

Perspectives



Over long periods of time, months and years, arterial PCO_2 and PO_2 are closely regulated, but over shorter periods, constancy of arterial blood gas tensions is perhaps an impractical or even an undesirable objective. It is now appreciated that fluctuation within limits is an inherent feature of normal function and that there are cycles of activity and rest that modify respiratory regulation as well as other regulatory processes (1, 2). Many of these cycles, like the sleep-waking cycle, are circadian, with a period of ~ 24 h, and seem to be keyed to the revolution of the earth.

Sleep, like breathing, seems to be essential to health, and adverse physiological and psychological consequences occur with sleep deprivation (3, 4). However, the need to adjust breathing to physiological requirements during both sleep and wakefulness complicates the task of the respiratory control system because sleep alters the response characteristics of the respiratory controller and the performance of the respiratory muscles. There may be a hierarchy of neurological organization that governs physiological regulations that determines priorities and arbitrates among conflicting demands as activity levels change.

In some individuals with the sleep apnea syndrome, adequate sleep and sufficiently stable breathing, both necessary to prevent dangerous fluctuations in blood gas tensions, seem to be incompatible (5, 6). Sleep is interspersed with periods when airflow stops and profound hypoxemia develops. Sometimes it seems as if death is averted only by arousal and the termination of sleep. While the biochemical basis of neither sleep nor breathing are known, much has been learned in recent years about sleep and about the mechanisms by which it affects respiratory control. Several effective methods of treatment of the sleep apnea syndrome have been developed based on our understanding of the effects of sleep on breathing.

Breathing during sleep. Neither sleep nor wakefulness are uniform states. Even in awake individuals, cyclic changes in breathing with both long and short periods can be obvious at altitude and can be discerned at sea level by sophisticated math-

Sleep Apnea and Its Causes

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ematical approaches and averaging techniques (7, 8). During sleep, these cycles may be even more apparent (but it is interesting that thus far no attempt has been made to examine the relationship between cyclic respiratory phenomena in wakefulness and sleep).

On the basis of EEG criteria, sleep has been divided into rapid eye movement (REM)¹ sleep and nonrapid eye movement (NREM) sleep (9, 10). During NREM sleep there is a synchronization of the EEG pattern with a reduction of its frequency. Sleep usually begins in the NREM stage, which itself has been divided into four substages characterized by a progressive slowing in EEG frequencies. REM sleep (the stage in which dreaming tends to occur) usually follows the NREM states. It is characterized by the occurrence of a desynchronized EEG and periods of rapid side-to-side movement of the eyes. Usually these eye movements are accompanied by spiking electrical waves which, in animals, are particularly prominent in the pons, geniculate body, and occipital cortex (PGO waves). REM sleep is also accompanied by inhibition of motor neurons, which leads to a profound loss of muscle force. By recording the EEG, electromyogram, and eye movements, REM sleep can be distinguished from NREM sleep.

Sleep can occur in the decorticate animal, but the normal alternation of sleep and wakefulness seems to depend on complex interconnections between the hypothalamus, the reticular formation, the raphe nuclei, and the locus coeruleus (11). In rats, destruction of the suprachiasmatic nuclei of the hypothalamus destroys the circadian sleep-wake cycle (12). Although within a 24-h period the same amount of sleep occurs as before, sleep occurs randomly rather than in well-defined blocks. The REM circadian cycle persists even after destruction of the SCN.

With respect to respiration in healthy humans, ventilation tends to decrease during NREM sleep but remains regular (9, 10). Arterial PCO_2 increases, while arterial PO_2 falls slightly. In REM sleep, breathing is irregular but apneas are usually short, less than a few seconds, and on average the arterial levels of blood gases do not vary much from that seen in NREM sleep.

In contrast, patients with the sleep apnea syndrome may spend much of the night not breathing, and may experience troubled sleep frequently interrupted by arousals.

The sleep apnea syndrome. The interruptions that occur in

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1. Abbreviations used in this paper: NREM, nonrapid eye movement; REM, rapid eye movement.

breathing during the night have been divided into two types, central apneas and obstructive apneas (5, 6). In central apneas there is no sign of respiratory activity—some central mechanism seems to be at fault. In obstructive apneas, respiratory efforts continue but there is no flow of air at either the nose or mouth. It is believed that a block in the upper airway occurs that prevents the movement of air into the lungs.

The distinction between obstructive and central apnea is not always clear. Frequently apneas are mixed in type, beginning with a central component and followed by an obstructive period where respiratory movements reappear but are ineffectual in producing ventilation because of upper airway occlusion. Many patients have both kinds of apnea even within the same night. Also, therapeutic interventions which are designed to prevent the occurrence of one or the other forms of apnea may substitute one type for the other (13).

Particular subjects seem to be especially prone to sleep apneas, which are most frequent in the lighter forms of NREM (stage I and II) and REM sleep (10). Apneas are most often seen in the elderly and in males; they occur infrequently in premenopausal women. Many, but not all, adult patients with sleep apnea are obese, and some have an anatomical abnormality that narrows the upper airway (14, 15, 16). Whether or not sleep apneas of infancy are related to the sleep apneas in adults is unclear. It used to be believed that the apneas of infancy were central in type, but it is now recognized that many of them are obstructive (17).

There also seem to be differences in patients in the temporal pattern of distribution of apneas. Some patients experience randomly during the night episodes of prolonged apnea associated with hypoxemia and the development of abnormal cardiac rhythms such as bradycardia, asystoles, A-V block, and ventricular ectopic beats (18). In other patients the apneas appear in clusters with a pattern highly reminiscent or identical to that seen in Cheyne-Stokes breathing (19). Individual episodes of apnea may be relatively short but the mean level of PO_2 experienced during the night is reduced by the recurrent nature of the apnea, and the mean level of PCO_2 is elevated.

It is believed, but not proven, that the sleep apnea syndrome has several adverse consequences. One of these, the lethal cardiac arrhythmias, is triggered by single episodes of prolonged apnea (19). The episodic hypoxemia in recurrent apneas could also produce pulmonary hypertension and right ventricular failure, while hypercapnia could induce bicarbonate retention and, ultimately, chronic and persistent alveolar hypoventilation (16, 20). Intermittent hypoxia and hypercapnia in animal models produce pulmonary vasoconstriction and increase hemoglobin levels (21). Certainly there are many reports of a return to normal of waking ventilatory responses and of a normalization of circulatory function with successful treatment of the sleep apnea syndrome (14, 16, 22). Also, studies of populations of snorers (snoring is due to partial upper airway obstruction) suggest that disturbed breathing during sleep predisposes to systemic hypertension (23). This could be due to the more frequent oc-

currence of both hypertension and obstructive sleep apnea in the obese.

Patients with sleep apnea frequently complain of psychological problems (4). Irritability and daytime hypersomnolence are common and may be caused by the fragmentation of sleep and by changes in body chemistry produced by the arousals that are sometimes associated with the apneas. The hypersomnolence and poor sleep may contribute to the reduced ventilatory responsiveness to CO_2 and hypoxia that are frequently seen in these patients even when they are awake (24).

It is not clear whether sleep apnea patients are fundamentally different from normal subjects. The bulk of the evidence suggests that they are not and that the syndrome arises from quantitatively exaggerated effects of sleep on respiratory control, which is reviewed in the next section.

Respiratory control. The normal sequence of inspiration and expiration depends on the presence of a tonic excitatory input to medullary respiratory neurons. The level of PO_2 and PCO_2 are probably the two most important factors that set the magnitude of this input. Both are believed to act on specific chemoreceptors that are directly connected to respiratory neurons (25). Hypercapnia and hypoxia lose their excitatory effects on breathing when these chemoreceptors are eliminated. Ventilation also is closely tied to metabolic rate, but the signal and the receptors that participate in this linkage remain obscure (26). Baroreceptors in high and low pressure areas of the circulation can also influence breathing, at least in anesthetized animals (27).

While rhythmic respiratory activity is maintained in the medullary animal, it is clear that supramedullary structures can also affect respiration. Many stimuli, such as pain, changes in light intensity, noise level, or hyperthermia can excite breathing through an effect on higher centers (28). During wakefulness such stimuli have a definite and substantial action on breathing patterns and ventilation levels (29). It is not clear whether these excitatory respiratory effects require the presence of some minimal level of chemical stimulation (30). With increasing stimulation there is an increase in discharge rates of medullary respiratory neurons, but, in addition, more and more neurons in the medulla and at other levels of the central nervous system develop a respiratory rhythm (11). There are greater numbers of neurons with respiratory rhythmicity in awake animals than in sleeping animals. It is likely that some of the respiratory effects of "less respiratory specific" stimuli, e.g., light and sound, are due to their arousing action. Hypoxia and hypercapnia also have an arousing effect that may be independent of their action on breathing, and which also seems to be mediated in part by higher brain centers (31).

The diaphragm is considered to be the major muscle of respiration. As respiratory stimulation becomes greater, the force of contraction of the diaphragm increases, and new muscles are recruited to assist it. These include chest wall muscles like the intercostals and the abdominal muscles, which help prevent the diaphragm from becoming ineffectual as a pressure generator

because of excessive shortening, avert the occurrence of fatigue, and prevent distortion of the chest wall or the dissipation of diaphragm force (32). Upper airway muscles that dilate the pharyngeal air passages assist in reducing the resistance to airflow as stimulus levels increase (33). They may also help offset any tendency for the upper airway to collapse as a result of the negative intrapharyngeal produced by the contraction of inspiratory chest wall muscles (34). This last action may be particularly important during sleep.

It is much more difficult in awake people and animals than it is during their sleep or with anesthesia to stop breathing simply by reducing the level of PCO_2 or by raising the level of PO_2 (28). Breathing seems to persist because of the respiratory excitatory effect of environmental stimuli, and possibly because of a slowly dissipating excitatory discharge in respiratory neurons that develops with active respiration (35).

During NREM sleep or anesthesia, when the effects of stimulation from the environment are reduced, apnea occurs much more easily with hyperventilation (36). In these states it can be shown that, as drives to breathing are reduced, there is a progressive cessation of activity in groups of respiratory muscles; diaphragm activity is the last to disappear (37). During REM sleep there seems to be internally generated stimuli that affect respiration, and hyperventilation may not by itself be enough to produce diaphragm apnea (37). However, REM sleep tends to be more fragile than NREM sleep, and studies of the effects of hyperventilation in this form of sleep are scarce.

Both REM and NREM sleep seem to reduce the sensitivity of the ventilatory response to hypoxia and hypercapnia; that is, the change in ventilation produced a change in PCO_2 or PO_2 (38, 39, 40, 41). This might mean that chemoreceptors operate differently in sleep. But this reduced sensitivity might also occur because of changes in lung and airway mechanics during sleep that impede the lung inflation or because nonspecific environmental stimuli no longer amplify the response to chemical stimuli (42, 43, 44). In any case, sleep seems to depress the activity of the accessory muscles of respiration (like the upper airway muscles) more than the diaphragm.

Responses to mechanoreceptor stimuli are also altered by sleep. For example, compensatory responses to airway obstruction are reduced (45). Laryngeal irritation that produces cough in the awake state may produce apnea in REM sleep (46). Whether other respiratory inhibitory reflex effects are more prominent in sleeping than in awake states is unclear. The reaction of different sets of muscles to stimulation, be it chemical or reflex, is not identical in anesthetized and awake animals, and this may also be true in sleep. In addition to different thresholds of activation, response curves can be different (47). Many reflexes, e.g., baroreceptor and irritant reflexes, seem to affect some upper airway muscles much more than they do the diaphragm (26, 27).

It has also been shown that responses of muscles may depend on the receptor stimulated. For example, in anesthetized animals, hypercapnia inhibits the adductor muscles that close the larynx

(48). But hypoxia, on the other hand, seems to exert an excitatory effect on laryngeal adductors and narrows the laryngeal aperture (48). Bruce has suggested that CO_2 , acting on peripheral chemoreceptors, excites the muscles of the tongue innervated by the hypoglossal nerve more than muscles innervated by the phrenic—but the reverse occurs if CO_2 is allowed to stimulate only central chemoreceptors (49). Whether or not the same differences exist during sleep are unknown, but it is conceivable that they do.

Finally, mechanical changes that occur during sleep seem to interfere with breathing. Airway resistance, for example, seems to increase (44). The supine posture adopted during sleep tends to promote airway collapse by gravitational forces and might allow respiratory pressures to displace mobile structures like the tongue so that they occlude the upper airway (6, 34). Sleep itself, particularly in its REM form, increases upper airway flaccidity. Preexisting anatomical changes like micrognathia or increased retropharyngeal fat in obese individuals would enhance the likelihood for airway obstruction (14, 15).

Hence, sleep and breathing are in many ways antagonistic. Sleep decreases respiratory stimulating effects and can alter reflex responses so that central apneas are more common. The decrease in drive may silence upper airway muscles before it stops the diaphragm and create an imbalance of forces that allows negative inspiratory pressure to produce airway obstruction. Finally, the changes in the alignment of the respiratory muscles in the upper airway and the effects of gravity tend to increase the forces needed to maintain breathing and airway patency; this in turn can lead to obstruction. On the other hand, the swings in blood gas tensions that occur with apnea, and the increased efforts to breathe that occur in obstructive apneas produce arousal and terminate sleep (40, 41). While these opposing tendencies are normally reconciled, sleep apnea patients seem unable to arrive at an adequate compromise.

Causes of repetitive clusters of apnea. Inhibitory reflexes arising from mechanoreceptors in the airways or in the circulatory system or momentary episodes of hyperventilation might easily explain randomly occurring isolated prolonged apneas. Whether the apneas were central or obstructive might depend on the nature or the intensity of the stimulus change.

However, it is difficult to explain why these stimuli should lead to repetitive apneas, that is, why the effects of a disturbance that caused an apnea should not disappear with time.

There are at least two possible explanations for recurrent apneas in sleep. One possibility is that sleep makes the cyclic oscillations that are discernible during wakefulness more obvious by eliminating the random superimposed effects of environmental changes in illumination and noise level. This idea is shown diagrammatically in Fig. 1. Apnea occurs, rather than just swings in ventilation, because sleep, in addition to reducing the respiratory stimulatory effects of hypoxia and hypercapnia, also depresses metabolic rate and the overall level of respiratory excitatory input (26, 28). Subjects with depressed chemoreceptor function would be more likely to develop apneas, and the nature

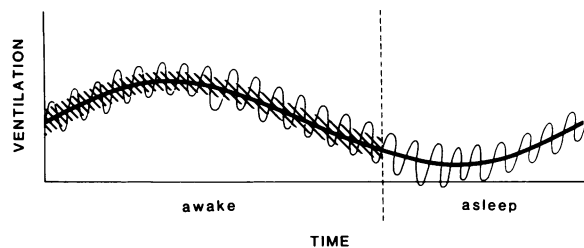


Figure 1. Oscillatory changes in ventilation over a day. Horizontal line represents zero ventilation. Heavy line shows a possible circadian change in ventilation level, while thin line sine waves show shorter spontaneously occurring breathing oscillations. When awake, short-term periodic oscillations in ventilation occur that are obscured by nonspecific environmental stimuli (-----). These oscillations become more apparent during sleep when the effects of environmental stimuli are minimized. Also, with the sleeping decrease in ventilation, the shorter fluctuations in ventilation are sufficient to cause apnea or near apnea.

of the apnea might depend on the specific chemoreceptor defect. Theoretically, if this explanation were correct, respiratory stimulants should prevent apnea. While some, such as progesterone and strychnine, have been used successfully in some patients, others have had no effect on the number of apneas found (50, 51).

Oscillations might also occur as a result of decreased damping in the feedback control system that regulates breathing (52). Physical feedback control system can be underdamped and unstable so that the output they produce is cycling rather than steady. Cheyne-Stokes breathing can result from such an instability in respiratory control. The factors that decrease the stability of respiratory control include increased controller gains, increased levels of resting CO_2 when breathing CO_2 -free gas, prolonged circulation time, and decreased storage in the body tissues of O_2 and CO_2 (19).

Neither of these two possibilities is mutually exclusive, since there are in physiological systems both pacemakers and feedback control loops, and both kinds of oscillations might occur together.

Respiratory physiologists are often not very clear about what they mean by reduced chemosensitivity, and this complicates the interpretation of data obtained during sleep. The problem is illustrated in Fig. 2.

Chemosensitivity is often evaluated in normal people by measuring the increase in ventilation produced by a change in arterial PCO_2 . This response is usually linear, and the slope of the relating ventilation to PCO_2 is often used as a measure of responsiveness. According to control theory, the greater the slope of this line the less the damping and the more likely it is for the respiratory system to become unstable. A decrease in slope tends to increase damping. Respiratory depressants may decrease the slope of the response line, i.e. decrease responsiveness. However, they can also shift the response line, as shown in Fig. 2, to the right, so that resting arterial PCO_2 is elevated and resting ventilation is reduced. In general, such rightward shifts, even though

they are produced by respiratory depressants, increase tendencies for instability. The cause of the instability is due in this case to an overall increase in the responsiveness ("loop gain") of the entire system (52). The hyperbolic line in the figure shows the change in P_ACO_2 caused by a given change in alveolar ventilation. When the resting arterial PCO_2 is higher, a change in ventilation will produce a greater change in PCO_2 than when the resting CO_2 is lower, so that apnea, for example, is more likely to occur. Sleep, like many respiratory depressants, has both effects: it increases the resting PCO_2 and it decreases the response slope. These changes have opposite actions on loop gain. Similarly, respiratory stimulants, by increasing responsiveness, can increase the propensity to instability, but by decreasing the resting PCO_2 can stabilize breathing. Hypoxia is one example of a respiratory stimulant that is believed to have its main effect by increasing the CO_2 response slope. How stable breathing is when sleep occurs or when drugs are used to alter chemosensitivity will depend on the relative degree of the two changes and their overall effect on "loop gain".

Bulow has reported an increase in central apneas in those normal individuals who had the greatest increase in resting PCO_2 with sleep (53). In animals, interventions that decrease damping of the control system by increasing circulation time or increasing controller gains or resting PCO_2 produce clusters of apnea and hyperventilation similar to that seen in sleep apneas (54, 55). The differences in responses of upper airway and chest wall muscles to different stimuli and to chemoreceptor inputs described earlier could lead to obstructive as well as central apneas. Some of the quantitative relationships needed to produce this kind of instability in breathing during sleep have already been described (19).

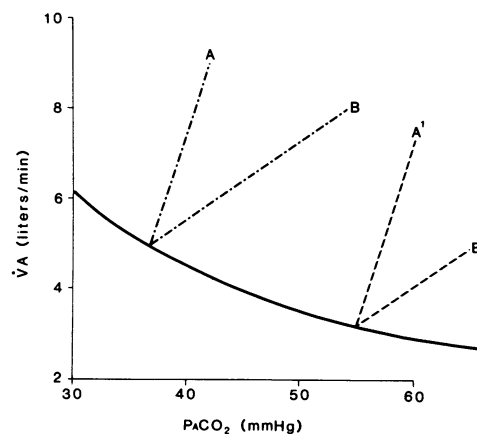


Figure 2. Heavy line shows the effect of ventilation (\dot{V}_A) on P_ACO_2 . Broken lines show the effect of changes in P_ACO_2 on ventilation (controller response). An increase in controller response from B to A decreases control system stability. A shift in controller responses from A to A', or B to B', also increases the possibility for oscillations in ventilation to occur as a result of instability in the respiratory feedback control system.

Control system instability could explain the mixed effect of respiratory-stimulating agents. Stimulants that acted to increase the slope of the ventilatory CO₂ response line would enhance instability and be of no benefit in preventing apnea. On the other hand, stimulants that act additively to CO₂ that have the same effect at all levels of drive (hence no effect on gain) should stabilize breathing.

But, there are still other considerations. First, the responsiveness of respiratory chemoreceptors to stimuli at or below the usual resting level has been little studied. It may be that as CO₂ is lowered below its usual arterial level of 40 mmHg, responsiveness changes, becoming greater or less. The responsiveness of different muscle groups may change in different ways as CO₂ is varied about the resting level (37). There is little information on the effects of pharmacological agents on these aspects of chemosensitivity in any one muscle or on comparative effects in different respiratory muscles. Agents, for example, that increase the resting level of activity of just the diaphragm but not the upper airway muscles, may convert recurrent central apneas to obstructive apneas. On the other hand, agents that increase the activity of upper airway muscles but not chest wall muscles may convert obstructive to central apneas.

Diagnosis and treatment. The diagnosis of sleep apnea requires confirmation by a sleep study in which heart rate and blood gas tensions are monitored in addition to breathing movements and EEG. Apneas during sleep are not necessarily dangerous, nor do they necessarily require treatment. In patients with life-threatening apneas, a search should be made for correctable anatomical defects that narrow the airways. This may include X-rays of the upper airway or CAT scanning. It should be remembered though that only static pictures will be obtained, and that what appears to be a narrow upper airway when visualized during expiration may be of adequate size if visualized during inspiration. Obesity itself can be a cause of upper airway narrowing that can be remedied by weight loss (13, 14). Plastic surgical procedures have been developed to correct other anatomical abnormalities (56).

Simple mechanical devices may also help widen the upper airway if the cause is functional rather than anatomical. These include devices to open the upper airways by keeping the tongue in a forward position or to allow a positive pressure to be maintained in the upper airways all through the breathing cycle (57, 58). To the degree that instabilities caused sleep apneas, a number of other interventions might prevent apnea. These include improvement of cardiac function with reduction in circulation time and drugs that appropriately alter the chemosensitivity of the upper airway and chest wall muscles (57, 58).

The effects of different interventions might also depend on the nature of sleep. It is not at all clear that sleep is always produced in the same way. A variety of sleep-promoting factors have been identified. These include a number of monamines, polypeptides (such as substance S-delta sleep-inducing peptide, muramyl depeptide, and interleukin -1), and prostaglandin D₂ (59, 60). While it is not clear whether any of these agents are

responsible for "natural" sleep, it is possible that natural sleep varies in its cause and that this cause is not always the same even when EEG patterns appear identical. Sleep may be produced by different combinations of these substances in different individuals. It is even possible that only some sleep-inducing substances are capable of producing the functional changes that lead to sleep apnea and that apneas depend ultimately on differences in the mix of the biochemical agents producing sleep.

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