Control of breathing during sleep

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Introduction
There has been a recent awakening of interest in breathing during sleep, due largely to two factors. Firstly, the recognition that some patients become apnoeic intermittently during sleep and that this can produce the sleep apnoea syndrome in adults [1] and may be related to the sudden infant death syndrome [2]. Secondly, the development of accurate ear oximeters [3] which allow the continual recording of oxygenation during sleep, and have led to the recognition of intermittent sleep-related severe hypoxaemia in patients with pre-existing lung disease [4, 5]. These observations have led to interest in the control of breathing during sleep. As both the apnoeic and hypoxaemic episodes are specific to sleep and occur most frequently during certain electroencephalographic stages of sleep, there follows a brief outline of the physiology of sleep.

Wakefulness is a state of cortical activation recognized by the occurrence of alpha waves on the electroencephalogram (EEG) and of high muscle tone. The cortical activation is maintained by tonic activity of the reticular activating system, which both directly stimulates the cortex [6] and also facilitates thalamic relay neurons, allowing onward passage of sensory information to the cortex [7]. Sleep is a state in which alpha activity is lost and muscle tone reduced. It can be subclassified into different stages [8] according to the frequency and voltage of the EEG and electromyogram (EMG) and the occurrence of eye movements on an electro-oculogram. Sleep is a cyclical process which in normal adults always starts with non-REM sleep, with rapid eye movement (REM) sleep cycles interspersed approximately every 90 min throughout non-REM sleep, each REM period lasting 15-30 min and tending to be longer later in the night.

Non-REM (stages 1-4) sleep is characterized by inhibition of the reticular activating system, resulting in cortical suppression and functional deafferentation. In REM sleep, the reticular activating system is reactivated, producing cortical stimulation [9]. In contrast to wakefulness, both sensory and motor functions are impaired during REM sleep. There is both pre- and post-synaptic inhibition of afferent neurons [10] resulting in raised arousal thresholds to external stimuli [9] and postsynaptic inhibition of motor neurons [11] which produces the postural atonia typical of REM sleep [12].

Normal breathing during sleep
It has been known for more than a century that ventilation is reduced during sleep [13]. Subsequent studies confirmed that ventilation was decreased in either presumed [14, 15] or documented [16-19] non-REM sleep. Although these findings have been challenged [20, 21], because of difficulties in obtaining basal levels of ventilation in awake subjects and because the facial instrumentation used might alter ventilation [22, 23], hypoventilation in non-REM sleep has been confirmed in many studies performed without facial instrumentation which showed either decreased thoraco-abdominal movement [18, 24] or arterial hypoxaemia [25-27] and hypercapnia [26-28]. As metabolic rate falls slightly during non-REM sleep [29, 30] the hypoxaemia and hypercapnia must reflect hypoventilation. The hypoventilation in non-REM sleep is due to a lower tidal volume [14, 16-19, 24] with either no change [14, 24, 31] or a slight increase [16, 17, 19] in breathing frequency compared with wakefulness.

In REM sleep the dominant feature is extreme variability in ventilation [17, 19, 32]. This is so marked that discussion of the average level of ventilation in REM sleep is of limited value. Douglas et al. [19] recently reported that minute
ventilation was lower in REM than non-REM sleep, averaging 84% of the level in wakefulness. Krieger et al. [33] also found a tendency for ventilation to be lower in REM than non-REM sleep, but this difference was not significant.

In teenagers Tabachnik et al. [34] found no difference in ventilation between REM and non-REM sleep, but they used an inductive plethysmograph which may not be accurate in REM sleep because of differences in relative contributions and phase relationships [35, 36] of the chest and abdomen. Some of these discrepancies may reflect the heterogeneous nature of REM sleep as there is some evidence that ventilation may be lowest during the periods of REM sleep in which eye movements are most common [24]. Almost all measurements of ventilation in our study [19] were made during frequent eye movements (phasic REM) but the frequency of eye movements is not reported in these other studies.

**Ventilatory control during sleep**

**Hypoxic ventilatory response**

Earlier claims that the hypoxic ventilatory response was preserved during sleep [17, 37] were based on studies which were inadequate by current criteria [38]. Four recent investigations [31, 38-40] found that the isocapnic ventilatory response decreases during sleep in adult men, all finding the lowest responses in REM sleep when it fell to as low as one-third of the level during wakefulness [38]. In one study this decrease between REM and non-REM sleep was not significant [39].

In non-REM sleep the hypoxic ventilatory response was lower than in wakefulness in two [38, 39] of the four studies. This discrepancy may be explained by the observation [41] that the hypoxic ventilatory response is lower in non-REM sleep than in wakefulness in men but not in women, as the studies showing no change in hypoxic ventilatory response in non-REM sleep included female subjects [31, 40]. It is unclear why men and women should differ in this respect, but it may be because the hypoxic ventilatory response in men reflects metabolic rate [42] which decreases in men when they sleep [30], but in women the hypoxic ventilatory response is not correlated with metabolic rate [42].

One study [31] finding no change in hypoxic response between non-REM sleep and wakefulness not only included female subjects, but also studies were performed without isocapnia and after sleep deprivation, both factors which decrease the awake ventilatory response [43-45], making the detection of a subsequent decrease more difficult.

Thus in adult men the hypoxic ventilatory response in non-REM sleep is approximately two-thirds of that in wakefulness, falling to one-third of the waking level in REM sleep. In adult women, there is no change in the hypoxic ventilatory response between wakefulness and non-REM sleep, but the response in REM sleep is about one-half that in the other stages.

**Hypercapnic ventilatory response**

The hypercapnic ventilatory response is also depressed during sleep. Studies performed either in EEG documented [16-18, 46] or presumed [14, 15, 47] non-REM sleep show a decreased slope of the ventilatory response to hypercapnia. Two recent studies [40, 48] found no change in the hypercapnic response during non-REM sleep, but one is internally inconsistent as there was a decreased slope of the metabolic hyperbola \( (V_t/P_{aco,}) \) yet no change in the hypercapnic response nor in the ratio of the slope of the hypercapnic ventilatory response to that of the metabolic hyperbola (controller gain). These two studies [40, 48] both measured hypercapnic response over a narrow \( CO_2 \) range and a high noise-to-signal ratio probably explains the failure to detect a change in hypercapnic response slope.

Two groups [49-51] had earlier reported that the slope of the hypercapnic ventilatory response was unchanged by sleep, but that there was a parallel shift to higher \( CO_2 \) levels during sleep. However, neither group presents evidence that the slope was unchanged, and the data of Reed & Kellogg [49, 50] suggest a decreased slope in most studies.

Furthermore, this is not a major discrepancy as either a parallel shift [49-51] or a decreased slope [14-18, 46, 47] may mean that the \( CO_2 \) increment (i.e. tolerance) from awake alveolar \( CO_2 \) to the \( CO_2 \) response line is increased by sleep [46]. This increased laxity may help explain hypoventilation and breathing irregularities during sleep (see below).

The hypercapnic ventilatory response has recently been shown to be lower in REM than non-REM sleep in adult man [46]. In REM sleep the hypercapnic response is approximately one-third of the level of wakefulness.

Douglas et al. [46] found no difference between the sexes in the effect of sleep on the hypercapnic ventilatory response. This contrasts with the conclusion of Davis et al. [52], who reported higher hypercapnic responses during sleep in women than in men. However, Newsom Davis et al. did not measure the hypercapnic response of their subjects when they were
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awake and so the reported differences may have antedated sleep, as there is a wide normal range of hypercapnic ventilatory response [53].

Thus, the hypercapnic ventilatory response in non-REM sleep is approximately two-thirds of that in wakefulness, falling to about one-third of the waking level in REM sleep.

The decreased ventilatory responses in non-REM sleep presumably reflect loss of cortical activation [6, 7] which may provide a 'wakefulness' drive to breathing. The further reduction during REM sleep results from the REM sleep specific inhibition of both sensory and motor functions [10, 11].

Responses to loaded breathing

There are few data on the ventilatory response to respiratory loads during sleep. Iber et al. [54] recently showed that the ventilatory response to an inspired load was diminished in non-REM sleep in normal man, but no measurements have been made during REM sleep.

Arousal responses

It is difficult to assess arousal thresholds to respiratory stimuli in man as the instrumentation required to deliver the stimuli usually impairs sleep and produces spontaneous arousal. Thus, the variable results often obtained may mean that many arousals were spontaneous, that the stimulus itself did not result in arousal, or that the arousal threshold was truly variable.

In normal subjects, hypoxia appears to be a poor stimulus to arousal [31, 38-40] with variable arousal thresholds and many subjects remaining asleep with arterial saturations as low as 70% (Pao2, approx. 5 kPa). Hypercapnia also produces arousal at variable levels [40, 46], but it appears to be a more potent stimulus to arousal as most subjects arouse before end-tidal Pco2 has risen by 2 kPa above the level in wakefulness. There is no difference between sleep stages in the arousal response to either hypoxia [38, 39] or hypercapnia [46]. These results in normal man contrast with those in dogs [55, 56] and cats [57], and in patients with the sleep apnoea syndrome [58] in whom arousal sensitivity appears to be decreased in REM sleep.

Both the addition of an inspiratory resistance [54] and the occlusion of inspiration [59] results in arousal from sleep. The arousal from REM sleep with airway occlusion [59] is far more rapid [6.2 ± 2.7 (sd) s] than from non-REM sleep (20.4 ± 7.6 s; P < 0.001) but the reason for this uncharacteristic increase in sensitivity in REM sleep is unclear.

Breathing rhythm

Breathing is irregular throughout REM sleep in all subjects [17, 19, 32] and in most subjects is irregular in non-REM sleep soon after sleep onset and after arousals [17, 19]. Although these dysrhythmias reflect variability in both respiratory timing and tidal volume, interest in the sleep apnoea syndrome has meant that the former has received most attention.

Breathing irregularities in non-REM sleep

Bulow [17] found that periodic breathing was commoner in subjects who had the greatest rightward shifts in hypercapnic ventilatory response and that apnoeas occurred only when the alveolar Pco2 was well to the left of the CO2 response line, suggesting that laxity in CO2 control when the CO2 response line moves abruptly rightwards at sleep onset may explain these irregularities. Similarly, reducing the end-tidal CO2 level during non-REM sleep to the level found in wakefulness produces apnoeas in normal subjects [60]. However, relative hypocapnia is not the entire explanation as increasing the CO2 by up to 2 kPa does not regularize breathing [46], and the same small study was also unable to confirm any correlation between right shift in the CO2 response line and breathing irregularities. Oxygenation appears to have a complex inter-relationship with irregular breathing during non-REM sleep [61] as it has been reported that hypoxia abolishes hypocapnia-induced apnoeas [60] and that hyperoxia can reduce spontaneous apnoeas during sleep [61]. It has been suggested [46] that the preservation of the hypoxic but not the hypercapnic response at waking levels in non-REM sleep may stabilize breathing and explain why pre-menopausal women breathe relatively regularly during sleep. However, too few individuals have been studied in detail to confirm or refute this proposal. It seems most likely that the explanation for breathing irregularities during non-REM sleep is multi-factorial and that important factors include not only relative changes in the hypoxic and hypercapnic ventilatory responses, but also [62] the combination of differences between O2 and CO2 control systems (Paco2 control being linear with respect to ventilation, whereas Pao2 is hyperbolic), and damping (body O2 stores being far smaller than CO2 stores, and therefore, Pao2 changing far more rapidly than Paco2 when ventilation changes).
Breathing irregularities in REM sleep

During REM sleep irregular breathing is the norm and neither hypoxia nor hypercapnia [46] influences the pattern of breathing. Similarly in animals, hypoxia [56], hyperoxia [63], hypercapnia [64], metabolic alkalosis [63], carotid body resection [65] and vagotomy [66–68] do not produce regular breathing in REM sleep.

It has been suggested [69] that these irregularities relate to the influence of behavioural factors, but there is no direct evidence to support this contention. In cats, Orem [70] found a positive correlation between the activity of some medullary respiratory motor neurons in REM sleep with pontine generated discharges termed ponto-geniculo-occipital waves. These waves are held to be one of the most basic electrophysiological phenomena of REM sleep and may be associated with the irregular rapid eye movements themselves. Thus, the dysrhythmic nature of breathing in REM sleep may relate directly to the dysrhythmic nature of REM sleep itself.

Clinical relevance of altered respiratory control during sleep

Patients with respiratory disease

Arterial oxygen tension falls by approximately 2 kPa in everybody during sleep [71], but while this is of little consequence in normal subjects, patients who are already markedly hypoxic when awake become severely hypoxic during sleep with directly measured arterial PaO₂ falling as low as 3.6 kPa [5]. The approximately 2 kPa decrease in PaO₂ results in little change in SaO₂ in normal subjects, who, when awake, lie on the flat summit of the haemoglobin-oxygen dissociation curve, but produces marked desaturation in hypoxic patients who lie on the steep slope of the curve when awake. Such REM-related nocturnal desaturation has been reported in hypoxic patients with chronic bronchitis and emphysema [5, 24, 72–74], cystic fibrosis [75, 76], kyphoscoliosis [77], diaphragmatic palsy [78] and chronic mountain sickness [79]. REM-related hypoventilation [19] permitted by decreased ventilatory responses to both hypoxia [38] and hypercapnia [46] is probably the dominant cause of the hypoxia [71] but a decrease in functional residual capacity [80, 81] and an increased dispersion of V/Q matching [5, 72] may contribute. Upper airway narrowing also probably occurs during these REM-related episodes [82], but this merely reflects the general hypotonia in REM sleep and is probably not a significant cause of REM-related hypoxia in non-obese patients with hypoxic pulmonary disease.

The REM-related desaturation in hypoxic patients results in an elevation of the pulmonary arterial pressure [5, 83, 84] and it has been suggested [5] that nightly repetition of these elevations of pulmonary arterial pressure might contribute to the development of cor pulmonale and sustained pulmonary hypertension in these patients. Similarly, as the red cell mass reflects oxygen saturation [85], the nocturnal desaturation may contribute to the development of polycythaemia in such patients, a hypothesis supported by the observation that repetitive transient hypoxaemia of similar magnitude may increase the red cell mass, at least in rats [86]. Both nocturnal oxygen [5, 87, 88] and ventilatory stimulants [24, 89] can decrease nocturnal hypoxia in such patients.

Ascent to altitude

Rapid ascent to altitude produces periodic breathing and apnoeas during sleep [90]. As such ascent results in a respiratory alkalosis, the tolerance in CO₂ between the awake resting level and the sleep ventilatory response line may be transiently increased, thus permitting such breathing irregularity. However, this is not the entire explanation as breathing a hyperoxic mixture stabilizes respiration in minutes whereas the alkalosis would be far more persistent. Acetazolamide can decrease the alkalosis and reduces the irregular breathing [91] and thus it appears that both hypoxia and the respiratory alkalosis are important in the pathogenesis of irregular breathing on ascent to altitude.

Sleep apnoea syndrome

The apnoeas in this condition result from lack of contraction of either the intercostals and diaphragm (central apnoeas) or, more commonly, of the upper airway opening muscles (obstructive apnoeas). The pressure within the upper airways is subatmospheric during inspiration (to suck air into the lungs) and the floppy supraglottic airway would collapse during each inspiration but for phasic activity of upper airway opening muscles including genioglossus [92], geniohyoid, tensor palatini and the medial pterygoids. These muscles are true respiratory muscles, contracting during each inspiration and increasing their activity when respiration is chemostimulated [93, 94]. Like other muscle groups, these muscles exhibit relative hypotonia during sleep and in some individuals this is sufficient to allow upper airway collapse.
and so obstructive apnoeas. Any factor which narrows the upper airway, including a short mandible [27] or nasal stenosis will mean that stronger suction is required for inspiration and thus will predispose to obstructive apnoeas. Narrowing due to submucosal infiltration in obesity, acromegaly or hypothyroidism may thus will predispose to obstructive apnoeas. The apnoeas often continue until the patient arouses [58], thus restoring upper airway muscle tone.

The neurophysiology of apnoea is not understood but it seems probable that the pathogenesis of obstructive and central apnoeas are similar: (1) many patients have both types of apnoeas [1]; (2) both types of apnoea occur during periodic breathing at sleep onset and during irregular breathing in REM sleep [95]; (3) some apnoeas consist of central followed by obstructive components, ‘mixed apnoeas’ [1]; (4) there is a parallel reduction in muscle tone in the diaphragm and upper airway opening muscles during obstructive apnoeas [96]; (5) both the treatment of central apnoeas with diahragmatic pacing [97] and the treatment of obstructive apnoeas by tracheostomy [98] can increase the alternative type of apnoea. Alternatively, as many suppose, the aetiology of central and obstructive apnoeas could be distinct, but this seems unlikely.

The apnoeas secondarily reduce ventilatory drive both by causing arousals and thus sleep deprivation and fragmentation which decrease ventilatory drive [44, 45] and also by producing a repetitive hypoxic and hypercapnic load blunting respiratory drive. Thus, ventilatory responses during wakefulness which are reduced in such patients return to normal after appropriate treatment [99].

In the treatment of the sleep apnoea syndrome, it is important to avoid ingestion of alcohol or other respiratory depressant drugs as these may increase the frequency and duration of apnoeas [100]. Patients with dominantly central apnoeas are rare and therapeutic trials are uncommon, but it appears that central respiratory stimulation with positive expiratory airway pressure alone can also reduce such apnoeas [108].

Conclusions

Hypoventilation and breathing irregularities are common during sleep and are clinically important. Although it is now known that sleep decreases both the hypoxic and hypercapnic drives to breathing, we are a long way from understanding the breathing irregularities which occur during sleep.

References

Disease, on breathing pattern. Emili, J.

Coccagna, Bristow, J.D., Honour, A.J., Picketing, T.G.

balance.

Changes in ventilation and chest wall mechanics during sleep in normal adolescents.

Hudgel, D.W.

E., Hedemark, L.L.

Berssenbrugge, A.

ventilation and chest wall mechanics during sleep in normal men.

White, D.P., Pickett, C.K., Zwillich, C.W.


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Sleep in diaphragmatic paralysis. American Review of Respiratory Disease, 121, 587-593.