The Association Between Daytime Sleepiness and Sleep-Disordered Breathing in NREM and REM Sleep

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Background: Daytime sleepiness is common in patients with sleep-disordered breathing. Although respiratory events during sleep are associated with the occurrence of daytime sleepiness, the differential impact of these events during non-rapid eye movement (NREM) and rapid eye movement (REM) sleep on daytime sleepiness has not been well characterized.

Study Objectives: To determine the effect of respiratory events during REM sleep and NREM sleep on daytime sleepiness, as assessed by the multiple sleep latency test (MSLT).

Design: Cross-sectional study.

Setting: University-based sleep disorders laboratory.

Participants: Patients referred for polysomnography and daytime MSLT (n=1,821).

Interventions: N/A

Measurements and Results: The study sample was initially divided into quartiles based on the level of the apnea-hypopnea index (AHI) during NREM sleep. Within the first NREM-AHI quartile (NREM-AHI < 8.3 events/hr), the association between REM-related respiratory events and daytime sleepiness was examined using the method of Kaplan-Meier analysis and Cox proportional hazards regression. After adjusting for age, gender, body mass index, and the duration of NREM and REM sleep, REM-AHI was not associated with daytime sleepiness (Relative Risk: 1.01; 95%CI: 0.94–1.10). Similarly, no significant association was observed between REM-AHI and the MSLT in patients within the second through fourth NREM-AHI quartiles. In contrast, increasing severity of disordered breathing during NREM sleep was associated with daytime sleepiness. For a 10-point increase in NREM-AHI, the adjusted relative risks for daytime sleepiness in the second through fourth NREM-AHI quartile were 1.21 (95%CI: 1.01–1.46), 1.20 (95%CI: 1.05–1.37), and 1.10 (95%CI: 1.04–1.16), respectively.

Conclusion: Sleep-disordered breathing during NREM sleep, but not REM sleep, is associated with increased risk of daytime sleepiness.

Key words: Sleep-disordered breathing; sleep apnea; daytime sleepiness; multiple sleep latency test; rapid eye movement sleep; non-rapid eye movement sleep; survival analysis

INTRODUCTION

SLEEP-DISORDERED BREATHING IS CHARACTERIZED BY REPETITIVE EPISODES OF PARTIAL OR COMPLETE COLLAPSE OF THE UPPER AIRWAY DURING SLEEP. The resulting decrease or cessation in airflow is often associated with oxyhemoglobin desaturation and/or an arousal from sleep. In patients with sleep-disordered breathing, respiratory events may occur throughout non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. The typical finding is that respiratory events during REM sleep are longer and are associated with a greater degree of hypoxemia than events that occur during NREM sleep. These characteristics may be related to the marked differences in arousal responses to respiratory stimuli (i.e., hypoxemia and hypercapnia) between REM and NREM sleep. In general, greater stimulus intensities are required to elicit an arousal from REM than NREM sleep.[1] Therefore, substantial differences exist in the characteristics of disordered breathing episodes during REM and NREM sleep.

It is well recognized that episodes of disordered breathing can alter sleep architecture. Respiratory events during NREM sleep can interfere with the normal cycling of REM periods throughout the night and may even prevent the progression to REM sleep. Moreover, respiratory events during REM sleep may truncate the amount of REM sleep achieved during any particular REM cycle. Therefore, respiratory events in either stage can reduce the total amount of REM sleep.

Excessive daytime sleepiness is one of the major clinical consequences of sleep-disordered breathing. In a study of patients with sleep-disordered breathing,[2] we have recently demonstrated that the apnea-hypopnea index, degree of sleep fragmentation, and severity of nocturnal hypoxemia are independently associated with increased risk of daytime sleepiness, as assessed by the multiple sleep latency test (MSLT). However, the differential impact of sleep-disordered breathing during NREM and REM sleep on clinical sequelae, such as daytime sleepiness, remains to be determined.[3,4]

Although respiratory events may be more severe during REM sleep, their impact on daytime sleepiness may be offset by the shorter duration of REM sleep compared to NREM sleep. In addition, respiratory events in NREM sleep may further decrease the exposure to disordered breathing in REM sleep. In the current study, we explored the relationships between daytime sleepiness and disordered breathing during NREM and REM sleep. We hypothesized that respiratory events during NREM sleep, but not REM sleep, would be associated with daytime sleepiness. Specifically, we predicted that respiratory events in REM sleep would not be associated with reductions in the MSLT either (a)

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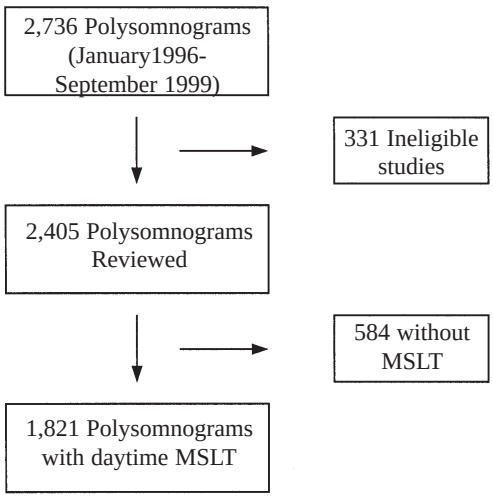

Figure 1—Selection of the study sample

in the absence of respiratory events during NREM sleep or (b) in the presence of respiratory events during NREM sleep. In contrast, we hypothesized that respiratory events in NREM sleep would be associated with reductions in the MSLT. To test these predictions, we modeled the impact of these events on the results of the MSLT in a sample of patients referred for clinical evaluation.

METHODS

Sample Selection

All consecutive patients (age ≥18 years) who underwent an overnight polysomnogram in our sleep laboratory from January 1996 through September 1999 were identified (n=2,736). Exclusionary criteria included split-night (<6 hrs) or extended (> 9 hrs) recordings (n=234), participation in ongoing research protocols (n=9), the use of supplemental oxygen (O_2) during any part of the study (n=33), and polysomnography during the day (n=4) or while on positive airway pressure therapy (n=51). Of the remaining 2,405 patients, 584 patients did not have an MSLT (Figure 1). The patient sample included in the present study is an expanded cohort of patients that includes the previously reported sample.[2] Approval for the use of the clinical data for the current study was obtained from the institutional review board on human research.

Polysomnography and Multiple Sleep Latency Test

The overnight study consisted of continuous recordings (Model 78d, Grass Instruments, Quincy, MA) of a modified electrocardiographic (V_6) lead, right and left electrooculographic leads, submental and bilateral anterior tibialis surface electromyograms, and two electroencephalographic leads (C3-A2, C3-O1). Respiration was monitored throughout the night with thermocouples (Protech, Woodinville, WA) at the nose and mouth, and with thoracic and abdominal strain gauges (Piezocrystals, EPM Systems, MidLothiam, VA). Continuous recording of the oxyhemoglobin saturation (SaO_2) was obtained with an oximeter (Ohmeda 3700; Englewood, CO). Physiologic signals were digitized (Sandman, Melville Software Ltd, Ontario, Canada) for off line analysis of sleep and breathing patterns. Sleep-stage scoring was performed on 30-second epochs according to standard criteria.[5] Apnea was defined as complete cessation of airflow for at least 10 seconds. Hypopnea was defined as any reduction in airflow that was associated with an electroencephalographic arousal or a 4% drop in the SaO_2. The apnea-hypopnea index (AHI) was calculated as the total number of apneas and hypopneas per hour of total sleep time. Sleep-state dependent indices (i.e., NREM-AHI and REM-AHI) were also determined by dividing the number of events in NREM and REM sleep by the amount of NREM and REM time, respectively.

The MSLT, which consisted of a series of four 20-minute nap trials at two-hour intervals, was performed in accordance with the recommended guidelines by the American Academy of Sleep Medicine.[6,7] The recording montage during the MSLT was similar to overnight study except that patients did not wear the thoracic and abdominal strain gauges. Each nap trial lasted 20 minutes if sleep did not occur. If the patient did fall asleep within 20 minutes, the trial was terminated 15 minutes after sleep onset. Between naps the patients were instructed not to sleep and were monitored by trained technicians. The sleep latency for each nap trial was defined as the time to the first 30-second epoch composed of at least 15 seconds of sleep stage 1.

The records of the study sample were reviewed and the following demographic information was obtained: age, gender, and body mass index (BMI). Information from the sleep study included: time in bed, total sleep time, the apnea-hypopnea index (AHI), sleep-state dependent AHI (i.e., NREM-AHI and REM-AHI), and time in NREM (sleep stages 1, 2, 3, and 4) and REM sleep. Daytime sleepiness was assessed with the median and mean sleep latency from the four MSLT naps. However, the median sleep latency was used as the primary outcome variable instead of the mean sleep latency for the following reasons. Since each nap during the MSLT has a truncated distribution with a maximum value of 20 minutes, the median is a better measure of central tendency than the mean as it is less likely to be influenced by extreme values.[8] Moreover, given that there were no differences in the findings based on using either the median or mean sleep latency from the four naps, analyses using the median are presented.

Statistical Analysis

General Approach for Analyzing the MSLT

The dependent variable of interest was the time to sleep onset during the MSLT. Since the MSLT measures the time to an event (sleep onset), techniques of survival analysis, including Kaplan-Meier product-limit analysis[9] and Cox proportional hazards regression,[10] were used to examine the associations between the results of MSLT and indices of sleep-disordered breathing severity during REM and NREM sleep. Although the methods of survival analysis were initially developed to study predictors of time to death, other events including time to sleep onset can also be studied with these techniques. In the context of sleep onset, the construction of a Kaplan-Meier curve consists of plotting the proportion of individuals that remain awake at each time point

Table 1—Descriptive statistics for patients with and without and MSLT

Characteristic	Study Sample PSG with MSLT (n=1821)	Excluded Patients PSG without MSLT (n=584)
Males, %	1232 (67.7%)	397 (68.0%)
Age, yr*	49.5±13.2	52.5±14.4
BMI, kg/m^2	34.1±8.5	33.3±9.2
AHI, events/hr	38.4±32.7	37.6±37.8
NREM-AHI, events/hr	37.9±34.3	37.2±39.4
REM-AHI, events/hr	38.6±30.3	36.6±31.6
Time in bed, min*	435.0±35.4	419.4±44.1
Total sleep time, min*	367.0±58.3	332.9±73.7
Sleep efficiency, %*	84.4±11.8	79.5±16.4
NREM sleep, % TST*	83.9±7.7	85.0±8.4
REM sleep, % TST*	16.1±7.7	15.1±8.4

*p<0.05 for comparisons between patients with and without an MSLT; TST=Total sleep time

throughout the course of the MSLT. For example, if 10 individuals out of sample of 100 have a sleep latency ≤1 minute, then the proportion of individuals remaining awake beyond the first minute would be 0.90. If another 10 individuals in that sample have sleep latency in the range of one to two minutes, then the proportion remaining awake beyond the second minute would be 0.80. If there is no interim censoring or loss to follow up, as is the case for the MSLT, the Kaplan-Meier curve is constructed by plotting these computed values at each respective time point. Separate Kaplan-Meier survival curves can be constructed to examine whether patients grouped by a predictor of interest (i.e., AHI) have different degrees of daytime sleepiness. Cox proportional hazards regression can be then used to mathematically model these survivorship functions and assess whether a variable, such as AHI, is associated with increased risk of daytime sleepiness.

Development of Multivariable Models for the Daytime Sleepiness

To model the impact of respiratory events on daytime sleepiness, a number of separate and staged analyses were conducted using the aforementioned techniques. First, the association between daytime sleepiness and REM-related respiratory events was examined in patients without evidence of disordered breathing in NREM sleep. Second, the association between REM-related respiratory events and daytime sleepiness was assessed in patients with evidence of disordered breathing in NREM sleep. Finally, the independent effect of respiratory events during NREM sleep and daytime sleepiness was also examined.

The effect of sleep-disordered breathing severity on daytime sleepiness was modeled using event rates in each sleep state (REM-AHI and NREM-AHI) as the primary exposure variable. Duration of NREM and REM sleep was then included in the analysis to account for the potential influence of respiratory events on sleep stage distribution. We also modeled the interaction between event rates and sleep stage times using cross product terms between sleep stage-specific rates (i.e., REM-AHI and NREM-AHI) and sleep stage times (REM-time and NREM-time). Hierarchical models were developed to test these interactions in models that contained event rates and sleep stage times. Variables that could have a confounding influence were included in all multivariable models. These variables included age, gender, BMI, and time in bed.

The statistical significance of all relative risks was determined by the two-sided test of the beta coefficient with a p-value of 0.05. While continuous and categorical forms of each variable were used in the model building process, results from the continuous analyses are presented for maximizing power. The log-rank test was used to determine the statistical significance of differences in Kaplan-Meier curves across ordered categories of each predictor variable. The likelihood ratio test was used at each stage to compare multivariable Cox regression models with and without the predictor variable of interest.[11] The assumption of proportional hazards for Cox regression was tested by plotting the In(-In[S(t)]) against In(time) where S(t) is the survivorship function.[12] Inspection of these plots suggested that the hazard functions for different strata of REM-AHI (and NREM-AHI) were not proportional after a sleep latency of 10 minutes. Therefore, a threshold of 10 minutes in the median sleep latency was used for the purpose of censoring observations. The cut-point in the MSLT of 10 minutes is also clinically relevant since it is generally accepted that differences in MSLT below 10 minutes are used to discriminate differences in the severity of daytime sleepiness.[6,7] All statistical analyses were conducted using the STATA 7.0 statistical software package (STATA Inc., College Station, TX).

RESULTS

Patient Characteristics

The characteristics of the study sample are summarized in Table 1. The sample consisted of 1,232 men (67.7%) and 589 women (33.3%) with a mean age of 49.5 years (SD: 13.2). Since the sample was comprised of patients referred for clinical evaluation, it was not surprising that these patients were obese with a mean BMI of 34.1 kg/m^2 (SD: 8.5) and had evidence of moderate to severe sleep-disordered breathing with a mean AHI of 38.4 events/hr (SD: 32.7). Sleep architecture data revealed the following average sleep stage distribution: 22.9% of sleep stage 1, 58.2% of sleep stage 2, 2.8% of slow-wave sleep, and 16.1 % of REM sleep. Results of the MSLT demonstrated significant daytime sleepiness with an average median sleep latency of 6.6 minutes (SD: 5.0). Comparing the patients in the study sample to the subgroup of patients excluded for not having an MSLT, we found no significant differences in the distribution of gender or the severity of disordered breathing (Table 1). However, patients without an MSLT were older and less obese compared to those with an MSLT. In addition, statistically significant differences in time in bed, total sleep time, and sleep efficiency were noted between the two patient groups.

As expected, there was a moderate correlation in the study sample between NREM-AHI and REM-AHI (r=0.69, 95% CI: 0.66 to 0.71). Nevertheless, as shown in Figure 2, considerable variability in REM-AHI was still evident within quartiles of

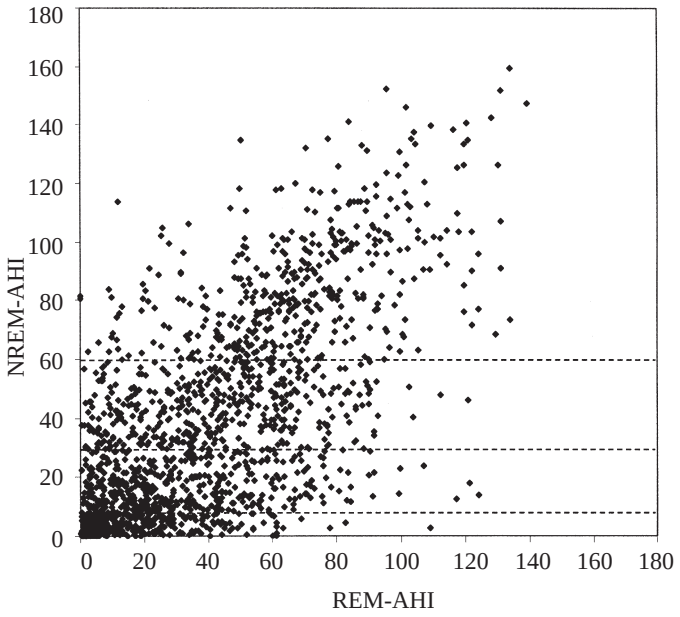

Figure 2—Scatter plot of NREM-AHI and REM-AHI (dashed lines represent cut-points for NREM-AHI quartiles)

NREM-AHI. There also was significant variability in NREM-AHI within the third and fourth quartiles. Table 2 shows the descriptive statistics of the study sample by NREM-AHI quartile. Not surprisingly, with increasing NREM-AHI, there was a decrease in the percentage of REM sleep and a concomitant increase in the amount of NREM sleep.

REM-Disordered Breathing and Daytime Sleepiness

Since the primary objective of this study was to examine whether respiratory events during REM sleep were associated with reduction in the MSLT, either in the absence or in combination with events during NREM sleep, the study sample was initially divided into quartiles based on the distribution of NREM-AHI. The first quartile (NREM-AHI <8.3 events/hr) was used to define the subgroup of patients without significant disordered breathing during NREM sleep. Alternative thresholds in the absolute value of NREM-AHI (<5 and <10 events/hr) were also examined. Since the results did not vary across these different samples, we constructed the Kaplan-Meier survival curves for quartiles of REM-AHI within the first stratum of NREM-AHI (< 8.3 events/hr). As shown in Figure 3(a), REM-AHI was not associated with increased risk of daytime sleepiness, as reflected by the MSLT. Cox proportional hazards modeling revealed that the unadjusted relative risk for a 10-point increase in REM-AHI was 1.03 (95% CI: 0.96 to 1.11). No significant change in the relative risk for REM-AHI was noted (relative risk: 1.01, 95% CI: 0.94 to 1.10) after adjusting for age, gender, BMI, and time in bed (Table 3). Furthermore, hierarchical models that included the interaction between REM-AHI and REM sleep time showed no improvement in predicting daytime sleepiness.

To explore the effects of REM-related hypoxemia and arousals on daytime sleepiness, separate multivariable Cox regression models were developed for these indices within the first NREM-AHI quartile (n=454). The unadjusted relative risk for a 4% drop in oxygen saturation during REM sleep was 1.18 (95% CI: 0.97 to 1.44). The relative risk remained unchanged (relative risk: 1.16; 95% CI: 0.91 to 1.49) after adjusting for variables including age, gender, BMI, and time in NREM and REM sleep. The association of daytime sleepiness with respiratory-related arousals during REM sleep also was assessed within the first NREM-AHI quartile. Multivariable Cox regression analysis showed that the relative risk for a 10-point increase in the arousal rate during REM sleep was 1.03 (95% CI: 0.91 to 1.17), demonstrating that respiratory-related arousals during REM sleep were not associated with daytime sleepiness after adjusting for age, BMI, time in bed, and time in NREM and REM sleep.

NREM- and REM- Disordered Breathing and Daytime Sleepiness

Data derived from patients in the second through fourth NREM-AHI quartiles were used to investigate the association between respiratory events during REM sleep and daytime sleepiness in patients with evidence of respiratory events during NREM sleep. The decision to use stratified analyses was motivated by our hypothesis that the association between respiratory events during REM sleep and daytime sleepiness may vary across levels of NREM-AHI. In addition, the stratified approach allowed us to model the effects of clinical variables (i.e., BMI, age, gender) on daytime sleepiness across different levels of NREM-AHI.

For each of the second through fourth NREM-AHI quartile, patients were further grouped based on the distribution of REM-AHI within that quartile. Kaplan-Meier analysis revealed no statistically significant relationship between REM-AHI and daytime sleepiness in the second NREM-AHI quartile (Figure 3b). In contrast, there was a weak but statistically significant association between REM-AHI and daytime sleepiness in the third and fourth NREM-AHI quartiles (Figure 3c and 3d). However, multivariable models showed that, after adjusting for NREM and REM time within these quartiles, the association between REM-AHI and daytime sleepiness was no longer significant (Table 4a). Interestingly, within each of the NREM-AHI quartiles (II, III, and IV), a statistically significant relationship (Table 4b) was noted between NREM-AHI and daytime sleepiness.

NREM-Disordered Breathing and Daytime Sleepiness

To assess the relative impact of disordered breathing during NREM sleep on daytime sleepiness, we conducted a parallel analysis reversing the roles of REM-AHI and NREM-AHI as predictors of daytime sleepiness. We began by developing quartiles of REM-AHI using the full study sample (n=1,821). The cut points for REM-AHI quartiles were as follows: <11.0 (I), 11.0 to 33.7 (II), 33.8 to 60.2 (III), and ≥60.3 (IV). Stratified proportional hazards models were developed within these REM-AHI quartiles to assess the association between NREM-AHI and the results of the MLST after adjusting for the following variables: age, gender, BMI, time in bed, and NREM and REM sleep time. The adjusted relative risks for a 10-point increase in NREM-AHI within the four REM-AHI quartiles were 1.11 (95% CI: 1.02 to 1.20), 1.06 (95% CI: 1.01 to 1.12), 1.09 (95% CI: 1.05 to 1.14), and 1.11 (95% CI: 1.07 to 1.15), respectively. These results suggest a relatively consistent and an independent effect of NREM-related respiratory events on daytime sleepiness across the spec-

Table 2—Mean values and interquartile ranges for clinical and polysomnographic data

Variable	NREM-AHI Quartile I (<8.3 events/hr)	II (8.3 - 29.2 events/hr)	III (29.3 - 59.8 events/hr)	IV (≥59.9 events/hr)
Age, years	45.0 (36 - 54)	50.5 (41 - 59)	53.1 (45 - 63)	49.3 (41 - 58)
BMI, kg/m^2	31.2 (25.6 - 35.4)	33.0 (28.0 - 36.7)	33.5 (27.8 - 37.2)	38.7 (32.4 - 43.1)
REM-AHI, events/hr	14.1 (2.8 - 20.4)	31.4 (13.1 - 44.7)	41.7 (22.8 - 59.8)	68.9 (51.9 - 86.3)
NREM-AHI, events/hr	3.1 (0.9 - 5.0)	17.1 (12.0 - 21.6)	43.6 (35.9 - 50.4)	87.5 (70.9 - 99.8)
NREM time, % of TST	80.3 (75.1 - 84.8)	82.4 (77.8 - 86.7)	84.8 (79.6 - 89.9)	87.9 (83.1 - 92.7)
REM time, % of TST	19.7 (15.2 - 24.9)	17.6 (13.3 - 22.2)	15.2 (10.1 - 20.4)	12.1 (7.3 - 16.9)
Time in Bed, minutes	436.9 (413.5 - 462.5)	435.9 (411.0 - 463.0)	435.4 (412.5 - 459.0)	432.1 (408.5 - 457.5)
Sleep Efficiency, %	85.6 (81.6 - 93.5)	85.2 (80.2 - 93.1)	82.9 (77.4 - 92.4)	83.9 (79.0 - 92.8)

TST=Total Sleep Time

trum of REM-disordered breathing severity.

DISCUSSION

The purpose of this study was to determine whether disordered breathing in REM sleep or NREM sleep was associated with daytime sleepiness, as assessed by the MSLT. Using the techniques of survival analysis to analyze the results of the MSLT, we found that respiratory events during REM sleep were not associated with daytime sleepiness in the absence of or in combination with respiratory events in NREM sleep. We also found that other measures of the severity of disordered breathing during REM sleep, including the degree of intermittent hypoxemia and the frequency of arousals, did not contribute to daytime sleepiness. Finally, we noted that disordered breathing in NREM sleep was independently associated with an increased risk of daytime sleepiness. The findings of our study suggest that the impact of respiratory events during NREM sleep on daytime sleepiness is greater than the impact of respiratory events during REM sleep.

The results of our current study are consistent with a previous report by Chervin et al.[4] demonstrating that REM-related disordered breathing is not associated with daytime sleepiness, as reflected by the MSLT. Despite the similarity in conclusions between the two studies, there are several features that contrast the current study from the previous work. First, associations between daytime sleepiness with other physiologic indices of disordered breathing during REM sleep (i.e., hypoxemia and arousal rate) were not assessed in the previous study. We have recently shown that hypoxemia and sleep fragmentation are independently associated with increased risk of daytime sleepiness. The results of our current study suggest that, in the absence of respiratory events during NREM sleep, REM-related events and their physiologic consequences are not associated with daytime sleepiness. Second, the relationship between REM-AHI and daytime sleepiness was not examined across different levels of NREM-AHI in the previous study. Finally, our use of survival analysis is in marked contrast to the analytic techniques that previously have been employed to analyze the results of the MSLT. Since the MSLT measures time to an event, survival analysis methods provide a more robust approach for analyzing such data. The primary advantage of survival analysis is its ability to handle censored observations. Classical regression techniques require the elimination or randomization of censored observations to one of two outcomes and can thus bias or introduce error into the analysis.

In contrast with the results of our study, Kass et al.[3] have suggested that REM-related respiratory events are associated with daytime sleepiness. In a group of symptomatic patients with an overall AHI of less than 10 events/hr, a modest correlation (r= -0.35) was observed between REM-AHI and the results of MSLT. However, given the relatively small number of patients (n=34) and the restricted range of disease severity, the generalizability of their results is limited. Moreover, no confounding variables (i.e., age, gender, BMI, and time in NREM and REM sleep) were adjusted for in their analyses. Using a relatively large sample with significant heterogeneity in disordered breathing severity, we were able to systematically examine the independent effects

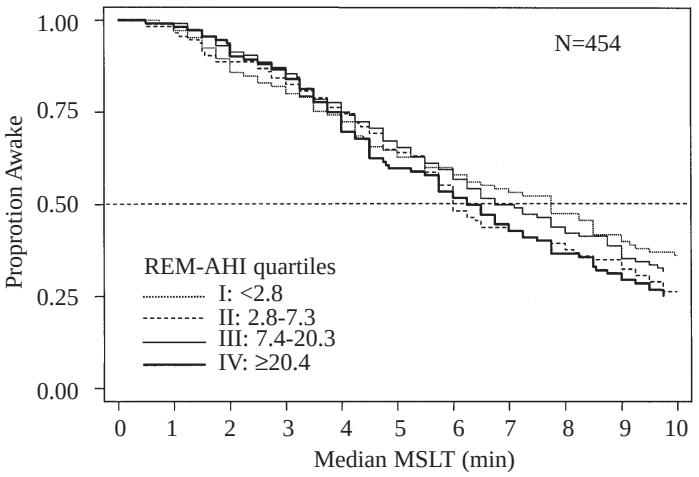

Figure 3(a)—Kaplan-Meier survival curves by REM-AHI (NREM-AHI <8.3)

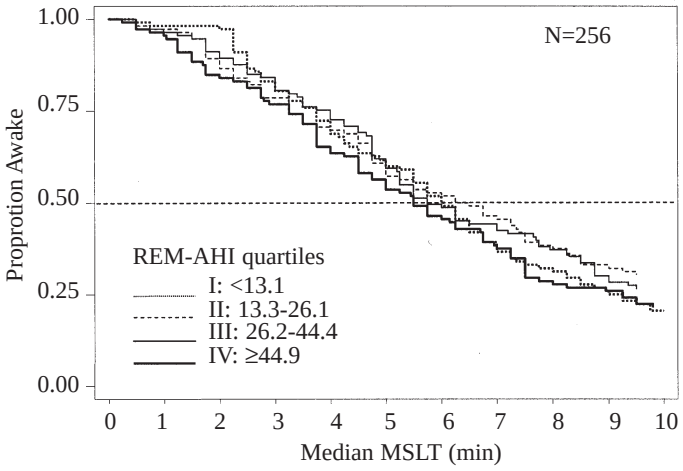

Figure 3(b)—Kaplan-Meier survival curves by REM-AHI (NREM-AHI: 8.3 – 29.2)

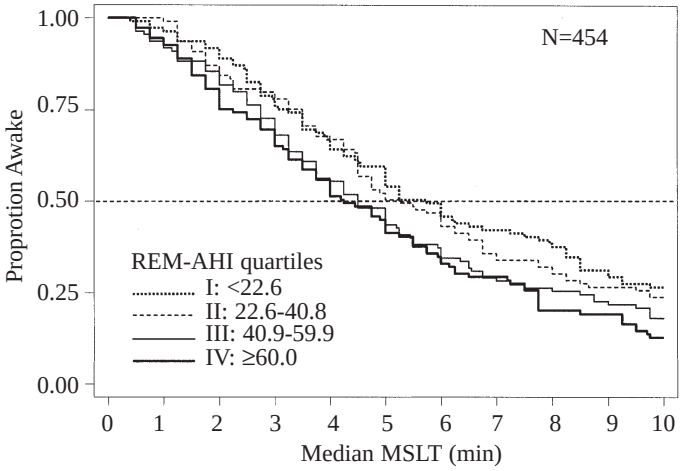

Figure 3(c)—Kaplan-Meier survival curves by REM-AHI (NREM-AHI: 29.3 – 59.8)

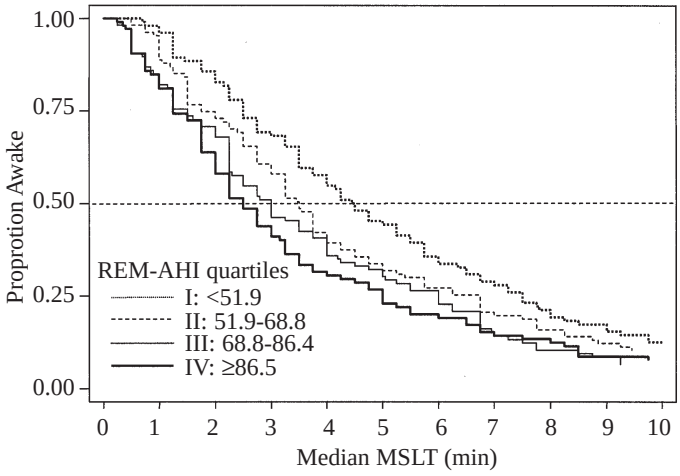

Figure 3(d)—Kaplan-Meier survival curves by REM-AHI (NREM-AHI > 59.9)

of NREM- and REM-related sleep-disordered breathing and daytime sleepiness. Our results indicate that respiratory events during NREM sleep have a greater impact on daytime sleepiness than respiratory events during REM sleep.

The differential effect of NREM- and REM-related respiratory events on daytime sleepiness was not surprising. Since NREM sleep typically constitutes 75% to 85% of total sleep time, any process that disrupts continuity of sleep during this stage will increase the likelihood of daytime sleepiness. Moreover, measures of disease severity based on NREM sleep will approximate the overall process of disordered breathing during sleep. Therefore, indices of disease severity during NREM sleep would better predict daytime sleepiness than indices of disease severity during REM sleep. Alternatively, the effects of respiratory events in NREM and REM sleep may, in fact, be dissimilar. Available data indicate that the responses to upper-airway collapse differ between NREM and REM sleep.[1] Although REM sleep is characterized by activation of the central nervous system, arousal responses to various stimuli (i.e., hypercapnia, hypoxia, and airway occlusion) are considerably diminished during REM sleep compared to NREM sleep. Therefore, the differential impact of sleep-disordered breathing during NREM and REM sleep may be related to the quantitative and/or qualitative characteristics of respiratory events in these sleep stages.

The absence of an association between respiratory-related arousals during REM sleep and daytime sleepiness is further supported by experimental data on the selective loss of REM sleep. Although initial studies on REM deprivation were inconclusive, accumulating data indicate that REM sleep disruption appears to have little impact on daytime sleepiness. Recently, Nykamp and coworkers[13] have shown that normal individuals selectively deprived of REM sleep do not manifest the same degree of daytime sleepiness, as assessed by the MSLT, compared to subjects deprived of NREM sleep. In fact, individuals deprived of REM sleep in that study had relatively little change in their MSLT results compared to baseline.

Several limitations should be considered in the interpretation of our results. Although the present study included a large number of patients across the spectrum of sleep-disordered breathing

Table 3—Multivariable proportional hazards model and relative risks for patients (n=454) within the first NREM-AHI quartile (<8.3 events/hr)

Predictor Variable	Relative Risk†	95% CI
Age, years	**1.07**	**1.02 - 1.12**
Gender, (M vs. F)	0.94	0.74 - 1.18
BMI, kg/m^2	1.04	0.96 - 1.12
Time in bed, minutes	**0.74**	**0.66 - 0.84**
NREM time, minutes	**1.32**	**1.18 - 1.46**
REM time, minutes	**1.42**	**1.25 - 1.61**
REM-AHI, events/hr	1.01	0.94 - 1.10

†Adjusted relative risks are for a 5-year increment in age; 5-unit increase in BMI; 30-minute increase in time in bed, NREM and REM time; and a 10-point increase in REM-AHI

severity, causality cannot be inferred based on our cross-sectional data. Definitive assessment of causality would require a controlled study of treatment in patients with REM-related disease and daytime sleepiness. However, until such studies are available, the data presented herein suggest that REM-related sleep-disordered breathing is not associated with daytime sleepiness. A second limitation is the selection of only those patients who underwent MSLT. While there were statistically significant differences in sleep architecture between patients with and without an MSLT, no differences were observed in the severity of disordered breathing between the two groups. Finally, our assessments of nocturnal sleep and daytime sleepiness were based on methods (i.e., polysomnography and MSLT) that can be influenced by a number of factors. It is well established that unfamiliar surroundings of the sleep laboratory and night-to-night biological variability can introduce bias in the physiologic characterization of sleep with an in-lab polysomnogram.[14,15] Similarly, a number of factors including duration of prior sleep, circadian rhythms, and neurobehavioral and motivational factors, can have a significant impact on the results of the MSLT. However, at present the in-lab polysomnogram and the MSLT represent standardized methods for the assessment of sleep and daytime sleepiness.

Despite the aforementioned limitations, this study has several strengths. The inclusion of a large sample of patients across the spectrum of disordered breathing severity allowed us to investigate, using a unique analytical approach, the associations between daytime sleepiness and NREM- and REM-related respiratory events. Moreover, given the substantial variability in sleep-disordered breathing severity during NREM and REM sleep in our study sample, we were able to thoroughly explore the independent effects of respiratory events in each sleep stage. Finally, the use of the MSLT in the current study provided an objective measure of daytime sleepiness. Despite the controversy surrounding the appropriate and ideal method for assessing daytime sleepiness,[16,17] the MSLT is a widely accepted method for quantifying the level of daytime sleepiness.[6,7]

Although the MSLT provides valuable information in the evaluation of patients with a primary hypersomnia, its role in patients with sleep-disordered breathing remains controversial. At the present, there are no outcome studies examining the clinical utility of the MSLT in patients with sleep-disordered breathing. In patients with severe underlying disease, clinical decisions are usually based on subjective reports of daytime sleepiness and the risk for cardiovascular disease. Thus, objective documentation of daytime sleepiness may not be necessary. However, in patients with mild to moderate sleep-disordered breathing, the MSLT can help identify severe daytime sleepiness in individuals that either deny or fail to recognize this symptom. Moreover, it may also help in the assessment of whether the level of daytime sleepiness can be attributed to the underlying apnea or possibly to another sleep-related disorder.

There are several implications of the current study. From the standpoint of disease classification, our results support the concept that the severity of sleep-disordered breathing should be assessed separately with NREM and REM indices. A composite or summary measure, such as the overall AHI, may inaccurately classify the severity of underlying disease. For example, using a composite index that weighs NREM and REM events equally, a patient with a minimal number of disordered breathing events in NREM sleep and a high number in REM sleep could be classified as having moderate sleep-disordered breathing. Conversely, a patient with a high number of disordered breathing events in NREM sleep and none in REM sleep has the potential of being classified as having milder disease. The use of sleep-state dependent indices (NREM-AHI and REM-AHI) provides a better characterization of disease severity than the use of an overall summary measure. Finally, from a clinical perspective, our study suggests that there is a direct relationship between daytime sleepiness and the severity of sleep-disordered breathing during NREM sleep. Therefore, in an excessively sleepy patient with mild sleep-disordered breathing during NREM sleep or sleep-disordered breathing exclusively in REM sleep, other potential causes of daytime sleepiness should be considered. The question of whether patients with isolated REM-related respiratory events require treatment is unknown since the impact of these events on other outcomes, such as neurocognitive and psychological function, remains to be determined.

In conclusion, our results indicate that disordered breathing episodes during REM sleep are not associated with daytime sleepiness. In contrast, disordered breathing episodes during NREM sleep are associated with increased risk of daytime sleepiness. Based on our findings, we recommend that, as clinical and epidemiologic studies assess the impact of respiratory disturbance during sleep, sleep-disordered breathing should be characterized using separate sleep state dependent indices.

Table 4(a)—Stratified multivariable proportional hazards models and adjusted relative risks† for daytime sleepiness by NREM-AHI quartile

	NREM-AHI Quartile		
Predictor Variable	**II**	**III**	**IV**
REM time‡, minutes	**1.31 (1.15 - 1.49)**	**1.20 (1.06 - 1.36)**	**1.25 (1.10 - 1.43)**
NREM time‡, minutes	**1.31 (1.18 - 1.47)**	**1.20 (1.10 - 1.31)**	**1.29 (1.19 - 1.41)**
REM-AHI‡, events/hr	1.02 (0.97 - 1.07)	1.04 (0.99 - 1.09)	1.03 (0.99 - 1.07)

†Adjusted for age, gender, BMI, and time in bed
‡Relative risks for a 30-minute increase in REM and NREM time; and 10-point increase in REM-AHI

Table 4(b)—Stratified multivariable proportional hazards models and adjusted relative risks† for daytime sleepiness by NREM-AHI quartile

	NREM-AHI Quartile		
Predictor Variable	**II**	**III**	**IV**
REM time‡, minutes	**1.33 (1.17 - 1.52)**	**1.21 (1.07 - 1.37)**	**1.28 (1.12 - 1.46)**
NREM time‡, minutes	**1.31 (1.17 - 1.47)**	**1.21 (1.11 - 1.32)**	**1.30 (1.20 - 1.41)**
NREM-AHI‡, events/hr	**1.21 (1.01 - 1.46)**	**1.20 (1.05 - 1.37)**	**1.10 (1.04 - 1.16)**
REM-AHI‡, events/hr	1.01 (0.96 - 1.06)	1.02 (0.97 - 1.07)	1.01 (0.96 - 1.05)

†Adjusted for age, gender, BMI, and time in bed
‡Relative risks for a 30-minute increase in REM and NREM time; and 10-point increase in REM- and NREM-AHI

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