

Complex Sleep Apnea: It Isn't Really a Disease

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Complex apnea is not a disease but comprises a vaguely defined group of entities with varying etiologies.¹ Many of its forms (e.g., treatment-emergent central apneas) are generally innocuous and self-limited.² The term “complex apnea” has recently gained popularity, despite its unclear definition. Various researchers and practitioners use the term to refer to a range of pathophysiological phenomena. A debate has ensued as to whether we should be “lumpers” or “splitters” with our terminology. The lumpers suggest using the term complex apnea to refer to any of a group of conditions in which patients with obstructive sleep apnea are refractory to treatment with CPAP. In contrast, splitters suggest the term be reserved specifically for patients with treatment-emergent central apnea. We are splitters because we believe the terminology should signify the underlying mechanism. If 2 different mechanisms are responsible for CPAP refractoriness, then 2 different terms should be used, particularly if they require different treatments. Splitting eliminates confusion and facilitates targeted treatment, rather than a “one size fits all” model/approach. In this article, we will first review the differential diagnosis of the various forms of complex apnea (or CPAP refractoriness), then summarize the possible underlying pathophysiological mechanisms, and finally conclude with some clinical recommendations and remaining questions.

A number of entities are frequently lumped into the term complex apnea, shown in Table 1. We have seen many cases in which patients were labeled as having complex sleep apnea, with little consideration given to the underlying cause. For instance, inadequate or excessive titration and weight gain may lead to persistent sleep disordered breathing despite CPAP. However, in most cases, the underlying problem can be addressed on an individual basis, without the use of expensive devices. In the case of inadequate or excessive titration, the breathing pattern can be stabilized by simply retitrating the patient using careful attention to detail. In the case of treatment-emergent central apneas, data suggest these events generally resolve spontaneously over time. If changes in body weight alter CPAP requirements, then adjustment in CPAP level and/or facilitating weight loss

may be the most advisable approach. In some cases, expensive devices are being used unnecessarily for problems that can be readily solved using straightforward means. Thus, the “literature” on complex apnea must be viewed cautiously as a result of this heterogeneity.

In many studies, complex apnea is defined by the development of central apnea in the OSA patient during the initial CPAP titration,^{3,4} previously described as treatment-emergent central apnea. Clinical experience has suggested that these events resolve spontaneously over time, since ongoing CPAP therapy is not a recognized cause of central sleep apnea. The pathogenesis of treatment-emergent central apnea, however, is unknown and is poorly studied.⁵ Several theories have emerged, based largely on speculation. One hypothesis is that changes in CO₂ excretion occur with the relief of upper airway obstruction. That is, a high upper airway resistance can damp the ventilatory control system, reducing the efficiency of CO₂ excretion.⁶ With the application of CPAP, the upper airway is opened, making the arterial CO₂ tension lower for any given set of ventilatory conditions. If the fall in PaCO₂ yields a value below the so-called CO₂ apnea threshold, then central apnea would be expected.⁷ Over the course of several days to weeks, the CO₂ apnea threshold is known to change, resulting in resolution of the central apnea. A similar phenomenon has been reported at high altitude and following tracheostomy, whereby central apnea and/or periodic breathing is well known to resolve spontaneously over time.^{8,9} Retrospective studies exploring these patterns must be viewed cautiously, since the most problematic cases are typically the individuals who undergo repeated sleep studies and thus bias the results. Large prospective studies now being performed have thus far confirmed that treatment-emergent central apneas rarely persist on follow-up polysomnography, reinforcing the idea that treatment-emergent central apneas are usually self-limited.¹⁷

Several other hypotheses have also been proposed for the emergence of central apnea following the initiation of CPAP therapy. First, overtitration of CPAP is thought to lead to central apnea, although the mechanisms are poorly understood. One factor may be the activation of lung stretch receptors, which may inhibit central respiratory motor output. Another possibility is that washout of CO₂ from the anatomical dead space may occur if mask leak or mouth breathing develop at high CPAP levels. However, dead space could increase on CPAP by raising the transmural pressure across the trachea and pharynx if no leak is occurring. Such CPAP overtitration may occur if there is an overreliance on nasal

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Table 1—

Problem	Solution
Inadequate titration	retitrate, adjust CPAP level
Overtitration	reduce CPAP level
Substantial mask leak leaving residual events	adjust interface
Treatment-emergent central apnea	wait until it goes away
Residual sleepiness on CPAP	consider modafanil
Change in CPAP requirements due to body weight	lose weight, adjust CPAP level
Sleep transition apneas upon CPAP initiation	observation, consider hypnotic
Narcotic induced central apneas	reduce narcotic dose, alternative analgesic
Other causes of sleepiness	increase total sleep time, stimulants etc

pressure flattening as the impetus for raising CPAP level. Nasal pressure flattening is a good surrogate for inspiratory flow limitation during spontaneous breathing,¹⁰ but it is poorly validated and potentially misleading during CPAP delivery. Second, initiation of CPAP can worsen sleep quality, and transitions from sleep to wake to sleep can contribute to central apneas associated with state instability.¹¹ In such cases, the ventilatory response to arousal can drive the PaCO₂ below the CO₂ apnea threshold, yielding central apnea during subsequent sleep. This sleep disruption at the initiation of CPAP and the associated CO₂ fluctuations also tend to resolve over time as patients habituate to the interface and the application of positive pressure. Although sleep is also fragmented prior to initiation of CPAP, presumably it is the application of CPAP that exaggerates the overshoots in ventilation by reducing pharyngeal resistance and augmenting the ventilatory response to arousal. Third, despite the lack of evidence for the superiority of bilevel positive airway pressure compared with standard CPAP for treatment of OSA, many laboratories use bilevel quite frequently. With bilevel PAP, inspiratory positive airway pressure titration can lead to augmented tidal volumes, which drive down arterial CO₂ tensions.^{12,13} If the resulting PaCO₂ falls below the CO₂ apnea threshold, then central apnea will occur.^{14,15} Thus, a variety of phenomena can theoretically contribute to fluctuations of CO₂, all of which are easily treated with careful attention to mechanism; none require the development of new nomenclature.

Regarding clinical outcome data, 2 phase III randomized trials are generally required to change the standard of care. That is, 2 multicenter trials showing superior outcome with newer devices compared to standard of care (CPAP) need to be accomplished. At present, the existing outcome data for newer devices to treat complex apnea are sparse. Because the natural history of many forms of central apnea is resolution, careful well-controlled longitudinal studies are essential to draw any conclusions regarding optimal treatment. Because no long-term randomized clinical studies currently exist for complex apnea, the best available evidence is based on data from physiological studies. In these studies, physiologists have been careful to classify mechanisms of apnea based on underlying pathogenesis, and therefore the most prudent approach would be to treat breathing abnormalities based on underlying cause.

For the scientist, several questions remain unanswered, including: (1) what is the mechanism underlying CPAP-induced central apnea? (2) how/why does the CO₂ apnea threshold change over time? and (3) can the upper airway can be stabilized without yielding unstable ventilatory control?

For the clinician, some of the remaining questions include: (1) how should the rare, truly refractory cases (central apneas which persist on reassessment) be managed? (2) can the emergence of central apnea (albeit transient) influence long term CPAP adherence by worsening the initial experience with CPAP? (3) how/when should the new generation devices which have been developed by industry be used clinically? and (4) does emergence of central apnea carry any prognostic utility since existing studies are equivocal?^{2,16}

The lumpers vs. splitters argument will continue as to whether complex apnea is a disease or a sign common to a diverse group of etiologies. The arguments come down to a semantic debate regarding what constitutes a disease. The bottom line is that if we were to call complex apnea a disease, we would have a myriad of treatments based on different underlying pathophysiological processes. If we were to limit the definition of complex apnea to treatment-emergent central apneas, the bulk of the evidence suggests that this “disease” is transient and inconsequential. The use of expensive new generation devices is currently unproven in such cases.

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REFERENCES

- Gilmartin GS, Daly RW, Thomas RJ. Recognition and management of complex sleep-disordered breathing. *Curr Opin Pulm Med* 2005;11:485-93.
- Dernaika T, Tawk M, Nazir S, Younis W, Kinaseswitz GT. The significance and outcome of continuous positive airway pressure-related central sleep apnea during split-night sleep studies. *Chest* 2007;132:81-7.
- Morgenthaler TI, Gay PC, Gordon N, Brown LK. Adaptive servoventilation versus noninvasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. *Sleep* 2007;30:468-75.
- Morgenthaler TI, Kagramanov V, Hanak V, Decker PA. Complex sleep apnea syndrome: is it a unique clinical syndrome? *Sleep* 2006;29:1203-9.
- Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. *Chest* 2007;131:595-607.
- Skatrud J, Dempsey J, Badr S, Begle R. Effect of airway imped-

- ance on CO₂ retention and respiratory muscle activity during NREM sleep. *J Appl Physiol* 1988;65:1676-85.
7. Dempsey JA. Crossing the apnoeic threshold: causes and consequences. *Exp Physiol* 2005;90:13-24.
 8. Guilleminault C, Cummiskey J. Progressive improvement of apnea index and ventilatory response to CO₂ after tracheostomy in obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1982;126:14-20.
 9. White DP, Gleeson K, Pickett CK, Rannels AM, Cymerman A, Weil JV. Altitude acclimatization: influence on periodic breathing and chemoresponsiveness during sleep. *J Appl Physiol* 1987;63:401-12.
 10. Hosselet JJ, Norman RG, Ayappa I, Rapoport DM. Detection of flow limitation with a nasal cannula/pressure transducer. *Am J Respir Crit Care Med* 1998;157:1461-7.
 11. Jordan AS, McEvoy RD, Edwards JK, et al. The influence of gender and upper airway resistance on the ventilatory response to arousal in obstructive sleep apnoea in humans. *J Physiol* 2004;558:993-1004.
 12. Meza S, Mendez M, Ostrowski M, Younes M. Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. *J Appl Physiol* 1998;85:1929-1940.
 13. Johnson KG, Johnson DC. Bilevel positive airway pressure worsens central apneas during sleep. *Chest* 2005;128:2141-50.
 14. Malhotra A, Jordan AS. Did fat boy Joe need hormone replacement? *Sleep* 2006;29:16-8.
 15. Rowley JA, Zhou XS, Diamond MP, Badr MS. The determinants of the apnea threshold during NREM sleep in normal subjects. *Sleep* 2006;29:95-103.
 16. Lehman S, Antic NA, Thompson C, Catcheside PG, Mercer J, McEvoy RD. Central sleep apnea on commencement of continuous positive airway pressure in patients with a primary diagnosis of obstructive sleep apnea-hypopnea. *J Clin Sleep Med* 2007;3:462-6.
 17. Javeheri, S. Rare persistence of central events upon re-evaluation after initial emergence on CPAP, personal communication.