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The effects of healthy aging on cerebral hemodynamic responses to posture change

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Abstract
Aging is associated with an increased incidence of orthostatic hypotension, impairment of the baroreceptor reflex and lower baseline cerebral blood flow. The effect of aging on cerebrovascular autoregulation, however, remains to be fully elucidated. We used a novel optical instrument to assess microvascular cerebral hemodynamics in the frontal lobe cortex of 60 healthy subjects ranging from ages 20–78. Diffuse correlation spectroscopy (DCS) and near-infrared spectroscopy (NIRS) were used to measure relative cerebral blood flow (rCBF), total hemoglobin concentration (THC), oxyhemoglobin concentration (HbO_2) and deoxyhemoglobin concentration (Hb). Cerebral hemodynamics were monitored for 5 min at each of the following postures: head-of-bed 30°, supine, standing and supine. Supine-to-standing posture change caused significant declines in rCBF, THC and HbO_2, and an increase in Hb, across the age continuum ($p < 0.01$). Healthy aging did not alter postural changes in frontal cortical rCBF ($p = 0.23$) and was associated with a smaller magnitude of decline in HbO_2 ($p < 0.05$) during supine-to-standing posture change. We conclude that healthy aging does not alter postural changes in frontal cortical perfusion.

Keywords: aging, cerebral blood flow, autoregulation, diffuse correlation spectroscopy, near-infrared spectroscopy

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1. Introduction

Posture change evokes hemodynamic responses in the cerebral and systemic vasculature aimed at maintaining cerebral perfusion. Venous return of blood flow to the heart is altered, leading to dynamic changes in vascular tone and the initiation of the systemic baroreceptor reflex. These cerebral and systemic hemodynamic responses occur in close temporal relation to maintain cerebral blood flow (CBF) across a mean arterial pressure (MAP) range of approximately 60–160 mmHg in normotensive people. Studies of healthy subjects have demonstrated that the systemic response to postural change, the baroreceptor reflex, is impaired with aging (Gribbin *et al* 1971). In addition, aging is associated with lower baseline blood flow velocities in the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) (Krejza *et al* 1999), as well as lower baseline CBF (Matsuda *et al* 1984) and an increased incidence of orthostatic hypotension (Shibao *et al* 2007). The effect of healthy aging on cerebrovascular autoregulation (CA), however, has yet to be fully elucidated.

The most commonly used modality for assessing the effect of aging on CA has been transcranial Doppler (TCD) ultrasonography. TCD experiments have demonstrated that healthy elderly subjects maintain adequate autoregulatory function under both dynamic (Carey *et al* 2003, Lipsitz *et al* 2000, Sorond *et al* 2005) and static conditions (Carey *et al* 2003, Lipsitz *et al* 2000, Yam *et al* 2005). These TCD findings may be explained by a pronounced vasodilatory response to decreased cerebral perfusion pressures in elderly subjects during acute orthostatic stress (Sorond *et al* 2005). However, while TCD studies have generally yielded consistent results about the absence of an aging effect in CA, these studies rely on an assumption that macrovascular CBF velocity is indicative of microvascular CBF.

The application of near-infrared spectroscopy (NIRS) to CA studies has provided an opportunity to evaluate this key assumption. Studies of healthy subjects using TCD and NIRS concurrently have generally validated the correlation between macrovascular CBF velocity and microvascular oxygenation during steady-state conditions (Reinhard *et al* 2006), during alterations in end-tidal CO_2 ($EtCO_2$) (Smielewski *et al* 1995) and during orthostatic stress (Krakow *et al* 2000). However, data from several NIRS studies have conflicted with TCD data regarding the effect of healthy aging on autoregulatory function. For example, Mehagnoul-Schipper *et al* (2000) found that elderly (mean age 74 years), but not young (mean age 27 years) subjects experienced significant declines in frontal cortical blood oxygenation and blood volume during supine-to-standing posture change. This finding was reproduced in a follow-up experiment in which serial NIRS measurements were performed in elderly subjects (mean age 75 years) during orthostatic stress (Mehagnoul-Schipper *et al* 2001). Hunt *et al* (2006) studied ten healthy subjects of mean age 60 years and demonstrated a significant postural decline in the ratio of oxygenated hemoglobin to total tissue hemoglobin concentration. The lack of concordance between TCD and NIRS data in autoregulation studies may reflect differences in measured parameters and underscores the importance of developing a modality that can directly measure microvascular CBF to more completely characterize autoregulatory function.

Diffuse correlation spectroscopy (DCS) is a novel optical technology that was developed to measure blood flow directly at the microvascular level (Boas *et al* 1995, Durduran 2004). Like NIRS, DCS is a near-infrared optical technique that utilizes photon absorption and scattering in tissues; the two techniques share the same advantages of light penetration in tissue that facilitates *in vivo* monitoring. However, the physiological parameters measured by NIRS and DCS differ. DCS detects the temporal intensity fluctuations of light scattered from moving red blood cells to provide measurements of relative CBF (rCBF) (Durduran 2004). By contrast, NIRS detects differential photon absorption from oxyhemoglobin and

deoxyhemoglobin to provide measurements of microvascular total hemoglobin concentration (THC), oxyhemoglobin concentration (HbO_2) and deoxyhemogobin concentration (Hb). Thus, while NIRS measurements of HbO_2 provide a surrogate marker of CBF that is only valid if arterial oxygen content and cerebral metabolic rate remain constant, DCS provides a direct measurement of microvascular CBF.

In this prospective observational study, we aimed to explore the effects of healthy aging on cerebral hemodynamic responses to posture change by utilizing a hybrid DCS/NIRS optical technique for comprehensive cerebrovascular hemodynamic monitoring. We studied a large cohort of subjects across the age continuum, rather than examining cerebral hemodynamics at the extremes of age. We also examined the correlation between DCS measurements of rCBF and NIRS measurements of THC, HbO_2 and Hb in order to assess whether the DCS/NIRS hybrid technique provides additional information about cerebral hemodynamics that cannot be obtained by NIRS alone. Finally, by defining the normative response of cerebral hemodynamics to posture change across the age continuum, we aimed to establish a control data set for comparison with clinical populations.

2. Methods

2.1. Study design and subject enrollment

This study was conducted at the Hospital of the University of Pennsylvania. The study protocol was approved by the institutional review board at the University of Pennsylvania. Written informed consent was provided by all subjects, who were recruited by posting fliers in the Hospital of the University of Pennsylvania and from a database maintained by the Center for Cognitive Neuroimaging at the University of Pennsylvania. Subjects were excluded from the study if they had a history of hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, congestive heart failure, coronary artery disease, previous myocardial infarction, previous stroke, previous transient ischemic attack, carotid artery disease, current smoking, previous smoking within 5 years, pulmonary disease, renal disease, or recent administration of vasoactive medications. The target enrollment was 60 subjects. Subjects were enrolled across the age continuum, with a minimum age of 18 years old. The National Institutes of Health Stroke Scale (NIHSS) was performed prior to study initiation for all subjects.

2.2. Diffuse correlation and near-infrared spectroscopies: background and analysis

Both DCS and NIRS utilize near-infrared light within the therapeutic spectral window (i.e. wavelengths between ∼650 nm and ∼950 nm) and rely on the absorption and scattering of photons in human tissue. In the near-infrared range, photon absorption is mainly due to hemoglobins, water molecules and lipids. Photon scattering is caused by intracellular organelles and mitochondria, as well as red blood cells (RBCs). When photons emitted from an optical probe are scattered by moving RBCs, the primary moving light scatterers in human tissue, subtle temporal variations in the intensity of scattered light can be detected at the surface of the scalp. A cerebral flow-index of rCBF is readily derived from this signal by calculating a temporal auto-correlation function of the intensity of the detected light (Boas *et al* 1995, Durduran 2004).

The 'detection volume' of cortical tissue from which NIRS measurements are recorded depends on the source–detector separation (Germon *et al* 1999, Choi *et al* 2004) and the optical properties of the tissue (i.e. the number and density of photon scatterers and absorbers). In the present investigation, the detection volume was standardized by utilizing a source–detector separation of 2.5 cm for all subjects. Although larger source–detector distances have been used

for some NIRS studies (Mehagnoul-Schipper *et al* 2000, Tachtsidis *et al* 2004), a separation distance of 2.5 cm has been utilized effectively in several NIRS studies of the brain (Durduran *et al* 2004, 2009, Li *et al* 2005, Kim *et al* 2009a) and provides a better signal for transcranial DCS than larger distances. Since the light path of DCS is approximately the same as that of NIRS due to the similar wavelengths that are utilized, both methods sample essentially the same tissue volume.

With regard to the DCS detection volume, thus far five published studies have quantitatively examined the penetration of DCS signals into the brain at the 2.5 cm source–detector separation. First, in a study by Durduran (2004), a human skull was used to verify experimentally that DCS penetrates the skull and interrogates the underlying tissue properties. In this same study, hypercapnia-induced changes in intracranial blood flow were also detected and were shown to be distinct from concurrent laser Doppler flowmetry measurements of scalp blood flow. Second, Li *et al* (2005) produced experimentally similar findings to Durduran (2004) using a three-layer model of the skull. Third, Gagnon *et al* (2008) utilized analytic two-layer solutions, Monte Carlo simulations derived from segmented MRI images and experiments on layered phantoms to verify that DCS is able to penetrate through the scalp and skull using a source–detector separation of approximately 2.5 cm. A fourth study validated DCS measurements of rCBF using a 2.5 cm source–detector separation with concurrent Xenon-CT measurements of rCBF in patients (mean age 48, range 18–82) with traumatic brain injury, aneurysmal subarachnoid hemorrhage and acute ischemic stroke (Kim *et al* 2009a). This clinical study provided direct validation of DCS against an established diagnostic modality for measuring cerebral blood flow. Finally, a 2.5 cm source–detector separation has also been used in a clinical study that utilized DCS to characterize autoregulatory impairment in acute, ischemic stroke patients and to investigate CA in subjects with vascular risk factors such as hypertension and diabetes (Durduran *et al* 2009). While the research described above clearly indicates that light from the DCS probe penetrates through the skull and into the cortex, in the future, it will be desirable to design probes with both small and large source–detector separations in order to definitively account for scalp and skull signals.

2.3. Procedure and instrumentation

A portable, custom-built instrument was used to measure rCBF, THC, HbO_2 and Hb using DCS and NIRS (Durduran 2004). Two optical probes were secured on both sides of the forehead with medical grade adhesive materials and a head strap. The probes were covered with a loose-fitting black cloth to minimize ambient light interference with the optical signal. The regions of frontal cortical tissue investigated by each probe were approximately 4–5 cm apart. Each probe consisted of one light source and two detectors—one for DCS detection and the other for NIRS detection. The distance between the light source and detectors was 2.5 cm.

Four high-speed, high-sensitivity avalanche photo-diodes were used as photon counting detectors for DCS. Data output from these photo diodes were sent to a multi-tau hardware correlator for calculation of auto-correlation functions in real time. The correlator produces an independent autocorrelation curve every 0.04 s. However, we used an averaging time of 3 s for each of the two probes, allowing for one frame of DCS data to be acquired every 6 s. This 6 s DCS data acquisition interval was followed by a 1 s NIRS data acquisition interval for both probes. Thus, a new set of DCS and NIRS cerebral hemodynamic data was acquired every 7 s.

The DCS light source consisted of a long coherence length, continuous wave laser (785 nm). Concurrent NIRS data were obtained using three lasers (690 nm, 785 nm and 830 nm), whose intensities were modulated at 70 MHz. A modified Beer–Lambert law was

used for NIRS analysis, with a differential pathlength factor (DPF) of 5.86 and 6.51 for wavelengths of 830 nm and 690 nm, respectively (Duncan *et al* 1996).

Blood pressure and heart rate (HR) were measured by a BpTRU Vital Signs Monitor (VSM MedTech Devices Inc., model BPM-300; Brooklyn, NY) prior to study initiation with subjects resting in the seated position. A FinaPres (FINger Arterial PRESsure, Finapres Medical Systems, Finometer Pro Model 1 with BeatScope PC-based software; Amsterdam, The Netherlands) device was then secured non-invasively on the right third finger for continuous beat-to-beat measurement of HR, mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP). Imholz *et al* (1998) have comprehensively reviewed the FinaPres technology and its validation with intra-arterial blood pressure measurement.

An adjustable armrest was used to keep the subject's right third finger at the level of the right atrium (fourth intercostal space, mid-axillary line) throughout the study. Finger position was confirmed using the FinaPres automated height monitor, after zeroing the finger to the level of the right atrium at the beginning of the study. The FinaPres device factors finger height into its hemodynamic measurements to correct for any hand movements that may occur with respect to the heart level. A loose-fitting, black piece of cloth was placed over the patient's right hand in order to minimize ambient light interference with the FinaPres signal. Measurements were performed in a quiet room with dim light at room temperature.

After the optical probes were placed securely on the forehead and when a stable FinaPres signal was obtained, a disposable rubber mouthpiece was placed in the subject's mouth with an $EtCO_2$ monitor attached to the opening of the mouthpiece (Micro-Capnograph CI240, Columbus Instruments; Columbus, OH). A nose clip was placed over the nares to prevent nose breathing. The capnograph was used to record $EtCO_2$ continuously. A pulse oximeter (Nellcor; Boulder, CO) was placed on the index finger of the patient's right hand to record peripheral arterial oxygen saturation (O_2Sat). Cerebral hemodynamics, systemic hemodynamics, O_2Sat and $EtCO_2$ were then monitored for 5 min each at the following postures: head-of-bed angle 30°, supine (initial supine), standing and supine (recovery supine).

The supine and standing positions were chosen for the protocol so that healthy subjects would be evaluated in natural postures. The head-of-bed 30° position was included to provide normative, control data for future studies of clinical populations since this is a posture at which many stroke and neurointensive care patients are kept to minimize aspiration risk or decrease intracranial pressure. The head of the hospital bed was lowered from a 30° to a 0° angle during the transition to the initial supine position, and then the subject was asked to stand up and lie back down for the subsequent transitions to the standing and recovery supine positions. Confirmation of optical probe placement, FinaPres finger level and $EtCO_2$ monitor placement was performed at the time of all posture changes, which occurred over the span of 5–10 s for the transition from head-of-bed 30° to initial supine and 30 s to 1 min for the transitions from initial supine to standing and standing to recovery supine. Subjects fasted and avoided caffeine intake for 3 h before the study and were also asked to void urine prior to study initiation.

2.4. Statistical analysis

Analyses were carried out using library(nlme) and library(gregmisc) in R version 2.8.1 (R Core Development Team 2008). Two-sided hypothesis tests were carried out with a type I error rate of 0.05. For each subject, the outcome of interest for rCBF was quantified relative to the initial supine position, as follows:

$$\Delta\text{rCBF}_i = (\text{CBF}_i - \text{CBF}_{\text{initial supine}})/\text{CBF}_{\text{initial supine}}$$

where CBF_i is CBF measured at the ith position (i = head-of-bed 30°, standing, or recovery supine). The outcomes of interest for all other cerebral and systemic hemodynamic parameters

(THC, HbO_2, Hb, MAP, SBP, DBP, HR, O_2Sat and $EtCO_2$) were normalized as follows:

$$\Delta Y_i = Y_i - Y_{\text{initial supine}},$$

where Y is the parameter of interest measured at the ith position.

A running Gaussian filter was used to smooth the DCS/NIRS time series data, with a window size of 4. At each body position, the DCS/NIRS, FinaPres, O_2Sat and $EtCO_2$ data were then averaged over the 5 min period. The beginning and ending time-points of the transitions between each posture were marked on both the FinaPres and optical data. The cerebral and systemic hemodynamic data acquired during these transitions between postures are not reported because the study aimed to examine postural cerebral hemodynamic changes, not dynamic autoregulatory changes.

Our study yielded repeated measures data on individual subjects. To account for, and take advantage of the correlation between repeated measures on the same individual, a linear mixed effects model was used to estimate the effect of body posture and age on changes in the outcomes of interest (Pinheiro and Bates 2000). The linear mixed effects model allowed for heterogeneity in the variance of the outcome at each position. As there was no significant hemispheric difference in any of the cerebral hemodynamic parameters at any of the body positions, hemisphere (left or right) was not included as a covariate in the model. Rather, measurements from the different hemispheres were analyzed as repeated measurements at each body position. Model fit was assessed using residuals.

We assessed the overall effect of body position on each hemodynamic parameter. We then built models that included postural effects as well as both age and gender effects that were allowed to vary by position. There was no *a priori* hypothesis regarding an effect of gender on postural changes in cerebrovascular hemodynamics, but gender was included in the model as a possible confounder. We used a global likelihood ratio test to ask whether postural changes associated with age or gender were significant, by comparing the full model to a reduced model without the term of interest. If the global likelihood ratio test showed either strict ($p < 0.05$) or marginal ($p < 0.10$) evidence of statistical significance, a Wald test was used to determine which specific postures might be associated with changes from the initial supine posture. Specifically, we tested for nonzero age or gender effects at each posture. This approach of comparing specific body postures to the initial supine posture only if there was evidence of a global effect meant that a small number of statistical tests were conducted, hence reducing the possibility of spurious false positive findings.

In order to account for other potential confounders, the correlation of age with body mass index (BMI), baseline hemodynamics and baseline $EtCO_2$ in the study population was assessed using a Pearson's correlation coefficient. There was no evidence of a significant association of age with the baseline hemodynamics or baseline $EtCO_2$ ($p > 0.05$ for all variables), but there was a trend toward an association between increasing age and increasing BMI ($p < 0.10$). We therefore included BMI as a covariate in our models to explore the possibility that age effects were confounded by BMI. However, inclusion of BMI in the models had little impact on the significance of the age effect, so results from the models that included BMI as a covariate are not reported.

Associations between postural changes in DCS measurements of rCBF and NIRS measurements of THC, HbO_2, Hb and HbDiff were explored using Pearson's correlation coefficient. HbDiff is calculated as [HbO_2 − Hb] and has been shown to be a better indicator of regional CBF than THC when O_2Sat is kept constant (Tsuji *et al* 1998). We also investigated associations between the supine-to-standing changes in systemic and cerebral hemodynamics using Pearson's correlation coefficient. These correlation analyses excluded six subjects whose NIRS data were not analyzed because of poor optical fiber-to-detector connection in the NIRS

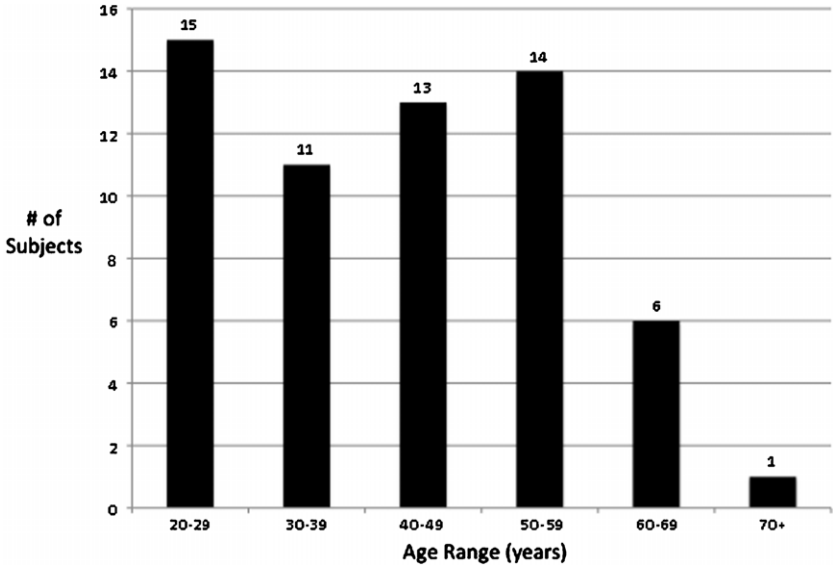

Figure 1. Bar graphs demonstrating the number of subjects in each age range, by decade.

Table 1. Demographic information and baseline characteristics of study population ($N = 60$).

Variable	Mean ± SEM
Male:female	28:32
Age (years)	42.3 (range 20–78)
BMI (kg m^{-2})	24.7 ± 0.5
SBP (mmHg)	115.4 ± 1.9
DBP (mmHg)	74.5 ± 1.4
HR (bpm)	71.3 ± 1.4
$EtCO_2$ (mmHg)	39.4 ± 0.5
NIH Stroke Scale	All subjects scored 0

instrument. Three subjects had poor quality $EtCO_2$ data due to capnograph malfunction, and two had poor quality systemic hemodynamic data due to low FinaPres signal. These subjects were excluded from the analyses of body posture effects on $EtCO_2$ and systemic hemodynamics, respectively.

3. Results

3.1. Subject characteristics

The demographic and baseline hemodynamic characteristics of the 60 healthy subjects are presented in table 1. Age ranged from 20 to 78 years old (see figure 1), with a mean of 42.3 years. The mean BMI was 24.7 kg m^{-2}, with a baseline BP of 115.4/74.5 mmHg and HR of 71.3 beats per minute. None of the subjects experienced syncope or reported pre-syncopal symptoms during the study.

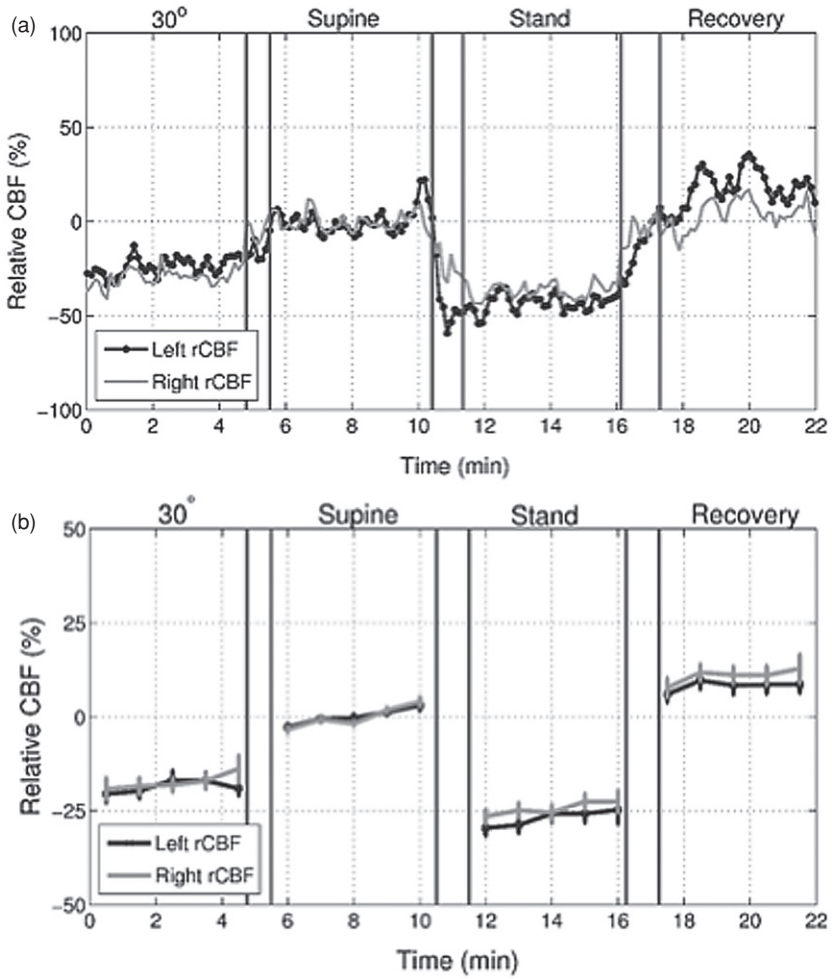

Figure 2. (a) Time series data of rCBF for a representative subject. (b) Time series data of rCBF averaged at 1 min intervals for the entire study population. Standard error bars are provided at each 1 min interval. The solid vertical lines between each posture in (a) and (b) represent the transition periods between body postures.

3.2. Postural changes in cerebral hemodynamics

Figure 2(a) displays time-series data of rCBF from a sample subject. Figure 2(b) displays time-series data of rCBF averaged over the entire study population on a minute-by-minute basis. Table 2 shows the mean changes in rCBF, THC, HbO_2 and Hb that occurred with each posture change across all subjects.

All cerebral hemodynamic parameters varied significantly with body posture ($p < 0.0001$ for all parameters). Supine-to-standing posture change led to significant decreases in rCBF, THC and HbO_2, as well as a significant increase in Hb, across the age continuum ($p < 0.01$ for all parameters). Changes in rCBF, THC and HbO_2 were also significant during the transition from head-of-bed 30° position to supine position. All of the cerebral hemodynamic parameters except Hb differed significantly between the initial supine position

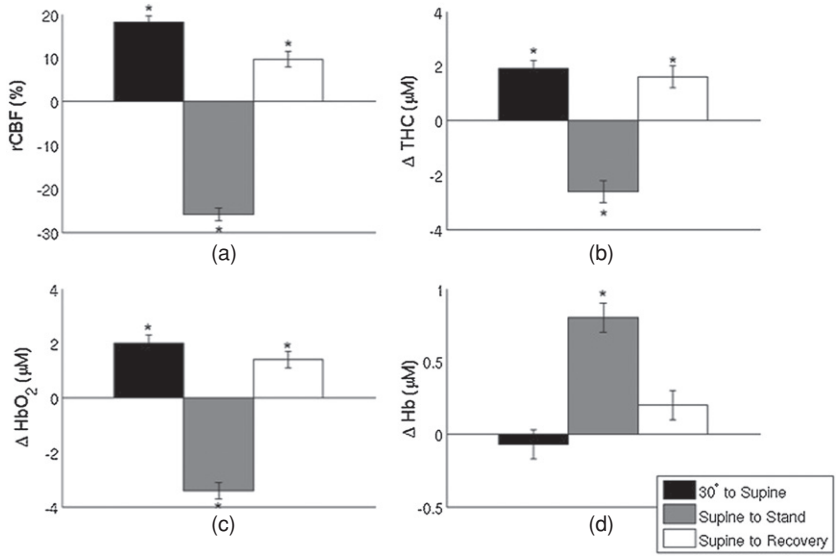

Figure 3. Bar graphs for mean changes in (a) rCBF, (b) THC, (c) HbO_2 and (d) Hb with each posture change for the entire population. Vertical bars represent standard errors from the mean. Asterisk (*) indicates significant change from the initial supine value.

Table 2. Postural changes in cerebral and systemic hemodynamics for all subjects ($N = 60$).

Hemodynamic parameter	Head-of-bed 30° to supine	Supine to stand	Initial supine to recovery supine
ΔrCBF (%)	18.2 (1.5)*	−25.9 (1.5)*	9.7 (1.8)*
ΔTHC (μmol L^{-1})	1.9 (0.3)*	−2.6 (0.4)*	1.6 (0.4)*
ΔHbO_2 (μmol L^{-1})	2.0 (0.3)*	−3.4 (0.3)*	1.4 (0.3)*
ΔHb (μmol L^{-1})	−0.07 (0.1)	0.8 (0.1)*	0.2 (0.1)
ΔMAP (mmHg)	−0.9 (0.8)	5.4 (1.0)*	6.3 (0.7)*
ΔSBP (mmHg)	0.2 (1.0)	1.3 (1.3)	7.9 (1.0)*
ΔDBP (mmHg)	−1.3 (0.7)	8.6 (0.8)*	4.2 (0.6)*
ΔHR (bpm)	−0.2 (1.4)	12.4 (0.9)*	−2.2 (0.3)*
ΔO_2Sat (%)	−0.1 (0.1)	0.8 (0.2)*	0.0 (0.1)
Δ$EtCO_2$ (mmHg)	−0.1 (0.2)	−2.0 (0.3)*	0.0 (0.2)

Data are expressed as mean (standard error).
* Significant change with new posture, $p < 0.01$.

(after transition from head-of-bed 30°) and the recovery supine position (after transition from standing, $p < 0.01$ for each parameter). Figure 3 provides bar graphs for average changes in rCBF, THC, HbO_2 and Hb with each posture change for the entire study population.

Among the four cerebral hemodynamic parameters considered, age did not significantly alter the magnitude of postural changes in rCBF ($p = 0.25$), THC ($p = 0.34$) or Hb ($p = 0.60$) in an initial global likelihood ratio test. This test, however, provided evidence of a trend toward significance for age-related HbO_2 postural responses ($p = 0.058$). Subsequent

Table 3. Postural changes in cerebral and systemic hemodynamics for males (M) and females (F) ($N = 60$).

Hemodynamic parameter	Head-of-bed 30° to supine		Supine to stand		Initial supine to recovery supine		Gender effect overall p-value
	M	F	M	F	M	F	
ΔrCBF (%)	−21.3 (2.1)[#]	−15.2 (2.0)[#]	−28.8 (2.1)	−23.8 (2.0)	14.0 (2.6)[#]	5.8 (2.4)[#]	<0.01
ΔTHC (μmol L^{-1})	−2.9 (0.4)[#]	−1.3 (0.4)[#]	−3.2 (0.6)	−2.4 (0.5)	2.6 (0.5)[#]	0.9 (0.5)[#]	<0.01
ΔHbO_2 (μmol L^{-1})	−2.7 (0.4)[#]	−1.5 (0.3)[#]	−4.0 (0.5)	−3.2 (0.4)	2.3 (0.4)[*]	0.7 (0.4)[*]	<0.01
ΔHb (μmol L^{-1})	−0.1 (0.1)[#]	0.2 (0.1)[#]	0.8 (0.2)	0.8 (0.2)	0.3 (0.2)	0.1 (0.1)	0.09
ΔMAP (mmHg)	2.0 (1.2)	0.2 (1.1)	6.8 (1.4)	4.5 (1.3)	6.0 (1.1)	6.4 (1.0)	0.40
ΔSBP (mmHg)	0.9 (1.5)	−0.9 (1.4)	2.2 (2.0)	0.5 (1.8)	7.0 (1.4)	8.2 (1.3)	0.50
ΔDBP (mmHg)	2.2 (1.0)	0.7 (0.9)	10.5 (1.2)	7.4 (1.1)	4.5 (0.8)	4.0 (0.8)	0.23
ΔHR (bpm)	0.5 (0.6)	0.2 (0.4)	15.2 (1.1)[*]	12.4 (0.9)[*]	−2.0 (0.5)	−2.2 (0.3)	0.03
ΔO_2Sat (%)	−0.007 (0.2)	0.2 (0.2)	0.7 (0.2)	0.7 (0.2)	−1.7 (0.2)[*]	0.4 (0.2)[*]	<0.01
Δ$EtCO_2$ (mmHg)	−0.3 (0.3)	0.4 (0.3)	−2.7 (0.4)	−1.7 (0.4)	−0.1 (0.3)	0.2 (0.2)	0.18

Data are expressed as mean (standard error). Values are for the average 40-year-old male versus the average 40-year-old female based on the fit of the linear mixed effects model.
[#] Significant gender effect on postural change, $p < 0.05$.
[*] Significant gender effect on postural change, $p < 0.01$.

investigations of specific postural changes indicated a significant association between age and HbO_2 change during supine-to-standing posture change ($p = 0.01$). Specifically, the magnitude of decline in HbO_2 during the supine-to-standing posture change decreased significantly with age.

Gender was associated with significant differences in overall postural changes in rCBF, THC and HbO_2 ($p < 0.01$ for all parameters) and showed a trend toward an effect on postural changes in Hb ($p < 0.10$) (see table 3). Subsequent investigations of specific postural changes did not demonstrate differences between men and women in the supine-to-standing postural changes for any cerebral hemodynamics parameter. However, women experienced a smaller magnitude of postural change in rCBF, THC and HbO_2 during the transition from head-of-bed 30° to supine position ($p < 0.05$ for the gender effect on all parameters) and during the transition from initial supine to recovery supine position ($p < 0.05$ for the gender effect on rCBF and THC, $p < 0.01$ for the gender effect on HbO_2).

Figure 4 provides scatter plots of the data with fitted lines representing the mean supine-to-standing postural changes in each cerebral hemodynamic parameter for both genders, as predicted from the fitted models. The y-intercepts indicate the mean postural hemodynamic changes for a subject of age 20, while the slopes represent age effects. As discussed above, gender effects were not statistically significant for the supine-to-standing postural changes in any cerebral hemodynamic parameter but were included here so that the models would be consistent for all postural changes. For HbO_2, supine-to-standing postural declines were substantially larger for younger than for older subjects. For example, at age 30, the linear model predicted a mean HbO_2 change for males and females of -4.59 μmol L^{-1} and -3.75 μmol L^{-1}, respectively, while at age 60 the model predicted a mean HbO_2 change for males and females of -2.85 μmol L^{-1} and -2.01 μmol L^{-1}, respectively.

DCS measurements of rCBF correlated weakly, but highly significantly, with NIRS measurements of THC ($R = 0.25$, $p = 0.008$), HbO_2 ($R = 0.30$, $p = 0.002$) and HbDiff ($R = 0.30$, $p = 0.002$) during the supine-to-standing posture change. DCS measurements of rCBF did not correlate with NIRS measurements of Hb ($R = 0.045$, $p = 0.64$).

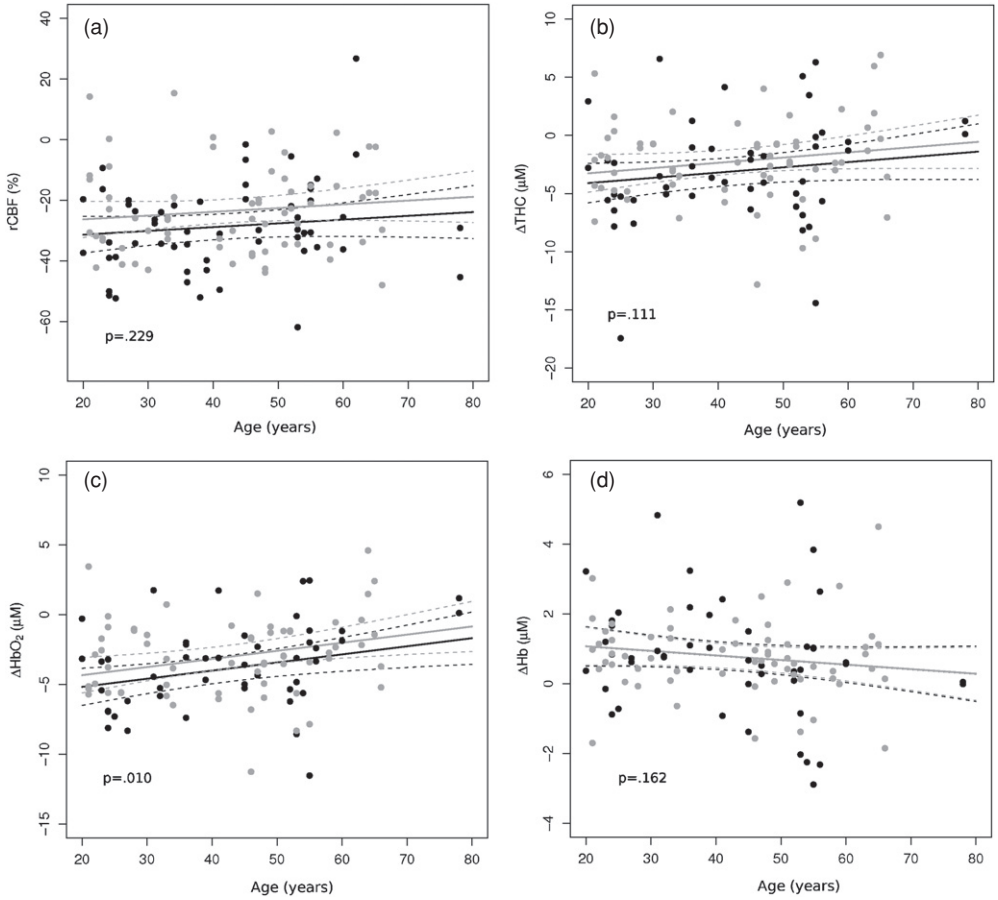

Figure 4. Effect of age on the supine-to-standing postural change in (a) rCBF, (b) THC, (c) HbO_2 and (d) Hb. All data are presented for males (black) and females (gray). Left and right hemisphere values for each subject are shown as separate points. Lines represent the predicted value of a given cerebral hemodynamic parameter as a function of age for men (black) and women (gray). 95% confidence intervals based on our model are shown as dashed lines for men (black) and women (gray), along with *p*-values for the association between age and supine-to-standing posture change in each cerebral hemodynamic parameter. The age effect is only significant for the supine-to-standing postural change on HbO_2 ($p = 0.01$). No significant gender effect was observed for any supine-to-standing postural hemodynamic changes ($p > 0.05$ for all parameters).

3.3. Postural changes in systemic hemodynamics

Table 2 shows the changes in MAP, SBP, DBP, HR, O_2Sat and $EtCO_2$ that occurred with each posture change. All systemic hemodynamic parameters varied significantly with body posture ($p < 0.0001$ for all parameters). No significant changes occurred in the transition from head-of-bed 30° to supine position, but during the supine-to-standing posture change subjects across the age continuum experienced a significant increase in MAP, DBP, HR and O_2Sat ($p < 0.01$ for all parameters). $EtCO_2$ decreased significantly with transition from supine to standing posture across the age continuum ($p < 0.01$). MAP, SBP, DBP and HR all differed significantly between the initial supine position and the recovery supine position ($p < 0.01$ for all parameters).

Age significantly altered the postural changes in HR ($p = 0.002$) and $EtCO_2$ ($p = 0.01$) but not the postural changes in MAP, SBP, DBP or O_2Sat. Older subjects experienced smaller magnitudes of change in HR and $EtCO_2$ during the supine-to-standing posture change. Gender was associated with significant alterations in the magnitude of postural change in HR and O_2Sat, with women having a smaller increase in HR during the supine-to-standing posture change ($p < 0.01$) and a small increase, rather than a decline, in O_2Sat at the recovery supine position, as compared to the initial supine position ($p < 0.01$) (see table 3).

3.4. Correlations between cerebral and systemic hemodynamics

Pearson's correlations demonstrated that mean supine-to-standing changes in rCBF were significantly associated with mean changes in SBP ($R = 0.3$, $p = 0.02$). Postural changes in frontal cortical rCBF, THC, HbO_2 and Hb were not associated with any of the other systemic hemodynamic parameters during the supine-to-standing position change.

4. Discussion

This study provides new insights into the effects of healthy aging on cerebral hemodynamic responses to posture change. The main finding of the study is that healthy aging alters the magnitude of change in frontal cortical HbO_2, but not rCBF, THC or Hb, during supine-to-standing posture change. This age effect was found to be continuous, not one that only becomes significant at the extremes of age. We also demonstrated that posture change significantly alters frontal cortical rCBF, THC, HbO_2 and Hb across the age continuum. This is the first time that the DCS optical technique has been used in conjunction with NIRS to study cerebral hemodynamics in a healthy population. To our knowledge, this study also provides the largest cohort of normative optical data on postural hemodynamic changes in a healthy population, which can serve as a reference for comparative analysis in clinical populations.

The absence of an age-related effect on the magnitude of postural changes in rCBF suggests that aging is not associated with a decline in global autoregulatory function, or more specifically, a decline in the autoregulatory capacity of the anterior cerebrovascular circulation. However, we did demonstrate that aging attenuates the magnitude of frontal cortical HbO_2 decline during supine-to-standing position change, a finding that is consistent with NIRS measurements of postural HbO_2 changes from a recent CA aging study by Kim *et al* (2009b). The incongruity between age-related postural changes in rCBF and HbO_2 may be partly explained by considering prior studies that demonstrate an age-dependent decrease in baseline CBF (Matsuda *et al* 1984, Krejza *et al* 1999). Although our optical instrument does not measure absolute changes in CBF, our observation that there is no age effect on postural changes in relative CBF, when considered in the context of a higher baseline CBF in younger subjects, suggests that there are age-dependent changes in absolute CBF with posture change. Specifically, one would expect a larger absolute decline in CBF during supine-to-standing posture change in younger as compared to older subjects. Assuming no change in frontal cortical oxygen metabolism with posture change (Ouchi *et al* 1999), a larger magnitude of decline in absolute frontal CBF during supine-to-standing posture change may be expected to cause a statistically significant, but clinically insignificant, increase in the magnitude of decline in frontal HbO_2 in young subjects.

Another possible explanation for the incongruity between age-related postural changes in rCBF and HbO_2 is that there are age-dependent effects on shunting of blood around the circle of Willis during posture change. Indeed, a redistribution of cerebral perfusion to the posterior circulation during supine-to-head-up tilt posture change has been demonstrated

across the age spectrum (Warkentin *et al* 1992). Furthermore, there is TCD evidence that posterior circulation, but not anterior circulation, autoregulatory function is compromised in older subjects (Haubrich *et al* 2004, Sorond *et al* 2005), suggesting that older subjects may be less able to redirect perfusion from the anterior to the posterior circulation during posture change.

Other potential explanations for the difference between age-related postural changes in rCBF and HbO_2, such as age-related postural changes in frontal cortical metabolic rate or arterial oxygen saturation, are less likely. With regard to the former, there is no evidence to suggest that frontal cortical metabolic rate is altered by posture change even independent of age. Rather, positron emission tomography experiments have shown that increased metabolism occurs primarily in the cerebellum, visual cortex and midbrain in subjects standing still with eyes open, not in the frontal lobe cortex (Ouchi *et al* 1999). Indeed, we might have expected to observe an age effect on postural changes in Hb, independent of any change in THC, if there were an age-related postural change in frontal cortical metabolic rate. By contrast, we observed statistically significant declines in THC and increases in Hb during the supine-to-standing posture change that were similar for all subjects across the age continuum. With regard to the possibility of age-related changes in arterial oxygen saturation, our pulse oximetry data did not demonstrate any age-related effect on postural changes in O_2Sat ($p = 0.44$).

An implication of the observed incongruity between age-related postural changes in rCBF and HbO_2 is that the hybrid DCS/NIRS optical technique provides an advantage over using NIRS alone for cerebral hemodynamic monitoring because NIRS measurements of HbO_2 are not adequate surrogates for DCS measurements of rCBF. This advantage of the hybrid DCS/NIRS optical technique is underscored by our correlation analyses, which demonstrated that changes in rCBF only weakly correlated with changes in HbO_2 ($R = 0.3$, $p = 0.002$), HbDiff ($R = 0.3$, $p = 0.002$) and THC ($R = 0.25$, $p = 0.008$) during the supine-to-standing posture change. Although these correlations were statistically significant, the relatively low R-values indicate that microvascular rCBF responses are only partially explained by HbO_2 and THC responses. Similar findings were observed in a recent study by Schytz *et al* (2009) in which calculation of a blood flow index using continuous wave NIRS in conjunction with an intravenous tracer did not correlate with ^{133}Xe-SPECT measurements of CBF in a healthy population ($R = 0.133$, $p = 0.732$).

The physiological basis for the weak correlations between DCS and NIRS measurements in healthy populations is not completely clear, but discrepancies are certainly expected in clinical populations for whom perturbations in cortical metabolic rate, intracranial pressure, arterial inflow or venous drainage complicate the relationship between CBF, THC, HbO_2 and Hb. Indeed, absent or weak correlations between postural changes in frontal cortical rCBF and THC have previously been demonstrated in acute ischemic stroke patients ($R = 0.11$, $p = 0.3$) (Durduran *et al* 2009), as well as traumatic brain injury and aneurysmal subarachnoid hemorrhage patients ($R = 0.3$, $p = 0.01$) (Kim *et al* 2009a). These data suggest that DCS measurements of microvascular rCBF cannot be predicted by NIRS measurements of microvascular THC or HbO_2 in either healthy or clinical populations. The DCS/NIRS hybrid optical technique thus may provide a more comprehensive assessment of cerebral microvascular hemodynamics than can be obtained by using NIRS alone.

An unexpected finding in this study was the relatively large magnitude of the mean decline in rCBF during supine-to-standing posture change across the age continuum ($25.9 \pm 1.5\%$). Notably, none of our subjects experienced pre-syncopal symptoms upon standing, and the 95% confidence interval of the postural rCBF decline (23.3 to 28.8%) does not approach the 40% threshold that is associated with onset of pre-syncopal symptoms in healthy young and healthy old subjects (Finnerty *et al* 1954). While there are no prior DCS studies of healthy

subjects to which our data can be compared, TCD studies have found declines in MCA CBF velocity ranging from 15 to 20% in healthy subjects during orthostatic stress (Carey *et al* 2003, Lipsitz *et al* 2000, Sorond *et al* 2005).

In addition, Kim *et al* (2009b) observed an MCA blood flow velocity decline of 16–29% immediately following a supine-to-standing posture change, though this decline was attenuated to 6–15% after 5 min of standing. Alperin *et al* (2005) observed a 12% average decline in global CBF using a vertical gap MRI during supine-to-sitting posture change in ten healthy subjects (average age 39 years old). Though this magnitude of CBF change is smaller than the supine-to-standing rCBF change observed in our study, one would expect that standing causes a larger CBF decline than sitting since venous return of blood to the heart is more compromised in the standing position. It should also be highlighted that our data pertain only to frontal cortical CBF, and there may be regional variations in CBF that contribute differently to the overall effects of posture on global perfusion. Finally, the magnitudes of frontal cortical HbO_2 change (-3.4 ± 0.3 μmol L^{-1}) and Hb change (0.8 ± 0.1 μmol L^{-1}) during supine-to-standing posture change found in our NIRS measurements are consistent with data from prior NIRS studies (Mehagnoul-Schipper *et al* 2000, 2001), suggesting that our optical instrumentation protocol was not systematically flawed.

In order to further evaluate the validity of our optical instrumentation, we performed a *post hoc* comparative analysis of our NIRS measurements with those of two prior NIRS studies. We selected the ten 'young' subjects from our study population whose average age (27.1 years) and age distribution (22–45 years) best match the ages of the young cohorts in the Mehagnoul-Schipper *et al* (2000) and Tachtsidis *et al* (2004) studies. The cohorts from the three studies had similar average BMI (21.9–23.4 kg m^{-2}), SBP (110–118 mmHg), DBP (70–77 mmHg) and HR (61–71 bpm). The supine-to-standing postural changes in the NIRS measurements of ΔTHC, ΔHbO_2 and ΔHb in our study had distributions that were broadly overlapping with all of the NIRS measurements performed in the other two studies except for the ΔHbO_2 changes found by Tachtsidis *et al* (2004) (see table 4). While the results from our study are generally consistent with these prior NIRS data, two possible explanations for the small differences may be that the duration of time at each posture varied between the studies, and the source–detector separation for our study was 2.5 cm, whereas Mehagnoul-Schipper *et al* (2000) and Tachtsidis *et al* (2004) utilized source–detector separations of 5.5 cm and 5 cm, respectively.

The observed 25.9% decline in rCBF is partly attributable to the significant decline in $EtCO_2$ that was found with postural change across the age spectrum, consistent with previous studies of $EtCO_2$ changes during orthostatic stress (Carey *et al* 2003). Assuming that CBF changes by approximately 2–4% for every mmHg change in $EtCO_2$ (Sokoloff 1960), an rCBF change of 4–8% would be expected from the 2.0 ± 0.3 mmHg mean decline in $EtCO_2$ that was found in our study population. Also contributing to the large postural decline in rCBF is the presumed decline in cerebral perfusion pressure, despite the increase in MAP that was measured at the level of the heart. As demonstrated by Harms *et al* (2000), even when MAP measured at the level of the heart remains constant or increases slightly in healthy subjects during supine-to-standing posture change, the calculated MAP at the level of the MCA declines by an average of 19 mmHg after 1 min and 14 mmHg after 5 min. Meanwhile, the postural decline in intracranial pressure is likely smaller (Alperin *et al* 2005), suggesting that the overall effect of supine-to-standing posture change in healthy subjects is a decrease in cerebral perfusion pressure.

We also found significant differences between all cerebral and systemic hemodynamic parameters, except Hb, O_2Sat and $EtCO_2$, at the initial supine position as compared to the recovery supine position. In a *post hoc* analysis we examined the Pearson correlation between

Table 4. Comparisons between 'young' cohorts in the present study, Mehagnoul-Schipper *et al* (2000) and Tachtsidis *et al* (2004)

Variable	Study cohort	Mehagnoul-Schipper *et al* (2000)	Tachtsidis *et al* (2004)
	Baseline characteristics and systemic hemodynamics		
N	10	10	10
Gender	4M, 6F	4M, 6F	8M, 2F
Age (age)	27.1 ± 7.2	27.1 ± 6.9	24 ± 6
Age range (years)	22–45	22–45	Not provided
BMI (kg m^{-2})	23.4 ± 3.2	21.9 ± 3.2	Not provided
SBP (mmHg)	110 ± 15	118 ± 7	Not provided
DBP (mmHg)	70 ± 10	77 ± 6	Not provided
HR (bpm)	71 ± 13	61 ± 7	Not provided
	Supine-to-standing changes in NIRS measurements		
ΔTHC (μmol L^{-1})	−3.1 ± 1.3	0.2 ± 4.9	1.0 ± 2.93
ΔHbO_2 (μmol L^{-1})	−3.9 ± 1.1	−1.2 ± 5.4	−0.57 ± 1.96
ΔHb (μmol L^{-1})	0.7 ± 0.3	1.4 ± 2.4	Not provided

Data are expressed as mean ± SD.

cerebral hemodynamic parameters at the two supine positions. This analysis indicated strong correlations ($R = 0.67$–0.76, $p < 0.05$) for all of the cerebral hemodynamic parameters at the two supine positions, suggesting good reproducibility of the DCS/NIRS measurements. These strong correlations are expected given that the light paths of DCS and NIRS are similar. Durduran *et al* (2009) recently found a similarly high degree of reproducibility in repeated measurements at the supine position in a population of acute, ischemic stroke patients using the same DCS/NIRS apparatus. The significant differences in cerebral hemodynamics at the two supine positions are therefore likely physiological in nature, not due to instrument error. A plausible physiological mechanism that explains these findings is an 'overshoot phenomenon', whereby cerebral perfusion, blood volume and oxygenation all increase transiently when the subject transitions to the supine position from standing. It is likely that if we had observed our subjects for longer than 5 min at the recovery supine position, rCBF, THC and HbO_2 would have ultimately trended down to the levels observed at the initial supine position.

The systemic hemodynamic responses to posture change observed in this study are in general agreement with previous studies showing that aging significantly alters changes in HR, but not MAP, DBP or SBP, during posture change (Jansen *et al* 1989, Mehagnoul-Schipper *et al* 2000). Our finding that only SBP correlated strongly with changes in rCBF during the supine-to-standing posture change differed from the correlations between postural changes in HbO_2 and Hb, and DBP and HR, found by Mehagnoul-Schipper *et al* (2000). A possible explanation for this difference is that the standard error of the mean was quite low for the baseline SBP of our study population, suggesting that our older subjects may have been healthier than the older subjects in the Mehagnoul-Schipper *et al* (2000) cohort. Additionally, whereas Mehagnoul-Schipper compared 18 subjects over 70 years old to 10 subjects under 45 years old, our study included only one subject over 70 years of age.

The observed gender effect on several of the cerebral and systemic hemodynamic parameters was a finding for which we did not generate an *a priori* hypothesis. We included gender effects in our statistical model in order to ensure that any effects we observed for age were independent of gender effects. We are not aware of prior studies of the effect of gender on

cerebral hemodynamic postural changes in a healthy population. It is possible that differences in behavior between the men and women in our study population, such as frequency of exercise, may have affected our cerebral and systemic hemodynamic measurements. We consider our observation of gender effects on postural hemodynamic responses to be a finding that may form the basis for hypothesis generation in future investigations of cerebral hemodynamics.

An important technical consideration relating to our optical instrumentation protocol is that we used the same DPF value in NIRS measurements for all subjects. Prior NIRS aging studies have similarly utilized an age-independent DPF (Mehagnoul-Schipper *et al* 2000, 2001, Tachtsidis *et al* 2004), yet Duncan *et al* (1996) have shown that the DPF may change as a function of age. We therefore performed a *post hoc* analysis to determine whether the utilization of age-specific DPFs from the Duncan *et al* (1996) study would alter our results. For our youngest subject (20 years old), DPFs of 6.06 and 5.39 were used for the 690 nm and 830 nm wavelength calculations. For our oldest subject (78 years old), DPFs of 7.62 and 6.87 were used. The postural changes in HbO_2 and Hb that were calculated for our oldest and youngest subject using these age-specific DPFs all had error bars that included the postural changes that were calculated with our standard DPFs of 6.51 (at 690 nm) and 5.86 (at 830 nm). It therefore appears that the utilization of age-specific DPF values would have had little substantive effect on our results and would have made it difficult to compare our findings with prior NIRS studies that used age-independent DPF values.

Another technical consideration in optical studies of cerebral hemodynamics is variability in skull thickness and cerebrospinal fluid (CSF) layer thickness between subjects. Okada and Delpy (2003) demonstrated with a Monte Carlo simulation model that variations in skull thickness and CSF layer thickness may alter the NIRS detection volume. In analyzing our results to derive physiological property variations, we have assumed that the interrogated brain tissue volumes are determined solely by tissue optical properties and are not age or gender dependent. We do not believe that skull thickness is a factor for our measurements or conclusions. Skull thickness has been shown to vary randomly between subjects in an age-independent and gender-independent manner (Lynnerup 2001) and would not therefore be expected to confound an analysis of age-related postural changes in the optical signal. On the other hand, cerebral cortex thickness has been shown to decrease (Scahill *et al* 2003, Rettmann *et al* 2006) and CSF layer thickness to increase (Murphy *et al* 1992, Gur *et al* 1991) as a function of age-related cerebral atrophy. Similarly, gender may also affect the scalp-to-brain distance, with women being found to have smaller age-related changes in intracranial CSF volume and left hemispheric atrophy than men (Gur *et al* 1991). Finally, intracranial CSF volume may change during posture changes (Alperin *et al* 2005).

From an experimental standpoint, serial radiological imaging of all subjects at different postures to determine inter-subject or postural variations in skull and CSF layer thickness is impractical. Thus, it is extremely difficult to discern whether a substantive systematic error in our study could have been introduced by these age-, gender- or posture-related detection volume physiological changes. Nevertheless, we expect the effects of these potential methodological errors to be ameliorated by the fact that each subject effectively acted as his or her own control. The importance of absolute detection volume is reduced because we are probing the relative changes in cerebral hemodynamics in the same volumes at different postures. As a result, many of the random physiological effects that modify the absolute optical signals are self-normalized. We therefore believe that the present study, as with other optical studies, is accurate to within the methodological limitations of diffuse optics (Hillman 2007).

Another consideration in optical measurements of cerebral hemodynamics is the possibility of extracranial blood flow influencing the optical signal. Our analysis implicitly

assumes that measured differential signals are due only to cortical tissue responses. With our present probe-pad configuration, we believe that there is substantial evidence to suggest that the potential effects of scalp blood flow are minimal. Previous studies performed by our laboratory with the same probe apparatus and source–detector separation have validated DCS measurements of rCBF in critically ill adults using an established tool for measuring CBF, Xenon CT (Kim *et al* 2009a), and have demonstrated in acute stroke patients that postural changes in rCBF differ significantly between the infarcted and non-infarcted cerebral hemispheres (Durduran *et al* 2009). Postural changes in scalp blood flow, which would be expected to be similar on the left and right sides of the head, cannot account for this observed association between the presence of infarction and unilateral alterations in postural rCBF changes. Together, these studies performed in clinical populations indicate that DCS investigates cortical CBF despite potential confounding by scalp blood flow changes.

It should also be noted that our optical instrumentation protocol was designed to provide an assessment of postural changes in cerebral hemodynamics, not an assessment of static or dynamic CA. Static CA is measured by comparing CBF at two steady states after an isolated change in MAP. Dynamic CA has been quantified using a variety of different methodologies, such as by measuring the degree to which acute manipulations in MAP impact CBF, the speed with which CBF returns to baseline after a change in MAP, or the transfer function between spontaneous oscillations in MAP and oscillations in CBF (van Beek *et al* 2008). In contrast to static CA or dynamic CA protocols, our posture change protocol produced additional physiological changes in HR, O_2Sat and $EtCO_2$, not just changes in MAP. We chose this protocol because posture change is an intervention that is commonly performed to alter cerebral perfusion in the clinical setting, and we specifically aimed to provide a normative data set for comparative studies between healthy populations and clinical populations.

5. Conclusion

In summary, this study suggests that healthy subjects across the age spectrum experience significant postural declines in frontal cortical rCBF but that aging does not alter the magnitude of this postural rCBF decline. We demonstrated that the DCS/NIRS hybrid optical technique can be readily used for studying healthy populations in natural postures and that DCS provides cerebral hemodynamic data that cannot be obtained from NIRS measurements alone. Our optical data also provide normative values of frontal cortical microvascular hemodynamics across the age spectrum, to which pathological values can be compared in future studies of clinical populations.

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