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Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment

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Eckert DJ, Younes MK. Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. J Appl Physiol 116: 302–313, 2014. First published August 29, 2013; doi:10.1152/japplphysiol.00649.2013.—Historically, brief awakenings from sleep (cortical arousals) have been assumed to be vitally important in restoring airflow and blood-gas disturbances at the end of obstructive sleep apnea (OSA) breathing events. Indeed, in patients with blunted chemical drive (e.g., obesity hypoventilation syndrome) and in instances when other defensive mechanisms fail, cortical arousal likely serves an important protective role. However, recent insight into the pathogenesis of OSA indicates that a substantial proportion of respiratory events do not terminate with a cortical arousal from sleep. In many cases, cortical arousals may actually perpetuate blood-gas disturbances, breathing instability, and subsequent upper airway closure during sleep. This brief review summarizes the current understanding of the mechanisms mediating respiratory-induced cortical arousal, the physiological factors that influence the propensity for cortical arousal, and the potential dual roles that cortical arousal may play in OSA pathogenesis. Finally, the extent to which existing sedative agents decrease the propensity for cortical arousal and their potential to be therapeutically beneficial for certain OSA patients are highlighted.

arousal threshold; upper airway; sleep-disordered breathing

OBSTRUCTIVE SLEEP APNEA (OSA) is a common breathing disorder and, in the absence of treatment, is associated with major adverse health outcomes (98, 111, 121). OSA is characterized by intermittent narrowing and collapse of the pharyngeal airway during sleep. These interruptions to breathing cause blood-gas disturbances, are often associated with brief awakening (cortical arousal), and thereby disrupt sleep continuity. The term “arousal” can refer to a broad range of physiological responses. Different levels or intensity of arousal may have quite different effects on sleep and breathing (31). Throughout this paper, unless stated otherwise, the term arousal refers to cortical arousal defined according to the conventional definition as an abrupt shift in the electroencephalogram lasting greater than 3 s (1). The pathophysiological causes of OSA are likely to be quite different between patients (42, 105–107, 112–114, 118). Other articles in this Highlighted Topics Series on the upper airway describe some of these causes and potential treatment approaches (18, 46, 57, 90). This brief review focuses on the potential dual roles that arousal from sleep has in OSA pathogenesis. Specifically, it highlights how some aspects of arousal may be beneficial under certain circumstances for some patients, whereas other components are likely to be deleterious and destabilize breathing during sleep for others.

HISTORICAL BACKGROUND ON THE ROLE OF AROUSALS IN OSA

A detailed review of this topic has recently appeared (108). Briefly, in the first detailed study on the mechanism of OSA, Remmers and colleagues (88) observed that the airway does not open until a cortical arousal occurred. Genioglossus muscle activity, the largest upper airway dilator, increased before the arousal, but the airway remained closed until there was a disproportionate increase in genioglossus activity associated with the arousal. Remmers and colleagues (88) proposed the “balance-of-forces” theory, whereby the gradual increase in dilator muscle activity during the obstructive phase is offset by the gradual increase in pharyngeal collapsing (negative) pressure, such that there is no effective dilating force. Only when dilator muscle activity increases disproportionally, through arousal, does the dilating force prevail and the airway opens.

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The notion that cortical arousal is required for the airway to open was rapidly accepted and became an integral part of the pathogenesis. It was so firmly believed that, when the airway opened without cortical arousal, it was assumed that arousal must have occurred somewhere but escaped detection [e.g., in an unmonitored electrode (79) or below the cortex (see Ref. 108 for references)]. For over 30 yr, arousal was assigned a “life-saving” role. It was considered malpractice to administer arousal-suppressing agents (sedatives, hypnotics) to OSA patients.

The patients studied by Remmers and colleagues (88) represented what we now call “obesity-hypoventilation syndrome” (OHS): very obese, somnolent, and with daytime hypercapnia. Although the need for arousal may still apply to such patients and in other OSA patients under certain circumstances, the type of patient who is now diagnosed and treated for OSA has changed dramatically. OHS represents <10% of OSA patients, and the typical patient nowadays has brief obstructive events with mild reductions in oxyhemoglobin saturation and no daytime hypercapnia. A reexamination of the role of arousals in the current population of OSA patients has not only shown that arousals may be unnecessary in many OSA patients, but that they may in fact aggravate the disorder (see Negative, below).

UNDERLYING MECHANISMS OF RESPIRATORY-INDUCED AROUSAL

Cortical arousals can be induced by a variety of stimuli, including noise, touch, pain, vibration, and respiratory-related inputs. The sensory inputs responsible for respiratory-induced cortical arousals have been extensively studied (see Ref. 9 for review). In a landmark study in normal subjects, Gleeson and colleagues (47) found that the esophageal pressure reached just before arousal is roughly the same, within an individual, whether respiratory stimulation was induced by hypercapnia, hypoxia, or by addition of a resistive load. This finding provided a unified mechanism for generating respiratory arousals, namely arousal occurs when a certain level of inspiratory effort is reached (47). Esophageal pressure just before arousal following induced [normal subjects (13, 14)] or spontaneous [OSA (67)] obstructions is also the same whether an individual breathes oxygen or a hypercapnic mixture before obstruction; changing the gas mixture simply alters the duration of obstruction required to reach the threshold pressure. It remains unclear, however, whether the direct arousal stimulus is related to pressure (i.e., mechanoreceptor input) or the central respiratory drive responsible for generating the observed esophageal pressure (9). There is no doubt that an increase in chemical drive alone, without loading, can elicit arousal (2, 16, 17, 51, 118). Experiments with upper airway anesthesia also provide convincing evidence that upper airway mechanoreceptors contribute to arousal in the presence of upper airway obstruction (6, 11, 30). However, studies investigating the possible role of chest wall mechanoreceptors in mediating respiratory sensation (likely the awake counterpart of arousals) suggest that chest wall mechanoreceptors may not play such an important role. Banzett and colleagues (4) found that the level of respiratory distress induced by CO2 breathing was the same whether or not chest wall muscles were paralyzed. Also, in human experiments, where mechanical loads could be applied selectively to the upper airway, the chest wall, or to both, the threshold for detecting added loads was not different whether the chest wall was included or not, whereas the detection threshold was considerably elevated (300–500%) when the chest wall alone was loaded (83, 115). Thus it is likely that the main inputs for respiratory arousals arise from the central respiratory drive and, when the upper airway is obstructed, from airway mechanoreceptors.

Arousals often follow, rather than precede, upper airway opening in OSA patients (113). In many such examples, there is a loud “snort” 0.5 to 1.0 s before the onset of the cortical arousal. Thus pharyngeal vibration or the loud noise associated with airway opening might be the source of, or at least contribute to, arousal in some patients (113).

HOW OFTEN IS UPPER AIRWAY OPENING THE RESULT OF AROUSAL?

Cortical arousals are observed near the end of the vast majority of obstructive events. This association provided much support for the idea that arousals are required in order for the upper airway to open. However, recent developments suggest the opposite may be true, at least in some patients. That is, airway opening may be produced via reflex (i.e., arousal-unrelated) activation of pharyngeal dilator muscles, and the association between airway opening and arousals may well be coincidental. Support for this concept is outlined below.

1) Cortical arousal is not observed at or near the time of airway opening in 10–25% of obstructive events (9, 35, 36, 87, 99, 113). While it is possible that cortical arousal may occur at unmonitored sites (31, 79), this possibility was not supported by the findings of an earlier study (76). It has also been proposed that airway opening in the absence of detectable cortical arousal may reflect “arousal” below the cortex (subcortical, brain stem, or autonomic arousals) (31, 35, 63, 87, 99). This was based on the observation that heart rate increases following upper airway opening, even in the absence of cortical arousal (35, 63, 87, 99). However, in a recent study Azarbarzin and colleagues (3) induced brief (3 breaths) obstructive events of different severities, including minimal hypopneas (flow rate 60–90% baseline), by lowering continuous positive airway pressure (CPAP) to different levels, and measured heart rate following deliberate relief of the obstruction, well before the airway would have opened spontaneously. They found that heart rate increased following all degrees of hypopnea severity (i.e., with no apparent threshold), and the magnitude of response increased as a function of hypopnea severity. Furthermore, the onset of tachycardia and peak heart rate occurred at the same times relative to end of obstruction, regardless of severity or duration of the preceding obstruction, even though respiratory drive would have been quite different (3). These observations indicate that postevent tachycardia is not consistent with an arousal response, which requires a threshold increase in arousal stimuli, but is another example of automatic (i.e., arousal-unrelated) regulation of heart rate in response to the ventilatory and hemodynamic changes that occur at the time of airway opening. Such automatic control of heart rate is well documented, even in deep anesthesia, and is well illustrated during sleep by sinus arrhythmia, as well as periodic, random [e.g., in rapid eye movement (REM) sleep], and overnight changes in heart rate. These authors (3) con-
cluded that an increase in heart rate following obstructive events could not be used to infer arousal in the absence of cortical changes. By extension, upper airway opening that is unassociated with cortical arousal cannot be attributed to arousal. If arousals cannot account for airway opening in observations without cortical arousal, then patients who display such events [40% of patients according to Younes (113; see Fig. 1 and supplement)] are capable of opening their airway without cortical arousal.

2) In another substantial fraction of obstructive events (~20% (113)], arousal begins after airway opening (Type 2), indicating that the arousal was secondary to airway opening (see UNDERLYING MECHANISMS OF RESPIRATORY-INDUCED AROUSAL, above) or was coincidental. In total, 75% of patients displayed events in which there was either no arousal (Type 1) or the arousal occurred after airway opening (Fig. 1).

3) Except in a small minority of patients, even when arousals occur at or before airway opening (Type 3), genioglossus activity typically gradually increases before the onset of arousal, reflecting reflex activation (117). Just before arousal appears, this progressive recruitment reaches a level just shy of the level required to open the airway (117). Considering the rate at which genioglossus activity was increasing before arousal, the airway would have opened spontaneously had arousal been delayed by only a few seconds (117).

4) The relation between arousal onset and the time of upper airway opening varies greatly within the same subject (Fig. 1). The frequency of events without arousals (Type 1) increases, while the frequency of Type 3 events decreases as sleep becomes deeper (113). Thus, as arousal threshold (TA) increases, arousals occur later or not at all. However, the time of upper airway opening, relative to the onset of obstruction, does not change as a function of sleep depth (113).

Collectively, these observations suggest that, in the majority of patients, reflex mechanisms are capable of opening the airway, and that arousals may not be necessary to restore airflow in many cases. The occurrence of arousal near the end of events may be largely coincidental and related to the fact that stimuli that evoke arousals and stimuli that are needed to reflexly recruit the upper airway dilator muscles are the same (increased respiratory drive and negative pharyngeal pressure), and these stimuli progressively increase with time in the course of obstruction. A certain amount of these stimuli is required to evoke arousals (TA). Likewise, a certain amount of the same stimuli is required to recruit pharyngeal dilators enough to open the airway [effective recruitment threshold (TER) (114, 118)]. TA varies over a wide range between individuals (9, 41, 42, 47, 113) (see below) and within the same individual (7, 93). TER varies over a wide range between patients, but is fairly constant in the same individual (72, 118). The interrelationship between these two thresholds determines whether arousals will occur before, after, or not at all at the time of airway opening (Fig. 2). If at some point in time TA is well above TER, TER will be reached first, and no arousal occurs (Type 1). If TA is only slightly above TER, opening occurs first, but, because chemical drive continues to increase for several seconds beyond opening (circulation delay), arousal may still occur after opening (Type 2). Furthermore, opening is often associated with loud noise.

Fig. 1. Time difference between upper airway (UA) opening and onset of arousal (ΔT) in individual dial-downs in 82 obstructive sleep apnea patients. Patients are arranged in order of increasing apnea-hypopnea index (AHI) during polysomnography. The AHI at selected patient numbers (Pt #) is shown on the bottom. ● Type 3 responses; ○ Type 2 responses; □ Type 1 responses (no arousal). ΔT values greater than 6 and less than −6 are assigned a single value to help expand the vertical axis. Note that most patients demonstrated more than one type, and that ΔT was highly inconsistent between and within patients. There is no tendency for the mix of types to change as AHI increases. Refer to the text for further detail. [Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. From Younes (113), online supplement.]
and throat vibration, which may trigger arousal after opening (Type 2). When $T_A$ is below $T_{ER}$, arousal occurs first. Because arousal is associated with an increase in dilator muscle activity, the airway opens at or soon after arousal (Type 3 events).

Whether coincidental or not, arousals do occur frequently in OSA patients. We now discuss the possible consequences of arousals on the pathogenesis and manifestations of the disorder.

AROUSAL FROM SLEEP MAY HAVE DUAL ROLES IN OSA PATHOGENESIS (CONCEPTUAL BASIS)

Positive

The sudden reintroduction of wakefulness that occurs with arousal from sleep is associated with rapid recruitment of inspiratory upper airway motoneurons (63, 109). In the case of obstructed breathing, rapid recruitment of upper airway dilator muscle activity will assist in quickly reopening the upper airway (e.g., Type 3 events). Once the upper airway is re-opened, there is a marked increase in airflow that occurs with arousal, known as the ventilatory response to arousal (58, 62, 64, 110). This enables rapid restoration of blood oxygen levels and dissipation of the excess carbon dioxide that builds up during obstructive breathing events. During transient occluded breathing, reflex inhibition of inspiratory respiratory motoneurons occurs (29, 40, 60). The brief reduction in drive may act to minimize moment-to-moment increases in the work of breathing during airflow limitation (29, 40, 60). It is possible that brief arousals may also play a beneficial role via rapidly alleviating the increased work of breathing that occurs during obstructive respiratory events.

Collectively, these initial physiological responses that occur with arousal may serve important roles in maintaining homeostasis. Indeed, when a patient experiences major blood-gas disturbances during sleep (e.g., OHS or during severe prolonged obstructions in OSA), the initial physiological changes that take place with arousal likely serve as a last line of defense to help restore airflow without which serious adverse effects may occur (37) (see Fig. 3). Within an individual patient, the beneficial effects associated with arousal may be important at certain times of the night (e.g., certain body positions and sleep states) but not others (see FACTORS INFLUENCING THE RESPIRATORY $T_s$ section below). However, as mentioned, OSA patients who are crucially reliant on arousal to restore adequate airflow during sleep likely represent a minority of the current OSA patient population. Rather, for many OSA patients, the initial transient responses that occur with arousal are often excessive or occur prematurely, and the subsequent physiological changes that take place in the period following arousal are likely to perpetuate further breathing instability and OSA (as outlined below).

Negative

Whereas early termination of obstructive events by arousal may reduce the associated hypoxemia, such early termination may increase the frequency of subsequent respiratory events through a number of mechanisms.

1) By reducing the duration of individual events, arousals increase the number of events per hour (cycling frequency). In many patients, event duration is $<15$ s, and events are associated with minimal hypoxemia [e.g., 3–6% decrease in arterial $O_2$ saturation from pulse oximetry ($SpO_2$)]. If arousal were not to occur in such patients, event duration may be longer, the apnea/hypopnea index (AHI) would decrease, but the decrease in $SpO_2$ would be somewhat [likely slightly (5, 113, 117)] higher. It is not clear which is more important with respect to cardiovascular risk: the number of events, or the extent of reduction in $SpO_2$, within a modest range of hypoxemia (86). However, it is clear that shorter duration events with arousals will be associated with a higher arousal index and, by extension, more complications related to sleep fragmentation. For example, isolated sleep fragmentation (i.e., without OSA) has wide spread negative effects, including excessive somnolence (23), decreased psychomotor performance (19, 20, 96), changes in several hormone levels (24), negative mood, and increased irritability and anger (22, 32, 76). Indeed, sleep fragmentation at the rate of 60/min (comparable with an AHI of $\sim 70$/min) was found to have similar effects on Multiple Sleep Latency Test (71), nap latency (21), and vigilance (21) as total sleep deprivation.
2) Frequent arousals interfere with progression of sleep to deeper stages. The tendency to develop OSA is considerably reduced in deeper sleep (84).

3) There is an impact of arousals on ventilatory stability. By definition, recurrent obstructive events are a manifestation of unstable ventilatory control, whereby the response to one event sets the stage for the development of another event. The instability in OSA occurs primarily because of the ventilatory overshoot that occurs at airway opening, which eliminates the stimuli needed to open and keep open the airway (i.e., chemical drive, negative pharyngeal pressure, arousal) (108, 114, 119). On the other hand, the destabilizing influence of a large ventilatory overshoot may be mitigated by neural memory phenomena, such as short-term potentiation and long-term facilitation. These memory phenomena would result in sustained postevent increases in dilator muscle activity after the disappearance of the excitatory stimuli that increased activity in the first place, thereby mitigating the development of another event. Accordingly, whether arousals at the end of respiratory events promote or mitigate instability depends on the following: 1) whether the occurrence of arousal is associated with a greater ventilatory overshoot than would occur if reflex mechanisms were given the opportunity to independently open the airway, and 2) whether arousals promote or inhibit memory phenomena (neuroplasticity). There is currently no information on the effect of arousals on memory phenomena. By contrast, there are compelling theoretical reasons, and some experimental evidence, that arousals promote a greater ventilatory overshoot.

Impact of arousal on the ventilatory overshoot. Figure 4 is a schema of the events leading to and following upper airway opening (from Ref. 108). The reduction in dilator muscle activity at sleep onset results in an obstructive event in susceptible individuals (i.e., those in whom upper airway patency is dependent on dilator muscle activity) (108, 114, 119).

Fig. 3. Schematic highlighting the potentially beneficial vs. destabilizing physiological changes associated with respiratory-induced arousals in obstructive sleep apnea. During obstructive breathing, oxygen levels decrease and carbon dioxide levels increase. Breathing effort (negative intrathoracic pressure) increases, and, if the arousal threshold (TA) is crossed, a cortical arousal from sleep occurs (dark shaded oval). This is associated with several immediate (1–2 breaths) beneficial effects for the sleep apnea patient with an obstructed UA indicated in the light shaded ovals to the left of the vertical dashed line. These include the following: recruitment of UA motoneurons, UA opening, increased airflow, and rapid reductions in breathing effort, reoxygenation, and dissipation of hypercapnia. However, in contrast to the immediate beneficial effects associated with arousal, secondary destabilizing effects can also arise, indicated in the white open ovals to the right of the vertical dashed line. These include disrupted sleep continuity, prevention of deeper, more stable, sleep, excessive reductions in carbon dioxide, and decreased respiratory drive and UA muscle tone. These effects are likely to contribute to the development of subsequent respiratory events. On balance, while the secondary destabilizing effects remain, the immediate beneficial effects of arousal are essential in patients with obesity hypoventilation syndrome (indicated by the shaded triangle seesaw). Conversely, on balance, the secondary destabilizing effects of arousal likely outweigh the beneficial effects for sleep apnea patients with a low TA (indicated by the open triangle seesaw). The magnitude of each of the physiological changes associated with arousal likely varies considerably between sleep apnea patients and is influenced by multiple factors. Accordingly, the balance between beneficial and destabilizing effects of arousal is also likely to vary considerably (refer to the text for further detail).
The magnitude of the overshoot at the time of airway opening is determined by how negative intrathoracic pressure is at the time of opening (inspiratory effort) and the resistance of the upper airway during the open phase. When opening occurs without arousal, intrathoracic pressure at opening is at the time of opening (inspiratory effort) and the resistance of the upper airway during the open phase. When opening occurs without arousal, intrathoracic pressure at opening is determined by $T_{ER}$. Thus a high $T_{ER}$ promotes a greater overshoot, and vice versa. However, the amount of dilator muscle activity would be at or slightly above the opening threshold (Fig. 4), with the result that airway resistance may remain sufficiently high in the open phase to restrain the overshoot.

When the $T_A$ is below $T_{ER}$, arousal will occur before the airway could open spontaneously. Chemical drive is necessarily lower than in the case where arousal did not occur first (Fig. 4). However, arousal per se provides an additional respiratory drive that increases inspiratory effort over and above what would result from the chemical drive alone (58, 59, 100, 101). The independent arousal stimulus to the respiratory muscles is large, amounting to $\sim 5$ l/min of ventilation on average (100). Thus inspiratory effort with arousal would be the sum of contributions of chemical drive and arousal (100). When arousal occurs at or before airway opening, chemical drive is only slightly below $T_{ER}$ (117) (Fig. 4). The addition of the larger arousal stimulus to breathing is almost certain to offset this deficit, so that inspiratory effort is likely to be the same or higher than in the case without arousal. More importantly, dilator muscle activity increases disproportionately with arousal (88) and may greatly exceed the level required to just open the airway (117). Upper airway resistance during the open phase is bound to be lower or much lower than in the absence of arousal, resulting in a greater overshoot.

As indicated earlier, arousal often follows spontaneous opening ($T_A > T_{ER}$) (113). In this case, the effect of arousal on the overshoot would be both to increase inspiratory effort over and above $T_{ER}$ and to decrease airway resistance even further. The effect on the overshoot would be compounded.

Experimental data on the effect of arousals on the ventilatory overshoot are scarce and at times contradictory. Younes (113) induced obstructive events by lowering CPAP to 1 cmH$_2$O and maintaining the low pressure until the event terminated with or without arousal. Most of the events were complete obstructions (44%) or severe hypopneas (flow <25% of baseline; 20% of events). Peak flow at the time of airway opening was only 131% of baseline flow (on CPAP) in observations without arousal, whereas it was 227% of baseline flow in observations with arousals [recalculated from reference (113)]. Interestingly, the magnitude of the overshoot increased progressively with the intensity of arousals, reaching an average 327% of baseline with very intense arousals. Arousals that just met the American Sleep Disorders Association criteria (1) had only minimally higher overshoot than observations without arousals. In the same study (113), it was found that the severity of a second event (undershoot) was significantly greater if an arousal occurred following the first event. Severity of the second event increased with intensity of the preceding arousal, even when severity of the initial event was matched (113).

By contrast, Jordan and colleagues (63) measured postevent ventilation in observations with and without arousals using a protocol in which CPAP was reduced to different levels to matching baseline CPAP flow (5 l/min), and the intensity of arousals was not defined. Thus, although theoretical considerations strongly argue that arousals increase the postevent overshoot, more experimental work is needed to confirm the theoretical expectations.

![Fig. 4. Sequence of events following the onset of an obstructive event. At eupneic drive, dilator activity during sleep is less than the level required to keep the airway open. A hypopnea or apnea develops. Chemical drive increases. At a certain chemical drive (recruitment threshold), the dilators begin responding to further increases in drive. Activity increases until the level required to open the airway (dilator opening threshold) is reached. Activity increases for one or two breaths beyond the point of opening and then begins declining as chemical drive decreases. In the declining phase, activity is higher than at the same drive in the rising phase as a result of short-term potentiation [STP (116)]. The chemical drive at which dilator activity reaches dilator opening threshold is referred as $T_{ER}$. This sequence can be interrupted if the $T_A$ is less than $T_{ER}$. [From White and Younes (108).]
In summary, the bulk of evidence suggests that the net effect of arousal on the severity of OSA is negative except in patients who fail to open their airway spontaneously, despite major deterioration in blood-gas tensions. Further support for this conclusion is derived from clinical trials on the use of sedatives in certain OSA patients, which will be reviewed below. A schematic summarizing potential positive and negative effects of arousal in OSA is displayed in Fig. 3.

**FACTORS INFLUENCING THE RESPIRATORY T_A**

As highlighted, the extent to which the balance between positive and negative factors associated with arousal contributes to OSA pathogenesis varies between patients and potentially within patients at different times during the night. For some OSA patients, upper airway anatomy/collapsibility and poor muscle responsiveness during sleep are key contributors, whereas respiratory control instability and the T_A are particularly important in others (42, 118). The role of the T_A in OSA pathogenesis is likely to be influenced by many factors, including sleep pressure/sleep deprivation, sleep state, and severity and duration of disease.

**Presence of OSA/Sleep Deprivation and Treatment**

Sleep fragmentation/deprivation associated with OSA has been postulated to increase the T_A (48). Indeed, CPAP treatment reduces the respiratory T_A in severe OSA patients (12, 26, 49, 72) (Fig. 5A). However, despite objective CPAP compliance of more than 6 h/night for over 3 mo, recent findings indicate that the T_A remains elevated compared with that in healthy controls (42), albeit slightly (average values: −18 vs. −12 cmH_2O) and to within the normal range (Table 1, Fig. 5A). In fact, the T_A post-CPAP treatment is quite low relative to mean values in untreated patients (Table 2). This finding suggests that a small component of the elevated T_A in severe OSA patients is either inherent or slowly/incompletely reversible. Nonetheless, it is clear that there is substantial between-subject variability in the T_A in both OSA patients and controls (42) (Tables 1 and 2). Interestingly, one-third of untreated OSA patients have a low T_A, and this proportion appears to be minimally affected by CPAP treatment (41, 42, 72). In these patients, the interaction between a collapsible upper airway and a low T_A is likely to importantly contribute to their pathogenesis (42). Thus the response of T_A to untreated OSA is quite variable, and, when it is high, it is largely reversible.

**Sleep State Effects**

Earlier data derived primarily from very severe OSA patients indicates that the T_A is ~38% higher (harder to wake up) in non-REM (stage 2 sleep and slow-wave sleep combined) compared with REM sleep (Fig. 5B). More recently, the T_A has been shown to increase by ~45% from stage 2 to slow-wave sleep (85). This is likely to facilitate increased genioglossus muscle activity and breathing stability (66, 84, 85). Conversely, the T_A in light stage 1 sleep is similar to REM sleep: ~37% lower in stage 1 compared with stage 2 sleep (41). This is likely to contribute to the increased propensity for sleep-disordered breathing during light sleep (84).

**Other Factors and Gaps in Knowledge**

Derived from data in over 500 OSA patients, Fig. 5C displays the relationship between OSA severity as measured by the AHI and the respiratory T_A. Despite different methodolo-
gious to measure the TA between studies, a robust relationship exists such that the TA is increased with increasing OSA severity. Similar relationships between the TA and the AHI as well as other markers of OSA severity, including hypoxemia and the arousal index, have been reported within some of these studies (68, 97). The increase in respiratory effort before arousal in very severe OSA is likely explained, at least in part, by increased sleep pressure (due to sleep fragmentation). It is also likely that brief arousals are ineffective at adequately eliminating increased respiratory drive in very severe OSA patients, such that greater negative intrathoracic pressure is reached, at least in part, by increased sleep pressure (28, 38, 53). Upper airway with progression of and following general anesthesia promote airway closure (28, 38, 53). However, during natural sleep, given that frequent or premature arousal can 1) limit the ability to effectively recruit dilator muscle activity and reach TER, 2) disrupt sleep continuity and the ability to obtain deeper more stable sleep, and 3) perpetuate respiratory control instability, particularly with large arousals, delaying or minimizing the intensity of arousals may be therapeutically beneficial for certain OSA patients. As stated, the concept of increasing the threshold for arousal to minimize the impact of these negative effects has been supported by animal data (80, 120), physiological models (75, 105), and observations that 1) periods of breathing stability in OSA are associated with an increase in the TA and elevated dilator muscle activity (66, 112); and 2) the TA increases with deeper sleep, which is associated with improved breathing stability (84, 85). Most recently, a standard dose of the sedative eszopiclone increased the respiratory TA in stage 2 sleep and increased the proportion of deeper vs. lighter sleep (stage 1 vs. stage 2) in OSA patients who did not experience major overnight hypoxemia at baseline (nadir SpO2 > 70%). This was associated with an ~45% reduction in the AHI in OSA patients with a low TA, without worsening hypoxemia (41). However, muscle activity and other important phenotypic traits, including upper airway collapsibility, were not measured in this study.

Nonetheless, these data provide convincing support for the importance of arousal in OSA pathogenesis and the potential for certain sedatives to be of therapeutic benefit at least in some patients. However, obtaining the optimal balance between retaining the beneficial components of arousal for potential times of need (e.g., during marked hypoxemia) vs. minimizing the negative effects of too frequent arousal (e.g., during less severe respiratory events) remains a delicate balance. Other factors, such as individual drug sensitivities and potential interaction with other drugs, also need to be carefully considered. Ultimately, the ability of certain sedatives to promote stable breathing will be dependent on 1) their effects on dilator muscle activity and responsiveness to respiratory stimuli; 2) the extent to which the agent increases the TA/diminishes arousal frequency and promotes deeper sleep; and 3) individual patient pathophysiology. A brief summary of the present understanding of each of these factors is highlighted below.

Effects of Sedatives on Dilator Muscles

To be therapeutically effective, sedatives must increase the TA without impairing dilator muscle function in appropriately selected patients. Historically, benzodiazepines and other depressants used during anesthesia have been associated with reduced upper airway muscle tone (including during the postoperative period) (25, 34, 70). However, it is not clear from such observations whether reductions in dilator muscle activity are the result of falling asleep (i.e., sleep-induced) or are due to a specific inhibitory effect of the drug. In sleeping rats, admin-

### Table 1. Summary of arousal threshold studies derived using an epiglottic or an esophageal pressure catheter in non-OSA controls

<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Arousal Threshold, cmH2O Range, cmH2O</th>
<th>No. Participants (No. Men)</th>
<th>AHI (No. Events/h Sleep)</th>
<th>CPAP Treated</th>
<th>Stimulus</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NREM</td>
<td>18 ± 2 (SE) 13–27</td>
<td>8 (all)</td>
<td>?</td>
<td>N/A</td>
<td>Added resistive load</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>17 ± 3 (SE) 8–25</td>
<td>5 (all)</td>
<td>?</td>
<td>N/A</td>
<td>Occlusion</td>
<td>8</td>
</tr>
<tr>
<td>SWS</td>
<td>24 ± 2 (SE) 20–30</td>
<td>5 (all)</td>
<td>?</td>
<td>N/A</td>
<td>Occlusion</td>
<td>8</td>
</tr>
<tr>
<td>NREM</td>
<td>28 ± 2 (SE) 20–38</td>
<td>6 (all)</td>
<td>?</td>
<td>N/A</td>
<td>Occlusion</td>
<td>13</td>
</tr>
<tr>
<td>NREM</td>
<td>20 ± 1 (SE) 15–25</td>
<td>6 (all)</td>
<td>?</td>
<td>N/A</td>
<td>Occlusion</td>
<td>15</td>
</tr>
<tr>
<td>SWS</td>
<td>20 ± 4 (SD) 15–28</td>
<td>6 (all)</td>
<td>?</td>
<td>N/A</td>
<td>Occlusion</td>
<td>14</td>
</tr>
<tr>
<td>NREM</td>
<td>15 ± 2 (SE) ? 12 (all)</td>
<td>?</td>
<td>N/A</td>
<td>Occlusion</td>
<td>Added resistive load</td>
<td>54</td>
</tr>
<tr>
<td>NREM</td>
<td>14 ± 2 (SE) ? 12 (all)</td>
<td>?</td>
<td>N/A</td>
<td>Occlusion</td>
<td>CPAP drops</td>
<td>42</td>
</tr>
<tr>
<td>NREM</td>
<td>–21 ± 9 (SD) ? 18 (&lt;13)</td>
<td>3 (0–9)</td>
<td>N/A</td>
<td>Occlusion</td>
<td>Added resistive load</td>
<td>54</td>
</tr>
<tr>
<td>NREM</td>
<td>12 ± 6 (SD) 5–22</td>
<td>17 (7)</td>
<td>?</td>
<td>N/A</td>
<td>Occlusion</td>
<td>45</td>
</tr>
</tbody>
</table>

Values are means ± SD or SE. OSA, obstructive sleep apnea; AHI, apnea/hypopnea index, quoted numbers are mean values (range), where available; CPAP, continuous positive airway pressure; NREM, non-rapid eye movement sleep; SWS, slow-wave sleep. Bolded rows highlight where data have been collected across different sleep stages or to different stimuli in the same study. Studies are listed in chronological order.
intrusion of pentobarbital is not followed by genioglossus inhibition relative to unmedicated sleep (120). Ketamine may preferentially increase genioglossus activity compared with propofol in rats (44). The antidepressant trazodone, the most commonly prescribed sedative in the United States, does not impair upper airway muscle activity in an English bulldog model of OSA (102). Preliminary work suggests that this is also the case in sleeping OSA patients (39). Using CPAP dial-downs, the responsiveness of two upper airway dilator muscles (genioglossus and tensor palatini) to increasing negative pharyngeal pressure was not impaired in response to a single 100 mg of trazodone (39). In healthy individuals, pentobarbital does not impair the genioglossus negative pressure reflex during wakefulness and, during sleep, delays arousal to enable increased genioglossus muscle activity, although upper airway resistance is increased (43). Finally, zopiclone appears to minimally affect genioglossus muscle activity during sleep in OSA patients (73). Thus, while further work is required, certain sedatives appear not to adversely affect upper airway muscle responses while increasing the $T_A$.

### Effects of Sedatives on the $T_A$

Flurazepam and trazodone reduce arousal responses to increasing $CO_2$ in healthy individuals and OSA patients, respectively (50, 52). Pentobarbital delays arousal to experimentally induced airway narrowing in healthy individuals (43). Using an esophageal or an epiglottic pressure catheter, the $T_A$ increases with 0.25 mg of triazolam by ~33% in healthy individuals (15) and by 24% in severe OSA patients (10), 100 mg of trazodone by 33% in OSA patients with a low $T_A$ (39), and 3 mg of eszopiclone by ~29% in OSA patients with low-moderate $T_A$ values (41). Increases in the $T_A$ of these magnitudes without impairing dilator muscle function are likely to be beneficial for

<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Arousal Threshold, cmH$_2$O</th>
<th>Range, cmH$_2$O</th>
<th>No. Participants (No. Men)</th>
<th>AHI (No. Events/h Sleep)</th>
<th>CPAP Treated</th>
<th>Stimulus</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM</td>
<td>−50 ± 4 (SE)</td>
<td>−30 to −110</td>
<td>22 (all)</td>
<td>98 (all &gt;60)</td>
<td>No</td>
<td>Natural events</td>
<td>92</td>
</tr>
<tr>
<td>REM</td>
<td>−57 ± 5 (SE)</td>
<td>−30 to −66</td>
<td>12 (all)</td>
<td>78</td>
<td>Yes</td>
<td>Natural events</td>
<td>10</td>
</tr>
<tr>
<td>REM</td>
<td>−55 ± 1 (SE)</td>
<td>−38 to −78</td>
<td>6 (all)</td>
<td>88</td>
<td>No*</td>
<td>Natural events</td>
<td>12</td>
</tr>
<tr>
<td>REM</td>
<td>−57 ± 5 (SE)</td>
<td>−30 to −124</td>
<td>25 (all)</td>
<td>94 (all &gt;30)</td>
<td>No</td>
<td>Natural events</td>
<td>26</td>
</tr>
<tr>
<td>REM</td>
<td>−30 ± 3 (SE)</td>
<td>−13 to −124</td>
<td>9 (6)</td>
<td>93 (42–110)</td>
<td>No</td>
<td>Natural events</td>
<td>30</td>
</tr>
<tr>
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<td>−52 ± 11 (SE)</td>
<td>−10 to −100</td>
<td>38 (all)</td>
<td>80 (18–128)</td>
<td>No</td>
<td>Natural events</td>
<td>26</td>
</tr>
<tr>
<td>REM</td>
<td>−50 ± 3 (SE)</td>
<td>−10 to −100</td>
<td>30 (all)</td>
<td>91</td>
<td>No</td>
<td>Natural events</td>
<td>91</td>
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<tr>
<td>REM</td>
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<td>−10 to −100</td>
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<td>90 (37–137)</td>
<td>No</td>
<td>Natural events</td>
<td>68</td>
</tr>
<tr>
<td>REM</td>
<td>−40 ± 2 (SE)</td>
<td>−10 to −100</td>
<td>88 (7)</td>
<td>87</td>
<td>?</td>
<td>Natural events</td>
<td>7</td>
</tr>
<tr>
<td>REM</td>
<td>−46 ± 5 (SE)</td>
<td>−10 to −100</td>
<td>9 (7)</td>
<td>87</td>
<td>?</td>
<td>Natural events</td>
<td>7</td>
</tr>
<tr>
<td>REM</td>
<td>−32 ± 4 (SE)</td>
<td>−10 to −100</td>
<td>9 (7)</td>
<td>87</td>
<td>?</td>
<td>Natural events</td>
<td>7</td>
</tr>
<tr>
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<td>−40 to −57 (1–7 h) (SE)</td>
<td>−10 to −100</td>
<td>9 (all)</td>
<td>86 (55–128)</td>
<td>No</td>
<td>Natural events</td>
<td>94</td>
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<tr>
<td>REM</td>
<td>−30 to −40 (1–7 h) (SE)</td>
<td>−10 to −100</td>
<td>37 (29)</td>
<td>77 (53–112)</td>
<td>No</td>
<td>Natural events</td>
<td>93</td>
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<tr>
<td>REM</td>
<td>−38 ± 2 (SE)</td>
<td>−10 to −100</td>
<td>108 (83–140)</td>
<td>12 (14–180)</td>
<td>No</td>
<td>Natural events</td>
<td>95</td>
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<tr>
<td>REM</td>
<td>−29 ± 2</td>
<td>−13 to −124</td>
<td>5 (all)</td>
<td>49</td>
<td>?</td>
<td>Natural events</td>
<td>104</td>
</tr>
<tr>
<td>REM</td>
<td>−33 ± 2</td>
<td>−13 to −124</td>
<td>6 (5)</td>
<td>16</td>
<td>?</td>
<td>Natural events</td>
<td>104</td>
</tr>
<tr>
<td>SWS</td>
<td>−49 ± 15 (SD)</td>
<td>−23 to −78*</td>
<td>32 (26)</td>
<td>57</td>
<td>No</td>
<td>Natural events</td>
<td>82</td>
</tr>
<tr>
<td>REM</td>
<td>−47 ± 14 (SD)</td>
<td>−23 to −78*</td>
<td>20 (?)</td>
<td>87</td>
<td>?</td>
<td>Natural events</td>
<td>82</td>
</tr>
<tr>
<td>REM</td>
<td>−32 ± 11 (SD)</td>
<td>−23 to −78*</td>
<td>29 (?)</td>
<td>87</td>
<td>?</td>
<td>Natural events</td>
<td>82</td>
</tr>
<tr>
<td>REM</td>
<td>−48 ± 22 (SD)</td>
<td>−23 to −78*</td>
<td>10 (all)</td>
<td>108 (83–140)</td>
<td>No</td>
<td>Natural events</td>
<td>49</td>
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<tr>
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<td>−35 ± 13 (SD)</td>
<td>−23 to −78*</td>
<td>10 (all)</td>
<td>108 (83–140)</td>
<td>1 night CPAP occlusions</td>
<td>49</td>
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<td>−32 ± 6 (SD)</td>
<td>−23 to −78*</td>
<td>10 (all)</td>
<td>108 (83–140)</td>
<td>7 nights CPAP occlusions</td>
<td>49</td>
<td></td>
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<td>−34 ± 16 (SD)</td>
<td>−23 to −78*</td>
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<td>108 (83–140)</td>
<td>30 nights CPAP occlusions</td>
<td>49</td>
<td></td>
</tr>
<tr>
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<td>−27 ± 12 (SD)</td>
<td>−23 to −78*</td>
<td>10 (all)</td>
<td>108 (83–140)</td>
<td>90 nights CPAP occlusions</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>REM</td>
<td>−54 ± 3 (SE)</td>
<td>−23 to −78*</td>
<td>74 (63)</td>
<td>47 (8–110)</td>
<td>No*</td>
<td>Natural events</td>
<td>97</td>
</tr>
<tr>
<td>REM</td>
<td>−17 ± 6 (SD)</td>
<td>−23 to −78*</td>
<td>9 (6)</td>
<td>52 (24–99)</td>
<td>Yes CPAP drops</td>
<td>52</td>
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<tr>
<td>REM</td>
<td>−20 ± 2 (SE)</td>
<td>−23 to −78*</td>
<td>10 (all)</td>
<td>50</td>
<td>Yes CPAP drops</td>
<td>85</td>
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<tr>
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<td>−29 ± 3 (SE)</td>
<td>−23 to −78*</td>
<td>10 (all)</td>
<td>50</td>
<td>Yes CPAP drops</td>
<td>85</td>
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</tr>
<tr>
<td>REM</td>
<td>−10 [−15 to −8] (IQR)</td>
<td>7–37</td>
<td>17 (8–82)</td>
<td>31 (8–82)</td>
<td>No</td>
<td>Natural events</td>
<td>41</td>
</tr>
<tr>
<td>REM</td>
<td>−16 [−20 to −13] (IQR)</td>
<td>7–37</td>
<td>17 (8–82)</td>
<td>31 (8–82)</td>
<td>No</td>
<td>Natural events</td>
<td>41</td>
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<tr>
<td>REM</td>
<td>−11 [−15 to −10] (IQR)</td>
<td>8–21</td>
<td>12 (8–134)</td>
<td>25 (8–134)</td>
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<td>Natural events</td>
<td>41</td>
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<tr>
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<td>−18 ± 7 (SD)</td>
<td>−8 to −42</td>
<td>57 (42)</td>
<td>46 (10–112)</td>
<td>Yes CPAP drops</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD or SE. While in some instances the goal of these studies was not to derive the arousal threshold per se, an epiglottic or esophageal pressure catheter was used in each case that enabled the arousal threshold to be estimated. *The range value was derived across all sleep stages. #Three nights CPAP withdrawal. †Absence of treatment confirmed via direct correspondence with author. IQR, median value and interquartile range; REM, rapid eye movement sleep. Bolded rows highlight where data have been collected across different sleep stages or before and after CPAP treatment in the same study. Studies are listed in chronological order. Note the progressive reduction in arousal threshold values with time, reflecting the shift from the obesity hyperventilation phenotype to the current OSA patient population, many of whom have low arousal thresholds.
some OSA patients, while others may require much larger increases to achieve stable breathing. The ability of various sedatives to reduce arousal frequency, the intensity/duration of arousals, and their ability to promote deeper sleep in the context of OSA have been minimally studied and may differ with drug type and dose.

**Individual Patient Pathophysiology**

In addition to the factors highlighted above, the effect of a particular sedative to alter OSA severity will depend on underlying pathophysiology on a per-patient basis. Delaying arousal may be deleterious in patients with already blunted arousal responses and advantageous in others who wake up prematurely (Fig. 3). Indeed, while the number of study participants has been small, most studies investigating the effects of sedatives on OSA severity do not show systematic changes in AH1 in unslected OSA patients (55, 69, 74, 77, 89, 103). Thus patient selection according to underlying pathophysiology and the type of sedative used are crucial in determining their effect on OSA severity (41). Recent findings suggest that over one-third of OSA patients have a low TA (42), and many patients arouse very close to their TIR (117). Strategies to increase the TA with non-myorelaxant sedatives are likely to be highly effective in these patients, particularly in those with only modestly collapsible upper airways (42). Detailed physiological and carefully designed clinical studies are required to determine the potential clinical utility of this approach.

**SUMMARY**

Arousal from sleep has important implications for OSA pathogenesis with potential dual roles. The immediate physiological changes that occur with cortical arousal are likely to be beneficial, and the type of sedative used are crucial in determining their effect on OSA severity (41). Recent findings suggest that over one-third of OSA patients have a low TA (42), and many patients arouse very close to their TIR (117). Strategies to increase the TA with non-myorelaxant sedatives are likely to be highly effective in these patients, particularly in those with only modestly collapsible upper airways (42). Detailed physiological and carefully designed clinical studies are required to determine the potential clinical utility of this approach.

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**DISCLOSURES**

D. J. Eckert received consulting income from Apnex Medical in 2009/10 unrelated to the topic covered in this review. M. K. Younes is majority owner of YRT Ltd., a Winnipeg R&D company that develops devices for the diagnosis of sleep disorders and management of respiratory failure.

**AUTHOR CONTRIBUTIONS**

Author contributions: D.J.E. and M.K.Y. conception and design of research; D.J.E. and M.K.Y. interpreted results of experiments; D.J.E. and M.K.Y. prepared figures; D.J.E. and M.K.Y. drafted manuscript; D.J.E. and M.K.Y. edited and revised manuscript; D.J.E. and M.K.Y. approved final version of manuscript.

**REFERENCES**

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