The Influence of Menstrual Status, Body Weight and Hypothalamic Function on Nocturnal Respiration in Women

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A disorder of breathing during sleep with episodes of haemoglobin oxygen desaturation and apnoea has been described in asymptomatic men of all ages and normal weight postmenopausal women; an increase in body weight in either group is associated with a greater fall in oxygen saturation and an increased frequency of apnoea[1,2]. In contrast, obese women with regular menstrual cycles show a less severe fall in oxygen saturation during sleep and do not show sleep apnoea[3]. It has been proposed that the higher plasma progesterone levels in women with regular menstrual cycles is a protective factor against the development of sleep-disordered breathing[2], but, more recently, it has been suggested that sleep-breathing abnormalities are related to the age rather than the sex of a patient[4]. We have recently reported evidence that the hypothalamus is also important for the control of nocturnal respiration[3].

We have now investigated the relationship of body weight and central factors to sleep-breathing patterns in asymptomatic normal weight and obese postmenopausal women and six younger women with amenorrhoea and obesity due to a hypothalamic-pituitary disorder, whose only complaint was progressive weight gain.

Subjects and Methods

Tables 1 and 2 give details of the subjects studied. The obese patients were volunteers who had become obese either as a teenager or during adult life and were attending the Obesity Clinic; the control group of women were volunteers from the hospital staff. All of the subjects had normal thyroid function, were non-smokers and were not taking any form of medication. They had experienced regular menstrual cycles until the time of the menopause which had occurred at least two years prior to study. The patients with hypothalamic-pituitary disorders (Table 2) attended the Endocrine Clinic and were characterised by an insatiable appetite, progressive weight gain and amen-

Table 1. Details of women studied. W/H² weight (kg)/height² (m); VC: Vital capacity; FEV: forced expiratory volume in one second; PEFR: peak flow rate, expressed as a percentage of predicted normal.
Patient no. 1–9 : postmenopausal normal weight women
    „   no. 10–15: postmenopausal obese women
    „   no. 16–21: hypothalamic-pituitary disorders.

Patient no.	Age (yr)	Weight (kg)	W/H²	VC	FEV₁	PEFR
1	62	67	23	104	98	94
2	50	74	25	94	90	88
3	51	64	22	86	92	95
4	55	67	24	102	96	92
5	65	65	22	111	102	94
6	52	65	24	98	94	98
7	50	65	24	90	88	82
8	55	63	22	85	77	80
9	50	63	24	95	100	89
Mean ± SEM	54	66(± 1)	23	96	93	90
10	54	96	35	96	93	92
11	60	80	31	107	114	91
12	55	115	46	89	83	91
13	48	96	34	85	92	110
14	53	107	43	80	80	97
15	52	90	32	94	110	96
Mean ± SEM	54	98(± 6)	37	92	95	96
16	35	104	40	75	75	76
17	44	106	42	84	85	81
18	48	115	44	92	90	104
19	60	106	37	80	85	95
20	30	85	31	95	98	110
21	58	112	44	79	78	81
Mean ± SEM	45	105(± 4)	40	84	85	91

Table 2. Details of patients with hypothalamic-pituitary disorders.

Patient no.	Age at diagnosis	Diagnosis	Current treatment (daily dosage)
16	23	Craniopharyngioma treated by hypophysectomy and external radiotherapy	Hydrocortisone (30mg), thyroxine (200μg) and nasal DDAVP (0.2ml)
17	38	Hypopituitary after surgery and external radiotherapy for invasive chromophobe adenoma	Hydrocortisone (30mg), thyroxine (200μg) and nasal DDAVP (0.2ml)
18	48	'Hypothalamic syndrome'—unexplained hyperphagia and somnolence with hyperprolactinaemia. Normal CT cranial scan, menopause at age 45 years	Nil
19	45	Acromegaly treated by external radiotherapy. Subsequent pituitary apoplexy and rapid increase in weight	Hydrocortisone (25mg), thyroxine (150μg)
20	29	Hypopituitary following 2nd pregnancy with subsequent rapid weight gain	Hydrocortisone (30mg), thyroxine (200μg)
21	57	Progressive weight gain with daytime somnolence. Normal anterior pituitary function, CT cranial scan suggests a partially empty sella. Menopause at age 46 years	Nil

orrhoea; those patients requiring pituitary hormone replacement treatment were taking physiological doses and no patient was taking an oestrogen preparation. All the subjects were asymptomatic and none had a past history of a respiratory disorder. The hypothalamic-pituitary patients were investigated because of their progressive weight gain; none of them complained of hypersomnolence, severe snoring or extreme tiredness. It was only after investigation that a history of these complaints was confirmed by their husbands. Pulmonary function was assessed using a Wright peak flow-meter and a Vitalograph dry spirometer. Body index was defined as weight (kg) divided by height in metres^2 (normal female range 19–24). We considered patients to be obese if their body index exceeded a value of 26.

The methods for monitoring respiration during sleep were identical to those we have previously reported[3]. Obese subjects were studied for two nights but it was only possible to study the lean subjects for one. Airflow at the nose and mouth were sensed with a laryngeal microphone, movement of the chest and abdomen was assessed with inductance bands (Respitrace) which show the movement of chest and abdomen separately.

Apnoea was defined as a pause in airflow for more than 10 seconds; obstructive apnoea was characterised by increased respiratory effort with paradoxical collapse of the chest during inspiration with no airflow due to obstruction at the pharynx or larynx; central apnoea was indicated by the absence of airflow with no abdominal or chest movement and mixed apnoea if there was no movement early in the episode of apnoea and unsuccessful movement later in the episode[5]. Haemoglobin oxygen saturation (SaO_2) was measured with a Hewlett Packard ear lobe oximeter with the patient in the supine position. Sleep was staged with an electroencephalogram (C_4A_1), electro-oculogram and submental electromyogram using standard methods. Time to sleep (Ts) was defined as the time (in minutes) from the start of the study until the onset of sleep. Time to REM (TREM) was the time from onset of sleep until REM sleep. The number of episodes of waking (W) for periods of longer than one minute was also recorded. One of the investigators remained at the bedside throughout, noting the subjects' behaviour, such as snoring or restlessness, and recording this on the tracing. Timing of the events was also recorded on the tracing and each tracing was reviewed in detail and correlated with the stage of sleep. Statistical analysis was by a Wilcoxon non-parametric test, because the results were not normally distributed, and Spearman rank correlation test. Each subject gave fully informed written consent and the study was approved by the hospital's ethical committee.

Results

Pulmonary Function Tests (Table 1)

All the patients and controls had normal spirometric values—that is, between 75 per cent and 125 per cent of predicted normal.

Sleep Study

Time awake during the night and times for sleep stages I, II, III/IV, REM and REM latency and the number of arousals (W) during the night are given in Table 3. The mean time spent in the stages was not significantly different between the three groups but only 4 of 9 normal subjects, 2 of 6 obese and none of the hypothalamic-pituitary group showed stage III/IV. There was no significant difference found between the indices of sleep latency (Ts), TREM, number of arousals and percentage time of sleep spent in REM sleep. Two of the patients had numerous apnoeas, one of these (patient 18) had very poor sleep (90 minutes without REM) and 32 arousals, the other (patient 19) slept well but with 12 arousals and only 10 minutes of REM sleep.

Apnoea (Table 4)

Obstructive apnoea was not seen in the normal weight or obese subjects but three of the hypothalamic-pituitary patients showed this (cases 16, 18, and 19) and in cases 18

Table 3. Duration of sleep stage and analysis of sleep pattern in the women studied. Wake T: total time awake during night; Ts: time from start of study until onset of sleep; TREM: time from onset of sleep until REM sleep; W: number of episodes of waking >1 minute during night.
Patient no. 1–9: postmenopausal normal weight
„ no. 10–15: postmenopausal obese
„ no. 16–21: hypothalamic-pituitary disorders.

Patient no.	Sleep stage (min)					Total sleep time (min)	REM/(%) total sleep	Ts	TREM (min)	W
	Wake T	I	II	III/IV	REM					
1	121	118	98	6	55	273	20	105	47	3
2	237	67	101	9	10	187	5	147	185	4
3	111	111	135	–	8	254	3	25	260	5
4	14	51	259	55	42	407	10	5	290	4
5	14	188	183	–	77	448	17	7	97	2
6	153	129	136	–	22	287	8	12	215	6
7	187	45	87	11	14	122	11	5	175	5
8	172	39	165	–	34	237	14	35	215	5
9	127	24	175	–	35	232	15	10	45	6
Mean ± SEM	126 ± 25	86 ± 18	149 ± 18		33 ± 8	272 ± 34	11 ± 2	39 ± 17	170 ± 29	4
10	243	79	97	–	25	201	12	94	85	5
11	246	48	109	–	17	174	9	150	183	9
12	202	65	117	–	11	193	6	115	208	7
13	162	27	163	5	12	207	6	15	175	8
14	142	21	196	4	50	271	18	102	72	6
15	158	75	172	–	32	275	12	51	82	6
Mean ± SEM	192 ± 19	52 ± 10	142 ± 17		24.5 ± 6	220 ± 18	10.5 ± 2	88 ± 20	134 ± 25	7
16	56	45	273	–	33	351	9	4	119	4
17	216	43	124	–	35	202	17	17	134	5
18	330	53	37	–	0	90	–	167	–	32
19	149	79	159	–	10	248	4	42	285	12
20	145	78	114	–	68	260	26	21	108	5
21	97	32	151	–	51	234	22	31	230	3
Mean ± SEM	165 ± 40	55 ± 8	143 ± 32		33 ± 10	231 ± 35	13 ± 4	47 ± 25	146 ± 42	10

and 19 this was very frequent. In addition, case 19 showed mixed apnoea. The duration of apnoea was variable, patient 19 showing long apnoea (mean duration 24.5 ± 12, range 14–60 sec), patient 18 shorter apnoea (mean duration 18.2 ± 5, range 11–40 sec) and other patients showing no apnoeas longer than 25 sec.

Haemoglobin Oxygen Saturation (SaO₂)

All measurements were made in the supine position and are given in Table 4. The mean awake saturation did not differ significantly between the three groups. Oxygen saturation fell in all subjects on falling asleep but the mean asleep value was not significantly different between the three groups. In all subjects except patient 18 (in whom there was no REM sleep), the minimum oxygen saturation was seen during REM sleep. The mean minimum saturation value did not differ significantly between the normal weight and obese subjects but was significantly less in the hypothalamic-pituitary women ($P<0.01$ versus normals, $P<0.05$ versus obese). The lowest values were seen in the two hypothalamic-pituitary women with numerous apnoeas (cases 18 and 19) and case 21 in whom severe desaturation occurred during periodic breathing without apnoea.

Time spent asleep with SaO_2 less than 95 per cent was similar in the three groups, but the hypothalamic-pituitary group spent significantly longer time with SaO_2 less than 90 per cent ($P<0.01$). Two of these women had an oxygen saturation less than 90 per cent for greater than 60 minutes during the night, case 17 without apnoea and case 19 with apnoea.

There was no significant correlation in the 18 non-apnoeic women between body index or body weight, and total sleep time, total REM time, time awake or oxygen saturations. The narrow distribution of the patients' ages made it impossible to analyse the effect of age on sleep and nocturnal oxygen saturation.

Discussion

We have previously reported that premenopausal obese women have periods of oxygen desaturation but not

Table 4. Haemoglobin oxygen saturation values (%), number and types of apnoea during sleep in the women studied. Apnoea index: no. of episodes of apnoea/hours of sleep.
Patient no. 1–9: postmenopausal normal weight
  „   no. 10–15: postmenopausal obese
  „   no. 16–21: hypothalamic-pituitary disorders.

Patient no.	Mean awake	Mean asleep	Minimum asleep	Time <95% (min)	Time <90% (min)	Total no. of apnoeas	Type of apnoea			Apnoea index
							central	obst.	mixed	
1	94	92	91	all	0	0				
2	94	93	90	all	0	0				
3	98	97	94	4	0	0				
4	95	93	85	207	5	2	2			0.4
5	94	92	90	all	0	1	1			0.1
6	95.5	94	90	140	0	0				
7	97	96	95	0	0	0				
8	96	94	90	185	0	0				
9	98	98	97	0	0	0				
Mean ± SEM	96 ± 0.5	94 ± 0.7	91 ± 1							
10	94	92	82	all	6	0				
11	94	92	84	all	8	6	6			2
12	97	95	94	11	0	1	1			0.3
13	97	96	93	3	0	0				
14	96	95	94	7	0	0				
15	96	94	92	176	0	0				
Mean ± SEM	96 ± 0.6	94 ± 0.7	89 ± 2							
16	98	94	80	82	12	34	0	34	0	5.5
17	94	90	81	all	62	0	0	0	0	
18	97	93	87	63	3	277	97	180	0	186
19	95	89	76	290	184	217	29	126	62	55
20	95	92	85	216	9	0	0	0	0	
21	93	90	72	all	17	4	4	4	4	0.7
Mean ± SEM	95 ± 0.7	91 ± 0.8	80 ± 2.3							

apnoeic episodes during sleep[3]. The fall in oxygen saturation seen in these women occurs predominantly during REM sleep and is much less severe than that reported in obese men of comparable weight[1]. We found no abnormality of sleep-breathing patterns in premenopausal women of normal weight, the minimum oxygen saturation recorded in this group during sleep being 95 per cent[3]. We now find that normal weight postmenopausal women show a fall in oxygen saturation when asleep and in 8 of the 9 women studied, the minimum SaO_2 measured was less than that seen in the lean premenopausal women. These results are similar to those reported by Block and colleagues[2]. Our obese postmenopausal women similarly show lower oxygen saturation during sleep. An increased amount of fat in the chest wall and abdomen has the predictable mass loading effect on the chest and diaphragm and leads to a reduction in vital capacity, expiratory reserve volume and chest wall compliance[6,7]. This effect is substantially magnified when an obese subject lies flat[8,9], but posture alone does not explain the findings in our patients because all of the subjects, both obese and normal weight, were studied only in the supine position. However, the mean awake

and mean asleep oxygen saturation values found in the postmenopausal obese women are both significantly less than the values we previously reported in similarly obese premenopausal women ($P < 0.01$). This finding supports the hypothesis that increasing age is an important determinant for the development of abnormal sleep-breathing patterns[4].

Extremely obese subjects show an increased ventilatory response to hypoxia but a decreased response to hypercapnia and this finding may explain the association of alveolar hypoventilation during sleep at which time central respiratory drive is decreased[10,12]. Obstructive sleep apnoea syndrome is particularly common in obese men but only a minority of such men develop the obesity-hypoventilation syndrome (OHS) characterised by hypoventilation, hypercapnia and hypersomnolence[13,14]. An increase of alveolar ventilation is seen in women during pregnancy and during the luteal phase of the menstrual cycle and this appears to parallel the increase in plasma progesterone concentrations[15,16]. Some patients with OHS have been treated successfully with medroxyprogesterone, which probably has a direct stimulatory effect on the central respiratory centre[17]. The

differences in nocturnal oxygen saturation found by us between the pre- and postmenopausal women support the concept that plasma progesterone has a protective effect on the maintenance of oxygen saturation during sleep.

We have previously proposed a relationship between hypothalamic function and respiratory control during sleep[3]. We found that obese premenopausal women with an absent prolactin response to insulin-induced hypoglycaemia, a possible marker of abnormal hypothalamic function, showed a significantly greater fall in oxygen saturation during sleep than equally obese premenopausal women with a normal prolactin response. In the current study, the six women with proven hypothalamic-pituitary disorders had a greater number of apnoeas and lower oxygen saturation than those older subjects with simple obesity. Insulin tolerance tests were not considered justifiable in the latter group in view of their age. This difference cannot be explained by body weight or body index because these differ little between the two groups. The results from the women with hypothalamic-pituitary obesity show a variety of disorders of sleep-breathing, in particular cases 18 and 19 whose sleep-breathing patterns were typical of obstructive sleep apnoea and case 22 whose oxygen saturation fell to 72 per cent during REM sleep without apnoea. We consider that centrally mediated relaxation of the larynx during sleep leading to reversible obstruction may explain the obstructive apnoea seen in our patients. No evidence of an obstructive lesion was found in any patient on direct laryngoscopy; nor was there any narrowing from an increase in adipose tissue distributed around the larynx, which has been suggested as a cause of obstructive apnoea in obese patients[18]. None of these women gave a history of disturbed sleep, daytime somnolence or lethargy to suggest such disturbances and the only reason for investigation was the complaint of progressive weight gain dating from the onset of their illness. The husbands of cases 18 and 19 confirmed that the patients snored loudly and were restless during sleep. Despite the heterogeneity of the hypothalamic-pituitary group, the finding that their breathing during sleep is more disordered than that of obese women suggests the importance of central factors for nocturnal respiratory control.

We conclude that a decrease in oxygen saturation and apnoea occurs in postmenopausal women during sleep irrespective of body weight but is significantly more severe in women who become amenorrhoeic at a younger age as the result of a hypothalamic-pituitary disorder, and subsequently become extremely obese. These findings, when considered with previous reports, suggest that the sex, menstrual status, weight of the patient and hypothalamic function, may individually be important factors which influence the control of nocturnal breathing.

Summary

We have previously reported that obese women with regular menstrual cycles show a fall in haemoglobin oxygen saturation when asleep. It has been suggested that the menstrual cycle, as well as body weight, may influence sleep-breathing patterns: we have investigated this by studying respiration during sleep in nine postmenopausal women of normal body weight, six postmenopausal women who were obese and six women who had become amenorrhoeic and obese following a hypothalamic-pituitary disorder. All of the postmenopausal women showed a decrease in oxygen saturation during sleep, the fall being similar between the lean and obese groups. In comparison, the women with hypothalamic-pituitary disorders showed more disturbed sleep-breathing patterns with a significantly greater fall in oxygen saturation ($P < 0.01$ versus lean postmenopausal $P < 0.05$ versus obese postmenopausal). Three of the hypothalamic-pituitary women had frequent apnoeic episodes during sleep and one had severe oxygen desaturation unassociated with apnoea. We conclude that a patient's sex, menstrual status, body weight and hypothalamic function are individually important factors for the control of respiration during sleep.

Acknowledgements

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