Arousals in Sleep-disordered Breathing: Patterns and Implications

Robert Joseph Thomas, MD
Beth Israel Deaconess Medical Center

Study Objective: To describe the whole spectrum of electroencephalographic (EEG) transients associated with the termination and recovery of obstructed respiratory events and, thus, widen the recognized spectrum of arousal phenomena from sleep.

Design: Retrospective review of diagnostic polysomnograms.

Setting: American Academy of Sleep Medicine (AASM)-accredited multidisciplinary sleep disorders center.

Patients: 17 patients with obstructive sleep-disordered breathing.

Interventions: None.

Measurements and Results: Nasal airflow using a nasal-cannula–pressure-transducer system and oral flow by a thermistor were used to score apneas and hypopneas; the latter included flow-limitation events. The EEG patterns that crested or occurred within 2 to 3 seconds of respiratory recovery were recorded, and posthoc categories were created for the purpose of tabulation ranging from an AASM 3-second arousal to a single K-complex with no electromyographic increase. Chi-square statistic was calculated to assess the difference in EEG patterns at event termination between apneas and hypopneas. Score-rescore agreement was tested. Apneas were significantly more likely to be associated with a 3-second arousal than were hypopneas, but all types of EEG change were seen with both types of events. Spindles were rarely seen with arousal-linked K-complexes. The majority of events in rapid eye movement sleep were terminated with visible electromyography tone increase.

Conclusions: The spectrum of EEG change associated with the termination of respiratory events identified by using a nasal-cannula–pressure-transducer system is wider than that recognized as arousal phenomena by the 1992 AASM criteria. Scoring arousals with the 3-second rule may falsely minimize the apparent impact of abnormal breathing on sleep. The time may be right to update arousal recognition rules.

Key Words: arousals, nasal pressure, sleep apnea

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INTRODUCTION

ONE OF THE MORE CONTROVERSIAL ISSUES IN CLINICAL SLEEP DISORDERS IS THE CONCEPT OF A TRANSIENT AROUSAL FROM SLEEP. Recurrent sleep disruption results in abnormalities of attention, mood, memory, and performance. The standard sleep-staging rules are not applicable for arousal scoring, which occurs on a timeframe of a few seconds. A number of arousal definitions have been published and are summarized in Table 1. The American Sleep Disorders Association (now the American Academy of Sleep Medicine, AASM) 3-second rule is the most widely used definition but was determined by consensus and practical utility rather that a specific biologic basis for the required type or duration of frequency changes. Although these criteria provided a useful framework when none existed, several limitations have become obvious with clinical use. The most important of these is that the termination of respiratory events detected by techniques more sensitive than the thermistor shows a wider range of patterns than the 3-second rule acknowledges.

Monitoring fluctuations of air pressure at the nose through a simple nasal-cannula–pressure-transducer system (NC-PT) has been shown to have an excellent correlation with pneumotachograph flow or obstructive respiratory events as defined by esophageal-pressure recordings. This technique allows an accurate estimate of the burden of sleep-disordered breathing, showing a spectrum of respiratory abnormalities that is not evident when using the thermistor or effort bands. It also allows for a more accurate visualization of patterns of transient polysomnographic change around the termination of individual events than was possible in the past. This may be conceptualized as an “event termination complex,” with changes noted in virtually all polysomnographic variables, as well as hemodynamic and behavior measures (Table 2). The purpose of this study was to define the polysomnographic patterns of electroencephalogram (EEG) transients associated with the termination of obstructive respiratory events identified using an NC-PT system. A relevant literature review was performed to support the concept of a spectrum of arousal-linked phenomena.

METHODS

Polysomnography

The diagnostic polysomnograms of 17 medication-free patients with obstructive sleep apnea were prospectively reviewed. The EEG (C4-A1, C3-A2, O2-A1, O1-A2), left and right electrooculograms, submental electromyogram (EMG), oral and nasal flow, respiratory effort by piezoelectric effort bands, oximetry, and right and left anterior tibialis electromyogram were recorded. All studies monitored nasal airflow with an NC-PT system and oral flow by a thermistor. Periodic leg movements were not further considered for this analysis. Studies were performed at sleep laboratories at the Beth Israel Deaconess Medical Center, Boston, or the Deaconess Glover Hospital, Needham, both in Massachusetts. The institutional review board approved this review of polysomnographic data.

Scoring of Respiratory Events

An obstructive apnea was defined as an absence of airflow on the nasal cannula and a reduction in the oral thermistor signal to less than 10% of baseline, with continued respiratory effort. Central apneas were scored when there was no evidence of effort. An obstructive hypopnea was defined as any clearly evident reduction in amplitude of the nasal pressure signal, or flattening of the inspiratory flow profile, for 3 or more consecutive breaths that were abruptly terminated, with a return to a rounded or sinusoidal flow profile or a large recovery breath.

Scoring of EEG Event-Termination Patterns

Six non-rapid eye movement (NREM) EEG patterns or grades that occurred within 2 to 3 seconds of respiratory recovery were recorded:

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Address correspondence to: Robert Joseph Thomas, MD, CC-866, Sleep Unit, Beth Israel Deaconess Medical Center, East Campus, 330 Brookline Avenue, Boston MA 02215; Tel: 617-667-3237; Fax: 617-975-5506; E-mail: rthomas1@caregroup.harvard.edu
(1) an AASM-defined 3-second arousal, (2) less than 3 seconds of visible arousal-alpha intrusions, (3) a delta burst (2 or more delta waves) with an EMG increase greater than 50% of the ongoing baseline, (4) a single K-complex with EMG elevation, (5) a delta burst with no EMG increase, and (6) a single K-complex with no EMG increase. A progressive hierarchy was assumed for the purpose of tabulation only, from grade 1 through grade 6, of increasing severity of adverse impact. The frequencies of occurrence of sleep spindles in relationship to spontaneous or respiratory event termination-related K-complexes were assessed by tabulating this phenomenon in 1000 complexes; 100 consecutive complexes from 10 separate polysonograms were evaluated. The temporal relationship of K-complexes and recovery breaths were visually assessed for these same events. For events termination in rapid eye movement (REM) sleep, the duration of EMG elevation of greater than or less than 3 seconds was tabulated.

Sleep Staging

Sleep was staged using conventional Rechtschaffen and Kales stages.

Score-rescore Test

All studies were independently scored by a certified polysomnographic technician and twice by the author, the latter by opening up a new digital scoring file. Event-by-event comparisons were made in the following categories: (1) scoring with EEG and respiratory signals, (2) scoring with EEG signals alone, and (3) scoring with respiratory signals alone.

Statistical Methods

Data were tabulated and summarized as mean and SD or percentages. A $\chi^2$ statistic was calculated to assess difference in EEG patterns at event termination between apneas and hypopneas. A $\kappa$ statistic was generated for event-by-event interscorer and intrascorer agreement.

RESULTS

Patient Characteristics

The mean age of patients was 46.3 ± 6.2 years, the mean respiratory disturbance index was 54 ± 14, and the mean minimum oxygen saturation was 78% ± 10.4%. Ten of the 17 patients were men. Seven patients maintained nocturnal oxygen saturation above 90%.

<table>
<thead>
<tr>
<th>Table 1—Arousal Definitions</th>
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<tr>
<td>Author</td>
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<td>R &amp; K$^2$</td>
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<td>Cheshire$^4$</td>
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<td>Collard$^5$ (movement arousals)</td>
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<td>Tsai$^6$</td>
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Respiratory Events

A total of 2956 events in NREM sleep were identified: 1217 obstructive apneas and 1739 hypopneas. Central apneas were not tabulated. In REM sleep, 220 apneas and 363 hypopneas were identified.

Apnea Versus Hypopnea Termination in NREM Sleep

Apnea termination grades were 56.6%, 15%, 18.6%, 2.6%, 1.7%, and 4.9%, respectively, for grades 1 through 6 (Figure 1); 0.6% of the events were unclassifiable. Hypopnea termination grades were 17.6%, 22.1%, 21.28%, 22.6%, 10.1%, and 6.1%, respectively, for grades 1 through 6; 0.2% of events were unclassifiable. The $\chi^2$ statistic was highly significant ($P < .0001$) as an estimate of differences (higher grades with apnea) in event termination grades between apneas and hypopneas.

Apnea Versus Hypopnea Termination in REM Sleep

The majority of events, 99% of apneas and 91% of hypopneas, were terminated with visible EMG tone increase; 87% of apneas and 77% of hypopneas had a 3-second or greater duration of EMG tone increase at termination.

Spindles and Arousal-linked K-complexes

Only 74 of the 552 (13.4%) respiratory-event-related K-complexes had a contiguous visually identifiable spindle, while 311 of the 448 (69.4%) spontaneous K-complexes had a contiguous spindle.

Score-rescore Analysis

Event-by-event agreement was 93.8% for the repeat scoring by the author and 90.5% for the technologist-author comparison for identification of all respiratory event terminations with both EEG and respiratory signals available. Agreement dropped to 67.3% and 58.7% when the EEG signal alone was used to score arousals, as the “cue” effect of respiratory recovery was absent. Scoring of the respiratory signal alone provided agreement of 90.3% and 88.6% for NREM sleep but 80.8% and 70.6% during REM sleep.

DISCUSSION

The spectrum of EEG transients that are associated with respiratory event termination are presented. The purpose of this study was not to propose or develop a new classification of arousals nor to validate a new arousal scoring system, but to document the spectrum of EEG transients that surround respiratory event termination, accurately assessed using the nasal pressure signal. Without this context, only alpha intrusions can be reliably scored as arousals, with acceptable interscorer reliability.
Reliability of arousal-type scoring, irrespective of the classification system used, may be even poorer and, unless there is a significant clinical correlation with outcome, would provide no further useful information.

The sample is a reasonable representation of the severity spectrum, including patients with and without nocturnal hypoxia and the entire spectrum of respiratory events—apneas, hypopneas, and “flow-limitation events.” There is a spectrum of change temporally linked to the termination of respiratory events that goes beyond the standard in current use: the AASM 3-second rule. The hierarchy of EEG termination pattern used was somewhat arbitrary (eg, K-complex with EMG increase versus delta burst without EMG increase) and was intended as a measure to categorize changes, not to be a stated new classification system. Interscorer variability in scoring AASM arousals is high but best when linked to respiratory events or periodic limb movements of sleep that cue attention to a possible arousal, and the presented data support that.11,12 The EEG signal was especially useful when identifying pathologic respiratory events during REM sleep, as flow limitation and respiratory-rhythm and -rate irregularity may normally be seen during REM sleep. In our data set, apneas, compared to hypopneas, were more likely to be associated with typical AASM arousals, which supports the concept of a hierarchal relationship of sleep responses to potentially disruptive influences. The implications of a wider concept of arousal scoring are discussed below.

Consequences of Disrupted Sleep

Sleep fragmentation is adequate, in the absence of hypoxemia, to cause excessive daytime sleepiness in patients with sleep-disordered breathing.13 Other studies have reported correlations between the apnea-hypopnea index, nocturnal hypoxemia, and sleep fragmentation with daytime hypersomnolence and with continuous positive airway pressure (CPAP) response.14-16 These correlations have been in the .3 range; a more sensitive and clinically realistic arousal definition may result in stronger links between respiratory events and their consequences. Significant objective excessive daytime sleepiness can persist following apparently good use of CPAP.17-19 Several reasons have been postulated, including long-term effects of hypoxia or sleep fragmentation. However, this could as easily be due to inaccurate scoring of hypopneas (requiring a 4% desaturation or a 3-second AASM arousal and a 50% reduction in thermistor signal) and not using normalization of flow as the titration endpoint. In essence, treatment converts patients from having obstructive sleep apnea syndrome to upper airway resistance syndrome. Using the AASM definition for arousals can underestimate the impact of disordered breathing on sleep.20 Success following surgical approaches or oral appliance therapy may seem less obvious with more precise measures of respiratory monitoring and arousal scoring.21

K-complexes in Relation to Arousals

K-complexes were an important component of EEG transients associated with respiratory event termination in our data set. This transient can appear spontaneously or may be triggered by various stimuli and has been suggested to represent signs of arousal or to represent a defensive or sleep-protective function.26,27 In a study using auditory sleep fragmentation, the incidence of both evoked and spontaneous K-complexes increased significantly on the recovery night, suggesting a sleep-maintenance function.27 However, in the current data set, they were a prominent component of EEG transients linked to respiratory event termination. The K-complex reflects, at the EEG level, the slow oscillation of cortical neurons.28 All K-complexes are not rhythmic, especially in the initial stages of sleep, when the cortical network is under the influence of arousing and sleep-inducing influences, resulting in asynchronous, arrhythmic, or isolated complexes.28 This type of instability would be...
quite prominent in patients with sleep-disordered breathing, who are continuously fluctuating between variable states of sleep depth and wake. In our data set, the K-complex was typically seen to just precede the respiratory event termination and was, in some instances, the sole overt EEG marker. Direct cortical stimulation elicits a monosynaptic excitatory postsynaptic potential followed by a long-lasting hyperpolarization—the rebound from the latter corresponds to a K-complex in the field potential tracing. This is the nature of the evoked K-complex. In a given recording, the greater the sleep-disturbing stimuli, the greater the number of evoked rather than spontaneous complexes. The slow oscillation is made up of an alternative pattern of hyperpolarization and depolarization of the neuronal membrane. In a straightforward situation of upper-airway obstruction, incremental effort will reach the threshold to evoke K-complexes, with incremental pressure swings resulting in more frequent and larger complexes, until the brainstem-forebrain arousal system terminates the sequence by a block of the slow potassium conductance necessary for the hyperpolarizations. Brainstem arousal and activating systems disrupt the slow oscillation by abolishing the hyperpolarizing phase through cholinergic and noradrenergic mechanisms—both acetylcholine and norepinephrine block slow potassium currents. This explains the absence while awake and the fact that the vast majority of K-complexes in association with a respiratory event occurs just before the event termination, whether it be single complex or as part of a delta burst. Polygraphic delta waves have been described in association with the termination of apneas and hypopneas. Analysis of the EEG frequency has shown a progressive increase in EEG delta band starting several seconds after the onset of obstructive apneas during NREM but not REM sleep. This progressive increase in delta power may reflect the progressive induction of evoked K-complexes, as described above, since it (K-complex) contains delta-frequency waves.

Spindles in Relation to Arousal

Thalamocortical activity exhibits 2 distinct states determined by the level of hyperpolarization of the thalamocortical cells—the oscillatory mode during NREM sleep and the tonic firing mode during wake or REM sleep. The transition from the oscillatory to the tonic mode is associated with a progressive depolarization of thalamocortical cells. Spindle waves are generated in the thalamus, largely through a cyclic interaction between thalamocortical and thalamic reticular neurons. There is an inverse relationship between the incidence of sleep spindles and K-complexes without spindles, the latter showing a correlation with transient activation patterns on the EEG. The number of K-complexes seen with spindles increases when there is no transient activation in the preceding 10 seconds of sleep. Moreover, there is a suppression of delta (spindle) frequency activity immediately following an evoked K-complex. If a K-complex is part of the arousal response, the transient intrusion of wake and the resultant transient depolarization of the thalamic nuclei should make it impossible for a spindle to be associated with these K-complexes. This was indeed seen to be the case, as there was no visually identifiable sleep spindle in 86% of the K-complexes that were associated with a respiratory event termination.

The role of K-complexes as markers of arousal in respiratory sleep disorders is further supported by data from evoked responses and recordings of muscle sympathetic nerve activity (MSNA). In one study, auditory stimuli applied during sleep induced a burst of MSNA followed by a transient increase of arterial blood pressure but only when the stimuli elicited an arousal response in the EEG, such as a K-complex, transient EEG desynchronization, or a short train of alpha waves. This seems to be a specific response to an abrupt change in sleep state, as the same stimuli applied during wakefulness do not induce these changes in MSNA and in arterial blood pressure.

Arousals are Graded Responses

This study clearly shows that, in clinical practice, there exists a spectrum of EEG responses at event termination. Only a small percentage (≤ 1%) of respiratory event termination in our set had absolutely no visually detectable EEG change. Not surprisingly, apneas and hypopneas had differing “population distributions” of the types of EEG transients at termination, with the former more likely causing classic AASM-type arousals. Several reports have described a hierarchy of progressive sympathetic and EEG responses with auditory and respiratory stimuli. Fast Fourier transformations of the EEG in sleep apnea patients have shown increases in EEG frequency coincident with increases in blood pressure at the end of respiratory events whether or not they were terminated by AASM arousals. A study of induced transient arousal on obstructive apneas showed a graded reduction in apnea length from overt and subtle (< 3 seconds alpha) auditory-induced electrocortical transients.

Arousals in Nonobstructive Sleep-disordered Breathing

The literature on arousal patterns in central sleep apnea and periodic breathing is relatively less. The cyclic variability intrinsic to this condition can make the application of discrete scoring rules difficult. The respiratory cycle is associated with a rise in high-frequency EEG activity during the hyperpneic phase. Using a neural network to provide a second-by-second analysis of sleep depth, it has been shown that sleep deepens progressively during the apneic phase. In this study, AASM arousals were seen to terminate from 64% to 97% of events in different subjects. K-complexes were consistently noted to be superimposed on the EEG during early arousal initiation. Arousal was initiated at or before apnea termination and progressed through the breathing phase. The rise and fall in systolic blood pressure closely followed the rise and fall of EEG sleep depth. Though events may be less discrete that in patients with obstructive sleep apnea, using a criterion of EEG transients phase locked to airflow patterns may be clinically adequate.

Factors Determining the Arousal Pattern

I have described a range of polysomnographic changes associated with termination of respiratory events. Definitions limited to alpha intrusions are too restrictive and do not reflect the clinical reality or full burden of disease. Accurate event detection and scoring are crucial to appreciating the arousal spectrum. I do not believe this is possible without recording esophageal pressure or nasal pressure. Various patterns (slow, fast, or mixed types) of arousals may be seen within the same individual during the same night. The precise pattern of individual events is likely determined by a number of factors, including the sleep stage, delta power, hypercapnia, cyclic alternating pattern or noncyclic alternating pattern state, severity of the respiratory event, severity of prior sleep fragmentation or sleep deprivation, alcohol use, neurologic disorders such as stroke, age, medication effects, circadian effects, and individual factors. The arousal threshold increases during the course of the night, resulting in an increase in apnea duration.

What is an Arousal in the Context of Sleep-disordered Breathing?

An event-linked arousal identified only by a just-detectable alpha intrusion or an isolated K-complex just prior to the event termination may be less disruptive than is several seconds of wake or an AASM arousal. It seems a clinically superior strategy to recognize the various patterns of EEG change that are linked to event termination and then formulate an arousal definition, rather than create an arbitrary definition and struggle with poor clinical correlations. An accurate measure of respiration is a necessary component of such an approach. A number of temporally related events can help detect an arousal event—a brief burst of bruxism activity, periodic or aperiodic limb movements, submental tone elevations in NREM sleep, a REM (brief intrusion of wake), a slow eye movement (brief intrusion of stage 1 sleep or drowsiness), an abrupt increase in respiratory effort or flow signal, transient blood-pressure elevations, an acceleration-deceleration sequence of R-R variation, and
behavioral responses such as verbalization, motor activity or movement, eye opening, or eye blinks. Simultaneous monitoring for autonomic activation responses using pulse transit time

7. Norman RG, Ahmed MM, Walsleben JA, Rapoport DM. Detection of respiratory events in infants and in an experimental porcine model, suggesting that this is the rule in biologic systems.

A arousal definition that is appropriate for research may not have practical clinical utility. The number of parameters recorded will also possibly modify a definition, such as limited versus full polysomnography. Repetitive “large recovery breaths” may be a useful marker of arousal when recorded during sleep in the appropriate setting, though experimental evidence is controversial on the requirement for a cortical arousal as defined by alpha intrusion in the EEG.

A simple categorization of EEG-respiratory arousals could be as follows: absent (no EEG or autonomic marker change), subcortical (no EEG change but autonomic arousal), cortical-I (complexes or delta waves), and cortical-II (presence of alpha/beta frequencies). This is similar to the criteria proposed in association with periodic leg movements in sleep-related disordered breathing in the sleep apnoea/hypopnoea syndrome. Arch Intern Med 1992;152:538-41.


