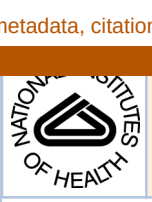

Published in final edited form as:

Biol Res Nurs. 2009 April ; 10(4): 307–317. doi:10.1177/1099800408330396.

Cerebrovascular Disease and Patterns of Cerebral Oxygenation during Sleep in Elders

Barbara Waag Carlson, RN, PhD [Assistant Professor, School of Nursing and Associate Director],
Biobehavioral Laboratory, The University of North Carolina at Chapel Hill, CB# 7460, Carrington Hall, Chapel Hill, NC 27599. PH: (919) 966-7598, FAX: (919) 843-9900, bcarlson@unc.edu

Virginia J. Neelon, RN, PhD [Associate Professor, School of Nursing and Director],
Biobehavioral Laboratory, The University of North Carolina at Chapel Hill,
vneelon@email.unc.edu

John R. Carlson, MS [Associate Research Professor],
School of Nursing, The University of North Carolina at Chapel Hill, carlsonj@email.unc.edu

Marilyn Hartman, PhD [Associate Professor], and
Institute on Aging, The University of North Carolina at Chapel Hill, hartman@email.unc.edu

Sunil Dogra, MBBS, FFARCSI [Clinical Associate Professor]
Department of Anesthesiology and Pain Management, School of Medicine, The University of North Carolina at Chapel Hill, sdogra@aims.unc.edu

Abstract

Purpose—The aim of this descriptive exploratory study was to describe patterns of cerebral oxygen reserves during sleep and their association with cerebrovascular risk factors in elders.

Methods—Participants--115 elders, age 70^{+} years--were monitored overnight using standard polysomnography. Measures included arterial oxyhemoglobin (SaO_2) and regional measures of percent cerebral oxyhemoglobin saturation ($rcSO_2$) via cerebral oximetry. Subjects were classified based on the magnitude of change in $rcSO_2$ from resting baseline to the end of the first non-rapid-eye-movement (NREM) period. One way ANOVA and Chi-square were used to test group differences in SaO_2 and the prevalence of cerebrovascular risk factors.

Findings—20 subjects (Group 1) experienced an increase in $rcSO_2$ during sleep along with sleeping $rcSO_2$ levels ≥ 55%; 95 subjects experienced a decline in $rcSO_2$; 72 subjects (Group 2) had sleeping $rcSO_2$ levels ≥ 55%; and 23 subjects had sleeping $rcSO_2$ levels < 55% (Group 3). Although all three groups had equivalent declines in SaO_2 levels during sleep, Group 3 had more cardiovascular comorbidity than Groups 1 and 2.

Conclusions—While SaO_2 levels decline in most people during sleep, compensatory vascular responses to these drops in SaO_2 are important for preventing $rcSO_2$ from falling during sleep. Those entering sleep with lower baseline $rcSO_2$ levels and those with greater declines in cerebral oxygenation during sleep may have greater cardiovascular burden and be at greater risk for stroke and other forms of disabling cerebrovascular disease.

Keywords

Aging; Sleep; Oxygenation; Cerebral; Arterial; Blood Flow; Instrumentation

Correspondence to: Barbara Waag Carlson.

Introduction

Cerebrovascular disease is commonly seen in and is a common cause of disability in older adults. Population studies indicate stroke affects approximately 12% of elders over age 70 years (Pleis & Lethbridge-Çejku, 2006). In addition, it has been estimated that an additional 28% of elders over age 70 and without any history of stroke have silent brain infarcts and subcortical white matter lesions (Vermeer, Longstreth, & Koudstaal, 2007). These silent brain infarcts and white matter lesions, which are thought to be due to ischemic processes, are associated not only with greater risk of future stroke (Vermeer et al., 2003), but also with neurological impairment (i.e., cognition, balance, and gait) and decline in neurological function in persons with no history of stroke (Prins et al., 2005; Rosano et al., 2005).

Neurons depend upon a constant delivery of oxygen and glucose to form adenosine triphosphate (ATP), a molecule of prime importance to cellular energy metabolism. On average, the brain extracts 40% of available oxygen from the blood passing though it; this leaves a substantial pool of available oxygen (the cerebral oxygen reserve) to cope with any increases in demand (Brown, Wade, & Marshall, 1985). Under resting wakeful conditions, cerebral oxygen reserves remain fairly stable because cerebral vessels regulate regional blood flow to accommodate changes in perfusion and arterial oxygen content (Derdeyn et al., 2002). With age, however, the size of the cerebral oxygen reserve declines because the cerebral blood flow declines by 5–10% between ages 40 and 75 (Larsson et al., 2001; Leenders et al., 1990). These age-associated declines in cerebral blood flow may be due to presence of occult cerebrovascular disease (Naritomi, Meyer, Sakai, Yamaguchi, & Shaw, 1979; Rossini et al., 2004), which eventually leads to either decreased capillary density or impaired vasodilation of local blood vessels (Derdeyn et al., 2002; Naritomi et al., 1979; Terborg, Gora, Weiller, & Rother, 2000). Regardless, the result is a diminished ability to increase blood flow in order to maintain cerebral oxygen metabolism and tissue function (Naritomi et al., 1979).

Figure 1 illustrates how measures of regional oxygenation could be used to identify individuals with diminishing cerebral oxygen reserves (Derdeyn et al., 2002; Nagata et al., 2000). In the early stages, often referred to as Phase I compensation, declines in perfusion and arterial oxygen content stimulate the regional blood vessels to dilate. During this stage, regional oxygen levels do not change as long as the vascular reserve is able to increase regional blood volume (and in effect, increase the supply of oxygen) enough to meet the oxygen needs of the cells. However, once the regional blood vessels reach maximal vasodilatory capacity, Phase II compensation begins.

In Phase II, more oxygen is extracted from the regional vascular compartment than the reserve can replenish. As a result regional oxygen levels decline as the cerebral oxygen reserves become increasingly depleted, which in Phase III can lead to states of increased oxidative stress, cytokine production, inflammation, and the typical markers seen in stroke and other forms of acute brain injury (neurofibrillary tangles, amyloid precursor protein, senile plaques). It is thought that in those with cerebrovascular disease, the ability to regulate regional blood volume declines and over time leads to greater decline in regional oxygen levels and greater risk of cerebral ischemia and stroke.

Previous studies suggest that the first sleep cycle may prove useful in studying cerebral oxygen reserves in older adults. The first sleep cycle corresponds with the period from sleep onset to the end of the first period of non-rapid-eye-movement sleep (NREM). In the frontal cortex, cerebral perfusion falls 5–15% during Stage 1 & 2 NREM sleep and 25–44% during Stage 3 & 4 NREM sleep (Hajak et al., 1994; Madsen, 1991). In addition, the percent arterial oxyhemoglobin saturation (SaO_2 as measured by pulse oximetry) declines by 1–2%

during sleep (Decker, Redline, Arnold, Masny, & Strohl, 1991; Gries & Brooks, 1996). This decline in SaO_2 at sleep onset is found in both old and young adults, but the old often have SaO_2 values that approach the lower limits of normal (95–96%) (Decker et al., 1991; Gries & Brooks, 1996; Naifeh, Severinghaus, & Kamiya, 1987). Not only do the old have lower SaO_2 levels, they tend to also have periods of desaturation during which SaO_2 falls below 90%, a level that previous studies suggest is sufficient for triggering regional compensatory dilation of the cerebral blood vessels (Gupta, Menon, Czosnyka, Smielewski, & Jones, 1997).

In addition, Doppler ultrasound studies in young adults indicate that cerebral blood flow declines during sleep (Hajak et al., 1994; Madsen, 1993) and that there is a marked reduction (of at least 70%) in regional blood flow in response to changing levels of carbon dioxide and oxygen during sleep (Corfield & Meadows, 2006). Given that those with cerebrovascular disease are likely to enter sleep with diminished blood flow, these state-associated declines in vascular compensation could lead to even lower levels of cerebral oxygenation and smaller cerebral oxygen reserves during sleep.

In fact, we have previously reported age-associated differences in cerebral oxygen reserves during sleep (Carlson, Neelon, Carlson, Hartman, & Dogra, 2008). In a study of 9 old (65–84 years) and 10 young (20–40 years) adults, we showed that, though arterial oxygenation (as measured by pulse oximetry) declined by 1–2% during the first sleep cycle in both groups, the old adults spent considerably more time with SaO_2 levels less than 90% (% time asleep: 26% versus 7%). Although the groups experienced similar declines in SaO_2 levels during sleep, we observed that regional measures of percent cerebral oxyhemoglobin saturation ($rcSO_2$) during sleep declined on average by 2.1% in the old while increasing by 2.1% in the young. This finding led us to hypothesize that the observed decline in $rcSO_2$ during sleep in the old was due to a limited ability of the cerebral blood vessels to increase flow in response to challenges such as hypoxemia (leading to Phase II compensation). That is, when arterial oxygen levels fell, oxygen extraction from capillary blood increased in order to maintain cerebral oxygen metabolism and tissue function, and this increased oxygen extraction was manifested as a decrease in regional cerebral oxygen reserves (Derdeyn et al., 2002). To explore this hypothesis, we examined patterns of cerebral oxygenation (primarily via measures of the change in $rcSO_2$) and their relationship to arterial oxygenation during sleep and cerebrovascular risk factors in a sample of 115 community dwelling older adults.

Methods

Participants

Volunteers over the age of 70 years were recruited by word of mouth, fliers posted at retirement communities and senior centers, and advertisements placed in local newspapers. Individuals with a history of a sleep disorder or chronic respiratory disease, such as asthma, COPD, or interstitial lung disease were excluded from participating, as were persons with a history of seizures, 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, periodic limb movements, or excessive daytime sleepiness as well as those currently using antidepressant medications, inhalers, narcotic analgesics, or sedative-hypnotic drugs were also excluded. The Institutional Committee for the Protection of Human Subjects approved the study and all participants gave informed consent.

Of the 167 volunteers that expressed an interest in participating, 38 were excluded because the person was under 70 years of age ($n = 25$) or had a history of sleep apnea, depression, or dementia ($n = 13$). An additional 11 were eligible but decided not to participate due to lack of interest ($n = 2$), acute change in health ($n = 6$) or scheduling conflicts ($n = 3$). A total of

118 completed a laboratory screen but 3 dropped out after the screen either due to acute changes in health ($n = 2$) or scheduling conflicts ($n = 1$).

The resulting study sample of 115 elders was predominantly female (64%) and Caucasian (86%), and their ages ranged from 70 to 92 years (mean = 78.3). All had normal cognitive and physical function, defined as a score above 27 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) and a score of 14 or more on the OARS Independent Activities of Daily Living Scale (Fillenbaum, 1978). All participants scored below 5 points on the Geriatric Depression Scale (Yesavage, 1983), indicating little or no depressive symptomology.

While 34% ($n = 39$) had poor sleep quality as indicated by a Pittsburgh Sleep Quality Index (Buysse, 1989) score > 5 points, none had a score > 8 points, which would have indicated severely disturbed sleep. Examination of their polysomnograms confirmed that our screening efforts were successful in excluding subjects with sleep apnea. The participants' sleep recordings further showed that all participants had a respiratory disturbance index of < 10, indicating that they had little or no sleep disordered breathing. Their mean SaO_2 during sleep was 95.9% ± 1.9%. Only one participant had a central sleep apnea index > 5 per hr.

Setting and Design

Participants spent two weekday nights (5pm–6am) at our laboratory. Each slept in a private bedroom, which was designed to emulate a hotel room. The bedroom was separate from the subject-monitoring station and was equipped with an infrared camera and room microphones for observing the participant.

Monitoring began at 11:00 pm and continued until 6:00 am the following morning . The first night served as a habituation night, allowing the participant to become familiar with sleeping in the laboratory prior to data collection on Night 2. On the day between study nights, participants were asked to maintain their typical daytime routines between the time they left the unit after breakfast (8:00 am) and returned for dinner (5:00 pm).

Subject Procedures

In the first 10 min of recording, the participant laid quietly with eyes closed and lights on, with the polysomnogram being used to verify that the subject remained awake during this initial period. Afterwards, the lights were turned off, and the participant was instructed to try to fall asleep. The participant was then awakened at 6:30 am.

Sleep monitoring included standard polysomonography (consisting of bilateral eye movement [EOG] channels, a central and an occipital electroencephalogram [EEG] channel, and one submental electromylogram [EMG] channel) and cardiorespiratory monitoring (electrocardiogram [ECG], oro-nasal thermocouple, inductance plethysmograph). Arterial oxyhemoglobin saturation (SaO_2) was measured every 3 s with a Nellcor pulse oximeter (Mallinckrodt, Inc., St. Louis, MO). Regional cerebral oxyhemoglobin saturation ($rcSO_2$) was measured every 4 s 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. These waveforms were stored to the file as the subject's polysomnogram.

The following procedures were performed to assure the accuracy of measurements (Carskadon, 1996; Keenan, 1999). Sensor impedances were checked manually at the start and end of each session to ensure that impedances remained between 1.0 and 5.0 kilohms. Instrument calibrations, using known standards, were done at the start and end of each session to ensure the accuracy of the EEG, EMG, EOG, pulse oximetry, and inductance

plethysomography measurements. A difference of no more than ± 2% from the standard was maintained across each night of study. Standard biological calibrations (blinking, close/open eyes, breath holding on inhalation/exhalation, a sigh and a cough) were also performed at the start and end of each study to ensure accurate detection of eye movements, alpha activity, body movements, and apneas.

Description of Near Infrared Spectroscopy

The INVOS 4100 uses a noninvasive optical technique called near infrared spectroscopy (NIRS) for measuring the relative change in cerebral oxygenation and blood volume. The method relies upon the differential absorption properties of hemoglobin in the near infrared region between 700 and 1000 nm. At 760 nm, hemoglobin occurs primarily in the deoxygenated form, while at 850 nm, it occurs in the oxygenated state. The INVOS uses the difference in absorbance of these two wavelengths to measure change in regional blood volume (or change in total hemoglobin). The ratio of the amount of oxygenated hemoglobin to total hemoglobin (oxygenated + deoxygenated) is used to estimate the percent oxyhemoglobin ($rcSO_2$). Since the venous blood accounts for approximately 80% of the regional vascular compartment, changes in $rcSO_2$ primarily reflect the pool of oxygen that remains after metabolism and ranges between 60% and 80% (Madsen & Secher, 1999).

The validity of NIRS in evaluating changes in $rcSO_2$ has been established under a variety of experimental conditions, including jugular bulb venous oxygen saturation, which is considered an index of mixed cerebral oxygenation (Pollard et al., 1996); blood oxygen level dependent changes as measured by blood oxygen-level dependent magnetic resonance imaging (Mehagnoul-Schipper et al., 2002); and cerebral blood flow as measured by transcranial Doppler sonography (Hirth, Obrig, Valdueza, Dirnagl, & Villringer, 1997). Although the INVOS 4100 measures only a small portion of the cortex, correlations with jugular venous bulb, a global measure of cerebral oxygenation, during carbon dioxide challenges range from .90 for within-subject changes to .77 for between-subject comparisons (Kim et al., 2000; Pollard et al., 1996).

Signal Processing and Data Analysis

Although we collected data for the entire night, we restricted our analysis to the first sleep cycle because previous studies of young adults (Madsen, 1993) found that the greatest changes in cerebral blood flow and metabolism occurred during the transition from wakefulness to NREM sleep. Additionally, our previous study found that $rcSO_2$ levels dropped significantly from wake baseline during the first NREM sleep cycle (Carlson et al., 2008).

The data streams were first screened for invalid observations and periods when subjects were out of bed. Standard scoring rules (Rechtschaffen & Kales, 1968) were used to identify sleep onset and to score each subsequent 30-s epoch into one of four states: the two major stages of NREM sleep (Stage 1 & 2 NREM sleep, Stage 3 & 4 NREM sleep), rapid-eye-movement (REM) sleep, and wake after sleep onset (WASO). A high level of interrater agreement (95%, Kappa = .92) was maintained across all records. Next, the 30-s epochs were aggregated into 5-min segments, and segments with at least 60% scored as sleep were used in the analysis. We then calculated the average SaO_2 and $rcSO_2$ for each valid 5-min segment. Differences from the average SaO_2 and $rcSO_2$ during baseline (the first 10 min just before lights out) were used to estimate the average change from baseline SaO_2 and $rcSO_2$ for each segment of sleep.

As in our previous study, we first examined how the baseline, sleeping and average change in $rcSO_2$ ($\Delta rcSO_2$) from wake baseline to sleep differed across subjects. We identified

variables and cutpoints for dividing the group into different patterns of cerebral oxygenation reserves. Using these categories of cerebral oxygen reserves, we then used repeated measures ANOVA to test for group differences in SaO_2 during sleep.

Since we were also interested in the potential application of this method for grading cerebrovascular pathology, we explored how the groups differed on the vascular, heart, and metabolic subscales from the Cumulative Illness Scale of Geriatrics (CIRS-G; Linn, Linn, & Gurel, 1968). The CIRS-G was administered by a certified geriatric nurse practitioner (NP), who scored the scale after a complete history and physical examination. For each subscale, the NP rated the participant's health based on a series of conditions. For example, the NP scored the heart subscale based on medical history (myocardial infarction, angioplasty or coronary artery bypass graft) and on physical exam findings (the presence of murmurs, atrial fibrillation, and blocks, and the number of cardiac medications). Each subscale ranges from 0 (no problem) through 2 (moderate disability/requires first-line therapy) to 4 (extremely severe/needs immediate treatment). In this analysis, we used a cutpoint of 2 points on each subscale to indicate clinically significant pathology. Chi-square statistics were used to test for group differences in cerebrovascular risk variables. Since the study was an 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.

Results

Trends in Cerebral Oxygenation During Sleep

On average, the sample took 16.8 min to fall asleep. Once asleep, they spent over 88% (range 70%–92%) of the first sleep cycle sleeping. As one would expect during the first sleep cycle, subjects spent over 85% of their time in NREM sleep. The range of $rcSO_2$ at baseline and during sleep was 43% to 81%. The mean $rcSO_2$ at baseline was 61.5% ± 7.4%; on average, the mean $rcSO_2$ fell to 60.7% ± 7.7% in sleep ($t_{df=2} = -3.22$, $p = .002$).

Figure 2 shows the mean right, the mean left and the average of right- and left-sided $rcSO_2$ measures of subjects at wake baseline, during the major stages of sleep, and during periods of WASO. The shaded area extending along the y-axis marks the area that represents $rcSO_2$ values within ± 1 standard deviation from wake baseline. Using the shaded area as a point of comparison, the greatest change in $rcSO_2$ occurred during both stages of NREM sleep. On average, $rcSO_2$ levels fell by 1.0% during Stage 1 & 2 NREM sleep and by 0.7% during Stage 3 & 4 NREM sleep. Segments of REM sleep were essentially equal to baseline (Δ $rcSO_2 = -0.2\%$), and the values were slightly higher (Δ $rcSO_2 = +.40\%$) than baseline levels in segments of WASO.

The $rcSO_2$ levels were slightly lower on the right side than on the left, but the difference was negligible ($p = .98$). Since previous studies (Hajak et al., 1994; Madsen, 1991) found that changes in blood flow and cerebral metabolism occurred equally on both sides of the frontal cortex (which corresponds to the cortical areas located directly under our sensors), we elected to use the mean of right and left, rather than one side alone, to characterize patterns of $rcSO_2$ during sleep. Since the greatest change in $rcSO_2$ was observed during Stage NREM sleep, we also limited our analyses to segments of NREM sleep.

Patterns of Cerebral Oxygenation During Sleep: Baseline and Sleep

Using the same procedure as in our previous studies (Carlson, Neelon, Carlson, Hartman, & Dogra, 2005; Carlson et al., 2008), we divided the subjects into groups based on whether the $rcSO_2$ rose during sleep or not. Figure 3 shows how the mean $rcSO_2$ and change from baseline $rcSO_2$ during sleep varied across subjects. Depending upon the individual subject,

the average change the in $rcSO_2$ varied from −7.5% to +6.5% (y-axis). The average $rcSO_2$ during sleep ranged from 38% to 81% (x-axis).

An increase in $rcSO_2$ was defined as an average $\Delta rcSO_2$ >1%. We used this cutpoint because the repeatability of $rcSO_2$ measures from the INVOS is reported to be within ±1% (http://www.somanetics.com). Although our within-night repeatability of baseline $rcSO_2$ measurements was much smaller, at ± 0.39% (Carlson et al., 2007), we decided to use this more conservative cutpoint in order to prevent miscoding increases in rcSO2.

Only 20 subjects experienced a rise in $rcSO_2$ during sleep (Group 1); all of these subjects had $rcSO_2 \geq 55\%$ both at baseline and during sleep. Of those who experienced no rise or a decline in $rcSO_2$ during sleep ($n = 95$), most ($n = 72$) also had sleeping $rcSO_2$ values ≥ 55% (Group 2). Since none of the subjects in Group 1 had $rcSO_2$ levels below 55%, a level which is 5% lower than the expected range for $rcSO_2$, we used an empirical cutpoint of < 55% to identify a third group in whom $rcSO_2$ declined during sleep and average $rcSO_2$ values were < 55% (Group 3).

As one would expect, significant differences between groups were observed both at baseline ($F_{(2, 113)} = 50.8$, $p < .0001$) and during sleep ($F_{(2, 113)} = 54.7$, $p < .0001$). Post-hoc comparisons (Tukey's method) showed that Group 3 had significantly lower $rcSO_2$ levels than the other groups during both periods. The mean $rcSO_2$ in Group 3 was 52.3% ± 4.7% at baseline (range: 43%–60%) and 49.9% (range: 37%–55%) during sleep. Although Groups 1 and 2 had equivalent $rcSO_2$ levels during sleep, Group 1 had significantly lower baseline $rcSO_2$ values than Group 2 (61.7% ± 6.9% versus 64.6% ± 7.1%, $F_{(1, 89)} = 78.4$, $p < .0001$). Although Groups 2 and 3 both experienced a decline in $rcSO_2$, the magnitude of decline in $rcSO_2$ during sleep was significantly greater in Group 3 than in Group 2 (−2.4% ± 2.4% versus −1.0% ± 1.6%, $F_{(1, 92)} = 9.0$ $p = .004$).

Arterial Oxyhemoglobin Saturation in Cerebral Oxygen Patterns

Figure 4 shows group differences in the average arterial oxygenation (SaO_2) at baseline and during sleep. The groups entered sleep with equivalent SaO_2 levels (baseline average: 96.5% ± 1.5%), and once asleep they dropped by similar amounts, on average to 95.9% ± 2.1%. Approximately a third of the subjects in each group had mean SaO_2 level < 95%, which is considered to be the lower limit of normal (95–96%). Not shown in Figure 4, however, is the fact that Groups 2 and 3 spent significantly more time asleep with SaO_2 levels < 90% than Group 1 ($F_{(2, 113)} = 32.4$, $p < .001$). On average, Groups 2 and 3 spent 10–15% of the time asleep with $SaO_2 < 90$, while no subject in Group 1 spent more than 5% of the time asleep with SaO_2 levels < 90%.

Cerebrovascular Risk Factors

Table 1 lists the prevalence of cerebrovascular risk factors for the three groups. Compared to the other groups, Group 3 had a higher degree of illness burden as indicated by the total scores on the Cumulative Illness Rating Scale for Geriatrics ($F_{[df=2, 114]} = 3.6$, $p = .01$). Since we specifically excluded persons with a debilitating level of illness (3 or higher on any item), higher total scores primarily reflect a greater number of organ systems with mild to moderate levels of severity. Hypertension and cardiac disease was equally prevalent in all three groups, but Group 3 had significantly more persons with diabetes ($X^2_{(df=20)} = 7.5$, $p = .02$). As a result, individuals in Group 3 were more likely to have both hypertension and diabetes ($X^2_{(2, 115)} = 9.5$, $p < .004$).

Discussion

The current study findings are consistent with our earlier report (Carlson et al., 2008) indicating that cerebral oxygenation, as defined by $rcSO_2$, declines in most older adults during sleep (all but 20 adults in our current sample). Despite the disparate trends we observed in $rcSO_2$, SaO_2 fell in all three groups. Consistent with previous reports (Decker et al., 1991; Gries & Brooks, 1996; Naifeh et al., 1987), these levels declined, on average, by 1%. As in our previous study, the trends in $rcSO_2$ did not necessarily parallel changes in SaO_2 levels during sleep. These findings suggest that even in the face of lower SaO_2 levels, cerebral oxygen levels decline only when cerebrovascular mechanisms become impaired.

Our primary measure of cerebral oxygenation, $rcSO_2$, reflects the amount of regional oxyhemoglobin per volume of blood; thus, changes in either regional oxyhemoglobin or regional blood flow can affect this measure. For example, in young adults with orthostatic hypotension, $rcSO_2$ drops in parallel with drops in regional blood flow, as measured by transcranial Doppler (Harms et al., 2000). In studies involving experimentally induced hypoxemia, which would cause SaO_2 levels much lower than seen in this study (Shah et al., 2000), $rcSO_2$ has been shown to fall in parallel with changes in jugular bulb venous oxygen saturation, which reflects change in global cerebral oxygen extraction.

In this sample of 115 older adults, only 20 subjects (17%) experienced an increase in $rcSO_2$ during sleep (Group 1). This group shared many characteristics with the young adults (age 20–40 years) in our previous study, who also experienced a rise in $rcSO_2$ during sleep. As with the young adults, Group 1 had fewer desaturations that resulted in drops in SaO_2 levels to 90%. While further research is necessary to determine the significance of this finding, the fact that this pattern of cerebral oxygenation is also found in young adults may suggest that this pattern reflects a cerebral vasculature that is functioning optimally to maintain its reserve of regional oxygen.

Compared to Group 1, Groups 2 and 3 were more likely to have SaO_2 levels < 90%. A previous study showed this reduction to be sufficient to evoke regional vasodilation of the cerebral capillaries (Gupta et al., 1997). Although both groups experienced a decline in $rcSO_2$ during sleep, subjects in Group 2 appeared to be able to mount an adequate compensatory vascular response to the drops in SaO_2 because they were able to maintain $rcSO_2$ levels above 55%. In contrast, Group 3 may have had more severe disturbance in regional blood flow regulation because, although their baseline SaO_2 levels did not differ from the others at baseline, they had $rcSO_2$ levels < 55% at baseline and their $rcSO_2$ levels dropped even more (by another 1–8%) as their SaO_2 levels dropped during sleep.. While not conclusive, this finding suggests that those in Group 3 had lost some of their ability to increase regional blood flow in response to hypoxemia during sleep.

The observation that Group 3 had significantly higher levels of illness burden, particularly hypertension and diabetes, may help to explain the significant declines in their $rcSO_2$ levels. In hypertension, atherosclerotic changes occur in the large and small cerebral arteries. Together with reduced autoregulation, these changes can result in regional decreases in cerebral blood flow, which ultimately leads to a rise in the amount of oxygen extracted from the circulating blood (Derdeyn et al., 2002). In addition, the risk of an ischemic stroke is increased in patients with diabetes mellitus, and outcomes after stroke in diabetics are worse compared to those of nondiabetic subjects (Kaarisalo et al., 2005). Whether through chronic states of hyperglycemia or insulin resistance, diabetes appears to have adverse effects on endothelial function and permeability of the blood-brain barrier (Jimenez-Bonilla et al., 2001; Last et al., 2007). In addition, chronic hyperglycemia and insulin resistance also leads to increased anaerobic metabolism, which can further exacerbate existing cerebral ischemia

via the release of oxidative stress mediators and other cell-damaging pathways (Newman, Bang, Hussain, & Toole, 2007). Of relevance to this study, diabetes is associated with significant declines in regional blood flow within the frontal regions of the brain (Jimenez-Bonilla et al., 2001; Last et al., 2007).

The fact that Group 2 experienced declines in $rcSO_2$ is also relevant when one considers that cerebral disease is a chronic condition whereby atherosclerotic plaques and endothelial changes develop over several years before diagnosis. Although Group 2 had less cardiovascular comorbidities than Group 3, the fact that $rcSO_2$ levels fell in Group 2 suggests that the mechanisms that regulate regional blood volume are being taxed. Perhaps, if not treated, many of the subjects in Group 2 would eventually develop significant disease and begin to spend more time with $rcSO_2$ levels less than 55%.

The clinical implications of these findings are many. While it is known that traditional cardiovascular risk factors (hypertension, smoking, dyslipidemia, and diabetes) are associated with increased risk of vascular dementia, a growing body of work is suggesting that cerebrovascular disease also adds to the risk of developing Alzheimer's disease (Launer et al., 2000; Ott et al., 2004; Ott et al., 1999). At the time of this study, there were few techniques for evaluating the status of cerebral blood vessel function. However, with the introduction of methods that can be used to measure various aspects of small-vessel resistance (i.e., arterial stiffness) and more sensitive techniques for evaluating cerebral small-vessel disease (e.g., diffusion tensor imaging) and oxygen extraction (e.g., blood-oxygen-level-dependent magnetic resonance imaging), it may be possible to determine the clinical significance of the group differences observed in this study.

Although cerebral oximetry has been criticized for its low spatial resolution (it measures only a 1 mm path of tissue and not the entire brain), the technique does have a higher time resolution (< .01 s) than many functional neuroimaging methodologies, including positron-emission tomography and functional magnetic resonance imaging. In addition, it provides only relative measures of change, but that is true of many radiographic measures. However, with the development of multidistance, frequency-based NIRS (Wolf et al., 2003) and more sophisticated continuous-wave three wavelength NIRS (Rais-Bahrami, Rivera, & Short, 2006) researchers and clinicians will be able to track changes in the components of $rcSO_2$ in absolute units (oxy-, deoxy- and total hemoglobin). As with its predecessors, like the INVOS 4100, these systems can be easily transported and provide low-cost, portable methods for tracking changes in oxygenation status.

Clearly, longitudinal studies that incorporate measures of vascular and cognitive function over years would allow for a more comprehensive understanding of the complex relationships among changes in arterial oxygenation, cerebral blood flow, cerebral blood volume, and cerebral oxygen reserves during sleep. At present, we do not know whether the observed differences in cerebral oxygenation are associated with cognitive decline, but it seems likely given prior studies that reported a link between declines in frontal blood flow and declines in cognition (Prins et al., 2005; Rosano et al., 2005). Given that there are interventions for reducing the effects of vascular disease, the identification of clinical markers of diminished cerebral blood flow or impaired cerebral oxygenation is important for identifying cases that can benefit from early intervention. Thus, simple repetitive measurements made with minimally intrusive instruments, such as those obtained by cerebral oximetry, may provide clinicians with a way to track falling cerebral oxygen reserves and, perhaps, intervene before significant injury and disability have occurred.

Acknowledgments

This study was funded by grants from the National Institute of Nursing Research (NR08032) and General Clinical Research Center, UNC Hospitals (RR0046).

References

Brown MM, Wade JP, Marshall J. Fundamental importance of arterial oxygen content in the regulation of cerebral blood flow in man. Brain. 1985; 108(Pt 1):81–93. [PubMed: 3978400]

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kuper DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Research. 1989; 28:193–213. [PubMed: 2748771]

Carlson BW, Neelon VJ, Carlson JR, Hartman M, Dogra S. Cerebral oxygen reserves during sleep in old and young adults. Gerontologist. 2005; 45(Special Issue 1):498–499.

Carlson BW, Neelon VJ, Carlson JR, Hartman M, Dogra S. Exploratory analysis of cerebral oxygen reserves during sleep onset in old and young adults. Journal of the American Geriatric Society. 2008; 56(5):914–919.

Corfield DR, Meadows GE. Control of cerebral blood flow during sleep and the effects of hypoxia. Advances in Experimental Medicine and Biology. 2006; 588:65–73. [PubMed: 17089880]

Decker MJ, Redline S, Arnold JL, Masny J, Strohl KP. Normative values of oxygen saturation over time. Journal of Ambulatory Monitoring. 1991; 4(4):297–304.

Derdeyn CP, Videen TO, Yundt KD, Fritsch SM, Carpenter DA, Grubb RL, et al. Variability of cerebral blood volume and oxygen extraction: Stages of cerebral haemodynamic impairment revisited. Brain. 2002; 125(Pt 3):595–607. [PubMed: 11872616]

Fillenbaum, GG. Center for the Study of Aging and Human Development. Multifactorial functional assessment questionnairre. Durham, NC: Duke University Press; 1978.

Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State" A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975; 12(3):189–198. [PubMed: 1202204]

Gries RE, Brooks LJ. Normal oxyhemoglobin saturation during sleep. How low does it go? Chest. 1996; 110(6):1489–1492. [PubMed: 8989066]

Gupta AK, Menon DK, Czosnyka M, Smielewski P, Jones JG. Thresholds for hypoxic cerebral vasodilation in volunteers. Anesthesia and Analgesia. 1997; 85(4):817–820. [PubMed: 9322461]

Hajak G, Klingelhofer J, Schulz-Varszegi M, Matzander G, Sander D, Conrad B, et al. Relationship between cerebral blood flow velocities and cerebral electrical activity in sleep. Sleep. 1994; 17(1): 11–19. [PubMed: 7910702]

Harms MP, Colier WN, Wieling W, Lenders JW, Secher NH, van Lieshout JJ. Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. Stroke. 2000; 31(7): 1608–1614. [PubMed: 10884461]

Hirth C, Obrig H, Valdueza J, Dirnagl U, Villringer A. Simultaneous assessment of cerebral oxygenation and hemodynamics during a motor task. A combined near infrared and transcranial Doppler sonography study. Advances in Experimental Medicine and Biology. 1997; 411:461–469. [PubMed: 9269463]

Jimenez-Bonilla JF, Quirce R, Hernandez A, Vallina NK, Guede C, Banzo I, et al. Assessment of cerebral perfusion and cerebrovascular reserve in insulin-dependent diabetic patients without central neurological symptoms by means of 99mTc-HMPAO SPET with acetazolamide. European Journal of Nuclear Medicine. 2001; 28(11):1647–1655. [PubMed: 11702106]

Kaarisalo MM, Raiha I, Sivenius J, Immonen-Raiha P, Lehtonen A, Sarti C, et al. Diabetes worsens the outcome of acute ischemic stroke. Diabetes Research and Clinical Practice. 2005; 69(3):293–298. [PubMed: 16098927]

Kim MB, Ward DS, Cartwright CR, Kolano J, Chlebowski S, Henson LC. Estimation of jugular venous O_2 saturation from cerebral oximetry or arterial O_2 saturation during isocapnic hypoxia. Journal of Clinical Monitoring and Computing. 2000; 16(3):191–199. [PubMed: 12578103]

Larsson A, Skoog I, Aevarsson, Arlig A, Jacobsson L, Larsson L, et al. Regional cerebral blood flow in normal individuals aged 40, 75 and 88 years studied by 99Tc(m)-d,l-HMPAO SPET. Nuclear Medicine Communications. 2001; 22(7):741–746. [PubMed: 11453045]

Last D, Alsop DC, Abduljalil AM, Marquis RP, de Bazelaire C, Hu K, et al. Global and regional effects of type 2 diabetes on brain tissue volumes and cerebral vasoreactivity. Diabetes Care. 2007; 30(5):1193–1199. [PubMed: 17290035]

Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: The Honolulu-Asia aging study. Neurobiology of Aging. 2000; 21(1):49–55. [PubMed: 10794848]

Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJ, et al. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. Brain. 1990; 113(Pt 1):27–47. [PubMed: 2302536]

Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. Journal of the American Geriatric Society. 1968; 16(622–626)

Madsen PL. Cerebral blood flow and metabolism during sleep. Cerebrovascular and Brain Metabolism Reviews. 1991; 3(4):281–296. [PubMed: 1772738]

Madsen PL. Blood flow and oxygen uptake in the human brain during various states of sleep and wakefulness. Acta Neurologica Scandinavica. Supplementum. 1993; 148:3–27. [PubMed: 8273451]

Madsen PL, Secher NH. Near-infrared oximetry of the brain. Progress in Neurobiology. 1999; 58(6): 541–560. [PubMed: 10408656]

Mehagnoul-Schipper DJ, van der Kallen BF, Colier WN, van der Sluijs MC, van Erning LJ, Thijssen HO, et al. Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. Human Brain Mapping. 2002; 16(1):14–23. [PubMed: 11870923]

Nagata K, Kondoh Y, Atchison R, Sato M, Satoh Y, Watahiki Y, et al. Vascular and metabolic reserve in Alzheimer's disease. Neurobiology of Aging. 2000; 21(2):301–307. [PubMed: 10867215]

Naifeh KH, Severinghaus JW, Kamiya J. Effect of aging on sleep-related changes in respiratory variables. Sleep. 1987; 10(2):160–171. [PubMed: 3589328]

Naritomi H, Meyer JS, Sakai F, Yamaguchi F, Shaw T. Effects of advancing age on regional cerebral blood flow. Studies in normal subjects and subjects with risk factors for atherothrombotic stroke. Archives of Neurology. 1979; 36(7):410–416. [PubMed: 454246]

Newman GC, Bang H, Hussain SI, Toole JF. Association of diabetes, homocysteine, and HDL with cognition and disability after stroke. Neurology. 2007; 69(22):2054–2062. [PubMed: 18040011]

Ott A, Andersen K, Dewey ME, Letenneur L, Brayne C, Copeland JR, et al. Effect of smoking on global cognitive function in nondemented elderly. Neurology. 2004; 62(6):920–924. [PubMed: 15037693]

Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999; 53(9):1937–1942. [PubMed: 10599761]

Pleis, JR.; Lethbridge-Çejku, M. Summary health statistics for U.S. adults: National Health Interview Survey, 2005 (Vol. 10): National Center for Health Statistics Vital Health Statistics. 2006.

Pollard V, Prough DS, DeMelo AE, Deyo DJ, Uchida T, Stoddart HF. Validation in volunteers of a near-infrared spectroscope for monitoring brain oxygenation in vivo. Anesthesia and Analgesia. 1996; 82(2):269–277. [PubMed: 8561326]

Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Jolles J, Koudstaal PJ, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. Brain. 2005; 128(Pt 9):2034–2041. [PubMed: 15947059]

Rais-Bahrami K, Rivera O, Short BL. Validation of a noninvasive neonatal optical cerebral oximeter in veno-venous ECMO patients with a cephalad catheter. Journal of Perinatology. 2006; 26(10): 628–635. [PubMed: 16900202]

Rechtschaffen, A.; Kales, A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Los Angeles: National Institute of Neurobiological Diseases and Blindness: Neurological Information Network; 1968.

Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT Jr, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. Journal of the American Geriatric Society. 2005; 53(4):649–654.

Rossini PM, Altamura C, Ferretti A, Vernieri F, Zappasodi F, Caulo M, et al. Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? Brain. 2004; 127(Pt 1):99–110. [PubMed: 14570819]

Shah N, Trivedi NK, Clack SL, Shah M, Shah PP, Barker S. Impact of hypoxemia on the performance of cerebral oximeter in volunteer subjects. Journal of Neurosurgical Anesthesiology. 2000; 12(3): 201–209. [PubMed: 10905567]

Terborg C, Gora F, Weiller C, Rother J. Reduced vasomotor reactivity in cerebral microangiopathy: A study with near-infrared spectroscopy and transcranial Doppler sonography. Stroke. 2000; 31(4): 924–929. [PubMed: 10754000]

Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: The Rotterdam Scan Study. Stroke. 2003; 34(5):1126–1129. [PubMed: 12690219]

Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: A systematic review. Lancet Neurology. 2007; 6(7):611–619. [PubMed: 17582361]

Wolf M, Franceschini MA, Paunescu LA, Toronov V, Michalos A, Wolf U, et al. Absolute frequency-domain pulse oximetry of the brain: Methodology and measurements. Advances in Experimental Medicine and Biology. 2003; 530:61–73. [PubMed: 14562705]

Yesavage JA, Brink TL. Development and validation of a geriatric depression screening scale: A preliminary report. Journal of Psychiatric Research. 1983; 17(1):37–49. [PubMed: 7183759]

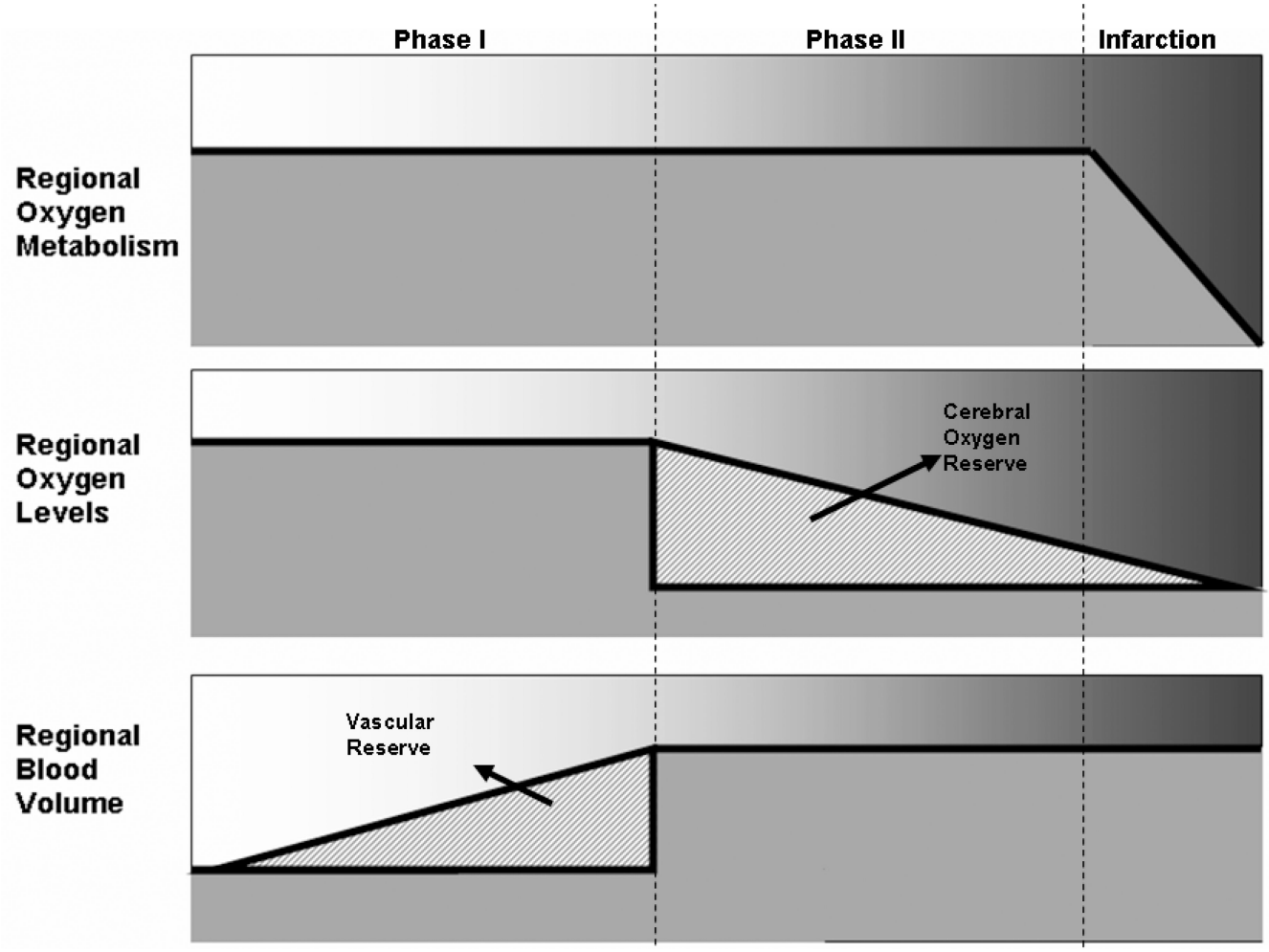

Figure 1.

Phases of cerebral vascular compensation. In cases of low resting cerebral blood flow (Phase 1), cerebral blood flow is maintained during challenges (like decline in SaO_2) by the dilatation of resistance vessels (vascular reserve), which leads to increases in regional blood volume. As cerebral blood flow continues to fall (Phase 2), the resistance vessel cannot dilate any further, and regional blood flow begins to fall. Despite this fall in regional flow, regional oxygen metabolism is maintained by removing more oxygen from the circulating blood (cerebral oxygen reserve). However, as blood flow declines even more, the cerebral oxygen reserve becomes depleted, which will eventually lead to cerebral infarction and injury (Phase 3). Figure adapted from Derdeyn, C. P., Videen, T. O., Yundt, K. D., Fritsch, S. M., Carpenter, D. A., Grubb, R. L., et al. (2002). Variability of cerebral blood volume and oxygen extraction: Stages of cerebral haemodynamic impairment revisited. *Brain, 125*(Pt 3), 595–607, by permission of Oxford University Press.

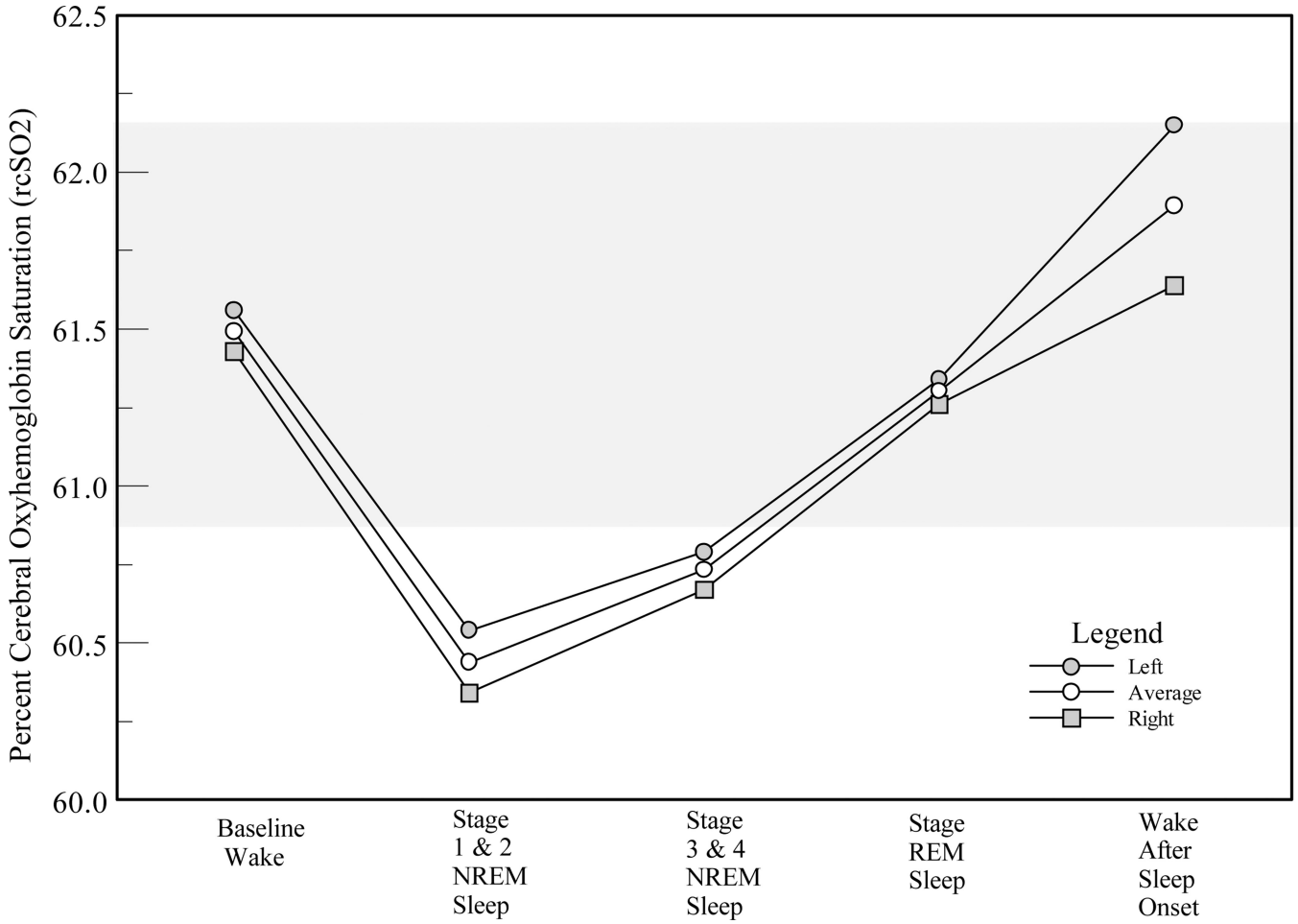

Figure 2.

Trends in cerebral oxyhemoglobin saturation ($rcSO_2$) at presleep baseline, during sleep, and with waking after sleep onset (WASO). The shaded area extending along the y-axis marks the area that represents $rcSO_2$ values within ± 1 standard deviation from wake baseline. Using the shaded area as a point of comparison, the greatest change in $rcSO_2$ occurred during both stages of NREM sleep. The filled circles and squares indicate the mean left and right $rcSO_2$ values for each state, respectively. The open circles indicate average of left- and right-sided $rcSO_2$ values.

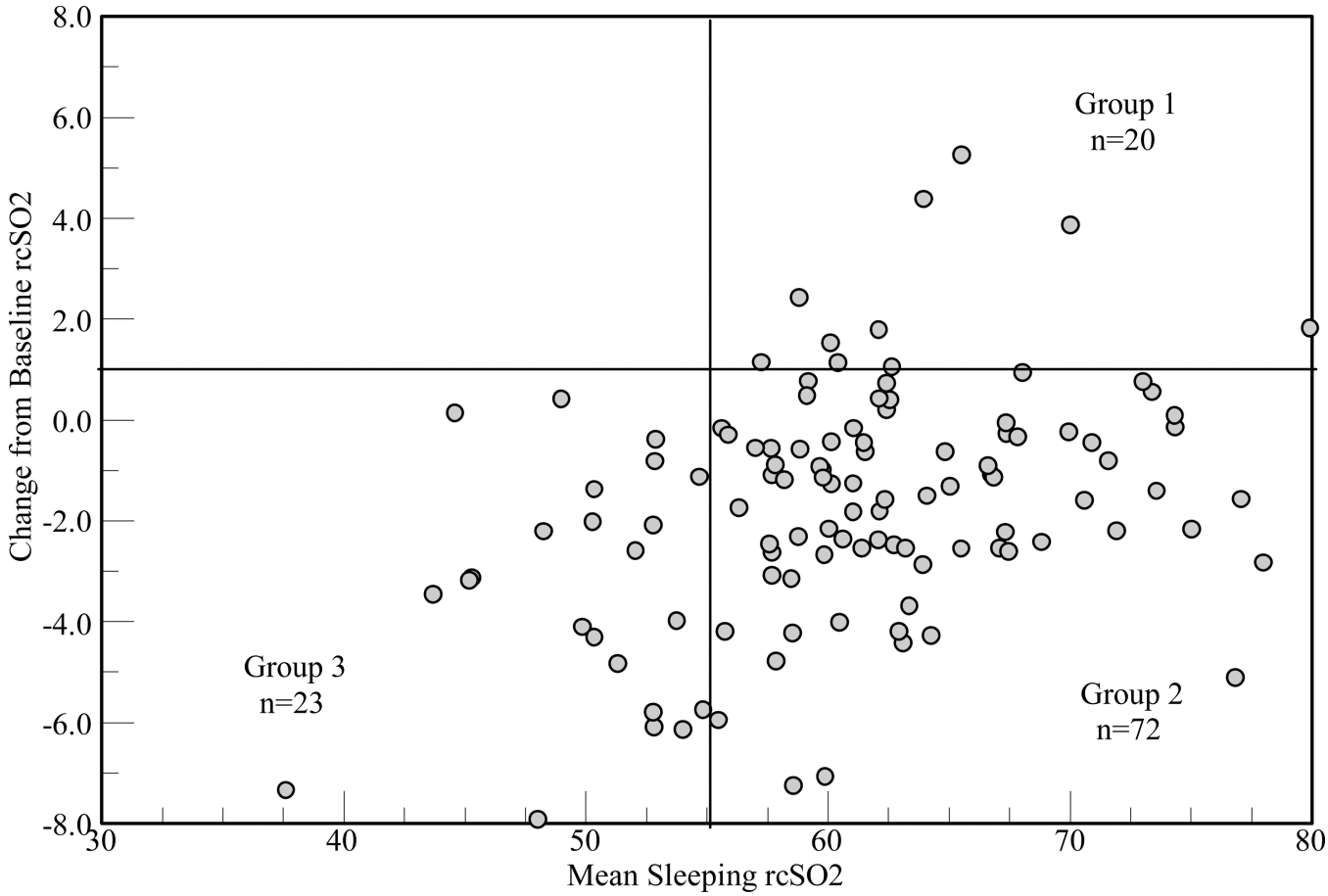

Figure 3.
Relationship between change in $rcSO_2$ and mean $rcSO_2$ levels during sleep ($n = 115$).

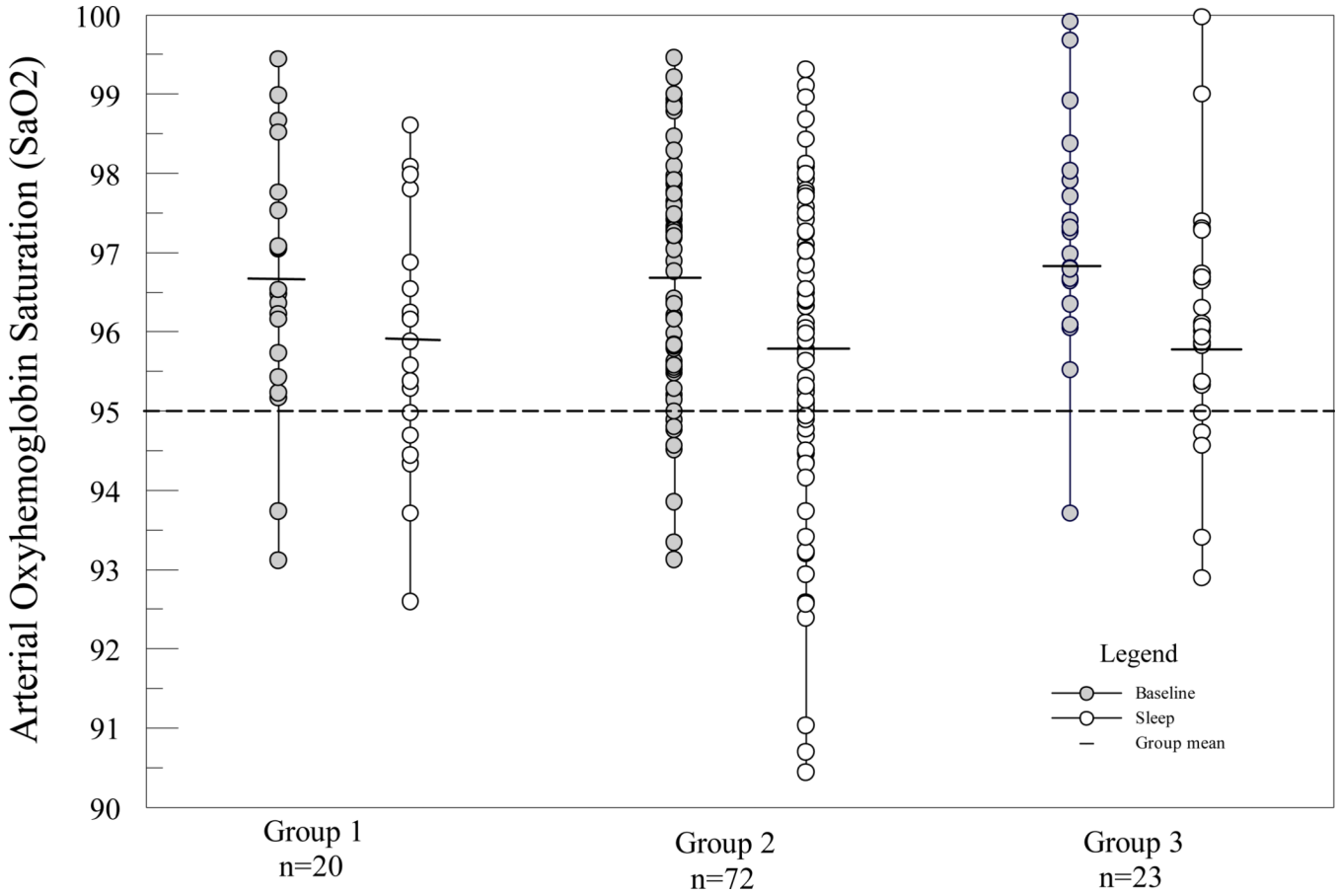

Figure 4.

Group differences in the arterial oxyhemoglobin saturation (SaO_2) at baseline and during NREM sleep. Each circle represents the mean SaO_2 for a subject. The filled circles indicate their average SaO_2 at baseline. The open circles indicate their average SaO_2 during sleep. The horizontal lines indicate the mean SaO_2 of the group.

Table 1

Prevalence of Cerebrovascular Risk Factors by Pattern of Cerebral Oxygen Reserve

	All Subjects	Group 1	Group 2	Group 3
n	115	20	72	23
% Heart disease	18.6%	15%	18%	23%
% Hypertension	50.9%	45%	50%	57%
% Diabetes*	7.6%	10%	3%	19%

Note. Group 1 = $rcSO_2 \geq 55\%$ and increased during sleep; Group 2 = $rcSO_2 \geq 55\%$ and decreased during sleep; Group 3 = $rcSO_2 < 55\%$ and decreased during sleep.

*Compared to the other groups, Group 3 had significantly more persons with diabetes ($X^2_{(df=20)} = 7.5$, $p = .02$)