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Editorial

How knowledge of cyclic alternating pattern improves continuous positive airway pressure titration in the management of sleep-disordered breathing

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by recurrent upper airway collapse producing apneas and hypopneas. The repetitive runs of respiratory events are terminated by EEG arousals; the more respiratory events, the more sleep fragmentation contributing to daytime sleepiness. The main therapeutic outcome – to abolish respiratory events and restore effective ventilation – can be achieved with continuous positive airway pressure (CPAP) titration, which relieves upper airway obstruction and reestablishes sleep continuity. Since sleep is adversely affected by respiratory events, severity and improvement of sleep fragmentation can be determined by monitoring respiratory events.

The pivotal role of ventilation during sleep has allowed us to increase our knowledge of sleep physiology and clarify some major clinical aspects of sleep medicine, in particular, the impact of OSAS on sleep, sleepiness and health. According to the ASDA scoring rules [1], EEG arousals punctuate sleep in patients with a number of disorders including OSAS. However, arousals are not necessarily a manifestation of a respiratory disturbance or a movement disorder, but may be, to a certain extent, physiological age-related components of sleep [2,3]. Still, arousals are basically considered as EEG markers of breathing irregularities.

To better appreciate the causes of arousals, it is important to define the role of arousals in undisturbed sleep as well as in sleep disorders. Arousals are brief intrusions of wakefulness into sleep accompanied by an important activation of cardiac, respiratory and motor functions. However, cerebral, neurovegetative and motor activation can also appear associated with sleep-preserving EEG features such as K-complexes or delta bursts [4,5]. In this case, the magnitude of activation is lower compared to conventional arousals, but is nevertheless significantly higher compared to the baseline condition [6] and may have adverse repercussions on daytime functioning [7]. These findings indicate that some delta-like EEG features, which do not fit the conventional definition of arousal, are endowed with both activating effects and sleep maintenance properties. The cyclic alternating pattern (CAP) is the microstructural framework that ties together both sleep-disrupting (ASDA arousals) and sleep-preserving EEG features (low-frequency high-amplitude bursts) within a <1 min periodicity dimension [8]. Composed of a pattern of repetitive activation (phase A) and deactivation (phase B), CAP is a marker of unstable sleep, while the absence of CAP (non-CAP) reflects a condition of sustained sleep stability. While stable sleep is associated with stable autonomic function assessed by polygraphic monitoring, unstable EEG sleep runs with fluctuations of neurovegetative activities [9]. In the close relationship between EEG and neurovegetative swings, CAP stands as a marker of both sleep instability and cyclic autonomic activation and is consistently associated with respiratory instability as it occurs in sleep apnea [10,11].

Robert Thomas' article in this issue [12] illustrates the practical implications of using the CAP methodology for manual pressure titration in patients with severe OSAS. Pressure adjustments were monitored throughout the night, particularly when the pattern of inspiratory flow limitation was 'stable', (persistent and non-progressive for at least 10 min) and when, within the same time range, the pattern was 'unstable' (characterized by repeated increases of the inspiratory flow limitation terminating in arousals). These breathing patterns were analyzed during non-rapid eye movement (NREM) sleep as defined by the R&K criteria and during CAP and non-CAP [13]. A total of 50 periods were identified. Thirty periods showed stable flow limitation and all but one corresponded to non-CAP on the EEG. Twenty periods showed unstable flow limitation and all but one were associated with CAP. All the increases of endonasal pressure accomplished during the non-CAP periods were ineffective on the flow profile. On the contrary, 2/3 of the pressure increments carried out during the CAP periods improved the airflow. The message is clear. Sleep EEG analysis in terms of CAP and non-CAP provides guiding feedback for CPAP titration.

Flow-limitation events are transient episodes of elevated upper airway resistance identified by characteristic flattening on the flow/time tracing. It is known that stable flow limitation can be found in deep NREM sleep, which basically reflects a condition of non-CAP. In other words, a stable pattern of flow limitation is compatible with a period of stable sleep (non-CAP), which reflects an overall balance among the neural, autonomic and chronobiological systems involved in sleep regulation. On the contrary, the presence of CAP indicates a period of unstable sleep resulting from

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instability in one or more systems of sleep regulation including the respiratory function. Since the central and peripheral systems are connected in a looping circuitry, it becomes a barren chicken–egg dilemma to question whether the unstable pattern of flow limitation is the outcome of an arousal-mediated instability or whether unstable breathing triggers sleep instability. As long as the anatomic or functional continuity is preserved, the mutual interaction between CAP and the regulatory mechanisms of respiration continue to operate.

The hypothesis of a widespread neural network is supported by evidence that multiple autonomic functions, including arterial pressure, heart rate and respiration undergo periodic variations at a frequency around 20–40 s as part of an endogenous rhythm that modulates many physiological functions. Thus, it is not surprising that a number of periodic events occurring during NREM sleep (sleep apneas, periodic limb movements) present a rhythm similar to CAP; this 20–40 s periodicity is a spontaneous rhythm of NREM sleep, frequently linked to the production of slow wave activity [14,15] and to the build-up of the sleep cycle [16].

In conclusion, the sleeping brain expresses a period of instability during CAP involving cerebral, autonomic and motor activities. In practical terms, the application of CAP not only improves the procedure of pressure titration in severe OSAS, but may also offer a sensitive tool for analyzing those puzzling cases where, despite unappreciated breathing irregularities, the patient appears sleepy and functionally impaired. It is probably in situations of mild upper airway dysfunction (which are the most frequent and most difficult to manage) that the investigation of sleep microstructure may uncover unexpected surprises.

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