HIGHLIGHTED TOPIC | Upper Airway Control and Function: Implications for Sleep-Disordered Breathing

The human upper airway: more than a floppy tube

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Upper airway anatomy and neuromuscular control in quadrupeds and bipeds is unique (7, 12). Genioglossus, the largest extrinsic tongue muscle, is the most extensively studied upper airway muscle, yet the tongue is comprised of four intrinsic and four extrinsic muscles (7). Ultimately, many factors influence neural control and the mechanical properties of the upper airway. These factors alter upper airway size, shape, and dynamic function (see Fig. 1).

At sleep onset and during rapid-eye-movement (REM) sleep, particularly when active eye movements are present, there is a profound loss of drive to the upper airway muscles. Not surprisingly, upper airway closure is common during these periods. As discussed in the mini-review on state-dependent and reflex drives to the upper airway (9), recent work by Horner and others has provided insight into the mechanisms mediating genioglossus muscle inhibition during REM sleep, the source of inspiratory drive to hypoglossal motoneurons, and the possibility that motor suppression in sleep and drug-induced sedation share common neural pathways and cellular mechanisms.

Approximately one-third of OSA patients generate minimal or no neural activation of genioglossus during non-REM sleep in response to experimentally induced apneas and hypopneas (5, 6). One therapeutic approach to overcome major reductions in response to experimentally induced apneas and hypopneas (5, 6). One therapeutic approach to overcome major reductions in response to experimentally induced apneas and hypopneas (5, 6). One therapeutic approach to overcome major reductions in response to experimentally induced apneas and hypopneas (5, 6). One therapeutic approach to overcome major reductions in response to experimentally induced apneas and hypopneas (5, 6).
in upper airway muscle tone during sleep, as covered by Schwartz and colleagues (13) in their mini-review on electrical stimulation of the hypoglossal nerve, is artificial stimulation of the upper airway dilator muscles. Until recently, this therapeutic approach has been quite limited but there are now several ongoing trials (13). This has been possible because of advances in neurostimulation technology. Conceptually, individuals with severe impairments in upper airway muscle tone during sleep would be expected to respond to this approach. Development of simple and accurate tools to identify which patients benefit from neurostimulation is a challenge.

In contrast, a substantial proportion of OSA patients can develop large increases in neural drive to genioglossus during natural sleep, yet this neural drive fails to alleviate the OSA (5). There are several possibilities, including biomechanical considerations, as highlighted by Bilston and Gandevia (1) in their mini-review on the biomechanical properties of the human upper airway and their effect on its behavior during breathing and in OSA, that may explain why large increases in neural drive are sometimes insufficient to open the upper airway. Possibilities include 1) severely compromised upper airway anatomy, 2) non-tube-like behavior whereby driving pressure exceeds upper airway dilatation to reduce airflow (negative effort dependence), 3) poor coordination of upper airway muscles, 4) counterproductive bidirectional movement of the upper airway muscles, or 5) dynamic changes in other surrounding structures such as epiglottic closure (1, 2, 4, 10, 13). Interestingly, artificial stimulation of the upper airway muscles can overcome the dissociation between already naturally high levels of neural output and upper airway closure (4). However, the ability to deliver the required level of electrical stimulation in these individuals may cause frequent arousals from sleep.

Although clinical data indicate that nightly neurostimulation of upper airway dilators can reduce OSA severity, with reductions maintained for at least 1 year (13), the long-term physiological effects on the upper airway muscles are unknown. Theoretically, long-term stimulation may yield beneficial effects via muscle plasticity (e.g., enhanced endurance) or deleterious effects via muscle hypertrophy in an already crowded airway (11). There are many plausible physiological changes that could occur with neurostimulation of the upper airway muscles, but they have not yet been formally tested. Similarly, there is clinical data demonstrating reductions in OSA severity with training (8), yet how training affects upper airway muscle physiology has not been investigated.

There is also important variation between patients as well as variability in the physiology within a patient in upper airway size, shape, and dynamic function. Both the anatomical and nonanatomical causes of OSA vary between patients (3, 5). Some anatomical compromise is required for the upper airway to collapse during sleep. However, as covered in several of the reviews, many factors influence static upper airway anatomy and dynamic function (Fig. 1). Indeed, Pcrit, a functional measure of the upper airway collapsibility during sleep, varies substantially between OSA patients, with some patients requiring suction pressures up to −5 cmH2O with others requiring in excess of +5 cmH2O to close the upper airway (5). In addition to an inability of the upper airway muscles to respond to airflow narrowing either via insufficient neural drive or translation of increased neural drive to airway opening, other nonanatomical traits including respiratory control stability can contribute to OSA. As outlined in the mini-review by Eckert and Younes (6) on arousal from sleep and its implications for obstructive sleep apnea pathogenesis and treatment, the propensity for awakening during airway narrowing (the respiratory arousal threshold) can have dual roles in OSA pathogenesis. Awakening too easily, that is a low arousal threshold (present in one-third of OSA patients) may increase OSA severity by 1) preventing deeper more stable sleep, 2) limiting buildup of respiratory stimuli required to increase neural drive to the upper airway muscles, and 3) perpetuating respiratory control instability (5, 16). In these individuals, strategies to increase the arousal threshold and promote sleep are likely to be helpful. Conversely, difficulty in awakening may prolong respiratory events and worsen sleep-disordered breathing in other patients (6).

Given the variety of factors that can influence the dynamic function of the upper airway and the heterogeneity of OSA pathophysiology, new models and techniques are being developed to estimate key contributing traits (14, 15). The goal of this work is to deliver targeted therapies according to underlying pathophysiology on a per-patient basis. Curiously, some individuals do not develop OSA despite abnormalities in anatomical or nonanatomical traits. Understanding how these individuals are protected from OSA is also likely to provide insight into OSA pathogenesis and treatment.

REFERENCES


