

# Effects of Menopause and Nasal Occlusion on Breathing during Sleep

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Prevalence of sleep-disordered breathing (SDB) is reported to increase in menopausal women. We examined response to a nocturnal respiratory challenge (nasal occlusion) during overnight polysomnography in 31 women (45 to 55 yr). Thirteen were premenopausal, four perimenopausal, and 14 postmenopausal by history and hormonal assay. Nasal occlusion increased the apnea hypopnea index (AHI) (occlusion mean =  $6.6 \pm 8.0$  versus baseline mean =  $1.6 \pm 2.6$ ,  $p < 0.01$ ) and arousal index (occlusion mean =  $35.1 \pm 20.1$  versus baseline mean =  $20.7 \pm 11.6$ ,  $p < 0.001$ ), but did not change the oxygen saturation nadir in those with respiratory events (occlusion mean =  $91.8 \pm 4.2$  versus baseline mean =  $92.0 \pm 11.6$ ). Menopausal groups did not differ on AHI, arousal index, or oxygen saturation nadir in either condition. Key variables were compared between occlusion responders ( $n = 11$ ) and nonresponders ( $n = 20$ ). Responders and nonresponders were not distinguished by age, menopausal status, nor several cephalometric or anthropometric variables. Body mass index ( $31.1 \pm 8.5$  versus  $24.3 \pm 3.4$ ,  $p < 0.003$ ), neck circumference ( $34.0 \pm 2.5$  versus  $32.5 \pm 1.7$  cm,  $p < 0.05$ ), and mandibular-hyoid distance ( $18.5 \pm 3.8$  versus  $14.5 \pm 5.7$  mm,  $p < 0.05$ ) were greater in responders. These findings suggest hormonal factors may be less important than weight and facial morphology in midlife development of SDB in women. **Carskadon MA, Bearpark HM, Sharkey KM, Millman RP, Rosenberg C, Cavallo A, Carlisle C, Acebo C. Effects of menopause and nasal occlusion on breathing during sleep.**

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The majority of patients diagnosed with sleep-disordered breathing (SDB) are men (1), a sex bias confirmed in epidemiologic studies in the United States (2, 3), Scandinavia (4, 5), and Australia (6, 7). The reasons for this sex difference are not well understood. One hypothesis is that female hormones may protect women from developing SDB (8), based on observations that SDB appears to be more common in menopausal than in menstruating women (9). Several alternative explanations have also been put forth. For example, body fat is highly correlated with SDB in men (2, 10), and the prevalence of sleep apnea is high in obese women (11). Furthermore, in a patient population of women with obstructive sleep apnea syndrome, body mass index (BMI) was reported to be more important than menstrual status (determined by self-report) as a predictor of apnea severity (12). These data suggest that increases in body mass or changes in weight distribution associated with menopause may promote postmenopausal development of SDB. Increasing age per se may also be a risk factor for the development of SDB in women, linked

perhaps to age-related changes in the tone of the upper airway or to chemoreceptor responsiveness.

The present study examines susceptibility to SDB as a function of menopause with age controlled. Because age and menopausal status are highly correlated, subjects were selected from a restricted age range in an attempt to minimize the potentially confounding effect of age on the relationship between SDB and menopausal status. Because occluding the nasal airway in normal male subjects leads to an increase in episodes of apnea and hypopnea during sleep (13, 14), nocturnal nasal occlusion was used as a challenge to assess susceptibility to SDB in these women.

A secondary aim of the study was to examine the relationship of SDB susceptibility to age, anthropometric, and cephalometric variables in this sample. Finally, the possible relationship between menopausal status and susceptibility to upper airway resistance syndrome (UARS), a breathing disturbance in sleep characterized by arousals not accompanied by frank apneic episodes (15), was also examined by assessing arousal responses to nocturnal challenge. Thus, we assumed that any relationship found between SDB and menopausal status may also extend to the minimally disordered breathing found in UARS.

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## METHODS

### Subjects

Subjects were recruited by newspaper advertisements and flyers which briefly described the study and invited interested women 45 to 55 yr of

age with no history of sleep disorders to telephone the laboratory. Potential subjects were then screened by telephone interview. Exclusion criteria were: surgical menopause, current use of hormone replacement treatment, pregnancy, use of medication affecting the central nervous or respiratory systems, self-report of sleeping < 7 h per night, report of sleep disorders or major sleep problems (women who reported snoring were not excluded), current or recent (within 1 yr) smoking, high caffeine intake (i.e., unable to reduce consumption to  $\leq 2$  cups of caffeinated beverage per day during the study), having full dentures, undergoing orthodontic treatment requiring braces, or major physical illness such as epilepsy (assessed during later examination by a physician). We attempted to include only those women who were clearly either pre- or postmenopausal. Potential volunteers who reported fluctuations in menstrual cycle length in conjunction with other menopausal symptoms, such as hot flashes, were considered perimenopausal and excluded. (Despite this exclusion four subjects were later found to be perimenopausal as described subsequently.) Thirty-two women fulfilling the above criteria were recruited. One woman was unable to tolerate the occlusion procedure, and her data were excluded from this report.

### Selection of Variables

An *a priori* decision was made to examine a limited number of variables to describe the responses to nocturnal nasal occlusion and to attempt to explain such responses. Thus, we chose three major dependent variables: apnea hypopnea index (AHI, number of apneas and hypopneas per hour of sleep), arousal index (number of transient arousals and awakenings per hour of sleep), and oxygen saturation ( $\text{SaO}_2$ ) nadir. These measures are commonly used to characterize SDB. Our independent or predictor variables were selected on the basis of existing data indicating their contributions to SDB in epidemiologic or clinical studies. Menopausal status was the chief independent variable. BMI was selected as it has been consistently related to SDB across populations (2-7). Among cephalometric parameters, posterior airway space (PAS) and vertical position of the hyoid (MP-H) were chosen as they have shown the most consistent relationships to obstructive sleep apnea syndrome (16). In addition, we chose several anthropometric measures for which evidence of a relation to SDB was available. These variables included neck circumference, neck skinfold, and skinfold sum (triceps + subscapular), each of which has been reported to be elevated in association with SDB (17, 18).

### Menopausal Status

Subjects completed a questionnaire and were interviewed about their menstrual history to determine frequency and regularity of menstrual periods, length of time since last menstrual period, and occurrence of hot flashes. In addition, all subjects still menstruating kept a menstrual cycle diary for at least two menstrual cycles. Women with irregular menses kept diaries for up to four cycles. Each subject had a morning blood sample drawn for hormonal measures following the overnight sleep study. Serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were determined by Smith-Kline Beecham Laboratories using a fluoroimmunoassay (Delfia Pharmacia, Turku, Finland). Normal adult female ranges of concentrations from the low levels of the luteal phase to the high levels of the ovulatory peak are 0.6 to 13.3 mIU/ml for FSH and 0.5 to 71.8 mIU/ml for LH. Postmenopausal ranges of concentration are 31.0 to 134.0 mIU/ml for FSH and 15.0 to 64.0 mIU/ml for LH. Serum estradiol and progesterone concentrations were determined by radioimmunoassay using reagents from Diagnostic Products Corporation, Los Angeles, California. Normal adult female ranges for serum to estradiol in all phases of the menstrual cycle combined are 10 to 375 pg/ml, and in postmenopausal women older than 60 yr values range from nondetectable to 14 pg/ml. In premenopausal women in the follicular phase of the menstrual cycle, normal values for progesterone range from 0.1 to 1.5 ng/ml. In women in the luteal phase, the normal range is 2.5 to 28.0 ng/ml. Postmenopausal women have progesterone values ranging from nondetectable to 0.7 ng/ml.

### Anthropometric Measures

Anthropometric measures were performed by a trained nurse researcher (CC) while subjects wore only an examination gown. Height and weight were measured using a standard balance beam scale and sliding height

measure; body mass index ( $\text{BMI} = \text{kg}/\text{m}^2$ ) was calculated for each subject. Skinfold thickness was measured at the triceps, subscapular, and neck with Lange skinfold calipers (Cambridge Scientific Instruments, Cambridge, MA). Each measure was determined three times and an average value calculated to the nearest millimeter. "Skinfold sum" was calculated as triceps skinfold + subscapular skinfold. Three measures of neck circumference were made just inferior to the laryngeal prominence, and a mean value calculated to the nearest centimeter.

### Medical History and Physical Examination

A physician on the research team (RPM) obtained a detailed medical history and carried out a general physical examination on each subject.

### Cephalometric Measures

A lateral projection of the skull was obtained with the subject's head secured in a cephalostat using a film focus distance of 5 feet. All cephalograms were recorded using a mirror eye reference position and a natural head posture while the subject was standing. An Oralix Ceph unit (Philips Dental Systems, Shelton, CT), with a technique of 71 kVp and 10 mA at 0.8 s exposure time, Kodak T-mat G film, and Lanex rare earth screens were used. Soft tissue and bony structure points from the radiographs were digitized using Quick-Ceph cephalometric software (Orthodontic Processing, Chula Vista, CA), and tracings were constructed. This method is highly reproducible (19) and allows superimposition of serial radiographs. Among measures obtained from these procedures were MP-H (mm) and PAS (mm).

### Procedure

**Polysomnography and nasal occlusion.** Three consecutive nights of polysomnography (PSG) were performed on each subject. All recordings began between 10:00 P.M. and 11:00 P.M. Recording time (i.e., lights out to lights on) ranged from 7.4 to 8.0 h (mean =  $7.9 \pm 0.1$  h). Twelve subjects in the premenopausal group were studied during the follicular phase of their menstrual cycle and two in the late luteal phase. The following variables were measured during the continuous nocturnal recordings: electroencephalogram (EEG) (from C3/A2 or C4/A1 and O1/A2 or O2/A1), right and left electro-oculogram (EOG), electromyogram (EMG) submental, nasal and oral airflow by thermistors or thermocouples, respiratory effort using mercury-filled or piezocrystal strain gauges taped to the chest and abdomen.  $\text{SaO}_2$  was measured with an Ohmeda Biox 3740 or Biox III pulse oximeter using a finger probe, and electrocardiogram (ECG) was recorded from a modified lead II position with electrodes taped to the right shoulder and left side. All recordings were made on Grass Instruments polygraphs at a paper speed of 10 mm/s. No intervention was carried out during Night 1 (adaptation night) or Night 2 (baseline night). On Night 3 (occlusion night), the nose of each subject was occluded by placing a piece of gauze impregnated with petroleum jelly just inside the nasal vestibule bilaterally and covering the nares with tape, a technique described by Olsen and coworkers (13).

Sleep was scored visually in 30-s epochs using standard criteria (20). Transient arousals ( $\geq 3$  s) were determined according to the criteria of the American Sleep Disorders Association (21). Arousals  $\geq 15$  s in duration were classified as awakenings. An apnea was scored when airflow fell below 20% of the preceding steady-state respiration amplitude for at least 10 s during sleep. An hypopnea was scored when the airflow signal dropped to between 20 and 50% of the preceding steady-state amplitude for at least 10 s, accompanied either by an arousal or a  $\geq 4\%$  drop in oxygen saturation. The following indices were calculated: AHI and number of arousals plus number of awakenings per hour of sleep (arousal index). In subjects with respiratory disturbance, the  $\text{SaO}_2$  nadir recorded overnight was noted.

**Data analysis.** Data were analyzed using Systat (22). The effects of menopausal group and nasal occlusion on the dependent variables were examined using repeated-measures analysis of variance (ANOVA) with group as a between-subjects variable and night (baseline or occlusion) as a within-subject variable. In most analyses, a probability value of 0.05 was considered significant, but Bonferroni adjustment of the probability value was used when multiple comparisons were made. Mean data are presented  $\pm$  standard deviation (SD).

TABLE 1  
RANGE, MEAN, AND STANDARD DEVIATION VALUES OF LUTEINIZING HORMONE,  
FOLLICLE-STIMULATING HORMONE, ESTRADIOL (E2) AND PROGESTERONE IN BLOOD SERUM

	Premenopausal (n = 14)		Perimenopausal (n = 4)		Postmenopausal (n = 13)	
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
FSH, mIU/ml	2.5–13.7	6.6 ± 3.9	19.1–74.2	39.1 ± 24.2	25.2–129.8	63.5 ± 28.4
LH, mIU/ml	1.7–10.1	5.3 ± 2.1	13.4–59.1	32.9 ± 21.0	16.3–70.8	37.0 ± 14.0
Estradiol (E2), pg/ml*	27.4–230.1	89.3 ± 65.5	15.9–153.3	84.6 ± 97.2	20.5–45.2	30.1 ± 8.8
Progesterone, ng/ml*	0.2–0.6	0.4 ± 0.2	0.4–1.6	1.0 ± 0.8	0.2–0.4	0.3 ± 0.1

\* The estradiol and progesterone assays were conducted in a subgroup of 19 subjects; eight were premenstrual (recorded during the follicular phase of the menstrual cycle), two were perimenopausal, and seven were postmenopausal. In addition, two premenopausal women were recorded during the late luteal phase of their menstrual cycle. The values for these two subjects (not reported in the above table) were 2.3 ng/ml and 9.5 ng/ml for progesterone, and 65.6 pg/ml and 63.3 pg/ml for estradiol.

## RESULTS

### Menopausal Status

On the basis of menstrual cycle history and hormonal results, 14 subjects were premenopausal, 13 were postmenopausal, and four were perimenopausal. The hormonal results are summarized in Table 1. In women classified as premenopausal, menstrual diaries indicated regular menses (range of cycle length, 24.5 to 35.0 d, mean  $28.1 \pm 3$  d), FSH and LH concentrations in the normal adult female range, and FSH to LH ratio  $< 1$ . The postmenopausal women reported absence of menses for a mean  $2.9 \pm 1.7$  yr (range 11 mo to 6.5 yr), had menopausal levels of FSH and LH, and FSH to LH ratio  $> 1$ . According to their menstrual diaries, three of the perimenopausal women had irregular cycles. Cycle lengths ranged from 21 to 37 d in one woman, to 17 to 47 d in another. One woman had last had a complete menstrual period 9 mo prior to the study, but reported minor bleeding in the week before the study. All three reported menopausal symptoms, and had intermediate levels of FSH and LH, with FSH to LH ratio  $> 1$ . The fourth woman in the perimenopausal group had regular menses (cycle length 30.3 d), but reported menopausal symptoms and had high concentrations of FSH (19.1) and LH (13.4), with an FSH to LH ratio  $> 1$ . Serum estradiol levels and progesterone levels were not applied to determine subject classification, rather they were used to assess present hormonal status. Results of both serum estradiol and serum progesterone were available for 10 premenopausal, seven menopausal, and two perimenopausal women. The menopausal women had

significantly lower estradiol concentrations than the other two groups, but all subjects had measurable levels above the range described for older menopausal women. Progesterone levels were low in all women, except the two premenopausal women who were studied during the late luteal phase of the menstrual cycle.

### Age

Although the age range was restricted to one decade to minimize potentially confounding effects of age, significant differences in mean ages were found across menopausal groups ( $F_{2,28} = 21.5$ ,  $p < 0.001$ ). The menopausal women were older than pre- and perimenopausal women, but the latter groups did not differ (see Table 2).

### Anthropometric and Cephalometric Measures

BMI values ranged from 18.6 to 48.9 (mean =  $26.7 \pm 6.5$ ). Of the 31 women studied, 18 had BMI values  $< 25$ , six had BMI values between 25 and 29.9, and seven had BMI values  $\geq 30$ . BMI did not differ among menopausal groups. Furthermore, no differences were detected on the basis of menopausal group in PAS, MP-H, neck circumference, neck skinfold, or skinfold sum (Table 2). There was no correlation between any of the hormonal measures and either BMI or neck circumference.

### Breathing and Arousal Measures on the Adaptation and Baseline Nights

To determine if the occlusion challenge test used in this study

TABLE 2  
ANTHROPOMETRIC AND CEPHALOMETRIC MEASURES\*

	Premenopausal (n = 14)	Perimenopausal (n = 4)	Postmenopausal (n = 13)
Age <sup>†</sup> , yr	46.9 ± 0.5	48.8 ± 2.5	52.7 ± 2.6
BMI	25.8 ± 5.3	26.4 ± 3.5	27.4 ± 8.0
Neck circumference, cm	32.9 ± 2.0	34.4 ± 2.0	32.8 ± 2.2
Neck skinfold, mm	13.8 ± 4.8	11.0 ± 4.5	13.1 ± 5.0
Skinfold sum			
Triceps + subscapular, mm	68.3 ± 14.9	56.4 ± 21.1	63.2 ± 20.7
MP-H, mm	16.4 ± 5.9	13.3 ± 1.6	16.2 ± 5.7
PAS, mm	13.6 ± 3.9	14.1 ± 4.2	12.9 ± 2.5

Definition of abbreviations: BMI = body mass index; MP-H = vertical position of hyoid; PAS = posterior airway space.

\* Results are expressed as mean ± SD.

† Significant effect of group ( $p < 0.001$ ). Pre- versus postmenopause,  $p < 0.001$ ; peri- versus postmenopause,  $p = 0.02$ ; peri- versus premenopause, ns. There were no significant differences between groups on any other variables.

TABLE 3  
BREATHING AND AROUSAL MEASURES ON ADAPTATION,  
BASELINE, AND OCCLUSION NIGHTS\*

	Premenopausal (n = 14)			Perimenopausal (n = 4)			Postmenopausal (n = 13)		
	Adaptation	Baseline	Occlusion	Adaptation	Baseline <sup>†</sup>	Occlusion	Adaptation	Baseline	Occlusion
AHI	0.7 ± 1.2	1.2 ± 1.8	7.8 ± 11.0	0.3 ± 0.3	0.3 ± 0.1	4.4 ± 5.9	2.0 ± 5.1	2.5 ± 3.5	5.9 ± 4.3
Nadir SaO <sub>2</sub>	93.6 ± 2.8	92.6 ± 2.3	92.6 ± 2.6	93.5 ± 2.1	94.8 ± 1.3	93.8 ± 2.1	92.5 ± 3.2	90.4 ± 6.6	90.2 ± 5.5
Arousal index	23.2 ± 9.7	20.4 ± 9.3	36.9 ± 21.7	13.4 ± 3.5	12.1 ± 2.0	23.4 ± 12.7	25.2 ± 16.7	23.6 ± 14.3	36.8 ± 20.1

Definition of abbreviations: AHI = apnea hypopnea index.

\* Results are mean ± SD. Adaptation and baseline nights did not differ for AHI, nadir SaO<sub>2</sub>, or arousal index; however, all three variables differed significantly between baseline and occlusion nights as described in the text.

produced more respiratory disturbance than could be attributed to night-to-night variability alone, AHI, SaO<sub>2</sub> nadir, and arousal index values recorded on the baseline night were compared with those recorded on the adaptation night to determine night-to-night variability. We found no differences between adaptation and baseline values for these measures (Table 3). Data collected on the adaptation night are not discussed further in this study. Data collected on the baseline night are considered "baseline data" in subsequent analyses.

At baseline only two subjects had sleep-disordered breathing, defined as AHI > 5. The first, a premenopausal subject, had AHI of 6.5, was 50.2 yr old, and had a BMI of 23.8. The second was in the menopausal group, with AHI of 12.8, was 50.8 yr old, and had a BMI of 24.3. For all subjects, neither SDB nor arousal frequency at baseline differed among menopausal groups (see Table 3).

#### Relationship between Menopausal Status and Response to Occlusion

ANOVA was used to examine the effect of menopausal group on response to occlusion. No effect of menopausal group was found for AHI, arousal index, or SaO<sub>2</sub> nadir (Table 3). Furthermore, there was no relationship between AHI on the occlusion night and either progesterone or estradiol.

#### Effect of Occlusion on Breathing and Arousal Measures

Nasal occlusion had a significant main effect on breathing and arousals. Mean AHI increased from 1.6 (± 2.6) at baseline to 6.6 (± 8.0) with nasal occlusion ( $F_{1,28} = 7.2$ ,  $p = 0.01$ ); mean arousal index increased from 20.7 (± 11.6) on baseline to 35.1 (± 20.4) with nasal occlusion ( $F_{1,28} = 13.1$ ,  $p < 0.001$ ). SaO<sub>2</sub> nadir, however, was not affected by nasal occlusion (baseline mean = 92.0 ± 4.8; occlusion = 91.8 ± 4.2) in subjects with evidence of respiratory disturbance. There were no significant group by night interactions on any of the analyses.

#### Effect of Occlusion on Sleep Measures

Compared with baseline, total sleep time (TST) was reduced on the occlusion night ( $F_{1,30} = 16.5$ ,  $p < 0.001$ ). The reduction in sleep time occurred both in non-rapid eye movement (NREM) sleep ( $F_{1,30} = 5.6$ ,  $p < 0.05$ ) and in REM sleep ( $F_{1,30} = 10.4$ ,  $p < 0.01$ ). To explore the possibility that the sleep disturbance produced by the intervention may have influenced AHI change unrelated to upper airway obstruction per se, we correlated AHI change (the difference in AHI between baseline and occlusion nights) with time in NREM and in REM sleep on the occlusion night. There was no correlation between AHI change and amount of either NREM ( $r = -0.03$ ,  $p = ns$ ) or REM sleep ( $r = -0.2$ ,  $p = ns$ ).

#### Predictors of Response to Nasal Occlusion

Independent of menopausal status, several subjects had striking responses to the nocturnal nasal occlusion procedure (Figure 1). Additional analyses collapsing across groups were undertaken

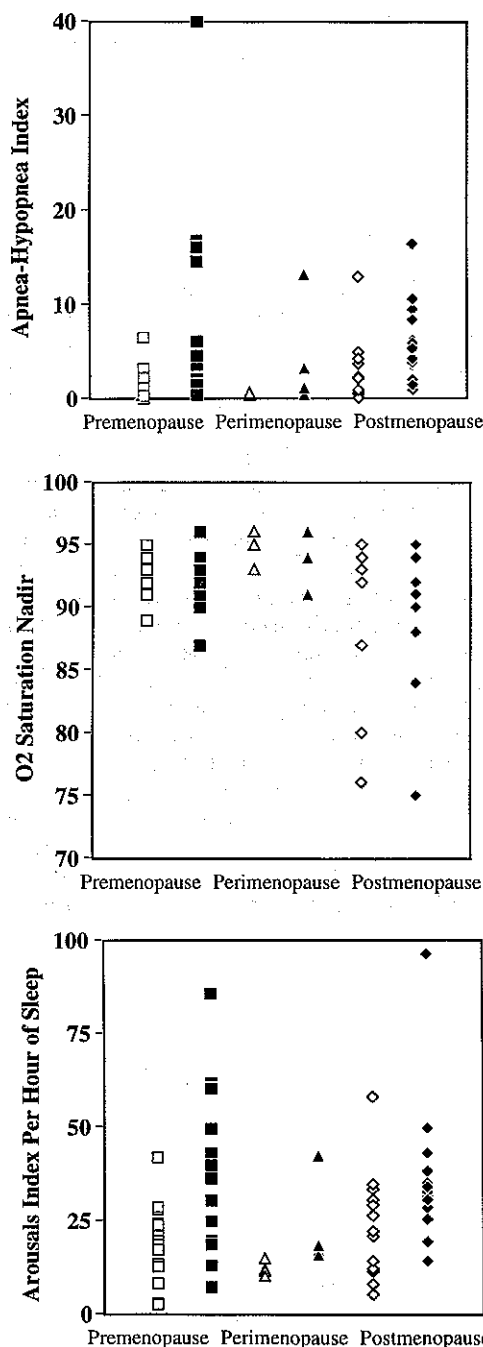


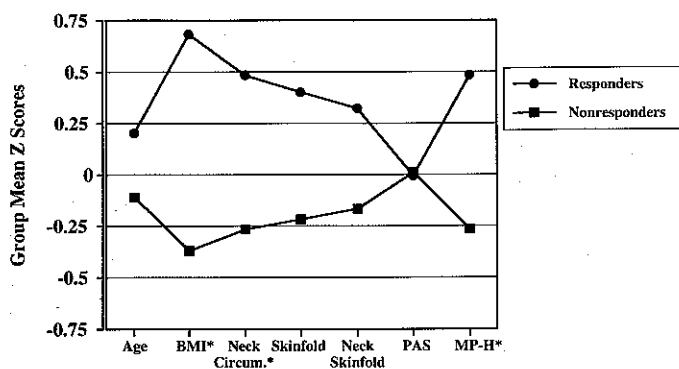
Figure 1. Responses to the occlusion procedure in individual subjects, grouped according to menopausal status. Values recorded on the baseline study night are represented by open (white) symbols and those on the occlusion night by closed (black) symbols. While some subjects clearly responded to the nasal occlusion procedure, this response was independent of menopausal status.

to identify factors that might predict response to the respiratory challenge. Responders to nasal occlusion were identified on the basis of two measures: (1) AHI increase of at least five events per hour on the occlusion night compared with the baseline night; or (2) an increase in arousals on the occlusion night exceeding one standard deviation of the group mean change value (i.e., increase from baseline of 32 or more arousals per hour of sleep). Eleven subjects were identified as responders to the occlusion procedure using these criteria. Three subjects fulfilled both the AHI and arousal criteria, six were included on the basis of increased AHI alone, and two subjects on the basis of arousal index alone. Of the eleven responders, five were in the premenopausal group, five were postmenopausal, and one was perimenopausal. Neither of the two premenopausal women studied during the late luteal phase of the menstrual cycle responded to the occlusion challenge. There was no difference between responders and nonresponders on any of the hormonal variables, nor was there any difference in TST on the occlusion night between responders and nonresponders.

A profile analysis was used to examine the pattern of variables potentially predictive of SDB in responders compared with nonresponders. Dependent variables assessed in the profile were age, BMI, neck circumference, neck skinfold, skinfold sum, MP-H, and PAS. To facilitate comparison among variables, z scores were computed for each variable used in the profile analysis. A main effect for group was found ( $F_{1,29} = 10.7, p < 0.01$ ), indicating a significant difference in the overall height of the profiles of responders and nonresponders. Figure 2 illustrates the responder and nonresponder group profiles derived from the z scores. Post hoc analyses showed that the responder group had a higher mean BMI than the nonresponders ( $31.1 \pm 8.5$  versus  $24.3 \pm 3.4, p < 0.003$ ), larger mean neck circumference ( $34.0 \pm 2.5$  cm versus  $32.5 \pm 1.7$  cm,  $p < 0.05$ ), and higher mean MP-H values ( $18.5 \pm 3.8$  mm versus  $14.5 \pm 5.7$  mm,  $p < 0.05$ ).

## DISCUSSION

We found no effect of menopausal status on women's responses to nocturnal nasal occlusion, a respiratory challenge delivered in sleep. This technique, previously shown to elicit SDB in men (13, 14), was also successful in inducing SDB in these female sub-



**Figure 2.** Z-score profiles of responders and nonresponders to nocturnal nasal occlusion. This figure shows the profiles of seven variables converted to z-scores in subjects who responded to the nasal occlusion challenge compared with nonresponders. Responders had a higher mean BMI ( $p < 0.003$ ) and larger mean neck circumference ( $p < 0.05$ ) than nonresponders. Responders also had higher mean MP-H values ( $p < 0.05$ ), indicating a more inferiorly positioned hyoid bone relative to the mandibular plane.

jects, leading to increased AHI and arousals compared with baseline values. Response to the procedure, however, did not differ in pre-, peri-, and postmenopausal women, indicating that menopausal status was not an important predictor of responsiveness to the challenge.

The most parsimonious explanation for this finding is that menopausal status does not affect response to nasal occlusion in sleep. This conclusion is supported by several studies in which no relationship between menopausal status and increased SDB in women has been found; several investigators have been unable to demonstrate the presence of a clear relationship between menopausal status and the prevalence of SDB either in a community population (2, 6), or in a patient population of obese women (12). Furthermore, Cistulli and colleagues (23) compared the occurrence of SDB in postmenopausal women with and without hormone replacement therapy in a repeated-measures design and were unable to demonstrate a difference in SDB severity when patients were taking hormonal supplements. Thus, menopausal status may not be a risk factor for the development of SDB, and the observed increase in SDB in older women may be due to other factors. Our findings support this interpretation. By recording women during the follicular phase, however, when progesterone values are low, we may have limited the putative "protective" value of progesterone in the premenopausal group.

On the other hand, the hormonal changes that accompany menopause occur over time, and it is possible that the previously hypothesized hormonal protection against SDB afforded to menstruating women does not stop abruptly when menses cease but rather diminishes across time. If so, perhaps insufficient time had elapsed for menopausal women in this study to have developed an increased susceptibility to the SDB challenge, as most had been menopausal for 3 yr or less and they still had circulating estradiol concentrations above the ranges typically described for postmenopausal women.

One might also query whether the nocturnal nasal occlusion challenge was adequate to examine menopausal susceptibility to SDB. The nasal airway is occluded in this challenge; however, the hormonal changes associated with menopause may affect other structures in the upper airway, or menopausal changes may alter the neurochemical control of breathing in sleep. Thus, critical structures or systems may not be challenged by nasal occlusion. For example, one subject in this study had moderate SDB (AHI = 12.5) before nasal occlusion and did not respond to the nocturnal challenge with an increase in either AHI or number of arousals per hour. Thus, one might argue that nasal occlusion may not be an appropriate challenge test to detect increased susceptibility to SDB in this population. Furthermore, although the arousal index may provide evidence of upper airway resistance syndrome not captured by the AHI, it is also possible that the two subjects who experienced a marked increase in arousals without an increase in AHI experienced sleep disruption unrelated to airway obstruction. As the procedure occluded the airway, however, the most likely explanation is that the arousals were associated with alterations in respiration.

Although no relation to menopausal status was detected, the nocturnal occlusion challenge produced a striking response in approximately one-third of the women in this sample. Our assessment of a set of predictor variables indicated that obesity (BMI) and structural features potentially affecting the upper airway (specifically hyoid position and neck circumference) were elevated in the responder group. It is notable that all measures of adiposity were much lower in this study than in another study of 25 female obstructive sleep apnea (OSA) patients of similar age (mean = 46.6 yr) in which no differences were found for anthropometric measurements of pre- versus postmenopausal patients (18). For example, in that study mean BMI was 34.5 (SEM = 1.6) in the postmenopausal patients and 36.9 (SEM =

2.8) in their premenopausal group compared with a value of 31.1 ( $\pm 8.5$ ) found in responders in the present study. Similarly, mean neck circumference was 39.8 cm (SEM = 1.2) in postmenopausal OSA women, and 37.5 cm (SEM = 0.9) in the premenopausal OSA patients compared with neck circumference values in our responders of 34.0 ( $\pm 2.5$ ) cm. These findings suggest that a sleep-disordered breathing continuum may exist, based on adiposity, and that the women who responded to the occlusion challenge in this study may be exhibiting early signs of the potential to develop SDB.

Also of interest is that the neck circumference measure was more strongly associated with SDB in our subjects than were the skinfold measures. This finding may indicate either that neck circumference is more reliably measured than skinfold or that neck circumference may serve as a better marker of the factors related to susceptibility to nasal occlusion. The latter seems likely as magnetic resonance imagery has detected a relationship between AHI and the amount of adipose tissue found adjacent to the pharyngeal airway in men (24).

MPH was higher in responders than nonresponders, indicating a more inferiorly positioned hyoid bone relative to the mandibular plane. Increased MPH has previously been reported in OSA patients (12, 25). That we have found such an association in women who respond to a respiratory challenge, but who do not have any evidence of sleep apnea under normal conditions, suggests that the position of the hyoid may be a risk factor for the development of SDB in women. Of additional interest was the lack of association between PAS and SDB susceptibility in our sample. This finding suggests that, in women, the size of the airway at the base of the tongue may be a less important predictor than the position of the hyoid, but confirmation is required in a clinical population.

The generalizability of the findings in this study is limited to some extent because the sample was relatively small and the age range was restricted by the study design. Nevertheless, subjects were a heterogeneous group in terms of BMI, and subjects were not excluded from the study on the basis of minor problems, such as reported snoring. Furthermore, although none of the women studied had major illnesses, we did not attempt to recruit a "super-healthy" sample. We therefore feel that the data collected are likely to be generalizable to other populations of healthy women in midlife.

In conclusion, our data do not support a role for menopause per se in susceptibility to SDB; however, as with other clinical and epidemiologic studies, we find that obesity and structural factors make significant contributions to SDB susceptibility in midlife women, specifically in response to a nocturnal nasal occlusion challenge.

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