP, mmHg             | 30 ± 10     | 36 ± 11     | 30 ± 11       | 31 ± 10       | 0.269   |
| RAP, mmHg·(cm·s⁻¹)⁻¹   | 0.8 ± 0.3   | 1.0 ± 0.3   | 1.2 ± 0.2*    | 1.3 ± 0.6*    | <0.001§ |
| PI, ratio              | 0.9 ± 0.2   | 0.9 ± 0.1   | 0.9 ± 0.2     | 1.0 ± 0.2     | 0.147   |

Extracranial hemodynamics

| MBFICA, (ml·min⁻¹)m⁻² | 162 ± 42    | 142 ± 38    | 158 ± 42      | 139 ± 40      | 0.258   |
| CVRICA, mmHg·(l·min⁻¹)⁻¹m⁻² | 161 ± 55     | 190 ± 58*   | 207 ± 70*     | 248 ± 76*†    | 0.176   |
| CrCPICA, mmHg          | 11 ± 10     | 24 ± 13     | 20 ± 15       | 14 ± 7        | 0.176   |
| RAPICA, mmHg·(l·min⁻¹)⁻¹m⁻² | 2.2 ± 0.3     | 1.9 ± 0.5   | 2.5 ± 0.9     | 2.8 ± 0.8     | 0.081   |

Values are means ± SD. SBP, DBP, MAP, and PP are systolic, diastolic, mean, and pulsatile arterial blood pressure; PetCO2, end-tidal pressure of carbon dioxide; HR, heart rate; SVi, stroke volume index; COi, cardiac output index; TPRi, total peripheral resistance index; MFV, mean flow velocity; CVRi, cerebral vascular resistance index; CrCP, critical closing pressure; RAP, resistance area product; PI, pulsatility index; ICA, internal carotid artery; MBF, mean blood flow; CVR, carotid vascular resistance. Technical limitations limited sample sizes in YNG/OLD/cHTN/uHTN to 23/17/21/10 for MBFICA and CVRICA, and to 6/10/12/5 for CrCPICA and RAPICA. P value determined by one-way ANOVA across groups (§significance across groups). Post hoc analyses identified the indicated group differences: *vs. YNG, P < 0.05; †vs. OLD, P < 0.05; ‡vs. cHTN, P < 0.05.

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A drop compared with YNG (Fig. 2B, Table 3). Despite the reduction in CVRi, MFV was lower in all groups during sitting and standing compared with supine (group-by-posture interaction: P = 0.012; Fig. 2C). Of note, women had higher MFV than men, which was consistent across all groups. Data were averaged across sex for all analyses.

Similar to the beat-by-beat hemodynamic measures reported above, group differences in the response to posture change were observed for within-beat characteristics. Notably, arterial PP was reduced with upright posture in YNG, but elevated in uHTN (group-by-posture interaction; P = 0.022; Fig. 3A). In the cerebral circulation, RAP was stable across all postures for YNG, OLD, and cHTN, but increased with upright postures in uHTN (group-by-posture interaction: P = 0.024; Fig. 3B), while in contrast, CVRi was dropping (compare with Fig. 2B). The change in CrCP paralleled that of CVRi (group-by-posture interaction: P < 0.001; Fig. 3C). Specifically, a larger drop in CrCP was observed for each group of older adults compared with YNG, with OLD and uHTN having significantly different effects.

Carbon dioxide, cardiac output, heart rate, and stroke volume were examined as possible confounding factors which may have influenced the cerebrovascular responses (Table 3). The change from supine lying to a standing posture was associated with a consistent reduction in PetCO2 in all groups. Likewise, no influence of group on the posture-related change in cardiac output index was observed. Of note, the absence of a group effect for cardiac output index was subsequent to opposing influences of heart rate and stroke volume index. Heart rate was elevated during upright posture in YNG, but this increase was attenuated in older adults with and without hypertension. In contrast, stroke volume index decreased during standing in YNG, and this drop was tempered in cHTN and uHTN. The group effects on heart rate and stroke volume index, but not cardiac output index, are notable given their inherent impact on the pulsatile hemodynamic profile.

Fig. 2. Mean arterial blood pressure (BPICA; A), cerebrovascular resistance index (CVRi; B), and mean blood flow velocity (MFV; C) in the middle cerebral artery (MCA) while lying supine (SUP), sitting (SIT), and standing (STA) in young (YNG), older normotensive (OLD, ○), controlled hypertensive (cHTN, †), and uncontrolled hypertensive adults (uHTN, △). Values are means ± SD. ANOVA statistics are reported in RESULTS. Post hoc analysis of paired differences at each posture are indicated here by: * vs. YNG, P < 0.05.
Thus the attenuated heart rate response of older and hypertensive adults contributed to the relative maintenance of stroke volume and greater PP, independent of BPMCA. These associations provide evidence that the cerebrovascular response should also consider both mean and pulsatile components. Indeed, posture-related changes in both PP and BPMCA were associated with changes in CrCP and RAP. The change in PP was directly related to the change in RAP (Fig. 4A) and inversely related to the change in CrCP (Fig. 4C). In contrast, the change in BPMCA, a nonpulsatile characteristic, was directly related to

A pooled analysis (N = 80) was performed to examine the association of posture-related changes in both mean and pulsatile pressure characteristics with cerebral hemodynamics. Posture-induced changes in both BPMCA and PP were associated with the change in stroke volume index (BPMCA: r = −0.43, P < 0.001; PP: r = 0.35, P = 0.002), while only the change in BPMCA was related to a change in cardiac output (BPMCA: r = −0.41, P < 0.001; PP: r = 0.16, P = 0.162). Consequently, individual heart rate, and thereby stroke volume, responses likely influence the PP response to upright posture. Multiple linear regression showed that the change in PP was a function of both the change in heart rate (β = −0.74, P < 0.001) and the change in BPMCA (β = 0.36, P = 0.002). Thus the attenuated heart rate response of older and hypertensive adults contributed to the relative maintenance of stroke volume and greater PP, independent of BPMCA. These associations provide evidence that the cerebrovascular response should also consider both mean and pulsatile components. Indeed, posture-related changes in both PP and BPMCA were associated with changes in CrCP and RAP. The change in PP was directly related to the change in RAP (Fig. 4A) and inversely related to the change in CrCP (Fig. 4C). In contrast, the change in BPMCA, a nonpulsatile characteristic, was directly related to

Fig. 3. Arterial pulse pressure (PP; A), resistance area product (RAP; B), and critical closing pressure (CrCP; C) while lying supine (SUP), sitting (SIT) and standing (STA). CrCP and RAP reflect characteristics of the middle cerebral artery. Values are means ± SD. * vs. YNG, P < 0.05; † vs. OLD, P < 0.05. See Fig. 2 legend for definitions.

Fig. 4. Scatterplots and Pearson correlation coefficients showing the relationship between posture-induced changes in blood pressure and middle cerebral artery characteristics. Changes in pulse pressure (ΔPP; A and C) and mean blood pressure (ΔBPMCA; B and D) are compared with changes in resistance area product (ΔRAP) and critical closing pressure (ΔCrCP). Data were pooled for analysis (N = 80), including young (●), older normotensive (○), controlled hypertensive (▲), and uncontrolled hypertensive adults (△).
both the change in RAP (Fig. 4B) and CrCP (Fig. 4D). After adjusting for age, cardiac output index, and \( \text{PetCO}_2 \), multiple linear regression revealed that changes in PP and \( \text{BP}_{\text{MCA}} \) were independently associated with changes in \( \text{R} \) (PP: \( \beta = 0.008 \pm 0.002, P < 0.001; \text{BP}_{\text{MCA}}: \beta = 0.080 \pm 0.002, P = 0.003 \)) and CrCP (PP: \( \beta = -0.54 \pm 0.11, P < 0.001; \text{BP}_{\text{MCA}}: \beta = 0.59 \pm 0.12, P < 0.001 \)), demonstrating important links between both pulsatile and nonpulsatile central hemodynamics and the cerebral circulation. Replacing cardiac output index with stroke volume index in this model did not alter the results (not shown).

Static CA characteristics were assessed by within-person linear regression examining the relative changes in MFV, \( \text{CVR}_{\text{I}} \), CrCP, and RAP as a function of the relative change in \( \text{BP}_{\text{MCA}} \) between supine, sitting, and standing (Table 4). In the \( \text{BP}_{\text{MCA}} \rightarrow \text{MFV} \) relationship, YNG had a higher gain than each group of older adults, and greater explained variance than the uHTN group, suggesting that sCA was enhanced in the older, hypertensive adults compared with YNG. Group differences in the \( \text{BP}_{\text{MCA}} \rightarrow \text{CVR}_{\text{I}} \) model were also noted between YNG and uHTN; however, no group differences were observed in the relationship between \( \text{BP}_{\text{MCA}} \) and either RAP or CrCP. To assess whether the group differences in posture-related changes in \( \text{PetCO}_2 \) influenced sCA, individual MFV values were adjusted for changes in \( \text{PetCO}_2 \) assuming a gain of 3%/mmHg in \( \text{PetCO}_2 \) influenced sCA, individual MFV values were adjusted for changes in \( \text{PetCO}_2 \), assuming a gain of 3%/mmHg CO\(_2\) (22). In the adjusted model (\( \text{BP}_{\text{MCA}} \rightarrow \text{MFV}_{\text{adjCO}_2} \)), sCA parameter estimates were reduced compared with the unadjusted model (\( P < 0.001 \); i.e., enhanced autoregulation) and the group differences that were present in younger adults were abolished. \( \text{PetCO}_2 \)-adjusted analyses were also run for \( \text{CVR}_{\text{I}} \), CrCP, and RAP based on published CO\(_2\) reactivity values (20); however, the results were unchanged (not shown).

Static CA measures within the extracranial ICA were computed from the slope of hemodynamic measures between supine lying and sitting (Table 5). No group differences were observed, despite a trend for enhanced gain of CrCP in YNG. In a supplementary analysis, the change in CrCP relative to \( \text{BP}_{\text{MCA}} \) was greater in YNG than in the combined group of all older adults (YNG: 19 ± 25 vs. all older adults: 2 ± 16; \( P = 0.045 \)).

### DISCUSSION

The present study revealed several novel findings that provide insight into cerebral hemodynamics in aging and hypertension. First, supine resting RAP, which is a measure of cerebrovascular resistance derived from intrabreath pulse wave characteristics, was elevated in older hypertensive adults compared with young healthy participants. In contrast, an indicator of cerebrovascular wall tension (i.e., CrCP) was not different across groups. Second, both RAP and CrCP were involved in the sCA response to the hypotensive stimulus of upright posture, with a decrease in CrCP playing a dominant role. Contrary to our hypothesis, the autoregulatory responses characterized by relative changes in CrCP and RAP with reduced blood pressure were similar in young adults and older adults with and without hypertension. The absolute changes in CrCP and RAP, however, were different between groups and significantly related to absolute changes in both the pulsatile and mean components of arterial pressure. Thus underlying hypertension may influence the cerebrovascular response through altered central regulation.

Despite noted increases in central arterial stiffness and reduced distensibility, hypertensive adults demonstrate a maintained, or even augmented, ability to attenuate fluctuations in MFV due to BP within the cerebral circulation (12, 45, 53). In the present study, we evaluated the regulation of RAP and CrCP as an alternative approach to target the effects of stiffening arteries and increased pulsatility on sCA. RAP and CrCP comprise separate components of cerebrovascular resistance.

### Table 4. Linear regression of \( \text{BP}_{\text{MCA}} \) on middle cerebral artery hemodynamics across supine, sitting, and standing postures

<table>
<thead>
<tr>
<th>Dependent Variable (% Δ)</th>
<th>Independent Variable (% Δ)</th>
<th>Parameters</th>
<th>YNG (n = 23)</th>
<th>OLD (n = 22)</th>
<th>cHTN (n = 23)</th>
<th>uHTN (n = 12)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CVR}_{\text{MCA}} )</td>
<td>( \text{BP}_{\text{MCA}} )</td>
<td>( \beta ) coefficient</td>
<td>0.45 ± 0.38</td>
<td>0.72 ± 0.27*</td>
<td>0.69 ± 0.29*</td>
<td>0.73 ± 0.19</td>
<td>0.009§</td>
</tr>
<tr>
<td>( \text{CrCP}_{\text{MCA}} )</td>
<td>( \text{BP}_{\text{MCA}} )</td>
<td>( \beta ) coefficient</td>
<td>0.30 ± 0.22</td>
<td>2.3 ± 0.7</td>
<td>3.0 ± 1.5</td>
<td>3.6 ± 2.2</td>
<td>0.252</td>
</tr>
<tr>
<td>( \text{RAP}_{\text{MCA}} )</td>
<td>( \text{BP}_{\text{MCA}} )</td>
<td>( \beta ) coefficient</td>
<td>−0.47 ± 0.73</td>
<td>−0.18 ± 0.63</td>
<td>−0.21 ± 0.67</td>
<td>−0.20 ± 0.93</td>
<td>0.491</td>
</tr>
<tr>
<td>( \text{MFV}_{\text{MCA}} )</td>
<td>( \text{BP}_{\text{MCA}} )</td>
<td>( \beta ) coefficient</td>
<td>0.59 ± 0.36</td>
<td>0.62 ± 0.35</td>
<td>0.61 ± 0.34</td>
<td>0.41 ± 0.34</td>
<td>0.334</td>
</tr>
<tr>
<td>( \text{MFV}_{\text{CO2adj}} )</td>
<td>( \text{BP}_{\text{MCA}} )</td>
<td>( \beta ) coefficient</td>
<td>0.81 ± 0.20</td>
<td>0.74 ± 0.29</td>
<td>0.67 ± 0.25</td>
<td>0.52 ± 0.37*</td>
<td>0.022§</td>
</tr>
</tbody>
</table>

Values are group means ± SD. Technical limitations limited sample sizes in YNG/OLD/cHTN/uHTN to 23/17/21/10 for \( \text{MBF}_{\text{ICA}} \) and \( \text{CrCP}_{\text{ICA}} \), and to 6/10/25 for \( \text{CrCP}_{\text{ICA}} \) and \( \text{RAP}_{\text{ICA}} \). \( P \) value determined by one-way ANOVA across groups.
that are derived from the instantaneous relationship between blood pressure and CBF (35). Increased baseline pulsatility in older hypertensive adults (range of mean ages: 73–76 yr) was associated with an elevated RAP, but not CrCP. This observation contrasts with a recent report which found older (mean age: 57 yr) normotensive adults to have a similar RAP, but a reduced CrCP, compared with a younger cohort (32). The study by Ogoh et al. reported no group differences in resting MFV between young and older adults, which might be a consequence of the relatively younger ages of their participants, as MFV is attenuated with aging and hypertension (2, 25), and likely contributed to the contrasting observations regarding RAP and CrCP in the present study. Our observation of a relationship between RAP and CVRi at rest agrees with a previous report within a group of young adults (20). Specifically, RAP describes the relationship between pulsatile blood pressure and pulsatile cerebral blood flow velocity. Although the variables in the current study are derived from noninvasive measures, increased RAP in hypertension is consistent with rodent models, which link exposure to elevated pulse pressure with hypertrophy and increased distensibility in cerebral arterioles (5). Independent of RAP, CrCP has been described as a marker of the effective downstream pressure, which is determined by cerebrovascular wall tension in the absence of intracranial hypertension (52). Our observation that hypertensive adults have raised RAP, but similar CrCP, suggests that chronic adaptations to elevated blood pressure involve alterations in vascular distensibility rather than increased vascular smooth muscle tone (i.e., structural vs. functional).

Following a change to upright postures, CBF was reduced in all groups. The drops in MBFICA and MFVMCA across the entire sample was ~8% (ranging from 7% in OLD to 10% in uHTN). This decrease is consistent with previously reported measurements of MBF and MFV during upright posture in healthy adults, ranging from 4 to 14% (3, 33, 41, 42). The consistency of these findings is in agreement with the notion that intact sCA does not connotes constant CBF, but rather an attenuation of the impact of changes in blood pressure on cerebral perfusion. In older adults with and without hypertension, the gain of the resistance model (i.e., BPmCA → CVRi) was ~0.7, which agrees with prior work in similar populations in which hypotensive stimuli were induced by lower body negative pressure (12) and sodium nitroprusside infusion (26). The drop in BPmCA induced by orthostatic stress in the present study was in excess of 20 mmHg, providing important evidence that the window of autoregulatory control encompasses blood pressure deviations common to stresses of daily living, such as posture change, in older adults with controlled and uncontrolled hypertension. Further, the BFmCA → MFV and BPmCA → CVRi models suggested that sCA was more tightly regulated in older and hypertensive adults than in younger adults. Enhanced autoregulation in older hypertensive adults using MFV and CVRi variables has been reported previously (25, 45, 53). Importantly, interpretation of sCA during postural transitions is complicated by coincident, and variable, changes in arterial PCO2 (13). After adjusting MFV by the posture-related change in PETCO2, using a common value of 3%/mmHg, sCA differences between groups were eliminated.

In a transfer function approach targeting the cardiac frequency to isolate the influence of arterial stiffening, the gain of the relationship between oscillations in BPmCA and MFV was found to be attenuated in hypertensive patients compared with healthy older adults (45). In the current study, the hypothesis that models of sCA involving CrCP and RAP would be more sensitive to differences between young, older, or hypertensive adults was not supported. Static CA models, characterizing the relative change in CrCP and RAP for the relative change in BPmCA, were similar across all groups. Interestingly, while CVRi was related to RAP at rest, the change in CVRi induced by upright posture was most closely mirrored in CrCP, corroborating recent results during head-up tilt in healthy young men (55). The greater role of CrCP, compared with RAP, within posture-related changes may be reflective of differences in the regulatory mechanisms underlying each variable. CrCP is an umbrella characteristic describing the collective action of multiple effectors of downstream pressure (52). This effective pressure is influenced by passive changes in venous and/or surrounding intracranial pressure, and by active changes in vascular wall tension. In addition, postulations that CrCP is sensitive to metabolic influences (36) and PCO2 (7, 55) provide evidence that autoregulatory responses driven by CrCP likely rely on multiple factors on top of fluctuations in arterial pressure. In opposition of the current findings, prior research has reported elevations in CrCP during seated and head-up tilt postures (4, 8); however, it appears these studies used central pressure in the estimation of CrCP, rather than BPmCA. Increased CrCP in response to lower arterial pressure would exaggerate the reduction in cerebral perfusion pressure and lower CBF given a constant resistance, a paradoxical autoregulatory response. Importantly, the estimation of CrCP relies on local arterial pressures. In upright posture, central arterial pressure is mostly stable or slightly increased, while the orthostatic gradient created between the heart and the brain results in lower BPmCA. Thus relying on central pressure may mislead the interpretation of local regulation. Although the current analysis relies on the assumption of a constant orthostatic effect on arterial pressure throughout the cardiac cycle, the reduction in CrCP, alongside stable or increased RAP, with upright posture is consistent with theoretical autoregulatory mechanisms to maintain perfusion while sitting and standing. Further, insight into the role of the siphon effect on cerebral perfusion pressure can be found in the debate in the American Journal of Physiology (16, 19). The siphon theory suggests that, in a closed loop, parallel fluctuations in the arterial and venous vasculature maintains perfusion pressure and precludes the necessity for hydrostatic adjustment when the head is elevated above the heart. Here, the orthostatic decrease in BPmCA was slightly greater than the decrease in estimated CrCP in all groups except the older hypertensive adults (Table 3). As CrCP reflects effective downstream pressure, the discrepancy between posture-related changes in BPmCA and CrCP provides support to the theory that the vasculature does not act like a rigid siphon and hydrostatic changes should be considered.

Whereas the relative changes in CrCP and RAP reflected in the models of sCA were similar across groups, differences in the absolute change in CrCP between old and young adults, and in RAP between hypertensive and young adults, suggest altered regulation related to variances in the absolute change in BPmCA and PP. A pooled regression analysis of the posture-induced changes in pulsatile and mean hemodynamic variables revealed important independent relationships that provide in-
sight into CBF regulation in aging and hypertension. Posture-related changes in RAP and CrCP were independently associated with both pulsatile and mean components of the arterial pressure wave. We observed a group-by-posture interaction in which upright PP was reduced in young adults, but increased in uncontrolled hypertension. Differences in the PP response were directly related to group differences in the heart rate response to upright posture. Age-related attenuation of the increases in heart rate have been reported previously (13), and result in smaller increases in diastolic pressure, and thus differential PP responses, while standing. Arterial stiffness, which is elevated in aging and hypertension, is an important determinant of PP, with the impact of central arterial stiffening on cerebrovascular health now being realized (30, 38, 51). Hence, we propose that further evaluation of pulsatile characteristics within the cerebral circulation with respect to their role in autoregulatory mechanisms is warranted.

*Autoregulation in the internal carotid artery.* The ICA is a major conduit artery, supplying ~75% of CBF bilaterally (43), and has recently received attention as a relevant extracranial site for assessment of both dynamic (40) and static CA (26). Examination of the ICA offers the benefits of ameliorated ultrasound access to the vessel with certain knowledge of Doppler angle and vessel diameter, allowing for more exact quantification of cerebral hemodynamics. In supine lying, no differences in MBFICA were noted between groups. Increased arterial pressures in older, hypertensive adults were matched by increasing CVRICA. Similar to observations in the MCA, increased baseline resistance was associated with elevated RAP rather than CrCP, although group differences in RAP were only a trend. We found no group differences for sCA estimates using the ICA measures. A comparison of extracranial and intracranial hemodynamics has suggested that variables derived from the MCA may underestimate true autoregulatory capacity (26). The current sCA estimates from MBFICA tended to suggest better regulation than those from MFVICA, with an exception in older hypertensive adults. In contrast, sCA estimates from CVR and CVRi were similar between the extracranial and intracranial vasculature. Although the ICA has previously been shown to be a reliable vessel for the assessment of sCA, we believe this to be the first report of CrCP and RAP derived from the ICA waveform. With regard to these measures, autoregulatory responses primarily involved changes in CrCP rather than RAP. When the three groups of older adults were combined for analysis, the relative change in CrCP was greater in younger adults. Mechanisms underlying the possibility of a more sensitive CrCP response in younger adults are unknown. Since this variable is believed to be influenced by metabolic demand and arterial blood gases (36), it reflects downstream adaptation within the cerebral arterioles rather than ICA characteristics. Contributions to the autoregulatory response from within the ICA vessel wall need to be clarified (26). Caution is advised given the small sample size and that ICA estimates of sCA were based on the slope of only supine and sitting data points. Replication is necessary prior to definitive conclusions.

**Methodological considerations.** Estimation of CrCP needs to be interpreted cautiously as it does not account for the nonlinear pressure-flow relationship, relies on extrapolation outside the limits of normal physiological variability, and uses peripheral pressure as a surrogate for pulse waves in the brain. We used a two-point (mean-diastolic) estimation method to determine CrCP, which has performed well in static regulatory analyses and was recently shown to have less variation and fewer instances of negative values, compared with other estimation strategies (37). In addition to attenuating noise, this estimation method reduces any amplification bias involved in using peripheral blood pressure as a noninvasive surrogate for the pressure waves in the brain. Unlike the systolic peak of the arterial pulse, mean and diastolic pressures are relatively stable between the aorta and resistance arterioles (31). In addition, the use of peripheral PP to reflect changes in cerebral PP is supported by the observation of a strong correlation between posture-related changes in peripheral and central PP (50).

The direct influence of PCO2 on cerebral vasculature is well-described (22, 27). Thus PCO2-related effects might supersede autoregulatory changes in the MCA and ICA to give the illusion of a pressure-passive system. After adjusting MFV for the posture-related change in PETCO2, assuming a cerebrovascular reactivity of 3%/mmHg CO2, no group differences in sCA were noted. We used a constant value for CO2 reactivity across all participants; however, there is evidence of age-related reductions in this variable (23, 45) and individual differences probably require an alternative strategy to overcome the CO2 effects on assessment of sCA (26). The gain for the BPmca → MFVadjCO2 model in young adults was only slightly lower than that found in unadjusted models of older and hypertensive adults. Hence, even if the CO2 reactivity was individually accounted for or controlled in older adults, they would have retained sCA similar to the young cohort, maintaining our conclusion that sCA is not affected by aging and hypertension.

The autoregulatory responses in the present study were related to an acute reduction in arterial pressure, protecting the brain from hypoperfusion. Evidence from the animal literature suggests that hypertension in the context of aging may disrupt mechanisms protecting against elevations in blood pressure (49). Pharmacological manipulation of pressure has been used to assess hypertensive stimuli in humans despite the potential for direct action on the cerebrovasculature to confound results. A recent investigation of older adults with well-controlled hypertension found autoregulatory responses to be preserved against increasing pressures (26). Future work within newly diagnosed hypertensive patients, or medically homogeneous populations, may be necessary to untangle these distinctions between animal and clinical research.

**Conclusions.** In agreement with the literature, sCA efficiency was similar in young, older, and hypertensive adults. CrCP and RAP were shown to reflect independent resistive characteristics of the cerebral circulation which had different responses to posture change in aging and hypertension. RAP was the primary determinant of cerebrovascular resistance at rest, whereas, upon moving to upright posture, RAP was relatively stable and CrCP decreased to help compensate for reduced arterial pressure in the brain. Relative changes in RAP and CrCP in response to hypotension were similar in young and older hypertensive adults; however, significant independent associations with both mean and pulsatile pressure changes suggest the cerebrovascular response is dependent on central cardiovascular dynamics. Heart rate and stroke volume responses contributed to differential changes in the pulsatile and mean components of arterial pressure between groups.
Both PP and BP MCA were independently associated with the CrCP and RAP response, suggesting within-beat characteristics are an important aspect of cerebral autoregulation. As the population ages and the prevalence of hypertension and arterial stiffening increases, the role of PP in cerebrovascular regulation will be an important area of study.

**Perspectives and significance.** Cerebral autoregulation is commonly assessed through the examination of beat-by-beat changes in mean cerebrovascular indexes (e.g., MFV or CVR). However, these variables may not account for changes in pulsatile hemodynamics associated with aging and hypertension. As the impact of arterial stiffness on the brain is realized (24, 51), the importance of understanding pulsatile regulatory mechanisms of cerebral hemodynamics will become essential. CrCP and RAP are sensitive to both pulsatile and mean characteristics of the pressure wave. In this study, we found that while autoregulatory responses to upright posture are preserved in aging and hypertension, the responses of CrCP and RAP, in particular, are sensitive to both the mean and pulsatile characteristics of the hypertensive stimulus. We suggest that proposed differences in the physiological mechanisms underlying CrCP and RAP (36) may provide insight into how mechanisms of cerebral autoregulation are maintained in aging and hypertension.

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