Alternative Approaches to Treatment of Central Sleep Apnea

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KEYWORDS

• Carbon dioxide • Oxygen rebreathing • Acetazolamide • Provent • Winx • Multimodal complex • Central apnea • Periodic breathing

KEY POINTS

- The phenotype that reflects heightened respiratory chemoreflex activation is non–rapid eye movement (NREM)-dominant sleep apnea. Conventional scoring may categorize many of these patients as obstructive.
- Targeting respiratory chemoreflex sensitivity or effects, and sleep fragmentation, can provide useful alternative or adjunctive therapy for central sleep apnea syndromes.
- CO_2 is the dominant driver of sleep respiration, and manipulation of CO_2 has the greatest potential for clinical effects. The primary challenges are simultaneously technical and biological: how to keep the CO_2 levels just above the NREM sleep CO_2 threshold. As these levels are not hypercapnic, sympathoexcitation would not occur.
- Treatments for obstructive components of sleep apnea that may be less prone to destabilize respiratory control include Provent, oral appliances, and Winx. However, residual disease is common and requires adjunctive therapies.
- Reducing the impact of arousals and inducing a stable form of NREM sleep may be achieved by sedatives, including the classic benzodiazepines and the nonbenzodiazepines such as zolpidem.
- Multimodality approaches to the treatment of sleep apnea are especially important for central sleep apnea syndromes.

INTRODUCTION

The treatment of central sleep apnea syndromes, especially the hypocapnic type characterized by a hyperactive respiratory chemoreflex, is challenging. The adaptive servoventilators target respiratory rhythm besides providing upper airway support, and are described in other articles in this issue. In this article alternative approaches to management are described, which in some instances may be used as adjuncts to positive airway pressure (PAP). As the hypocapnic central sleep apnea syndromes are characterized by specific pathologic rhythms of respiration, accurate polysomnographic recognition of driving chemoreflex influences is critical in dosing primary and adjunctive/alternative therapies. Phenotyping of

Disclosures: Dr Thomas is: (1) coinventor of the ECG-spectrogram technique to phenotype sleep and sleep apnea. This technology is licensed by the Beth Israel Deaconess Medical Center to MyCardio, LLC; (2) coinventor of the Positive Airway Pressure Gas Modulator, a device that treats central/complex apnea with low concentration CO_2 added to positive pressure therapy. He consults for DeVilbiss in the development of a new-generation auto-CPAP.

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the contributory components of sleep apnea is central to phenotype-driven therapy. The phenotypes that have current treatment options are upper airway collapsibility, chemoreflex activation level, and sleep fragmentation propensity.

POLYSOMNOGRAPHIC RECOGNITION OF A HEIGHTENED RESPIRATORY CHEMOREFLEX

Scoring of respiratory events in sleep apnea patients have traditionally been biased toward an obstructive phenotype, although the recent update of the 2007 American Academy of Sleep Medicine (AASM) guidelines has criteria for scoring central hypopneas and short sequences of periodic breathing/Cheyne-Stokes respiration.[1] The guidelines state that central hypopneas should not be scored in the presence of flow limitation, but obstruction is a common feature of central events,[2] even at simulated altitude,[3] the latter being a relatively pure model of chemoreflex-driven sleep apnea. Direct visualization of the upper airway shows collapse at the nadir of the cycle to be common even in polysomnographic central disease.[4] Expiratory pharyngeal narrowing occurs during central hypocapnic hypopnea,[5] directly supporting the concept that the presence of flow limitation alone cannot be used to distinguish obstructive and central hypopneas.[3] Complex sleep apnea as currently defined requires a central apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) of 5 or more, with centrally mediated respiratory events constituting 50% or more of all respiratory events during continuous positive airway pressure (CPAP) titration, in those who do not fulfill criteria for primary central sleep apnea or periodic breathing on the diagnostic polysomnogram. However, publications of complex apnea did not score central hypopneas or periodic breathing. Descriptions of low (<5%) persistence of complex apnea may be inaccurate and reflect reliance solely on scoring classic central apneas.[6,7] The guideline for recognition of Cheyne-Stokes respiration also require a cycle duration of at least 40 seconds, but the author has shown that even shorter cycle times in the range of 20 to 25 seconds is typical of non–rapid eye movement (NREM)-dominant sleep apnea,[8] reminiscent of high-altitude periodic breathing. The most characteristic feature of chemoreflex-driven events is not the morphology of individual events but NREM dominance and timing/morphology of sequential events (nearly identical) in a consecutive series of events.[9]

A related dimension is the criteria used for estimating success of therapies. For example, if 4% oxygen desaturation is used to score hypopneas (used in most treatment reports, and which continues to be the recommendation of the AASM), significant degrees of baseline and residual disease can be missed. Moreover, adaptive servoventilators distort the conventional polysomnogram signals and, unless the pressure output of the devices are used to score events, inappropriate success may be declared. When periodic breathing is not adequately controlled, the primary marker on the polysomnogram is pressure cycling associated with arousals. Scoring respiratory events during adaptive servoventilation needs to use the pressure output signal from the ventilator, which is roughly equal and opposite to the patient's abnormality. When pressure cycling persists, sleep fragmentation is usually severe even if respiration is improved by conventional criteria.

ADVANCED PHENOTYPING OF CHEMOREFLEX INFLUENCES ON SLEEP RESPIRATION

The NREM sleep CO_2 reserve can be exposed inadvertently during bilevel positive pressure titration in the sleep laboratory, when central apneas or periodic breathing may emerge even if continuous positive pressure is well tolerated and efficacious. An experimentally precise version of this approach uses bilevel ventilation with measurement of end-tidal CO_2 ($ETCO_2$), the difference between stable breathing and the level just before bilevel-induced periodic breathing or central apneas. The CO_2 reserve is smaller (2–3 mm Hg) in those with heart failure and predominantly central sleep apnea.[10] Proportional assist ventilation may also be used to estimate the ease of induction of central apnea and periodic breathing, and thus quantify the contribution of enhanced respiratory chemoreflexes to sleep apnea severity.[11–15] This technique requires considerable expertise and is not readily applicable to a clinical laboratory environment.

Time series analysis of the electrocardiogram (ECG) (using heart-rate variability and heart rate/respiratory coupling) can provide a map of sleep-state oscillations, with the spectral dispersion providing phenotyping information regarding chemoreflex influences.[9] The technique, the ECG-spectrogram, maps coupled oscillations of heart-rate variability and respiratory R-wave ECG amplitude modulation. The ECG-derived sleep spectrogram can detect low-frequency coupled oscillations with 2 primary patterns: broad band and narrow band. Elevated narrow-band coupling, which detects sequences of central apneas and periodic breathing, is noted in patients with complex sleep apnea. Those with the ECG-spectrogram