Sleep Apnoea in Myxoedema

DAVID MACKAY, MD, MRCP(UK), Senior Registrar
ROSEMARY A. COOPER, MB, FRCP, Consultant in Clinical Neurophysiology
SUSAN BRADBURY, Chief Technician
DAVID J. GAWKRODGER, MB, MRCP (UK), Registrar
KEITH PROWSE*, MD, FRCP, Consultant Physician
WALTER VAN'T HOFF, MB, FRCP, Consultant Physician
North Staffordshire Hospital Centre, Stoke-on-Trent, Staffordshire

Lethargy and daytime somnolence are common symptoms in myxoedema but these complaints may also be associated with sleep apnoea[1]. There have been previous reports of obstructive sleep apnoea in patients with severe myxoedema[2-4], but such studies have come from Sleep Study Centres to which patients had been referred because of sleep difficulties. In contrast, we have studied patients taken consecutively from the endocrine clinic and referred for other reasons, in an attempt to determine the occurrence and severity of sleep apnoea in this condition.

Patients and Methods

We studied nine patients (3 men and 6 women) with a mean age of 49 years (range 17-69). Their clinical details are given in Table 1. Their free thyroxine index (FTI) ranged from 1-36 (normal 68-185) and their plasma thyroid stimulating hormone (TSH) concentrations ranged from 30-142 mU/litre (normal value <10 mU/litre). These measurements were made at the time of the sleep record. All were newly diagnosed and had not received treatment. None had large goitres or evidence of retrosternal thyroid extension. One patient (case 8) gave a history of chronic bronchitis and one (case 9) had received diuretic therapy for mild left ventricular failure. The patients were questioned about daytime somnolence, and a history of snoring was taken from their bed partner. Prolactin levels were measured at 9 a.m. in seven of the nine patients (cases 1, 2, 4, 5, 6, 7 and 8). Spirometry was performed with a low resistance spirometer with the patient seated, and the total lung capacity estimated by a closed-circuit multibreath helium dilution technique. Transfer factor was measured by the single breath technique.

The patients were studied during nocturnal sleep in a quiet darkened room. A trained observer was present throughout the seven-hour recording period of sleep to check instrument sitting and annotate the trace, where necessary. No hypnotic or sedative drugs were given before the study. Simultaneous recordings were made of airflow at the nose and mouth, thoracic and abdominal movement, electrocardiogram (ECG), ear oxygen saturation, submental electromyogram (EMG), electro-oculogram (EOG) and electroencephalogram (EEG). The methods used have been described previously[5,6].

Each trace was analysed by two independent observers. Sleep apnoea was defined as cessation of airflow at the nose and mouth lasting for at least 10 seconds[1]. Apnoea was classified as obstructive if abdominal and thoracic movements continued, central if thoracic and abdominal movements were absent, and mixed if there was no movement early in the episode of apnoea and unsuccessful movement later in the episode[1]. Sleep stage was classified according to standard criteria[7]. (Stage 0 refers to periods in which the patient appeared asleep clinically with some muscle activity in submental EMG, no REM but 90 per cent or more of an epoch was occupied by alpha rhythm. It is distinguished from periods when the patient was actually awake.) Arousal frequency was also measured, and was defined as arousal to Stage 0 or to wakefulness. The relationship of arousal to episodes of apnoea was recorded.

Results

Details of daytime somnolence, excessive nocturnal snoring and lung function are given in Table 2 in which the patients are ranked according to apnoea index (number of episodes of apnoea per hour). Five patients had three or more episodes of daytime sleep, for example falling asleep after meals or while watching television. None of these patients had sleep paralysis, cataplexy or hypnagogic hallucinations. One of these hypersonomnolent patients (case 8) had excessive snoring as judged by his bed partner. One patient (case 6) complained of suddenly occurring
awakening during the night with a feeling of anxiety. The remaining three patients were asymptomatic. The sleep studies in all the symptomatic patients showed episodes of sleep apnoea. Five patients had an appreciable number of episodes of sleep apnoea (cases 5-9). Three female patients had 22-28 apnoeic episodes during sleep (well outside the normal range of less than five in women quoted in an earlier study which did not, however, take account of age and weight[1]). Two patients, one male and one female, had severe sleep apnoea with an apnoea index over 5.0 (9.1 and 20.7 respectively). The other male patient had more apnoeic episodes overnight than the asymptomatic patients but the number was still within the normal range of less than 25 episodes in men[1]. One asymptomatic patient showed sleep apnoea, with four episodes, only one of which occurred during Stage II sleep (Table 3).

The group of five patients with 22-137 apnoeic episodes overnight did not differ significantly from the other group in terms of mean age, body weight, FTI or TSH concentration. The mean known duration of symptoms of myxoedema in those with an appreciable number of apnoeic episodes was 16 months compared with three months in those with a normal number \(P<0.02\) Mann-Whitney U test[8]). The male patient with sleep apnoea had moderate airway obstruction, but did not show the marked hypoxaemia which may occur during REM sleep in subjects with chronic bronchitis[9]. Flow-volume loops in the nine patients showed no evidence of upper airway obstruction. All prolactin levels were below 650 mU/litre and were considered to be within normal limits.

Table 3 shows the duration of each sleep stage and the number of apnoeic episodes in each stage. All five patients with an appreciable number of episodes of sleep apnoea (cases 5-9) showed grossly disturbed sleep patterns.

Table 4 gives details of the apnoeic episodes. The apnoea was predominantly central in type. Of the 253 apnoeic episodes seen in five patients, only 21 were obstructive and 17 mixed in type. The patient with the history of excessive snoring (case 8) showed a number of obstructive episodes. In three patients (cases 4, 5 and 6) apnoea was associated with significant changes in heart rate. In two patients (cases 7 and 9) the apnoeic episodes caused small but significant falls in ear oxygen saturation. The number of arousals is shown in Table 5. Only those
Table 3. Duration of each sleep stage and number of apnoeic episodes in each stage in eight patients with myxoedema. (Case 2 excluded because of technical problems.)

| Case No. | Apnoea Index | Sleep stage I | Sleep stage II | Sleep stage III | Sleep stage IV | REM | Total sleep stages |
|----------|--------------|---------------|----------------|----------------|----------------|-----|--------------------|
| 1        | 0            | 12            | 137            | 17             | 24             | 30  | 233                |
| 2        | 0.6          | 24            | 206            | 47             | 31             | 61  | 397                |
| 3        | 2.8          | 98            | 173            | 7              | 2              | 19  | 341                |
| 4        | 3.7          | 75            | 138            | 48             | 5              | 6   | 356                |
| 5        | 4.3          | 65            | 143            | 12             | 2              | 9   | 349                |
| 6        | 4.4          | 77            | 153            | 32             | 11             | 48  | 384                |
| 7        | 4.4          | 7             | 34             | 5              | 0              | 85  | 277                |
| 8        | 9.1          | 26            | 132            | 5              | 0              | 28  | 137                |
| 9        | 20.7         | 96            | 197            | 9              | 4              | 29  | 397                |

Table 4. Details of the apnoeic episodes experienced by seven patients.

| Case No. | Apnoea Index | Type of Apnoea | Mean (± SD) duration of apnoea (s) | Mean (± SD) change in heart rate (beats/min) | Mean (± SD) change in oxygen saturation (%) |
|----------|--------------|----------------|-----------------------------------|---------------------------------------------|---------------------------------------------|
|          |              | Obstructive    | Central                           |                                             |                                             |
| 3        | 0.6          | 3              | 11 ± 1                            | 5 ± 37                                      | 0                                           |
| 4        | 2.8          | 2              | 15 ± 5                            | 3 ± 4*                                      | 0 ± 1                                       |
| 5        | 3.7          | 0              | 14 ± 4                            | -2 ± 3**                                    | -1 ± 3                                      |
| 6†       | 4.3          | 0              | 15 ± 4                            | 8 ± 7***                                    | 4 ± 3***                                    |
| 7        | 4.4          | 0              | 15 ± 4                            | 3 ± 8                                       | 4 ± 4*                                      |
| 8        | 9.1          | 7              | 13 ± 3                            | 0                                           | -1 ± 2                                      |
| 9        | 20.7         | 14             | 17 ± 5                            | 0                                           | -4 ± 4*                                     |

†Ear oxygen saturation was not measured.
* * P<0.05
** P<0.02
*** P<0.001

Table 5. Frequency of arousals after the first epoch of Stage II sleep. Arousal was defined as achieving Stage 0 sleep (see text) or frank wakefulness.

| Patient | Arousal | Following Apnoea |
|---------|---------|------------------|
|         | Total   |                  |
| 1       | 11      | 0                |
| 2       | 22      | 3                |
| 3       | 30      | 0                |
| 4       | 54      | 0                |
| 5       | 110     | 7                |
| 6       | 23      | 2                |
| 7       | 29      | 7                |
| 8       | 23      | 7                |

Table 6. Body weight before and after thyroxine therapy.

| Group                  | Average weight pre-treatment (mean ± SD) | Average weight post-treatment (mean ± SD) |
|------------------------|------------------------------------------|------------------------------------------|
| All patients (n = 9)   | 74.3 ± 16.3                              | 71.9 ± 15.2                              |
| Patients without apnoa (n = 4) | 78.0 ± 8.2                              | 77.0 ± 11.4                              |
| Patients with apnoa (n = 5) | 71.4 ± 20.1                              | 67.8 ± 16.6                              |

arousals occurring after the first epoch of Stage II sleep are included. Arousal did not appear to be related to the occurrence of apnoea. When arousal occurred immediately after apnoea it was not related to the duration of the apnoeic episode.

Those patients who showed episodes of sleep apnoea lost slightly more weight on thyroxine than patients without apnoea (mean weight loss 3.6 kg versus 1.0 kg respectively), but this difference was not statistically significant (Table 6).

The male patient with sleep apnoea died from myocardial infarction six months after the study. Repeat studies were carried out in the four female patients with excessive sleep apnoea when they were clinically and biochemically euthyroid. Symptoms of hypersomnolence and excessive snoring had disappeared. These studies showed an increase in sleep time averaging 50 minutes with normal sleep patterns. Three patients had no apnoeic episodes and the other had only four apnoeic episodes (Table 7). In
all patients but one (case 7) the number of arousals was less.

Discussion

An appreciable number of apnoeic episodes occurred during overnight sleep in five out of nine patients with myxoedema. Two of the five patients had severe sleep apnoea with an apnoea index of over 5.0. The episodes were predominantly central in type in contrast to previous reports of obstructive sleep apnoea in myxoedema[2-4]. The division into central and obstructive types was made on the basis of the polygraphic criteria set out by Guilleminault and colleagues[1]. In our patients with central sleep apnoea, respiratory efforts, even if they were made, were insufficient to cause movement of the thorax and abdominal wall but the occurrence of minor respiratory efforts such as may be detected by oesophageal catheter[10] cannot be excluded. It seems more likely that the difference between our findings and previous reports reflects the selection of patients, our patients being taken consecutively from the endocrine clinic rather than being referred primarily because of sleep difficulties.

The five patients with apnoeic episodes all gave a history of sleep complaints. Four had hypersomnia (one in association with heavy snoring) and the other (case 6) complained of sudden awakening during the night with a feeling of anxiety. The latter complaint has been reported in four out of 10 patients with central sleep apnoea of non-endocrine origin[1], and our patient (case 6) showed the greatest number of arousals (see Table 5). The patient (case 8) with the history of excessive snoring had the greatest number of obstructive episodes. He was also overweight and had moderately severe chronic bronchitis, both conditions that may be associated with obstructive sleep apnoea. He did not, however, show episodes of hypoxaemia during REM sleep such as occur in chronic bronchitis when sleep-disordered breathing is present[9].

The fall in oxygen saturation in the male subjects was within the range of the normal subjects described by Block et al.[10]. Two female patients showed a small but significant fall in arterial oxygen saturation (maximum mean fall 4 per cent). This was certainly abnormal because normal women do not show a fall in oxygen saturation during overnight sleep[10]. The decrease was less marked than we have found in previous studies in acromegaly[5] and it is of doubtful pathological significance.

Neither of the two patients with the greatest number of apnoeic episodes showed significant changes in heart rate, although such changes were present in the other three patients with sleep apnoea but were small in absolute terms. This casts doubt on the value of 24-hour ECG monitoring as a screening test for sleep apnoea syndrome[11]. Three of the five patients with apnoeic episodes were over 65 years old, including the two who had the most severe apnoea. A study of home sleep recordings in volunteers has suggested that about 25 per cent of persons aged 65 and over will have sleep apnoea with an apnoea index of at least 5.0[12]. Our four female patients with apnoea were re-studied when euthyroid. Their hypersomnia and apnoea had disappeared. Although two of these patients were over 65, all four had improved when euthyroid, indicating that the apnoeic episodes were related to thyroid status rather than age. Weight is unlikely to be a factor in the difference in the occurrence of apnoea between the two groups, as there was no significant difference in initial weight or amount of weight lost during thyroxine therapy. The obstructive episodes reported in previous studies were attributed to myxoedematous swelling producing upper airway obstruction, and also responded to thyroxine therapy[2,3]. Thus both types of sleep apnoea seen in myxoedema respond to thyroxine.

The mechanism of central sleep apnoea in our patients is uncertain. The occurrence of apnoea was not related to thyroxine levels, obesity and age. There was a correlation between sleep apnoea and the duration of symptoms of myxoedema. Sleep apnoea occurred in those with the longer histories but the patient’s assessment of symptom duration in myxoedema is notoriously unreliable. Episodes of central sleep apnoea may be associated with the disordered breathing of obstructive sleep apnoea[4]. This is an unlikely factor in our cases because obstructive episodes were few compared to central ones in the two most severely affected patients, and did not occur at all in the other three.

There have been previous reports of disordered ventilatory control in patients with myxoedema[13-15]. It is
possible that changes in ventilatory drive during sleep may have predisposed to central apnoeic episodes but we have no measurements to support this view. A recent case report has described central sleep apnoea in a 45-year-old man with hypothyroidism[16]. This patient showed abnormal responses to hypoxia and hypercapnia while awake but again no measurements were made during sleep. Both the apnoea and ventilatory abnormalities were corrected by thyroxine. This further supports the view that sleep apnoea in hypothyroidism can be secondary to central changes as well as to changes in the upper airway.

Acknowledgements
We wish to thank Dr John Stainforth and Mr Albert Allen for their help with the sleep recordings and Mrs B. M. Cartlidge for typing the manuscript.

References
1. Guilleminault, C., Van den Hoed, J. and Milter, M. M. (1978) In Sleep Apnoea Syndromes, p. 1. (ed C. Guilleminault and W. C. Dement.) New York: Academic Press.
2. Yamamoto, T., Hirose, N. and Miyoshi, K. (1977) European Neurology, 15, 188.
3. Orr, W. C., Males, J. L. and Imes, N. K. (1981) American Journal of Medicine, 70, 1061.
4. Rajagopal, K. R., Derderian, S. S., Jabber, B., Burman, K. D. and Hunt, K. K. Jr. (1981) American Review of Respiratory Disease, 123 (suppl.), 188.
5. Perks, W. H., Horrocks, P. M., Cooper, R. A. et al. (1980) British Medical Journal, 280, 894.
6. Perks, W. H., Cooper, R. A., Bradbury, S. et al. (1980) Thorax, 35, 85.
7. Rechtschaffen, A. and Kales, A. (1968) Manual of standardized terminology, techniques and scoring system for sleep stages in human subjects. Bethesda, Maryland: National Institute of Neurological Disease and Blindness.
8. Siegel, S. (1956) Non-parametric statistics for the behavioral sciences. New York: McGraw-Hill.
9. Douglas, N. J., Calverley, P. M. A., Leggett, J. E., Brash, H. M., Fienley, D. C. and Brezinova, V. (1969) Lancet, 1, 1.
10. Block, J. A., Boyson, P. G., Wynne, J. W. and Lung, L. A. (1979) New England Journal of Medicine, 300, 313.
11. Tilkian, A. G., Motta, J. and Guilleminault, C. (1978) In Sleep Apnoea Syndromes, p. 197. (ed C. Guilleminault and W. C. Dement.) New York: Academic Press.
12. Kripke, D. F. and Ancoli-Israel, S. (1983) In Sleep/Wake Disorders: Natural History, Epidemiology and Long-term Evolution, p. 137. (ed C. Guilleminault and E. Lugaresti.) New York: Raven Press.
13. Wilson, W. R. and Beddle, G. N. (1960) Journal of Clinical Investigation, 39, 42.
14. Massumi, R. A. and Winnacker, J. L. (1964) American Journal of Medicine, 36, 876.
15. Zwick, C. S., Pierson, D. J., Hofeldt, F. D., Lupkin, E. G. and Weil, J. V. (1975) New England Journal of Medicine, 292, 662.
16. Millman, R. P., Bevilacqua, J., Peterson, D. D. and Pack, A. I. (1983) American Review of Respiratory Disease, 127, 504.

continued from page 247

century (1811 and 1841), and then not again until an abridgement appeared in 1952. In it the editor wrote: 'Except for his assiduity in collecting material, much would have been lost to us ... He would endure contentedly an hour's or more impertinence from any aged church officer or other superannuated person for the gleaning of two lines to his purpose. A great deal of the material thus quarrried has found its way into our standard compilations ... The more the matter is studied, the more surprising it appears that there has been such long neglect of the most lively of antiquaries, who wrote the most readable of all works of collective biography.'

LEONARD PAYNE