Influence of Sex and Age on Duration and Frequency of Sleep Apnea Events

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Objectives: Differences between men and women potentially provide insight into the regulation sleep apnea events. This study, therefore, examined how apnea frequency and duration varied according to age, sex, and sleep stage in a clinical population.
Design: NA
Setting: NA
Patients: Patients were 215 women and 215 men referred to a sleep disorders center with symptoms of obstructive sleep apnea and matched for BMI. Apnea events were compared across three age groups (18-39, 40-59, and 60-88 years) in stage 2 and in REM sleep.
Interventions: NA
Results: In stage 2 sleep, young and middle aged women were similar averaging 15 and 13 apnea events per hour respectively. Men had significantly more events averaging 27 and 30 events per hour for the corresponding age groups. The apnea frequency doubled from middle age to older women, and the sex difference narrowed between the older males and females to a non significant difference (26 events per hour for women versus 34 events per hour for men). Apnea duration was significantly longer in men than in women. Stage 2 apnea duration increased significantly with age for men (20.1, 21.5, 23.8 s) and women (16.7, 18.3, 20.6 s) across the three age groups. This also occurred in REM sleep in for men (22.8, 26.5, 29.8 s) and women (19.3, 22.4, 26.6 s).
Conclusions: Duration did not demonstrate the marked "menopausal effect" that there was for apnea frequency. Female gender and younger age conferred benefit primarily by preventing airway collapse (reduced apnea frequency) with less of an effect on apnea duration, i.e., the ability to end the apnea. Compared to stage 2 sleep, REM sleep reduced the differences between men and women in apnea frequency. One explanation may be that differences in muscle tone of the upper airway account for the sex differences in apnea frequency.
Key words: Obstructive sleep apnea; apnea duration; menopause; sex differences; rem sleep; sleep, bmi

INTRODUCTION

IN A LARGE MIDDLE AGE WORKING POPULATION-BASED STUDY, men were 2.0 to 3.7 times more likely than women were to have apnea.[1] For patients presenting to a sleep disorders center, the male-female ratio often has been even larger.[2] This sex difference appears to be less in older patients with the change occurring somewhere in the middle age to older years.[3,4] Although women do appear to have shorter apnea events,[5] studies generally focus on differences in apnea frequency with less attention paid to apnea event duration. By comparing changes in sleep apnea event duration and frequency across different ages in men and women, we sought to gain insight into factors that affect the severity of obstructive apnea. Several possibilities may account for the difference in apnea observed in men and women including differences in respiratory drive,[6] upper airway muscle tone or upper airway anatomy.

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METHODS

Subjects

Physician-referred patients to an accredited sleep disorders center comprised the initial subject pool. Data for this study came from polysomnographic studies recorded over an approximate three-year period (1989–1991). Unlike recent diagnostic polysomnograms, most of these older studies were not divided into diagnostic and nasal CPAP titration portions (split-night studies). Patients from this pool composed the six study groups described below.

The inclusion criteria were 1) a history suggesting the possibility of obstructive sleep apnea; 2) an age of at least 18 years; 3) a total sleep time (time in bed minus time awake) of more than four hours; 4) a REM sleep percentage of at least five percent of the sleep period time (the time from the initial sleep onset to final awakening); 5) apnea events in both stage 2 and REM sleep, (i.e. an apnea/hypopnea index [AHI] in both stage 2 and REM sleep of at least one); and 6) apnea events that were primarily obstructive in nature, (i.e., obstructive events composed more than 60% of the total events). Excluded were patients who began nasal CPAP during the study or who had previously been studied polysomnographically for any reason.

Of the 840 subjects who met the inclusion and exclusion criteria, 610 were men (male to female ratio 2.7 to 1). Within this group the women were significantly older (49 vs. 45 years), heavier (34 vs. 31 BMI) and had fewer apnea events (16 vs. 26 AHI). They also had slightly less REM sleep percentage (15 versus 16). Women and men did not differ on total sleep time (388 vs. 399 min) or mean low oxygen saturation (79% for both).

These patients were then divided into three age groups that generally corresponded for women to premenopause, perimenopause/menopause, and postmenopause (18–39, 40–59, and 60–88 years). When the relationship of age and sex to BMI (kg/m^2) was examined, not only did an analysis of variance (ANOVA) indicate that women had a greater BMI ($F_{(1,834)}=47.87$, $p<0.001$), the difference was greatest for the younger women as indicated by a significant age by BMI interaction ($F_{(2,834)}=3.032$, $p=0.049$).

Table 1.—Final study groups: means and + standard errors for age, BMI, total sleep time (TST), and percentage of REM sleep

Age	18 - 40 yr.	40-59 yr.	60-88 yr.
Women			
N	54	120	41
Age	33 + 0.8	50 + 0.5*	68 + 1.0 *
BMI	34 + 1.0	33 + 0.7	31 + 0.8 †
TST	413 + 7.1	385 + 5.0	364 + 7.4 #
REM %	16 + 0.7	16 + 0.6	14 + 0.8
Men			
N	54	120	41
Mean Age	33 + 0.7	47 + 0.5	66 + 0.8
Mean BMI	34 + 1.0	33 + 0.7	31 + 0.8 †
TST	400 + 6.9	389 + 4.8	370 + 7.6 #
REM %	17 + 0.7	15 + 0.5	14 + 0.7

* = Significantly older than men in same age group.
† = Significantly lower BMI than the next youngest age group.
# = TST significantly decreased with age.

To control for BMI differences between men and women, we attempted to match each of the 230 women with a male within the same age group who was within two BMI units. However, five women were dropped from the youngest group (BMI = 50, 52, 62, 66 and 70), four women were dropped from the 40–59 year age group (BMI = of 50, 53, 53 and 60), and six women were dropped from the oldest group (BMI = 38, 39, 39, 42, 48, 49) because of a lack of matching men. The non-matching men also were dropped from the final study group. The matching was blind regarding the polysomnographic variables.

The final study group of 430 patients consisted of 215 women and 215 men. Compared to the pre-matched groups, the matching resulted in the BMI of women being somewhat less and that of men somewhat greater. Although matching reduced the BMI range among groups, BMI decreased with age. In addition, middle age and older women who were slightly older than men were in the corresponding age group (Table 1).

Polysomnography

Patients reported to the sleep disorders center approximately two hours before their usual bedtime. They completed a presleep questionnaire asking about medications and daytime activities. After preparation for bed, technicians attached transducers to measure EEG (C3 - A2), EOG (LOC and ROC), EKG, EMG (chin, anterior tibialis, surface intercostal/diaphragmatic), nasal airflow, and oxygen saturation from pulse oximetry. We recorded relative tidal volume as measured with inductance plethysmography (Respitrace®) calibrated with an iso-volume maneuver during the trial run.

Following an all night study, an experienced technician visually scored the PSG record for sleep stages and apnea/hypopnea episodes. When more than one sleep stage occurred in an epoch, the technician scored the predominant stage; or, if no one stage predominated, the technician scored the epoch as the sleep stage from which the apnea event originated. The duration of the apnea periods was measured from the end of exhalation to the beginning of inhalation as determined from the tidal volume channel. Criteria for scoring a hypopnea event were a drop in tidal volume by at least 50%, an oxygen desaturation of at least two percentage points, and an EEG arousal or EEG movement artifact on the EEG that lasted at least two seconds. The scoring technician counted respiratory events lasting ten seconds or longer. Apnea and hypopnea events were combined at the time of scoring and constitute the AHI. Thus, references to apnea refer to the apnea-hypopnea index. The sleep and apnea results were entered into a computer that calculated the various sleep stage parameters and the relationship to sleep apnea events. A diplomate of the American Board of Sleep Medicine then reviewed the PSG record and scoring. The data were stored on comput-

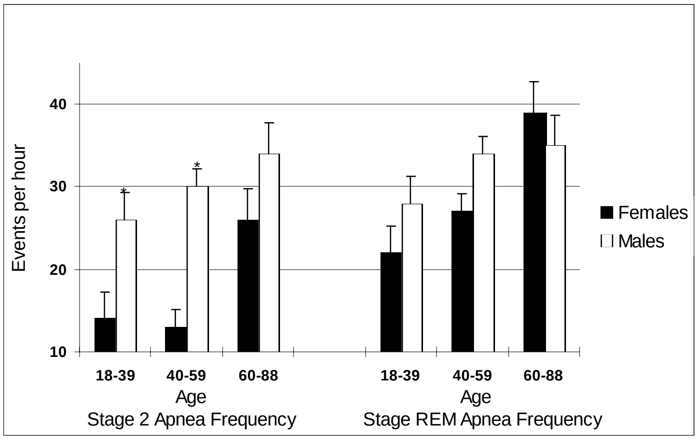

Figure 1.—The figure illustrates apnea event frequency (means and SEM bars) for Sex, Age groups, and Sleep Stage. Men had more apnea than women did in stage 2 sleep ($F_{(1, 423)} = 18.03$ $p < 0.001$). Apnea frequency increased with age for men and women ($F_{(2, 423)} = 5.95$, $p = 0.003$). Paired comparisons indicated that only for the young and middle age groups did men have more apnea than women did. A * indicates a significant difference between men and women for that age group.

er disk at the time of scoring and later retrieved for this study.

Data Analysis

The software program SYSTAT® performed all statistical analyses. The primary analysis consisted of performing an ANOVA for each of the two dependent variables (apnea duration and apnea frequency). The design was 2 (gender) by 3 (age groups) by 2 (sleep stage) with sleep stage analyzed as a repeated measures factor. Probabilities of less than 0.05 were considered significant.

Because BMI decreased with age, it was used as a covariate for analyzing apnea frequency and duration variables. Because the overall AHI positively correlated with apnea duration ($r=0.36$, $p<0.001$), AHI was used as a covariate in the ANOVA examining the effects of age and sex on duration. Where appropriate, t tests were used for paired comparisons. An ANOVA also was performed on the low oxygen desaturation with BMI used as a covariate.

To further examine the relationship with BMI, a regression analysis was performed with each of the dependent variables, stage 2 apnea index (S2I), stage REM apnea index (RI), Stage 2 apnea duration (S2D) and stage REM apnea duration (RD). A Bonferroni correction was applied to the overall F value probability to correct for the multiple tests. Finally, in a post hoc analysis, we computed the correlation between overall AHI and the difference between the mean duration of apnea in stage REM and apnea in stage 2 sleep.

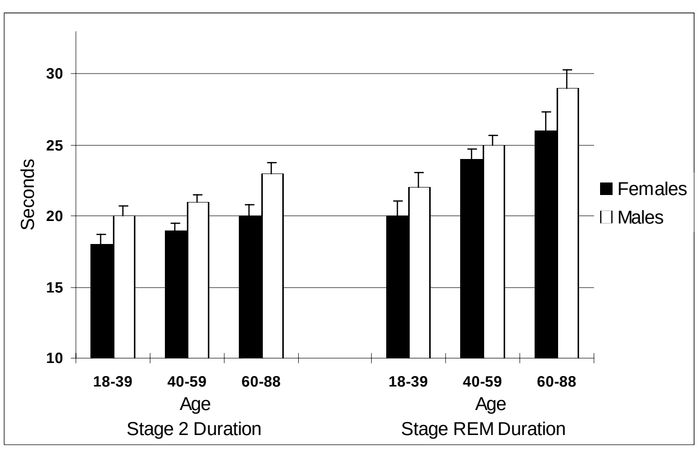

Figure 2.—The figure illustrates apnea event duration (means and SEM bars) for Sex, Age Groups, and Sleep Stage. Men had significantly longer apnea events than women ($F_{(1, 422)}=12.23$, $p=0.001$). Duration significantly increased with age ($F_{(2, 422)}=13.17$, $p<0.001$). The older the subjects, the greater was the difference between REM sleep and stage 2 sleep ($F_{(1,422)}=6.39$, $p=0.002$). Unlike with apnea frequency, men and women did not differ at specific age groups.

RESULTS

Apnea Frequency (Figure 1)

Only in stage 2 sleep and not in REM sleep did men have more frequent apnea events than women. This was reflected by an interaction between sleep stage and sex ($F_{(1,423)}=18.03$ $p<0.001$). The frequency of the apnea events significantly increased with age in stage 2 and REM sleep for both men and women ($F_{(2,423)}=5.95$, $p=0.003$). Paired comparisons among the female groups indicated that only the 60–88 year old group differed from the two younger groups ($p<0.05$). Also, only for the oldest group was there no significant difference in apnea frequency between the men and women.

The covariate BMI was significantly and positively related to apnea frequency ($F_{(1,423)}=53.13$, $p<0.001$). Also BMI interacted with sleep stage ($F_{(1,423)}=16.14$, $p<0.001$) in that increased BMI was related to increased apnea frequency in REM sleep more than in stage 2 sleep.

Apnea Duration (Figure 2)

The duration of the apnea events also increased with age ($F_{(2,422)}=13.17$, $p<0.001$). Men had slightly longer apnea events than women ($F_{(1,422)}=12.23$, $p=0.001$). There was not a significant difference between REM and stage 2 sleep ($F_{(1,422)}=3.36$, $p=0.067$) although there was a significant interaction between sleep stage and age ($F_{(1,422)}=6.39$, $p=0.002$). The older subjects had a greater difference between REM sleep and stage 2 sleep duration. The covariate, BMI, did interact with sleep stage ($F_{(1,422)}=15.53$, $p<0.001$). Increased BMI was associated with longer apnea events in REM sleep.

Low Oxygen Desaturation

In addition to a significant ANOVA indicating that overall women did not have as severe a desaturation as men (79.5 vs. 74.8, $F_{(1,423)}$=11.20, p=0.001), there was an interaction between Sex and Age Groups ($F_{(2,423)}$=3.36, p= 0.036). For women, mean low oxygen desaturation declined with age (83.7, 79.9, and 74.9) with the oldest group's value approaching that of men. For women, paired comparisons indicated that the groups did differ significantly except between the youngest and middle age groups that did not significantly differ (p=0.074). For men, mean low oxygen desaturation did not decrease with age (74.4, 74.8, 75.4).

Regression Analyses (Table 2)

In stage 2 sleep, only in men was BMI significantly related to the frequency of apnea. As BMI increased, so did the apnea frequency. In REM sleep, more frequent apnea events accompanied increasing BMI for both men and women.

For apnea duration measures, there was less of a relationship with BMI. In stage 2 sleep, women with a greater BMI had slightly shorter apnea events. Apnea duration in men also slightly decreased with increasing BMI although this was not significant. Conversely, in REM sleep, apnea duration increased with BMI. This relationship was significant only in the male subjects.

DISCUSSION

If women had a less collapsible airway as the result of greater muscle tone, then REM sleep and aging, both typically accompanied by decreases in muscle tone, should reduce the sex difference in apnea frequency more that duration. This appears to be the case. Other findings are that apnea events in men are more sensitive to changes in BMI (i.e., increasing weight is more likely to increase apnea frequency in REM sleep and in stage 2 sleep); and, REM apnea events become longer than stage 2 apnea events as the respiratory system is apparently stressed by aging, frequent apnea events, and obesity.

Apnea Frequency

Young and middle age women did not differ from each other but had far fewer apnea events than did men. Older women had more frequent apnea events than the two younger groups. The difference was dramatic with approximately twice the apnea frequency in the older group. Unlike women, men had a near linear increase in the apnea frequency across the three age groups. Therefore, young to middle age status helped to shield women against airway collapse while older women were similar to older men.

Although we did not determine the menopause status of the women, the median age of women at the time of menopause is 50–51 years with a typical range of 48–55 years. Menopause related changes begin even earlier with a decrease in ovarian sensitivity to gonadotropin stimulation, a decrease in conception rate and a reduced pregnancy rate after the age of 40.[7] In addition, an increase in LH and FSH may precede menopause by four to six years respectively.[8] Therefore, if a change in the hormonal environment directly determined the change in apnea frequency, some increased apnea frequency should be apparent in the 40–59 year old group. This lack of immediate response suggests a complex effect that is consistent with the poor response to short-term treatment of sleep apnea syndrome with estrogen replacement.[9]

Because changes in apnea duration with age were not particularly unique for women, differences in arousal or termination of apnea events are unlikely related to the fac-

Table 2.—Regression analyses for BMI against the stage 2 apnea index, stage REM apnea index, stage 2 apnea duration and REM duration.

	Females (N = 215)			Males (N = 215)		
Dependent Measures	Y intercept	Slope	*p*	Y intercept	Slope	*p*
Stage 2 Index	6.0	0.3	ns	-8.1	1.2	<0.001
Stage REM Index	-5.6	0.2	<0.001	-20.3	1.6	<0.001
Stage 2 Duration	23.0	-0.1	0.033	23.7	-0.1	ns
Stage REM Duration	20.5	0.1	ns	21.3	0.2	ns

ns = not significant. The *p* values are for the slope value after a Bonferroni correction. For each unit change in BMI, the slope gives the expected change in apnea variables. For example, a one-unit increase in BMI will increase the apnea index in REM sleep in men by 1.6.

tors responsible for sex differences in apnea frequency. Instead, the differences in apnea frequency suggest that airway collapsibility, possibly mediated through change in soft tissue composition, fat distribution or muscle function, contribute to the sex differences. Upper airway muscle tone may account for sex, age, and sleep stage differences in apnea frequency. At least during wakefulness, women do appear to have greater genioglossal muscle tone.[10] In REM sleep, women have an apnea frequency closer to that of the men. Thus, age and REM sleep, both accompanied by reduced muscle tone reduce apnea event differences between men and women.

Apnea Duration

Although apnea event duration is greater in older men during REM sleep, the duration actually varied within a relatively narrow range compared to apnea frequency. Men averaged apnea events that were about three seconds longer than women; age was associated with increased duration in a linear fashion from approximately 19–23 seconds; and, the age effect was greater in REM sleep than in stage 2 sleep by about three seconds. The narrow range even within these pathological groups reflects the success of the probably redundant systems for ending apnea events.

An increase in apnea duration may reflect a number of changes. These include 1) A breakdown in sensing apnea events (e.g., loss of chemoreceptor sensitivity with aging);[11,12] 2) A reduction of the stimulus that triggers an arousal (e.g., reduced proprioception because of loss of muscle fibers occurring with aging);[13,14] 3) Greater sleepiness that counteracts the arousal stimuli.[15,16] Because sleep deprivation results in a greater increase in apnea duration in REM sleep than in NREM sleep,[17] the greater duration in REM sleep for the older groups may result from increased sleepiness. Apnea events were not necessarily longer in REM sleep particularly in young subjects with few apnea events. Long REM sleep events appear related to stressors of age, obesity and apnea frequency. Without these, apnea duration in REM and NREM sleep is similar.

Study Design Issues

Because this was a non-randomized cross sectional study, physicians may have used different criteria for referring men and women to the sleep disorders center; or, older patients may have had a higher complaint threshold, (i.e., less likely to complain to their physician), and women may have had a lower complaint threshold. However, biased sampling is unlikely to entirely explain the dramatic increase from middle age to older women only for apnea frequency and not for other measures. Also, despite differences in methodology, the ratio of men to women with sleep apnea was close to that of the Wisconsin population-based study.[1]

Two findings suggest that a harvesting effect of older more severely ill patients occurred that could have decreased the apparent effects of aging and sex. The mean BMI declined with age suggesting that obesity increased mortality. Also, the frequency of REM apnea events in the oldest men plateaued and therefore did not show the increase it did between the young and middle age groups.

Finally, because this study did not take into account factors such as other disease states and medications,[18] the increased duration of apnea events with age may have been affected by either or both of these, perhaps with REM sleep more susceptible. These factors may have blunted respiratory center sensitivity thus delaying the arousal response. Thus the results potentially reflect a combination of age-dependent changes (those directly related to aging) and age-related changes (those related to comorbid conditions).

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