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COMMENTARY

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Multimodality Therapy for Sleep Apnea Syndromes

Commentary on Chowdhuri et al. Treatment of central sleep apnea in US veterans. J Clin Sleep Med 2012;8:555-563.

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The fixation on unimodal approaches to management of "sleep apnea" defies biological reality. Perhaps the incredible success of continuous positive airway pressure (CPAP) for obstructive sleep apnea is at least partially to blame, but the increasing evidence for sleep apnea phenotypes have not resulted in a meaningful translation to patient care. Taking obstructive sleep apnea, studies compare CPAP with an oral appliance, or with weight loss, or placebo, depending on the precise scientific question and the desire to show "equivalence" or at least clinical effectiveness (e.g., hypoglossal nerve stimulation, Provent) for aid to marketing and FDA approval.[1]

However, sleep apnea in a wider sense is the end result of interactive pathophysiological processes. These include sleep fragmentation propensity, upper airway obstruction, and respiratory chemoreflex under- or over-responsiveness.[2,3] Then why is it that there is so little data on combination therapies? Was there ever a clinical trial of myocardial infarction or congestive heart failure comparing unimodal therapies? Typically a pathophysiology-driven "basic cocktail" is tested against a new add-on. The need for improved management strategies for sleep apnea syndromes is evident—not more than 50% compliance/adherence for an apparently gold standard treatment that almost always shows sleep laboratory effectiveness, in patients seeking help for debilitating symptoms, should raise the possibility that maybe our gold is a metal of lesser worth. The clinical challenge is even greater in those with central or complex apnea and hypoventilation syndromes, where advanced modes of ventilation are being evaluated as stand-alone therapies, such as adaptive ventilation in congestive heart failure-associated periodic breathing.[4] If there is one condition where sleep fragmentation, obstructive elements, and respiratory decontrol interact, it is in heart failure patients.

The paper by Chaudhuri et al.[5] in this issue of the journal is an important one. Though not randomized, it seems to reasonably support the beneficial effect of supplemental oxygen in improving sleep-respiration in those with significant central sleep apnea, using a threshold of a central apnea index $\geq$ 5/hour of sleep. The delay in response is intriguing and likely reflects an interaction of sleep state effects (REM, stable NREM rebound) and direct biological effects of oxygen, including plausible changes in redox state. Looking closely at the data shows that stage N1 remains high, and some important information about the characteristics of the "optimal response" are missing (duration, sleep stage, and state). The definition of the optimal response also leaves something to be desired: is getting the CAI under 5/hour really a valid biological target? Other limitations of the paper include not scoring respiratory effort related arousals and hypopneas that do not have a 50% signal reduction. During titration, getting rid of major discrete events is relatively easier than normalizing sleep-breathing, and use of the alternate criteria when supplemental oxygen is added (thus directly modifying one of the scoring tags) can overestimate efficacy. Though periodic breathing was recognized, using the 10-minute criterion (which has no specific biological basis) will exclude shorter bursts of periodic breathing that are common in those with mixed apnea and have been well described at high altitude, the quintessential chemoreflex-induced sleep apnea model. Nevertheless, the study is a very important contribution to the literature and was just begging to be done.

Table 1 lists some of the options available to target the different pathophysiological processes in sleep disordered breathing syndromes. The therapies available to overcome obstruction are relatively straightforward, and some combinations are logical (weight loss + CPAP). However, the oral appliance vs. CPAP story has taken a gladiatorial color—what about combined therapy, especially those who have high pressure requirements? Most centers probably offer this on a case-by-case basis, as we do, but there may be additional potential benefits of minimizing mouth breathing and preventing an oronasal mask from pushing the jaw backwards during sleep. Positive pressure + a sedative are a logical approach to the anxious patient and those with severely fragmented sleep, and a subset of patients could benefit over the long term. The sedative could also improve blood pressure dipping,[6] which is frequently abnormal in sleep apnea patients. In hypoventilation syndromes and in those with pulmonary pathology affecting gas exchange such as chronic obstructive lung disease, supplemental oxygen could be a useful adjunct to bilevel ventilation by allowing targeting both CO_2 and O_2 end-points; adding O_2 is commonly done in clinical practice, but is there an advantage to keep the saturations closer to 98% vs. 90%? The latter target results in vulnerability to significant desaturations with changes in body position, sleep stage, mask or mouth leak, and minor respiratory events. Part of the effectiveness of Provent may relate to minimizing hypocapnia.[7]

The approach to management of various hyperresponsive chemoreflex syndromes (central and complex sleep apnea, peri-

Table 1—Targeting therapy to pathology in sleep apnea management

Pathophysiological target	Modality
Upper airway obstruction	Positive pressure (various), oral appliance, various soft tissue and bone-based surgeries, Provent, oral negative pressure, hypoglossal nerve stimulation, weight loss including bariatric surgery, body positioning (non-supine), lower body negative pressure
Sleep fragmentation propensity	Sleep hygiene, treating circadian phase abnormalities, sedatives
Hyporesponsive respiratory chemoreflex	Bilevel ventilation, volume-target pressure support ventilation, acetazolamide, weight loss including bariatric surgery, O_2
Hyperresponsive respiratory chemoreflex	Adaptive ventilation, sedatives, acetazolamide, O_2, CO_2 based approaches including dead space, body positioning, Provent (?), cardiac pacing, lower body negative pressure (?)
Disordered integration (opiates, brain stem pathologies)	Adaptive ventilation, O_2, CO_2 modulation

odic breathing) is challenging and unlikely to be solved by unimodal therapy. First, the disease needs to be properly quantified. Scoring event-by-event introduces a strong bias in the direction of obstruction, as flow-limitation is common in periodic breathing sequences. The update of respiratory scoring criteria have made a real effort to aid us in characterizing central hypopneas,[8] yet leave it optional—why should anything considered important be optional? If it is assumed, as stated in the article, that "separation of hypopneas into central or obstructive is not clinically indicated in the majority of patients," then we are never going to accurately phenotype sleep apnea. It is likely that there was far more "central" disease both before and after treatment in these patients than that quantified by a central apnea count. Using a 10-minute threshold to tag periodic breathing minimizes the recognition of this pattern; the new criteria more readily enable identifying periodic breathing.[8] The REM vs. NREM severity difference is blurred when global apnea-hypopnea or respiratory-disturbance indices are computed; NREM dominance is characteristic of strong respiratory chemoreflex effects. The bimodality of NREM sleep, where periods of stable breathing can occur during N2, can result in the premature declaration of CPAP success in NREM-dominant sleep apnea syndromes. Second, we should have greater expectations from the definition of success. In fact, the end point of success should be the same for obstruction or central sleep apnea syndromes—elimination of all respiratory events including respiratory effort related arousals, normalizing sleep quality, and optimal clinical outcomes (e.g., daytime sleepiness and fatigue, blood pressure dipping). In the Chaudhuri study, stage N1 remained markedly elevated—in all probability, there was significant residual sleep apnea subthreshold to the scoring criteria used. Equally possible is that these patients have an increase in sleep fragmentation propensity independent of sleep apnea, as has been noted in complex apnea[9] and congestive heart failure.[10] A "sleep stabilizer" (aka sedative) would be a logical addition here.

Hypocapnia driven respiratory instability is the most important factor in central apnea syndromes—rebreathing approaches[9] and acetazolamide are logical adjuncts, even to adaptive ventilation. The sad part is that much of the above may well remain devoid of high levels of evidence—there is little incentive to study these systematically, never mind the enormous cost and little return to the use of freely available generic drugs. Sedatives have been traditionally abhorrent entities in sleep apnea management. Perhaps it is time to revisit this dogma, given: (1) the availability of sedatives with acceptable impact on respiration[11] (moreover, positive pressure will protect if used at the same time); (2) the recognition of the role of arousals in amplifying sleep apnea severity; (3) induction of blood pressure dipping; and (4) beneficial effects in central apnea at sea level[12] and at high-altitude,[13] thus a logical option as adjunctive therapy in the hyperresponsive chemoreflex syndromes. It would make clinical sense to avoid sedatives in REM-dominant obstructive sleep apnea and reserve this approach to NREM-dominant central/complex apnea.

Targeting ataxic respiration such as may occur with the use of opiates, brainstem disorders, or Parkinson disease follows no simple rule, and various combinations of positive (including adaptive) pressure, O_2 and CO_2 modulation, and perhaps acetazolamide, may be required.

How can the field evaluate multimodality treatment options? It may require prospective clinical trials by consortia whose members are the average sleep center, who more than anyone else, have an incentive to accurately phenotype sleep apnea and use all appropriate available options.

CITATION

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DISCLOSURE STATEMENT

Dr. Thomas is a patent holder of an approach to use adjunctive CO_2 added to positive airway pressure for treatment of central and complex sleep apnea; co-patent holder/license (To MyCardio, LLC) for technology using the ECG to detect and quantify sleep apnea phenotypes. **Off-label use:** Multimodality approaches to sleep apnea treatment involve off-label use of FDA approved products (masks) and drugs (e.g., acetazolamide, sedatives).