Effect of Aging on Dynamic Cerebral Autoregulation During Head-Up Tilt

Brian J. Carey, MD; Ronney B. Panerai, PhD; John F. Potter, DM

Background and Purpose—Physiological aging is associated with many changes in the cardiovascular and cerebrovascular systems, but dynamic cerebral autoregulation (CA) during supine rest shows no age-related changes. Because syncopal syndromes usually occur during orthostatic stress and their prevalence increases with age, it is important to define the effect of aging on dynamic CA during orthostatic stress.

Methods—Twenty-five younger subjects (±40 years) and 25 sex-matched older subjects (±60 years) underwent 70° head-up tilt for 30 minutes. Bilateral middle cerebral artery blood flow velocities were measured with transcranial Doppler ultrasound, along with noninvasive continuous measurements of arterial blood pressure, heart rate, and transcutaneous and end-tidal carbon dioxide concentrations. By comparing actual changes in cerebral blood flow velocity to changes predicted by a model based on arterial blood pressure changes, we derived dynamic autoregulatory indexes for each subject for periods before, during, and after tilt.

Results—Younger subjects were a mean of 40 years younger than older subjects (28±8 versus 69±10 years). Although cerebral blood flow velocity (P<0.001) and baroreceptor sensitivity (P<0.001) were significantly lower at rest in older subjects, autoregulatory indexes were similar in younger and older subjects at all times before, during, and after tilt (P=0.62).

Conclusions—Although increasing age is associated with lower cardiac baroreceptor sensitivity and cerebral blood flow velocity, dynamic CA during orthostatic stress is unaffected by physiological aging. (Stroke. 2003;34:1871-1875.)

Key Words: aging ■ cerebrovascular circulation ■ syncope ■ ultrasonics

Normal aging is associated with many well-recognized changes in the cardiovascular system such as increases in systolic blood pressure (BP) and decreases in systemic artery compliance and cardiac baroreceptor sensitivity (BRS).1–3 The cerebral vasculature also undergoes age-related changes as evidenced by the decline in cerebral blood flow (CBF) and CBF velocity (CBFV) with advancing years.4,5

Cerebral autoregulation (CA) refers to the inherent ability of cerebral blood vessels to keep CBF constant over a wide range of perfusion pressures.6 Dynamic CA refers to the ability to maintain CBF in the face of rapid changes in perfusion pressure occurring over a matter of seconds; static CA refers to CBF adjustments in response to steady-state changes in perfusion pressure.6 Dynamic CA may have different control mechanisms than static CA and may be more susceptible to impairment in certain disease states such as seen after acute ischemic stroke.7

Dynamic CA has been shown to be impaired during presyncope, and this impairment probably contributes to the fall in CBF that ultimately results in loss of consciousness during syncope.8 Syncope syndromes become more prevalent with age, and it has been hypothesized that a physiological age-related deterioration in CA may account for this increased prevalence. Dynamic CA has previously been shown to be preserved in normal subjects during orthostatic stress, but no age-related deterioration has been demonstrated in dynamic CA in normal subjects during supine rest.8,9 Most syncopal syndromes, however, occur during orthostatic stress, and an age-related deterioration of dynamic cerebral autoregulatory responses to orthostasis could explain the rising prevalence of syncope syndromes with age.10 This study investigated the effect of aging on dynamic CA in normal subjects during orthostatic stress induced by head-up tilt, hypothesizing that dynamic CA during orthostasis would be impaired in older subjects.

Subjects and Methods
Subjects were recruited from a volunteer register in the department and from department staff. All were healthy, on no medications, and free of cardiovascular, cerebrovascular, and autonomic disease on the basis of history, clinical examination, and standard autonomic function tests.11 Significant silent carotid stenosis was excluded by bilateral neck auscultation and the absence of typical transcranial Doppler ultrasound findings.12

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Subjects were assigned by age to a younger group (≤40 years) and an older group (≥60 years) and were pair matched for sex and body mass index to within 2.0 kg/m².

Subjects avoided caffeine-containing products, nicotine, and alcohol for at least 12 hours before the study and attended a temperature-controlled (21°C to 24°C) laboratory between 9 and 11 AM. A 2-hour rest after a light breakfast. Subjects lay supine on a padded table capable of being manually tilted with their head supported by 2 pillows. After 10 minutes of supine rest, 3 semiautomated BP readings were taken 1 minute apart (Omron 711). The mean of the last 2 readings, if values differed by <10 mm Hg, was taken as the baseline casual BP measurement. A surface 3-lead ECG and noninvasive beat-to-beat arterial BP measurements (Finapres 2300, Ohmeda) were recorded, with the BP cuff kept at right atrial level while supine and during tilt with a custom-made, adjustable arm rest. Transcutaneous CO₂ partial pressure was measured with a previously validated transcutaneous gas monitor (TINA, Radiometer), with the probe placed at heart level in the anterior axillary line. End-tidal CO₂ was measured via a gas monitor (TINA, Radiometer), with the probe placed at heart level. Subjects were assigned by age to a younger group (40 years) and an older group (≥60 years) and were pair matched for sex and body mass index to within 2.0 kg/m². Using methods described previously, we calculated dynamic autoregulatory index (ARI) values ranging from 0 (absent) to 9 (most efficient) for the 1-minute period before tilt, first and third minutes after tilt, first and last minutes after returning supine, and first and third minutes after returning supine for each subject. In short, actual CBFV changes were compared with CBFV changes predicted by a model based on arterial BP changes proposed by Tiecks et al. This model was fitted to each of the 1-minute data segments by selecting the value of ARI leading to the minimum quadratic error between measured CBFV and the model-predicted CBFV. In addition, the model allowed calculation of correlation coefficients assessing how closely the measured CBFV fitted the model-predicted velocity for each subject during each time period. Cardiac BRS was derived for each subject from the 5-minute baseline recording using fast Fourier transform spectral analysis methods as described by Robinson et al.

### Statistical Analysis

Demographic details and baseline characteristics of the younger and older groups were compared by use of 2-sample Student’s t tests. The between-group and within-subject changes in the groups were modeled for each outcome measure with a mixed model for repeated-measures data. A normal distribution was assumed, and a good approximation of this was demonstrated by a plot of residuals. Model selection was by changes in the log likelihood, and denominator degrees of freedom were calculated with Satterthwaite’s method. Different covariance patterns were investigated with Akaike’s information criterion. Data were analyzed with the SAS version 6.12 and Minitab 12 software packages. Statistical significance was set at P<0.05.

The study was approved by the local research ethics committee, and fully informed, written consent was obtained from each subject.

### Results

Demographic and baseline data of the younger (n=25) and older (n=25) groups are given in Table 1. The mixed model did not detect any differences between results obtained from the 2 sexes; therefore, sex was removed from the model, and results are presented without sex bias. Similarly, no differences were detected between results obtained for the right and left MCAs, so this distinction was also excluded from the model. Five very elderly (≥75 years) subjects are included in the older group and were analyzed with the rest of the older group because their results did not differ at any stage. Baseline CBFV (P<0.001) and cardiac BRS (P<0.001) values were significantly higher in the younger group, and baseline systolic (P<0.001) and diastolic (P<0.001) BPs were significantly higher in the older group.
ARI values of the 8 syncopal subjects were significantly lower than those of nonsyncopal subjects in the last minute before (1.8 versus 5.3; difference, 3.5; 95% CI, 1.9 to 4.5; \( P<0.05 \)) and first minute after (1.5 versus 5.5; difference, 4.0; 95% CI, 1.8 to 4.8; \( P<0.05 \)) returning supine but were similar at all other times. Apart from the predicted cardiovascular changes during presyncope, no differences were demonstrated in any parameter at any other time between the 8 syncopal subjects and the nonsyncopal subjects.

**Discussion**

Dynamic CA has been shown to be impaired during presyncope; therefore, the hypothesis that an age-related deterioration in CA accounts for the rise in prevalence of syncope syndromes with age is attractive. One previous study did not show any age-related deterioration in dynamic CA in normal subjects during supine rest, whereas another demonstrated that dynamic CA is preserved in normal subjects during orthostatic stress induced by head-up tilt. Because most syncope syndromes occur during orthostatic stress, it is important to know whether normal aging impairs dynamic CA during orthostasis.

We therefore hypothesized that dynamic CA would be impaired in healthy older subjects during head-up tilt, thereby supporting the notion that an age-related deterioration in CA accounts for the rise in prevalence of syncope syndromes with age. We did not demonstrate any deterioration in indexes of dynamic CA during orthostatic stress in older subjects, however, despite the presence of normal cardiovascular aging, as evidenced by lower cardiac BRS and CBFV and higher arterial BP. Moreover, we found that autoregulatory responses in older healthy subjects are similar to those of younger healthy subjects during supine rest and during presyncope, as well as during head-up tilt.

**TABLE 2. Mean MAP, Mean CBFV, Pulse Interval, Transcutaneous and End-Tidal CO₂, and ARI Values of the Younger and Older Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CBFV, cm/s</td>
<td>Younger</td>
<td>61±14</td>
<td>51±12*</td>
<td>49±15*</td>
<td>50±15*</td>
<td>52±13*</td>
<td>56±13</td>
<td>59±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>49±13</td>
<td>40±11*</td>
<td>40±9*</td>
<td>42±13*</td>
<td>41±11*</td>
<td>47±14</td>
<td>50±14</td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>Younger</td>
<td>88±17</td>
<td>92±15</td>
<td>93±11</td>
<td>88±14</td>
<td>87±15</td>
<td>90±11</td>
<td>92±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>96±12</td>
<td>99±14</td>
<td>100±15</td>
<td>94±16</td>
<td>95±16</td>
<td>97±14</td>
<td>100±17</td>
<td></td>
</tr>
<tr>
<td>Pulse interval, ms</td>
<td>Younger</td>
<td>920±121</td>
<td>776±150*</td>
<td>759±131*</td>
<td>713±95*</td>
<td>709±104*</td>
<td>935±100</td>
<td>915±123</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>887±88</td>
<td>740±111*</td>
<td>722±158*</td>
<td>691±81*</td>
<td>687±117*</td>
<td>909±142</td>
<td>893±133</td>
<td></td>
</tr>
<tr>
<td>Transcutaneous CO₂</td>
<td>Younger</td>
<td>41.1±5.8</td>
<td>39.8±6.0†</td>
<td>38.7±6.3†</td>
<td>39.2±5.7†</td>
<td>39.3±6.2†</td>
<td>40.0±6.5</td>
<td>40.3±6.3</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>42.0±6.1</td>
<td>40.7±5.9</td>
<td>39.5±6.1</td>
<td>39.8±6.4†</td>
<td>40.0±6.6†</td>
<td>41.0±6.5</td>
<td>41.4±5.9</td>
<td></td>
</tr>
<tr>
<td>End-tidal CO₂</td>
<td>Younger</td>
<td>41.5±7.1</td>
<td>38.8±6.2†</td>
<td>38.2±7.7†</td>
<td>38.2±7.7†</td>
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<td>38.2±7.7†</td>
<td></td>
<td>0.74</td>
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<tr>
<td></td>
<td>Older</td>
<td>41.1±5.6</td>
<td>37.9±5.8†</td>
<td>37.7±6.5†</td>
<td>37.7±6.5†</td>
<td>37.7±6.5†</td>
<td>37.7±6.5†</td>
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<td></td>
</tr>
<tr>
<td>ARI</td>
<td>Younger</td>
<td>5.0±2.2</td>
<td>5.6±2.0</td>
<td>5.5±1.9</td>
<td>5.3±1.5</td>
<td>5.3±2.1</td>
<td>5.4±2.4</td>
<td>5.1±1.9</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>4.9±2.3</td>
<td>5.7±1.7</td>
<td>5.5±1.7</td>
<td>5.6±2.0</td>
<td>5.2±1.8</td>
<td>5.6±2.7</td>
<td>5.3±2.2</td>
<td></td>
</tr>
</tbody>
</table>

A indicates last minute before tilt (baseline); B, first minute after head-up tilt; C, third minute after head-up tilt; D, third last minute of head-up tilt; E, last minute of head-up tilt; F, first minute after returning supine; and G, third minute after returning supine. Probability value represents overall difference between younger and older groups detected with the mixed model. 

*Significant difference from baseline (\( P<0.001 \)).
†Significant difference from baseline (\( P<0.05 \)).

Data record of a 22-year-old female subject who underwent head-up tilt at time 0 showing the right MCA Doppler waveform, finger plethysmograph pressure waveform, ECG trace, and end-tidal and transcutaneous CO₂ recordings.

Five younger subjects and 3 older subjects developed imminent vasovagal syncope during head-up tilt and were replaced supine before the end of the 30-minute period. These subjects were excluded from the mixed model, but inclusion or exclusion did not affect the overall results.

To indicate the type and quality of raw data gathered, we have included the Figure to demonstrate the actual data record of a young female subject around the point of head-up tilt.

Changes in parameters from baseline for both groups are given in Table 2. Mean CBFV (\( P<0.001 \)) and transcutaneous (\( P<0.05 \)) and end-tidal (\( P<0.05 \)) CO₂ levels were significantly lower in both groups during head-up tilt and recovered to baseline levels after head-up tilt.

ARI values were similar in both groups at all times, with the overall estimated difference in ARI values between the younger and older groups being −0.2 (95% confidence interval [CI], −0.7 to 0.3; \( P=0.62 \)).
CBFV values in the younger and older groups were comparable to values reported previously\textsuperscript{5,7-9} and demonstrate the significant age-related decline that one would expect. CBFV and transcutaneous and end-tidal CO\textsubscript{2} levels declined significantly in both groups during head-up tilt, and these are normal physiological changes that have been well demonstrated.\textsuperscript{8,17} Indeed, Cencetti et al\textsuperscript{18} have shown a direct link between the fall in CBFV and relative hypocapnia during orthostatic stress.

The model proposed by Tiecks et al\textsuperscript{15} was initially developed using hypotension induced by rapid thigh cuff deflation, but this model has previously been applied to spontaneous BP changes at rest and during head-up tilt and shown to be valid.\textsuperscript{7-9} The model has been used to demonstrate impaired CA in patients with severe carotid artery stenosis,\textsuperscript{19} during presyncope,\textsuperscript{8} and after acute ischemic stroke.\textsuperscript{7} In addition, the model has been validated using low extremes of CBFV and cerebral perfusion pressure.\textsuperscript{8} The ARI values obtained during this study are comparable to values obtained during similar studies,\textsuperscript{7-9} and the decline in ARI values in syncopal subjects during and after presyncope was expected, having previously been demonstrated in normal subjects and patients with recurrent vasovagal syncope.\textsuperscript{8} We have found an overall ARI difference between younger and older groups of \texttext{-0.2 (95\% CI, \texttext{-0.7 to 0.3). We believe that the CI is of a magnitude that suggests that there is no clinically significant age-related deterioration in dynamic CA in healthy older subjects during orthostatic stress.}

The lower cardiac BRS and CBFV values and higher arterial BP levels in the older group at baseline reflect, we believe, normal physiological aging in this group.\textsuperscript{1,3,5,20} There is no evidence that increases in systemic BP facilitate dynamic CA, and it is most unlikely that the higher systemic arterial BP levels in the older group led to improved dynamic CA during head-up tilt. If anything, the opposite might have been expected.

Results of the 5 very elderly (\texttext{\geq}75 years) subjects were similar to those of older subjects between 60 and 75 years of age, but the numbers involved are too small to draw any meaningful conclusions. It is conceivable that dynamic CA in very elderly subjects no longer performs as efficiently as in young or young elderly subjects, and another study looking at a larger very elderly group may be a worthwhile exercise. Significant differences in cerebral Doppler blood flow parameters exist between younger men and women,\textsuperscript{20} but the mixed model did not detect any sex differences in autoregulatory responses at any stage. It is still possible that sex differences in autoregulatory responses to orthostatic stress exist but that this study was not adequately powered to detect such differences.

The major limiting factor of our work remains the indirect measure of MCA pressure. Although arterial pressure waveforms change with head-up tilt, noninvasive plethysmography correlates very well with intra-arterial pressure recordings during head-up tilt.\textsuperscript{21} These methods have previously been used when assessing dynamic CA during head-up tilt and have been found to be reliable and consistent.\textsuperscript{4} A direct measurement of MCA pressure is impossible without very invasive procedures that, in themselves, would affect the interpretation of our work. Because original work with the model used MCA pressure derived from Finapres monitoring as the input parameter and assumed that fluctuations in perfusion pressure were reflected mainly by MCA pressure fluctuations,\textsuperscript{7-9,15,19} it is important to use MCA pressure when calculating ARI values. Intracranial pressure changes after head-up tilt are likely to be relatively small and similar in syncopal and nonsyncopal subjects alike,\textsuperscript{22} and changes in venous pressure will occur to an equal and proportionate degree as arterial pressure. In the absence of better, noninvasive alternatives, therefore, we believe that our calculations using noninvasive plethysmography provide acceptable estimates of MCA pressure.

Our calculations also assume that MCA diameter remains constant during head-up tilt and presyncope. MCA caliber does not change during simulated orthostatic stress, and changes in CO\textsubscript{2} concentrations to the degree demonstrated here would not be expected to affect MCA diameter significantly.\textsuperscript{23,24} Profound hypotension during presyncope, however, could potentially cause MCA myogenic vasodilation and influence CBFV, but our methods did not allow us to assess this possibility. Because we did not measure MCA diameter during this study, caution must be exercised when our results are interpreted.

Transcutaneous CO\textsubscript{2} measurements correlate highly with arterial CO\textsubscript{2} levels but rely on gas diffusion and thus have poor dynamic response characteristics. In addition, doubts exist about the accuracy of end-tidal and transcutaneous CO\textsubscript{2} measurements during changes in cardiac output.\textsuperscript{25} Our CO\textsubscript{2} findings, however, are consistent with our previous findings and those of other researchers and are a reasonable reflection of arterial CO\textsubscript{2} levels in our subjects.\textsuperscript{8,17,18}

Because we were dealing with healthy subjects, we did not use carotid duplex scanning to exclude significant internal carotid artery stenosis in our subjects; instead, we used a combination of neck auscultation and the transcranial Doppler findings. Significant internal carotid artery stenosis is not reliably excluded by neck auscultation, and transcranial Doppler findings have not yet been validated or used widely in these circumstances. Thus, our results must be interpreted with caution.

In summary, we have found that normal aging does not appear to affect dynamic cerebral autoregulatory function during orthostatic stress or supine rest. We do not believe, therefore, that the increased prevalence of syncope syndromes with age can be explained by an age-related deterioration in dynamic CA.

References


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