Exploratory Analysis of Cerebral Oxygen Reserves During Sleep Onset in Older and Younger Adults

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OBJECTIVES: To explore differences in cerebral oxygen reserves during sleep in old and young adults.

DESIGN: Descriptive cross-sectional study.

SETTING: General clinical research center.

PARTICIPANTS: Nine old (aged 65–84) and 10 young (aged 21–39) adults.

MEASUREMENTS: Subjects were monitored during the first nightly sleep cycle using standard polysomnography, including measures of arterial oxyhemoglobin saturation (SaO₂). Changes in regional cerebral oxymoglobin saturation (rcSO₂) were used to estimate cerebral oxygen reserves. General linear models were used to test group differences in the change in SaO₂ and rcSO₂ during sleep.

RESULTS: Older subjects had lower SaO₂ than young subjects before sleep (baseline) (F(1,18) = 5.1, P = .04) and during sleep (F(1,18) = 10.7, P = .01). During sleep, half of the older subjects and none of the younger ones had SaO₂ values below 95%. In addition, the older subjects had more periods of oxygen desaturation (drops in SaO₂ ≥4%) (chi-square = 24.3, P = .01) and lower SaO₂ levels during desaturation (F(1,18) = 11.1, P < .01). Although baseline values were similar, rcSO₂ decreased during sleep 2.1% in older subjects (F(1,8) = 3.8, P = .05) but increased 2.1% during sleep in younger subjects (F(1,9) = 4.6, P = .04). When the older subjects awakened from sleep, rcSO₂, but not SaO₂, returned to baseline; both returned to baseline in younger subjects.

CONCLUSION: This exploratory analysis generated the hypothesis that lower SaO₂, combined with declines in regional blood flow, contributes to decline in cerebral oxygen reserves during sleep in older subjects. Further study will assess the effects of factors (e.g., medical conditions, subclinical disorders, and sleep architecture) that might account for these differences. J Am Geriat Soc 56:914–919, 2008.

Key words: brain hypoxia; hypoxemia; aging; sleep; oximetry

H uman cerebral function depends upon an uninterrupted oxygen supply. Although the brain accounts for only 2% of body weight, it accounts for nearly 20% of oxygen consumption. On average, 40% of available oxygen is removed from the blood as it passes through the brain, but this still leaves a substantial pool of oxygen (the cerebral oxygen reserve) available for any increases in demand. 1,2 Under normal circumstances, the cerebral oxygen reserve remains fairly stable, because the cerebral vessels regulate regional blood flow to accommodate changes in cerebral perfusion and arterial oxygenation, 3,4 but with age, the cerebral vessels lose some of their ability to maintain this reserve of oxygen, which declines on average by 5% to 10% between the ages of 40 and 75. 5,6 Age-associated reductions in regional blood volume are most often seen in brain areas important for cognition and motor function, namely, the frontal, basal temporal, parietal, and motor cortices. 5

The age-associated decline in cerebral oxygen reserve is more likely to be seen during the first sleep cycle, a period characterized by an overall decline in arterial oxygenation as well as frequent and recurrent fluctuations in arterial oxygenation. 7,8 In general, arterial oxygenation (measured according to pulse oximetry) declines by 1% to 2% during sleep, beginning with Stage 1 and 2 non-rapid eye movement (NREM) sleep. During the transition from wakefulness to sleep, arterial oxygenation fluctuates most during Stage 1 and 2 NREM sleep and then stabilizes at a lower level upon reaching Stage 3 and 4 NREM sleep. This pattern of change in arterial oxygenation during sleep is found in younger and older adults, but older adults are more likely than younger people to have average arterial oxyhemoglobin saturation (SaO₂) values that approach the lower limits of normal (95–96%) and to have periods of desaturation during which SaO₂ levels fall to 92% or less. 9–11
In addition, Doppler ultrasound studies in young adults indicate that the regulation of regional blood flow in response to changing levels of carbon dioxide and oxygen is significantly lower during sleep. Given that older people generally have lower resting cerebral blood flow than younger people, inability of older people to compensate for sleep-related declines in SaO2 would lead to lower levels of cerebral oxygen and smaller cerebral oxygen reserves during sleep than in younger people. In this study, cerebral oximetry was combined with standard polysomnography to evaluate how cerebral oxygen reserves change in old and young adults during the first sleep cycle.

METHODS

Subjects
Nine old (5 men, mean age 76.4) and 10 young (4 men, mean age 25.5) adults were recruited from public advertisements and a subject pool maintained by the Department of Psychology at the University of North Carolina at Chapel Hill. Persons were excluded if they reported lung disorders, myocardial infarction, stroke, diabetes mellitus, seizures, cardiac failure, substance abuse, or exposure to general anesthesia within the previous 6 months. Persons being treated for insomnia or with self-reported symptoms of sleep apnea (snoring or pauses in breathing during sleep, waking with feelings of anxiety or dread), periodic limb movements (kicking or restlessness during sleep or bed linens in disarray), or excessive daytime sleepiness (Epworth Sleepiness Scale score > 10 points) and those currently using antidepressant medications, narcotic analgesics, or sedative–hypnotic drugs were also excluded.

All subjects had normal everyday function, as defined by a Mini-Mental State Examination score of 26 points or higher, an Older Adults Resource Services Activity of Daily Living Scale score of 26 or higher, and a Center for Epidemiologic Studies Depression Scale score less than 15 points. Examination of their polysomnograms (2 hours) showed that all subjects had a respiratory disturbance index of less than five per hour, well below the criteria for sleep apnea. Their central apnea indices were less than three per hour, suggesting that none had severe cardiac disease. On average, both groups had normal body mass indices (BMIs mean ± standard deviation; old, 21.9 ± 3.7 kg/m²; young, 20.4 ± 4.3 kg/m²); only one young adult and none of older subjects had a BMI of 27.0 kg/m² or higher. The university’s institutional committee for the protection of human subjects approved the study. All subjects gave informed consent.

Procedure
The study was conducted at a general clinical research unit funded by the National Institutes of Health. Monitoring began at 10:00 p.m. During the first 10 minutes of recording, subjects lay quietly with eyes closed and lights on. After an uninterrupted 10-minute period of wakefulness, the lights were turned off, and subjects were instructed to fall asleep. Subjects were awakened after completing their first bout of Stage 3 and 4 NREM sleep. At this time, the recording was stopped, the sensors were removed, and the subject left the research unit. Total recording periods ranged from 2.0 to 2.5 hours.

Instrumentation
A standard polysomnogram (consisting of one central and one occipital electroencephalography (EEG) channel, a right and left eye movement channel, and one submental electromyography channel) was used to score sleep states. Standard measures and criteria set by the American Academy of Sleep Medicine were used to detect desaturations, as well as apneas and hypopneas. SaO2 was measured every 0.33 seconds using a Nellcor pulse oximeter (Malinckrodt Inc., St. Louis, MO). Airflow at the nose and mouth was monitored using a single-channel oronasal thermocouple (Pro Tech, Woodville, WA). Respiratory effort was recorded using a respiratory inductance plethysmograph (Ambulatory Monitoring, Ardsdale, NJ).

Regional oxyhemoglobin saturations (rcSO2) were collected every 4 seconds using the INVOS 4100 cerebral oximeter (Somanetics, Troy, MI). The INVOS sensors were applied directly to the forehead, 2 cm above the eyebrow and 2 cm to the right and left of midline. The INVOS 4100 uses near-infrared spectroscopy (NIRS), a noninvasive optical technique, to record regional changes in rcSO2. The validity of NIRS as a means of evaluating changes in rcSO2 has been established under a number of experimental conditions, including measurement of jugular bulb venous oxygen saturation, which is considered an index of mixed cerebral oxygenation; correlation of blood oxygen level with oxygen-level dependent magnetic resonance imaging; and cerebral blood flow as measured using transcranial Doppler sonography. Recent studies using the INVOS 4100 in elderly subjects undergoing surgical procedures indicate that declines of greater than 15% or rcSO2 values of 55% or less are associated with significant declines in cognition. In the present study, the average of rcSO2 values and the average change in rcSO2 from resting baseline to sleep, were used to characterize group differences in cerebral oxygen reserves.

Waveform Processing and Data Analysis
The signals were processed using standard bioelectric amplifiers (Gould Instruments Inc., Akron, OH) and stored to a computer at a sampling rate of 250 samples per second using the Windaq Waveform Acquisition Program (Dataq Instruments Inc., Akron, OH). Standard scoring rules were used to identify sleep onset and to score each subsequent 30-second epoch into one of four states (Stage 1 and 2 NREM sleep, Stage 3 and 4 NREM sleep, REM sleep, and wake after sleep onset (WASO)). Other standard criteria were used to identify segments with EEG arousals and to score the severity of desaturations.

The 30-second epochs were aggregated into 5-minute segments, and the percentage of time spent in each state was calculated for each segment. In 90% of the segments, one state accounted for more than 70% of the segment, and this was the state assigned to that segment. In the remaining 10%, the deepest stage of sleep was assigned to each segment (Stage 3 and 4 NREM, then Stage 1 and 2 NREM, then REM, and then WASO). The average SaO2 and rcSO2 for each 5-minute segment from lights out was then calculated. Differences from the average SaO2 and rcSO2 during baseline (the 10 minutes just before lights out) were used
Subjects (70.3/C6 a result, older subjects spent less time asleep than younger (X2old[df = 2, NREM, Stage 3 and 4 NREM, and WASO. Before each analysis, the data were examined for possible outliers and when found, the analysis was performed with and without the suspected outlier. Because the study was a small-sample exploratory study in an undeveloped area of inquiry, hypothesis generation was favored over strict control of Type I error, and corrections were not used for multiple tests.

Because neither group spent much time in REM sleep (old, 3.1 ± 1.0 minutes; young, 4.5 ± 2.9 minutes), only the segments of NREM sleep were used in this analysis. In addition, the initial analyses indicated that the right- and left-sided measures did not differ from one another overall or in interactions with age group and state. Thus, only the results of the right-side measurements are reported here.

RESULTS

Sleep Measures

Older subjects took longer to fall asleep (26.5 ± 18.7 vs 18.3 ± 7.0 minutes). Although having the same number of periods of wakefulness as younger subjects (2.0 ± 1.8 vs 2.0 ± 0.87), older subjects took almost three times as long to fall back asleep (30.0 ± 27.1 vs 10.6 ± 8.4 minutes). As a result, older subjects spent less time asleep than younger subjects (70.3 ± 31.5 vs 96.0 ± 30.6 minutes, F(1, 18) = 4.5, P = .03). Older subjects spent less time in Stage 1 and 2 NREM sleep (33.3 ± 22.5 vs 49.2 ± 15.8 minutes) but about the same amount of time in Stage 3 and 4 NREM sleep (36.1 ± 18.0 vs 37.2 ± 19.5 minutes). In both groups, EEG arousals were more likely to occur during Stage 1 and 2 NREM sleep than Stage 3 and 4 NREM sleep (X2old[df = 1] = 10.5, P < .01; X2young[df = 1] = 16.7, P < .01).

Arterial Oxyhemoglobin Saturation

Figure 1 shows the distribution of SaO2 values in older and younger adults. Older subjects had lower SaO2 levels at baseline (96.5% ± 0.91% vs 97.5% ± 1.0%) and during Stage 1 and 2 NREM sleep (94.7% ± 1.4% vs 96.7% ± 1.1%) and Stage 3 and 4 NREM sleep (94.7% ± 1.0% vs 96.3% ± 1.1%) than younger subjects. In the total sample, SaO2 levels declined from baseline during Stage 1 and 2 NREM sleep (F(1,18) = 31.0, P < .01) but did not differ significantly between Stage 1 and 2 NREM sleep and Stage 3 and 4 NREM sleep. These trends in SaO2 did not differ between older and younger subjects until WASO, during which SaO2 returned to baseline levels in younger subjects but remained lower than baseline in older subjects (F(1, 8) = 12.1, P < .01). Older subjects also had more segments with desaturations than younger subjects (45.9% vs 18.2%, chi-square = 24.3, P = .01). The majority of desaturations (old, 68%; young, 73%) occurred during Stage 1 and 2 NREM sleep. EEG arousals accompanied slightly more than half of segments with desaturations (old, 64%; young, 63%). Duration of desaturations in older subjects was slightly shorter but essentially equivalent to those in younger subjects (6.9 seconds vs 7.7 seconds). In segments with desaturation, SaO2 values were also lower in older subjects than in younger subjects (mean minimum SaO2: 91.4% ± 1.2% vs 93.3% ± 1.1%, F(1,14) = 11.11, P < .01). Older subjects spent approximately 26% of the time with SaO2 levels less than 92%, while younger subjects spent approximately 7% of their time with SaO2 levels less than 92%.

Cerebral Oxygenation Reserves

As shown in Figure 2, the two groups had similar rSO2 values at baseline (66.8% ± 4.5% in old vs 71.3% ± 6.0% in young), but once asleep, older subjects had significantly lower rSO2 values during Stage 1 and 2 NREM (64.7% ± 1.7% vs 73.5% ± 2.0%), Stage 3 and 4 NREM (63.8% ± 1.9% vs 74.4% ± 1.8%), and WASO (66.5% ± 1.0% vs 71.8% ± 2.3%). Although rSO2 values may range from 15% to 95%, values in healthy populations typically range between 60% and 80%. Two older subjects and none of the younger subjects had mean rSO2 values below 60% during sleep. One young adult and none of the older subjects had a mean rSO2 above 80%.

Upon falling asleep, the two groups exhibited different trends in rSO2 (F(1, 18) = 10.0, P = .006). During Stage 1 and 2 NREM sleep, the mean rSO2 of younger subjects increased 2.2% ± 3.2% from baseline (F(1, 9) = 4.6, P = .04). Although not significantly different from Stage 1 and 2 NREM sleep, during Stage 3 and 4 NREM sleep, the
mean rcSO₂ of younger subjects increased another 0.9%, reaching 74.4% ± 1.8%. (In four subjects, the increase in rcSO₂ was as high as 5.0% and 9.5% during Stage 3 and 4 NREM sleep.) The young subjects’ rcSO₂ returned to baseline levels during WASO (0.8% ± 2.6%). In contrast, the mean rcSO₂ in older subjects decreased 2.1% ± 2.4% (F(1, 8) = 3.8, P = .05) during Stage 1 and 2 NREM sleep and dropped another 0.9% during Stage 3 and 4 NREM sleep. Three older subjects had declines of rcSO₂ between 9% and 11%. Similar as in younger subjects, rcSO₂ during Stage 3 and 4 NREM sleep was not significantly different from Stage 1 and 2 NREM sleep. As with younger subjects, the mean rcSO₂ in older subjects returned to baseline levels during WASO (−0.3% ± 2.7%, F(1, 8) = 0.23).

**DISCUSSION**
To the authors’ knowledge, this study is the first to show that cerebral oxygen reserves, as defined according to rcSO₂, decline during sleep in older adults but increase during sleep in younger adults. Despite these disparate trends in rcSO₂, SaO₂ fell in both groups during sleep. Consistent with previous reports, it was found that SaO₂ levels declined 1% in older and younger subjects. Because older subjects had lower SaO₂ before sleep, they were more likely the reach low SaO₂ levels during sleep. In this study, none of the younger subjects, but half of the older subjects, had a mean SaO₂ less than 95%, a finding that is similar to the reports of others.

Older subjects also had more episodes of oxygen desaturation, but not necessarily longer periods of desaturation, during sleep; overall, older subjects spent more time with SaO₂ levels less than 92%. The average minimum SaO₂ in older subjects was 91.4%, whereas in younger subjects, the average minimum value was 93.3%. This group difference in the percentage of time spent with SaO₂ levels below 92% is important, because studies using transcranial Doppler ultrasound in humans demonstrate that the threshold for compensatory regional vasodilation response to hypoxia occurs at SaO₂ levels much higher than previously reported in animals (at or near a SaO₂ of 90%). The observation that the two older subjects with SaO₂ levels just above 95% at baseline showed the greatest decline in rcSO₂ as they progressed to the deeper stages of NREM sleep further support the idea that low SaO₂ levels introduce a challenge to regional cerebral blood vessels. Thus, although both groups experienced similar declines in SaO₂ during sleep, lower baseline SaO₂ levels and more-severe desaturations make older subjects more likely to experience mild-to-moderate hypoxemia and invoke regional vasodilation to maintain cerebral oxygen reserves during sleep. The primary measure of cerebral oxygenation, rcSO₂, reflects the amount of regional oxyhemoglobin per volume of blood; thus, any change in rcSO₂ represents a change in regional oxyhemoglobin relative to regional blood volume. SaO₂ levels in younger subjects remained well above the threshold required to evoke regional vasodilation, but in at least a few of the older subjects, SaO₂ fell below 90%. It therefore follows that, in some of the older subjects, the decline in rcSO₂ represented a decline in regional oxyhemoglobin that exceeded any rise in regional blood volume. Differences in baseline regional blood volumes might also account for the disparate trends in rcSO₂ in old and young. At least two studies using positron emission scanning reported that resting blood flow to certain regions of the brain declines 5% to 10% between the ages of 40 and 75. Pertinent to the present study is the finding that the frontal cortex exhibits one of the greatest age-related declines in blood flow. Such regional decreases in blood flow may result from a regional decrease in capillary density or from disturbed vasodilatation of local blood vessels. In any case, the result is a limited ability to increase flow in response to challenges like hypoxemia. As a result, oxygen extraction from capillary blood must increase to maintain cerebral oxygen metabolism and tissue function, and this increased oxygen extraction is reflected as a decrease in measured rcSO₂. At least one study indicated that declines in frontal lobe perfusion predict the development of mild cognitive decline in older adults.

Differences in regional oxygen metabolism may also account for the disparate trends in rcSO₂ in old and younger adults. In general, cerebral blood flow is thought to mirror changes in cerebral metabolism. In the frontal cortex, regional brain metabolism in young adults declines from baseline by 5% to 15% during Stage 1 and 2 NREM sleep and 25% to 44% during Stage 3 and 4 NREM sleep. The one exception is during awakenings from sleep, during which, for a few seconds, cerebral blood volume increases above that needed to maintain oxygen metabolism and thus leads to increases in regional oxygen levels.

The finding that rcSO₂ levels in younger subjects increase from waking baseline into the deeper states of NREM sleep suggests that the observed drop in regional blood volume does not occur until the regional oxygen level drops to critical threshold. Until that time, blood volume...
remains at waking levels or lags behind the drop in cerebral metabolism. The observation that rsCO2 levels fell and then returned to baseline levels upon awakening from sleep further suggests that, when one awakens from sleep, regional blood flow is quick to adjust to increases in metabolism and restore regional oxygenation to resting levels.

Unlike in younger subjects, the mean rsCO2 of older subjects declined 2.5% during State 1 and 2 NREM sleep another 1% during Stage 3 and 4 NREM sleep. Although the change in rsCO2 for the group averages were only 2.5%, during Stage 3 and 4 NREM sleep, two of the older subjects had declines in rsCO2 of 9% and 11%. Given that these subjects had resting baseline levels of 60% to 61%, these changes represent a 15% to 18% decline from their baseline rsCO2 values. Given that previous studies have reported that declines of 15% or more from resting baseline are associated with impaired cognition, these modest declines may mark individuals who are at risk for cognitive decline. The fact that rsCO2—but not SaO2—returned to baseline levels upon waking suggests that, although sleep may add to age-associated decline in cerebral oxygen reserves, the ability to awaken from sleep is important for restoring vascular response to hypoxemia in older persons.

Although these data regarding sleep and arterial oxygenation are consistent with those from previous reports, the modest sample size limits the ability to generalize to all older adults. As a necessary first step, a cross-sectional design was used to compare differences between older and younger adults; at present, it cannot be definitively concluded that the observed differences reflect aging per se as opposed to some undiagnosed subclinical disorder in older subjects. Given the interest in examining age-associated differences in cerebral oxygen reserves, the older adults in this study were screened to be in relatively good health and without any apparent functional decline. Although none of the subjects had rsCO2 levels below 55%, a few of the older subjects experienced a fall of more than 15%, levels that previous studies report can also predict functional decline.21–23 Such a finding suggests that these downward trends in cerebral oxygenation during sleep may reflect a preclinical state that marks individuals at risk for functional decline. Following a larger, more-diverse sample over years would allow a comprehensive definition of the clinical significance of the complex relationship between changes in arterial oxygenation, cerebral blood flow, cerebral blood volume, and cerebral oxygen reserves during sleep. Simple, repetitive measurements made with minimally intrusive instruments, like those provided by cerebral oximetry, may provide a way to track falling cerebral oxygen reserves and, perhaps, intervene before significant injury has occurred.

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