Cerebral Oxygenation Declines in Healthy Elderly Subjects in Response to Assuming the Upright Position

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Background and Purpose—With increasing age, assuming the upright position is more often accompanied by symptoms such as dizziness and lightheadedness, possibly as a result of a diminished oxygen supply to the brain due to impaired cerebral autoregulation. We aimed to quantify postural changes in cerebral oxygenation and systemic hemodynamics in healthy elderly and young subjects.

Methods—In 18 healthy elderly subjects (aged 70 to 83 years) and 10 healthy young subjects (aged 22 to 45 years), frontal cortical oxygenation and hemodynamic responses were continuously monitored by near infrared spectroscopy and Finapres, respectively, before and during 10 minutes of active standing.

Results—Cortical oxyhemoglobin concentration \([O_2\text{Hb}]\) decreased by \(-4.6 \pm 2.2 \, \mu\text{mol/L} \) (\(P<0.001\)) and cortical deoxyhemoglobin concentration increased by \(1.5 \pm 2.4 \, \mu\text{mol/L} \) (\(P<0.05\)) in the elderly subjects after posture change, whereas these variables did not change significantly in the young subjects. The postural hemodynamic changes tended to be attenuated in the elderly subjects, except for the increases in systolic blood pressure (BP). Smaller postural increases in diastolic BP were related to larger \([O_2\text{Hb}]\) decreases (\(r=0.53, P<0.01\), corrected for the age effect).

Conclusions—Assuming the upright position evokes an asymptomatic decrease in frontal cortical oxygenation in healthy elderly subjects but not in healthy young subjects. Cortical \([O_2\text{Hb}]\) changes are affected by diastolic BP changes. These findings may indicate that regulation of cerebral oxygenation alters with increasing age. (Stroke. 2000;31:1615-1620.)

Key Words: aging ■ cerebral circulation ■ hypotension, orthostatic ■ oxygen ■ spectroscopy, near-infrared

Cardiovascular responses and hemodynamic compensatory mechanisms become impaired with increasing age. As a result, assuming the upright position may evoke orthostatic hypotension and cerebral symptoms, such as dizziness, lightheadedness, falls, or even syncope in elderly people. Postural diastolic blood pressure (BP) decreases even predict excess cerebrovascular mortality rates. Postural cerebral symptoms depend on the extent to which cerebral perfusion and oxygen supply become compromised. Because cerebral autoregulation, normally providing a stable cerebral blood flow within certain variations of systemic BP, and cerebral blood flow may become impaired with aging and with increasing BP levels, postural changes in cerebral perfusion and oxygen supply may vary between elderly subjects and young subjects.

Several studies, using transcranial Doppler sonography (TCD), examined cerebral blood flow velocity during orthostatic stress in healthy adult subjects. Some of these studies have shown cerebral vasocostriction and a lower cerebral perfusion, whereas others have found stable cerebral hemodynamics. Two other studies, performed with the use of near infrared spectroscopy (NIRS), showed changes in frontal cortical oxygenation in healthy adult subjects during head-up tilt.

Whereas the TCD method aims at indirect assessment of cerebral tissue perfusion changes through measurement of blood flow velocity changes in the large cerebral arteries, the NIRS method directly assesses cerebral oxygenation changes on the cerebral cortical tissue level. The NIRS technique is based on the relative transparency of human tissue to near-infrared light and on the oxygenation-dependent light absorption changes caused by the chromophores oxyhemoglobin \([O_2\text{Hb}]\) and deoxyhemoglobin \([HHb]\). Application of a modified Lambert-Beer law offers the opportunity to quantify absolute changes in \([O_2\text{Hb}]\) and \([HHb]\) as the result of the different optical absorption spectra of these chromophores. In the last decade, NIRS has become a suitable and easily manageable method to monitor cerebral cortical oxygenation continuously and noninvasively, for example, during orthostatic stress or brain activation.

Since postural symptoms such as dizziness and lightheadedness occur more often with aging, we hypothesized that postural decreases in cerebral oxygenation are larger in elderly subjects than in young subjects, making elderly...
Subjects and Methods

Subjects
Healthy elderly subjects were recruited by means of an advertisement in a local newspaper. Preset inclusion criteria for healthy elderly subjects were age ≥70 years; a medical history free of cardiovascular, pulmonary, renal, endocrinological, and neurological disorders; no use of cardiovascular medications; and an active and independent life. Thirty-three responders were invited for a screening visit. Fifteen elderly subjects were excluded by preset exclusion criteria: cardiac rhythm disturbances (n = 4); systolic BP > 170 mm Hg and/or diastolic BP > 95 mm Hg (n = 5); orthostatic hypotension, defined as a drop in systolic BP ≥20 mm Hg after at least 1 minute of standing (n = 4); forced expiratory volume in 1.0 second < 1.5 L/s (n = 1); or an abnormal outcome on computer-controlled automatic function testing 19 (n = 1).

Ten healthy young subjects were recruited from the academic and hospital staff and from acquaintances of the investigators. Preset inclusion criteria for the healthy young subjects were an age of ≤45 years; a medical history free of cardiovascular, pulmonary, renal, endocrinological, and neurological disorders; no use of cardiovascular medications; no cardiac rhythm disturbances; and no orthostatic hypotension. The young subjects were familiar with participation in research.

All young and elderly subjects regularly performed physical exercise, such as walking, cycling, or swimming, and ate a normal diet without salt restriction. All subjects gave their written informed consent to this study. The investigation was approved by the ethics committee for research on human subjects of the University Medical Center, Nijmegen, the Netherlands.

Procedure and Instrumentation
Cerebral oxygenation was measured continuously by a pulsed, continuous-wave NIRS device, which produces 3 light bundles with wavelengths of 775 nm, 845 nm, and 904 nm, respectively (OXYMON, Department of Physiology and Biomedical Engineering, University Medical Center, Nijmegen, the Netherlands). For estimation of absolute changes in oxyhemoglobin concentration [O_2Hb] and deoxyhemoglobin concentration [HHb] over the frontal cortex, a differential path-length factor of 6.0 and Livera’s algorithm were used.15,21 The NIRS optodes were placed on C4 and approximately F4 according to the 10 to 20 system for standard electrode positions with an interoptode distance of 5.5 cm.22 The optodes were attached with tight elastic headbands to press them against the skin. Changes in [O_2Hb], [HHb], and in total hemoglobin concentration [tHb], defined as the sum of the changes in [O_2Hb] and [HHb] and considered a measure of cerebral blood volume, were sampled every second and stored on disk for offline analysis.

BP was measured beat-to-beat at the middle finger of the nondominant hand with the use of a Finapres device (FINger Arterial PRESSure; TNO).23,24 The finger was kept at heart level at all times. A height detector (Department of Biomedical Engineering, University Medical Center, Nijmegen, the Netherlands) comparing finger level and heart level at the fourth intercostal space in midaxillar line corrected the BP signal for small hydrostatic pressure artifacts according to the formula BP (mm Hg) = finger BP (mm Hg) + 74 (mm Hg/m) × height (m). The BP signal was recorded with a sample frequency of 100 Hz. Absolute changes in systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), pulse pressure (PP), heart rate (HR), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) were calculated offline from the finger arterial BP waveform by the FAST-mf system software program Modelflow (TNO).23–27 Modelflow is a 3-element model of the arterial input impedance, including continuous correction for variations in the diameter and the compliance of the aorta, describing the relation between aortic flow and pressure and computing SV.25–27 CO is computed by multiplying SV and HR, and TPR is calculated for each heartbeat as the quotient of MAP and CO.25–27

On the day of testing, the subjects arrived at the hospital in the morning after a fast of at least 3 hours. The tests took place in a quiet room at an ambient room temperature of 21°C to 24°C. All subjects voided before start of the test and were familiarized with the study protocol. After instrumentation and when a stable Finapres signal was obtained, the subjects assumed a supine position for at least 10 minutes, after which they stood up within 10 seconds and remained standing for 10 minutes.

Statistical Analysis
Statistical analysis was performed with SPSS for Windows 8.0 (SPSS Inc, 1998). A value of P < 0.05 was taken as the level of significance. The results are expressed as mean ± SD.

Subject characteristics on screening were compared by means of 1-way ANOVA. During the standing-up tests, 1-minute averages of changes in [O_2Hb], [HHb], [tHb], BP, PP, HR, SV, CO, and TPR were calculated. Baseline values were defined as the last 1-minute averages before the posture change from supine to upright position. Two-way repeated-measures ANOVA was applied to examine the effect of time and time-by-group interaction on the postural changes versus baseline. The dependence of average postural changes in [O_2Hb], [HHb], and [tHb] on sex, baseline BP level, and average postural changes in BP, PP, HR, SV, CO, and TPR was determined with Pearson’s correlation tests and stepwise multiple linear regression analysis incorporating dichotomized age as a fixed covariant.

Results

Subject Characteristics
The characteristics of the 18 healthy elderly subjects and the 10 healthy young subjects on screening are presented in Table 1.

Postural Changes in Cerebral Oxygenation
Figure 1 and Table 2 show the postural changes in frontal cortical [O_2Hb], [HHb], and [tHb] in the healthy elderly and young subjects. Changes in cerebral oxygenation took place within the first 2 minutes of standing and remained essentially unchanged during prolonged standing.

Frontal [O_2Hb] and [tHb] decreased in the elderly subjects but not in the young subjects, the 2 groups differing signifi-

TABLE 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Healthy Elderly Subjects (n = 18)</th>
<th>Healthy Young Subjects (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>9/9</td>
<td>4/6</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.9 ± 3.6</td>
<td>21.9 ± 3.2‡</td>
</tr>
<tr>
<td>Quetelet index, kg/m²</td>
<td>26.3 ± 2.3</td>
<td>21.9 ± 3.2‡</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>147 ± 17</td>
<td>118 ± 7‡</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84 ± 8</td>
<td>77 ± 6*</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>64 ± 12</td>
<td>41 ± 8†</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>70 ± 8</td>
<td>61 ± 7†</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD; * P < 0.01, † P < 0.001 compared with healthy elderly subjects.
Significantly in their responses of [O$_2$Hb] and [tHb]. Frontal [HHb] increased in the elderly subjects, but the [HHb] rise did not reach significance in the young subjects ($P < 0.06$). The changes in frontal [HHb] were not significantly different between the 2 groups (Figure 1 and Table 2).

None of the elderly or young subjects showed obvious cerebral symptoms such as dizziness or lightheadedness after the posture change.

Postural Changes in Systemic Hemodynamics
Figure 2 and Table 2 show the changes of SBP, DBP, MAP, and PP in the healthy elderly and young subjects after standing. In addition, Figure 3 and Table 2 represent the postural changes of HR, SV, CO, and TPR in the 2 groups. Systemic hemodynamics changed immediately after standing up, but after the second minute of standing, no further change was present. None of the subjects had orthostatic hypotension.

Both groups showed rises in SBP, DBP, and MAP during standing, and significant differences were not present between their responses. When the BP changes over time were calculated in terms of percentage in view of the significantly different BP levels between the young and elderly subjects, the BP curves remained essentially the same and were not significantly different between the 2 groups either. The PP responses did differ significantly between the 2 groups (Figure 2 and Table 2).

HR increased significantly more in the young subjects than in the elderly subjects after standing, whereas SV decreased significantly more in the former group. However, the postural changes in CO were not significantly different between the 2 groups, nor did the TPR responses differ significantly (Figure 3 and Table 2).

Correlations Between Cortical Oxygenation, Systemic Hemodynamics, and Sex
Pearson’s correlation tests showed that the mean postural changes in [O$_2$Hb] and [tHb] were significantly related to the mean changes in DBP, HR, SV, and CO ($P < 0.05$), whereas the mean postural changes in [HHb] were not related to changes in systemic hemodynamics. Sex did not affect any of the variable changes, although the postural decreases in [O$_2$Hb] tended to be smaller in women ($P = 0.08$). Multiple linear regression analysis with correction for the age effect

<table>
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<tr>
<th>TABLE 2. Postural Changes in Cerebral Oxygenation and Systemic Hemodynamics in the Second Minute of Standing Versus Baseline</th>
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</thead>
<tbody>
<tr>
<td>Elderly Subjects ($n=18$)</td>
</tr>
<tr>
<td>Frontal cortical [O$_2$Hb], $\mu$mol/L</td>
</tr>
<tr>
<td>Frontal cortical [HHb], $\mu$mol/L</td>
</tr>
<tr>
<td>Frontal cortical [tHb], $\mu$mol/L</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
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<td>DBP, mm Hg</td>
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<td>MAP, mm Hg</td>
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<tr>
<td>PP, mm Hg</td>
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<tr>
<td>HR, bpm</td>
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<tr>
<td>SV, mL</td>
</tr>
<tr>
<td>CO, L/min</td>
</tr>
<tr>
<td>Total peripheral resistance, dyne · s · cm$^{-5}$</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD; *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ vs baseline.
revealed that mainly the mean changes in DBP predicted the mean changes in [O2Hb] (r = 0.53, P < 0.01) and [tHb] (r = 0.47, P < 0.05) after standing.

**Discussion**

The main findings of this study are that frontal cortical oxygenation and blood volume, expressed by changes in [O2Hb] and [tHb], respectively, declined in healthy elderly subjects after standing in the absence of decreases in orthostatic BP. No such changes were found in healthy young subjects. Postural decreases in cortical [O2Hb] and [tHb] were not only significantly related to advanced age, but they were also independently related to smaller postural increases in DBP. Postural increases in cortical [HHb] were not affected by age or hemodynamic changes.

The present study evaluated the postural changes in cortical oxygenation and blood volume in healthy elderly and young subjects by NIRS. NIRS is a noninvasive method with relatively high temporal resolution for continuous and direct assessment of changes in cerebral cortical tissue oxygenation and blood volume.12,15 TCD, which has been frequently used for measuring cerebral perfusion changes, is also a noninvasive method, providing an indirect estimation of changes in cerebral tissue perfusion by assessing blood flow velocity changes. The TCD method has, however, some disadvantages. First, TCD concerns perfusion changes on the level of larger vessels. Second, the measurements may be biased by changes in diameter of the insonated arteries. Third, the insonation of cerebral arteries is very difficult in some subjects and during posture change. NIRS, on the other hand, is a simply applicable method that measures the (mis)balance of oxygen supply and oxygen demand directly on capillary level in the cerebral cortical tissue.10–12,15 Therefore, NIRS is a promising technique to investigate responses of cerebral
cortical oxygenation and blood volume to a stimulus. However, NIRS cannot quantify oxygenation changes in deeper subcortical areas or the brain stem. In addition, contributions from extracranial tissue to NIRS measurements cannot be completely ruled out, although these contributions have been demonstrated to be relatively small providing the interoptode distance is at least 5.0 cm.13,14,28

In the present study, the postural changes in frontal [O₂Hb], [HHb], and [tHb] observed by NIRS in the elderly subjects were not associated with cerebral symptoms. The oxygenation changes might be relatively small (<5 μmol/L) compared with the total cerebral [tHb] estimated 70 to 100 μmol/L and might be clinically irrelevant to such an extent.11 Since none of the subjects had orthostatic symptoms, oxygen supply apparently still met the functional oxygen demand in the central brain areas and the brain stem after assuming the upright position. Unfortunately, these areas cannot be assessed with NIRS. Frontal cortical oxygenation and blood volume did diminish in elderly subjects during standing, however, indicating that elderly subjects might be more vulnerable to cerebral ischemic symptoms than young subjects in case of additional adverse effects of disorders or medication on cerebral oxygenation.

The postural decreases in frontal [O₂Hb] and [tHb] that were present in the elderly subjects might indicate that the regulation of cerebral oxygenation alters with increasing age. However, it remains unclear whether it involves mainly a larger instability in cerebral perfusion or a different cerebral flow redistribution pattern in upright position with aging, since several explanations are possible for the postural changes in frontal cortical oxygenation. First, oxygen supply may be lower in the upright position because of a diminished cerebral perfusion. The diminished cerebral perfusion may result from a lower perfusion pressure in the cerebral arteries caused by hydrostatic changes11,29 or from a paradoxical increase in vascular resistance on standing.7 A change in systemic arterial saturation or an enhanced functional oxygen demand in the frontal brain areas is unlikely.10 Cortical [HHb], considered as a reflection of the balance between oxygen consumption and delivery, increased but relatively less than [O₂Hb] decreased in the elderly subjects. Therefore, we conclude that cerebral oxygen supply was probably lower in the elderly subjects during standing. A second explanation for the postural decrease in frontal cortical oxygenation in elderly subjects may be that the oxygenation decrease is merely local because of redistribution of oxygen supply to other brain or brain stem areas to protect vital functions or after functional brain activation during active standing.20,30 A previous study, performed with the 133Xe inhalation method, has shown a redistribution of cerebral blood flow with a lower frontal flow in healthy adults after a posture change.30 Since we measured cerebral oxygenation changes only at the frontal brain area, further studies investigating several cortical brain areas simultaneously are needed to provide more insight into this issue.

The hemodynamic variables in this study changed in accordance with previous studies performing orthostatic tests in healthy young and elderly subjects.3,31,32 Supine levels of BP and HR were higher and postural changes in HR and SV were attenuated in elderly subjects, but the postural BP changes were not significantly different between the 2 age groups.

Larger postural increases in DBP were significantly related to smaller postural decreases in [O₂Hb] and [tHb], independent of the age effect on changes in cerebral oxygenation and blood volume. This finding might indicate that higher DBP levels during standing are beneficial for counteracting cerebral perfusion decrements in the upright position. In addition, this finding may emphasize the importance of assessing not only SBP but also DBP for the diagnosis of orthostatic hypotension, as recommended by the American Autonomic Society and the American Academy of Neurology.33 The changes in cortical [HHb], reflecting the matching between oxygen consumption and delivery, were not related to BP changes. In addition, the [HHb] changes were smaller and showed less variation than the [O₂Hb] or [tHb] changes.

The present study has several limitations. First, the numbers of subjects included are relatively small in view of the large interindividual response variation. However, we did find significant changes in hemodynamics and cerebral oxygenation between the 2 age groups. Second, we were not able to examine whether aging has a gradual effect on postural responses of cerebral oxygenation because we did not include subjects in a continuum of age. Further, although we attached the optodes with tight elastic headbands to press them against the skin of the head, we could not fully rule out a possible contamination of the NIRS measurements by the extracranial blood flow in the skin tissue. Nevertheless, we are confident that the behavior of the present oxygenation changes most probably reflected the brain tissue oxygenation changes due to the interoptode distance of 5.5 cm.28 Finally, we were not able to measure cerebral oxygenation changes over several brain areas simultaneously. Future studies are needed to provide additional insight into the issue of cerebral oxygenation changes over several brain areas in response to assuming the upright position.

In conclusion, in the absence of orthostatic BP decreases, frontal cortical oxygenation declined remarkably in healthy elderly subjects after standing but not in healthy young subjects. The cerebral oxygen supply apparently remained sufficient, because no cerebral symptoms were present in either group during standing. Higher postural increases in DBP attenuated frontal cortical decreases in [O₂Hb] and [tHb] during standing but did not affect postural changes in [HHb]. This outcome may indicate that regulation of cerebral oxygenation alters with increasing age. Consequently, we speculate that elderly subjects might be more vulnerable to ischemic cerebral symptoms than young subjects.

Acknowledgments

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