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State of the Art Review

Respiratory Arousal From Sleep: Mechanisms and Significance

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Summary: The mechanisms by which respiratory stimuli induce arousal from sleep and the clinical significance of these arousals have been explored by numerous studies in the last two decades. Evidence to date suggests that the arousal stimulus in nonrapid eye movement sleep (NREM) is related to the level of inspiratory effort rather than the individual stimuli that contribute to ventilatory drive. A component of the arousal stimulus proportional to the level of inspiratory effort may originate in mechanoreceptors either in the upper airway or respiratory pump. Medullary centers responsible for ventilatory drive may also send a signal proportionate to the level of drive to higher centers in the brain which are responsible for arousal. Thus, the arousal stimulus may consist of multiple components, each increasing as inspiratory effort increases. The level of effort triggering arousal is an index of the arousability of the brain (arousal threshold). A deeper stage of sleep, central nervous system depressants, prior sleep fragmentation, and the presence of obstructive sleep apnea (OSA) have been observed to increase the arousal threshold to airway occlusion. Less information is available concerning the mechanisms of arousal from rapid eye movement (REM) sleep. While REM sleep is associated with the longest obstructive apneas in patients with OSA, normal human subjects appear to have a similar or lower arousal threshold to respiratory stimuli in REM compared to NREM sleep. Recent studies have challenged the assumption that the termination of all obstructive apnea is dependent on arousal from sleep. Improvements in methods to detect and quantitate changes in the cortical electroencephalogram (EEG) may better define the relationship between arousal and apnea termination. This may result in improved criteria for identifying EEG changes of clinical significance. While little is known concerning the mechanisms of arousal in central sleep apnea, arousal may play an important role in inducing this type of apnea in some patients. **Key Words:** Arousal—Sleep apnea syndrome—Respiration—Mechanoreceptors—Sleep.

Arousal from sleep is a frequent occurrence in patients with the sleep apnea syndromes and other respiratory disorders that interrupt sleep. Although arousal was previously regarded as the "forgotten response" to respiratory stimuli (1), the last decade has seen a renewed interest in research concerning both the mechanisms by which respiratory stimuli produce arousal from sleep and the clinical significance of these arousals. The purpose of this review is to summarize what it is known about the mechanisms and clinical significance of arousal resulting from respiratory stimuli, to propose a series of simple models to structure the experimental facts, and to highlight some of the many questions that remain unanswered.

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DEFINITION OF AROUSAL AND RESPIRATORY AROUSAL FROM SLEEP

The term "arousal from sleep" denotes the change from a state of sleep to a state of wakefulness (1,2). Arousals may disrupt sleep by producing prolonged awakenings and thus shortening total sleep time. However, frequent brief arousals can also result in increases in daytime sleepiness without substantially reducing total sleep time (3–6). Therefore, determining the frequency of arousals has become a standard part of the analysis of sleep architecture. Until recently, there has not been a clear consensus on the minimum changes that must be present in the electroencephalogram (EEG) and electromyogram (EMG) to score an arousal. A preliminary report from the Atlas Task Force of the American Sleep Disorders Association (ASDA) (7) recommended that an arousal be scored in nonrapid eye movement (NREM) sleep when there is "an

abrupt shift in EEG frequency, which may include theta, alpha, and/or frequencies greater than 16 Hz, but not spindles" of 3 seconds or greater in duration. The 3-second duration was chosen for methodological reasons; shorter arousals may also have physiological importance. To be scored as an arousal, the shift in EEG frequency must follow at least 10 continuous seconds of any stage of sleep. Arousals in NREM sleep may occur without a concurrent increase in the submental EMG amplitude. But, in order to be scored as an arousal in rapid eye movement (REM) sleep, the required EEG changes must be accompanied by a concurrent increase in EMG amplitude. This extra criterion is necessary because spontaneous bursts of alpha rhythm are a fairly common occurrence in REM (but not NREM) sleep. Finally, according to these preliminary recommendations, increases in the chin EMG in the absence of EEG changes are not considered evidence of arousal in either NREM or REM sleep. Similarly, sudden bursts of delta activity in the absence of other changes also do not qualify as evidence of arousal. Because cortical EEG changes must be present to meet the above definition of arousal, such events are also termed electrocortical arousals. It should be noted that the preliminary ASDA guidelines represent a consensus on events likely to be of physiological significance. The committee recognized that other EEG phenomenon, such as delta bursts, may also represent evidence of arousal in certain contexts.

Despite these efforts to standardize the definition of arousals, a number of problems still remain. For example, the scoring of arousals still remains somewhat subjective. With the use of computerized techniques such as spectral analysis of the EEG signal, a more quantitative definition of arousal may someday be possible. Of greater concern is the possibility that the cortical EEG criteria currently employed to define arousal from sleep (7) overlook the potential importance of subcortical arousal. Whether this type of arousal does occur, how it might be defined, and what its clinical importance might be are currently unknown; these questions are the subject of ongoing research efforts.

In this review we will focus on respiratory arousal. We will define such events as arousal from sleep associated with progressive increases in stimuli related to respiration (hypoxia, hypercapnia, and respiratory effort). However, we acknowledge that in the absence of a more specific definition, there is no way to discern whether a given arousal from sleep is actually produced by stimuli associated with respiration or actually occurs for other reasons that are coincidental with, but not the result of, respiratory stimulation (e.g. spontaneous arousal). As many of the works cited in this review were performed before the above ASDA arousal-scoring guidelines were published, these studies often used slightly different criteria to define arousal. Therefore, we will use the term "respiratory arousal" in a somewhat broader sense than specified by the above ASDA criteria.

TABLE 1. *Arousal stimuli related to respiration*

A. Chemical (chemoreceptors)
Hypoxia
Hypercapnia
Net ventilatory drive
B. Mechanical (mechanoreceptors)
Upper and lower airways
Respiratory muscles
Chest wall

RESPIRATORY AROUSAL DURING NREM SLEEP

Arousal to hypoxic and hypercapnic stimuli

In simple terms, an arousal response occurs once the arousal stimulus exceeds the arousal threshold. The stimuli related to respiration that might possibly trigger arousal are listed in Table 1. Early studies focused on hypoxia or hypercapnia individually, determining arousal thresholds as the values of PO_2 (or SaO_2) below which, or PCO_2 above which, arousal from sleep occurred. Arousal from from NREM sleep secondary to hypoxia without airway occlusion, whether isocapnic (8–10) or hypocapnic (11), is surprisingly inconsistent. In one study, normal human subjects failed to arouse from sleep during about half of the isocapnic hypoxia trials even when the arterial oxygen saturation (SaO_2) fell as low as 70% (8). In another study (10), isocapnic hypoxia induced arousal in only 5/8 subjects when the alveolar PO_2 fell as low as 40 mm Hg. Hypocapnic hypoxia appears to be even less likely to induce arousal with normal subjects arousing from NREM sleep only about one-third of the time (11). In contrast to humans, arousal from sleep due to experimental hypoxia occurs consistently in dogs (12).

Hypercapnia is a much more potent arousal stimulus than hypoxia (10,13,14). Studies of hyperoxic hypercapnia have found that arousal tends to occur when the end tidal PCO_2 reaches 10–15 mm Hg above the baseline waking level. The values of the CO_2 arousal threshold vary between individuals and also depend on the method used to induce hypercapnia. Not surprisingly, the combination of hypercapnia and hypoxemia is a more potent stimulus to arousal than hypoxia alone (12,15).

The importance of chemoreceptors to the arousal response to eucapnic hypoxia was demonstrated by studying the arousal response in dogs before and after

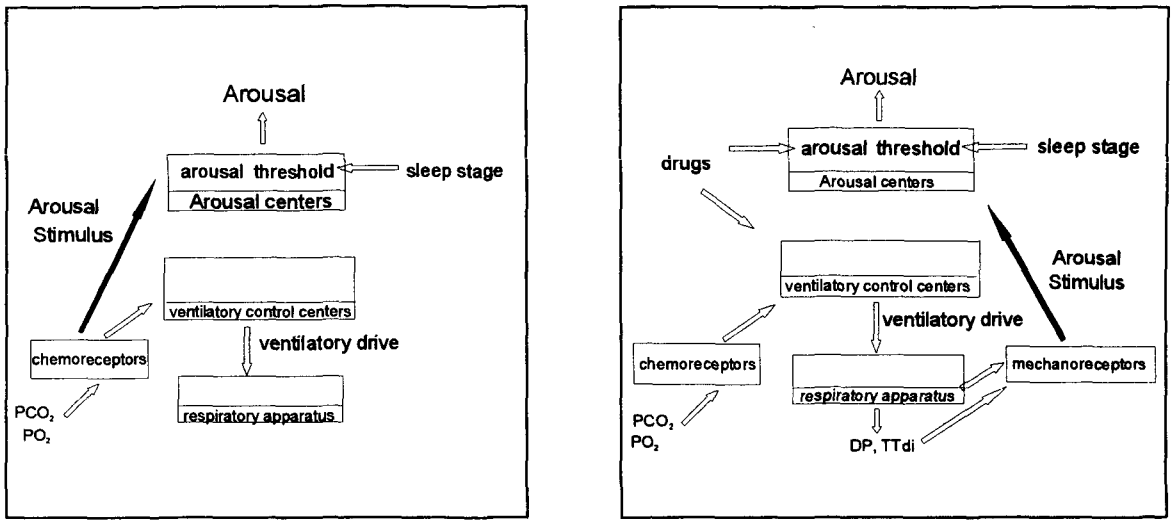

FIG. 1. (Model A) A simple model of the arousal response to respiratory stimuli. Information from the chemoreceptors forms the arousal stimulus. Arousal occurs when the arousal stimulus exceeds the arousal threshold. (Model B) In this model, the arousal stimulus is information from mechanoreceptors. The receptors are stimulated by the act of inspiration. The arousal stimulus increases as the level of inspiratory effort increases. Here the esophageal pressure deflection (DP) or the tension time index of the diaphragm (TTdi) are assumed to reflect the level of inspiratory effort and are therefore indices of the magnitude of the arousal stimulus. The maximum values of DP or TTdi are indices of the arousal threshold.

carotid body denervation (16). The SaO_2 associated with arousal from NREM sleep decreased from 83% to less than 60% and in REM sleep from 70% to less than 50% after carotid body denervation. These results could be explained by a simple model of respiratory arousal in which the chemoreceptors project directly to areas of the brain responsible for arousal, such as the reticular activating system (Fig. 1, model A). When the stimulus transmitted from the chemoreceptors exceeds the arousal threshold, arousal occurs. As the areas of the brain responsible for arousal remain poorly defined, we will refer to them collectively as the arousal centers. In accord with this model, removal of the carotid body input (important chemoreceptors) would decrease the arousal stimulus for a given level of arterial hypoxia and hypercapnia, but would not change the arousal threshold (sensitivity of the arousal centers). Conversely, the observed differences in the levels of hypoxia triggering arousal from NREM and REM sleep would be due to changes in the arousal centers (the arousal threshold) inherent to these different sleep stages.

Arousal from airway occlusion

Obstructive sleep apnea and experimental airway occlusion

Hypercapnic hypoxemia develops during periods of obstructive apnea (airway occlusion) or hypopnea (airway narrowing) of sufficient length or severity to result in hypoventilation. Thus, chemoreceptor input to the central nervous system would be expected to be an important arousal stimulus during airway occlusion/narrowing. Bowes and coworkers (17) documented the importance of the carotid bodies (important peripheral chemoreceptors) in the arousal response to tracheal occlusion in dogs. After carotid body denervation (CBD), arousal from slow wave sleep was greatly delayed and the arterial oxygen saturations at arousal were <60%.

However, arousal from upper airway narrowing or occlusion appears to involve more stimuli than the arterial blood gas changes alone, as arousal can occur at the termination of apneas or hypopneas that are too brief for substantial asphyxic blood gas changes to develop. Thus, the act of inspiring against a narrowed or occluded airway might by itself contribute to the arousal stimulus. Possible mediators of this effect might be mechanoreceptors in or near the respiratory tract that are activated by increasing respiratory effort. The interaction between mechanical and chemical stimuli to arousal was demonstrated by Yasuma and coworkers (18) in dogs. In this study, arousal was induced by isocapnic hypoxia (rebreathing) with and without an added expiratory load. With other factors being the same, arousal occurred at a higher SaO_2 in the loaded condition, demonstrating that mechanical factors contribute to the arousal stimulus. This study suggests that information from both chemoreceptors and mechanoreceptors can contribute to the arousal stimulus during airway occlusion.

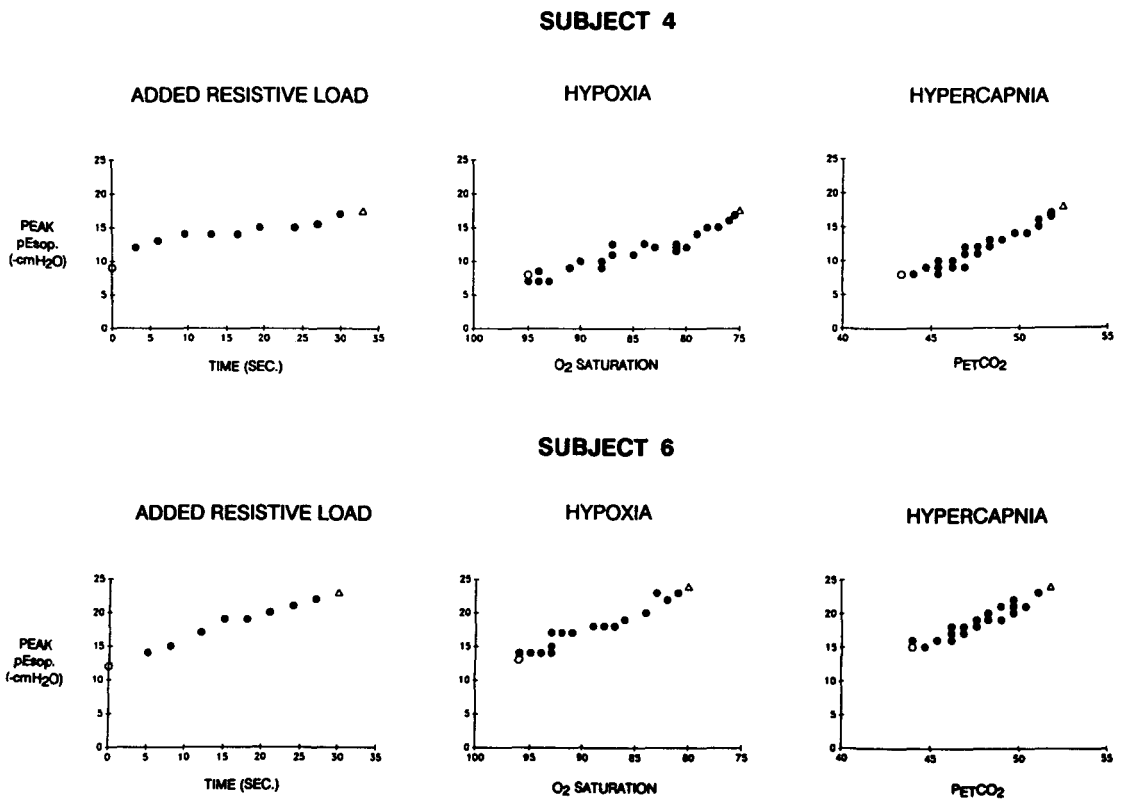

FIG. 2. Shown are plots of peak negative inspiratory esophageal pressure for three different respiratory stimuli at baseline (open circles), during stimulated ventilation (closed circles), and for the breath preceding arousal from sleep (open triangles) for two different subjects. Peak negative esophageal pressure begins at similar baseline levels and progressively rises until arousal results at a level that is similar within, but different between, the two subjects. (Printed with permission: *Am Rev Respir Dis* 1990;142:295–300).

If mechanoreceptors do contribute to the arousal stimulus, it would be expected that the input to the arousal centers would correlate with the amount of negative pressure generated by the inspiratory effort during obstructed inspiration. To investigate this correlation, several studies of airway occlusion focused on the level of inspiratory effort associated with arousal. Vincken and coworkers (19) found that patients with obstructive sleep apnea (OSA) tended to arouse from NREM sleep when the tension time index of the diaphragm (TTdi) reached the range associated with muscle fatigue (0.15–0.18). The authors concluded from this data that diaphragmatic muscle fatigue might trigger arousal. Subsequently, Wilcox and coworkers (20) found arousal from sleep to occur in some patients with OSA at lower levels of TTdi. These data, and the fact that muscle fatigue occurs only after prolonged contraction in the fatiguing range (21), suggest that the hypothesis that muscle fatigue triggers arousal is untenable. However, the results from these two studies suggest that individual patients arouse repeatedly once a certain TTdi level is reached. Thus, although the level of TTdi prior to arousal varies among patients, it is consistent within individual patients.

These observations in patients with OSA suggest that the arousal stimulus during airway obstruction in NREM sleep might be related to the level of inspiratory effort irrespective of the specific combination of PCO_2 and PO_2 values stimulating ventilatory drive. However, no measures were taken in these studies to separate the effects of increasing arterial PCO_2, decreasing PO_2, and mechanical factors upon arousal from sleep. These variables were systematically controlled in a study of normal subjects by Gleeson and coworkers (22). Using the peak negative esophageal pressure as an index of inspiratory effort, these investigators evaluated three stimuli for inducing arousal from sleep (hypoxemia, hypercapnia, and resistive loading). The ventilatory responses to the three stimuli, the SaO_2, and end tidal PCO_2 values at arousal from the three stimuli were different. However, arousal tended to occur at the same peak negative esophageal pressure in a given patient independently of the method of respiratory stimulation (Fig. 2). Thus, regardless of the stimulus to increasing respiration, arousal occurred at the same level of respiratory effort.

The relationship between inspiratory intrathoracic pressure changes and arousal from sleep in normal humans has been further studied using experimental airflow (mask) occlusion. During mask occlusion in nor-

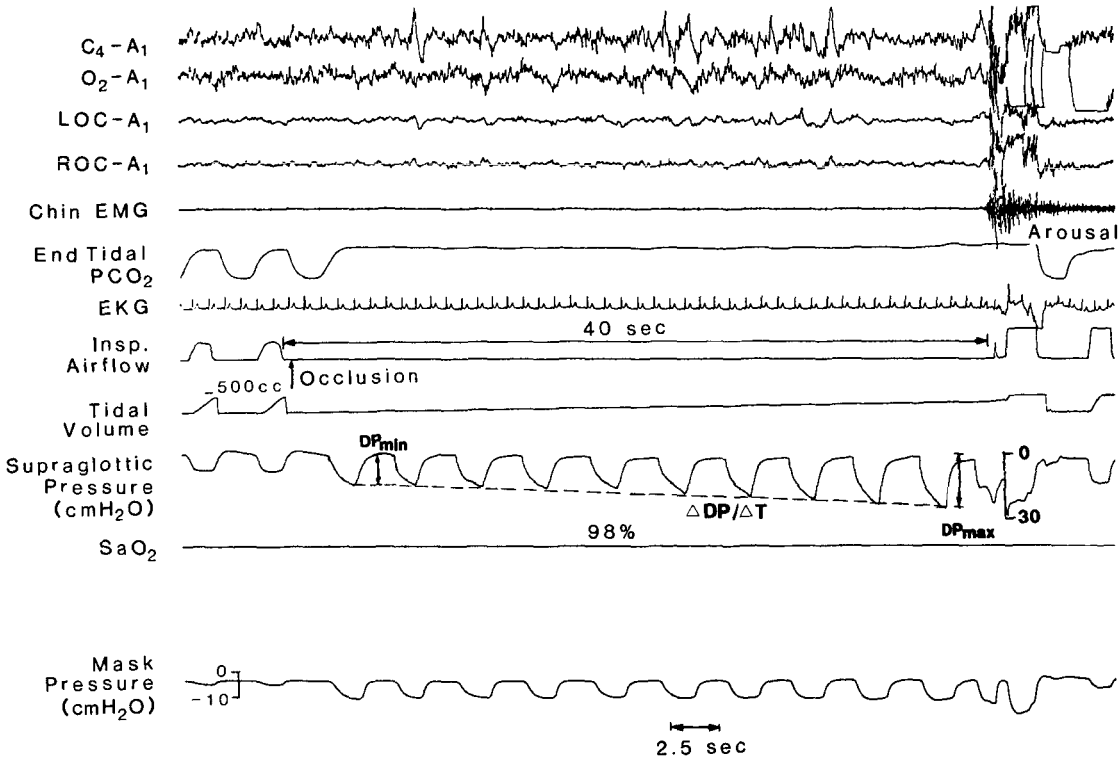

FIG. 3. Mask occlusion in a normal subject during nonrapid eye movement (NREM) sleep under hyperoxic conditions. The supraglottic pressure deflections (DP) increase until arousal. The initial (minimum) pressure deflection (DP_{min}), the maximum deflection prior to arousal (DP_{max}), and the mean rate of increase in the pressure deflection (DP) with time ($\Delta DP/\Delta T$) are illustrated. (Printed with permission: *Am Rev Respir Dis* 1992;145:445–452.)

mal subjects during NREM sleep, there is a progressive rise in the level of airway suction pressure until arousal occurs (23,24). Because upper airway collapse may occur using this technique (Fig. 3), it is necessary that respiratory pressure deflections be measured in the supraglottic area (below the site of collapse) rather than at the mask (24). In the absence of airflow, supraglottic pressure deflections are equivalent to intrathoracic changes and are therefore similar to pressure deflections measured in the esophagus (25). For simplicity, we will use DP (pressure deflection) to represent deflections in either supraglottic or esophageal pressure.

Examination of the time course of intrathoracic (airway) pressure changes during mask occlusion provides a basis for relating changes in inspiratory effort to the factors determining the time to arousal. One can designate DP_{min} as the pressure deflection during the first occluded breath and DP_{max} as the maximum deflection prior to arousal (Fig. 3). One can then define a rate of change in pressure deflection as $\Delta DP/\Delta T = (DP_{max} - DP_{min})/T$, where T is the time between DP_{min} and DP_{max}. The time course of pressure deflections can then be characterized by the three parameters: DP_{min}, DP_{max}, and $\Delta DP/\Delta T$. In accord with this concept, DP_{min} reflects the level of ventilatory drive at the time of airway occlusion, DP_{max} the arousal threshold (inspiratory pressure level at which arousal occurs), and $\Delta DP/\Delta T$ the respiratory response to airway occlusion.

Using this model, Berry and associates performed a series of experiments investigating the effects of various interventions on the time to arousal from NREM sleep (Table 2). Under hyperoxic conditions (26) during stable stage 3/4 sleep, the time interval between

TABLE 2. *Summary of studies of mask occlusion in normal subjects*

Condition versus control	Time to arousal	DP_{max}	$\Delta DP/\Delta T$	DP_{min}	Reference
Hyperoxia	Increased	No change	Decreased	No change	26
Hypercapnia	Decreased	No change	Increased	Increased	27
Ethanol	Increased	Increased	Decreased	Increased	24
Triazolam	Increased	Increased	No change	No change	28
Stage 3/4 versus 2	Increased	Increased	No change	No change	24

DP, deflection in pressure.

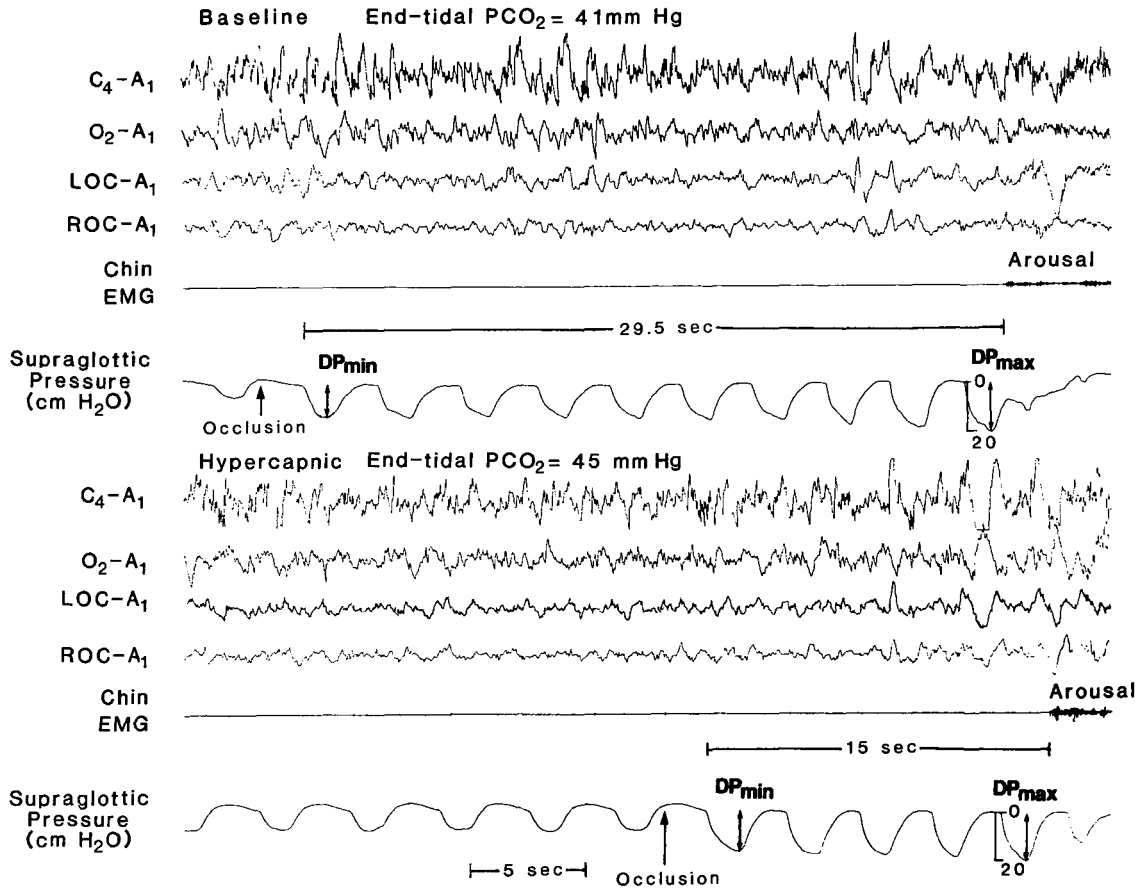

FIG. 4. The arousal response to mask occlusion in a normal subject during stage 3/4 nonrapid eye movement (NREM) sleep under hyperoxic conditions. The upper tracing is a control occlusion (preocclusion end-tidal PCO_2 = 41 mm Hg). The lower tracing is a hypercapnic occlusion (preocclusion PCO_2 = 45 mm Hg). Although preocclusion hypercapnia shortened the time to arousal, the maximum level of inspiratory effort preceding arousal (DP_{max}) was the same. The DP_{min} and $\Delta DP/\Delta T$ were higher when the preocclusion PCO_2 was higher. (Printed with permission: *J Appl Physiol* 1993;74:2269–2275.)

mask occlusion and arousal was increased compared to control occlusions. The amount of arterial oxygen desaturation following mask occlusion was greater in the control condition. However, the level of suction pressure associated with arousal (DP_{max}) was similar under both conditions. Hyperoxia delayed arousal by decreasing the respiratory response during occlusion ($\Delta DP/\Delta T$). In contrast, when mask occlusion was performed under hypercapnic conditions, the time to arousal was shortened compared to control conditions (27). Again, the DP_{max} under hypercapnia and control conditions did not differ. Preocclusion hypercapnia shortened the time to arousal by increasing ventilatory drive at the time of occlusion (DP_{min}) and by slightly increasing the respiratory response during occlusion ($\Delta DP/\Delta T$). A sample tracing of occlusions under control and hypercapnic conditions is illustrated in Fig. 4. Thus, similar to the findings of Gleeson and coworkers (22), arousal occurred once a certain level of inspiratory effort was reached, regardless of the blood gas changes. Therefore, DP_{max} could be viewed as an index of the arousal threshold, presumably reflecting the sensitivity of central nervous system arousal centers. The experimental manipulations (preocclusion hyperoxia or hypercapnia) altered the time course of inspiratory effort without changing the arousal threshold (DP_{max}). Alterations in the preocclusion ventilatory drive (DP_{min}) or the respiratory response to airway occlusion ($\Delta DP/\Delta T$) changed the time required for the developing level of inspiratory effort (DP) to reach DP_{max}.

In a second set of experiments, Berry et al. (24,28) demonstrated that it is also possible to alter the arousal response to airway occlusion by altering the arousal threshold (DP_{max}). If one assumes that DP_{max} reflects the level of sensitivity of the central nervous system to arousal stimuli from airway occlusion, it follows that drugs that decrease neural sensitivity (central nervous system depressants) would increase the arousal threshold and therefore increase the DP_{max}. In fact, when carefully studied, ethanol (24) and triazolam (28) each delayed arousal following experimental airway occlusion and increased DP_{max}. In addition, ethanol also decreased ($\Delta DP/\Delta T$) demonstrating an effect on both the arousal threshold and the respiratory response

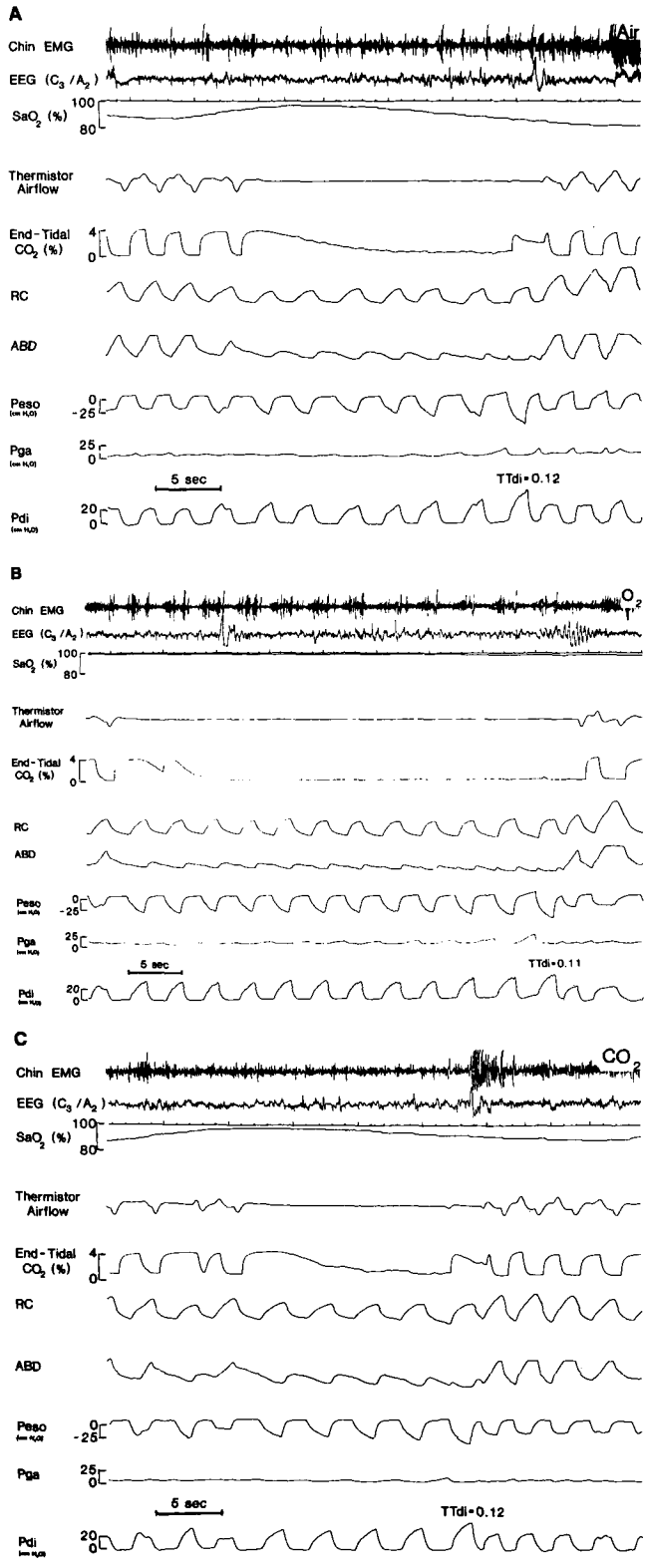

FIG. 5. Representative apneas from a patient in stage 2 sleep under three experimental conditions. (A) Apnea while breathing room air. Note that Pdi (the transdiaphragmatic pressure) and TTdi (the tension-time index) progressively increase during apnea, reaching a maximum on the last obstructed effort. (B) Apnea while breathing O2. There is no substantial oxygen desaturation, and the apnea duration is prolonged compared to that on room air. However, the TTdi ← value of the last obstructed effort is similar to that on room air. (C) Apnea while breathing CO_2. Pre and postapneic end-tidal PCO_2 are increased compared with values on air. Again, however, the TTdi achieved at end-apnea is the same as that achieved by breathing room air. (Printed with permission: *Am J Resp Crit Care Med* 1994; 149:707–14.)

to airway occlusion. In summary, it is clear that various interventions can alter either the time course of developing DP ($\Delta DP/\Delta T$), the arousal threshold (DP_{max}), or both factors simultaneously.

Comparable experiments have been performed in patients with OSA and have shown similar results. Kimoff and coworkers (29) found that experimental increases in the preapnea PO_2 and PCO_2 resulted in increases and decreases, respectively, in the apnea duration, but did not change the level of inspiratory effort (TTdi) associated with arousal (Fig. 5). Analogous to results in normal individuals, central nervous system depressants also appear to increase the level of inspiratory effort associated with arousal in OSA patients. For example, triazolam was found to increase both the apnea duration and the maximum deflection in esophageal pressure (DP_{max}) prior to arousal in OSA patients (30).

Although the results of studies of mask occlusion in normal subjects and OSA patients during NREM sleep are quite similar, some differences are notable. First, the level of inspiratory effort at arousal is higher in patients with OSA. The possible significance of this finding will be discussed below. Secondly, in the studies of normal subjects, mask occlusion is usually applied at a time of regular respiration and stable ventilatory drive. Following occlusion, there is a steady increase in suction pressure. In patients with OSA, airway occlusion occurs during a period of falling ventilatory drive. During some apneas, the esophageal DP may initially decrease, reach a minimum, and then increase until arousal. In this case, a modification of the previously discussed scheme for describing the time course of DP is necessary (Fig. 6). The initial fall in DP observed during apnea is probably due to the fact that while upper airway obstruction occurs during periods of falling ventilatory drive (31), apnea onset is not necessarily at the nadir in ventilatory drive. Thus, there is a phase shift between ventilatory drive and airway patency. However, this does not necessarily imply a phase shift between ventilatory drive to the upper airway and respiratory muscles. Onal and coworkers (31,32) have demonstrated that during preapneic breaths the EMG of the genioglossus (EMGge) and the diaphragm (EMGdi) both decrease proportionately. Airway patency depends on a complex balance between upper airway muscle tone (opening the airway)

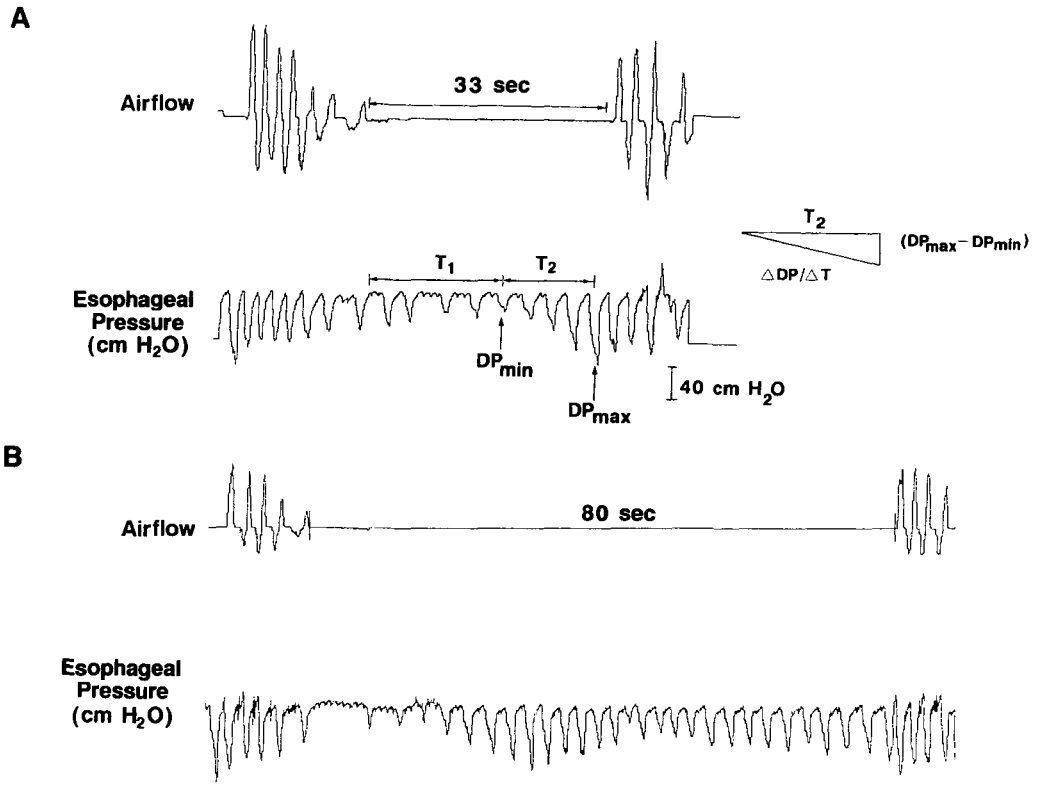

FIG. 6. Actual tracings of esophageal pressure deflections from a patient with obstructive sleep apnea (OSA) during nonrapid eye movement (NREM) sleep **(A)** and rapid eye movement (REM) sleep **(B)**. During NREM sleep **(A)**, the maximum esophageal pressure decreases initially, reaches a minimum value (DP_{min}), then increases until apnea termination. The time required to reach the maximum level of inspiratory effort depends on T1 [apnea onset to minimum deflection pressure (DP)], DP_{min}, and $\Delta DP/\Delta T$. Arousal coincided with the resumption of airflow. In REM sleep **(B)**, DP is erratic with no steady pattern of increase.

and other factors such as the transluminal pressure and the passive tendency of the airway to collapse (33). In susceptible patients, upper airway closure could occur before the nadir in upper airway muscle tone (or ventilatory drive). Therefore, apnea onset need not coincide with the nadir in ventilatory drive (or the minimum DP).

A third difference between mask occlusion in normal patients and spontaneous airway obstruction in patients with OSA is that the rate of increase in inspiratory effort magnitude during apnea [$\Delta DP/\Delta T$ or $\Delta(TTdi)/\Delta T$] is often much higher in the latter group (26,30). While the increase (with time) in suction pressure is often fairly linear after mask occlusion in normal patients, in those with OSA the slope increases quite rapidly toward apnea termination. This does not appear to be due to a nonlinearity in neuromechanical coupling between ventilatory drive and suction pressure. While the relationship between esophageal DP and EMGdi differs between the occlusive and nonocclusive phases of the apnea cycle (32,34), during the occlusive phase DP and Pdi (transdiaphragmatic pressure) vary linearly with increases in EMGdi. Therefore, the nonlinear increase (with time) in DP seen in some patients is probably due to a nonlinear increase in ventilatory drive that occurs due to the low and rapidly falling values of arterial PO_2 and elevated PCO_2 at apnea termination. In any case, this high rate of increasing DP in OSA patients means that interventions that produce an increase in DP_{max} will result in only a minimal increase in the time required to reach this higher level of inspiratory effort. Thus, interventions that increase the DP_{max} may result in relatively minor increases in the time to arousal (apnea duration).

Before we address the possible mechanisms by which respiratory stimuli might produce arousal in response to airway occlusion, some methodological issues need clarification. As noted above, some investigations have used TTdi and others the deflection in esophageal pressure (or airway pressure) as an index of the level of inspiratory effort. As studies using TTdi or DP have found similar results, there is no clear advantage of one over the other. The TTdi = ([mean Pdi/Pdi_{-max})(Ti/T_{tot}]) where the mean Pdi is the mean transdiaphragmatic (esophageal − gastric) pressure during the inspiratory effort, Pdi-max is the maximum voluntary Pdi, and Ti/T_{tot} is the ratio of inspiratory time (Ti) to the total cycle time (T_{tot} = 60/respiratory rate). The TTdi focuses upon the inspiratory activity of the diaphragm while DP reflects the product of the activity

of all the inspiratory muscles. While the TTdi is an established index to document a pattern of muscle contraction that is potentially fatiguing, it is not necessarily superior to changes in esophageal pressure as an index of the sensation of effort. For example, during awake resistive loading, the peak esophageal pressure (as a ratio of the maximum voluntary value) was more reflective of the sensation of dyspnea than the TTdi (35). If airway mechanoreceptors contribute to the arousal stimulus (see below), the change in airway pressure sensed by such receptors is likely to be more closely related to the change in esophageal pressure rather than to the transdiaphragmatic pressure (25). Alternatively, the TTdi has a component related to the rate of effort ($1/T_{tot}$). During obstructive apnea in an occasional patient, the esophageal pressure deflection may actually plateau while occluded inspiratory efforts become more rapid (the TTdi but not DP will therefore continue to increase) (20). In such a case, the TTdi may better reflect the increase in effort. The pressure time index, PTI = $(Pes/Pes_{max})(Ti/T_{tot})$, is yet another index of effort that has been measured during sleep (36). Here Pes is the mean esophageal pressure during an inspiratory effort and Pes_{max} is the maximum voluntary Pes. It is easier to measure than the TTdi and does include a rate related-factor. However, in most patients, during obstructive apnea, the change in Pdi is principally due to changes in esophageal pressure (20), and DP continues to increase until arousal. Thus, it is not surprising that studies using either DP or TTdi have reached similar conclusions. Furthermore, as discussed below, DP and TTdi are best viewed as indices of respiratory effort rather than the actual arousal stimulus.

Another point needing clarification is that the arousal threshold in a given normal individual or patient with sleep apnea does vary during a single night. Possible reasons for this variation will be discussed in a later section. In the studies discussed earlier (22,24,26–29), in which the arousal thresholds under various conditions were compared (for example room air vs. hyperoxia), the conditions to be compared were randomly repeated across the night in the same sleep stage. Thus, on the average, the arousal threshold in each condition should have been equivalent.

It should also be emphasized that the onset of arousal as determined visually does not always occur at the nadir in esophageal pressure, nor even necessarily during inspiration. In such cases, the previous effort is used to determine the maximum inspiratory effort preceding arousal. This emphasizes the point that DP or TTdi are best considered indices of the arousal stimulus. Furthermore, the time of termination of obstructive apnea may not precisely coincide with the onset of EEG changes meeting ASDA criteria for arousal. For example, apnea termination may coincide with a burst of high voltage delta activity. Prominent EEG speeding (meeting ASDA criteria for arousal) may follow one or more breaths later.

Mechanisms of the arousal response to airway occlusion

The above studies suggest that while changes in respiratory stimuli (PCO_2, PO_2, and mechanical factors) alter the time course of inspiratory effort (ventilatory drive) during airway occlusion, arousal is triggered once a given level of inspiratory effort is reached, independent of the combination of stimuli contributing to the ventilatory drive. What is the pathway by which increasing ventilatory effort (as an arousal stimulus) is transmitted to arousals centers in the brain? One possibility is shown in model B (Fig. 1). According to this model, the stimulus that produces arousal is mechanoreceptor output. If mechanoreceptor output increased in proportion to inspiratory effort, then arousal would be triggered at the same level of effort, independent of the combination of stimuli generating increased ventilatory drive, provided that the arousal threshold (state of the arousal centers) remained constant. Using this scheme, DP or TTdi would be an index of the stimulus to arousal, and the maximum values prior to arousal (DP_{max} or $[TTdi]_{max}$) would be an index of the arousal threshold. Thus, the time to arousal (apnea duration) would depend on both the arousal threshold and the respiratory response to airway occlusion [$\Delta DP/\Delta T$ or $\Delta(TTdi)/\Delta T$]. Central nervous system depressants (ethanol, triazolam) or a deeper stage of sleep (stage 3/4) would raise the arousal threshold, thus increasing the level of DP or TTdi required to trigger arousal (DP_{max}, $[TTdi]_{max}$).

While this model accounts for many experimental findings, it is based on the assumption that activation of the respiratory apparatus must occur to trigger arousal from respiratory stimuli. In other words, it does not allow for the possibility that increased respiratory drive may produce arousal from sleep independently of its effect upon the respiratory apparatus (the act of inspiration). There are no specific data available to address this issue, but several indirect lines of evidence suggest this possibility. Studies using respiratory muscle paralysis in awake humans (37) suggest that an increase in respiratory drive induced by hypercapnia can be perceived as dyspnea in the absence of active respiratory efforts. This suggests that the sensation of dyspnea may result from respiratory stimuli (such as hypercapnia), independent of increases in ventilatory effort, presumably due to stimulation of higher brain centers. While this might be explained by a direct projection of the chemoreceptors to higher

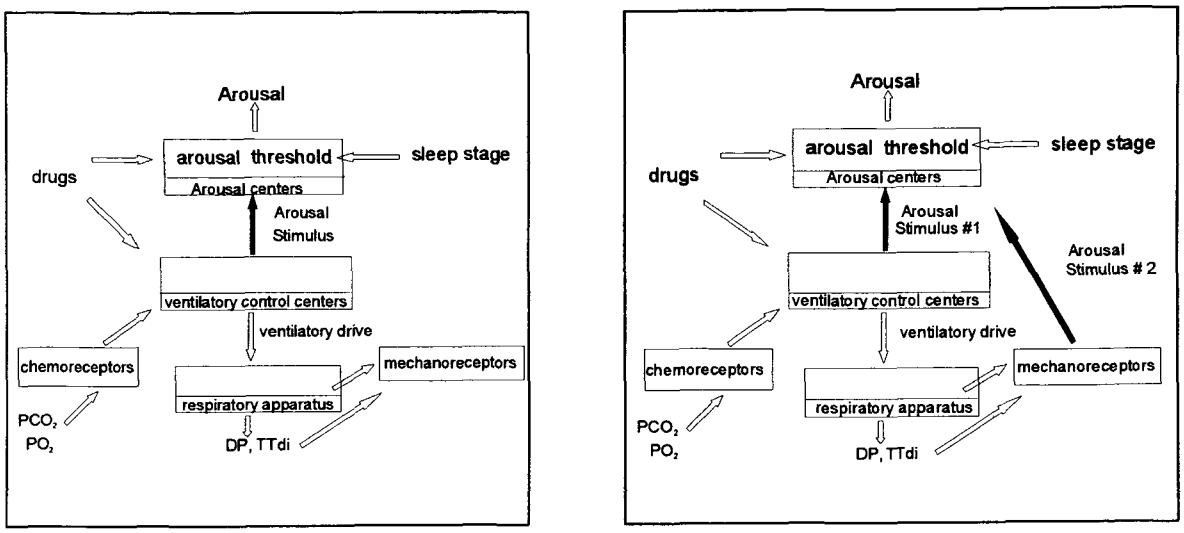

FIG. 7. (Model C) A schematic model of arousal in which the arousal stimulus is a signal from the ventilatory control centers to the arousal centers. The signal increases as ventilatory drive increases. Thus, the arousal stimulus increases as the esophageal pressure deflection (DP) and the tension time index of the diaphragm (TTdi) increase. (Model D). In this model the net arousal stimulus has two contributions. Arousal stimulus #1 is a signal from the ventilatory centers and arousal stimulus #2 is a signal from the mechanoreceptors. Although multiple mechanoreceptor sites are likely, for simplicity, only one is shown.

centers, work in animals suggests a direct connection between the portions of the brain generating respiratory drive (medullary respiratory motor neurons) and higher centers. Chen and coworkers (38) studied decerebrate, paralyzed, and ventilated cats with the vagi and carotid sinus nerves severed. They found that when ventilatory drive was increased above a certain threshold (either by continuous stimulation of the carotid sinus nerve or by hypercapnia), phasic neuronal activity was detected in the midbrain associated with each respiration (phrenic nerve firing). The threshold was approximately 50% of the maximum phrenic nerve activity. With progressive increases in ventilatory drive above this threshold, a further graded increase in phasic midbrain activity was noted. The authors' results suggested that the midbrain activity associated with increased ventilatory drive was the result of signals from the medullary respiratory motor neurons rather than from either central or peripheral chemoreceptors. This conclusion was based on the following reasoning. The experimental stimulation of the carotid sinus was continuous and the output of central chemoreceptors (hypercapnia) is not phasic at normal respiratory rates. However, these nonphasic stimuli to the respiratory upper motor neurons resulted in increases in the phasic activity of the phrenic nerve. The phasic midbrain activity during periods of increased ventilatory drive correlated precisely in timing and magnitude with the phasic phrenic activity. Thus, the only likely source of the phasic signal detected in the midbrain area was the medullary respiratory motor neurons. In an analogous fashion, when ventilatory drive is increased during sleep, this signal may be communicated from the medullary respiratory centers directly to higher centers, such as the reticular activating system. This signal could increase with further increases in respiratory effort and could trigger arousal once a threshold value is reached.

Model C (Fig. 7) presents a model that incorporates the possibility that a signal from areas of the brain controlling ventilatory drive is communicated to centers responsible for arousal. This signal is independent of, but proportionate to, the signals to the respiratory muscles (increasing DP and TTdi). This model thus allows for the occurrence of arousal once a given level of ventilatory center stimulation is reached, without requiring active inspiration. During muscle paralysis, the arousal stimulus would increase during ventilatory center stimulation even though no actual inspiratory effort was produced. If such communication between ventilatory control centers and arousal centers exists, then mechanoreceptor contributions to the arousal stimulus are not necessary to explain why a given level of inspiratory effort triggers arousal independent of the specific factors stimulating the centers responsible for ventilatory drive.

In model C, DP or TTdi are assumed to be indices of ventilatory drive (respiratory center excitation), with both increasing in a parallel fashion during the terminal portion of obstructive apnea. This does not ignore the fact that neuromechanical coupling of the diaphragm does change during the apnea cycle. For example, the ratio of Pdi (or DP) to the EMG of the diaphragm (EMGdi) is higher during the terminal (oc-

clusive) phase of apnea compared to the postapneic or early apneic phases (32,34). This appears to be due to recruitment of the abdominal muscles and an increase in gastric pressure. Nevertheless, both Pdi and DP vary linearly with EMGdi during the terminal occlusive phase of apnea. Thus, Pdi or DP remain valid indices of the level of ventilatory drive as long as comparisons are made between the terminal occlusive phases of different apneas.

It is also possible that the arousal stimulus could have contributions from both mechanoreceptors and ventilatory control centers (Fig. 7, model D). For simplicity, only one mechanoreceptor component to the arousal stimulus is shown in this figure. Provided that each contribution to the arousal stimulus increased in proportion to increasing inspiratory effort, the model can still account for the observation that arousal occurs at a threshold level of inspiratory effort. If the net arousal stimulus (sum of all contributions) exceeds the arousal threshold, then arousal occurs.

Note that in both models B and D, using a change in DP_{max} to infer a change in the arousal threshold [central nervous system (CNS) arousability] implicitly assumes that mechanoreceptor function (the relationship between DP and the mechanoreceptor related arousal stimulus) has not changed. In both models, a decrease in mechanoreceptor function would require an increased DP_{max} (but equivalent arousal stimulus) to trigger arousal even if the arousal threshold was unchanged. With respect to the ventilatory drive component of the arousal stimulus (models C, D), the important relationship for interpreting changes in DP_{max} is the relationship between DP and this component of the arousal stimulus rather than either chemoreceptor function or the relationship between chemical stimuli and ventilatory drive.

Chemoreceptors and arousal

In models B, C, and D, information from chemoreceptors is not directly a component of the arousal stimulus (unlike model A). This does not mean chemoreceptor function is unimportant for the arousal response. Impairment of chemoreceptors would be expected to decrease $\Delta DP/\Delta T$, thus delaying arousal. Greater asphyxia would also be needed to generate the same level of inspiratory effort. However, these models would still predict arousal at the same level of effort so long as the arousal threshold, mechanoreceptor function (models B, D), and the relationship of the ventilatory drive arousal stimulus to DP were unchanged (models C, D). In a related experiment, Bowes and coworkers studied the effects of carotid body denervation (CBD) on the arousal response to tracheal occlusion during slow-wave sleep in dogs (17). After CBD, the time to arousal was greatly increased and $\Delta DP/\Delta T$ was quite reduced. Unfortunately, only limited data on the tracheal pressure at arousal were published. In one animal, the DP_{max} after CBD was decreased compared to the control condition. This differs from the results of the effects of preocclusion hyperoxia in normal subjects (26) or patients with OSA (29), where $\Delta DP/\Delta T$ was decreased, but arousal occurred at the same level of inspiratory effort. If these observations in intact humans are valid, it implies either that: 1) CBD lowered the arousal threshold to respiratory stimuli (lower DP_{max}), or 2) arousal mechanisms not encompassed by models B–D were active. One should note that the very slow increase in DP after CBD resulted in a prolonged period of severe hypoxemia before arousal occurred. Thus, cerebral dysfunction may have been present during the terminal portion of the occlusions. The arousals after CBD were much briefer. Thus, it is possible that either hypoxic medullary dysfunction or CBD may have changed the relationship between the arousal stimulus and the level of inspiratory effort. In any case, intact carotid bodies appear essential for normal respiratory and arousal responses to airway occlusion.

Mechanoreceptors and arousal

Potential sites for mechanoreceptors that might contribute to the arousal stimulus during increased respiratory effort include the respiratory muscles, the chest wall, and the upper and lower airway. As noted above, the finding that arousal during airway occlusion occurs once a given level of inspiratory effort is reached independent of the specific respiratory stimuli generating the effort does not necessarily imply that mechanoreceptor input to the arousal centers is a component of (model D) or the entire (model B) arousal stimulus. What direct evidence is there that mechanoreceptors in the respiratory muscles do in fact contribute to the arousal stimulus? The question might be addressed by comparing the arousal threshold in humans or experimental animals before and during neuromuscular blockade, as alluded to above. If some mechanical consequence of increasing ventilatory effort was an important element of the arousal stimulus, then abolition of the ventilatory effort to a known respiratory stimulus (such as hypercapnia) should increase the threshold for arousal (arousal at a higher PCO_2). To our knowledge, such experiments have not been performed.

An alternative method for dissociating respiratory stimuli from the associated respiratory effort it produces is inspiratory muscle unloading. Kimoff and coworkers (39) provided mechanical volume ventilation (triggered just prior to the onset of spontaneous ventilation) in sleeping dogs during periods of stimulated

ventilation (hypercapnic and hypoxic challenges induced by a rebreathing circuit). By unloading the muscles (mechanical ventilation), respiratory muscle activation should be reduced for any level of increasing respiratory stimulation. Therefore, the mechanoreceptor output from the respiratory muscles should be reduced for a given level of respiratory stimulus. This would be predicted to increase the level of PCO_2 (hypercapnic challenge) or decrease the level of PO_2 (hypoxic challenge), triggering arousal. However, unloading the inspiratory muscles in this fashion resulted only in an increase in the arousal threshold for the hypercapnic stimulus during REM sleep. One reason that this technique may not have raised the arousal threshold more dramatically was that mechanical ventilation was found to augment expiratory muscle EMG. This may have offset the decreased activity of the inspiratory muscles. Another possible explanation is that in the control condition, the muscles were not significantly loaded, and therefore the mechanoreceptors may have contributed very little to the arousal stimulus. If this was true, unloading might have had the small effect that was observed. In a second related experiment (40), inspiratory pressure support (IPS) prolonged the time to arousal from both NREM and REM sleep in dogs after initiation of CO_2 administration (adjusted to maintain a constant end-tidal PCO_2). The EMG activity of the diaphragm was reduced by IPS compared to the control condition, but the activity of expiratory muscles (transversus abdominis) was unchanged. The EMG activity of muscles in both IPS and control conditions increased until arousal. However, at arousal, the EMG activity (ventilatory drive) was the same in both conditions. Thus, although the investigators proposed that these findings suggest that mechanoreceptors contribute to the arousal stimulus, another interpretation is that IPS merely slowed the rate of increase in ventilatory drive. If so, because arousal occurred at the same level of EMG activity in both IPS and control conditions, no conclusions about the nature or location of the arousal stimulus (mechanoreceptors or ventilatory control centers) can be drawn from these data.

A second site known to contain mechanoreceptors is the upper airway. Specifically, receptors responding to pressure, flow, and the respiratory activity of upper airway muscles are known to exist in the nasopharynx, oropharynx , hypopharynx, and in the laryngeal area (41,42). During respiratory efforts against an obstructed upper airway, the pressure receptors below the site of obstruction would be stimulated by negative intraluminal pressure. One method of determining if output from such mechanoreceptors contributes to the arousal stimulus is by decreasing their sensitivity with topical anesthesia (42). Basner and coworkers (43) found that upper airway anesthesia in normal subjects increased by 8.5 seconds the mean time to arousal during NREM sleep following mask occlusion. Mask pressure was measured, and the amount of suction pressure at arousal did not differ between the control and anesthesia conditions. Berry and coworkers (44) demonstrated in a group of patients with OSA that topical upper-airway anesthesia increased the apnea duration during NREM sleep and the level of inspiratory effort (DP_{max}) prior to arousal. This study utilized small fluid-filled catheters to measure deflections in esophageal pressure during apnea (DP). The authors hypothesized that upper-airway collapse may have prevented Basner and coworkers (43) from detecting a greater suction pressure prior to arousal after upper airway anesthesia. Both of these studies found no lidocaine-induced increase in the threshold to arousal by acoustic stimuli, making central effects of absorbed anesthetic an unlikely explanation for the results. These two studies suggest that sensation arising from the upper airway does contribute to the arousal stimulus during airway occlusion. The results of the study of lidocaine in patients with OSA are consistent with the predictions of the models B or D. In accord with these models, reduction of the arousal stimulus for a given level of DP would increase the level of effort (DP_{max}) associated with arousal.

However, not all investigations have documented an effect of upper airway anesthesia on event duration. Chadwick et al. (45) found an increase in the frequency, but not the duration, of obstructive events (apneas and hypopneas) when topical anesthesia was applied to the upper airways of a group of snorers. Deegan and coworkers (46) did not find an increase in apnea frequency or event duration after topical upper airway anesthesia in a group of patients with mild OSA. One explanation for the negative results is the difficulty in obtaining an adequate amount or duration of anesthesia from a single application of drug, even when a longer acting agent is used. Conversely, the study of Berry and coworkers (44) may have found an effect of lidocaine due to a reduction in tactile stimuli produced by the esophageal catheters. However, this explanation does not account for the increase in the time to arousal following upper airway anesthesia in the study of normal subjects who were not instrumented (43). While technical difficulties may explain the different findings, an alternative explanation is that the populations studied were very different (normal, snorers, mild/severe OSA). The magnitude of the contribution from upper airway mechanoreceptors to the arousal stimulus likely depends on both the nature of the receptors and the levels of airway pressure occurring prior to arousal (Fig. 8). Snorers and patients with mild apnea may arouse at levels of inspiratory effort

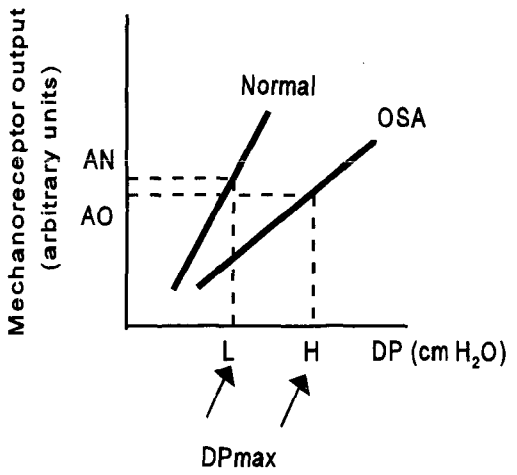

FIG. 8. Hypothetical relationship of upper airway mechanoreceptor output and airway suction pressure (esophageal pressure deflection = DP) in a normal subject and a patient with obstructive sleep apnea (OSA) during upper airway occlusion. Mechanoreceptor function is assumed to be impaired in the patient with OSA (less output for the same DP). However, the mechanoreceptor contribution to the arousal stimulus (AN) in a normal subject arousing at a low (L) level of inspiratory effort is similar to that of an OSA patient (AO) arousing at a much higher level of inspiratory effort (H). Both mechanoreceptor function and the arousal threshold determine the magnitude of the mechanoreceptor contribution to the arousal stimulus at the time of arousal.

only slightly higher than those levels that arouse normal nonsnorers. If their mechanoreceptors were impaired, the contributions to the arousal stimulus at such levels of effort could be minimal. Therefore, lidocaine would have little effect. In contrast, the contribution of upper airway receptors in normal individuals at such levels of effort might be greater. Lastly, patients with severe apnea, who also have altered mechanoreceptors, arouse at high levels of effort that might be sufficient to produce a significant contribution from the impaired mechanoreceptors. The evidence for impairment of upper airway mechanoreceptors in patients with OSA will be discussed below.

Another method of studying the effects of upper-airway mechanoreceptor input on arousal is to compare nasal and tracheal occlusions. This avenue of investigation assumes that any difference in the arousal responses following occlusion of the tracheal airway compared to those that follow occlusion of the upper airway must be due to upper airway mechanoreceptors. Issa and coworkers (47) performed airway occlusions via a nasal (snout) mask and tracheostomy tube in sleeping dogs. Tracheal occlusions prevented negative pressure changes from being sensed in the airway above the tracheal balloon. These investigators found that tracheal occlusions resulted in fewer early arousals compared to nasal occlusions (especially in REM sleep). In three of the four dogs, the time to arousal was longer during tracheal occlusions, although the difference reached statistical significance in only two dogs in NREM sleep.

TABLE 3. *Factors influencing the arousal threshold to airway occlusion*

Known:
Sleep stage
Prior sleep fragmentation
Central nervous system depressants
Possible:
Within-stage variations in depth of sleep
Time of night (circadian, sleep cycles)
Amount of accumulated sleep

In summary, the contribution of mechanoreceptors to the arousal stimulus seems likely but remains to be firmly documented. Arousal at a given level of inspiratory effort can be explained without invoking a mechanoreceptor component to the arousal stimulus (model C). If mechanoreceptors do contribute to the arousal stimulus, the relative importance of the contribution probably depends both on the location and properties of the receptor and the levels of effort (airway pressure) reached prior to arousal (arousal threshold).

The arousal threshold in NREM sleep

The arousal threshold to respiratory stimuli in NREM sleep varies between subjects and in the same subject during a single night. While some factors influencing the arousal threshold have been identified (Table 3), our understanding is still rudimentary. Differences in the arousal threshold between individuals could be intrinsic, acquired, or both. In addition, CNS depressants (such as ethanol and benzodiazepines) have been shown to increase the arousal threshold in experimental (24,28) and in naturally occurring (30,48,49) airway obstruction. As outlined above, the influence of drugs upon the arousal response to airway occlusion can be due either to alterations in the arousal threshold or to the respiratory response to airway occlusion (24).

The interval between the onset of experimental airway occlusion and arousal in normal subjects or apnea duration in apnea patients varies within an individual patient during the night in NREM sleep. This variability corresponds to similar variability in the level of inspiratory effort prior to arousal. This suggests that the arousal threshold to respiratory effort varies across the night. Some of this variability is undoubtedly due to the effect of sleep stage on the arousal threshold. Studies of the effect of sleep stage on the arousal threshold to nonrespiratory stimuli (e.g. sound) have generally shown higher thresholds in sleep stage 3/4 compared to sleep stage 2 (50). However, studies of

the influence of sleep stage on the levels of eucapnic/hypocapnic hypoxia or hypercapnia that trigger arousal have provided conflicting results. Douglas and coworkers found no indication of any differences in the arousal threshold to hypoxic stimulation between sleep stages 2 and 3/4 (9). Conflicting results have also been found for hypercapnia induced arousal. Bulow (51) found a higher arousal threshold (higher PCO_2 value) to hypercapnia in sleep stage 3/4 than in sleep stage 2. Berthon-Jones and Sullivan (13) found arousal occurred at progressively higher alveolar PCO_2 as the depth of NREM sleep increased from sleep stage 2 to sleep stage 4 in males but not females. However, Douglas et al. found no difference in the arousal threshold to hypercapnia between sleep stages 2, 3/4, and REM (14). These incongruous results of the effects of sleep stage on arousal produced by hypercapnia may be entirely explainable by the differences in experimental methods in these studies. In a study of the arousal response to experimental airway occlusion in normal subjects, Berry et al. (24) found a higher arousal threshold in stage 3/4 sleep compared to stage 2 sleep. Similarly, Gugger and coworkers found that addition of an inspiratory resistance during sleep in normal subjects resulted in arousal from sleep much less frequently in stage 3/4 sleep than stage 2 sleep (52).

Thus, taken in total, it appears that the arousal threshold to resistive loading, airway occlusion, and possibly hypercapnia is higher in stage 3/4 sleep than stage 2 sleep. Nevertheless, it remains important to note that even within the same sleep stage, considerable variability in the arousal threshold exists (23). Thus, sleep stage differences can account for only a portion of the variability in the arousal threshold over the night. One possible problem is that the categorization of NREM sleep into only four stages is an arbitrary and crude separation. Even applying the usual scoring rules for NREM sleep in patients with severe OSA is often problematic. Often, only brief periods of undisturbed sleep are recorded between arousals, with sleep stages 3 and 4 typically being absent. Unfortunately, better indices of the depth of sleep (as related to the arousal threshold), rather than those of sleep stage, remain to be defined. One possibility is that spectral analysis of the EEG signal may provide information about the depth of sleep. For example, Neckelmann and Ursin found that the arousal threshold to acoustic stimuli in rats was higher in epochs with a higher delta power (53).

Many other factors could potentially affect the arousal threshold in NREM sleep. These include the duration of the time interval since the last prolonged awakening, amount of accumulated sleep, time of night, or temporal proximity to REM sleep. At least

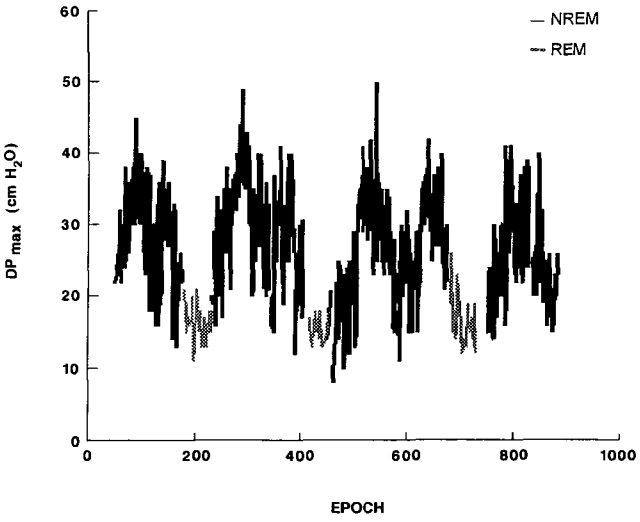

FIG. 9. This figure illustrates the variation in DP_{max} (the maximum deflection in esophageal pressure prior to arousal) over the night in a patient with obstructive sleep apnea (OSA). The absolute value of DP_{max} is shown (actual deflections were negative). The epochs were 30 seconds in duration. If DP_{max} is assumed to be an index of the arousal threshold, this threshold appears to vary in this patient in a cyclical manner during the night.

in some patients with OSA, the arousal threshold appears to vary in a cyclic fashion (Fig. 9). While the mean arousal threshold in most patients with OSA may be elevated, a much lower level of inspiratory effort can trigger arousal at certain times during the night. Certainly, much remains to be learned about the causes of variation in the arousal threshold during NREM sleep across the night.

Impaired arousal during NREM sleep in OSA

Normal subjects arouse from NREM sleep following mask occlusion at levels of inspiratory effort (DP_{max}) in the range of negative 20–30 cm H_2O (23,24,26–28) while patients with OSA typically arouse at much larger negative pressures (40–80 cm H_2O) (29,30). Two possible explanations are: 1) a higher arousal threshold in patients with OSA or, 2) impaired upper airway mechanoreceptors. A higher arousal threshold could be due to: 1) chronic sleep fragmentation, 2) nocturnal hypoxia, 3) habituation to the arousal stimulus, or 4) an intrinsically higher arousal threshold.

As discussed previously, patients with OSA have fragmented sleep due to the repeated arousals that terminate apneic events. Prior sleep fragmentation is known to cause increases in the arousal threshold to acoustic stimuli (50,54), and may be partly responsible for the high arousal thresholds of patients with OSA. Downey and Bonnet (54) showed that sleep fragmentation produced by repetitive exposure to acoustic

stimuli every minute resulted in a progressive rise in the arousal threshold in normal subjects during the first of two consecutive study nights. Bowes and coworkers (55) found that sleep fragmentation in dogs (induced by exposure to repetitive acoustic stimuli for two to three consecutive nights) impaired the arousal responses to hypercapnia and laryngeal stimulation but did not reduce the sleeping hypercapnic and hypoxic ventilatory responses. Fewell (56) found that in lambs, sleep fragmentation induced by auditory stimuli increased the time to arousal after airway occlusion by about 4 seconds in quiet (NREM) sleep. Guilleminault and Rosekind (57) evaluated the effects of a single night of total sleep deprivation (rather than sleep fragmentation) in four patients with mild OSA. They found a trend for prolongation of NREM events (14-second increase), suggesting a higher arousal threshold. O'Donnell et al. (58) found that prior sleep deprivation increased the time to arousal and the maximum suction pressure associated with arousal from NREM sleep induced by airway occlusion in tracheotomized dogs. Berry and coworkers (59) found that withdrawal of nasal continuous positive airway pressure (CPAP) (resulting in recurrence of sleep apnea and sleep fragmentation) for three nights resulted in a longer apnea duration and greater negative esophageal pressure deflection at the point of arousal from NREM sleep on a subsequent night. The patients in this study had severe OSA and had been using nasal CPAP for at least 6 months or longer. It is of interest that even before withdrawal of nasal CPAP therapy, the level of inspiratory effort prior to arousal was still much higher than levels typically associated with arousal in normal subjects during experimental airway occlusion. Boudewyns and coworkers (60) studied a group of OSA patients before initiation of CPAP and after 1 year of CPAP therapy. On the first night off CPAP, both the mean DP_{max} and apnea duration in NREM sleep were decreased compared to pretreatment values. Both of these studies imply that OSA impairs the arousal response to airway occlusion and that treatment can at least partially reverse the changes. One should note that as CPAP therapy improves oxygenation and prevents sleep fragmentation, these studies do not exclude hypoxemia as a contributing cause of impaired arousal in patients with OSA.

Another potential explanation for higher arousal threshold in OSA patients could be habituation to a repetitive arousal stimulus, regardless of its nature. It is axiomatic in psychobiology that repetitive presentation of any stimulus results in a decrease in the response and/or an increase in the threshold of stimulus magnitude required to elicit a response (61). Experiments designed to determine the effect of repetitive stimuli upon the threshold for arousal from sleep are unfortunately confounded by the increasing pressure for sleep produced by multiple arousals and by the possible resultant increase in the arousal threshold. With these limitations in mind, Downey and Bonnet found the threshold for arousal to an acoustic stimulus increased over one night but then reached a plateau (54). O'Donnell and coworkers found no evidence of an increase in the arousal threshold to tracheal occlusion in dogs repetitively occluded over a night following a previous period of sleep deprivation (58). Thus, while habituation to the stimulus of airway occlusion might in part explain the higher arousal thresholds in patients with OSA, it is difficult to discern the contribution of this factor above the relatively larger effects of sleep fragmentation.

A final possible explanation for a higher arousal threshold to inspiratory negative pressure changes in sleep apnea patients is that these patients have a native high threshold to respiratory arousal regardless of the fact that their upper airways are repeatedly obstructed during sleep. The most compelling evidence for this possibility is that effectively treated (nasal CPAP) patients with OSA still require greater negative pressure to trigger arousal than do normal subjects (59). However, it is also possible that years of apnea have produced changes that are not completely reversible by therapy with nasal CPAP or that compliance with or the effectiveness of nasal CPAP therapy is less than perfect. In any case, it is difficult to prove that OSA patients have an inherently higher arousal threshold than control non-OSA patients. This issue could be settled by prospectively determining DP_{max} (mask occlusion) in a group of normal subjects and then following them until a portion of the group develops sleep apnea. If the DP_{max} of the portion of the group developing apnea was higher than the DP_{max} of those who remained without OSA, one could conclude that OSA patients have innately higher arousal thresholds. The successful completion of such a study would obviously be very difficult.

While the finding that patients with OSA arouse at higher levels of inspiratory effort than do normal subjects undergoing mask occlusion suggests a higher arousal threshold, other interpretations are also possible. Recall that in models B or D, a higher DP_{max} at arousal could be due to a reduction of the mechanoreceptor contribution to the arousal stimulus (less arousal stimulus at the same DP) without a change in the arousal threshold. As previously mentioned, one study did find a higher DP_{max} after topical upper-airway anesthesia in patients with OSA (44). Thus, a higher level of inspiratory effort triggering arousal in OSA patients could be due to mechanoreceptor dysfunction as well as an increase in the arousal threshold. Long-term airway obstruction and trauma from snor-

ing could conceivably damage mechanoreceptors in the upper airway or decrease their response secondary to upper airway edema. There is independent, indirect evidence that suggests that patients with OSA may have impaired upper airway mechanoreceptor function. These patients have increased upper-airway edema (62) and impaired sensation in the upper airway (63). When negative pressure is applied to the upper airway of normal humans, there is a reflex increase in upper airway muscle tone that can be reduced by topical anesthesia (42). Thus, the afferent limb of this reflex is believed to depend upon upper airway mechanoreceptors. Treatment of patients with nasal CPAP increases this reflex (64), implying that the reflex was impaired prior to treatment. These studies suggest that untreated sleep apnea may decrease upper airway mechanoreceptor function, presumably due to direct damage to the mechanoreceptors or increased upper airway edema. Thus changes in upper airway mechanoreceptor function as well as sleep fragmentation might explain why nasal CPAP therapy decreases (60) and withdrawal of CPAP increases (59) the level of inspiratory effort associated with arousal. Irreversible changes in mechanoreceptors might also explain why some patients still require high levels of inspiratory effort to trigger arousal even after treatment with CPAP (59).

In summary, the higher levels of inspiratory effort (DP_{max}) associated with arousal in patients with OSA could be due to an increased arousal threshold or mechanoreceptor dysfunction. While the increase in the arousal threshold is likely due to a combination of factors, sleep fragmentation is probably a major cause. Longitudinal studies of arousal to both respiratory and nonrespiratory stimuli in patients with OSA before and after varying periods of therapy may help explain why arousal is impaired in these patients.

RESPIRATORY AROUSAL DURING REM SLEEP

Rapid eye movement sleep has important influences on the arousal response to respiratory stimuli. For example, patients with OSA have the longest events and most severe desaturation in REM sleep (65). In dogs, eucapnic hypoxemia induced arousal at a lower SaO_2 in REM than NREM sleep (12). Studies in dogs have found that arousal from tracheal (47,58) or nasal (47) occlusion took longer in REM than in NREM sleep. In another study, the amount of desaturation associated with arousal after tracheal occlusion in REM compared to that in NREM sleep was greater, although the difference did not reach statistical significance (17). Such data might lead one to believe that the arousal threshold to respiratory stimuli is increased in REM compared to NREM sleep. However, studies in normal human subjects have not consistently supported this conclusion. For example, Douglas et al. found no clear differences in the arousal threshold to eucapnic hypoxemia between NREM and REM sleep (9). Berthon-Jones and Sullivan (13) found that normal individuals subjected to hyperoxic hypercapnia aroused at similar alveolar PCO_2 values in REM and stage 2 sleep. Males aroused at a higher PCO_2 level from stage 3/4 sleep than from REM sleep. In a second study, Douglas et al. (14) found no difference in the level of hypercapnia inducing arousal between NREM and REM sleep. Mask occlusion in normal subjects actually elicits arousal from REM sleep very rapidly (23). Gugger and coworkers found that application of an inspiratory resistance in normal human subjects elicited an arousal response more quickly in REM sleep than either stage 2 or stage 3/4 NREM sleep (66). Thus in normal human subjects, the arousal threshold to mask occlusion or resistive loading in REM sleep is actually below that found in NREM sleep. The different results in dogs are most likely due to a species difference. However, the reasons why patients with OSA have longer apneas in REM sleep remain to be determined.

Compared to NREM sleep, little information is available about the mechanisms of arousal during REM sleep. In normal human subjects, arousal is often too rapid to study the time course of inspiratory effort. In dogs, the time to arousal after tracheal occlusions during REM sleep compared to NREM sleep is longer, but the maximum tracheal suction pressure prior to arousal does not differ (58). In contrast to NREM sleep, tracheal pressure swings did not progressively increase and were often erratic. In patients with OSA the time course of esophageal pressure swings is also often different in REM compared to NREM sleep (Fig. 6). While the level of inspiratory effort steadily increases during the terminal portion of the apnea during NREM sleep, this is not always the case during REM sleep. During REM obstructive apnea, the changes in the esophageal pressure swings are more erratic with decreased deflections frequently associated with phasic eye movements. This is similar to the reduction in tidal volume and pleural pressure swings that occur in normal subjects during phasic eye movements in REM sleep (phasic REM) (67). In addition, while arousal typically follows the highest level of inspiratory effort in NREM sleep, in REM sleep this is not always the case. Surprisingly little data is available to compare the level of effort at arousal in patients between NREM and REM sleep in patients with OSA. Vincken et al (19) found the mean maximum TTdi preceding arousal to be lower during REM than during NREM (0.15 vs. 0.19), despite a longer REM apnea duration in three patients with OSA. Wilcox et al. (20) found

the maximum TTdi during REM to be higher than NREM but the slope of the increase (with time) in TTdi to be less during REM sleep in one patient with OSA. Boudewyns et al. (60) determined DP_{max} and apnea length in 30 randomly selected apneas in NREM sleep and at least 10 apneas in REM sleep in a group of 25 patients with OSA. Although differences in DP_{max} and apnea length between NREM and REM were not statistically analyzed, DP_{max} tended to be lower in REM sleep, despite a longer event length. Based upon these limited data, the mean rate of increase in inspiratory effort during REM obstructive apnea appears to be slower and more erratic than in NREM sleep, and the level of inspiratory effort preceding arousal is not clearly higher (and may be lower) in REM compared to NREM sleep.

However, in REM sleep, the phrenic nerve output and esophageal pressure swings may not accurately reflect the magnitude of activity of the respiratory centers. Net phrenic nerve output may be decreased due to descending inhibitory influences, even though the activity of motor neurons in the respiratory motor centers is increased (68). For these reasons, the previously presented models in which TTdi or DP are used as indices of the arousal stimulus and the maximum values used as indices of the arousal threshold during airway occlusion are probably not valid for REM sleep. In addition, due to generalized muscle hypotonia during REM sleep, the same amount of neural drive may not result in the same pleural pressure changes in REM as in NREM sleep. Even if TTdi is used as an index of inspiratory effort, comparisons between NREM and REM sleep may not be valid, as the hypotonia of other respiratory muscles during REM sleep alters the efficiency of diaphragmatic pressure generation during airway obstruction (34). For these reasons, comparisons of the level of inspiratory effort preceding arousal between REM and NREM are not straightforward and make conclusions about differences in the arousal threshold to this stimulus difficult.

Given these difficulties in comparing the arousal response in NREM and REM sleep, what possible explanations exist for the longer apneas in REM sleep in patients with OSA? One possibility is that the erratic and perhaps slower increase in respiratory effort during REM apneas decreases the contribution to the arousal stimulus from mechanoreceptors. Another possibility is that unlike normal subjects, OSA patients have a higher arousal threshold in REM than in NREM sleep. Comparison of arousal thresholds to nonrespiratory stimuli in these patients in NREM and REM sleep may help answer this question. Alternatively, the transmission of the arousal stimulus from ventilatory center stimulation or from peripheral mechanoreceptors to the arousal centers may be inhibited by mechanisms generating REM sleep. This possibility will be difficult to evaluate until the basic mechanisms inducing REM sleep are better understood.

As discussed in a previous section, sleep fragmentation could be one cause of a higher arousal threshold during NREM sleep in patients with OSA compared to normal subjects. Does sleep fragmentation increase the threshold in REM more than in NREM in patients with OSA? Guilleminault and Rosekind (57) found that a single night of sleep deprivation increased apnea duration more in REM than in NREM sleep on a subsequent night in a small group of patients with OSA. By contrast, O'Donnell and coworkers did not find greater increases in event duration after sleep deprivation in REM than in NREM sleep in a study of tracheal occlusion in dogs (58). Much work remains to be done in understanding the mechanisms of arousal from REM sleep and the differences between the arousal response to airway occlusion during REM sleep in patients with OSA and experimentally induced airway obstruction in normal human subjects.

CLINICAL SIGNIFICANCE OF RESPIRATORY AROUSAL

For the patient with a respiratory-related sleep disorder, the arousal response has both benefits and disadvantages. Apnea termination may depend upon respiratory arousal. Viewed in this way, arousal from sleep is a lifesaving event. Unfortunately, if arousals are significantly frequent, sleep architecture is disrupted and sleep is not restorative, even if the total sleep time is near normal (3,54). There is now considerable evidence to suggest that daytime hypersomnolence, the cardinal manifestation of OSA, results directly from repetitive arousals from sleep. Those OSA patients with frequent arousals have reduced proportions of slow-wave and REM sleep (65). The daytime sleep latency (multiple sleep latency test) is abnormally short. With successful treatment, there is an initial increase (rebound) in the amounts of slow wave and REM sleep, rapid improvement in symptoms, and an increase in the daytime sleep latency (69). Although both repetitive episodes of arterial oxygen desaturation and respiratory arousals are typically present during sleep in these patients, it is now believed that nocturnal hypoxemia plays a small role, compared to that played by sleep fragmentation, in inducing daytime sleepiness. Treatment of OSA patients with supplemental oxygen may improve the nocturnal saturation, but it does not improve the sleep latency as measured by the MSLT (70). Conversely, experimental sleep fragmentation with brief arousals induced by nonrespiratory stimuli does not result in nocturnal hypoxia, but does induce severe daytime sleepiness (2,3,47).

The relationship between respiratory arousal and the termination of apnea during sleep is the subject of ongoing research. During the terminal portion of obstructive apnea, while the patient remains asleep, the muscle activity of both upper airway and respiratory muscles progressively increases, but the airway remains closed. The tendency of the upper airway muscles to restore airway patency is thus apparently balanced by increased suction pressure, and the airway remains obstructed. Airway opening is typically preceded by a preferential increase in upper airway muscle activity (compared to the diaphragm). The large increase in upper airway tone is usually preceded or coincident with evidence of arousal (71). This finding has resulted in the proposal that apnea is terminated by the arousal response to respiratory stimuli (1,71).

Recently, some investigators have challenged this thinking based on the observation that less than 100% of apnea terminations are associated with unambiguous evidence of arousal (defined by routine EEG monitoring). In fact, the percentage of obstructive apnea terminations that are associated with arousals defined by the usual criteria probably varies considerably from patient to patient. There are several possible explanations for apnea termination without arousal: 1) the criteria for arousal are too restrictive, 2) our methods for detecting cortical arousal are insensitive, 3) arousal is not necessary for apnea termination, and 4) apnea termination is a result of subcortical rather than cortical arousal.

Many episodes of apnea termination without apparent arousal are likely to be due to insensitive monitoring techniques and criteria for designating arousal rather than the actual absence of electrocortical activation. For example, the ability to detect cortical arousal is affected by the choice of the EEG recording montage utilized (use of an occipital lead facilitates detection of alpha waves). In addition, there is preliminary evidence that the routine use of frontal electrodes will increase the percentage of events associated with arousal. In one study of patients with frequent arousals (OSA and the upper airway resistance syndrome), only 74% of the respiratory events were associated with arousal from sleep (ASDA criteria) using central and occipital EEG derivations. However, when frontal EEG changes were also considered, this percentage rose to 95% (72). Detection of EEG frequency shifts by visual interpretation may also be much more difficult in patients who do not produce prominent alpha waves. In other patients, delta waves are seen at apnea termination and may obscure a shift in EEG frequency. At other times, alpha activity follows a delta burst but is <3 seconds in duration. Although delta waves are not considered indicative of arousal in the recently proposed criteria for arousal (7), some patients consistently produce them at apnea termination, usually associated with an abrupt increase in the submental EMG. Some of the problems identifying arousal could potentially be overcome by employing a more extensive montage and a sophisticated spectral analysis of EEG frequency using computer technology. For example, one could define arousal as an abrupt increase (absolute or relative) in the power in higher frequency bands. It is also likely that a broader definition of arousal may be clinically useful.

However, while sophisticated methods may identify more arousals at apnea termination, there is undoubtedly a fraction of obstructive apneas that terminate without electrocortical changes. In patients with obstructive apnea, ventilatory drive to the respiratory muscles and upper airway muscle activity fluctuates in a periodic fashion, falling before apnea onset and smoothly increasing at the time of apnea termination (31). If the increases in upper airway EMG muscle activity during sleep are sufficient to restore airway patency, then apnea termination can undoubtedly occur without arousal. However, if an abrupt increase in upper airway muscle activity is required to restore upper airway patency, this implies "a change in state" of the brainstem respiratory motor neurons controlling the upper airway muscles. If this change occurs in the absence of a generalized cortical activation (identified as an EEG arousal), this event might be called a "subcortical arousal". Although this concept has emerged, no clear definition of subcortical arousal has yet been advanced. One possible definition of subcortical arousal would be the global (widespread) activation of subcortical structures, manifested by an abrupt change in several brainstem functions (e.g. heart rate, arterial blood pressure) not associated with cortical (EEG) activation. According to this definition, an isolated change, such as the increase in submental EMG during snoring, would not be labeled as an "arousal". However, even this approach presents problems in REM sleep. During this sleep stage, phasic changes in many brain stem-controlled activities occur. In summary, it is likely that apnea termination can occur without generalized cortical arousal. In such cases, apnea termination following abrupt changes in brain stem functioning may reflect subcortical arousal. If so, then cortical arousal at apnea termination represents the subset of apnea termination in which the arousal process spreads to the cortex.

If cortical arousal is an associated phenomenon rather than the cause of apnea termination, do apneas with and without associated arousal differ? Rees and coworkers (73) found that neither apnea length, peak pleural pressure preceding apnea termination, nor the postapnea blood pressure increase differed between events with and without evidence of cortical arousal.

A possible confounding factor was the atypically high proportion of nonarousing events (66%) on the study night. During a noninstrumented night, only 33% of events were nonarousing. Further study of this issue is needed. Alternatively, if cortical arousal is not necessary for apnea termination, is repetitive subcortical arousal associated with apneas sufficient to result in daytime sleepiness? This important issue will undoubtedly be the subject of future research.

Recently, several investigations have sought to determine if nonrespiratory stimuli can influence ventilatory control and apnea termination without inducing cortical arousal. Carley and coworkers (74) demonstrated that acoustic stimuli that did not produce electrocortical arousal (as defined by sophisticated EEG spectral analysis) could alter the pattern of respiration during NREM sleep. Basner and coworkers (75) found that when a brief (0.5 second) acoustic stimulus was presented during obstructive apnea that the event was terminated within 2 seconds of the tone, 72% of the time when electrocortical arousal occurred and 17% of the time when no arousal was noted (using standard EEG criteria and both central and occipital scalp electrodes). These findings support the proposition that generalized cortical arousal is not required for apnea termination. Furthermore, nonrespiratory stimuli may be able to influence apnea termination without inducing cortical arousal. The relationships between upper airway function, obstructive apnea termination, and cortical/subcortical arousal remain to be determined.

CENTRAL SLEEP APNEA AND AROUSAL

While the majority of the previous discussion has focused on OSA, the termination of central apneas is also frequently associated with arousal. While these arousals may result in complaints of insomnia, in some series of central sleep apnea, complaints of daytime sleepiness were actually more common (76). Thus, the effects of arousals on sleep quality may have the same consequences as in patients with OSA. Relatively little work has specifically addressed the mechanisms of arousal in central apnea. In fact, more attention has been focused on the possibility that arousal may actually cause or perpetuate some forms of central apnea.

Central sleep apnea can be divided into two types: 1) those forms associated with awake hypoventilation and 2) those without hypercapnia (76). The former group usually has either a defect in the central control of respiration that worsens with sleep onset or a neuromuscular weakness. The nonhypercapnic group includes patients with idiopathic central apnea (77) in whom no apparent cause is present to explain the central apnea, and those with Cheyne–Stokes breathing (CSB) (usually due to neurological disease or congestive heart failure). In patients with idiopathic central apnea, apnea termination occurs coincident with arousal and ventilation postapnea abruptly increases. Central apnea can occur as isolated episodes or in repetitive cycles of apnea/hyperpnea (periodic breathing). In contrast, CSB (a specific type of periodic breathing) is characterized by periods of ventilation with a crescendo–decrescendo pattern interspersed with periods of central apnea or hypopnea. Arousals often do not occur at apnea termination but rather at the peak of the postapnea ventilatory phase (78). Patients with CSB due to heart failure usually have a much longer duration of ventilation between apneas than in patients with idiopathic sleep apnea who exhibit periodic breathing (79). In both idiopathic central sleep apnea and patients with CSB, central apnea is believed to occur because the arterial PCO_2 value is below the apneic threshold (the arterial PCO_2 required to generate respiratory effort during sleep). Indeed, both groups tend to have low awake PCO_2 values (77,80).

In idiopathic central sleep apnea, isolated episodes of central apnea may occur after a nonapnea-related arousal. Subsequent arousal at apnea termination may help to perpetuate cycles of central apnea/arousal. Xie et al. (77) found that the arousals followed by central apnea in this group were invariably associated with an increase in ventilation (thus reducing the PCO_2). The duration of apnea was also correlated with the magnitude of the preceding arousal (and the degree of hyperventilation). Thus, in this group, arousal is an indirect cause (via induced falls in PCO_2) as well as a consequence of apnea. Bonnet and coworkers found that triazolam, a short-acting hypnotic, reduced the amount of central apnea in a group of patients with idiopathic central sleep apnea (81). Presumably, triazolam decreased central apnea by decreasing the frequency of arousals or the amount of hyperventilation induced by arousal.

In patients with CSB, there is an underlying instability in ventilatory control resulting in oscillations in ventilatory drive (82). Thus hyperventilation and the subsequent hypocapnia may be less dependent on arousal. Biberdorf et al. studied the effects of temazepam, a benzodiazepine with an intermediate duration of action, in a group of patients with CSB due to congestive heart failure in a double-blind crossover protocol (83). Temazepam reduced the number of arousals per hour of sleep but did not change the apnea + hypopnea index or the amount of CSB. Thus, the nonarousal factors predisposing to periodic breathing may have been more important in this patient population.

The mechanisms leading to arousal in patients with central sleep apnea are unknown. When arousal occurs during periods of increased ventilatory effort (CSB), the same mechanisms that trigger arousal during OSA

could be at work. However, what triggers arousal when it precedes or coincides with the resumption of ventilatory effort (as is common in idiopathic central sleep apnea)? If chemoreceptor-related stimuli trigger both the resumption of ventilatory effort and arousal, this would imply a low arousal threshold. Apnea duration in idiopathic central sleep apnea appears to increase with the amount of preapneic hyperventilation (77). Thus, apnea termination and arousal might occur at similar levels of ventilatory drive (or PCO_2) with the initial PCO_2 determining the time to arousal (and apnea length). However, we know of no study addressing the level of inspiratory effort on the first breath after central apneas of variable length in these patients. Clearly, more investigation of arousal mechanisms in patients with central sleep apnea is needed.

FUTURE RESEARCH

In this review we have attempted to structure the considerable body of knowledge concerning respiratory arousal. There is obviously a need for more basic research to establish the neural pathways involved in the arousal response. In addition, the factors responsible for the within-night variability in the arousal threshold need to be identified. The role of mechanoreceptors in the arousal response also needs clarification. Such basic questions as why patients with OSA have longer events in REM sleep and arouse at higher levels of inspiratory effort in NREM sleep remain unanswered. Finally, the relationship of cortical EEG changes and apnea termination needs further clarification. If subcortical arousal exists, how should it be defined? These and many other questions posed by this review will undoubtedly be the subject of future investigations.

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