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Reflex Tachycardia with Airway Opening in Obstructive Sleep Apnea

Commentary on Azarbarzin et al. Contribution of arousal from sleep to post-event tachycardia in patients with obstructive sleep apnea. SLEEP 2013;36:881-889.

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Arousal from sleep is traditionally defined as a visually discernible shift to higher frequency activity in the sleep EEG lasting > 3 sec, with > 15-sec shifts considered full awakening.[1-3] Arousals can occur spontaneously without an obvious trigger or be elicited by virtually any sensory stimulus applied with sufficient intensity to reach the "arousal threshold," which varies between individuals and according to the "depth" or stage of sleep. Rather than simply a return to wakefulness, arousal appears to reflect a transiently activated state with altered responses to sensory inputs compared to wakefulness.[4] Rapid cortical re-activation along with augmented cardiorespiratory and metabolic activity accompanying arousal has clear survival advantages, since all may be required to support "fight or flight" responses to exogenous or endogenous threats arising during sleep.

Transient cardiorespiratory responses accompany both spontaneous and induced arousals and include brief tachycardia, peripheral vasoconstriction, a surge in blood pressure, and a burst of upper airway and ventilatory pump muscle activity.[5-15] These responses exhibit both all-or-none or "threshold" behavior, and graded responses in which arousal duration and the magnitude and duration of cardiovascular activation vary according to stimulus intensity. Often there is no visually discernible changes in the EEG while there is a clear cardiovascular response,[15-18] with peripheral vasoconstriction particularly prominent.[13] Such responses are commonly termed "autonomic" or "subcortical" arousals. However, it remains unclear if cortical activation implied by "arousal" contributes to them, or if responses simply reflect subcortical reflexes responding to a stimulus without arousal.

In this issue of *SLEEP*, Azarbarzin and colleagues[19] investigated relationships between tachycardia and airway opening, with and without arousal. This is an important area of investigation since the hierarchy of arousal versus cardiovascular activation responses during obstruction in sleep and relationships with cardiovascular health outcomes remain poorly understood. Azarbarzin et al. point out that in obstructive sleep apnea (OSA) tachycardia has been shown to accompany arousal and airway opening both with and without discernible arousal.[15-18] Tachycardia with airway opening in the absence of discernible EEG changes could indicate lower threshold activation responses with more subtle cortical involvement (or so-called subcortical arousals). Alternatively, tachycardia could predominantly reflect subcortical reflexes responding to the effects of sudden airway opening (such as airway and intrathoracic pressure changes and hemodynamic effects) largely independent of arousal.

Azarbarzin et al.[19] examined heart rate changes following severe airway obstruction induced by lowering constant positive airway pressure (CPAP) in patients with severe OSA, and compared heart rate responses accompanying spontaneous airway opening with arousals to responses from similar severity obstructions deliberately terminated earlier by rapidly increasing CPAP after 3 obstructed breaths. The investigators reasoned that if post-event tachycardia reflects autonomic reflex responses to airway opening rather than arousal, then post-event tachycardia should show a close temporal relationship to airway opening and a graded response increasing with obstruction severity irrespective of the presence or absence of arousal. Alternatively, if tachycardia reflects subcortical "arousal" with a lower threshold than more conventionally scored arousals, the authors suggest that tachycardia should only occur above a certain threshold of obstruction severity with timing unrelated to airway opening.

Azarbarzin and colleagues found that deliberate early termination of obstruction by increasing CPAP produced brisk tachycardia, with a close temporal relationship to airway opening and a graded response according to obstruction severity, largely independent of the presence or absence of arousal. These important findings support that tachycardia with airway opening in OSA may be dominated by subcortical reflexes with only a modest contribution from arousal. However, some caution is warranted in the interpretation of these data.

Azarbarzin et al. concluded that subcortical "arousal" does not contribute to post-event tachycardia and suggest that the terms "autonomic arousal" and "subcortical arousal" are misnomers that should be avoided in future studies. While this point is worth noting, the neural substrates for cardiovascular and arousal responses and their degree of interaction and overlap remain speculative. Human studies of arousal typically rely on surface EEG recordings, yet recent animal and human studies using concurrent intracranial and surface EEG recordings show marked temporal and spatial differences in the EEG—the so called local sleep phenomenon.[20] Importantly, the motor cortex can show frequent periods of wake-like EEG activity (> 10-s bursts of alpha activity), while scalp EEGs, including frontal leads,

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show slow wave activity.[21] This is consistent with regionalized cortical activation that may help balance homeostatic needs for uninterrupted sleep as a global process, with opposing needs of motor behaviors following sudden awakenings to a threatening stimulus.[21] Concurrent cardiovascular system activation could also occur without discernible arousal in scalp EEGs. Definitions are clearly important for standardisation in clinical practice, but given these data, measurement constraints and largely arbitrary definitions of arousal with uncertain clinical significance,[10,22,23] a clear distinction between subcortical reflexes and higher cortical activation responses may not be entirely meaningful or warranted.

It should also be considered that a rapid CPAP increase in the presence of obstruction could represent a potent sensory stimulus for both subcortical reflexes and arousal beyond intrathoracic pressure and hemodynamic effects. Similar to other sensory disturbances that evoke cardiovascular[11,13] and cortical[24,25] responses, sudden inspiratory muscle unloading and a rapid rise in airway and intrathoracic pressure, not necessarily specific to airway opening *per se*, could also produce graded cardiovascular and more subtle cortical evoked responses closely aligned with airway opening. The data reported by Azarbarzin et al.[19] are clearly consistent with subcortical reflex origins and a hierarchy of activation responses from subcortical reflexes, through to more substantial responses accompanying arousal and full awakening. However, this does not necessarily exclude cortical involvement without discernible arousal, in which the degree of cortical versus subcortical activation is largely governed by stimulus intensity, subcortical reflex sensitivity, and cortical excitability at the time of stimulus exposure.

In the context of obstructive sleep apnea (OSA), where the upper airway frequently either partially or completely collapses during sleep, sudden airway opening at the end of each obstruction is strongly associated with arousal and cardiorespiratory activation. Although it is tempting to suggest that arousal may be highly protective in OSA, Younes has previously shown that airway opening often occurs *before* and sometimes without discernible arousal, especially in deep sleep when arousal propensity is diminished.[26] Thus, arousal and airway opening may be largely incidental events, both arising from augmented inspiratory effort, with outcomes determined by factors such as arousal propensity, obstruction severity, and the effectiveness of upper airway muscle recruitment.[26,27] This view is consistent with the classic concept of an inspiratory effort arousal threshold largely independent of the respiratory stimulus.[28] By virtue of exaggerated hyperventilation, arousal could destabilize upper airway and ventilatory control stability.[26,27] More frequent obstruction in light sleep and reduced OSA severity with arousal suppression support this idea,[29,30] although augmented upper airway muscle activity with arousal could also help counteract these effects.[15,31]

Subcortical reflex activation of upper airway dilator muscles could play a role in resolving obstructive events with minimal sleep disturbance. Frequent cardiovascular system activation—when cardiorespiratory work and blood gases can be severely compromised during OSA events—could also have detrimental cardiovascular effects. Further studies are needed to examine upper airway muscle activity, airflow, tachycardia, and more sensitive markers of reflex cardiovascular activation with and without arousal, along with studies to examine potential effects of frequent cardiovascular activation on health outcomes in OSA.

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DISCLOSURE STATEMENT

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