Strong Chemoreflex Modulation of Sleep-Breathing: Some Answers but Even More Questions


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Long ago, in a universe that now seems far away, sleep apnea seemed so simple. There were obstructive apneas, and then there were central apneas. Medicare blessed the airway when there were 30 apneas, but not 29. There was Cheyne-Stokes respiration in those with advanced heart failure, and periodic breathing at altitude. Nary a worry about hypopneas requiring a specific reduction in a flow signal, nasal pressure or flow-limitation, 3-second arousals or arguments about “complex” sleep apnea. Since that peaceful time, much has moved in the world of obstructive sleep apnea. However, the polysomnographic characterization of chemoreflex influences on sleep-breathing has remained essentially stuck with the “straight line in everything for 10-seconds” central apnea or 10 continuous minutes of concordant waxing and waning effort and airflow. Flow-limitation has become the accepted practical biomarker of upper airway obstruction—thus the vast majority of scored events in clinical sleep medicine or research are categorized as obstructive.

There are problems with this more complicated but still relatively happy state of affairs. The upper airway can be closed during a central apnea, hypocapnia can be associated with flow-limitation, and the majority of new respiratory events at simulated altitude demonstrate flow-limitation. Loop gain is increased in patients with greater severities of obstructive sleep apnea, especially in those with a reduced contribution from upper airway collapsibility. Supplemental oxygen improves sleep apnea in non-hypoxic high loop gain individuals. Thus, there is a nagging feeling that the air we may be systematically underestimating the impact of chemoreflex influences on sleep apnea.

Does this matter? The idea of simultaneous and mixed physiologies (obstruction and chemoreflex) has been around for a while, with the term “complex sleep apnea” being introduced in 2005/2006. Looking beyond “believers vs. non-believers,” there is at least clinical appreciation of a subgroup of sleep apnea patients with certain characteristics that bode poorly for continuous positive airway pressure (CPAP) over the short term. These patients have non-rapid eye movement (NREM) sleep dominant obstructive sleep apnea and more readily yield classic central apneas on CPAP application, relative to REM-dominant obstructive sleep apnea. As can be expected, this conversion of mostly obstructive to mostly central sleep apnea with CPAP is associated with sleep fragmentation, where the arousals likely induce even more hypocapnia and respiratory instability. The size of this subgroup is as much a focal point of debate as is the long-term outcomes of those with acute CPAP-induced central sleep apnea, who are otherwise free of diseases such as congestive heart failure. These two questions are important. If these events are indeed rare and transient, we need not worry, but if common and persistent, our current treatment, tracking and device development paradigms need change.

To answer the question of prevalence and persistence, accurate measurement of strong chemoreflex influences on sleep-respiration is critical. The article by Javaheri et al. in this issue of JSCM used a threshold of 5 central apneas/hour of sleep; others have used different thresholds, including 10/hour of sleep and 5/hour of sleep + ≥ 50% of all events. Central hypopneas and periodic breathing are too difficult (time consuming and besieged with arbitrariness), it seems, for researchers to integrate into their assessments. These authors did show that of 1286 patients with a diagnosis of OSA, 6.5% had CPAP-emergent/persistent central sleep apnea. However, this phenomenon was generally transitory and was eliminated within 8 weeks after CPAP therapy. The prevalence of CPAP-persistent CSA was about 1.5%. Even though retrospective, the results do seem to suggest that we are worrying too much (if we do at all) about these patients, and that “time will heal.” I propose that is not the case for several reasons.

Thermistors were used in this study; a large number of respiratory events could have been missed on the diagnostic assessment. While this may not matter for counting traditional central apneas, it would if any attempt was made to try and score short periodic breathing sequences or central hypopneas. Table 5 shows that sleep quality remains impaired in those 42 subjects who had
A second CPAP evaluation, raising the possibility that all is not well. The question at the heart of the debate is the following— are there better ways to measure the chemoreflex contribution to sleep apnea and translate that into improved scoring and disease phenotyping? The continued use of classic central apneas only seems the mirror image of continuing to identify only classic obstructive apneas, a practice that is uniformly accepted as obsolete.

Meticulous scoring technique sensitive to central hypopneas and periodic breathing, esophageal manometry and pulse transit time have been suggested as methods to differentiate central and obstructive events. The morphology of the individual respiratory event is considered paramount, and not the timing characteristics of a series of events. Mapping coupled oscillations of heart rate variability and respiratory R-wave ECG amplitude modulation is yet one more method (the sleep spectrogram) that may provide both new insights into the interaction of chemoreflex modulation and obstructive influences and suggest caution in the continued exclusive use of central apnea counts.13

The ECG-derived sleep spectrogram can detect low frequency coupled oscillations with two primary patterns: broad band and narrow band. Narrow band coupling detects sequences of central apneas and periodic breathing at altitude, but also tags segments of polysomnograms traditionally scored with obstructive respiratory events. The technique has been applied to the 5247 polysomnograms from the Sleep Health Health Study. Those with the ECG-spectrogram biomarker of putative strong chemoreflex modulation of sleep respiration have more severe sleep apnea and greater degrees of sleep fragmentation. More tantalizing is the frequency and pervasiveness of the narrow band biomarker in the SHHS dataset: more than 30% of those with an AHI ≥ 5/hour of sleep, far higher than the prevalence of visually scored / identified periodic breathing or central sleep apnea.14 Thus, the technique seems to detect “obstructed periodic breathing.” If this is indeed a true marker of strong chemoreflex influences on sleep-respiration, then abandoning the concept of “complex” sleep apnea (a better term could be “chemoreflex modulated obstructive sleep apnea”) is premature.

Figure 1 demonstrates the effects of simulated altitude on sleep spectrogram-based phenotyping of sleep apnea, and the results should provoke thought. My own experience is that unshackling from the “central apnea index ≥ 5” rule allows identification of NREM-dominant obstructive periodic breathing in at least 10% of unselected sleep laboratory patients. The pattern is often readily apparent on the diagnostic polysomnogram. In our center, we may treat such patients with added dead space, adaptive ventilation, or both. It is my clinical impression that the phenotype of persistent NREM dominant obstructed periodic breathing (vs. relatively pure CPAP-induced central sleep apnea) resolves in only a minority of patients over time. Mining (rescorings, computational analysis) of data sets such as the Apnea Positive Pressure Long-Term Efficacy Study15 may provide further insights; besides central apnea counts and periodic breathing indices, outcomes in terms of compliance, sleepiness and cognition will be important. What Javaheri et. al. have usefully shown is that classic central apneas are likely to reduce with time on CPAP. What remains to be determined are the best ways to identify/score strong chemoreflex influences on sleep respiration and the short/long-term impact of such influences. Development of simpler ways to measure loop gain or CO₂ reserve in the clinical sleep laboratory could be useful, and open a practical window into this dimension of sleep physiology and pathology.

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REFERENCES