Dynamic Cerebral Autoregulation Is Unaffected by Aging

Brian J. Carey, MRCPI; Penelope J. Eames, MRCP; Melanie J. Blake, MRCP; Ronney B. Panerai, PhD; John F. Potter, DM

Background and Purpose—Normal aging is associated with marked changes in the cardiovascular and cerebrovascular systems. Although cerebral autoregulation (CA) is impaired in certain disease states, the effect of age per se on dynamic CA in humans is unknown and the focus of this study.

Methods—Twenty-seven young subjects (≤40 years) and 27 older subjects (≥55 years), matched for sex and systolic blood pressure (BP), underwent measurement of cerebral blood flow velocity by transcranial Doppler ultrasound and noninvasive beat-to-beat arterial BP measurement during induced and spontaneous dynamic BP stimuli. A standard dynamic autoregulatory index (ARI) was derived for each spontaneous and induced dynamic BP stimulus to include the step response, as well as cardiac baroreceptor sensitivity (BRS), for the 2 groups.

Results—The mean age of the young group was 29±5 years, and that of the older group was 68±5 years. Cardiac BRS was reduced in the older group (8.6±4.5 versus 16.9±8.8 ms/mm Hg; P<0.0001). However, no age-related differences were demonstrated in step response plots or in ARI values for any pressor or depressor dynamic BP stimulus (P=0.62), with mean ARI values for all stimuli combined being 4.9±1.8 for the young group and 5.0±2.3 for the older group.

Conclusions—Although increasing age is associated with a decrease in cardiac BRS, dynamic CA, as assessed by step response analysis as well as cerebral blood flow responses to transient and induced BP stimuli, is unaffected by aging.

Key Words: aging • autoregulation • cerebral circulation • ultrasonography, Doppler, transcranial

The cardiovascular system demonstrates many age-related changes, as evidenced by the well-recognized increase in systolic blood pressure (BP) and decreases in systemic artery compliance and cardiac baroreceptor sensitivity (BRS) with age. Aging may also be associated with changes in cerebrovascular hemodynamics, with both cerebral blood flow (CBF) volume and CBF velocity (CBFV) being reported as declining with advancing years.

Cerebral autoregulation (CA) refers to the inherent ability of the cerebral blood vessels to keep CBF constant for a wide range of systemic BP levels. CA occurs with a substantial degree of temporal heterogeneity in that physiological adjustments of CBF occur both quickly and slowly. Dynamic CA refers to the ability to maintain CBF in the face of BP changes occurring over a matter of seconds and reflects the latency of the cerebral vasoregulatory system. Static CA refers to CBF adjustments in response to more prolonged BP changes and is a measure of the overall efficiency of the system. Dynamic CA is impaired in a variety of disease states, including post–head injury disorders, subarachnoid hemorrhage, acute ischemic stroke, and carotid artery disease. It has been suggested that static and dynamic CA may have different control mechanisms and that dynamic CA may be more susceptible to damage in pathological states, as seen after acute ischemic stroke. Since disease states likely to affect CA are more common in the elderly, it is important to know whether aging per se affects CA.

The advent of transcranial Doppler ultrasonography has facilitated the noninvasive measurement of CBF hemodynamics by allowing CBFV changes in response to static and dynamic BP changes, and hence CA, to be calculated. Methods of CA estimation using spontaneous BP changes may have advantages over methods using induced BP changes. Such methods include the new step response methodology and do not induce sympathetic stimulation or hypocapnia, both of which may affect the integrity of CA. The use of spontaneous BP changes is also less noxious to subjects and poses less risk to patients potentially at risk from the induction of acute hypotensive or hypertensive changes, eg, patients after an episode of acute stroke or subarachnoid hemorrhage and those with carotid stenosis.

Although the effect of aging on CA has been studied in animals, we are unaware of any studies on the effects of physiological aging on dynamic CA in humans. This study was designed to assess the effect of human aging on dynamic CA in response to spontaneous and induced pressor and depressor stimuli.
Subjects and Methods

Subjects

Subjects were recruited from a volunteer register in the department and from departmental staff. All were healthy, on no medications, and free from cardiovascular, cerebrovascular, or autonomic disease as based on history and clinical examination. Significant silent carotid stenosis was excluded on the basis of bilateral neck auscultation and the absence of typical transcranial Doppler ultrasound findings.\(^2\) Subjects had 3 semiautomated BP readings taken 1 minute apart (Omron 711) after lying supine for 10 minutes; a cuff of an appropriate size was used. Mean baseline BP levels were taken as the average of the last 2 readings, provided that BP levels differed by <10 mm Hg.

The subjects were assigned by age to a young group (≤40 years) or an older group (≥55 years) and were pair-matched for sex, systolic BP (within 10 mm Hg), and body mass index (BMI) to within 2.0 kg/m².

Protocol and Measurements

Subjects avoided caffeine-containing products, nicotine, and alcohol for at least 12 hours before the study and wore loose, comfortable clothing, attending the sessions a minimum of 2 hours postprandially. All recordings were made in a dedicated research room kept at constant ambient temperature (21°C to 24°C), and external stimuli were minimized. Subjects lay supine on a couch with their head supported by 2 pillows. A surface 3-lead ECG was fitted, and arterial BP was measured noninvasively from the middle finger of the left hand with a servo-controlled plethysmograph (Finapres 2300, Ohmeda).\(^2\) An appropriate cuff size was chosen, and the hand was supported at the level of the right arm with a custom-made armrest. CO₂ levels were measured with a previously validated transcutaneous gas monitor (TINA, Radiometer).\(^2\) Middle cerebral artery blood flow velocity was measured with a transcranial Doppler ultrasound (SciMed QVL 842X). The Doppler frequency shift and the other parameters were recorded onto a digital tape (DAT, Sony PC-108M). Subjects lay supine for a minimum of 20 minutes, and recording was started when the Finapres and TINA values had stabilized (<10% variation over 5 minutes). Subjects were asked to remain supine and to refrain from talking during the recordings, and 2 baseline recordings of at least 5 minutes each were made. Subsequently, the dynamic pressor stimuli and depressor stimuli were applied in random order, with a baseline recording of 60 seconds between and after each test.

Dynamic Pressor BP Stimuli

Dynamic pressor BP stimuli included the following: (1) In lower body negative pressure release, the lower limbs of the subjects were sealed at the level of the iliac crests in a custom-designed box, and lower body negative pressure was applied (range, 15 to 58 mm Hg) to cause a fall of at least 10 mm Hg in systolic BP. After 5 minutes and when a steady state BP level had been achieved, atmospheric pressure was suddenly restored to the box by disconnecting the pressure box. (2) In the Valsalva maneuver, phase IV, subjects were asked to perform a Valsalva maneuver lasting 15 seconds while supine by blowing into a tube connected to a transducer that registered intrathoracic pressures to aid compliance. After completion, subjects lay quietly for 1 minute while recording continued. This procedure was repeated twice so that each subject performed 3 Valsalva maneuvers 1 minute apart. (3) Three spontaneous rises in BP (>5 mm Hg) were selected at random from each of the two 5-minute rest recordings. A total of 6 spontaneous pressor changes were therefore selected for each subject, and the mean value was taken.

Dynamic Depressor BP Stimuli

Dynamic depressor BP stimuli included the following: (1) For the thigh cuff release, bilateral thigh cuffs were applied and inflated to suprasystolic pressures for 90 seconds with thigh cuff pressure monitored with the use of a mercury sphygmomanometer. The cuffs were then rapidly deflated, and recording was continued for an additional minute. This test was repeated in some patients to increase the likelihood of obtaining a BP fall of >10 mm Hg. (2) Three spontaneous falls in BP (5 mm Hg) were selected at random from each of the 2 rest recordings. A total of 6 spontaneous depressor changes were therefore selected for each subject.

Data Analysis

Systolic BP, diastolic BP, mean BP, and middle cerebral artery blood flow velocity were calculated for each cardiac cycle by methodology previously used in our department.\(^1\)

Determination of Dynamic CA and Cardiac BRS

CA was graded by generating a dynamic autoregulatory index (ARI), ranging from 0 to 9, for each subject for each dynamic pressor and depressor stimulus according to the methods proposed by Tiecks et al\(^2\) with modifications previously used in our department.\(^1\) Each dynamic BP stimulus yielded an ARI for right and left middle cerebral arteries for each individual. The mean of the 2 ARI values thus obtained was taken to be the ARI for that individual for that dynamic BP stimulus. For thigh cuff release, Valsalva maneuver, spontaneous rises in BP, and spontaneous falls in BP, the mean of the ARI values derived for each adequate stimulus was taken to be the ARI for that dynamic BP stimulus.

Step response analysis was performed by the methods previously used by Panerai et al.\(^15\)\(^16\) In short, a fast Fourier transform method was used to define the arterial BP and CBFV spectra of the rest recordings. The frequency and phase responses of the transfer function were estimated with the average of 4 segments of data, each with 512 samples. The impulse response function was obtained from the inverse of the transfer function, and the step response was derived by integration of the impulse response function.\(^15\)\(^16\)

Cardiac BRS was derived with the baseline recordings and fast Fourier transform spectral analysis methods, as described by Robinson et al.\(^2\)

Statistical Analysis

With all 5 BP stimuli, it was assumed that missing data were lost in random fashion, i.e., that the probability of a missing ARI was not a function of the subject’s ARI. A normal distribution was assumed, and a good approximation of this was demonstrated by a plot of residuals. Using mixed modeling age by stimulus interaction, we calculated age effect, estimated difference (young versus old), and stimulus effect.

Since the 2 groups were pair-matched, Student’s paired t tests were used to compare ARI values derived for each BP stimulus between the 2 groups to determine whether any individual test demonstrated a difference.

The differences between ARI values derived from the 5 different stimuli were estimated with the use of a mixed model for repeated-measures data. Different covariance patterns were investigated with Akaike’s information criterion. Multiple pairwise testing was adjusted for by Tukey’s method.

Mean step responses and their standard errors were calculated for both young and older groups.\(^15\)\(^16\) The step responses at 5 seconds were compared between the 2 groups with Student’s paired t test.

Data were analyzed with the use of SAS version 6.12 and Minitab 12 software packages. Results are presented as mean±SD (range); statistical significance was set at the P<0.05 level. The study was approved by the local ethics committee, and all subjects gave informed consent.

Results

Demographic and baseline data for the young (n=27) and older groups (n=27) are contained in Table 1. Despite matching individual pairs for systolic BP and BMI, both parameters were significantly higher in the older group (P<0.001 and P=0.003, respectively), but mean arterial and
TABLE 1. Demographic Information and Baseline Characteristics of the Young and Older Groups

<table>
<thead>
<tr>
<th></th>
<th>Young Group</th>
<th>Older Group</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>15:12</td>
<td>15:12</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age, y</td>
<td>29 ± 5 (20–39)</td>
<td>68 ± 5 (55–79)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124 ± 11 (107–145)</td>
<td>130 ± 9 (107–147)</td>
<td>6 (5, 7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76 ± 8 (61–90)</td>
<td>76 ± 7 (58–89)</td>
<td>0 (–3, 3)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>92 ± 8 (76–104)</td>
<td>94 ± 8 (74–105)</td>
<td>2 (–4, 1)</td>
<td>0.10</td>
</tr>
<tr>
<td>Baseline heart rate, bpm</td>
<td>63.2 ± 10.2 (45.2–76.4)</td>
<td>59.6 ± 7.6 (42.7–81.1)</td>
<td>3.6 (–1.4, 8.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline CBFV, cm/s⁻¹</td>
<td>54.3 ± 14.8 (37.4–81.5)</td>
<td>42.5 ± 9.9 (20.6–55.2)</td>
<td>11.8 (3.5, 18.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.3 ± 1.6 (19.8–28.3)</td>
<td>25.6 ± 3.8 (19.5–34.6)</td>
<td>2.3 (0.9, 4.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline CO₂, mm Hg</td>
<td>41.4 ± 5.8 (35.4–48.9)</td>
<td>40.9 ± 4.4 (35.0–45.9)</td>
<td>0.5 (–3.4, 4.4)</td>
<td>0.80</td>
</tr>
<tr>
<td>Cardiac BRS, ms/mm Hg</td>
<td>6.9 ± 8.8 (7.0–44.0)</td>
<td>8.6 ± 4.5 (1.9–22.1)</td>
<td>8.4 (4.4, 12.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean ± SD, with ranges in parentheses for the group as a whole. Differences between groups are listed as mean differences.

Discussion

Certain important aspects of cerebral hemodynamics have been shown to change with age, with CBF volume and CBFV decreasing and cerebral arterial vessels widening in diameter. The reasons behind the decline in CBF and CBFV with age are unknown but may be due to the increase in arterial vessel diameter or decreasing metabolic demand. Dynamic, as opposed to static, CA has been shown to be the more vulnerable component to impairment in certain disease states, and, as pathological changes become more prevalent with age, it is important to know whether age per se causes deterioration in dynamic CA. That such changes take place is evident in the present study as dynamic CBFV and BRS were significantly lower in the older group than in the young group (difference = 1.27; 95% CI, 0.03 to 2.50; P = 0.042). The differences were found when all dynamic stimuli were combined, although no other significant differences were found. When all dynamic stimuli were combined, mean ARI values were 4.9 ± 1.8 for the young group and 5.0 ± 2.3 for the older group (difference = −0.1; 95% CI, −0.6 to 0.7; P = 0.88).

Mean step response plots for the 2 groups, including standard errors, are displayed in the Figure. No significant differences were shown between the step responses of the groups at 5 seconds (0.17 versus 0.14; difference = 0.03; P = 0.37).

TABLE 2. Differences Between Groups in Mean Arterial Pressure Changes and ARI Values for Each Dynamic BP Stimulus

<table>
<thead>
<tr>
<th>BP Stimulus</th>
<th>n</th>
<th>Younger BP Change, mm Hg</th>
<th>Older BP Change, mm Hg</th>
<th>Difference (95% CI)</th>
<th>P</th>
<th>Younger Mean ARI</th>
<th>Older Mean ARI</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous rises in BP</td>
<td>27</td>
<td>9 ± 3*</td>
<td>8 ± 2*</td>
<td>1 (–0.5, 2.5)</td>
<td>0.16</td>
<td>4.4 ± 1.5</td>
<td>4.0 ± 2.3</td>
<td>0.4 (–0.9, 1.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Spontaneous falls in BP</td>
<td>27</td>
<td>–9 ± 3*</td>
<td>–8 ± 4*</td>
<td>0 (–1.3, 2.1)</td>
<td>0.67</td>
<td>5.0 ± 1.9</td>
<td>4.7 ± 2.5</td>
<td>0.3 (–1.0, 1.4)</td>
<td>0.63</td>
</tr>
<tr>
<td>Thigh cuff release</td>
<td>19</td>
<td>16 ± 3†</td>
<td>16 ± 6†</td>
<td>0 (–1.3, 1.4)</td>
<td>0.91</td>
<td>5.4 ± 1.1</td>
<td>6.2 ± 2.4</td>
<td>–0.8 (–1.9, 1.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>LBNP release</td>
<td>11</td>
<td>7 ± 7</td>
<td>14 ± 3</td>
<td>3 (–0.9, 7.6)</td>
<td>0.11</td>
<td>4.1 ± 2.0</td>
<td>4.5 ± 2.6</td>
<td>0.4 (–2.3, 1.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Valsalva maneuver</td>
<td>16</td>
<td>28 ± 14‡</td>
<td>20 ± 6‡</td>
<td>8 (1.7, 13.9)</td>
<td>0.02</td>
<td>5.2 ± 2.6</td>
<td>5.2 ± 2.7</td>
<td>0 (–1.9, 2.0)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

LBNP indicates lower body negative pressure; n = number of matched pairs where data were available. Comparisons were made with Student’s paired t test. See Subjects and Methods for complete description of BP stimuli.

*Represents the mean of all values >5 mm Hg derived from the rest recordings.
†Represents the mean of all values >10 mm Hg derived from the thigh cuff recordings.
‡Represents the mean of all values >10 mm Hg derived from the 3 Valsalva recordings.
place in old age may have clinical importance and may help to explain, for example, the poor correlation between postural symptoms and systemic BP changes in response to standing in the elderly and in certain syncope syndromes. Despite the use of 2 different methodologies (Tiecks’ model and impulse response analysis), both pressor and depressor BP stimuli and induced and spontaneous BP changes, we have failed to show any difference in dynamic CA with age. Using similar methods, our group detected impaired dynamic CA in severe carotid artery stenosis,26 after acute ischemic stroke,11 in neonates,15 and during hypercapnia.16 We found that the older group had lower cardiac BRS and mean CBFV values than their younger counterparts, suggesting that the “normal” aging process in other cardiovascular and cerebrovascular parameters was present in our subjects.3,5,27

The Valsalva maneuver and thigh cuff release have previously been used as dynamic pressor and depressor stimuli, respectively, to assess CA.11–13,28 Thigh cuff release is probably the most widely applied dynamic BP stimulus, but it is unknown whether ARI values are dependent on the type of dynamic stimulus used, the direction of BP change (pressor or depressor), or the magnitude of BP change induced. To our knowledge, lower body negative pressure release and the use of spontaneous transient changes in BP at rest have not been used with Tiecks’ model to assess CA until now. Although we have demonstrated significant differences between ARI values derived by different dynamic BP stimuli (thigh cuff release and lower body negative pressure release), no age-related differences were found.

Although Tiecks’ ARI is an arbitrary model, it does provide important clinical information, eg, acute ischemic stroke patients have ARI values on the order of 2.0 lower than age- and BP-matched controls.11 Similar methods have shown ARI values to be a mean of 2.6 lower than control values in patients with carotid artery disease.13 Our ARI values are consistent with those published previously12,13,29 and demonstrate an ARI difference of only −0.18 between young and older groups, with a 95% CI of −0.93 to 0.56. We believe that our CIs are of a magnitude that suggest that there is no clinically significant age-related deterioration in dynamic CA.

The magnitudes of dynamic BP changes were significantly greater in the young for the Valsalva maneuver, but no differences were shown for any of the other dynamic BP stimuli. We did not find any significant correlation, however, between the magnitude of dynamic BP changes and ARI values in our subjects. It is also worth noting that the Valsalva maneuver caused the largest dynamic BP changes in both groups but yielded neither the highest nor lowest ARI values.

Step response analysis has been used to demonstrate impairment of dynamic CA in premature neonates, hypercapnia, and severe carotid artery stenosis.15,16,26 Step response plots characteristically demonstrate a return of CBFV to baseline values when dynamic CA is intact and higher values when impaired. The step response plots were remarkably similar for the 2 groups and indicate an active autoregulation in both groups.

Kastrup et al10 found that cerebrovascular CO2 reactivity was not affected by aging in men but decreased with age in women. A subanalysis of our female subjects demonstrated no differences in dynamic CA with age. It must be remembered, however, that CO2 reactivity and dynamic CA are different entities, the former possibly representing only one of the elements of the latter. If postmenopausal differences in CO2 reactivity truly exist, they do not appear to affect the integrity of dynamic CA.

We have failed to demonstrate any diminution of dynamic CA with age, a finding that we believe is of great interest, since this is the first study to show that aging does not impair CA while demonstrating that aging does alter other cardiovascular and cerebrovascular hemodynamic parameters, ie, cardiac BRS and CBFV. CA is a function of multiple physiological processes, including metabolic, myogenic, neuronal, and possibly nitric oxide– and endothelin-mediated endothelial mechanisms.31,32 It is interesting that, although arterial compliance, CBFV, CBF, and possibly endothelium-mediated vascular relaxation decline with age,2,4,5,33 the ability of the cerebrovasculature to compensate for acute BP changes remains undiminished. This suggests that the CA system may have a built-in reserve that allows for degeneration of the individual elements with time. If this is the case, it is possible that dynamic CA reserve may deteriorate with age and that impairment of dynamic CA may only be uncovered if the reserve is stretched to capacity, eg, at BP or age extremes, with large dynamic BP changes, or in disease states. The dynamic methods used in this study for assessing CA probably did not produce large enough BP changes, however, to exceed the upper and lower BP limits within which dynamic CA is active, and the possibility of a narrowing of the BP plateau with age cannot be addressed by our work.

CBFV values in the young and older groups were comparable to values reported elsewhere and demonstrated the significant age-related decline one would expect.5,27 It is unknown whether the magnitude of CBFV has any effect on dynamic CA, but it would appear not to be the case in this study since ARI values were similar in our young and old groups even though mean CBFV was significantly lower in the older group. Despite matching, the older group as a whole had a small although significantly higher systolic BP than the young group. There is no evidence that increases in systemic BP levels impair or facilitate dynamic CA,34 and, in any case, mean BP and diastolic BP were well matched between the
group pairs. Moreover, if systemic BP truly has an effect on dynamic CA, we might have expected detection of lower ARI values in the older group, but this was not seen. Similarly, there is no evidence that increases in BMI are associated with changes in dynamic CA. If such changes did occur with increasing BMI, one could hypothesize that they would be mediately by increases in arterial BP, but this parameter has been reasonably well controlled.

The major limitation of this work and, indeed, any work using similar methodology is that we have measured CBFV rather than CBF. Changes in CBF can only be reliably deduced from CBFV changes if the diameter of the insonated vessel remains unchanged, but reliable, noninvasive assessment of vessel diameter has proven notoriously elusive. A number of authors have used the spectral power of Doppler signals to show that middle cerebral artery diameter does not change during thigh cuff application and release and during hypocapnia and hypercapnia, but a recent study has cast doubt on the usefulness of this method of assessing vessel diameter. We believe, however, that significant change in middle cerebral artery diameter is unlikely during thigh cuff application and release, lower body negative pressure, Valsalva maneuver, or supine rest. Nevertheless, we have not directly measured middle cerebral artery diameter, and caution must therefore be exercised in interpreting our results.

In addition to inducing dynamic BP changes, the different dynamic stimuli may result in other important physiological changes such as hypocapnia secondary to hyperventilation, hypercapnia during the Valsalva maneuver due to apnea, and possibly varying degrees of increased sympathetic nervous system activity between stimuli. Hypocapnia has been shown to augment dynamic CA, but we found no age-related differences in CO2 levels at rest. The effect of increased systemic sympathetic nervous system activity on dynamic CA is unclear, nor is it known whether the effect of sympathetic nerves on cerebral blood vessels changes with aging. An age-related deterioration would, however, probably impair dynamic CA and result in lower ARI values in the older age group. Since the degree of change in CO2 and sympathetic nervous system activity and the effects on dynamic CA in response to thigh cuff release, Valsalva maneuver, and lower body negative pressure release are unknown, we used statistical methods that allowed for the fact that ARI values derived from different dynamic stimuli may not be directly comparable. In view of these uncertainties, however, methods of assessing dynamic CA using spontaneous BP changes at rest, Tiecks’ model, or step response analysis may appear more attractive.

Using induced and spontaneous dynamic pressor and depressor changes in systemic BP to alter CBFV, we have not demonstrated any deterioration in dynamic CA with age. This finding has clinical significance in suggesting that any deterioration in dynamic CA in older subjects detected by these methods is likely to be pathological rather than physiological in origin. We believe, however, that further studies using other methods of assessing CA are needed to confirm our findings.

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References


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