Carbon Dioxide in Sleep Medicine: The Next Frontier for Measurement, Manipulation, and Research

Commentary on Wang et al. Hypercapnia is a key correlate of EEG activation and daytime sleepiness in hypercapnic sleep disordered breathing patients. *J Clin Sleep Med* 2014;10:517-522.

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Carbon dioxide (CO₂) is the most important regulator of respiration and blood pH. Papers are published with scant new information every so often that largely focus on clinical descriptions of hypercapnic individuals, often obese. While there is intense basic science interest in CO₂ sensitive neurons in the brainstem, including the Phox2b/neurokinin-1 receptor (NK1R)-expressing neurons in the pre-Bötzinger complex (pre-Bötzc),¹ and exposing the carotid bodies to hypocapnia induces periodic breathing,^{2,3} the science and industry of sleep-breathing medicine has generally neglected CO₂. Much of the information on chronic exposure to elevated but low levels of CO₂ comes from submarine research, targeting sustained ambient concentrations in the low single digits.⁴⁻⁸ Acute exposure to high concentrations of CO₂ results in extreme dyspnea and death; the gas has anesthetic properties and can induce a reversible isoelectric EEG.⁹ Demonstrating slowing of EEG rhythms with hypercapnia¹⁰ and power loss in classic oscillatory bands¹¹ (besides increased slow wave sleep associated with respiratory failure¹²) is nonspecific and not informative on pathobiological mechanisms. Increased inhaled CO₂ does suppress cerebral metabolic rate of oxygen¹³ and reduces resting state functional connectivity.¹⁴ While sympathetic drive is reliably increased acutely by hypercapnia, acclimatization mechanisms at the cellular and neural circuit levels, which can be remarkably potent enabling life at otherwise lethal CO₂ levels, remain to be elucidated. We are not sure if there is a true CO₂ sensor equivalent to hypoxia-inducible factors vs. simply pH mediated changes, or if there are profound direct effects of CO₂ on inflammatory responses, the metabolome, the transcriptome, or epigenetic regulation. Widespread systemic dysregulation is plausible, and some data is suggestive. Hypercapnia can induce mitochondrial dysfunction through increased levels on microRNA-183, which decreases expression of isocitrate dehydrogenase.¹⁵ Hypoxia-hypercapnia cycles are neurotoxic.¹⁶ Obesity hypoventilation (vs. obese controls) was reported to show an increase in the pro-atherosclerotic RANTES chemokine, a decrease in the anti-inflammatory adipokine adiponectin, and impaired endothelial function.¹⁷

The paper by Wang et al. is a timely reminder that we neglect CO₂ to our peril.¹⁸ Though the study was not primarily designed to answer the specific question of CO₂ and EEG/sleepiness/cognition, and the therapeutic precision could have been better,

the data strongly suggest an adverse and partially reversible impact of hypercapnia on brain function in the context of sleep disordered breathing. Detailed neurocognitive assessments were not reported, and if done, perhaps will be in another publication. Hypercapnia will be seen increasingly in association with obesity in children and adults, and a range of hypoventilation syndromes from neuromuscular or pulmonary disorders. Do we have a relatively silent “hypercapnic dementia” epidemic coming, just a large number of individuals at second gear? Even if CO₂ is normal in the day, can we assume that moderate hypercapnic during sleep is harmless? We are largely blind to the degree and severity of hypercapnia in laboratory and home sleep testing. Hypoxia has always taken center stage in “sleep apnea medicine,” and the study of hypoxia biology is highly mature and constantly progressing. CO₂ has not lit the same exploratory fires under clinicians and scientists. Why is that so?

Measurements and the emerging differentiated phenotype drives therapeutic strategies, and the field seems to be largely marching in place clinically with regard to CO₂, even when the research data supports moving to new approaches and greater recognition of respiratory chemoreflex influences, hyperactive or hypoactive. A comparison of the approaches (**Table 1**) taken by the American Academy of Sleep Medicine’s scoring manual and International Classification of Sleep Disorders-3rd Edition (both available online at www.aasmnet.org), are reflective of some of the ambivalence we face. There are numerous problems with clinical application of both sets of criteria for accurate phenotyping. For Cheyne-Stokes respiration, the quintessential association of hyperactive respiratory chemoreflexes that usually result in hypocapnia: (1) The manual describes a pattern that is basically a diagnosis (a CSR index ≥ 5 /h of sleep), yet the ICSD-3 specifies that these should make up $\geq 50\%$ of all scored events. So, a CSR related index of 30 in a patient with an overall AHI of 61 will be considered obstructive apnea, which makes little clinical sense. (2) Central hypopnea scoring is “optional” in the scoring standards, yet recognition of CSR is recommended. The events which make up CSR are essentially strings of central apneas and hypopneas. How can this be reconciled? (3) The cycle length of 40 seconds is recommended as a minimum for a CSR event. However, events both at sea level (often) and high

Table 1—Determining hypercapnic and hypocapnic sleep disordered breathing phenotypes

Pattern	AASM Scoring Manual	ICSD-3
Cheyne-Stokes breathing	Score a respiratory event as Cheyne-Stokes breathing if BOTH of the following are met: a. There are episodes of ≥ 3 consecutive central apneas and/or central hypopneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of ≥ 40 seconds. b. There are ≥ 5 central apneas and/or central hypopneas per hour of sleep associated with the crescendo/decrecendo breathing pattern recorded over ≥ 2 hours of monitoring.	Criteria (A or B) + C + D must be met A. The presence of one or more of the following: 1. Sleepiness. 2. Difficulty initiating or maintaining sleep, frequent awakenings, or non-restorative sleep. 3. Awakening short of breath. 4. Snoring. 5. Witnessed apneas. B. The presence of atrial fibrillation/flutter, congestive heart failure, or a neurological disorder. C. PSG (during diagnostic or positive airway pressure titration) shows all of the following: 1. Five or more central apneas and/or central hypopneas per hour of sleep. 2. <i>The total number of central apneas and/or central hypopneas is $> 50\%$ of the total number of apneas and hypopneas.</i> 3. The pattern of ventilation meets criteria for Cheyne-Stokes breathing (CSB). D. The disorder is not better explained by another current sleep disorder, medication use (e.g., opioids), or substance use disorder.
Central hypopneas	If electing to score central hypopneas, score a hypopnea as central if NONE of the following criteria are met: a. Snoring during the event. b. Increased inspiratory flattening of the nasal pressure or PAP device flow signal compared to baseline breathing. c. Associated thoracoabdominal paradox occurs during the event but not during pre-event breathing	General criteria for central sleep apnea B. PSG demonstrates all of the following: 1. Five or more central apneas and/or central hypopneas per hour of sleep (PSG). 2. <i>The number of central apneas and/or central hypopneas is $> 50\%$ of the total number of apneas and hypopneas.</i> 3. Absence of CSB.
Sleep hypoventilation	If electing to score hypoventilation, score hypoventilation during sleep if EITHER of the below occur: a. There is an increase in the arterial PCO_2 (or surrogate) to a value > 55 mm Hg for ≥ 10 minutes. b. There is ≥ 10 mm Hg increase in arterial PCO_2 (or surrogate) during sleep (in comparison to an awake supine value) to a value exceeding 50 mm Hg for ≥ 10 minutes.	Criteria for obesity hypoventilation Criteria A-C must be met A. Presence of hypoventilation during wakefulness ($\text{PaCO}_2 > 45$ mm Hg) as measured by arterial PCO_2 , end-tidal PCO_2 , or transcutaneous PCO_2 . B. Presence of obesity ($\text{BMI} > 30$ kg/m ² ; > 95 th percentile for age and sex for children). C. Hypoventilation is not primarily due to lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder (other than mass loading from obesity), medication use, neurologic disorder, muscle weakness, or a known congenital or idiopathic central alveolar hypoventilation syndrome.

altitude (always) in patients with positive pressure induced or amplified respiratory instability have short cycles that are less than 30 seconds. If 40 seconds is a requirement, then these short-cycle events will be falsely characterized as obstructive (the default). (4) Flow limitation excludes a “central hypopnea” in the scoring manual yet this idea has been conclusively shown to be false from the following data: (a) at high-altitude, a pure chemoreflex form of sleep apnea, flow-limitation occurs frequently; (b) heart failure patients with otherwise classic CSR can demonstrate flow-limitation; (c) the airway can close during polysomnographic central apnea; (d) central hypopneas demonstrate flow-limitation.

In clinical practice, snoring can be seen in association with CSR—but usually occurs associated with the arousal—while in a more purely obstructive event, snoring occurs during the event and transiently resolves during the arousal. As phenotype determines our treatment approach, the current bias of scoring to obstructive events has the potential to result in inappropriate treatment choices. It is also important to note that periodic

breathing detection by therapeutic devices follows proprietary manufacturer-specified algorithms that do not match visual evaluation of waveform data in all instances. All these issues are germane to the new category of treatment-emergent central sleep apnea—small tweaks in the criteria or their application can result in vastly varying rates of “complex apnea,” and is one likely reason for the difference in opinion of clinical importance in the field. Hypocapnia minimization¹⁹⁻²¹ is a logical strategy to improve management of hypocapnic respiratory instability syndromes that span CSR, hypocapnic CSA in all its forms, and NREM dominant obstructive apnea, so this issue is of direct clinical relevance.

Moving to hypoventilation, there is a surprising lack of a requirement for any clinical symptom, or requirement by accredited sleep laboratories to be able to measure CO_2 . This reflects the neglect that hypercapnia has faced technologically (development of a cheap, rapidly responsive, and accurate monitor, similar to an oximeter), in clinical diagnostic application (not measured in the vast majority of sleep laboratories

dealing with adults patients), tracking of home treatment responses in the ventilation community, and research exploring the basic science of hypercapnia at local and systemic levels. Obesity hypoventilation requires daytime hypercapnia regardless of the severity of sleep hypercapnia—do we really need to wait until wake CO_2 regulation fails before recognizing an important dysfunction? The 10-minute threshold is fairly arbitrary—even if a reasonable minimum, surely some severity grading is necessary? Pediatric norms ($> 25\%$ of the total sleep time as measured by either the arterial PCO_2 or surrogate is spent with a $\text{PCO}_2 > 50$ mm Hg) are better defined from polysomnography, but the correlation of the degree of hypercapnia to cognitive and cardiovascular outcomes, if any, remain to be established. The present/absent approach suggested by the criteria constrains the relevance of various degrees of elevations, which can be stage specific. The lack of data (as it is not measured) keeps us at the status quo—a cycle that continues to feed our ignorance. What about high values during brief periods of REM sleep in a patient with neuromuscular disease that cause arousals (and thus a transient reduction in CO_2) without quite hitting the duration mark? In fact, when positive pressure ventilation is successfully used and sleep is no longer fragmented, severe hypercapnia can emerge—prior to treatment, arousals protected the patient. Is hypercapnia on treatment as acceptable as hypercapnia before treatment? Do we call this treatment-emergent hypercapnia? The majority of sleep laboratories do not have the technology (and thus not even the technical expertise) to manipulate CO_2 . How do bilevel ventilators and the new volume target ventilators specifically designed for hypoventilation receive FDA approval with no need to measure or track CO_2 during use? We would never use supplemental O_2 without oximetry assessments. The business practice of sleep medicine is a further barrier, with no additional reimbursement for CO_2 -tracking and manipulation, which surely requires greater expertise, training, and perhaps certification than standard continuous positive airway pressure titrations.

There is unfortunately no polysomnographic feature equivalent to CSR to suggest hypoventilation, other than disproportionate oxygen desaturation, which can have other causes such as ventilation-perfusion mismatch. Respiratory rate may be low (contributing to hypoventilation) or high (a response to hypercapnia) and thus not diagnostically useful in adults, though in children tachypnea during sleep can suggest disease. Patients on opiates have a relatively unique phenotype of ataxic respiration, central apnea propensity, and mild hypercapnia. I have seen rare patients with classic CSR who are mildly hypercapnic, especially when congestive heart failure develops in a previously hypercapnic patient.

There is currently little incentive to integrate cheap and accurate CO_2 monitoring into routine clinical sleep medicine practice, including follow-up of treatment effects. Transcutaneous and end-tidal measurements should be an integrated part of polysomnography and even perhaps cardiopulmonary monitoring equipment, which will surely drive down the current high costs. Measuring end-tidal CO_2 accurately during positive pressure titration is challenging but feasible.¹⁹ An oximeter which can also measure capillary CO_2 could cause a paradigm shift in medical practice by exposing this largely hidden pathology. For

now, clinical and research sleep teams should consider biting the bullet and absorbing the cost of routine CO_2 measurements. Titrations of hypercapnic patients should target normalization of CO_2 , and this may require more than one night. For a start we need to have a better sense of the extent and nature of the challenge. The Academy could consider a clinical and laboratory practice standard update to require CO_2 measuring capability at least in high risk individual.

CITATION

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