Chapter 1
Hypercapnic Obstructive Sleep Apnea

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Case

Case 1: An example of hypercarbic OSA associated with obesity hypoventilation

Ms. E is a 51-year-old woman with severe obesity (BMI 49 kg/m^2), hypertension (HTN), poorly controlled type 2 diabetes mellitus (T2DM), gastroesophageal reflux (GERD), and suspected asthma. She was seen in the pulmonary clinic 10 years prior for suspected asthma. At that time, she endorsed snoring and daytime sleepiness. She was provided with a bronchodilator for possible reactive airways and a proton pump inhibitor to treat GERD, which was felt to be contributing factor to her intermittent dyspnea and wheeze. A sleep study was recommended, but not pursued, and the patient was lost to follow up.

She represented to the pulmonary clinic for evaluation of several years progressive dyspnea, becoming short of breath (SOB) after walking a few feet and waking 2–3 times at night with SOB and orthopnea. On questioning, she endorsed loud snoring, witnessed apneas, and excessive daytime sleepiness (EDS). She routinely slept from 10 PM to 7 AM with multiple awakenings to urinate. She would doze throughout the day, including when conversing with her family, watching television, or sitting. She did not drive.

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She has never smoked, moved to the United States in 2001 from South Asia, and lives with her husband. They have three grown children and no pets. She works as a homemaker.

On presentation she was hypoxic, SpO_2 83% on room air, improved to 95–96% on 3LPM nasal cannula. Her blood pressure was 150/100 mmHg. Weight was 300 pounds, height 63 inches. Her physical exam was notable for a modified Mallampati class IV airway, macroglossia with tongue scalloping, and a thick, short neck of 19 inches circumference. Lungs had decreased basilar breath sounds. Heart had a regular rate and rhythm with loud, split P2. Her lower extremities had chronic venous stasis skin changes and 3+ pitting edema bilaterally to the knees. There was concern for volume overload with a suspected diastolic heart failure exacerbation and/or pulmonary hypertension as well as probable OSA and possible OHS. She was admitted to the inpatient medical service for further management.

Her inpatient work-up included:

Transthoracic echocardiogram (TTE) that revealed a mildly dilated right ventricle with borderline systolic function, symmetric left ventricular hypertrophy with normal global and regional left ventricular systolic function, and borderline pulmonary hypertension. A right heart catheterization that demonstrated mixed pre- and post-capillary pulmonary hypertension with pulmonary capillary wedge pressure of 21 mmHg. A contrast-induced TTE was also conducted and showed no evidence of intra or extra-cardiac shunt. Her laboratory values were notable for polycythemia (hemoglobin, Hgb15.6 g/dL, hematocrit, Hct 50%) and an elevated serum bicarbonate, HCO_3 (32 mEq/L). An arterial blood gas (ABG) performed while on supplemental oxygen showed pH 7.36/$PaCO_2$ 66 mmHg/PaO_2 66 mmHg.

Aggressive diuresis was performed. She remained hypoxemic and required 1–2 LPM supplemental O_2 to maintain her $SpO_2 > 90\%$ during the daytime. She continued to desaturate with sleep, despite supplemental O_2, for which the sleep medicine service was consulted. Per sleep medicine recommendations, she was started on empiric auto-bilevel positive airway pressure (BPAP), with EPAP 8; pressure support, PS 4; and maximum IPAP 20 cm H_2O with plan for outpatient sleep study and sleep medicine clinic follow-up.

A split night polysomnogram (PSG) with transcutaneous carbon dioxide ($TcCO_2$) monitoring took place (Figs. 1.1 and 1.2).

The baseline portion, limited by the absence of REM sleep, showed severe, supine dominant hypoxic sleep apnea (apnea-hypopnea index (AHI) 4% 33 events/h, sleep baseline SpO_2 was 78–83% with O_2 nadir 71%, and 20% of the total sleep time spent $\leq$88%). There was evidence of hypercarbia ($TcCO_2$ 58–60 mmHg) and mild transitional instability characterized by post-arousal central apneas, attributed to heightened chemosensitivity in the setting of longstanding hypoxia. The titration was partially successful, with BPAP 14/8 cm H_2O improving flow in lateral NREM sleep, while pressures higher than 19/12 cm H_2O were needed in REM sleep. Four LPM O_2 was added to PAP, but REM desaturations continued. BPAP 19/13 cm H_2O with 6 LPM O_2 was initiated with recommendation for elevated (head end) or lateral sleep.

After using BPAP for 1 month, the patient returned for an supervised titration conducted in a lateral position to ensure full optimization of breathing in REM. This

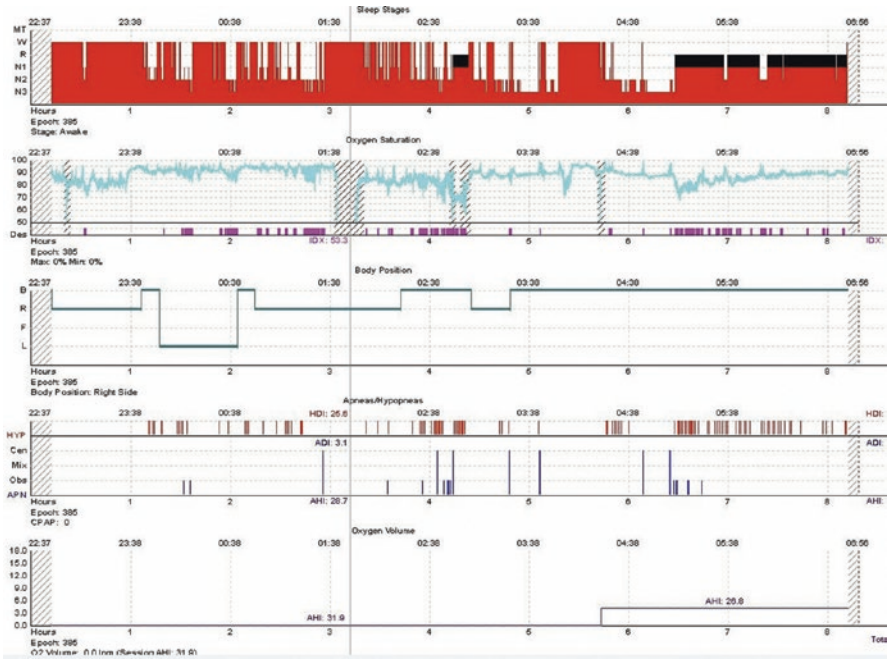

Fig. 1.1 Hypercapnic obstructive sleep apnea hypnogram. Notable abnormalities are severe sleep fragmentation and sustained hypoxia even when respiratory events are scarce. Though not in this figure, there was hypercapnia (see Fig. 1.2) associated with the hypoxia

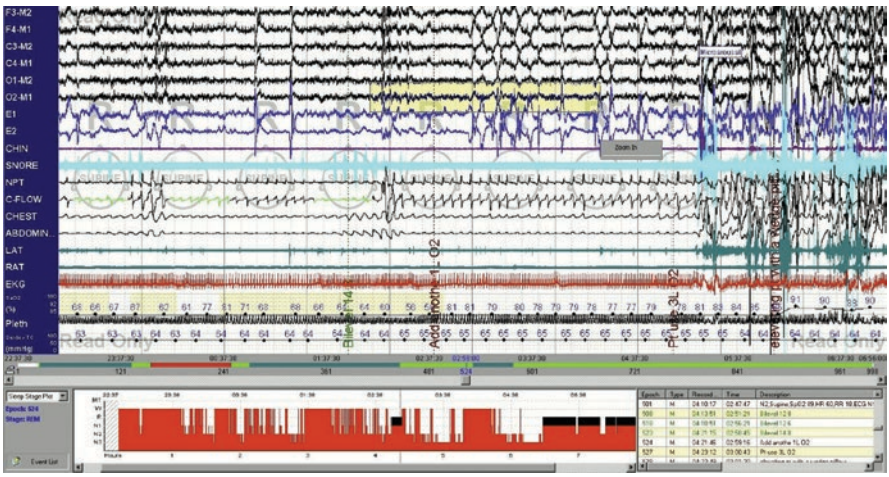

Fig. 1.2 Severe hypercapnia and hypoxia during positive pressure (bilevel) titration. The same patient as in Fig. 1.1. Though sleep is starting to show improved consolidation, there is severe hypoxia and substantial hypercapnia; this snapshot is from rapid eye movement sleep

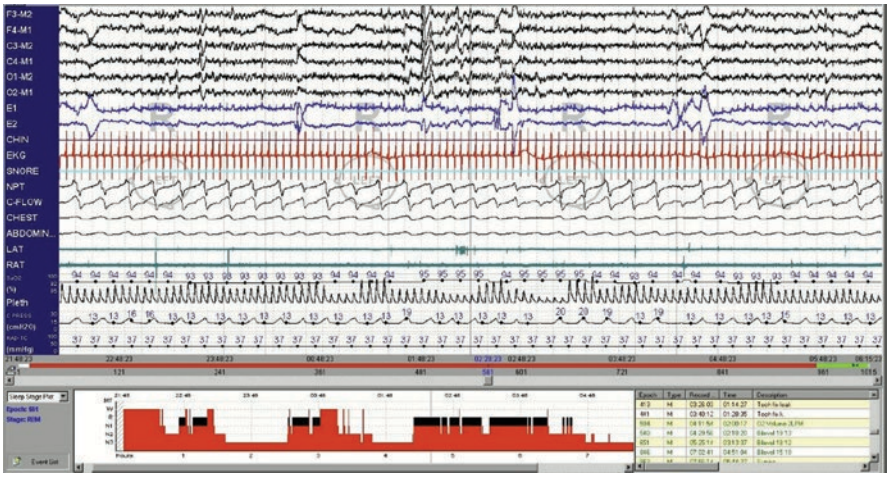

Fig. 1.3 Effect of positive airway pressure treatment on hypercapnic obstructive sleep apnea. Same patient as in Figs. 1.1 and 1.2, a repeat titration after 1 month of bilevel ventilation. Note the marked improvement of sleep consolidation, the persistence of slow wave sleep, and REM rebound and normalization of oxygen saturation and transcutaneous carbon dioxide levels

titration (Fig. 1.3) was successful, with SpO_2 maintained >90% on 4LPM O_2 and BPAP 19/13 cm H_2O controlling REM obstruction without destabilizing NREM breathing control. On BPAP, $TcCO_2$ improved (38–39 mmHg in wake, 37–38 mmHg during sleep).

The patient has continued to follow in sleep clinic. She has remained BPAP adherent with excellent clinical response and improvement in daytime alertness. Figure 1.4 shows Ms. E's BPAP device modem data from EncoreAnywhere™ (Respironics' remote server). A repeat ABG (conducted on room air after 2 months of nocturnal BPAP/O_2) showed pH 7.38/$PaCO_2$ 57 mmHg/PaO_2 47 mmHg. Polycythemia also improved with Hgb 12.1 g/dL and hematocrit 38%. The patient has had no subsequent hospitalizations. She is considering pursuing surgical weight loss.

Case 2: A unique phenotype of hypercarbic OSA, with coexistence of obstruction, hypoventilation, and high loop gain pathophysiology

Mr. P is a 59-year-old man with history of obesity (BMI 37 kg/m^2), COPD, HTN, heart failure with preserved ejection fraction (HFpEF), and pulmonary hypertension. Sleep apnea had been suspected for years, but he was never able to sleep in the laboratory during prior sleep study attempts and thus went undiagnosed and untreated. He presented to sleep medicine clinic with EDS and snoring and agreed to undergo another sleep study. A split-night PSG showed severe sleep apnea with severe intermittent hypoxia superimposed on baseline hypoxia (wake and sleep) (AHI 4% 72 events/h, RDI 87 events/h, O_2 nadir 56%) and hypoventilation ($TcCO_2$ ~ 70 mmHg). There was NREM variable cycle duration events and short cycle periodic breathing with obstructive features (flow limitation). Sleep hypoxia

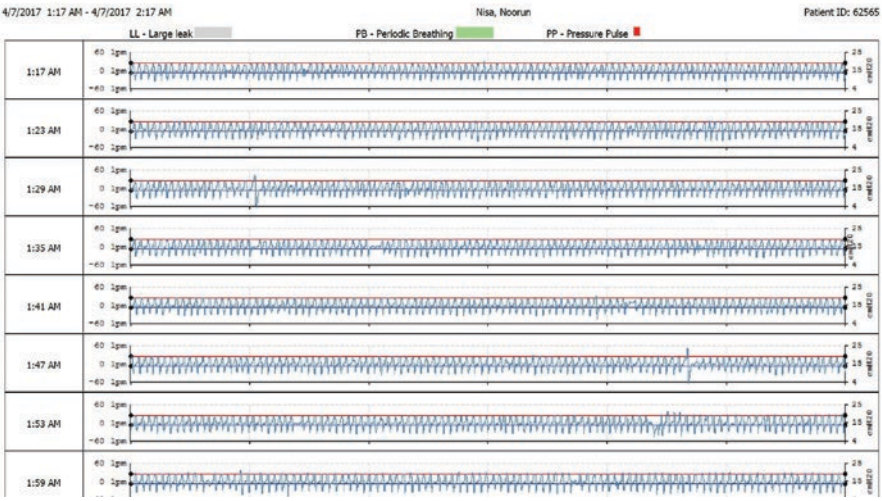

Fig. 1.4 Stable breathing on long-term bilevel ventilation. The same patient as in Figs. 1.1, 1.2, and 1.3. Stable breathing documented through the online EncoreAnywhere™ system. Each horizontal line is 6 min. Inspiratory pressure is the horizontal red line, expiratory pressure the horizontal blue line (19/13 cm H_2O)

was most pronounced during REM with V-shaped oximetry. The addition of supplemental oxygen improved but did not eliminate nocturnal desaturations, especially during REM.

The patient initially refused PAP, but due to repeated hospitalizations for acute on chronic heart and respiratory failure, he ultimately agreed to treatment and underwent a titration of BPAP and average volume-assured pressure support with auto-EPAP mode (AVAPS-AE). He was initiated on AVAPS-AE and oxygen with a recommendation for side or elevated (head end) sleep, weight management, optimization of volume status, and smoking cessation. Over time, he experienced clinical improvement with consistent use of AVAPS-AE. He quit smoking and remained treatment adherent to his congestive heart failure (CHF) regimen.

A repeat titration of PSGs was pursued to reassess optimal device settings. On repeat polysomnogram, high loop gain features and of NREM obstructive periodic breathing was pronounced, evident at baseline (Fig. 1.5) and worse with application of AVAPS-AE, while CPAP/O_2 with a non-vented mask (off label CO_2 modulation) provided superior control (Fig. 1.6, multistage hypnogram with AVAPS followed by CPAP titration; Fig. 1.7**,** NREM CPAP titration). Treatment was changed to CPAP 17 cm H_2O with a non-vented mask and 2LPM O_2 with addition of bedtime acetazolamide (125 mg).

His laboratory data improved over time. Prior to treatment with AVAPS-AE, his daytime ABG (on 4 LPM O_2) showed compensated respiratory acidosis – pH 7.37/$PaCO_2$ 73 mmHg/PaO_2 90 mmHg. Following the CPAP/O_2/non-vented mask titration and use, optimization of CHF, and smoking cessation, hypercarbia on his room

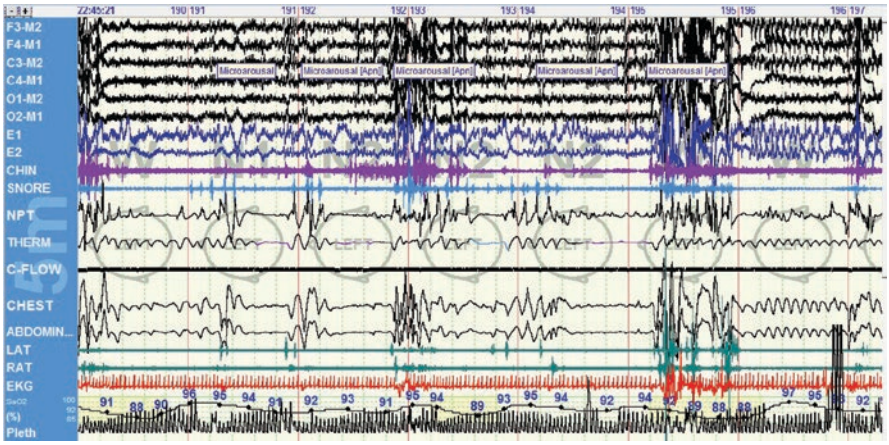

Fig. 1.5 Polysomnographic phenotype of high loop gain obstructive sleep apnea. Note the short cycle lengths (less than 30 s) and the free admixture of obstructive and central events, in non-rapid eye movement sleep

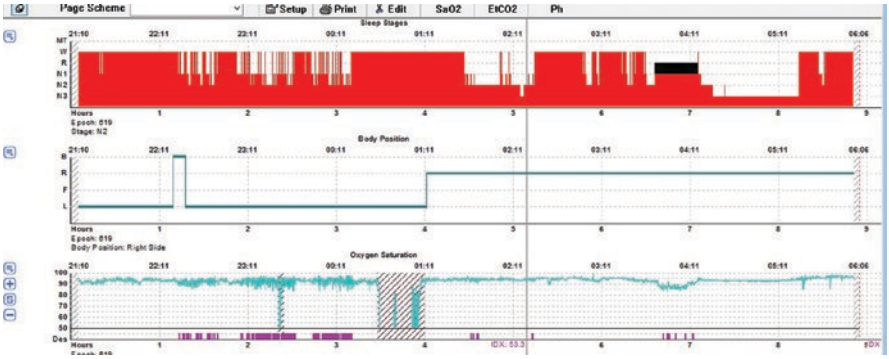

Fig. 1.6 Hypnogram of AVAPS followed by CPAP titration. High loop gain signal in a hypercarbic patient. The same patient as in Fig. 1.5 and this figure. The clue to a high loop gain is the pattern of oxygen desaturations – a "band-like" pattern, which occurs only in the presence of high loop gain and similar respiratory events, which is evident here during the AVAPS portion of the study. The patient is on their right side during CPAP titration, and despite CPAP 17 cm H_2O and supplemental oxygen, there is mild hypoxia in REM sleep. The pattern is distinctly different from the band-like desaturation seen before CPAP therapy

air ABG resolved – pH 7.38/ $PaCO_2$ 40 mmHg/ PaO_2 72. His serum bicarbonate similarly demonstrated normalization, decreasing from 40 mEq/L pre-PAP to 24 mEq/L after consistent use. Prior to PAP treatment (and also in the setting of smoking), he was polycythemic with hemoglobin of 18.8 g/dL and hematocrit of 60.5%, after smoking cessation and consistent PAP use this resolved – hemoglobin 14.1 g/dL, hematocrit 45.9%.

He has been clinically stable without further hospitalizations.

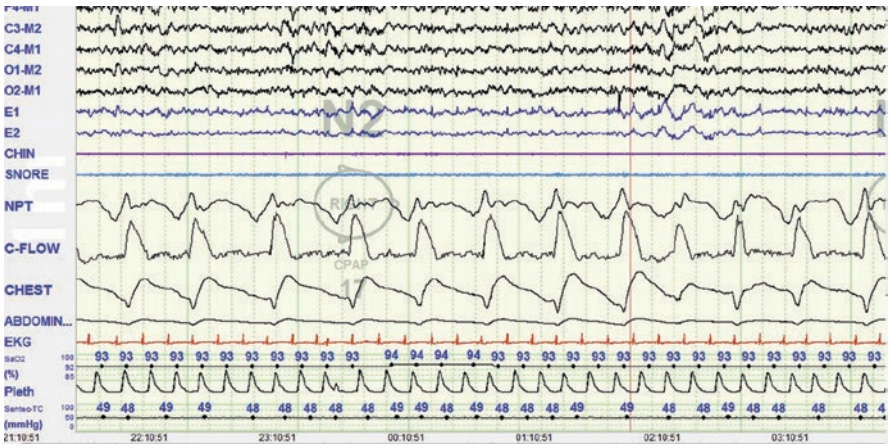

Fig. 1.7 Treatment of high loop gain hypercapnic OSA. CPAP, non-vented mask to buffer CO_2 fluctuations, and 2 L/min supplemental oxygen added to CPAP. This mask configuration reduces CO_2 fluctuations and thus aids in stabilization of respiratory motor output. Though stabilized, the patient is mildly hypercapnic. Typical high loop gain apnea including idiopathic central sleep apnea, periodic breathing, and complex/treatment-emergent apnea is as a group hypocapnic. The coexistence of multiple pathologies such as heart failure and chronic obstructive lung disease changes the stable state CO_2 needed to achieve respiratory rhythm stability

Discussion

Hypercapnic obstructive sleep apnea encompasses a variety of sleep apnea phenotypes which require varied management. Case 1 above illustrates an example of typical obesity hypoventilation with obstructive sleep apnea, controlled with the use of BPAP and supplemental oxygen. In contrast, in Case 2 above, the management is more complicated as the primary disease phenotype evolved over time. Since obesity hypoventilation syndrome is discussed in Chap. 11, our discussion will focus on hypercapnic OSA with periodic breathing, detailing the background pathophysiology and management strategies.

Hypocapnic periodic breathing or central sleep apnea typical of heart failure and idiopathic central sleep apnea, and hypercapnic central sleep apnea associated with hypercapnia typical of opioid use or advanced chronic obstructive lung disease are relatively intuitive and easy to conceptualize. Models of periodic breathing emphasize the interplay of elevated loop gain and airway collapsibility [1]. Hypercapnic periodic breathing is not intuitive and opens conflicts with key therapeutic principles. Specifically, hypocapnic periodic breathing requires targeting elevated loop gain and minimizing hypocapnia, while hypercapnic syndromes require ventilatory support and adequate opening of the upper airway. Reducing CO_2 destabilizes hypercapnic periodic breathing, but raising CO_2 further would seem to be undesirable in hypercapnic syndromes. How can this conflict be resolved?

Respiratory Chemoreflexes and Disease

The respiratory chemoreflexes have a profound role in the pathophysiology of several disease states. These include congenital and acquired hypoventilation syndromes [2, 3], obstructive sleep apnea [4], high-altitude illness [5], sympathetic activation in congestive heart failure, chronic obstructive lung disease, and chronic renal failure. A profound impact of heightened respiratory chemosensitivity is seen in congestive heart failure, where the slope of the hypercapnic ventilatory response is increased, which is in turn associated with sympathoexcitation, periodic breathing, and increased mortality [6, 7]. In healthy subjects, exposure to hypoxia across durations of hours to weeks, under natural or experimental conditions, reliably induces increases in blood pressure, muscle sympathetic activity, and catecholamines [8–10]. The effect of hypoxia can outlast the stimulus duration. Complex time scales of hypoxic responses have been described, but in conditions such as sleep apnea and chronic obstructive lung disease, marked sympathoexcitation is the typical result.

Trait Versus State Components of the Respiratory Chemoreflex

There is ample evidence of *genetic/trait* effects on respiratory chemoreflexes, although the effects on sleep respiration were not evaluated in many of these reports. Certain mice and rat strains are highly susceptible (or resistant) to periodic breathing following hypoxic exposure [11, 12]. Several knockout mice have altered (usually blunted) hypoxic and hypercapnic [13] sensitivity. Evidence in humans include (1) individual differences in hypoxic ventilatory sensitivity and its correlation with altitude-induced periodic breathing [14]; (2) familial clustering of chemoreflex sensitivity; and (3) ventilatory instability during sleep onset in healthy individuals being greater in those with high peripheral chemosensitivity [15].

State effects are also important as evidenced by:

1. Hypoxic ventilatory responses (HVR) change in response to sustained hypoxia including at altitude.
2. There is increased prevalence of mixed forms of sleep apnea post-stroke in heart failure, and increased chemoreflex sensitivity in periodic breathing associated with congestive heart failure or post-stroke [16, 17].
3. A reduction of periodic breathing occurs following cardiac transplantation [18, 19].
4. An increase of central apneas occurs with age. However, chemoreflexes have been reported to be reduced in the elderly, so the mechanisms are likely more complicated.
5. Post-tracheostomy central sleep apnea reduces in severity over time [20, 21].
6. Recent evidence from a dog model of acute pulmonary venous hypertension suggests that increases in left ventricular end-diastoic pressure (LVEDP) may reduce CO_2 reserve [22]. Of possible relevance, systolic and diastolic cardiac

dysfunction is common in severe sleep apnea [23, 24], but obesity, age, and hypertension are confounders [25].
7. A 30% overnight increase in chemoreflex sensitivities has been reported in sleep apnea, while in the non-apnea group, there was a significant overnight reduction in chemoreflex thresholds (approximately 5%), without changes in sensitivities [26].
8. Changes in hypercapnic ventilatory response (HCVR) (reduced sensitivity) have been reported following therapy of obstructive but not central sleep apnea. Reduction in HVR but not HCVR was reported following 4 weeks of positive airway pressure therapy for obstructive sleep apnea [27], while NREM CO_2 reserves improved within a month [28].

The trait vs. state dimension can only be speculated regarding hypercapnic periodic breathing. When heart failure is present, plausibly the high loop gain is acquired over a background of abnormal lung and chest wall mechanics, imparting the rhythm despite elevated CO_2. In those rare patients with morbid obesity without chronic obstructive lung disease or heart failure who show short-cycle hypercapnic periodic breathing, we suspect the elevated loop gain is probably genetic. Long-term tracking will be required to answer these questions. In the case of Mr. P, morbid obesity with COPD despite uncontrolled HFpEF allowed for the overriding phenotype to appear as OHS/OSA. Overtime, NREM high loop gain became more pronounced and required change in PAP mode and addition of strategies to minimize loop gain.

The Importance of Hypocapnia and the CO_2 Reserve in Central Sleep Apnea and Periodic Breathing

NREM sleep unmasks a highly sensitive hypocapnia-induced apneic threshold, whereby apnea is initiated by small transient reductions in arterial CO_2 ($PaCO_2$) below eupnea, and respiratory rhythm is not restored until $PaCO_2$ has risen significantly above eupneic levels. The CO_2 reserve varies inversely with both plant gain and the slope of the ventilatory response to reduced CO_2 below eupnea. The reserve is highly labile in NREM sleep [29]. Reductions in cerebrovascular responsiveness to CO_2 result in a gain in chemoreflex control of sleep breathing and may also play an important role in mediating respiratory instability during sleep. Both central ventral medullary and peripheral carotid body chemoreceptors are known to mediate chemoreflex control of respiration. Studies that have tried to dissociate the central and peripheral components suggest that rapid responses are dependent on the peripheral chemoreceptors [30–32].

Maintaining steady CO_2 levels stabilizes sleep respiration. In contrast, high concentrations of CO_2 fragment sleep by inducing arousals secondary to respiratory stimulation and sympathoexcitation [33, 34]. A key challenge has been delivery of CO_2 in a clinically adequate, tolerable, and precise manner. This involves holding the CO_2 steady and just above the NREM sleep CO_2 threshold – protecting the CO_2 reserve while maintaining sleep consolidation. A recent study confirmed the

stabilizing effects of CO_2 modulation in treating apnea syndromes with a substantial central component [35]. Thus, keeping the CO_2 above the NREM CO_2 threshold is critical for management of central apnea syndromes regardless of etiology or the proportion of the phenotype which is centrally mediated.

The addition of a closed volume (dead space) to exhale increases rebreathing of exhaled air and results in a rapid increase in CO_2 levels and an increased tidal volume and respiratory rate. This concept has been used in mechanical ventilation to reduce hypocapnia for several years, and, more recently, it has been successfully used to treat central sleep apnea with Cheyne-Stokes breathing in heart failure [34]. Combining hypocapnia minimization with positive pressure is logical, and we have shown that keeping CO_2 *jus*t above the apnea threshold with the use of dead space/enhanced expiratory rebreathing space (EERS) is an effective adjunct to PAP therapy [36]. There is only a small (1–3 mm Hg) increase in inspiratory CO_2 because of the positive pressure-induced washout and subtidal volume dead space. The physiological target for titrations with enhanced expiratory rebreathing space is to maintain $ETCO_2$ at the low normal range for sleep. Dynamic CO_2 manipulation (delivery restricted to a specific phase of the respiratory cycle) may, in future studies, improve on the stabilizing effects of CO_2 [37].

Hypercapnic periodic breathing seems to respond as well as hypocapnic periodic breathing to CO_2 stabilization. As these patients are chronically hypercapnic, holding the $ETCO_2$ close to wake levels is well tolerated, as it is the stable level of exposure for the patient. Dropping the $ETCO_2$ by even 2–3 mm Hg in NREM sleep in hypercapnic periodic breathing patients can markedly destabilize respiration. For Mr. P., AVAPS mode provided too much ventilatory support, resulting in relative hypocapnia, while CPAP had minimal impact on NREM $ETCO_2$.

Polysomnographic Recognition of High Loop Gain Sleep Apnea

A key requirement for treatment of hypercapnic periodic breathing is optimal recognition of high loop gain effects on sleep breathing, beyond pure Cheyne-Stokes and central apneas. Scoring of respiratory events in sleep apnea patients has traditionally been biased to an obstructive phenotype, though the recent update of the 2007 AASM guidelines has criteria for scoring central hypopneas and short sequences of periodic breathing/Cheyne-Stokes respiration [38]. 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 [39], even at simulated altitude [40], 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 [41]. Expiratory pharyngeal narrowing occurs during central hypocapnic hypopnea [42], directly supporting the concept that the presence of flow limitation alone cannot be used to distinguish obstructive and central hypopneas [40]. Treatment-emergent central sleep apnea as currently defined requires a central apnea-hypopnea index ≥5/h

of sleep with centrally mediated respiratory events constituting ≥50% of all respiratory events during CPAP titration, in those who do not fulfill criteria for primary central sleep apnea or periodic breathing on the diagnostic polysomnogram. However, publications of treatment-emergent central sleep apnea did not score central hypopneas or periodic breathing. *Thus, we believe that descriptions of low (<5%) persistence of "treatment-emergent central sleep apnea" are incorrect and reflect reliance solely on scoring classic central apneas* [43, 44]. The guideline for recognition of "Cheyne-Stokes respiration" require a cycle duration of at least 40 s, but we have shown that even shorter cycle times in the range of 20–25 s is typical of NREM-dominant sleep apnea [45], reminiscent of high-altitude periodic breathing. *The most characteristic feature of chemoreflex driving is not the morphology of individual events but NREM-dominance and timing/morphology of sequential events (nearly identical) in a consecutive series of events* [46]. *This key concept is relevant regardless of CO_2 levels.* More regular use of CO_2 monitoring would be required to even know the true prevalence of this pattern. As the cachexic heart failure caricature is replaced by the obese heart failure patient, it should be anticipated that hypercapnic periodic breathing will become more prevalent.

Carbonic Anhydrase Inhibition

Acetazolamide, a diuretic and carbonic anhydrase inhibitor, diminishes the ventilatory response of the peripheral chemoreceptors to hypoxia, decreases loop gain, and reduces the ventilatory response to arousals [47–50]. Its efficacy to reduce high-altitude periodic breathing and associated sleep fragmentation, a model of high loop gain effects on sleep, is well established. Other biological effects (e.g., aquaporin) of possible relevance occur [51]. In animal models, it has been shown to lower the $ETCO_2$ apnea threshold and widen the difference between the eupneic and $ETCO_2$ thresholds [52]. Acetazolamide has been used in treating non-hypercapnic CSA or CSR, in patients with and without chronic heart failure [53]. The drug may convert those with mixed obstructive and central sleep apnea to mostly obstructive (the reverse of CPAP-induced central sleep apnea). Acetazolamide has been successfully used as CPAP adjuncts at high-altitude [54, 55]. Zonisamide [56] and topiramate [57] have carbonic anhydrase inhibitory effects and could be used in the place of acetazolamide. New data suggests that the carbonic anhydrase inhibition effects are not key to reducing carotid body activity [58]. Recent data support a role for acetazolamide in improving intermediate outcomes in obstructive sleep apnea, suggesting benefits that may go beyond changes in the apnea-hypopnea index [59].

Acetazolamide is the single most important adjunct we have discovered for hypercapnic periodic breathing, used as a single 125–250 mg dose 30–60 min prior to bedtime. The effect is nearly immediate (within an hour) and thus can be tested in the sleep laboratory itself. The effect is not dependent on renal mechanism and may involve some combination of central stimulation and direct reduction of carotid body contribution to loop gain.

Oxygen as Adjunctive Therapy for Hypercapnic Periodic Breathing

Supplemental oxygen delivered by nasal cannula during sleep or through a positive pressure device is well tolerated. In studies in which O_2 was administered to patient with OSA, hypoxemia, but not the AHI or sleep quality is improved [60]. In a randomized controlled study of CPAP vs. O_2 in obstructive sleep apnea in patients with cardiovascular comorbidity, O_2 was not beneficial [61], suggesting that merely improving oxygenation is insufficient. Little is known regarding the effect of oxygen treatment for OSA on long-term cardiovascular risk.

In contrast to its effect in OSA, supplemental oxygen in patients with central sleep apnea has shown more consistent effectiveness, not only improving oxygenation but often leading to a reduction in the frequency of apneas and hypopneas, with a reported reduction in AHI of 40–75%. However, effectiveness is typically partial, and residual sleep apnea and sleep fragmentation are common. Adding oxygen to CPAP [62, 63] may benefit CSA and treatment-emergent CSA via a reduction in responsiveness of peripheral chemoreceptors and loop gain [64, 65]. A study in a US Veteran's population showed benefit in a predominantly CSA population, but the polysomnographic changes were delayed by as much as an hour or more [66]. Respiratory event cycles can lengthen with the use of O_2. Such a change may "reduce" the respiratory event index but not imply a true stabilization of respiration. In heart failure, reduced chemoreflex activation can provide additional benefits, but overall the likelihood that O_2 will be effective therapy alone is small. Oxygen therapy may expose the underlying obstructive components and cause a "shift" from central to obstructive events [67].

When oxygen is used as part of a "cocktail" to treat hypercapnic periodic breathing, there are potential synergistic mechanisms which could be harnessed: (1) eliminating hypoxia and (2) reducing elevated loop gain. Moreover, in the presence of positive airway pressure treatment, worsening of hypercapnic would not be expected as long as hyperoxia is avoided.

Adaptive Ventilation for Hypercapnic Periodic Breathing

Assessing therapeutic efficacy during the use of the adaptive servo ventilators (ASVs) is challenging. The devices provide anti-cyclic ventilatory support [68]; the flow and effort signals reflect combined patient and ventilator contributions and can thus give a false sense of success. "Pressure cycling" is a response of an ASV to ongoing periodic breathing. When pressure cycling persists, sleep fragmentation can be severe even if respiration is "improved" [69, 70]. This pattern means that the periodic breathing pathology is ongoing, necessitating the continued pressure response. When the ventilator enables stable respiration, cycling between the minimum and maximum pressure support zone is minimal. Bench testing of ASV algorithms shows device-specific response characteristics, but stable breathing does not

occur across a range of simulated central apnea patterns [71]. Long-range home ASV data assessment show some degree of persistent pressure cycling in the majority of patients, while the simultaneous device-calculated AHI can be zero or less than 1, suggesting overestimation of efficacy and underestimating maladaptive outcomes [72].

ASVs are powerful devices and, if there is patient-ventilatory asynchrony, may induce hypocapnia, excessive cycling of pressures, arousals, distorted flow patterns, and physical discomfort [72]. The Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF) study showed no benefit and increased mortality when an ASV was used in chronic heart failure patients with reduced ejection fraction [73]. The entry criteria were an ejection fraction ≤45% and AHI > 15/h with ≥50% central events and a central AHI ≥ 10/h. Hypocapnia, metabolic alkalosis, hemodynamic perturbations, and excessive sympathetic driving associated with excessive pressure cycling are speculated mechanisms of adverse outcomes [74].

Our limited experience with ASV in hypercapnic periodic breathing is that with expert manipulation of expiratory pressure support and driving inspiratory pressures, benefits can be obtained, but only in the presence of adjuncts such as acetazolamide and stabilizing CO_2. The Philips-Respironics BiPAP Auto SV Advanced™ offers somewhat greater customization of pressures and is our more commonly used ASV device for this group of patients.

Each patient is different and needs to be treated as such. Assuming that every hypercapnic patient can be optimized with BPAP or AVAPS does not recognize the biological challenges that such patients can demonstrate. Ms. E was managed with BPAP/O_2 for hypercapnic OSA due to OHS/OSA. However, Mr. P, a patient with HFpEF, COPD, obesity, and chronic hypercarbic respiratory failure, presented with a different hypercapnic OSA phenotype. In his case, optimal sleep breathing therapy could only be achieved with access to the correct data (PSG, CO_2), recognition of PSG phenotype (i.e., identifying NREM periodic breathing, even when obstructive), a balanced approach to treatment (i.e., tolerating mild REM hypoventilation rather than inducing NREM periodic breathing), and the use of adjunctive therapies (CO_2 via mask, acetazolamide).

Clinical Pearls

1. Sleep hypercarbia (REM > NREM) typically precedes daytime hypercarbic respiratory failure and can be seen in a variety of pathologies related to the lungs (COPD, ILD), thoracic cage (kyphosis, obesity), and respiratory muscles (NMD). Medications (sedatives, opioids) can also cause hypercarbia, due to suppression of respiratory drive that becomes most pronounced during sleep.
2. Hypercarbic OSA can therefore be seen in patients with comorbid lung disease, obesity, and NMD and in those who use chronic sedatives or opioid medication.

3. Hypercarbic OSA encompasses a variety of sleep apnea phenotypes. While obstruction is the most common, mixed obstruction and high loop gain physiology with NREM periodic breathing can also occur. Opioid-related dysrhythmic breathing and chronic heart failure induced high loop gain features can coexist with hypercarbic OSA. These combinations are more challenging to optimize and require attention to treatments that target breathing control in addition to those that attenuate airflow obstruction. Appropriate PSG phenotype recognition is key, as is a balanced approach to treatments and understanding of treatment conflicts. Adjunctive therapies are often needed, including off-label use of acetazolamide and/or application of small amounts of rebreathing space (CO_2 modulation). CPAP may be superior to BPAP or AVAPS in some cases (as shown in Case 2). Adaptive ventilation (in non-HFrEF conditions) can also be considered.
4. To diagnose and properly manage hypercarbic OSA, PSG and nocturnal CO_2 data is required. Baseline daytime ABG is also recommended.
5. The appropriate mode of nocturnal positive pressure support is based on assessment of sleep ventilation data with attention to OSA phenotype as well as underlying pathology, severity of hypercarbia, and/or nocturnal hypoxemia.
6. Over time, sleep breathing pathophysiology can evolve and change, also potentially impacting optimal therapy. As demonstrated in the two case examples, improvements in baseline hypercarbia and polycythemia may be seen with treatment adherence.

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