Age effects on brain oxygenation during hypercapnia

Rodolfo Gatto
University of Illinois at Chicago
Department of Neurosurgery
Chicago, Illinois 60612

William E. Hoffman
Mark Mueller
Chanannait Paisansathan
University of Illinois at Chicago
Department of Anesthesiology
Chicago, Illinois 60612

Fady Charbel
University of Illinois at Chicago
Department of Neurosurgery
Chicago, Illinois 60612

Abstract. Previous studies showed that the cerebrovasodilation response to hypercapnia is attenuated with aging. The purpose of this study was to determine if normal aging attenuates increases in brain oxygenation during hypercapnia. Prefrontal cortex oxyhemoglobin (OHb) and deoxyhemoglobin (HHb) concentrations were measured in 13 healthy subjects ages 26 to 59 years using a frequency domain tissue oximeter. Measurements were obtained under the following conditions: (1) subject awake breathing spontaneously, (2) during mask ventilation with 21% oxygen, (3) mask ventilation with 100% oxygen, (4) 100% oxygen in a rebreathing circuit to increase end-tidal CO_2. Under baseline conditions breathing room air, there was a negative correlation between baseline OHb and age ($r=-0.60$, $P<0.05$). Ventilation with 100% oxygen increased OHb without a change in total hemoglobin and no affect of age. During mask rebreathing, end-tidal CO_2 increased from 39.5 ± 5.0 mm Hg (millimeters of mercury) to 56.5 ± 5.7 mm Hg, which produced significant increases in OHb and total blood volume that were negatively correlated with age ($r=-0.67$, $P<0.05$) and positively correlated to baseline OHb ($r=0.60$, $P<0.05$). These results indicate that OHb concentrations decreased with age, consistent with attenuated cerebral vasodilation during hypercapnia. [DOI: 10.1117/1.2804705]

Keywords: near-infrared spectroscopy; brain oxygenation; hypercapnia; age.

Paper 07057SSRRR received Feb. 19, 2007; revised manuscript received May 8, 2007; accepted for publication May 9, 2007; published online Nov. 16, 2007.

1 Introduction

Frequency domain–near-infrared spectroscopy (FD-NIRS) allows the measurement of absolute brain oxyhemoglobin (OHb) and deoxyhemoglobin (HHb) concentrations.[1] Reports indicate that cerebral vasodilatory capacity during hypercapnia is decreased with aging.[2] Safonova et al.,[3] found that cerebral vasomotion is decreased and there is an attenuated increase in OHb during breath holding in volunteers aged 38 to 56 compared to younger subjects. Other reports indicate that increases in OHb related to mental stimulation are less in an aged population.[4] This suggests that cerebrovasodilation and enhanced brain oxygenation produced by brain stimulation or hypercapnia are attenuated with aging.

We hypothesized that decreases in baseline OHb and total hemoglobin (tHb) could be related to decreased blood flow and cerebrovasodilatory capacity in the aged.[5–7] The purpose of this study was to determine if baseline OHb concentration and OHb reactivity to hypercapnia are affected by aging. These results could be used to identify normal versus pathological cerebrovascular responses associated with aging.

2 Methods

These studies were approved by the institutional review board, and 13 healthy volunteers with no known cerebrovascular disease gave signed consent.

Address all correspondence to William E. Hoffman, PhD, University of Illinois at Chicago, Department of Anesthesiology, 1740 W. Taylor, Chicago, IL 60612; Tel: 312–996–4018; Fax: 312–996–9018; E-mail: whoffman@uic.edu

2.1 *Instrumentation*

The Oxiplex TS (ISS Inc., Champaign, Illinois) is a FD-NIRS oximeter with multidistance light sources to monitor OHb, HHb, and tHb concentrations.[8] This device utilized multidistance near-infrared light modulated at an RF frequency of 110 MHz to determine regional hemoglobin content in brain tissue in absolute concentration (μmol/L).[9]

Eight laser diodes were coupled to the oximeter by optical fibers that emitted light at wavelengths of either 690 or 830 nm and one detector. The four source-detector distances of the probe were 2.5, 3.0, 3.5, and 4.0 cm in all patients. The probe was placed on the right forehead 2 cm above the eyebrow and 1 cm lateral from the midline and shielded from outside light. OHb and HHb were determined every 2 s. The tHb was calculated as the sum of OHb and HHb and brain oxygen saturation (SbO_2) calculated as OHb divided by tHb and multiplied by 100.

Other data, including noninvasive mean blood pressure, heart rate, inspired oxygen fraction, and end-tidal CO_2 ($ETCO_2$) were collected by computer from a Datex-Ohmeda anesthetic monitor (General Electric, Madison, Wisconsin) every 10 s.

2.2 *Protocol*

Treatment 1 was made with the subject recumbent in a quiet room, with reduced ambient lighting and breathing room air

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Table 1 Brain tissue oxygenation, $ETCO_2$, blood pressure, and heart rate in 13 subjects expressed as mean ± standard deviation.

	Baseline (room air)	Mask (FiO_2 21%)	Mask (FiO_2 100%)	Mask (100% O_2 rebreathing)
SbO_2 (%)	57±7	57±7	62±7[a]	66±8[a]
OHb (μmol/L)	23.8±7.8	23.9±8.2	26.1±9.0[a]	30.1±10.6[a]
HHb (μmol/L)	18.0±7.2	17.7±7.2	15.8±6.5[a]	15.4±6.2
tHb (μmol/L)	41.7±13.6	41.6±14.1	41.8±14.1	45.5±14.7[a]
$ETCO_2$ (mm Hg)		39.9±4.4	39.5±5.0	56.5±5.7[a]
MABP (mm Hg)	109±13	110±13	114±13	124±13[a]
HR (min^{-1})	74+12	76+13	74+11	81+14[a]

[a] $p > 0.05$ compared to previous treatment.
FiO_2=fractional inspired oxygen concentration, MABP=mean arterial blood pressure, HR=heart rate.

for 10 min. Treatment 2 was made with the subject breathing via face mask from the circuit of a Narkomed 2B anesthesia machine (North American Dragger, Telford, Pennsylvania) with CO_2 absorbent removed and gas flow of medical air (21% oxygen) at 10 L/min for 10 min. In treatment 3, medical air was discontinued and 100% O_2 was given at 10 L/min for 10 min. In treatment 4, the gas flow of 100% oxygen was reduced to 200 to 500 cc/min and the adjustable pressure-limiting valve of the circle system was closed, and the subject was allowed to rebreath the gases in the circuit until the volunteer indicated a desire to stop. After rebreathing to an $ETCO_2$ of 50 mm Hg (millimeters of mercury) or greater, the face mask was removed and another 5 min breathing room air was allowed before the monitors were removed.

Data are reported as mean ± standard deviation. Data in each subject were compared over time using a repeated measures analysis of variance with Tukeys tests used for post hoc evaluation. Separate repeated measures analyses of covariance were used to investigate the impact of age, blood pressure, or heart rate on the change in OHb from baseline to the mask rebreathing treatment. OHb, HHb, tHb, and SbO_2 were correlated with age by Pearson product moment correlation. The group size ($n=13$) was calculated to detect a 5% change in total hemoglobin content with a power of 90%, assuming a standard deviation of 5% from normal levels of 40 μmol/L and a significance level of 0.05. The average baseline variation of total hemoglobin under steady state unanesthetized conditions in all patients was 2.0%.

3 Results

The age range of the 13 volunteers in this study was 26 to 59 years, and there were 10 males and 3 females. There were no changes in blood pressure or heart rate until mask rebreathing to increase $ETCO_2$, and this produced a significant increase in blood pressure and heart rate (Table 1). Under baseline conditions, breathing room air, volunteer age was negatively correlated to baseline OHb concentration ($r=-0.60$, $P<0.05$, Fig. 1).

Analysis of covariance indicated there was a significant increase in OHb from baseline to mask rebreathing (OHb: $F=14.48$, $P<0.05$) and this was significantly influenced by age (OHb × age: $F=3.97$, $P<0.05$). The increase in OHb per mm Hg change in CO_2 was negatively correlated with age ($r=-0.67$, $P<0.05$, Fig. 2) and positively correlated to baseline OHb ($r=0.60$, $P<0.05$). There was no significant effect of the increase in heart rate or blood pressure during

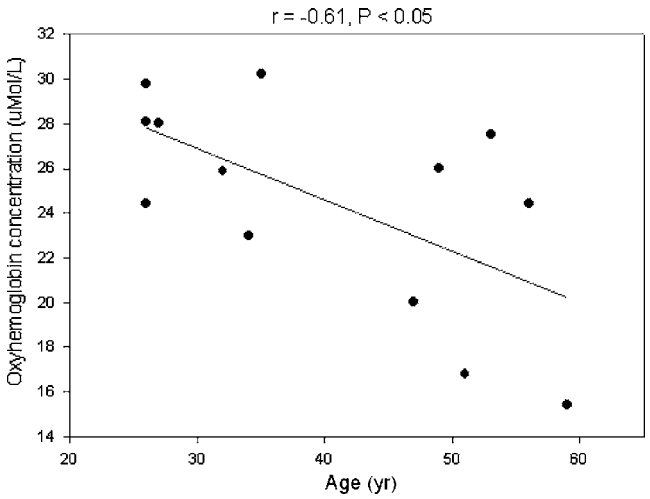


Fig. 1 Baseline brain oxyhemoglobin concentration plotted as a function of age. There was a negative correlation between OHb and age ($r=-0.61$) as indicated in the figure.

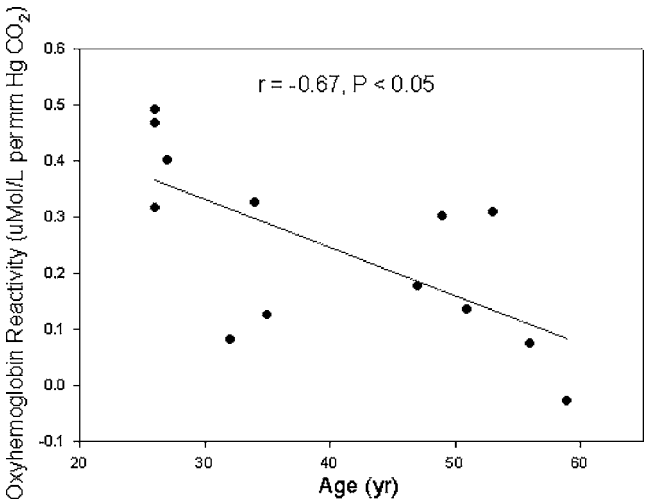


Fig. 2 OHb reactivity during hypercapnia, plotted as a function of age. There was a negative correlation ($r=-0.67$) as indicated in the figure.

hypercapnia and the increase in OHb as determined by analysis of covariance.

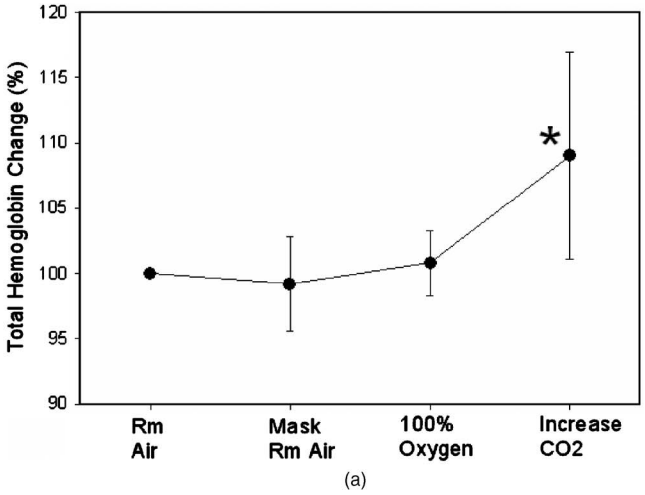
The tHb increased 9% during hypercapnia compared to baseline and this was negatively correlated with age (Fig. 3).

4 Discussion

These results indicate that OHb concentration decreased as a function of aging in volunteers under baseline conditions. There was no age-related effect on brain oxygenation during inspiration of 100% oxygen but the increase in OHb and tHb during hypercapnia was age dependent. The response to CO_2 was also correlated with baseline OHb concentration. These results are consistent with previous reports that cerebral blood flow and the cerebral vasodilatory response to CO_2 were attenuated with age.[2,3,10] Our data indicate that age-attenuated cerebral vasodilation during hypercapnia is related to decreased baseline OHb concentrations.

There is evidence that cerebral hemodynamic changes occur with aging that inhibit maintenance of brain oxygenation during anesthetic and physiological challenges. During brain stimulation produced by oculomotor activity or mental function tasks, cerebral vasodilation and increases in brain oxygenation are attenuated with aging.[11,12] Similarly, cerebral vasodilation produced by hypercapnia is attenuated in aged subjects.[2] During anesthesia, it is reported that aged patients are at greater risk for brain hypoxia due to an inability to maintain cerebral blood flow during decreases in arterial blood pressure.[13,14] Our data suggest that cerebrovascular reactivity and oxygenation during hypercapnia are attenuated with aging.

These results show OHb concentrations decreased with age. It is not clear whether age-related decreases in OHb concentration are linked to decreased cerebral vasodilatory capacity. Buxton[7] showed that enhanced brain oxygenation during brain stimulation is mediated by cerebral vasodilation and an increase in cerebral blood volume. Huppert et al.[15] confirmed this relationship and indicated that the ratio was 0.6 for the change in cerebral blood volume relative to the increase in cerebral blood flow. In this study, tHb, an indication of blood



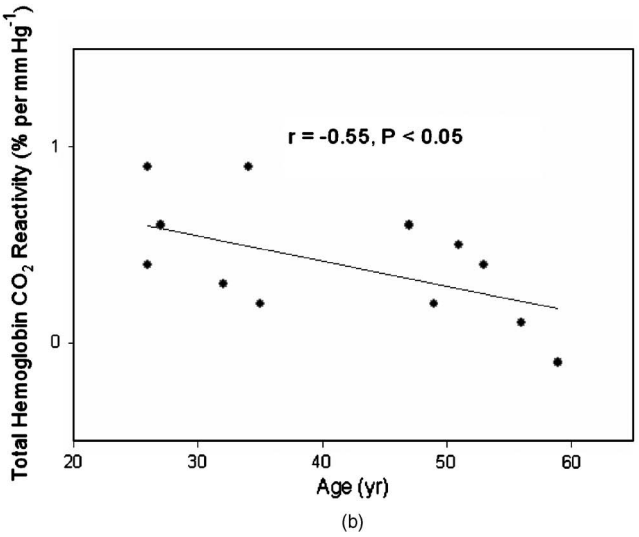


Fig. 3 (a) Total hemoglobin percent changes during oxygen and CO_2 challenges expressed as mean±standard deviation, $*=p<0.05$ compared to previous measure. (b) tHb CO_2 reactivity plotted as a function of age.

volume, increased during rebreathing. This is consistent with cerebral vasodilation. Because OHb decreased with age, this may indicate that decreased brain vascular volume under baseline conditions is related to lower vasodilatory capacity.

It is reported that normal aging can decrease cerebral blood flow in the forebrain and anterior cingulate gyrus.[5,6] This suggests that the decrease in OHb that was related to age may be related to a decrease in cerebral blood flow. In addition, attenuated cerebrovascular reactivity to CO_2 is reported in the aged.[10] The decrease in OHb and tHb reactivity to changes in CO_2 with age may be linked to decreased cerebral blood flow.

It is possible that changes in scalp blood flow during hypercapnia affected brain tissue measures. No attempt was made to correct for skin and scalp flow in this study. Noninvasive NIRS is complicated because the light path to the brain tissue is intersected by scalp, skull, and cerebrospinal fluid. Unless the layered structure is accounted for, measurements could be inaccurate.[16] The dominant factor in near-infrared tissue light transport is scattering, 10 times more probable than absorption. The problem is to determine the absorption

coefficient of hemoglobin separately from the scattering coefficient of the tissue. Steady state intensity near-infrared measurements ascertain the relative absorption of the tissues with no explicit knowledge of the scattering properties available.[9] FD-NIRS uses frequency modulated multidistance light arrays to measure scattering and absorption and determine absolute brain concentrations of OHb and HHb in brain tissue separate from scalp and skull.[1,8] These studies suggest that contamination from nonbrain tissue is minimal.

We noted in this study that there were two clusters of data points above and below the regression lines for baseline OHb—OHb reactivity and tHb reactivity with respect to age. This suggests that throughout the age range of this study, there is a biphasic grouping of subjects with high and low OHb and tHb reactivity, related to baseline OHb. Our finding agrees with a report that patients with low baseline OHb had an attenuated brain oxygenation response to stressful stimulation.[17] It is not clear why there is a biphasic grouping of subjects with high and low baseline OHb, but this is related to CO_2 reactivity.

It is a problem in this study that the sequence of treatments was the same in all subjects and was not randomized. An error of measurement may have occurred due to the systematic treatment. We did not observe a change in brain oxygenation when the volunteer breathed 21% oxygen spontaneously or by mask. This suggests there was stability in the measurement over time. We included 100% oxygen as one of the treatments in order to maintain adequate oxygen in the circuit and avoid any risk of hypoxia during the rebreathing procedure. The changes in OHb and HHb with 100% oxygen alone were consistent with our expectations that there was no age-related difference in the ability to provide oxygen to the brain. We did see age-related differences in brain oxygenation during hypercapnia. This is probably related to an attenuated cerebrovasodilatory to CO_2 in normal aging.[10]

It is possible that increases in blood pressure had an effect to increase OHb independent of the cerebral vasodilating effect of hypercapnia.[18] However, neither heart rate nor blood pressure were significantly related to the increase in OHb during hypercapnia by analysis of covariance. Also, increases in $ETCO_2$ would not disrupt autoregulation. However, increases in cerebral blood flow during hypercapnia may be enhanced by simultaneous increases in blood pressure. In this study, there was no age-related effect of hypercapnia on blood pressure, indicating that the age-related increase in OHb was not pressure related.

In conclusion, these results confirm that OHb decreased as a function of age and suggest that this is related to attenuated brain oxygenation during hypercapnia. The data suggest that baseline OHb concentrations may predict cerebral vasodilation during physiological challenges. This agrees with recent studies that brain hypoxia may occur in neurosurgical patients under normal anesthetic conditions if awake baseline OHb measures are low.[13] The clinical importance of future studies may be to identify the influence of brain pathology with respect to normal aging.

Acknowledgments

This study was funded by the departments of anesthesiology and neurosurgery, University of Illinois at Chicago.

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