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Exploratory Analysis of Cerebral Oxygen Reserves during Sleep Onset in Old and Young Adults

Barbara W. Carlson, RN, PhD[*], **Virginia J. Neelon, RN, PhD**[*], **John R. Carlson, MS**[†], **Marilyn Hartman, PhD**[‡], and **Sunil Dogra, MBBS**[§]

[*]Associate Professor, School of Nursing, The University of North Carolina at Chapel Hill, Chapel Hill, NC

[†]Research Associate Professor, School of Nursing, The University of North Carolina at Chapel Hill, Chapel Hill, NC

[‡]Research Associate Professor, Department of Psychology, The University of North Carolina at Chapel Hill, Chapel Hill, NC

[§]Clinical Associate Professor, School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

OBJECTIVE—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 (65–84yrs) and 10 young (21–39yrs) adults

MEASUREMENTS—Subjects were monitored during the first nightly sleep cycle using standard polysomnography, including measures of arterial oxyhemoglobin saturation (SaO_2). Changes in regional cerebral oxyhemoglobin saturation ($rcSO_2$) were used to estimate cerebral oxygen reserves. General linear models were used to test group differences in the change in SaO_2 and $rcSO_2$ during sleep.

RESULTS—Compared to young subjects, the old had reduced SaO_2, both before sleep (baseline) ($F_{(1,18)}$=5.1, p=.04) and when asleep ($F_{(1,18)}$=5.14, p=.04). During sleep, half of the old and none of the young had SaO_2 values below 95%. In addition, the old had more periods of oxygen desaturation (drops in $SaO_2 \geq 4\%$) (X^2=24.3, p=.01) and lower SaO_2 levels during desaturation ($F_{(1,18)}$=11.11, p<.01). Although baseline values were similar, $rcSO_2$ decreased during sleep by 2.1% in the old ($F_{(1,8)}$=3.8, p=.05) but increased by 2.1% during sleep in the young ($F_{(1,9)}$=4.6, p=.04). When the old awakened from sleep, the $rcSO_2$, but not the SaO_2, returned to baseline; both returned to baseline in the young.

Please address correspondence to Barbara W. Carlson PhD, RN, Assistant Professor, School of Nursing, The University of North Carolina at Chapel Hill, CB 7460 Carrington Hall, Chapel Hill, NC 27599, Phone: 919-966-9416, Fax: 919-966-7298, bcarlson@email.unc.edu. Alternatively, send correspondence to Virginia J. Neelon PhD, RN, Associate Professor, at the same address. Phone: 919-966-1410, Fax: 919-966-7298 vneelon@email.unc.edu.

Contributions: Dr. Carlson affirms that she has listed everyone who contributed significantly to the work. Dr. Carlson was the primary author and played a major role in study concept and design (including obtaining the funding for the work), data collection, analysis and interpretation of the data and preparation of the manuscript. Mr. Carlson performed the statistical analysis, and reviewed and revised the manuscript. Drs. Neelon, Hartman, and Dogra were involved in the study concept and with the interpretation of the results, and review and revision of the manuscript. All authors approved the manuscript.

CONCLUSION—This exploratory analysis generates the hypothesis that lower SaO_2, combined with declines in regional blood flow, contributes to the decline in cerebral oxygen reserves during sleep in the old. Further study will assess the effects of factors (e.g. medical conditions, subclinical disorders, and sleep architecture) that might account for these differences.

Keywords

Brain Hypoxia; Hypoxemia; Aging; Sleep; Oximetry

INTRODUCTION

Human 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 though the brain, but this still leaves a substantial pool of available oxygen (the cerebral oxygen reserve) to cope with 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] With age, however, the cerebral vessels lose some of their ability to maintain this reserve of oxygen, which declines on average by 5–10% between age 40 and age 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 by pulse oximetry) declines by 1–2% during sleep, beginning with the Stage 1 & 2 non-rapid eye movement (NREM) sleep. During the transition from wakefulness to sleep, arterial oxygenation fluctuates most during Stage 1 & 2 NREM sleep, 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 both in young and old adults, but the old are more likely than the young to have average SaO_2 values that approach the lower limits of normal (95–96%), and to have periods of desaturation during which SaO_2 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 diminished during sleep.[12] Given that the old generally have lower resting cerebral blood flow than the young, an inability of the old to compensate for sleep-related declines in SaO_2 would lead to lower levels of cerebral oxygen and smaller cerebral oxygen reserves during sleep when compared to the young. In this study, we combined cerebral oximetry 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 years) and 10 young (4 men, mean age = 25.5 years) adults were recruited from public advertisements and a subject pool maintained by the Department of Psychology. Persons were excluded if they reported lung disorders, myocardial infarction, stroke, diabetes, 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, wakening 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[13] >10 points) as well as 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 Status Examination score > 26 points,[14] an Older Adults Resource Services Activity of Daily Living Scale score > 26,[15] and a Center for Epidemiologic Studies Depression Scale score < 15 points.[16] Examination of their polysomnograms (2 hours) showed that all subjects had a respiratory disturbance index of < 5/hour, well below the criteria for sleep apnea. Their central apnea indices were less than 3/hour, suggesting that none had severe cardiac disease. On average, both groups had normal body mass indices (old = 21.9 ± 3.7 kg/m^2; young = 20.4 ± 4.3 kg/m^2); only one young adult and none of the old had a BMI >27 kg/m^2. 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 an NIH-funded General Clinical Research Unit. Monitoring began at 10:00 pm. During the first 10 minutes of recording, the subject lay quietly with eyes closed and lights on. After an uninterrupted 10-minute period of wakefulness, the lights were turned off and subject was instructed to fall asleep. The subject was awakened after completing their first bout of Stage 3 & 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 EEG channel, a right and left eye movement channel, and one submental EMG channel) was used to score sleep states. Standard measures and criteria set by the American Academy of Sleep Medicine[17] were used to detect desaturations as well as apneas and hypopneas. Arterial oxyhemoglobin saturation (SaO_2) was measured every 0.33 seconds with a Nellcor pulse oximeter (Mallinckrodt Inc, St. Louis, MO). Airflow at the nose and mouth was monitored with a single channel oro-nasal thermocouple (Pro Tech, Woodville WA). Respiratory effort was recorded with a respiratory inductance plethysmograph (Ambulatory Monitoring, Ardsdale NJ).

Regional oxyhemoglobin saturations ($rcSO_2$) 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 a non-invasive optical technique (near infrared spectroscopy or NIRS) to record regional changes in the percentage of oxyhemoglobin ($rcSO_2$). The validity of NIRS as a means of evaluating changes in $rcSO_2$ 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[18]; correlation of blood oxygen level with oxygen-level dependent magnetic resonance imaging[19]; and cerebral blood flow as measured by transcranial Doppler sonography[20]. Recent studies using the INVOS 4100 in elderly subjects undergoing surgical procedures indicate that declines of >15% or $rcSO_2$ values of 55% or less are associated with significant declines in cognition [21–23]. In the present study, we used the average of $rcSO_2$ values and the average change in regional

cerebral oxyhemoglobin saturation ($rcSO_2$), from resting baseline to sleep, 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 computer at a sampling rate of 250 samples per second using the Windaq Waveform Acquisition Program (Dataq Instruments Inc., Akron, OH). Standard scoring rules[24] were used to identify sleep onset and to score each subsequent 30 second epoch into one of four states (Stage 1 & 2 NREM sleep, Stage 3 & 4 NREM sleep, REM sleep, and Wake after Sleep Onset [WASO]). Other standard criteria were used to identify segments with EEG arousals[25] and to score the severity of desaturations.[26]

The 30-second epochs were aggregated into 5 minute segments and the percentage 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 (deepest: Stage 3 & 4 NREM, then Stage 1 & 2 NREM, then REM, and then, WASO). Next, we then calculated the average SaO_2 and $rcSO_2$ for each 5 minute segment from lights out. Differences from the average SaO_2 and $rcSO_2$ during baseline (the first 10 minutes just before lights out) were used to estimate the average change from baseline SaO_2 and $rcSO_2$ for each segment.

Statistical analyses were performed using SAS, version 8.0 (SAS Institute Inc., Cary, NC). A total of 240 segments from the young and 208 segments from the old subjects were analyzed. Chi Square and Student's *t* test statistics were used to describe group differences in state characteristics. Repeated measures ANOVA was used the compare group differences in the subjects' SaO_2 and $rcSO_2$ at baseline, Stage 1 & 2 NREM, Stage 3 & 4 NREM, and WASO. Prior to each to analysis, the data was examined for possible outliers and when found; we performed the analysis with and without the suspected outlier. Since the study is a small sample exploratory study in an undeveloped area of inquiry, hypothesis generation was favored over strict control of Type I error and we did not use corrections for multiple tests.

Since neither group spent much time in REM sleep (old = 3.1 ± 1.0 minutes, young = 4.5 ± 2.9 minutes), we used only the segments of NREM sleep in this analysis. In addition, our initial analyses indicated that the right and left sided measures did not differ from each other overall or in interactions with age group and state. Thus, we report here only the results of the right side measurements.

RESULTS

Sleep Measures

The old took longer to fall asleep (26.5 ± 18.7 versus 18.3 ± 7.0 minutes). Although having the same number of periods of wakefulness as the young (2.0 ± 1.8 versus 2.0 ± 0.87), the old took almost three times as long to fall back asleep (30.0 ± 27.1 versus 10.6 ± 8.4 minutes). As a result, the old spent less time asleep than the young (old = 70.3 ± 31.5 minutes, young = 96.0 ± 30.6 minutes, $F_{(1, 18)} = 4.5$, p=.03). The old spent less time in Stage 1 & 2 NREM sleep (33.3 ± 22.5 versus 49.2 ± 15.8 minutes) but about the same amount of time in Stage 3 & 4 NREM sleep (36.1 ± 18.0 versus 37.2 ± 19.5 minutes). In both groups, EEG arousals were more likely to occur during Stage 1 & 2 NREM sleep than Stage 3 & 4 NREM sleep ($X^2_{old[df=1]} = 10.5$, p<.01; $X^2_{young[df=1]} = 16.7$, p<.01).

Arterial Oxyhemoglobin Saturation

Figure 1 shows the distribution of SaO_2 values in old and young adults. Compared to the young, the old had lower SaO_2 levels at baseline (96.5% ± .91% versus 97.5% ± 1.0%) and during both Stage 1 & 2 NREM sleep (94.7% ± 1.4% verses 96.7% ± 1.1%) and Stage 3 & 4 NREM sleep (94.7% ± 1.0% verses 96.3% ± 1.1%). In the total sample, SaO_2 levels declined from baseline during Stage 1 & 2 NREM sleep ($F_{(1,18)} = 31.0$, $p < .01$), but did not differ significantly between Stage 1 & 2 NREM and Stage 3 & 4 NREM sleep. These trends in SaO_2 did not differ between old and young until WASO, where the SaO_2 returned to baseline levels in the young but remained lower than baseline in the old ($F_{(1, 8)} = 12.1$, $p < .01$).

Compared to the young, the old also had more segments with desaturations (old = 45.9%, young = 18.2%, $X^2 = 24.3$, $p = .01$). The majority of desaturations (old = 68%, young = 73%) occurred during Stage 1 & 2 NREM sleep. Slightly over one half of segments with desaturations 10 were accompanied by EEG arousals (old = 64%, young = 63%). Duration of desaturations in the old was slightly shorter but essentially equivalent to the young (6.9 seconds verses 7.7 seconds). In segments with desaturation, SaO_2 values were also lower in the old than in the young (mean minimum SaO_2: old = 91.4% ± 1.2%, young = 93.3% ± 1.1%, $F_{(1,14)} = 11.11$, $p < .01$). Compared to the young, the old spent approximately 26% of the time with SaO_2 levels less than 92%, while the young spent about 7% of their time with SaO_2 levels less than 92%.

Cerebral Oxygenation Reserves

Shown in Figure 2, the two groups had similar $rcSO_2$ values at baseline (66.8% ± 4.5% versus 71.3% ± 6.0%) but once asleep, the old had significantly lower $rcSO_2$ values during Stage 1 & 2 NREM (64.7% ± 1.7% versus 73.5% ± 2.0%), Stage 3 & 4 NREM (63.8% ± 1.9% versus 74.4% ± 1.8%) and WASO (66.5% ± 1.0% versus 71.8% ± 2.3%). While $rcSO_2$ values may range from 15 to 95%, values in healthy populations typically ranging between 60–80%. [27] Two of the old and none of the young had mean $rcSO_2$ values below 60% during sleep. One young adult and none of the old had a mean $rcSO_2$ above 80%.

Upon falling asleep, the two groups exhibited very different trends in $rcSO_2$ ($F_{(1, 18)} = 10.0$, $p = .006$). During Stage 1 and 2 NREM sleep, the mean $rcSO_2$ of the young increased from baseline by 2.2% ± 3.2% ($F_{(1, 9)} = 4.6$, $p = .04$). While not significantly different from Stage 1 & 2 NREM sleep, during Stage 3 & 4 NREM sleep, the mean $rcSO_2$ of the young increased by another 0.9%, reaching 74.4% ± 1.8% (in four subjects, the increase in $rcSO_2$ was as high as 5.0% and 9.5% during Stage 3 & 4 NREM sleep). The young subjects' $rcSO_2$ returned to baseline levels during WASO (0.8% ± 2.6%). In contrast, the mean $rcSO_2$ in the old decreased by 2.1% ± 2.4% ($F_{(1, 8)} = 3.8$, $p = .05$) during Stage 1 & 2 NREM sleep and dropped by another 0.9% during Stage 3 & 4 NREM sleep. Three of the old had declines of $rcSO_2$ between 9% and 11%. Similar to the young, $rcSO_2$ during Stage 3 & 4 NREM sleep was not significantly different from Stage 1 & 2 NREM sleep. As with the young, the mean $rcSO_2$ in the old returned to baseline levels during WASO (-0.3% ± 2.7%, $F_{(1, 8)} = 0.23$).

DISCUSSION

To our knowledge, this study is the first to show that cerebral oxygen reserves, as defined by $rcSO_2$, decline during sleep in older adults but increase during sleep in young adults. Despite these disparate trends in $rcSO_2$, SaO_2 fell in both groups during sleep. Consistent with previous reports,[10, 28, 29] we found that SaO2 levels declined by 1% in both old and young subjects. Since the old had lower SaO_2 before sleep, they were more likely the reach low

SaO_2 levels during sleep. In this study, none of the young but one half of the old subjects had mean SaO_2 less than 95%, a finding that is similar to the reports of others.[10, 28]

The old also had more episodes of oxygen desaturation, but not necessarily longer periods of desaturation, during sleep; overall, the old spent more time with SaO_2 levels less than 92%. The average minimum SaO_2 in the old was 91.4%, while in the young; the average minimum value was only 93.3%. This group difference in the percentage of time spent with SaO_2 levels below 92% is important because studies using transcranial Doppler ultrasound in humans[30] demonstrate that the threshold for compensatory regional vasodilation response to hypoxia occurs at SaO_2 levels much higher than previously reported in animals (at or near an SaO_2 of 90%). The observation that the two old subjects with SaO_2 levels just above 95% at baseline showed the greatest decline in $rcSO_2$ as they progressed to the deeper stages of NREM sleep, further support the idea that low SaO_2 levels introduce a challenge to regional cerebral blood vessels. Thus, although both groups experienced similar declines in SaO_2 during sleep, lower baseline SaO_2 levels and more severe desaturations make the old subjects more likely to experience mild-to-moderate hypoxemia and invoke regional vasodilatation in order to maintain cerebral oxygen reserves during sleep.

Our primary measure of cerebral oxygenation, $rcSO_2$, reflects the amount of regional oxyhemoglobin per volume of blood; thus, any change in $rcSO_2$ represents a change in regional oxyhemoglobin relative to regional blood volume. SaO_2 levels in the young remained well above the threshold required to evoke regional vasodilatation, but in at least a few of the old, SaO_2 fell below 90%. It therefore follows that, in some of the old, the decline in $rcSO_2$ represents a decline in regional oxyhemoglobin that exceeds any rise in regional blood volume.

Differences in baseline regional blood volumes might also account for the disparate trends in $rcSO_2$ in old and young. At least two studies using positron emission scanning[5, 6] report that resting blood flow to certain regions of the brain declines by 5–10% between age 40 and age 75 years. Pertinent to the present study is the finding the frontal cortex exhibits one of the greatest age-related declines in blood flow.[5, 6, 31, 32] Such regional decreases in blood flow may result from a regional decrease in either capillary density or from disturbed vasodilatation of local blood vessels.[4] 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 in order to maintain cerebral oxygen metabolism and tissue function, and this increased oxygen extraction is reflected as a decrease in measured $rcSO_2$. [33] At least one study indicates that declines in frontal lobe perfusion predict the development of mild cognitive decline in older adults.[31]

Differences in regional oxygen metabolism may also account for the disparate trends in $rcSO_2$ in old and young. 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 5–15% during Stage 1 & 2 NREM sleep and by 25–44% during Stage 3 & 4 NREM sleep.[34, 35] The one exception is during awakenings from sleep where, for a few seconds, cerebral blood volume increases above that needed to maintain oxygen metabolism and thus leads to increases in regional oxygen levels [2, 34, 35].

The finding that $rcSO_2$ levels in the young 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 either remains at waking levels or lags behind the drop in cerebral metabolism. The observation that $rcSO_2$ levels fell 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.

In contrast to the young, the mean $rcSO_2$ of the old declined by 2.5 percent during State 1 & 2 NREM sleep by another 1% during Stage 3 & 4 NREM sleep. Although the change in $rcSO_2$ for the group averages were only 2.5%, it is important to note that during Stage 3 & 4 NREM sleep, two of the old had declines in $rcSO_2$ of 9% and 11%. Given that these subjects had resting baseline levels of 60%–61%, these changes represent a 15%–18% decline from their baseline $rcSO_2$ values. Given that previous studies have reported that decline of 15% or more from resting baseline is associated with impaired cognition[21–23], these modest declines may mark individuals who are at increased risk for cognitive decline. The fact that $rcSO_2$—but not SaO_2—returned to baseline levels upon wakening, suggests that while sleep may add to the 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 our data regarding sleep and arterial oxygenation are consistent with previous reports, the modest sample size limits our ability to generalize to all older adults. As a necessary first step, we used a cross-sectional design to compare differences between old and young adults; at present, we cannot definitively conclude that our observed differences reflect aging *per se* as opposed to some undiagnosed subclinical disorder in the old. Given our 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. While none of our subjects had $rcSO_2$ levels below 55%, a few of the old experienced a fall of greater than 15%, levels that previous studies report can also predict functional decline.[22, 23] Such finding might suggest that these downward trends in cerebral oxygenation during sleep may reflect a preclinical state that marks individuals at risk for functional decline. Clearly, following a larger and 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 us with a way to track falling cerebral oxygen reserves and, perhaps, intervene before significant injury has occurred.

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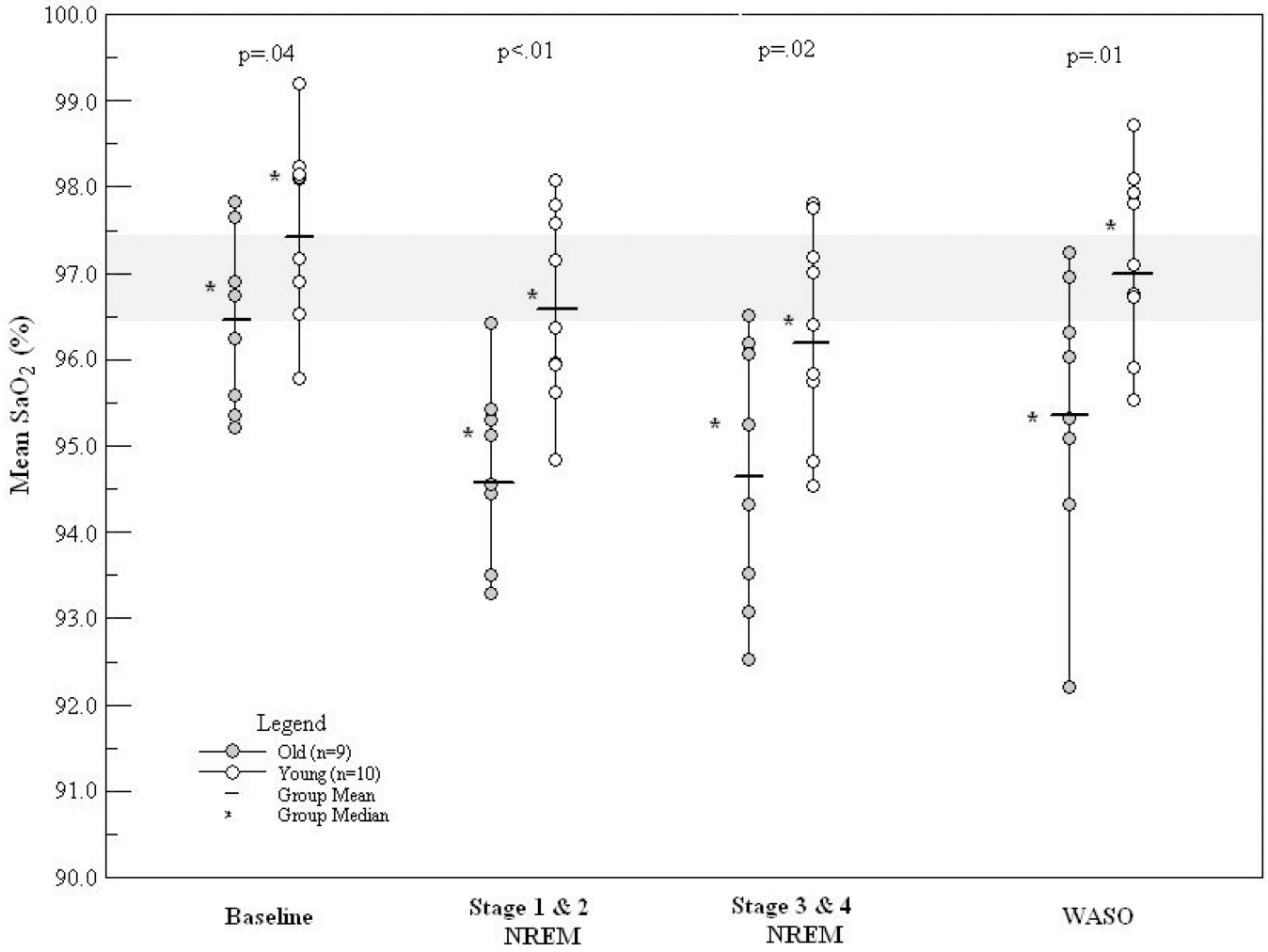

Figure 1.

Group differences in the percent arterial oxyhemoglobin saturation (SaO_2) at baseline, during NREM sleep (Stage 1 & 2 and Stage 3 & 4 NREM) and wake after sleep onset (WASO) in old (filled circles) and young (open circles) adults. The shaded area indicates the boundariesof mean baseline SaO_2 and the bars indicate the group means. The stars indicate the group medians. Within a state category, each point represents the mean SaO_2 of one subject. The values at the top of each category indicate the probability that SaO_2 differs between the two groups.

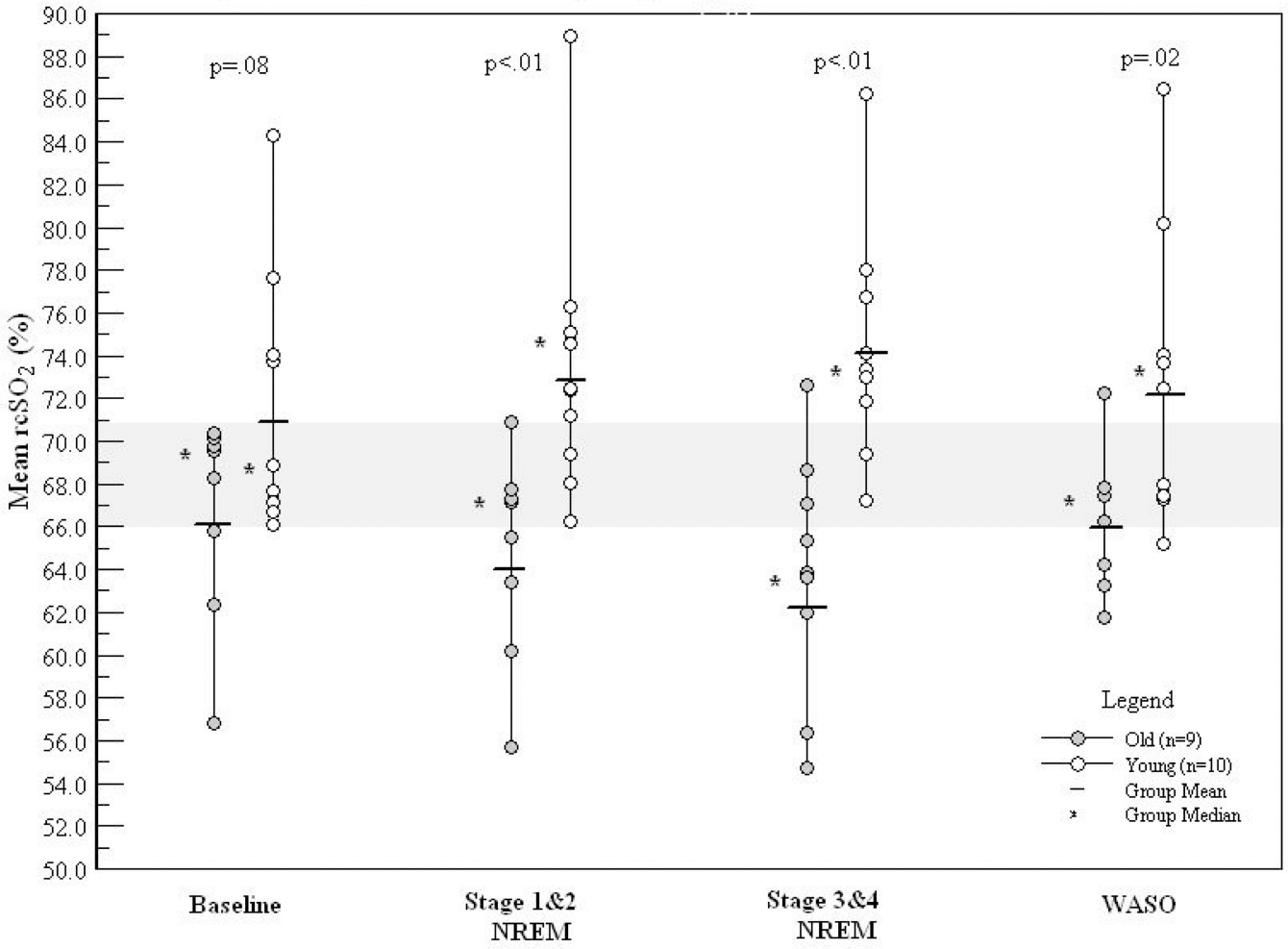

Figure 2.

Group differences in the percent cerebral oxyhemoglobin saturation ($rcSO_2$) at baseline, during NREM sleep (Stage 1 & 2 and Stage 3 & 4 NREM) and wake after sleep onset (WASO) in old (filled circles) and young (open circles) adults. The shaded area indicates the boundaries of mean baseline $rcSO_2$ and the bars indicate the group means. The stars indicate the group medians. Within a state category, each point represents the mean $rcSO_2$ of one subject. The values at the top of each category indicate the probability that $rcSO_2$ differs between the two groups.